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Original article

Omitting radiation therapy after lumpectomy for pure DCIS does not reduce the risk of salvage mastectomy

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ABSTRACT

Purpose: Radiation therapy (RT) after breast-conserving surgery (BCS) for Ductal Carcinoma in Situ (DCIS) halves the risk of local recurrence (LR). The omission of RT is often supported by the paradigm that patients who develop LR can be salvaged with further breast-conserving therapy leading to higher rates of breast preservation and improved quality of life. However, population-based, long-term rates of breast preservation in women treated by upfront BCS ± RT are unknown.

Methods and materials: Women diagnosed with pure DCIS from 1994 to 2003 treated with BCS ± RT in Ontario were identified. Median follow-up is 12 years. The development and treatment of LR and contralateral breast cancers were determined by administrative databases with validation. The 10-year mastectomy-free survival was calculated using the Kaplan-Meier method. The impact of RT on breast preservation was determined by propensity-adjusted cox proportional hazards model.

Results: The cohort includes 3303 women with DCIS; 1649 (50%) underwent BCS alone, 1654 (50%) underwent BCS + RT. Women treated by BCS alone were more likely to develop a LR compared to those treated by upfront BCS + RT (20.8% versus 15.5%, $p < 0.001$). Mastectomy was used to treat LR in 57.4% (197/343) of women who recurred after BCS alone and 67.6% (174/257) of those who recurred after BCS + RT. Women treated with upfront BCS + RT had higher rates of bilateral breast preservation at 10 years compared to those treated by BCS alone (87.3% vs. 82.7%, $p = 0.0096$).

Conclusion: Local Recurrence after BCS alone does not favor breast preservation.

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1. Introduction

Despite strong evidence that radiation therapy (RT) after breast-conserving surgery (BCS) for ductal carcinoma in situ (DCIS) halves the risk of local recurrence (LR) and invasive local recurrence [1–8], the benefit of RT in the management of DCIS continues to be a matter of controversy. One argument against the use of RT is that patients who develop LR can be salvaged with further breast-

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conserving therapy such that the upfront omission of RT will lead to higher rates of breast preservation and minimal exposure to RT compared to upfront treatment with RT [9]. Bilateral breast preservation is an important determinant of quality of life for women with early stage breast cancer and DCIS [10,11]. There is a paucity of data on the management of LR, the extent to which further BCS (versus mastectomy) is used, and the resultant long-term rates of bilateral breast preservation. Population-based data provide insight into the *actual* treatment received by women, representing an amalgamation of clinicians' recommendations and patient preferences. We report the use of mastectomy in the management of LR and the impact of RT on the long-term rates of (bilateral) breast preservation in a population of women with pure DCIS treated by BCS alone or BCS + RT.

2. Methods

2.1. Study cohort identification

Identification of the population cohort was previously described [8]. We obtained copies of all breast pathology reports held at the Ontario Cancer Registry (OCR) and excluded cases with a final diagnosis of invasive breast cancer or benign disease ($N = 118,905$). We excluded 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 ($N = 2332$). The population cohort includes 5077 women with pure DCIS; 1774 cases were treated by mastectomy were excluded from this analysis. The study cohort included 3303 treated by BCS. Pathology review was performed in 2536 of 3303 (77%) cases at the time of this analysis. For the remaining cases, we abstracted data from the original pathology reports. For the remaining cases, we abstracted data from the original pathology reports, including the tumor size (mm), nuclear grade (low, intermediate, high, unreported), comedo necrosis (present, absent, unreported), multifocality (present, absent, unreported) and resection margin status (positive, negative, unreported). Since the margin width was not consistently reported it was not abstracted [8].

2.2. Treatment

Identification of treatment and outcomes for the cohort was previously described (8). We linked the cohort to administrative databases held at the Institute for Clinical Evaluative Sciences (ICES) by deterministic 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 Ontario Cancer Registry (OCR). For each case, we identified all breast surgical procedures performed within 6 months of diagnosis. Postoperative RT was scored for patients receiving RT within 12 months of diagnosis. All surgical treatments and RT data were validated by chart review. The date of DCIS diagnosis is the date of the initial breast cancer surgery associated with a pathological diagnosis of DCIS. Tamoxifen usage in women over 65 years of age was identified through linkage with the Ontario Drug Benefit database. Tamoxifen usage in women <65 years of age was not available.

2.3. Outcomes and treatment of local recurrence

LR is defined by invasive breast cancer or DCIS that developed in the ipsilateral breast six months or more beyond the initial DCIS. Contralateral breast cancer is defined by DCIS or invasive breast

cancer that developed in the opposite breast beyond the diagnosis of DCIS. To determine the treatment of the LR or contralateral cancer we first identified all breast surgical procedures, categorized as breast-conserving surgery or mastectomy, performed 6 months or more beyond the date of DCIS diagnosis by deterministic linkage with CIHI. To determine the histology of the recurrence we linked each breast surgical procedure with the OCR, CIHI and reviewed individual pathology reports when available to determine if the recurrence was invasive breast cancer, DCIS or other (including benign and LCIS). We calculated the risk of 'ipsilateral' mastectomy by calculating the 10-year risk of mastectomy on the same side as the index DCIS lesion. To determine the overall rate of bilateral breast preservation, we calculated the 10-year risk of 'any' mastectomy performed in either breast for any reason (irrespective of the development of a subsequent breast event), to account for mastectomies that might have been performed for pain, cosmesis or patient preference. Overall mortality is estimated from the date of initial DCIS to the date of death from any cause determined from the RPDB. The last date of follow-up is March 31, 2014.

2.4. Statistical analysis

Descriptive analyses were conducted to examine differences in measured patient characteristics among women treated by BCS alone or BCS + RT. Chi-square tests were used for categorical variables and t-tests for continuous variables. We examined the impact of RT on: 1) the odds of salvage mastectomy for individuals who developed LR, 2) risk of ipsilateral mastectomy and 3) risk of any mastectomy. To account for systematic differences between women treated by BCS alone versus BCS + RT, we calculated each woman's propensity for receiving RT (propensity score). The propensity score for each patient was calculated as the linear component of the logistic regression model of the probability of receiving RT conditional on measured covariates: margins, surgery year, age, subtype, multifocality, nuclear grade, comedo necrosis. We adjusted for the propensity score in the multivariable regression analyses under a forward selection process to balance the distribution of observed baseline covariates between subjects treated with and without RT [12]. We calculated the 10-year rate of ipsilateral breast preservation (ipsilateral mastectomy-free survival) and 10-year rate of bilateral breast preservation (any mastectomy-free survival) using the Kaplan-Meier method and evaluated differences between curves by the log-rank test. The association between characteristics and the odds of salvage mastectomy was examined using multivariable logistic regression, and the association between characteristics and the hazard of ipsilateral mastectomy (and the hazard of any mastectomy) was examined using Cox proportional hazards regression models. SAS 9.4 was used for all analyses with p -value of <0.05 considered to be statistically significant.

3. Results

3303 women were diagnosed with pure DCIS and treated conservatively from 1994 to 2003; 1649 (50%) were treated by BCS alone and 1654 (50%) received BCS + RT. The mean follow-up was 11.2 years for patients treated by BCS alone and 12.7 years for those treated with BCS + RT. Women that were treated with BCS + RT were more likely to be younger (median age 56 vs 61; $p < 0.001$) and have lesions that were larger (median tumor size 8.85 vs 7.68; 0.014), necrotic (61.4% vs 50.9%; $p < 0.001$), high grade (38.2% vs 29.2%; $p < 0.001$), multifocal (22.0% vs 18.3%; $p = 0.008$) and less likely to have unknown margin status (20.1% vs. 26.0%, $p < 0.001$) compared to those treated by BCS alone (Table 1). Among women treated by BCS alone, 343 (20.8%) developed LR ($N = 202$ invasive (12.2%), $N = 141$ DCIS (8.6%)). Among women treated by BCS + RT,

Table 1
Patient characteristics by initial treatment of DCIS.

	BCS Only N = 1649	BCS + RT N = 1654	Whole Cohort N = 3303	p-Value ^a
Age at diagnosis				
median	61 (51–71)	56 (49–65)	58 (50–68)	<0.001
<40	27 (1.6%)	49 (3.0%)	76 (2.3%)	<0.001
40–50	307 (18.6%)	366 (22.1%)	673 (20.4%)	
50–60	416 (25.2%)	598 (36.2%)	1014 (30.7%)	
≥60	894 (54.2%)	639 (38.6%)	1533 (46.4%)	
missing	<=5 (0.3%)	<=5 (0.1%)	7 (0.2%)	
Tumor Size (mm)				
mean ± SD	7.68 ± 12.26	8.85 ± 12.27	8.28 ± 12.28	0.014
unknown	545 (33.1%)	445 (26.9%)	990 (30.0%)	<0.001
Necrosis				
Present	840 (50.9%)	1016 (61.4%)	1856 (56.2%)	<0.001
absent/	264 (16.0%)	193 (11.7%)	457 (13.8%)	
Nuclear grade				
Low	173 (10.5%)	99 (6.0%)	272 (8.2%)	<0.001
Moderate	769 (46.6%)	758 (45.8%)	1527 (46.2%)	
High	482 (29.2%)	632 (38.2%)	1114 (33.7%)	
Unknown	225 (13.6%)	165 (10.0%)	390 (11.8%)	
Multifocality				
Present	302 (18.3%)	364 (22.0%)	666 (20.2%)	0.008
absent	1347 (81.7%)	1290 (78.0%)	2637 (79.8%)	
Subtype				
Solid	959 (58.2%)	1146 (69.3%)	2105 (63.7%)	
Cribriform	470 (28.5%)	356 (21.5%)	826 (25.0%)	
Micropapillary	45 (2.7%)	34 (2.1%)	79 (2.4%)	
Other	54 (3.3%)	35 (2.1%)	89 (2.7%)	
Margin status				
Negative	1083 (65.7%)	1182 (71.5%)	2265 (68.6%)	<0.001
Positive	137 (8.3%)	139 (8.4%)	276 (8.4%)	
Unknown	429 (26.0%)	333 (20.1%)	762 (23.1%)	
Recurrence				
Ipsilateral	343 (20.8%)	257 (15.5%)	600 (18.2%)	<0.001
contralateral	110 (6.7%)	124 (7.5%)	234 (7.1%)	0.36
bilateral	17 (1.0%)	13 (0.8%)	30 (0.9%)	
unknown	29 (1.8%)	14 (0.8%)	43 (1.3%)	

^a p-value compares the BCS alone group to the BCS + RT group.

257 (15.5%) developed LR (N = 164 invasive (9.9%), N = 93 DCIS (5.6%)). The 10-year local recurrence, cause specific and overall survival rates were 20.1%, 97.9% and 84.1% for women treated by BCS alone and 13.0%, 97.9% and 91.3% for those treated by BCS + RT (Table 1).

3.1. The treatment of local recurrence

Overall, 599 women developed LR and 370 (62%) were treated by mastectomy. Salvage mastectomy was used in more than half (57.4% (197/343)) of LRs that developed after BCS alone and in two-thirds (67.6% (174/257)) of LRs that developed after BCS + RT (p = 0.01). Salvage mastectomy was used in 61% (123/202) of invasive LRs and 53% (74/141) DCIS LRs (p = 0.12) that developed after BCS alone and, in 71% (116/164) of cases with invasive LR and 62% (57/92) of those with DCIS LR that recurred after BCS + RT (p = 0.15). Among women who developed LR within 5 years of diagnosis, 224/352 (59.1%) were treated by salvage mastectomy compared to 146/247 (63.6%) for those who developed LR > 5 years from initial diagnosis (p = 0.26).

We examined the impact of year of diagnosis on the management of local recurrence. For women treated by BCS alone, there was a small decline in the proportion of LRs treated by mastectomy depending of the year of LR. Between 1994 and 2003, 63.1% of patients had mastectomy compared to 2004–2014 where 47.6% of patients had mastectomy (p = 0.01).

We performed univariate and multivariable analyses to determine the impact of initial RT on the use of salvage mastectomy for

Table 2
Factors associated with the use of salvage mastectomy as treatment of local recurrence.

	Odds Ratio	95% CI		P value
		lower	upper	
Univariate				
Radiation	1.55	1.10	2.17	0.012
Age at diagnosis	0.97	0.96	0.99	0.0005
High nuclear grade	1.51	1.07	2.13	0.019
Multifocality	1.62	1.09	2.39	0.016
Positive margins	1.18	0.83	1.67	0.36
Year of diagnosis	1.01	0.95	1.08	0.66
Multivariable				
Radiation	1.33	0.93	1.89	0.12
Age at diagnosis	0.99	0.96	1.01	0.30
Multifocality	1.59	1.06	2.38	0.024

LR. On multivariable analysis, adjusting for propensity score and year of diagnosis, treatment of the index DCIS lesion with RT was not associated with a greater likelihood salvage mastectomy for LR (HR = 1.33, 95%CI: 0.93, 1.89, p = 0.12). The only baseline pathological factor associated with an increased risk of salvage mastectomy for LR was the presence of multifocality (HR = 1.59, 95% CI: 1.06, 2.38, p = 0.02) (Table 2).

3.2. Long-term risk of ipsilateral mastectomy

We then assessed the impact of initial RT on the risk of ipsilateral mastectomy. On multivariable analysis (adjusting for propensity score and year of diagnosis), RT was associated with a 28% reduction in the 10-year risk of ipsilateral mastectomy (HR = 0.72, 95%CI: 0.6, 0.87, p = 0.007). In addition, the presence of high nuclear grade (HR = 1.42, 95%CI: 1.15, 1.75, p = 0.01), multifocality (HR = 1.43, 95%CI: 1.16, 1.78, p = 0.001), solid subtype (HR = 0.71, 95%CI: 0.56, 0.91, p = 0.006) and initial positive resection margins (HR = 1.52, 95%CI: 1.23, 1.87, p > 0.0001) were statistically significantly associated with an increased risk of ipsilateral mastectomy (Table 3). The 10-year cumulative ipsilateral mastectomy-free survival risk is 85.5% for women treated by BCS alone and 89% for those treated by BCS + RT (p = 0.047) (Fig. 1).

3.3. Bilateral breast preservation

To determine the rates of bilateral breast preservation we

Table 3
Factors associated with ipsilateral mastectomy in women with DCIS treated by breast-conserving surgery.

	HR	95% CI		P value
		Lower	upper	
Univariate				
Radiation	0.83	0.692	0.997	0.047
Age at diagnosis <50 yrs (vs. ≥ 50 years)	1.72	1.42	2.09	<0.0001
Necrosis	1.28	1.04	1.6	0.021
High nuclear grade	1.55	1.29	1.87	<0.0001
Multifocality	1.66	1.35	2.026	<0.0001
Solid subtype (vs. other)	1.09	0.89	1.32	0.41
Positive margins (vs. negative)	1.22	1.01	1.48	0.039
Year of diagnosis	0.94	0.91	0.97	0.0004
Multivariable				
Radiation	0.72	0.6	0.87	0.0007
Age at diagnosis <50 yrs (vs. ≥ 50 years)	1.16	0.88	1.53	0.28
High nuclear grade	1.42	1.15	1.75	0.001
Multifocality	1.43	1.16	1.78	0.001
Solid subtype (vs. other)	0.71	0.56	0.91	0.006
Positive margins (vs. negative)	1.52	1.23	1.87	<0.0001

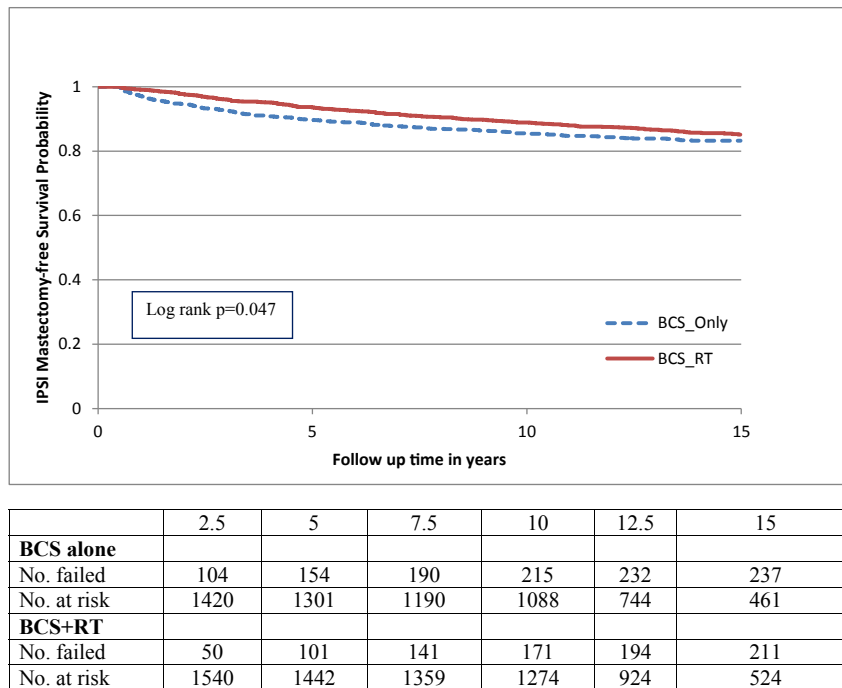


Fig. 1. Kaplan-Meier Ipsilateral Mastectomy-free Survival in Women with DCIS treated by Breast-conserving Surgery alone or Breast-conserving Surgery and Radiation. These curves depict the long-term probability of preservation of the ipsilateral breast. This analysis takes into account mastectomies performed on the same side as the index DCIS lesion. Patients whose index DCIS lesion was treated by BCS + RT had a higher ipsilateral mastectomy-free survival compared to those initially treated by BCS alone.

calculated the 10-year cumulative mastectomy-free survival taking into account mastectomies performed on either side for *any* reason including LR, contralateral disease, benign diagnoses, cosmetic purposes, patient preference or prophylaxis. For the whole cohort, 572 mastectomies were performed; the majority of mastectomies ($N = 553$ (97%)) were performed in individuals who developed LR (90%) or a contralateral breast cancer (7%). On multivariable analysis, treatment of the index DCIS lesion by BCS + RT was associated with a 29% reduction in the 10-year risk of *any* mastectomy ($HR = 0.71$, 95%CI: 0.60, 1.43, $p < 0.0001$) (Table 4).

Overall, the 10-year mastectomy-free survival rates (bilateral breast preservation) are 82.7% for women initially treated by BCS alone and 87.3% for those treated by BCS + RT ($p = 0.0096$) (Fig. 2).

Table 4
Factors associated with any Mastectomy in Women with DCIS Treated by Breast-conserving Surgery.

	HR	95% CI		P value
		Lower	Upper	
Univariate				
Radiation	0.803	0.681	0.946	0.0088
Age at diagnosis <50 yrs (v.s. ≥ 50 years)	1.692	1.421	2.015	<0.0001
Necrosis	1.12	0.97	1.43	0.093
High nuclear grade	1.429	1.209	1.688	<0.0001
Multifocality	1.564	1.302	1.88	<0.0001
Solid subtype (vs. other)	1.04	0.88	1.24	0.62
Positive margins (vs. negative)	1.17	0.985	1.391	0.07
Year of diagnosis	0.94	0.914	0.973	0.0002
Multivariable				
Radiation	0.71	0.60	0.84	<0.0001
Age at diagnosis <50 yrs (v.s. > 50 years)	1.16	0.91	1.43	0.23
High nuclear grade	1.3	1.08	1.57	0.007
Multifocality	1.39	1.15	1.69	0.0009
Solid subtype (vs. other)	0.72	0.58	0.89	0.0025
Positive margins (vs. negative)	1.40	1.16	1.70	0.0004
Year of diagnosis	0.92	0.89	0.95	<0.0001

4. Discussion

Minimizing the risk of LR and the risk of mastectomy are important determinants affecting the quality of life (QOL) of women with DCIS [11,13]. In one study evaluating the preferences of 120 women with DCIS and 240 unaffected women the fear of an invasive recurrence treated by salvage mastectomy was associated with the greatest detrimental effect on QOL [10]. In another study of 97 women with early, invasive breast cancer the fear of LR resulting in mastectomy was associated with a 7–10% reduction in QOL [11]. We previously reported the outcomes of a population of women with pure DCIS treated with breast-conserving surgery with or without RT [8]. We extended this analysis to assess the management of local recurrence, the impact of RT on the use of salvage mastectomy and to evaluate the long-term rates of bilateral breast preservation achieved after each therapeutic approach.

Overall, we found that women treated with RT had a 29% lower risk of mastectomy at 10 years compared to those treated by BCS alone ($HR = 0.71$, 95%CI: 0.60, 1.43, $p < 0.0001$). The cumulative 10-year mastectomy-free survival was 87.3% for women initially treated by BCS + RT and 82.7% for those treated by BCS alone ($p = 0.0096$). The higher rate of breast preservation is attributable to the lower risk of LR with RT and that a significant proportion of LRs (57.4% of LRs after BCS alone and 67.6% of LRs after BCS + RT) were treated with mastectomy, irrespective of histology, and year of LR. The probability of treatment by salvage mastectomy was similar for patients treated by BCS alone or BCS + RT ($HR = 1.33$, 95%CI: 0.93, 1.89, $p = 0.12$).

Our findings that most LRs are treated by salvage mastectomy are corroborated by published data from randomized trials and retrospective cohort studies of women with DCIS [1,4,14–17]. In the EORTC 10853 randomized trial of 1010 women treated by BCS with or without RT, 63% (94/149) of women who developed LR after BCS alone and 75% (64/85) of those who recurred after BCS + RT were

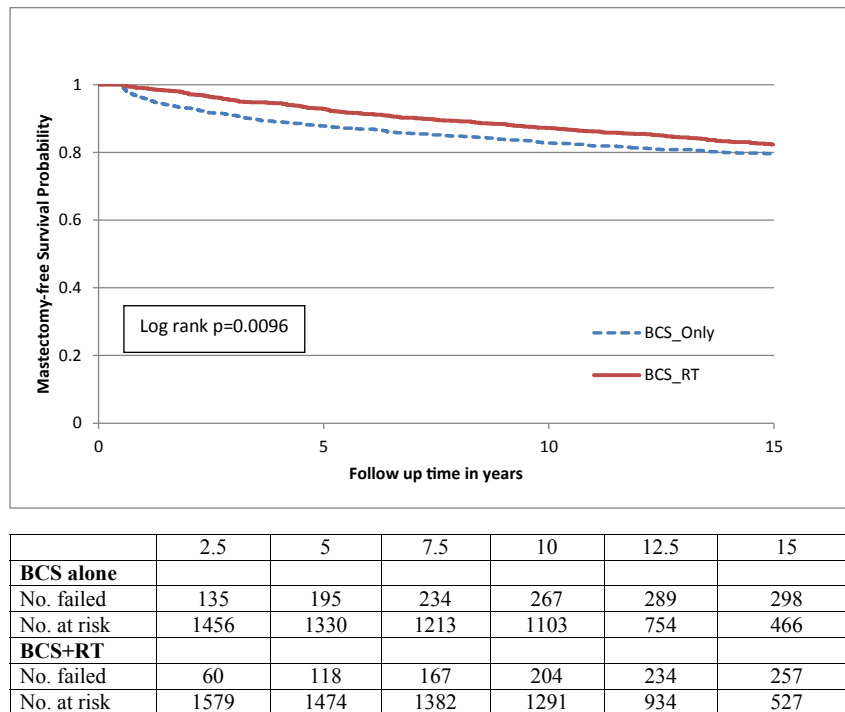


Fig. 2. Bilateral Breast Preservation in Women with DCIS treated by Breast-conserving surgery with and without Radiation: Kaplan-Meier Mastectomy-free Survival Estimates These curves depict the long-term probability of bilateral breast preservation by calculating the overall mastectomy-free survival rates. This analysis takes into account mastectomies performed on either breast performed for any reason. Patients whose index DCIS lesion was treated by BCS + RT had a higher probability of bilateral breast preservation (mastectomy-free survival) compared to those initially treated by BCS alone.

treated by salvage mastectomy [4]. Women treated by BCS alone had a higher probability of mastectomy at 15 years compared to those treated with BCS + RT (19% vs. 13%, HR = 0.66, 95% CI: 0.48, 0.90) [4]. In the NSABP B17 study which randomized 818 women to treatment by BCS alone or BCS + RT, 47% of women who developed LR after BCS alone and 57% of those who recurred after BCS + RT received salvage mastectomy [1]. In the ECOG E5194 cohort study of 670 selected women with favorable features of DCIS all of whom were treated by BCS alone, 56% of LRs were treated by mastectomy [14]. One study using data from the National Comprehensive Cancer Network identified 2939 women diagnosed with DCIS from 1997 to 2008 (80% received BCS + RT). Among 88 LRs, 85% (74/88) were treated by salvage mastectomy (with or without reconstruction). The investigators also reported the treatment of LR in 2995 women diagnosed with DCIS treated with BCS with or without RT from 1990 to 2001 identified from the Health Maintenance Organization Cancer Research Network. Among 182 LRs identified, 61% were treated by salvage mastectomy (with or without reconstruction) [17]. Overall, the proportion of women who receive salvage mastectomy as treatment of LR range from 48 to 58% for those who recur after upfront treatment by BCS alone and 57–84% for who recur after BCS + RT [1,4,14–17].

Our findings are in contrast to a previously published Markov model which concluded that treatment by BCS + RT for DCIS would lead to a lower long-term likelihood of breast preservation [9]. Inherent in this model was the assumption that one-quarter (ranging from 20 to 48% on sensitivity analysis) of women who recur (with stage 0 or I disease) after initial treatment by BCS alone and 100% of LRs that develop after BCS + RT will be treated by salvage mastectomy. In fact, our data, corroborated by data from randomized trials and cohort series found that a significantly higher proportion of LRs, ranging from 48 to 63%, that develop after BCS alone are treated by salvage mastectomy. It is also worth noting

that even among women who recurred between the years 2003–2014, half were treated by mastectomy. In addition, the discrepancy between our findings and the Markov model are further explained by the finding that mastectomy is not uniformly used in all women who recur after BCS + RT; up to a third of women will receive further breast – conserving therapy [1,4,14–17].

Several aspects of this study merit comment. This analysis is based on a very large population-based cohort with patients treated from 126 centres (academic and non-academic institutions) from a province with more than 13 million inhabitants. The analysis focused exclusively on patients treated with breast-conserving surgery, excluding those treated by primary mastectomy.

Treatment of the index lesion by BCS alone or BCS + RT was not randomly allocated but influenced by physicians' interpretation of the risks and benefits of radiation therapy, compliance with guidelines and patient preference. The proportion of patients receiving RT after BCS is well-balanced with those not receiving RT and the analysis was adjusted by the propensity to receive RT (propensity score), adjusting for imbalances between treatment groups. Being a population-based study, this represent outcomes reflective of patient's and surgeon's preferences (and hence a realistic picture of what happens to patients), while previous series were based on long term outcomes of randomized clinical trials and hence on a selection of patients subject to bias in term of treatment choice. Patients were treated from 1994 to 2003 and followed until 2014; the proportion of patients passing the 10 year mark is very large (11-year median follow-up), providing sufficient time to allow for the development of LR and strengthening the conclusion on long-term cosmetic consequences. Although data from the SEER registry report a temporal rise in the use of unilateral and bilateral mastectomy in the initial treatment for DCIS [18,19] we did not observe an increase in the rate of salvage mastectomy over time.

In summary, despite common belief, omitting radiation therapy

after breast-conserving surgery for pure DCIS does not result in a greater chance of breast preservation in case of local recurrence. Our findings suggest that patient attitudes and preferences are relevant both in the management of DCIS and in the management of local recurrence [20]. Women treated with RT, despite having higher risk factors, experienced a lower risk of LR and a greater likelihood of bilateral breast preservation at 10 years compared to women treated by BCS alone. Therefore, the argument of greater likelihood of breast preservation should not be part of the decision to omit RT after BCS.

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