Systematic review

Tamoxifen with radiotherapy compared with Tamoxifen alone in elderly women with early-stage breast cancer treated with breast conserving surgery: A systematic review and meta-analysis

Tyler R. Chesney, Jennifer Xin Yin, Nikoo Rajaee, Andrea C. Tricco, Anthony W. Fyles, Sergio A. Acuna, Adena S. Scheer

Division of General Surgery, Department of Surgery; Faculty of Medicine; Li Ka Shing Knowledge Institute and Department of Surgery, St. Michael’s Hospital; Epidemiology Division, Dalla Lana School of Public Health; Department of Radiation Oncology, Princess Margaret Cancer Centre; and Institute of Health Policy, Management, and Evaluation, University of Toronto, Canada

Abstract

Background: Our aim was to assess the effect of adjuvant radiotherapy on recurrence and survival for elderly women (>70) with early-stage hormone receptor-positive breast cancer treated with breast conserving surgery (BCS) and Tamoxifen.

Materials and methods: MEDLINE, EMBASE, and Evidence-Based Medicine Reviews were systematically searched through August 12, 2016 for randomized controlled trials (RCTs) comparing radiotherapy to no radiotherapy and presenting outcomes for women >70 years. Two investigators screened citations, abstracted results, and appraised studies using Cochrane Risk of Bias tool. Pooled risk ratios (RR) for breast, axillary, and distant recurrence, and overall survival were determined using weights from fixed-effects models.

Results: Four RCTs with low risk of bias were identified (2387 elderly women). Tamoxifen plus radiotherapy reduced breast recurrence compared to Tamoxifen alone from 60 to 10 (95% CI 6–20) per 1000 patients at 5 years (RR 0.18, 95% CI 0.10–0.34; 4 trials, 2387 patients). This effect was maintained at 10 years (RR 0.27, 95% CI 0.13–0.54; 2 trials, 891 patients). Radiotherapy minimally reduced axillary recurrence from 12 to 3 (95% CI 1–10) per 1000 at 5 years (RR 0.28, 95% CI 0.10–0.81; 3 trials, 2287 patients). Radiotherapy did not affect distant recurrence (RR 1.49, 95% CI 0.87–2.54; 3 trials, 2287 patients) or overall survival (RR 0.98, 95% CI 0.79–1.22; 3 trials, 2287 patients).

Conclusion: For elderly women (>70), radiotherapy reduces the risk of breast and axillary recurrence, but does not impact distant recurrence or overall survival in early-stage breast cancer treated with BCS and Tamoxifen. The value of this risk reduction must be weighed by women and their physicians when considering the omission of adjuvant radiotherapy.

© 2017 Elsevier B.V. All rights reserved. Radiotherapy and Oncology 123 (2017) 1–9

Early-stage breast cancer is amenable to breast conserving surgery (BCS) with equivalent survival to mastectomy if adjuvant radiotherapy is included [1–3]. Radiotherapy and a radiation boost to the tumor bed also reduce local recurrence, but this risk reduction declines with advancing age [4,5]. Additionally, elderly women more frequently have favorable tumor biology with a high frequency of low-grade, hormone receptor (HR) positive, HER2-negative tumors that respond to endocrine therapy potentially reducing the absolute benefit of radiotherapy [6–10].

Treatment of elderly breast cancer patients is often not guideline adherent with older women may receiving less radiotherapy following BCS, and variably more hormonal therapy [11–15]. Several randomized controlled trials (RCTs) have tested the safety of omitting radiotherapy, but the majority of women were younger than 65, and results had little initial impact on practice [16–18]. Available guidelines provide conflicting statements on the use of radiotherapy in elderly women after BCS. Two state that it is reasonable to omit radiotherapy, and the third states that there is no subgroup of fit older women in which radiotherapy can be systematically omitted [19–21].

Attempting to clarify this question, a previous systematic review was conducted [22]. Unfortunately, in order to include a greater number of studies by defining elderly as postmenopausal,
that review included many younger women, as young as 44 years. Further, it included one trial that had no women older than 69 years, and two trials with the majority of women under 65. The results are reported for the population as a whole without any outcomes reported specifically for elderly women.

Our current systematic review therefore aims to clarify the effect of adjuvant radiotherapy for elderly women (≥70 years) with early-stage HR-positive breast cancer treated with BCS and endocrine therapy by synthesizing outcomes from RCTs specific to this unique population.

Methods

We registered our protocol with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42015024598) [23]. We reported this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) standards [24].

Search strategy

We systematically searched the electronic databases MEDLINE and EMBASE from inception through August 12, 2016 with no restriction for language or publication status. We similarly searched the Evidence Based Medicine Reviews (EBMR) database combining searches of Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Cochrane CENTRAL, Cochrane Methodology Register (CMR), Health Technology Assessment (HTA), NHS Economic Evaluation Database (NHSEED), and ACP Journal Club. An information specialist developed a maximally sensitive search strategy to include terms for breast cancer, radiotherapy, and endocrine therapy (see Appendix Tables A1 and A2 for full search strategies). The search strategy was peer reviewed using the Peer Review of Electronic Search Strategies (PRESS) checklist [25]. Scanning of included studies and relevant reviews was conducted to ensure literature saturation.

Eligibility criteria and outcomes

We included RCTs comparing adjuvant radiotherapy to no radiotherapy in older women with early-stage breast cancer treated with BCS and adjuvant endocrine therapy. Early stage breast cancer included tumor stage T1 and T2, clinically node negative (N0) invasive breast cancers. Studies evaluating treatment of in-situ breast cancer, more advanced disease (T3/T4, clinically or biopsy-proven node positive), recurrent disease, or using neoadjuvant therapy were excluded. Primary outcomes included number of in-breast recurrences, axillary recurrences, distant recurrences, and all-cause deaths at 5 years, and 10 years if available. Studies were included only if at least one of our primary outcomes was available for older women defined as a group aged 70 years or above, or a group with median age of 70 years or above but no patients under 65 years. If these outcomes were not reported in the published manuscript, authors were contacted to obtain data for older women.

Study selection

After pilot-testing the eligibility criteria, two independent reviewers (TRC, JY) evaluated all citations for eligibility. Level 1 screening of titles and abstracts identified all potentially relevant citations, and level 2 screening evaluated these citations in full-text for final inclusion. When several citations reported on the same trial at different time points, the reports with 5-year outcomes and 10-year outcomes were retained for inclusion. Five-year outcomes were selected due to availability across all included studies, and 10-year outcomes were available for in-breast recurrence in 2 trials. Discordance between reviewers was resolved by discussion.

Data extraction

A data extraction form was developed a priori and pilot tested [26]. Two reviewers (TRC, JY) independently extracted data from each included study. Discordance was resolved by discussion.

Data were extracted on study-level information, inclusion and exclusion criteria, patient characteristics, intervention and comparator details, co-interventions, and outcomes. Outcomes were extracted from intention-to-treat analyses. For studies that only presented Kaplan–Meier survival curves, survival end points were extracted using Digitizelt software (Digitizelt, Brunschweig, Germany) [27]. Missing data were treated as “not reported”. Where possible, authors were contacted to obtain data not originally reported.

Risk of bias assessment

Risk of bias was assessed independently by two reviewers (TRC, JXY) using the Cochrane Risk of Bias tool [28]. Funnel plots for assessment of publication bias were not constructed as no outcome had at least ten RCTs contributing data [29].

Synthesis and statistical analysis

Descriptive synthesis was used to summarize study characteristics, patient characteristics, intervention details, and risk of bias results.

For our meta-analyses, risk ratios (RR) were selected as the measurement of effect for our primary outcomes. Although hazard ratios are the most appropriate statistic for meta-analysis of time-to-event outcomes, neither hazard ratios nor sufficient statistical information to estimate them (e.g., Kaplan–Meier survival curves, \( p \)-values for log-rank test) using established methods, were available across studies [30]. Therefore, RR with their respective 95% confidence intervals (CI) were estimated for dichotomous outcomes at 5 years for each study, and at 10 years where available. For studies with zero events, the standard continuity correction of 0.5 was applied [31].

Meta-analyses were performed using weights from fixed-effects models using Mantel–Haenszel methods due to low event rates, and reported with corresponding 95% CI [32]. The decision to use fixed-effects models was made a priori as the strict eligibility criteria used in RCTs were expected to create homogenous populations across studies. Heterogeneity of the data was evaluated visually using forest plots, and between-study statistical heterogeneity was assessed with Cochran’s Q test and quantified using the \( I^2 \) statistic [33]. \( I^2 \) values of 25%, 50% and 75% corresponded to cut-off points of low, moderate and high degrees of heterogeneity, respectively [34].

To ease communication of intervention effects we calculated clinically applicable absolute effect measures including comparative risk, which is expressed as number of events per 1000 patients at risk, and numbers needed to treat (NNT). These absolute effect measures were calculated using the pooled RR and the median Tamoxifen alone group risk across studies for each outcome [26,35].

Statistical analyses were performed using Review Manager (RevMan) 5.3 (Cochrane Collaboration, Copenhagen, Denmark) [36]. No pre-specified subgroup analysis or meta-regression was planned. To investigate the effect of radiotherapy on axillary recurrence in patients not having axillary lymph node dissection (ALND)
a post hoc subgroup analysis pooling outcomes from trials with a low proportion of ALND was conducted.

**Results**

**Systematic search**

Fig. 1 illustrates citation selection. Our initial search strategy yielded 7231 citations after removal of duplicates. Three citations were added after citation tracking. After level 2 screening of the remaining 28 full-text articles, 22 were excluded. Five were excluded as multiple reports of the same trial, 3 did not have available full texts, 1 did not use adjuvant endocrine therapy, 6 were not RCTs, 1 did not have the designated comparator group, 5 did not have outcome measures available for elderly women, and 1 included patients with node-positive disease. Ultimately, 6 articles reporting on 4 RCTs were included.

**Study and patient characteristics**

Study and patient characteristics are detailed in Tables 1 and 2. The four included RCTs reported on 2387 women aged 70 years and older with study periods ranging from 1989 to 2009. Two of these trials specifically recruited elderly women, one 70 years and older, and the other 65 years and older with a median age of 70 [37,38]. All patients from these two trials were included in the meta-analyses. The remaining two trials had outcomes available for the subgroup of elderly women (aged 70 years or older) [39,40]. Fisher reported these subgroup outcomes in the published manuscript (100 of 673 patients), and Fyles provided outcomes for this subgroup after contacting them (325 of 769 patients) [39,40].

Across studies, the tumor size cut-offs varied from 1 cm to 5 cm; however, these cutoffs still correspond to early-stage (T1-2) tumors. The proportion of T1 tumors ranged from 83 to 99% across studies. Two trials had limited inclusion to HR-positive tumors resulting in 97% and 99% HR-positive patients [37,38]. Two trials did not limit to only HR-positive tumors, but had HR-positive rates of 84% and 57% (with 30% unknown status) [39,40]. Tumor grade was reported in only two trials, but was largely grades 1 and 2 tumors with fewer than 20% of grade 3 tumors. Axillary staging requirements for inclusion varied across studies: one required either sentinel lymph node biopsy (SLNB) or ALND, two accepted clinical staging or pathological staging, and one required ALND. Actual axillary surgery ranged from 100% ALND in Fisher to 78% SLNB in PRIME II [37,39,40].

All women received BCS with a negative pathological margin defined as no tumor at inked margin in three trials, and ≥1 mm in PRIME II. Adherence to Tamoxifen was not reported in PRIME II and CALGB C9343, and was 99–100% in the other two trials [37,38]. All women in the intervention arm received adjuvant whole-breast radiotherapy at a dose of 40–50 Gy; three trials gave boosts of 10–14 Gy. Receipt of radiotherapy was reported in 98–100% of women in the intervention arm across trials. Women in the control arm did not receive adjuvant radiotherapy with no crossover in three trials and 0.6% crossover in Fyles [39].

**Risk of bias assessment**

Risk of bias assessment is summarized in Appendix Table A3. All trials are at low risk of bias overall; however, the use of blinding is not well reported in three trials. PRIME II did not blind patients to treatment received, but blinding was maintained for outcome assessors and data analysis. The remaining three trials did not report on blinding; nonetheless, as the outcomes of interest were objective outcomes, the risk of bias can be assumed to be low.

**Outcomes**

All trials provided data on in-breast recurrence for elderly women at 5 years. There is strong evidence that adjuvant Tamoxifen plus radiotherapy reduced in-breast recurrence compared to adjuvant Tamoxifen alone in elderly women with early-stage breast cancer following BCS (RR 0.18, 95% CI 0.10–0.34, p < 0.001; 22 full-text articles excluded
- Multiple reports on same trial (n=5)
- Full text unavailable (n=3)
- No adjuvant endocrine therapy (n=1)
- Not a randomized controlled trial (n=6)
- Different comparator group (n=1)
- No outcomes available for elderly women (n=5)
- Node positive disease (n=1)

Fig. 1. Study selection process.
2387 patients) with low heterogeneity ($I^2 = 0\%$, $p = 0.96$) (Fig. 2). The addition of radiotherapy to adjuvant Tamoxifen reduces the number of in-breast recurrences from 60 to 10 (95% CI 6–20) per 1000 patients at 5 years (Table 3). As such, 21 patients must be treated with radiotherapy to prevent one additional breast recurrence in 5 years (NNT 21). Two trials had 10-year follow-up outcomes for in-breast recurrence [41,42]. At 10 years of follow-up the effect of radiotherapy combined with adjuvant Tamoxifen compared with Tamoxifen alone following BCS is maintained (RR 0.27, 95% CI 0.13–0.54, $p < 0.001$; 891 patients) with low heterogeneity ($I^2 = 0\%$, $p = 0.44$) (Fig. 2). The addition of radiotherapy to adjuvant Tamoxifen reduces the number of in-breast recurrences from 80 to 20 (95% CI 10–40) per 1000 patients at 10 years (Table 3). Compared to 5 years where 21 patients must be treated with radiotherapy to prevent one additional breast recurrence, at 10 years 17 women must be treated with radiotherapy for the same effect (NNT 17).

Three trials provided data for axillary recurrence for elderly women at 5 years [37–39]. Adjuvant Tamoxifen plus radiotherapy reduced axillary recurrence compared to adjuvant Tamoxifen alone (RR 0.28, 95% CI 0.10–0.81, $p = 0.02$; 2287 patients) with low heterogeneity ($I^2 = 0\%$, $p = 0.81$) (Fig. 3). The number of axillary recurrences was reduced from 12 to 3 (95% CI 1–10) per 1000 patients with the addition of radiotherapy to adjuvant Tamoxifen (Table 3). The NNT is 116 to prevent one axillary recurrence in 5 years. Two trials provided data for our subgroup analysis of trials with low proportion of ALND: PRIME II had only 22% of patients with ALND, and CALGB 9343 had 36%. In this subgroup with low proportion of ALND, there was no statistical difference in the rate of axillary recurrence with the addition of radiotherapy (RR 0.34, 95% CI 0.10–1.13).

Three trials provided data for distant recurrence for elderly women at 5 years [37–39]. There is no clear evidence of a difference in distant recurrence with the addition of radiotherapy to adjuvant Tamoxifen compared to adjuvant Tamoxifen alone (RR 1.49, 95% CI 0.87–2.54, $p = 0.14$; 2287 patients) with low heterogeneity ($I^2 = 0\%$, $p = 0.60$) (Fig. 3). The three trials provided data for overall survival for elderly women at 5 years [37–39]. Similarly, there is an absence of evidence of effect on overall survival with the addition of radiotherapy to adjuvant Tamoxifen compared to adjuvant Tamoxifen alone (RR 0.98, 95% CI 0.79–1.22, $p = 0.89$; 2287 patients) with low heterogeneity ($I^2 = 0\%$, $p = 0.63$) (Fig. 3).

**Discussion**

We identified four RCTs of low overall risk of bias comparing adjuvant Tamoxifen plus radiotherapy to adjuvant Tamoxifen alone reporting outcomes specific for elderly women with early-stage breast cancer treated with breast conserving surgery. There is strong evidence that the addition of radiotherapy reduces the risk of breast and axillary recurrence. However, the absolute risk reduction with the addition of radiotherapy in this population is low. Radiotherapy reduces the risk of breast recurrence from 60 to 10 per 1000 patients at 5 years; an absolute risk reduction of 5% (95% CI 4–5%) or a NNT of 21 to prevent one in-breast recurrence. This effect is maintained at 10 years when the addition of radiotherapy reduces the risk of breast recurrence from 80 to 20 per 1000, an absolute risk reduction of 6% (95% CI 4–7%). More modest is the reduction in axillary recurrence from 12 to 3 per 1000, an absolute risk reduction of 1% (95% CI 0.2–1%) or a NNT of 116 to prevent one axillary recurrence. Additionally, the meta-analyses do not demonstrate evidence that the addition of radiotherapy has an effect on distant recurrence or overall survival. Overall, these findings are consistent with the conclusions of the included RCTs regarding a modest effect on locoregional recurrence at 5 and 10 years. However, the published risk difference in Fyles at 5 years is higher at 7.1%, likely due to the inclusion of younger women in this estimate [39]. Further, the individual RCTs were not powered for the outcome of axillary recurrence, which was significant in our meta-analysis albeit modest in effect size. Likewise, the included studies were not powered for the outcomes...
of distant recurrence or overall survival; thus, our meta-analysis improves the confidence in the null result.

Our systematic review has several strengths. Most notable is the inclusion of outcomes specifically for elderly women. We obtained published elderly subgroup outcomes from one trial and previously unpublished subgroup outcomes from another (Fyles [39,40]). By carefully restricting the age criterion for inclusion, we were able to produce a homogeneous study population with results directly applicable to elderly women. Other strengths include our rigorous methodology based on an a priori protocol. Usefully, we present results using absolute effects for ease of interpretation and clinical applicability.

Our review has several differences compared to the previous systematic review [22]. Our review includes outcomes specifically for elderly women not available in the previous review including published and unpublished subgroup outcomes, the results of PRIME II, and 10 year follow-up outcomes. The pooled estimates of effect were estimated at differing time-points across trials ranging from 4.5 to 13.7 years making the results difficult to interpret. Our review selected the clinically standard time-points of 5 and 10 years to estimate RRs. Additionally, odds ratios, as used in the prior review, can be difficult to interpret, and absolute estimates of effect should also be presented [35,43]. The prior review calculates risk differences from sums of events across trials, which does not account for weighting, rather than from the pooled estimate calculated by meta-analysis as is standardly done. Finally, the search strategy only utilizes two databases, and a risk of bias assessment is not included in this previous review.

In our systematic review, the included trials do not report on comorbidity or frailty. Prior cohort studies have observed the increased mortality from non-breast cancer causes and reduced absolute benefit of radiotherapy with increasing age and comorbidity or frailty. Prior cohort studies have observed the increased mortality from non-breast cancer causes and reduced absolute benefit of radiotherapy with increasing age and even more with increasing multimorbidity and frailty.

We could not calculate hazard ratios because sufficient data were not available across studies. Even though hazard ratios are important in accounting for censoring and competing risk, our results using RRs are similar to those reported by the time-to-event analyses available in the trials. Although censoring cannot be accounted for in dichotomous outcomes, the rate of censoring was not different between treatment arms when reported in the trials.

The included trials do not report on adverse effects or quality of life. Elderly women may also struggle with mobility, transporta-
tion, and other social supports that have not been measured. The literature evaluating the impact of radiotherapy on quality of life in elderly is limited. The PRIME RCT randomized women older than 65 years to standard adjuvant radiotherapy or no radiotherapy and

<table>
<thead>
<tr>
<th>Reference (year)</th>
<th>Treatment Arm</th>
<th>N</th>
<th>Age</th>
<th>Tumor Stage</th>
<th>HR+</th>
<th>Grade</th>
<th>BCS</th>
<th>Axillary Surgery</th>
<th>Received Tamoxifen</th>
<th>Received Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIME II [37] (2015)</td>
<td>TamRT</td>
<td>658</td>
<td>69 (IQR 67–73)</td>
<td>T1 584 (89%) T2 74 (11%)</td>
<td>1 292 (44%) 2 352 (33%) 3 13 (2%)</td>
<td>658</td>
<td>SLNB* 516 (78%) ALND 135 (21%)</td>
<td>NR</td>
<td>573/584 (98%)</td>
<td></td>
</tr>
<tr>
<td>Tam Alone</td>
<td>668</td>
<td>70 (IQR 67–74)</td>
<td>T1 584 (87%) T2 84 (13%)</td>
<td>1 271 (41%) 2 368 (35%) 3 23 (3%)</td>
<td>668</td>
<td>SLNB* 502 (75%) ALND 158 (24%)</td>
<td>NR</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CALGB 9314 [38] (2004)</td>
<td>TamRT</td>
<td>317</td>
<td>70–74 y 139 (44%) ≥75 y 178 (56%)</td>
<td>T1 312 (98%) T2 5 (2%)</td>
<td>308 (97%)</td>
<td>NR</td>
<td>317</td>
<td>ALND 117 (37%)</td>
<td>NR</td>
<td>317 (100%)</td>
</tr>
<tr>
<td>Tam Alone</td>
<td>319</td>
<td>70–74 y 146 (46%) ≥75 y 173 (54%)</td>
<td>T1 310 (97%) T2 9 (3%)</td>
<td>310 (97%)</td>
<td>NR</td>
<td>319</td>
<td>ALND 115 (36%)</td>
<td>NR</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Fyles [39] (2004)</td>
<td>TamRT</td>
<td>171</td>
<td>≥70</td>
<td>T1 142 (84%) T2 28 (17%)</td>
<td>161 (94%)</td>
<td>1 8/386 (22%) 2 179/386 (46%) 3 57/386 (15%)</td>
<td>171</td>
<td>118 (69%)</td>
<td>169 (99%)</td>
<td>167 (98%)</td>
</tr>
<tr>
<td>Tam Alone</td>
<td>154</td>
<td>≥70</td>
<td>T1 128 (83%) T2 25 (16%)</td>
<td>144 (94%)</td>
<td>1 8/383 (21%) 2 181/383 (47%) 3 67/383 (18%)</td>
<td>154</td>
<td>104 (68%)</td>
<td>153 (99%)</td>
<td>1 (0.6%)</td>
<td></td>
</tr>
<tr>
<td>Fisher [40] (2002)</td>
<td>TamRT</td>
<td>57</td>
<td>≥70</td>
<td>T1 332/334 (99%)</td>
<td>197/334 (59%) Unknown 54/334 (28%)</td>
<td>NR</td>
<td>57</td>
<td>ALND 57 (100%)</td>
<td>57 (100%)</td>
<td>57 (100%)</td>
</tr>
<tr>
<td>Tam Alone</td>
<td>43</td>
<td>≥70</td>
<td>T1 330/334 (99%)</td>
<td>181/334 (54%) Unknown 108/334 (32%)</td>
<td>NR</td>
<td>43</td>
<td>ALND 43 (100%)</td>
<td>43 (100%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>
found increased breast symptoms and fatigue in the radiotherapy group, but overall health-related quality of life was no different between groups [47].

Nevertheless, several advances in the delivery of radiotherapy have reduced the overall burden of radiotherapy. Intensity modulated radiation therapy (IMRT) improved cosmesis, fibrosis, toxicity and skin telangiectasia at 5 and 10 years in randomized trials [48–50]. Hypofractionation increases convenience by shortening treatment duration, and demonstrates reduced toxicity, edema, telangiectasia, fatigue, and trouble meeting family needs in RCTs [51–54]. Similarly, accelerated partial breast irradiation (APBI) is a localized form of radiation aimed at improving convenience for women with low-risk tumors [55–58]. A recent systematic review of 8653 women across 8 RCTs confirms the safety of APBI on regional, distant, and overall survival, with a small increase in breast recurrence (2.9% vs 0.6% at 5 years; HR 4.45, 95% CI: 1.78–11.61) [59]. Importantly, the impact of locoregional recurrence on quality of life should be considered when weighing this against the omission of radiotherapy, and women may alternatively opt for treatment with an alternative radiotherapy delivery technique to

---

### Table 3
**Summary of findings.**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks, per 1000 patients (95% CI)</th>
<th>Risk difference, per 1000 patients (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>NNT</th>
<th>No. of Participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk Tamoxifen Alone</td>
<td>Corresponding risk Tamoxifen and Radiotherapy</td>
<td>RR 0.18 (0.10 to 0.34)</td>
<td>21</td>
<td>2387 (4)</td>
</tr>
<tr>
<td></td>
<td>RR 0.27 (0.13 to 0.54)</td>
<td>RR 0.28 (0.10 to 0.81)</td>
<td>RR 1.49 (0.87 to 2.54)</td>
<td>17</td>
<td>891 (2)</td>
</tr>
<tr>
<td></td>
<td>RR 0.98 (0.79 to 1.22)</td>
<td>RR not significant</td>
<td>RR not significant</td>
<td>93</td>
<td>2287 (3)</td>
</tr>
<tr>
<td>In-breast Recurrence at 5 years</td>
<td>60</td>
<td>10 (6 to 20)</td>
<td>50 fewer (40 fewer to 54 fewer)</td>
<td>60 fewer (40 fewer to 70 fewer)</td>
<td>9 fewer (2 fewer to 11 fewer)</td>
</tr>
<tr>
<td>In-breast Recurrence at 10 years</td>
<td>80</td>
<td>20 (10 to 40)</td>
<td>60 fewer (40 fewer to 70 fewer)</td>
<td>9 fewer (2 fewer to 11 fewer)</td>
<td>8 more (28 more to 2 fewer)</td>
</tr>
<tr>
<td>Axillary Recurrence at 5 years</td>
<td>12</td>
<td>3 (1 to 10)</td>
<td>9 fewer (2 fewer to 11 fewer)</td>
<td>8 more (28 more to 2 fewer)</td>
<td>5 fewer (35 more to 35 fewer)</td>
</tr>
<tr>
<td>Distant Recurrence at 5 years</td>
<td>22</td>
<td>30 (20 to 50)</td>
<td>8 more (28 more to 2 fewer)</td>
<td>5 fewer (35 more to 35 fewer)</td>
<td>21</td>
</tr>
<tr>
<td>Overall Survival at 5 years</td>
<td>165</td>
<td>160 (130 to 200)</td>
<td>5 fewer (35 more to 35 fewer)</td>
<td>21</td>
<td>2387 (4)</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, Confidence interval; NNT, Number Needed to Treat; RR, Risk Ratio.

* The basis for the assumed risk was derived from median Tamoxifen alone group risk across studies. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the Tamoxifen group and the relative effect of the addition of radiotherapy (and its 95% CI). These are rounded for ease of interpretation.

* Pooled RRs taken from the meta-analyses.

* Calculated from the median Tamoxifen alone group risk across studies and RR: NNT = 1/(median Tamoxifen alone group risk × (1 – RR)). These are rounded to the nearest whole number by convention for ease of interpretation.

---

Fig. 2. Effect of radiotherapy plus Tamoxifen (Tam RT) compared to Tamoxifen alone (Tam) on breast recurrence at 5 years (A) and 10 years (B). Risk ratios were pooled using fixed-effects models.
reduce the burden of treatment. There are no studies directly reporting on elderly women’s preferences in weighing omission of radiotherapy against the risk of locoregional recurrence, nor are there published decision aids to assist women with this choice.

It is well known that elderly women are undertreated with BCS in favor of mastectomy [12–14]. There are many reasons for this such as logistical concerns related to radiotherapy; possibility of comorbidity, functional impairment, and frailty; ideas about body-image; among others. However, as long as this group of elderly patients who would otherwise underutilize BCS meets the selection criteria for this meta-analysis, they should expect to have similar outcomes as those reported in this meta-analysis, and this meta-analysis may improve the utilization of BCS in elderly women.

Finally, these results apply only to women who are treated with endocrine therapy. For postmenopausal women, adjuvant endocrine therapy for 5, and up to 10 years, is recommended to reduce the risk of local recurrence and breast cancer-related mortality [9,60,61]. Both Tamoxifen and aromatase inhibitors (AI) are options, but AIs have increased benefit [9,62]. Adverse effects are not common, but include thromboembolic events, endometrial hyperplasia, reduced bone density, musculoskeletal and sexual symptoms [9,60–62]. These can lead to poor adherence and non-persistence [63]. While several options for managing adverse effects exist, the option of omitting endocrine therapy has been proposed [60,64]. Two 2 × 2 factorial design RCTs demonstrate that adjuvant monotherapy with either Tamoxifen alone or radiotherapy alone had similar effects on reduction of local recurrence compared with no adjuvant treatment [65,66]. Conversely, GBCG-V observed no difference between monotherapy with either Tamoxifen or radiotherapy compared with combined endocrine and radiotherapy, while BASO II observed increased local recurrence with monotherapy compared with combined therapy [64,66]. Based on these results, women who cannot tolerate or opt to omit endocrine therapy, may favor the inclusion of adjuvant radiotherapy.
Omitting radiotherapy for early breast cancer in the elderly

Conclusion
Our meta-analysis provides the most robust estimate of effect for adjuvant radiotherapy, or its omission, in elderly women with early-stage breast cancer treated with BCS and adjuvant endocrine therapy. These findings provide precise estimates that can be included in guideline recommendations, can be used by patients and their physicians in shared decision-making, and provide data for the development of a decision aid to assist elderly women in making this choice. Indeed, the addition of adjuvant radiotherapy reduces the absolute risk of breast recurrence and axillary recurrence. However, the absolute reduction in the risk of breast recurrence is modest, and even less for that of axillary recurrence. Further, there is no demonstrable evidence that radiotherapy affects the risk of distance recurrence or overall survival. The value of this risk reduction must be weighed by elderly women and their physicians when considering the omission of adjuvant radiotherapy. Women may also consider the impact of omitting endocrine therapy or using alternative radiotherapy techniques as other options to reduce treatment burden. Ultimately, the inputs of a multidisciplinary team including a global assessment of risks and prognosis such as a comprehensive geriatric assessment will facilitate patient-centered decision making [21].

Funding source
Andrea C. Tricco is funded by a Tier 2 Canada Research Chair in Knowledge Synthesis.

Disclaimers
There are no conflicts of interest to disclose.

Acknowledgements
Christine Neilson, information specialist.
Bridget Morant, information specialist.

Appendix A. Supplementary data
Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2017.02.019.

References
[37] Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM, investigators PI. Breast-conserving surgery with or without irradiation in women aged 65 years.