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EPIDEMIOLOGY

Patterns of adjuvant care and outcomes of elderly women with stage I breast cancer after breast-conserving surgery: a population-based analysis

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Abstract

Purpose Randomized trials studying endocrine therapy (ET) with and without radiation therapy (RT) following breast-conserving surgery (BCS) have detected differences in local recurrence (LR) but not survival among elderly women with hormone receptor positive stage I breast cancer (BC). We assembled a population-based cohort of such women to examine the use and outcomes associated with or without the administration of adjuvant radiotherapy (RT) or ET.

Methods Women aged ≥ 65 years with stage I BC treated with BCS in Ontario between 2010 and 2016, their treatments and outcomes were ascertained using deterministic linkages of administrative databases. Multivariable Cox regression models were used to evaluate risks of ipsilateral LR and of any first in-breast event, categorizing women by their treatment.

Results 5076 women were treated with BCS followed by RT + ET ($n = 1964$), RT alone ($n = 1325$), ET alone ($n = 719$), or no adjuvant treatment ($n = 1068$). Median follow-up was 5 years. LR occurred in 0.9% after adjuvant RT + ET, 1.4% after RT alone, 3.1% after ET alone, and 9.4% after BCS alone ($p < 0.001$). The adjusted risk of LR was increased in those who received no adjuvant therapy (HR = 13.43, CI: 7.89, 22.85), or ET alone (HR = 4.03, CI: 2.14, 7.59). The adjusted risk of any first in-breast event was greatest among those without any adjuvant therapy (HR = 7.61, 95%CI: 5.21, 11.11, p < 0.0001). Absolute and adjusted risks of any first in-breast event were comparable between those with ET alone (HR = 2.09, 95%CI: 1.27, 3.43, $p = 0.0038$) and those with RT alone (HR = 1.91, 95% CI: 1.25, 2.91, $p = 0.0028$).

Conclusions Older women with stage I BC who receive no adjuvant therapy have a significant absolute risk of LR and any first in-breast event, whereas the absolute risk of these events among those with either RT alone or ET alone is only slightly higher than among those treated with both.

Keywords Breast cancer · Elderly · Population-based · Local recurrence · Radiotherapy · Patterns of care

Introduction

Greater than one-third of breast cancer (BC) cases in North America occur among elderly women [1, 2] and most present with stage I disease [3]. In elderly women, BC demonstrates less aggressive pathology [4] and is frequently Luminal subtype [5] with a lower risk of recurrence than younger women [6]. Furthermore, elderly women are more likely to have health issues influencing the tolerability and benefit of treatments. De-escalation of therapy that will achieve low risks of recurrence with minimal adverse effects is of interest to patients and their oncologists.

Most elderly women with stage I BC are treated with breast-conserving surgery (BCS) followed by adjuvant radiation therapy (RT) and endocrine therapy (ET) [7]. Recently two landmark trials aimed at de-escalating therapy by omitting RT in elderly women with Stage I, hormone sensitive BC treated by BCS and ET have been reported [8–10]. The PRIME II trial randomized women aged ≥ 65 years with tumors ≤ 3 cm and the CALGB 9343 trial randomized

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women ≥ 70 years at diagnosis, with node negative, estrogen receptor (ER), and/or progesterone receptor (PR) positive tumors treated with BCS to receive adjuvant RT and ET versus ET alone. The omission of RT resulted in higher 5 and 10 year risks of local recurrence (LR) (4% vs. 1% at 5 years [8, 10] or 9% vs. 2% at 10 years [9]) but the absolute benefit of RT was small. Furthermore, there was no difference in breast cancer-specific or overall survival rates between the two groups [8–10]. National Comprehensive Cancer Network guidelines now support the omission of adjuvant RT in women ≥ 70 years at diagnosis with Stage I BC and favorable tumor pathology (≤ 2 cm, node negative, ER +) if they receive 5 years of ET [11]. Another approach to de-escalation has been the omission of adjuvant ET. To date there have been few trials of this approach. The British Association of Surgical Oncology (BASO-2) clinical trial randomized women younger than 70 years with tumors < 2 cm, node negative, grade 1 histology or good prognosis subtype, to receive RT (yes/no) or ET (tamoxifen) (yes/no) using a 2 × 2 factorial design and demonstrated similarly low annual rates of LR in women treated with RT alone (0.7%) or ET alone (0.8%) [12].

The objective of this analysis is to evaluate treatment and outcomes in a population of elderly Ontario women (aged ≥ 65) with stage I BC treated with BCS, who received adjuvant RT and ET, either adjuvant modality alone (RT alone or ET alone) or no adjuvant therapy at all.

Methods

Cohort identification

The study population was identified by deterministic linkages of administrative databases held at ICES and Cancer Care Ontario (CCO) labeled by encrypted Ontario Health Insurance numbers. Cases with first time diagnosis of invasive BC, stage I, at age 65 or older, between 2010 and 2016 were identified from the Ontario Cancer Registry (OCR) by searching for International Classification of Diseases (ICD)-10 diagnosis code C50. Diagnosis code, date of diagnosis, tumor grade, biomarkers, age, sex, and date with cause of death were extracted. Cases coded as male or unknown sex ($n = 103$), or prior history of any invasive cancer including BC ($n = 2648$), and those with triple negative BC (ER and PR negative and Her2 negative) ($n = 195$), ER and PR negative and Her2 positive disease ($n = 41$), or those lacking any hormone receptor data ($n = 74$) were excluded. Cases with bilateral BC ($n = 9$) including those with contralateral BC within 6 months of index lesions ($n = 85$), and those with unknown laterality of the index lesion ($n = \leq 5$) were excluded. Women with ER and PR negative tumors but unknown Her2 status were included ($n = 121$).Cases were linked to the Canadian Institute for Health Information (CIHI) Discharge Abstract (DAD) and Same Day Surgery (SDS) databases to identify breast surgical procedures performed within 6 months following the diagnosis date with an associated ICD-10 BC diagnosis code (C50). Intervention code, laterality code, and date of admission were extracted. Patients treated by mastectomy ($n = 1819$) were excluded. All cases treated with chemotherapy or Herceptin between the diagnosis date and 6 months ($n = 3285$) were excluded by identifying chemotherapy, from the Ontario Health Insurance Plan (OHIP) physician billing claims, the New Drug Funding Program, and the CCO Activity Level Reporting (ALR) databases.

Socioeconomic status was ascertained using census data from the Registered Persons Database (RPDB). Adherence to mammographic screening prior to diagnosis was determined by the Ontario Breast Screening Program (OBSP) and OHIP physician billing codes and was defined as the presence of at least one mammogram at 7–30 months and at 24–48 months prior to diagnosis date within a minimum interval of 12 months.

Surgical and adjuvant treatment

Surgical procedures and laterality were identified from the CIHI DAD and SDS databases and intervention codes for BCS, axillary nodal dissection and sentinel node biopsy, and ICD-10 diagnosis code for invasive BC, C50. Adjuvant RT was defined by initiation of breast RT within 6 months of the diagnosis date, from records in the ALR database containing the anatomic code for breast RT, with laterality concordant with the ICD-10 diagnosis code, surgical intervention laterality code, and treatment delivery code corresponding to conventional or IMRT delivery. Receipt of ET was identified using the Ontario Drug Benefit Claims (ODB) database using dispensing records for Tamoxifen, Anastrozole, Letrozole, Exemestane, or Raloxifene if first dispense date occurred within 6 months following the diagnosis date. Women were categorized into four groups: no adjuvant therapy, RT only, ET only, or both (RT + ET). Adherence to ET in the subgroups of patients who received RT + ET or ET alone was captured using ODB claims to obtain the days supplied with the drug (yes/no), starting from a first dispense date within 6 months of the BC diagnosis date for 5 years. Patients were considered adherent at each time point covered by a prescription drug supply. The proportion of person-days adherent to ET over total follow-up days, for each 3-month period was plotted over time.

Outcomes

LR was defined as any invasive or non-invasive BC in the ipsilateral breast occurring ≥ 6 months from the date of

diagnosis of the index lesion. Recurrences were identified using OCR and CIHI databases and breast surgical intervention with an ICD-10 code C50 (invasive) or D051 (non-invasive), with the same laterality as initial lesion. Metachronous contralateral BC as a first event was similarly identified from records coded with the opposite laterality as the index event. Any first subsequent in-breast event was defined as the first event (invasive or non-invasive) occurring in the ipsilateral or contralateral breast $\geq$ 6 months after the diagnosis date.

Venous thromboembolism (VTE) was defined as deep vein thrombosis, defined by the OHIP billing code for venous doppler plus a dispense date for low-molecular weight heparin from 0–7 days following the service date of the doppler, or, pulmonary embolism (PE), captured using ICD-10 codes in the CIHI databases, occurring 30 days or more after the last breast surgery. Patients receiving any of the following anticoagulants at the time of diagnosis (Dalteparin, Enoxaparin, Tinzaparin, Rivaroxaban, Apixaban, Dabigatran, Edoxaban) and those with prior VTE or cerebral infarct were excluded from this analysis of VTE.

BC mortality was defined as death related to BC (ICD code C50) in (1) the OCR (2) ICES Vital Statistics and Death Registry (ORGD), and/or (3) CIHI DAD terminal admission most responsible diagnosis code during the follow-up period up to December 31, 2016. Other cause mortality was also determined over this same period of time and was considered a competing risk against BC mortality. Overall survival was computed as death due to any cause during the complete follow-up period to June 30, 2017.

Comorbidity adjustment

To adjust for comorbidities, the Charlson comorbidity index was calculated using Deyo's method [13]. Data for each case over the 60-month period prior to diagnosis date were identified from the CIHI DAD database.

Statistical analysis

Differences in baseline characteristics between the treatment groups were evaluated using Chi-Square testing for categorical variables and *t* tests for continuous variables. Time to LR, time to any first in-breast event and overall survival in each treatment group was evaluated using Kaplan–Meier curves and statistically significant differences between groups were calculated using the log-rank method. The risk of BC mortality was calculated using the cumulative incidence function approach, where death from other causes was considered a competing event. Time to LR and time to any first in-breast event was modeled using Cox proportional hazards regression using backward selection, retaining variables based on $p \leq 0.05$. Women with subsequent breast events of unknown laterality were censored on the date of such an event. When examining these outcomes among the group of women receiving ET, the Cox model included adherence to ET and proportion of time spent adherent to ET as time-varying covariates.

Results

The population cohort includes 5076 Ontario women with stage I BC diagnosed between January 1, 2010 and December 31, 2016 treated by BCS and selected to not receive adjuvant chemotherapy. The population, pathologic features, biomarkers, and treatments received are presented in Table 1. We observed that 4008 (79.0%) patients received adjuvant therapy; the most common being RT + ET in 1964 (38.7%), followed by RT alone in 1325 (26.1%) and ET alone in 719 (14.2%). The treatment groups were different with respect to age at diagnosis, baseline comorbidity, tumor grade, and biomarkers.

We examined the temporal pattern of the administration of adjuvant therapy for the cohort. We found a significant trend toward the omission of adjuvant RT + ET over time ($p = 0.00001$). Prior to 2014, 43.4% of women in the cohort received adjuvant RT + ET compared to only 28.7% of those diagnosed after 2014. This decrease was associated with an increase in the proportion of women who received no adjuvant therapy from 18.1% to 27.3% ($p < 0.001$) and a modest increase in the use of ET alone (13.0% to 16.7%, $p < 0.001$) or RT alone (25.5% to 27.3%, $p = 0.19$) (Table 2). In those women who received any ET, tamoxifen was prescribed 36% of the time, and this pattern of use remained stable over time ($p > 0.05$).

Local recurrence

After a median follow-up period of 5 years (interquartile range: 3–6 years) and median follow-up of 5 years for sub-cohorts RT + ET and RT alone, 4 years for ET alone, and 3 years for those who received no adjuvant therapy, ipsilateral LR (invasive or in situ) developed in 159 patients (2.8%) and contralateral BC developed in 83 patients (1.6%). The highest rate of LR occurred in women who received no adjuvant therapy ($n = 100$, 9.4%). LR developed in 22 (3.1%) women who received ET alone, in 19 (1.4%) women who received RT alone and in 18 (0.9%) women who received RT + ET ($p < 0.001$). The overall 5-year local recurrence-free survival (LRFS) rates were 89% in those who did not receive any adjuvant therapy, 97% in women treated with ET alone, 98% after RT alone, and 99% in those treated with RT + ET ($p < 0.0001$) (Fig. 1). Factors associated with an increased risk of ipsilateral LR include age at diagnosis (HR age 65–70 = 2.45, 95% CI:1.59, 3.79, $p < 0.0001$; HR age

Table 1 Patient characteristics

	No adjuvant therapy *N* (%)	RT + endocrine therapy *N* (%)	Endocrine therapy alone *N* (%)	RT only *N* (%)	Whole Cohort *N* (%)	*P* value
	N = 1068	*N* = 1964	*N* = 719	*N* = 1325	*N* = 5076	
Age at diagnosis Median (IQR)	76 (70–84)	70 (67–74)	74 (69–82)	71 (68–76)	72 (68–78)	< 0.001
65–70	277 (25.9%)	1001 (51.0%)	221 (30.7%)	593 (44.8%)	2092 (41.2%)	< 0.001
71–75	219 (20.5%)	591 (30.1%)	174 (24.2%)	394 (29.7%)	1378 (27.1%)	
76–79	141 (13.2%)	216 (11.0%)	99 (13.8%)	156 (11.8%)	612 (12.1%)	
≥ 80	431 (40.4%)	156 (7.9%)	225 (31.3%)	182 (13.7%)	994 (19.6%)	
Charlson score						
0	813 (76.1%)	1740 (88.6%)	575 (80.0%)	1128 (85.1%)	4256 (83.8%)	< 0.001
1	107 (10.0%)	154 (7.8%)	79 (11.0%)	127 (9.6%)	467 (9.2%)	
≥ 2	148 (13.9%)	70 (3.6%)	65 (9.0%)	70 (5.3%)	353 (7.0%)	
Axillary staging						
Sentinel node Biopsy	457 (42.8%)	1238 (63.0%)	341 (47.4%)	892 (67.3%)	2928 (57.7%)	< 0.001
Axillary dissection	175 (16.4%)	578 (29.4%)	174 (24.2%)	293 (22.1%)	1220 (24.0%)	
None	436 (40.8%)	148 (7.5%)	204 (28.4%)	140 (10.6%)	928 (18.3%)	
Tumor grade						
Low	388 (36.3%)	672 (34.2%)	280 (38.9%)	591 (44.6%)	1931 (38.0%)	< 0.001
Medium	429 (40.2%)	1071(54.5%)	333 (46.3%)	518 (39.1%)	2351 (46.3%)	
High	83 (7.8%)	168 (8.6%)	45 (6.3%)	88 (6.6%)	384 (7.6%)	
Unknown	168 (15.7%)	53 (2.7%)	61 (8.5%)	128 (9.7%)	410 (8.1%)	
Receptor status						
ER + and PR+	833 (78.0%)	1758 (89.5%)	645 (89.7%)	1065 (80.4%)	4301 (84.7%)	< 0.001
ER + or PR+	76 (7.1%)	167 (8.5%)	54 (7.5%)	116 (8.8%)	413 (8.1%)	
Other	159 (14.9%)	39 (2.0%)	20 (2.8%)	144 (10.9%)	362 (7.1%)	
Her2neu status						
Positive	16 (1.5%)	28 (1.4%)	14 (1.9%)	17 (1.3%)	75 (1.5%)	0.033
Negative	603 (56.5%)	1161 (59.1%)	445 (61.9%)	730 (55.1%)	2939 (57.9%)	
Unknown	449 (42.0%)	775 (39.5%)	260 (36.2%)	578 (43.6%)	2062 (40.6%)	
Breast RT					*N* = 3289	
Conventional		336 (17.1%)		308 (23.2%)	644 (19.6%)	
Hypofractionation		1609 (81.9%)		994 (75.0%)	2603 (79.1%)	
Other		19 (1.0%)		23 (1.7%)	42 (1.3%)	
Boost RT					*N* = 3289	
Prescribed		294 (15.0%)		216 (16.3%)	510 (15.5%)	
Not prescribed		1670 (85.0%)		1109 (83.7%)	2779 (84.5%)	

RT radiation therapy; *IQR* interquartile range; *ER* estrogen receptor; *PR* progesterone receptor

71–75 years = 1.98, 95% CI: 1.23, 3.18, $p = 0.005$), intermediate grade (HR = 2.01, 95% CI: 1.37, 2.94, $p = 0.0003$) or high grade disease (HR = 2.59, 95% CI: 1.44, 4.65, $p = 0.002$), and the omission of axillary nodal staging (HR = 2.89, 95% CI: 2.01, 4.14, $p < 0.0001$) (Table 3). Women who did not receive any adjuvant therapy had a 13-fold increased risk of developing LR (HR = 13.43, 95% CI: 7.89, 22.85, $p < 0.0001$) compared to those who received both RT + ET. The risk of an ipsilateral LR was relatively higher in women treated with ET alone compared to those who received RT + ET (HR = 4.02, 95% CI: 2.14, 7.57, $p < 0.0001$), but the absolute differences in the event rates were low (Table 3).

Contralateral BC developed as a first event in 2.2% of those who received no adjuvant therapy, 2.2% of cases treated with RT alone, 1.4% of women who received RT + ET and <1% of those treated with ET alone ($p = 0.016$). Most (85.7%) were invasive histology.

Table 2 Treatment following breast-conserving surgery by year of diagnosis

	Diagnosis year		
	2010–2013 $N=3464$	2014–2016 $N=1612$	P value
No adjuvant therapy	628 (18.1%)	440 (27.3%)	<0.00001
RT + ET	1502 (43.4%)	462 (28.7%)	<0.00001
Tamoxifen	511 (34.0%)	179 (38.7%)	0.063
Aromatase inhibitor	991 (66.0%)	283 (61.3%)	0.063
ET alone	449 (13.0%)	270 (16.7%)	0.0003
Tamoxifen	160 (35.6%)	107 (39.6%)	0.283
Aromatase inhibitor	289 (64.4%)	163 (60.4%)	0.283
RT alone	885 (25.5%)	440 (27.3%)	0.190

RT radiation therapy; *ET* endocrine therapy

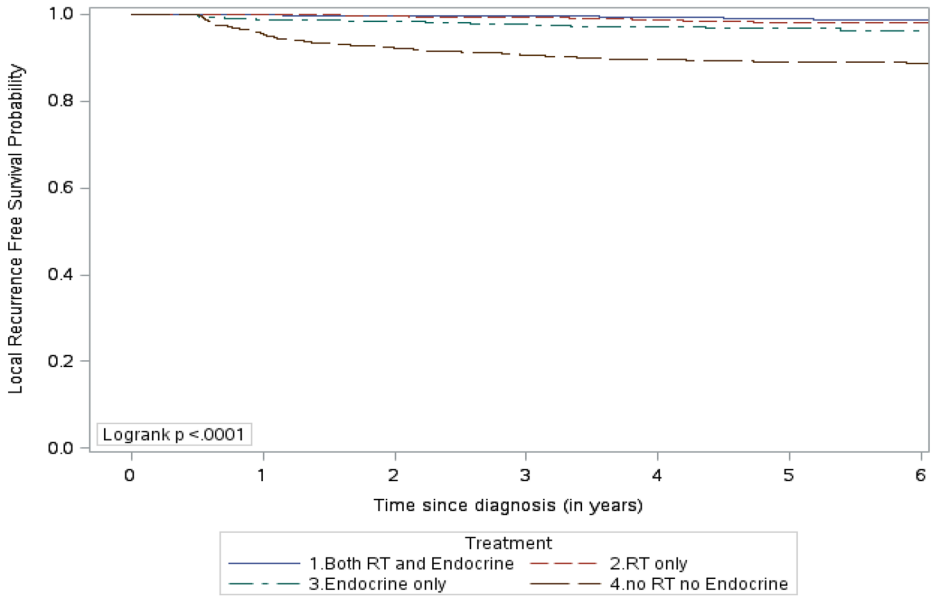

Fig. 1 Local recurrence-free survival following breast-conserving surgery with or without adjuvant therapy

No. at risk

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
RT+ET	1958	1851	1699	1437	1019	663
RT alone	1317	1131	995	820	618	433
ET alone	695	584	494	376	246	166
No adjuvant therapy	954	769	594	440	297	190

First in-breast event

Taking into account all subsequent in-breast events (ipsilateral or contralateral), significantly more women who received no adjuvant therapy developed an in-breast event ($n=122$, 11.4%). By comparison, 3.6% after ET alone ($n=26$) or 3.5% of women who received RT alone ($n=47$) developed an in-breast event. Treatment with RT alone was associated with a lower risk of a LR, whereas treatment with ET alone was associated with a lower risk of a contralateral event. Women who received both RT + ET had a slightly lower rate of any first subsequent in-breast event ($n=42$ (2.1%), $p<0.001$). The median time to any first in-breast event was 5 years for the whole group. The 5-year in-breast event-free survival rates were 86% in those who did not receive any adjuvant therapy, 96% in women treated with ET alone, 96% after RT alone, and 98% in those treated with RT + ET ($p<0.0001$) (Fig. 2). On multivariate analysis adjusted for year of diagnosis (Table 3), women who did not receive any adjuvant therapy had an eightfold increased risk of developing any first subsequent in-breast event (HR = 7.61, 95% CI: 5.21, 11.11, $p<0.0001$)

Table 3 Multivariable analysis of factors associated with ipsilateral local recurrence or any in-breast events in patients treated with breast-conserving surgery with or without radiation therapy or endocrine therapy

	Ipsilateral local recurrence				Any in-breast events			
	HR	95%CI lower	Upper	*P* value	HR	95%CI lower	Upper	*P* value
Treatment (vs. RT + ET)								
No RT or ET	13.43	7.89	22.85	< 0.0001	7.61	5.21	11.11	< 0.0001
ET only	4.02	2.14	7.57	< 0.0001	2.09	1.27	3.43	0.004
RT only	1.84	0.96	3.53	0.07	1.91	1.25	2.91	0.003
Age at diagnosis (years) (vs. ≥ 80 years)								
65–70	2.45	1.59	3.79	< 0.0001	1.92	1.32	2.78	0.0006
71–75	1.98	1.23	3.18	0.005	1.77	1.19	2.63	0.005
76–79	1.33	0.74	2.41	0.34	1.20	0.73	1.97	0.46
No axillary staging	2.89	2.01	4.14	< 0.0001	1.96	1.43	2.67	< 0.0001
Tumor grade (vs. low grade)								
Intermediate grade	2.01	1.37	2.94	0.0003	1.36	1.01	1.82	0.04
High grade	2.59	1.44	4.65	0.0015	1.63	0.99	2.67	0.05
Unknown grade	1.17	0.64	2.13	0.61	0.99	0.60	1.63	0.97
Hormone status (vs. ER + & PR +)								
ER + or PR+	0.84	0.45	1.56	0.58	0.71	0.41	1.23	0.22
ER- and PR-	1.37	0.68	2.73	0.38	1.13	0.61	2.10	0.70
ER unknown and/or PR unknown	0.95	0.49	1.82	0.87	0.88	0.50	1.57	0.67
Year of diagnosis (vs. year 2010–2013)								
2014–2016	1.04	0.72	1.51	0.84	1.08	0.79	1.49	0.62

HR hazard ratio; *CI* confidence interval; *RT* radiation therapy; *ET* Endocrine therapy; *ER* estrogen receptor; *PR* progesterone receptor

compared to those who received both RT + ET. By comparison, women treated with single modality therapy had a similar twofold increased risk of any first subsequent in-breast event compared to those treated with RT + ET (RT alone, HR = 1.91, 95% CI: 1.25, 2.91, $p = 0.003$; ET alone HR = 2.09, 95% CI: 1.27, 3.43, $p = 0.004$). Other factors associated with a higher risk of any first subsequent in-breast event include age at diagnosis (HR 65–70 years = 1.92, 95% CI: 1.32, 2.78, $p = 0.0006$; HR 71–75 years = 1.77, 95% CI: 1.19, 2.63, $p = 0.005$), intermediate tumor grade (HR = 1.36, 95% CI: 1.01, 1.82, $p = 0.04$), and no axillary intervention (HR = 1.96, 95% CI: 1.43, 2.67, $p < 0.0001$).

Overall survival and breast cancer mortality

The 5-year overall survival rates were 71.5% for women who received no adjuvant therapy, 81.6% after ET alone, 92.8% after RT alone, and 95.7% after RT + ET ($p < 0.0001$). The majority of deaths were not related to BC (Fig. 3). To minimize the effect of confounding due to selection bias and comorbid illnesses, we examined the rates of BC mortality in 1960 women who had no comorbidities (Charlson score of 0), with grade 1 or 2 ER or PR expressing, her2neu negative BC and confirmed node negative status by axillary staging. The rates of BC-related mortality were 1.7% in women who did not receive any adjuvant therapy, 1.4% in women treated with ET alone, 1.7% after RT alone, and 0.12% after RT + ET ($p = 0.05$).

Adherence to endocrine therapy

In women with ER and/or PR expressing tumors who received ET (i.e., RT + ET or ET alone), the proportion of women adherent to ET decreased over time. After 1- and 2-year follow-up 81% and 76% of women were adherent to ET, while at 5-year follow-up 66.8% of women were adherent (Fig. 4). Multivariate Cox modeling showed that a 10% increase in the proportion of time adherent to ET resulted in a 12–13% reduction in the risk of a subsequent in-breast event (HR = 0.88, 95%CI: 0.80, 0.96, $p = 0.006$) or LR (HR = 0.87, 95%CI: 0.77, 0.98, $p = 0.019$) (Table 4).

Venous thromboembolism

Overall, the development of VTE was more frequent among women who received ET (with or without RT) compared to women who did not. Among 2261 women who received adjuvant ET with no prior history of a thromboembolic event or anticoagulation, 83 (3.7%) experienced a VTE (of these, 48/83 (57.8%) were due to pulmonary embolus). By comparison, among 1988 women with no prior history of VTE who did not receive ET, 52 (2.6%) experienced VTE

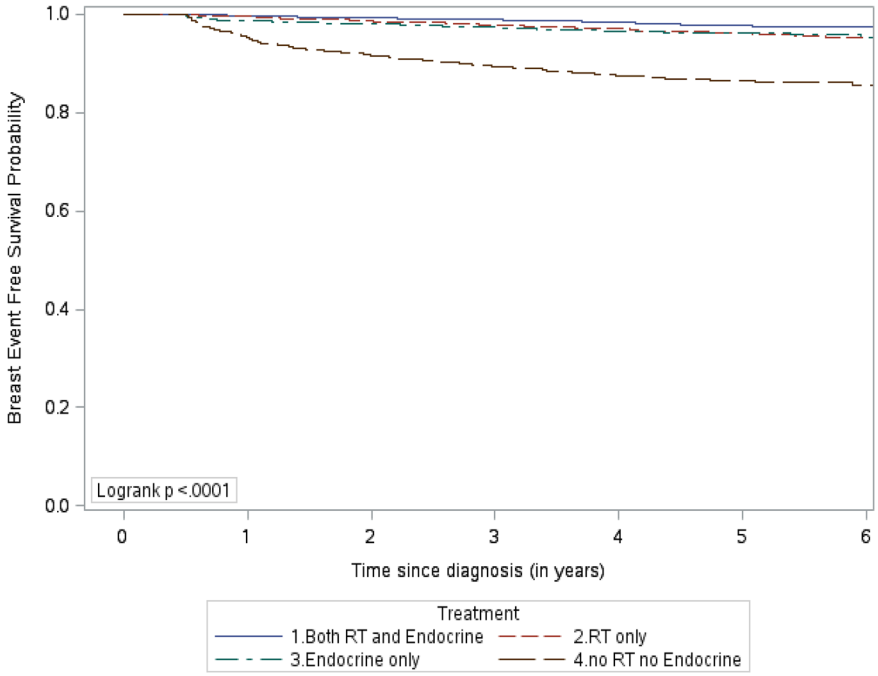

Fig. 2 Any in-breast event-free survival following breast-conserving surgery with or without adjuvant therapy

No. at risk

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
RT+ET	1954	1843	1687	1421	1002	652
RT alone	1314	1120	980	808	605	421
ET alone	693	582	492	373	244	164
No adjuvant therapy	952	765	585	431	289	181

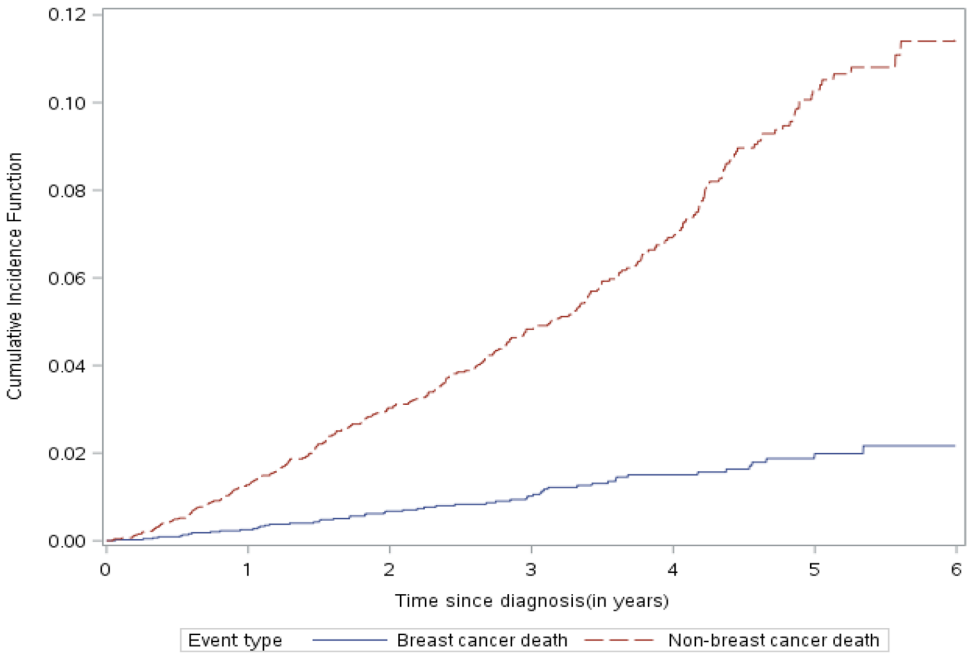

Fig. 3 Cumulative incidence of breast cancer-related and non-breast cancer-related deaths

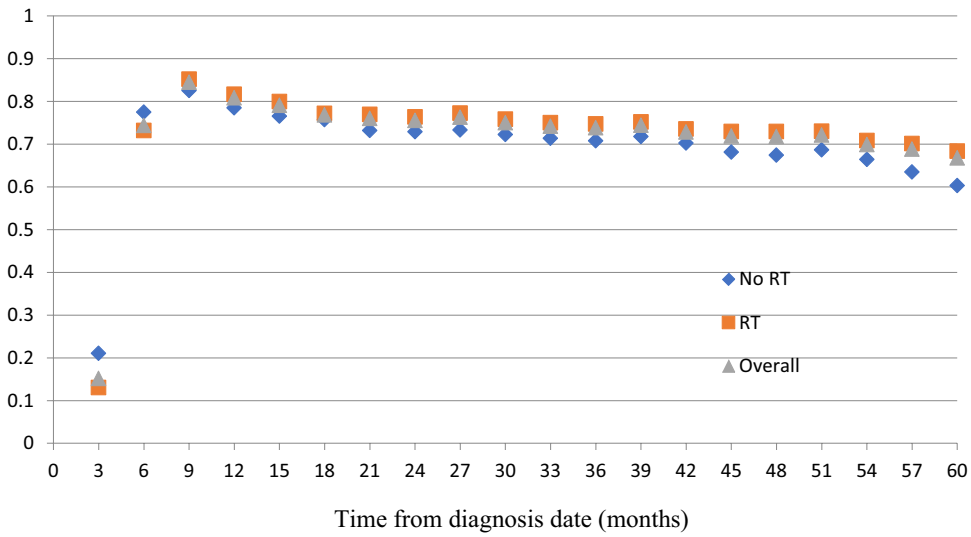

Fig. 4 Proportion of patients adherent to endocrine therapy after breast-conserving surgery with or without radiotherapy

Table 4 Multivariable analysis of factors associated with ipsilateral local recurrence or any in-breast events in patients treated with endocrine therapy

	Ipsilateral local recurrence				Any in-breast events			
	HR	95% CI lower	95% CI upper	*P* value	HR	95% CI lower	95% CI upper	*P* value
Adherent ET (vs. no)	1.63	0.75	3.57	0.22	1.54	0.83	2.85	0.17
RT (yes vs. no)	3.78	1.91	7.47	0.0001	1.89	1.10	3.25	0.02
Age at diagnosis (yrs) (vs. ≥ 80 years)								
65–70	0.99	0.38	2.61	0.99	0.71	0.32	1.58	0.40
71–75	0.99	0.36	2.74	0.99	1.10	0.50	2.41	0.82
76–79	0.92	0.29	2.91	0.88	1.15	0.47	2.83	0.76
No axillary staging	0.70	0.29	1.68	0.42	0.76	0.37	1.56	0.45
Tumor grade (vs. low grade)								
Intermediate	1.17	0.58	2.38	0.66	0.73	0.44	1.22	0.23
High	1.77	0.56	5.60	0.33	0.73	0.25	2.11	0.56
Unknown	1.60	0.42	6.13	0.49	1.03	0.34	3.09	0.96
Hormone status (vs. ER + and PR +)								
ER + or PR+	1.24	0.43	3.56	0.69	0.96	0.38	2.42	0.94
Both ER and PR unknown	1.60	0.36	7.05	0.53	1.95	0.68	5.60	0.21
Year of diagnosis (vs. year 2010–2013)								
2014–2016	0.45	0.13	1.62	0.22	0.48	0.18	1.27	0.14
SES (vs. Urban 1)								
Missing	0.00	0.00	0.00	0.99	0.00	0.00	0.00	0.98
Rural	0.61	0.12	3.14	0.55	1.19	0.40	3.58	0.75
Urban 2	1.24	0.40	3.84	0.71	1.77	0.72	4.32	0.21
Urban 3	1.14	0.36	3.63	0.82	1.03	0.38	2.77	0.96
Urban 4	1.32	0.44	3.99	0.62	1.61	0.66	3.94	0.30
Urban 5	1.14	0.38	3.43	0.81	1.12	0.44	2.82	0.81
Charlson group (vs. 0)								
1	0.50	0.15	1.71	0.27	0.88	0.39	1.98	0.75
≥ 2	0.36	0.05	2.71	0.32	0.30	0.04	2.21	0.24
Adherence to screening mammography	0.65	0.32	1.35	0.25	1.02	0.61	1.71	0.93
Proportion of time adherent to ET	0.87	0.77	0.98	0.019	0.88	0.80	0.96	0.006

HR hazard ratio; *CI* confidence interval; *ET* endocrine therapy; *RT* radiation therapy; *ER* estrogen receptor; *PR* progesterone receptor; *SES* socio-economic status

Table 5 Incidence of venous thromboembolic events

	No adjuvant therapy *N* (%) *n* = 853	RT and endocrine therapy *N* (%) *n* = 1680	Endocrine therapy only *N* (%) *n* = 581	RT only *N* (%) *n* = 1135	*P* value
DVT	8–11	25 (1.31%)	10–13	15 (1.18%)	
PE	11 (1.16%)	22 (1.16%)	17 (2.59%)	13–15	
DVT and PE	≤5	7 (0.37%)	≤5	≤5	
DVT or PE	21 (2.21%)	54 (2.84%)	29 (4.42%)	31 (2.44%)	0.039

RT Radiation therapy, *DVT* deep vein thrombosis, *PE* pulmonary embolism

(of these, 29 (55.8%) were due to pulmonary embolus) ($p = 0.05$). The rate of VTE was higher in women treated with adjuvant tamoxifen (4.4%) compared to those treated with an aromatase inhibitor (2.3%) ($p = 0.0036$). Among women who experienced a VTE, 56/135 (41.5%) were on tamoxifen and 37 (27.4%) were on an aromatase inhibitor prior to the event. Among women who did not experience a VTE during the follow-up period, 26.5% received tamoxifen and 36% who received an aromatase inhibitor. Incidence of VTE by adjuvant treatment received is described in Table 5.

Discussion

In this contemporary population-based cohort of 5076 women aged 65 years or older with stage T1N0 BC treated with BCS from 2010 to 2016, we observed that adjuvant therapy (RT, ET or both) was used in approximately 80% of patients. The use of adjuvant RT and ET alone or in combination following BCS decreased steadily with increasing age and with increasing Charlson comorbidity score.

The use of adjuvant RT and ET in combination following BCS decreased considerably over the study period from 43.4% prior to 2014 to 28.7% after 2014. This was accompanied by a modest increase in adjuvant ET or RT alone but a larger increase in the proportion of patients who did not receive any adjuvant therapy from (18.1 to 27.3%). These patterns of treatment utilization are consistent with selection for adjuvant therapies based on age and comorbidities and may reflect a perceived reduced recurrence risk in this patient population, or a perception of inability for these patients to tolerate side effects associated with individual or multiple adjuvant therapies. Although the reasons for de-escalation are not known, it may reflect patient and physician preferences in part influenced by the lack of survival difference between the various treatment strategies in this population.

Among women who commenced adjuvant ET (with or without RT), adherence to ET declined to 66% during the fifth year from diagnosis. Data from clinical trials report that 8–28% of trial patients do not complete 5 years of treatment [14–17]. In general practice settings, up to two-thirds do not complete the recommended 5 years of adjuvant hormonal therapy [18]. Women at the extremes of age at diagnosis and those who experience treatment-related side effects were significantly more likely to be non-adherent to ET [18]. We found that the proportion of time adherent to ET was associated with an increase in the relative risk of LR (HR = 0.87, 95% CI: 0.77, 0.98, $p = 0.019$). Overall the absolute rates of an in-breast event (ipsilateral and contralateral breast events combined) after treatment with adjuvant RT alone or ET alone were similar (3.5% and 3.6%). The temporal trend of decreasing use of combined adjuvant therapy, and its decreasing use with increasing age, suggests clinician and patient preferences toward single modality adjuvant therapy for elderly women with hormone receptor positive stage I BC treated with BCS.

It is notable that the development of a VTE was more frequent among women who received ET (with or without RT) compared to women who did not. The rate of VTE was highest in women treated with adjuvant tamoxifen (4.4%), whereas the rate of VTE among women treated with an aromatase inhibitor (2.3%) was similar to those who did not receive adjuvant ET (2.6%) ($p = 0.0036$). Furthermore, 60% of VTE were due to pulmonary embolism. The rates of VTE in our cohort are similar to those seen in the randomized clinical trial of anastrozole versus tamoxifen [19]. Additional data with longer term follow-up is needed to evaluate the rate of adverse events including osteoporotic fractures related to aromatase inhibitors, cardiac events, and second malignancies related to RT, to better weigh the therapeutic benefit of adjuvant therapies for individual patients.

The rates of LR at 5 years (1–3%) for patients treated with adjuvant therapy are similar to those reported in past clinical trials [8, 10, 12, 20]. The risk of LR without adjuvant therapy was substantially higher at 9%. Although we have no direct evidence that the absence of all adjuvant therapies in this population compromises overall survival, there is a burden of additional breast surgery under general anesthetic borne by this subpopulation during relatively short years of follow-up. Furthermore, over 70% remain alive 6 years after diagnosis and will continue to be at risk of further breast cancer events which might make the use of some adjuvant

therapy following BCS more attractive for many of these women.

In conclusion, we observed a decrease in the use of combination adjuvant RT and ET over time in elderly patients with Stage I breast cancer treated by BCS. This was accompanied by a modest increase in the use of ET or RT alone but a significant increase in the use of no adjuvant therapy. Patients treated with combination or single modality adjuvant therapy with RT or ET had relatively low absolute risks of LR or contralateral breast cancer following BCS. In contrast, patients that did not receive any adjuvant therapy were at a significant risk of any in-breast event. These data support that mono-adjuvant therapy with ET or RT alone provides considerable benefit even for elderly women with low risk breast cancer. Prospective study is required to define clinical and patient reported outcomes in this population, for whom the various options of adjuvant therapy, although not altering overall survival, may significantly influence adverse outcomes other than death, and alter the requirements for further surgery and its associated morbidity during advancing age.

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

Compliance with ethical standards

Conflict of interest All other authors declare no conflict of interest.

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

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

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