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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

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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.

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,

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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, JXY) 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, Bruanschweig, 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)