Recurrence and mortality after breast-conserving surgery without radiation

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ABSTRACT

Background Breast-conserving surgery (bcs) and radiation therapy (rt) are the standard of care for early breast cancer; studies have demonstrated that adjuvant rt confers a protective effect with respect to recurrence, although no randomized trials have shown a survival benefit.

Methods This retrospective cohort study used Ontario data linked through ICES to examine patients treated for breast cancer between 1 April 2007 and 31 March 2014. The primary outcome was death or recurrence. Outcomes were compared between patients who did and did not receive rt.

Results The total cohort size was 26,279. The hazard ratios (hrs) for various outcomes were significantly higher for patients who did not receive rt than for patients who did: recurrence or death combined (hr: 2.49; 95% confidence interval (ci): 2.25 to 2.75), recurrence (hr: 2.33; 95% ci: 1.91 to 2.84), and death (hr: 2.28; 95% ci: 2.03 to 2.56). The hr for death was 1.81 (95% ci: 1.65 to 1.99) for patients having stage ii cancer compared with those having stage i disease. The hr for death was 1.97 (95% ci: 1.74 to 2.22) for patients having high comorbidity compared with those having little comorbidity.

Conclusions Adjuvant rt carries a protective effect with respect to recurrence and survival in patients with early-stage breast cancer. That survival benefit has not been appreciated in previous randomized trials and underscores the importance of rt as a component of breast cancer treatment.

Key Words Breast cancer, radiation therapy, death, recurrence, breast-conserving therapy

INTRODUCTION

Breast-conserving therapy, consisting of breast-conserving surgery (bcs) followed by radiotherapy (rt), has been shown to be equivalent to mastectomy in terms of survival for early-stage breast cancer.1–10 The rate of adjuvant rt use after bcs ranges widely, from as low as 66% to as high as 99%.11,12 A previous study from our group found that 86% of patients are appropriately treated after bcs13.

The benefits of rt with respect to local recurrence have been shown from the earliest studies comparing mastectomy with breast-conserving therapy, in which patients who do not receive rt are at increased risk of recurrence.1–3,10,14 Much of the previously published data from randomized controlled trials have supported the notion that rt does not affect mortality; however, data from population-based studies and meta-analyses show a survival benefit conferred by the receipt of rt.1–3,11,14–19

The purpose of the present study was to determine the effect on recurrence and survival of adjuvant radiation after bcs on a population level (“real-world” scenario) in a single-payer health care system.

METHODS

Study Setting and Design The residents of the province of Ontario (2016 population: 13.98 million)20 have access to universal health care and their interactions with hospital and physician services are recorded in administrative databases. Relevant datasets were linked using unique, encoded identifiers and were analyzed at ICES.
In this retrospective population-wide cohort study, all patients with a diagnosis of breast cancer (Ontario Cancer Registry) who underwent bcs in Ontario between 1 April 2007 and 31 March 2014 were included in the initial cohort. The definition of bcs was a hospital procedure code for breast lumpectomy for cancer concurrent with an ohip (Ontario Health Insurance Program) physician billing code for bcs. In a stepwise manner, the following exclusion criteria were applied: male sex; age less than 16 or more than 105 years; non-Ontario residence; no physicianbilling record for bcs within 2 days of the procedure date; breast cancer diagnosis more than 1 year before bcs; Hodgkin lymphoma (the most likely cause for non-breast radiotherapy to the chest); previous lumpectomy or mastectomy (to exclude patients likely to have previously been irradiated); history of lupus, scleroderma, or dermatomyositis; previous rt; unknown laterality (for the index bcs); and breast cancer stage not i or ii at the time of diagnosis. Figure 1 illustrates the cohort build. Table 1 shows baseline variables for the cohort by receipt or non-receipt of rt. SupplementaryTable S1 presents this study’s records (Reporting of Studies Conducted Using Observational Routinely Collected Health Data) statement.

Data Sources
Data were obtained from 7 linked Ontario databases: the Discharge Abstract Database and the Same Day Surgery database maintained by the Canadian Institute for Health Information (cihi), the National Ambulatory Care Reporting System, the ohip claims database, the Registered Persons Database, the iccs physician database, and the Ontario Cancer Registry. Supplementary Table S2 presents the full list of databases used.

Outcomes and Baseline Variables
Patients were considered to have received rt if there was evidence of rt to the chest recorded in the Activity Level Reporting database within 1 year of bcs.

The primary outcome of the study was death or recurrence. Recurrence was defined as either: ipsilateral lumpectomy or mastectomy more than 1 year after bcs, or more than 3 radiotherapy visits more than 455 days after lumpectomy. Follow-up ended on 31 March 2016, yielding a follow-up period of 2–9 years after lumpectomy. Baseline characteristics collected included age, neighbourhood income quintile (surrogate for socioeconomic status, adjusted for household size and housing costs), patient comorbidity, rurality (community population <10,000, reflecting access to daily rt), cancer stage, time from diagnosis to lumpectomy, fiscal year of the index event, laterality, surgeon age, surgeon sex, surgeon years since medical school graduation (years of experience), and hospital setting (academic or community).

We determined patient comorbidity using the Johns Hopkins (Baltimore, MD, U.S.A.) Adjusted Clinical Groups system (version 10)21. This method of case-mix grouping captures all morbidities for which a patient receives care during a defined period—in this case, 2 years before the procedure date. The Adjusted Clinical Groups can be collapsed into 6 resource utilization bands (rubs) based on the expected use of health care resources. In the present study, we used the Discharge Abstract Database, the Same Day Surgery database, the National Ambulatory Care Reporting System, and ohip databases to calculate rubs, which are summarized as a 3-point ordinal variable because very few patients (0.565%) had a rub less than or equal to 2: 1, low (rub 0–3); 2, moderate (rub 4); and 3, high (rub 5). Supplementary Table S3 contains the full list of codes used to collect those data.

Results were stratified by time from the index bcs (within 2 years of, and >2 years after the bcs). Mortality and recurrence within 2 years of bcs were interpreted as representing residual primary disease and were not considered to be representative of recurrence secondary to lack of rt.

Statistical Analysis
Baseline differences between patients who did or did not receive rt were evaluated using a standardized difference. A standardized difference greater than 0.10 can be interpreted as a potentially meaningful between-group difference.

We used unadjusted and adjusted Cox proportional hazards models to investigate the effect of rt exposure on our outcomes. Patients were censored at the time of death, cancer recurrence, emigration (defined as no health care contact for 3 or more years before the end of follow-up), or at the end of the study period. Adjusted analyses included patient age, comorbidity score, cancer stage, and institution teaching status. We used previously described methods to assess the proportional hazards assumption for each covariate. Exposure to rt demonstrated non-proportionality, and therefore separate hazard ratios (hrs) were computed for several discrete time ranges. Each model also included an interaction term between age and time because of the non-proportionality of the effect of patient age. In models...
investigating each outcome separately, the alternative outcome was considered a competing event, and patients were censored using the methods described by Austin et al.24 Survival probabilities used to calculate the absolute risk difference and the number needed to treat were estimated from adjusted Cox proportional hazards models stratified by \textit{rt} exposure 25.

To ensure that the results were not affected by the decision to limit \textit{rt} exposure to within 1 year of lumpectomy, we conducted sensitivity analyses that permitted exposure for an additional 6 months. We also conducted subgroup analyses to explore potential differences in the effect of \textit{rt} between patients who were older and younger than 70 years at the time of lumpectomy. Finally, post hoc analyses were conducted in which patients who experienced death or recurrence within 2 years of \text{bcs} were excluded (\textit{rt} exposure was modelled as a single variable for those analyses). For all analyses, the reported \textit{p} values come from 2-tailed tests in which a value less than 0.05 was considered statistically significant. We performed all analyses using the SAS Enterprise Guide software application (version 7.1: SAS Institute, Cary, NC, U.S.A.).

**Ethics Approval**

The study was approved by the Sunnybrook Health Sciences Centre Research Ethics Board.

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**TABLE I** Baseline variables for patients who did and did not receive radiation therapy (\textit{rt}) within 1 year of breast-conserving surgery

| Variable | Overall | No RT | RT | Standardized difference | \( p \) Value |
|----------|---------|------|----|-------------------------|-------------|
| Patients (\( n \)) | 23,954 | 3,487 | 20,467 | | |
| Patient age (years) | | | | | |
| Median | 61.0 | 68.0 | 60.0 | 0.46 | <0.001 |
| IQR | 52.0–70.0 | 55.0–80.0 | 52.0–69.0 | | |
| Residence\(^a\) [\( n \) (\%)] rural | 2,657 (11.1) | 363 (10.4) | 2,294 (11.2) | 0.03 | 0.321 |
| Neighbourhood income quintile\(^b\) [\( n \) (%)] | | | | | |
| 1 | 3,894 (16.3) | 676 (19.4) | 3,218 (15.7) | 0.10 | <0.001 |
| 2 | 4,523 (18.9) | 666 (19.1) | 3,857 (18.8) | 0.01 | <0.001 |
| 3 | 4,734 (19.8) | 703 (20.2) | 4,031 (19.7) | 0.01 | <0.001 |
| 4 | 5,253 (21.9) | 728 (20.9) | 4,525 (22.1) | 0.03 | <0.001 |
| 5 | 5,471 (22.8) | 702 (20.1) | 4,769 (23.3) | 0.08 | <0.001 |
| Resource utilization band [\( n \) (%)] | | | | | |
| Low (0–3) | 10,143 (42.3) | 1,205 (34.6) | 8,938 (43.7) | 0.19 | <0.001 |
| Moderate (4) | 8,680 (36.2) | 1,213 (34.8) | 7,467 (36.5) | 0.04 | <0.001 |
| High (5) | 5,131 (21.4) | 1,069 (30.7) | 4,062 (19.8) | 0.25 | <0.001 |
| Cancer stage [\( n \) (%)] stage II | 9,701 (40.5) | 1,502 (43.1) | 8,199 (40.1) | 0.06 | <0.001 |
| Time since cancer diagnosis (days) | | | | | |
| Median | 33.0 | 32.0 | 33.0 | 0.04 | 0.015 |
| IQR | 22.0–46.0 | 19.0–48.0 | 22.0–46.0 | | |
| Institution status [\( n \) (%)] teaching | 6,679 (27.9) | 737 (21.1) | 5,942 (29.0) | 0.18 | <0.001 |
| Surgeon age (years) | | | | | |
| Median | 49.0 | 49.0 | 49.0 | 0.03 | 0.091 |
| IQR | 41.0–56.0 | 41.0–56.0 | 41.0–56.0 | | |
| Surgeon sex [\( n \) (%)] women | 8,105 (33.8) | 1,078 (30.9) | 7,027 (34.3) | 0.07 | <0.001 |
| Surgeon experience (years) | | | | | |
| Median | 24.0 | 23.0 | 24.0 | 0.02 | 0.176 |
| IQR | 15.0–30.0 | 15.0–30.0 | 15.0–30.0 | | |

\(^a\) Data missing for 2 patients.
\(^b\) Data missing for 79 patients.
\text{IQR} = 25\%–75\% interquartile range.
RESULTS

The initial cohort size was 41,790 patients. After applying the exclusion criteria (Figure 1), the included patients numbered 26,279. A further 2325 patients were excluded from the analysis because of death or recurrence within year 1. Patients who survived 1 year without recurrence tended to be older (mean age: 61.2 vs. 58.5 years; \( p < 0.001 \)), to have stage I rather than stage II disease (59.5% vs. 47.9%, \( p < 0.001 \)), and to have been treated in a teaching hospital (27.9% vs. 20.1%, \( p < 0.001 \)). Of the 23,954 patients included in the final cohort, 3487 (14.6%) did not receive \( rT \), and 20,467 did (85.4%). Compared with patients who did not receive \( rT \), those who did were more likely to have stage I disease (59.9% vs. 56.3%, \( p < 0.001 \)), to have been treated in a teaching hospital (29% vs. 21.1%, \( p < 0.001 \)), and to have fewer comorbidities (60.2 vs. 67.1, \( p < 0.001 \)), and to be younger (mean age: 61.2 vs. 58.5 years; \( p < 0.001 \)).

Survival analysis demonstrated that patients who did not receive \( rT \) were consistently more likely to have experienced recurrence or to have died at all time points studied (years 3, 4, and 5+ after \( bCS \); Table 1). The \( hr \) for death or recurrence ranged from 2.31 to 2.82 (\( p < 0.0001 \)) for years 3, 4, and 5+. That trend persisted in the subgroup analyses completed for patients less than 70 and 70 or more years of age to a significance level of \( p < 0.01 \). The \( hr \) for recurrence did not reach significance in years 3 or 5+, but did in year 4 (\( hr: 2.80; 95\% \) confidence interval (CI): 1.84 to 4.25). That trend persisted for all subgroups examined, with only year 4 reaching statistical significance. In the subgroup less than 70 years of age, the \( hr \) was 2.63 (95% CI: 1.56 to 4.45); in the subgroup 70 or more years of age, the \( hr \) was 3.35 (95% CI: 1.53 to 7.33). The \( hr \) for death ranged from 2.22 to 2.44 (\( p < 0.0001 \)) across years 3, 4, and 5+. That effect persisted in the subgroup 70 years of age and older, with \( hr s \) ranging from 2.00 to 2.48 (\( p < 0.0001 \)). However, in the subgroup less than 70 years of age, year 4 did not reach significance. Among patients less than 70 years of age, the year 3 \( hr \) was 1.95 (95% CI: 1.31 to 2.90), and the year 5+ \( hr \) was 1.84 (95% CI: 1.27 to 2.67).

The average effect of \( rT \) in patients beyond 2 years post-lumpectomy demonstrated similar trends for the primary outcomes: the \( hr \) for recurrence or death was 2.49 (\( p < 0.0001 \)), the \( hr \) for recurrence was 2.33 (\( p < 0.0001 \)), and the \( hr \) for death was 2.28 (\( p < 0.0001 \)). Within 5 years of \( bCS \), the absolute risk reduction for death or recurrence was 13.00%; for recurrence, 4.37%; and for death, 8.13% (Table III). Those values correspond to a number needed to treat of 8 for death or recurrence, 23 for recurrence, and 13 for death. Figure 2 illustrates the failure curves over time with respect to the primary outcomes.

Table II presents both the complete results of the primary outcomes with up to 9 years of follow-up and the results of primary outcomes beyond 2 years postoperatively. Primary outcome results for years 1 and 2 postoperatively are not presented because those recurrences and deaths were interpreted to represent failure of primary surgery (for recurrence) or competing causes of death near the time of the operation (that is, not affected by \( rT \)).

With respect to death, patient comorbidities and cancer stage were significant variables for the outcome. Compared with patients having a low comorbidity burden, those with moderate and high comorbidity scores were more likely to die: \( hr 1.29 \) for moderate comorbidity and \( hr 1.97 \) for high comorbidity (\( p < 0.0001 \)). Patients with stage II cancer were more likely than patients with stage I cancer to die (\( hr: 1.81; p < 0.0001 \)).

With respect to recurrence, comorbidity was nonsignificant in the overall cohort, although in the subgroup less than 70 years of age, increased age showed a small protective effect (\( hr: 0.92; p < 0.0001 \)).

The variables not listed in the tables (rurality, income quintile, laterality, time from diagnosis to treatment, fiscal year, surgeon age, surgeon sex, and surgeon experience) were excluded from the analysis because they were well balanced between the groups. In the delayed \( rT \) sensitivity analysis, none of the point estimates differed by more than 0.03 (data not shown).

DISCUSSION

Beyond 2 years after \( bCS \), several trends emerge with respect to death and recurrence in patients who do not receive \( rT \). Compared with patients who receive \( rT \), those who do not are more than twice as likely to die (all causes). That observation runs contrary to results from many previously published randomized controlled trials that found no difference in mortality between women who do and do not receive \( rT \). However, a number of larger-scale studies (both meta-analyses and population-based cohort studies) have demonstrated that \( rT \) confers a survival benefit in patients who receive \( bCS \) for breast cancer. Even among studies corroborating the benefit of radiation, the present study, compared with previous randomized trials, demonstrates a greater reduction in breast cancer death, perhaps because it analyzed real-world data rather than highly preselected cases, as in clinical trials. That hypothesis might suggest that the survival benefit conferred by \( rT \) is apparent only at high sample sizes, but is present nonetheless. The discrepancy might also be attributable to the fact that published randomized trials tend to use more restrictive inclusion criteria (for example, limits on comorbidity and age) and more extensive surgical resections (sector resection rather than lumpectomy).

Our findings also suggest that the observed survival benefit persists beyond 5 years after \( bCS \) and begins early. Some patients might not receive radiation based on a belief or counselling that the benefit of radiation is limited in early-stage breast cancer, because the recurrence rate is low and competing risks of death are high. Some studies have suggested that \( rT \) is unnecessary for certain groups of patients who can be treated with tamoxifen and that to radiate is to overtreat; others suggest that adjuvant therapies might not be needed at all for certain groups because of low rates of locoregional recurrence as long as 10 years after diagnosis. Our data demonstrate that \( rT \) confers an important and clinically significant survival advantage even after accounting for comorbidities and age. We could not define a group that does not benefit from \( rT \), including patients who are older and have more comorbidity.
### TABLE II  Primary outcomes

| Variable                      | Cohort overall (n=23,954) | Subgroup: <70 years of age (n=17,733) | Subgroup: ≥70 years of age (n=6,221) |
|-------------------------------|---------------------------|----------------------------------------|----------------------------------------|
|                               | Death or recurrence HR (95% CI) | Recurrence HR (95% CI) | Death HR (95% CI) | Death or recurrence HR (95% CI) | Recurrence HR (95% CI) | Death HR (95% CI) | Death or recurrence HR (95% CI) | Recurrence HR (95% CI) | Death HR (95% CI) |
| Radiation therapy exposure    |                           |                          |                           |                           |                          |                           |                           |                          |                           |
| Year 3                        | 2.35 (1.94 to 2.85)       | 1.66 (1.06 to 2.61)      | 2.22 (1.79 to 2.77)      | 1.97 (1.43 to 2.71)       | 1.78 (1.04 to 3.04)      | 1.95 (1.31 to 2.90)      | 2.12 (1.62 to 2.77)       | 1.57 (0.66 to 3.72)      | 2.04 (1.53 to 2.72) |
|                               | p<0.0001                  | p=0.0268                 | p<0.0001                 | p<0.0001                  | p=0.0349                 | p=0.001                  | p<0.0001                  | p=0.3104                 | p<0.0001          |
| Year 4                        | 2.82 (2.28 to 3.49)       | 2.80 (1.84 to 4.25)      | 2.44 (1.91 to 3.12)      | 2.17 (1.27 to 2.72)       | 2.63 (1.56 to 4.50)      | 1.24 (0.71 to 2.17)      | 2.80 (2.08 to 3.73)       | 3.35 (1.53 to 7.33)      | 2.48 (1.81 to 3.40) |
|                               | p<0.0001                  | p<0.0001                 | p<0.0001                 | p<0.0001                  | p=0.0014                 | p=0.0003                 | p<0.0001                  | p=0.0025                 | p<0.0001          |
| Year 5+                       | 2.31 (1.92 to 2.78)       | 1.26 (0.81 to 1.96)      | 2.22 (1.80 to 2.74)      | 1.73 (1.28 to 2.34)       | 1.31 (0.78 to 2.20)      | 1.84 (1.27 to 2.67)      | 2.25 (1.74 to 2.90)       | 1.46 (0.63 to 3.39)      | 2.00 (1.53 to 2.62) |
|                               | p<0.0001                  | p<0.0001                 | p<0.0001                 | p<0.0001                  | p=0.0004                 | p=0.0014                 | p<0.0001                  | p=0.0011                 | p<0.0001          |
| Age                           | 0.98 (0.96 to 0.99)       | 0.97 (0.94 to 1.00)      | 1.01 (0.98 to 1.04)      | 0.94 (0.90 to 0.97)       | 0.92 (0.88 to 0.96)      | 0.97 (0.91 to 1.04)      | 1.00 (0.94 to 1.06)       | 1.04 (0.92 to 1.17)      | 1.03 (0.97 to 1.10) |
|                               | p=0.0103                  | p=0.0116                 | p=0.4809                 | p=0.0003                  | p=0.0001                 | p=0.4421                 | p=0.9629                  | p=0.5731                 | p=0.2928          |
| Interaction: age*time         | 1.01 (1.01 to 1.01)       | 1.00 (1.00 to 1.01)      | 1.01 (1.00 to 1.01)      | 1.01 (1.01 to 1.02)       | 1.01 (1.00 to 1.02)      | 1.01 (1.00 to 1.02)      | 1.00 (1.00 to 1.02)       | 1.01 (0.97 to 1.01)      | 1.01 (1.00 to 1.02) |
|                               | p<0.0001                  | p=0.0424                 | p=0.0084                 | p=0.0002                  | p=0.0025                 | p=0.2189                 | p=0.0351                  | p=0.3743                 | p=0.1673          |
| Resource utilization band     |                           |                          |                           |                           |                           |                           |                           |                          |                           |
| Moderate vs. low              | 1.22 (1.11 to 1.34)       | 1.09 (0.93 to 1.29)      | 1.29 (1.14 to 1.45)      | 1.14 (1.01 to 1.29)       | 1.04 (0.86 to 1.24)      | 1.23 (1.04 to 1.45)      | 1.33 (1.13 to 1.56)       | 1.35 (0.92 to 1.97)      | 1.31 (1.10 to 1.56) |
|                               | p<0.0001                  | p=0.0275                 | p<0.0001                 | p<0.0001                  | p=0.04                   | p=0.7085                 | p=0.0167                  | p=0.0005                 | p=0.1279          |
| High vs. low                  | 1.72 (1.55 to 1.90)       | 1.13 (0.93 to 1.37)      | 1.97 (1.74 to 2.22)      | 1.70 (1.48 to 1.96)       | 1.14 (0.91 to 1.44)      | 2.17 (1.82 to 2.60)      | 1.73 (1.48 to 2.03)       | 1.19 (0.80 to 1.76)      | 1.82 (1.54 to 2.16) |
|                               | p<0.0001                  | p<0.0001                 | p<0.0001                 | p<0.0001                  | p=0.0264                 | p<0.0001                 | p<0.0001                  | p=0.4024                 | p<0.0001          |
| Cancer stage                  |                           |                          |                           |                           |                           |                           |                           |                          |                           |
| II vs. I                      | 1.65 (1.52 to 1.78)       | 1.15 (0.99 to 1.32)      | 1.81 (1.65 to 1.99)      | 1.66 (1.49 to 1.85)       | 1.78 (1.04 to 3.04)      | 2.21 (1.92 to 2.56)      | 1.42 (1.26 to 1.59)       | 1.27 (0.94 to 1.70)      | 1.41 (1.24 to 1.60) |
|                               | p=0.0001                  | p<0.0001                 | p=0.0001                 | p=0.0001                  | p=0.0001                 | p=0.0001                 | p=0.0001                  | p=0.0001                 | p=0.0001          |

**Primary outcomes**
### Table II  Continued

| Variable                      | Cohort overall (n=23,954) | Subgroup: <70 years of age (n=17,733) | Subgroup: ≥70 years of age (n=6,221) |
|-------------------------------|---------------------------|----------------------------------------|---------------------------------------|
|                               | Death or recurrence | Recurrence | Death | Death or recurrence | Recurrence | Death | Death or recurrence | Recurrence | Death |
|                               | HR (95% CI)          | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| **Primary outcomes continued**|                           |                           |                           |                           |                           |                           |                           |                           |                           |
| Teaching hospital             |                           |                           |                           |                           |                           |                           |                           |                           |                           |
| Yes vs. no                    | 1.01 (0.92 to 1.10)     | 1.16 (0.99 to 1.36)     | 0.93 (0.84 to 1.04)     | 1.02 (0.90 to 1.15)     | 2.63 (1.56 to 4.50)     | 0.96 (0.82 to 1.13)     | 1.01 (0.88 to 1.16)     | 1.35 (0.98 to 1.86)     | 0.92 (0.79 to 1.07)     |
|                              | p=0.8594               | p=0.0678               | p=0.216               | p=0.7413               | p=0.0003               | p=0.6328               | p=0.9023               | p=0.0642               | p=0.2696               |
| **Primary outcomes beyond**   |                           |                           |                           |                           |                           |                           |                           |                           |                           |
| 2 years after treatment⁵      |                           |                           |                           |                           |                           |                           |                           |                           |                           |
| Radiation therapy exposure    | 2.49 (2.25 to 2.75)     | 2.33 (1.91 to 2.84)     | 2.28 (2.03 to 2.56)     | 2.49 (2.25 to 2.75)     | 2.33 (1.91 to 2.84)     | 2.28 (2.03 to 2.56)     | 2.49 (2.25 to 2.75)     | 2.33 (1.91 to 2.84)     | 2.28 (2.03 to 2.56)     |
|                              | p<0.0001               | p<0.0001               | p<0.0001               | p<0.0001               | p<0.0001               | p<0.0001               | p<0.0001               | p<0.0001               | p<0.0001               |
| Age                          | 0.96 (0.92 to 1.01)     | 1.02 (0.94 to 1.11)     | 0.97 (0.91 to 1.04)     | 0.96 (0.92 to 1.01)     | 1.02 (0.94 to 1.11)     | 0.97 (0.91 to 1.04)     | 0.96 (0.92 to 1.01)     | 1.02 (0.94 to 1.11)     | 0.97 (0.91 to 1.04)     |
|                              | p=0.1007               | p=0.6333               | p=0.4074               | p=0.1007               | p=0.6333               | p=0.4074               | p=0.1007               | p=0.6333               | p=0.4074               |
| Interaction: age*time         | 1.01 (1.00 to 1.02)     | 1.00 (0.98 to 1.01)     | 1.01 (1.00 to 1.02)     | 1.01 (1.00 to 1.02)     | 1.00 (0.98 to 1.01)     | 1.01 (1.00 to 1.02)     | 1.01 (1.00 to 1.02)     | 1.00 (0.98 to 1.01)     | 1.01 (1.00 to 1.02)     |
|                              | p=0.0017               | p=0.443                | p=0.0137               | p=0.0017               | p=0.443                | p=0.0137               | p=0.0017               | p=0.443                | p=0.0137               |
| Resource utilization band     |                           |                           |                           |                           |                           |                           |                           |                           |                           |
| Moderate vs. low              | 1.23 (1.10 to 1.37)     | 1.16 (0.96 to 1.41)     | 1.26 (1.10 to 1.44)     | 1.23 (1.10 to 1.37)     | 1.16 (0.96 to 1.41)     | 1.26 (1.10 to 1.44)     | 1.23 (1.10 to 1.37)     | 1.16 (0.96 to 1.41)     | 1.26 (1.10 to 1.44)     |
|                              | p=0.0002               | p=0.0122               | p<0.0001               | p<0.0002               | p=0.0122               | p<0.0001               | p<0.0002               | p=0.0122               | p<0.0001               |
| High vs. low                  | 1.74 (1.55 to 1.95)     | 1.21 (0.96 to 1.52)     | 1.90 (1.66 to 2.17)     | 1.74 (1.55 to 1.95)     | 1.21 (0.96 to 1.52)     | 1.90 (1.66 to 2.17)     | 1.74 (1.55 to 1.95)     | 1.21 (0.96 to 1.52)     | 1.90 (1.66 to 2.17)     |
|                              | p<0.0001               | p<0.0001               | p<0.0001               | p<0.0001               | p<0.0001               | p<0.0001               | p<0.0001               | p<0.0001               | p<0.0001               |
| Cancer stage                  |                           |                           |                           |                           |                           |                           |                           |                           |                           |
| II vs. I                     | 1.62 (1.48 to 1.77)     | 1.05 (0.89 to 1.25)     | 1.81 (1.63 to 2.01)     | 1.62 (1.48 to 1.77)     | 1.05 (0.89 to 1.25)     | 1.81 (1.63 to 2.01)     | 1.62 (1.48 to 1.77)     | 1.05 (0.89 to 1.25)     | 1.81 (1.63 to 2.01)     |
|                              | p<0.0001               | p<0.0001               | p<0.0001               | p<0.0001               | p<0.0001               | p<0.0001               | p<0.0001               | p<0.0001               | p<0.0001               |

⁵ The hazard ratio is adjusted for age, radiation therapy exposure, diagnosis year, and interaction: age*time.
Our results suggest that, compared with patients who receive RT, those who do not are at increased risk of recurrence. That finding is consistent with results in previous studies which found that RT lowers the risk of local recurrence.\textsuperscript{2,4,10,14,19,26} However, our results further suggest that the benefit of RT with respect to recurrence might not persist beyond 6 years after BCS. Although reduced statistical power might partly account for that finding, it appears that most patients who experience recurrence do so within the first few years after BCS and that the benefit of adjuvant RT therefore declines over time. It might also be the case that patients who do not receive RT experience disease progression, but do not receive treatment and are instead captured as deaths. That hypothesis seems reasonable if the barriers to receipt of adjuvant RT are still present in those patients, potentially preventing them from receiving further treatment for recurrent disease.

\begin{table}[ht]
\centering
\begin{tabular}{|c|c|c|}
\hline
\textbf{Variable} & \textbf{Cohort overall (n=23,954)} & \textbf{Subgroup: <70 years of age (n=17,733)} & \textbf{Subgroup: \geq 70 years of age (n=6,221)} \\
\hline
Death or recurrence & Death & Death & Death or recurrence \\
HR & (95\% CI) & HR & (95\% CI) & HR & (95\% CI) \\
\hline
Teaching hospital & Yes vs. no & 0.92 to 1.13 & 0.97 to 1.41 & 0.85 to 1.08 & 0.4916 \\
\hline
\end{tabular}
\caption{Primary outcomes beyond 2 years after treatment continued.}
\end{table}

\textsuperscript{a} Estimates in the “Recurrence” and “Death” columns come from a sub-distribution model accounting for competing events.

\begin{figure}[ht]
\centering
\begin{minipage}{0.49\textwidth}
\textbf{A} Curve for death or recurrence failure combined (log-rank test: }p<0.0001\textit{) (B) Curve for recurrence failure (log-rank test: }p<0.0001\textit{). (C) Curve for death (log-rank test: }p<0.0001\textit{). RT = radiation therapy.}
\end{minipage}
\end{figure}
Limitations of all large administrative database analyses are their retrospective nature and the risk of incomplete data capture (including an inability to capture several potential confounders, and poor capture of recurrences), although province-wide health-related data are captured in a mandated reporting system that is considered to represent accurate population level data. Here, the issue of poor recurrence capture was addressed by two proxy markers: repeat surgery after 1 year or 3 radiation visits (of any kind) after 455 days. Surgery after 2 years was felt to represent repeat surgery for management of a recurrence. Unfortunately, radiation treatments are not captured individually in the databases used, and therefore any radiation oncology visit—including consultation, computed tomography simulation, or treatment—was counted as a “RT visit.” It was reasoned that 455 days (15 months) should be used as a cut-off for initial adjuvant treatment to allow for delays resulting from extended chemotherapy courses. Any subsequent treatment would be considered to represent recurrence. Because 3 or more RT visits is the minimum number required for a consultation, computed tomography simulation, and treatment delivery (even for palliative radiation), that number was felt to represent recurrence. This method does not capture patients who recur and receive no treatment, although such patients would progress and be captured in the “death” outcome.

It is possible that certain cohorts, more than others, benefit from RT in a way that has not been elucidated in large randomized controlled trials for adjuvant radiation in early-stage breast cancer. Recent publications have demonstrated that early-stage patients with circulating tumour cells treated by BCS obtain a survival benefit with radiation that patients without circulating tumour cells do not. That effect was not found to apply to early-stage patients treated with mastectomy. Clearly further work is required to differentiate the subset of patients that obtains the greatest survival benefit with the use of radiation in early-stage breast cancer treated with BCS—specifically, interrogating systemic chemotherapy and hormonal therapy use with tumour tissue and blood correlative studies, data that we were not able to access. We did not capture neoadjuvant, adjuvant, or palliative chemotherapy use, and we were not able to obtain hormonal therapy prescriptions or adherence.

**CONCLUSIONS**

Contrary to the results of previously published randomized trials in selected patients, the present study demonstrates that, compared with patients who receive RT within 1 year of BCS, those who do not receive adjuvant RT are more than twice as likely to die or to experience recurrence. That effect is present even when older patients are excluded from the cohort to eliminate the effect of competing causes of death and situations in which alternatives to radiation might be acceptable. The protective effect of RT with respect to recurrence was also again demonstrated. Radiation therapy after BCS confers a protective effect against recurrence and death, and should be systematically offered to eligible patients undergoing BCS for early-stage disease.

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**TABLE III Absolute risk reduction**

| Outcome                  | Follow-up (years) | Average probability of death (%) | Risk difference (%) | Number needed to treat |
|--------------------------|-------------------|----------------------------------|---------------------|------------------------|
|                          |                   | RT  | No RT  |                         |                        |
| Death or recurrence      | 1                 | 1.78| 4.78   | 3.00                  | 34                     |
|                          | 2                 | 3.68| 9.67   | 5.99                  | 17                     |
|                          | 3                 | 5.83| 14.95  | 9.12                  | 11                     |
|                          | 4                 | 8.02| 20.05  | 12.04                 | 9                      |
|                          | 5                 | 10.09| 24.67  | 14.58                 | 7                      |
| Recurrence               | 1                 | 1.72| 5.26   | 3.54                  | 29                     |
|                          | 2                 | 1.71| 5.23   | 3.52                  | 29                     |
|                          | 3                 | 1.53| 4.69   | 3.16                  | 32                     |
|                          | 4                 | 1.81| 5.53   | 3.72                  | 27                     |
|                          | 5                 | 1.93| 5.87   | 3.94                  | 26                     |
| Death                    | 1                 | 5.22| 11.81  | 6.59                  | 16                     |
|                          | 2                 | 5.17| 11.65  | 6.49                  | 16                     |
|                          | 3                 | 4.81| 10.83  | 6.02                  | 17                     |
|                          | 4                 | 3.13| 7.20   | 4.07                  | 25                     |
|                          | 5                 | 4.40| 10.07  | 5.68                  | 18                     |

RT = radiation therapy.
are independent from the funding sources. No endorsement by ICES, AMOSO, SSDM, LHI, or the Ontario Ministry is intended or should be inferred. Parts of this material are based on data or information compiled and provided by CIHI. However, the analyses, conclusions, opinions, and statements expressed in the material are those of the authors, and not necessarily those of CIHI. Parts of this material are based on data and information provided by Cancer Care Ontario (CCO). The opinions, results, views, and conclusions reported in this article are those of the authors and do not necessarily reflect those of CCO. No endorsement by CCO is intended or should be inferred.

**CONFLICT OF INTEREST DISCLOSURES**
We have read and understood Current Oncology's policy on disclosing conflicts of interest, and we declare that we have none.

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