Journal of Geriatric Oncology 8 (2017) 140–147

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

Review article

Omission of axillary staging in elderly patients with early stage breast cancer impacts regional control but not survival: A systematic review and meta-analysis

Shuyin Liang [a], Julie Hallet [a,b], Jory S. Simpson [a,c], Andrea C. Tricco [d,e], Adena S. Scheer [a,c,d,*]

[a] Department of Surgery, University of Toronto, Toronto, 500 University Avenue, Suite 602, Toronto, Ontario M5G 1V7, Canada
[b] Division of General Surgery, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada
[c] Division of General Surgery, St. Michael's Hospital, 30 Bond Street, Toronto, Ontario M5B1W8, Canada
[d] Li Ka Shing Knowledge Institute of St. Michael's Hospital, 209 Victoria Street, Toronto, Ontario M5B1W8, Canada
[e] Division of Epidemiology, Dalla Lana School of Public Health, University of Toronto, 155 College Street, 6th Floor, Toronto, Ontario M5T 3M7, Canada

ARTICLE INFO

Article history:
Received 20 July 2016
Received in revised form 11 November 2016
Accepted 1 December 2016
Available online 13 December 2016

Keywords:
Breast cancer
Axillary staging
Elderly
Systematic review
Meta-analysis

ABSTRACT

Introduction: Management of early breast cancer in the elderly population is challenging due to different breast cancer biology and limited tolerance to aggressive treatments. The aim of this study is to evaluate whether the omission of axillary staging impacts breast cancer outcomes in elderly patients.
Patients and Methods: A systematic review and meta-analysis was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. The electronic databases were searched in August 2014 using the following inclusion criteria:
Population Elderly patients (≥70 years) with early stage (T1/T2, N0) breast cancer.
Intervention Axillary staging with a sentinel node biopsy, axillary sampling or axillary node dissection.
Control No axillary surgery.
Outcomes Local-regional recurrence, disease-free survival, overall survival.
Study design RCTs.
Results: Two RCTs met the eligibility criteria and were included. A meta-analysis of the included RCTs of 692 patients found that axillary staging reduced the risk of axillary recurrence compared to no axillary staging (RR 0.24, 95% CI: 0.06 to 0.95, $I^2 = 0\%$, $p = 0.04$). There were no differences observed in in-breast recurrence or distant recurrence (RR 1.20, 95% CI: 0.55 to 2.64, $I^2 = 62\%$, $p = 0.65$, RR 1.17, 95% CI: 0.75 to 1.82, $I^2 = 0\%$, $p = 0.48$, respectively). There were no differences observed in overall or breast-cancer specific mortality (RR 0.99, 95% CI: 0.79 to 1.24, $I^2 = 0\%$, $p = 0.92$, RR 1.07, 95% CI: 0.72 to 1.57, $I^2 = 0\%$, $p = 0.75$, respectively).
Discussion: Omission of axillary staging in elderly patients with clinically negative axillae results in increased regional recurrence but does not appear to impact survival.

Contents

* Corresponding author at: 30 Bond Street, Room 3-005, Donnelly Wing, Toronto, Ontario M5B1W8, Canada. Tel.: +1 416 864 5804; fax: +1 416 864 5821.
E-mail address: scheera@smh.ca (A.S. Scheer).

http://dx.doi.org/10.1016/j.jgo.2016.12.003
1879-4068/

1. Introduction

Women above the age of 65 make up approximately 40% of new breast cancer diagnoses [1]. With an aging population, management of breast cancer in the elderly is a growing problem that general and specialized breast surgeons are increasingly facing. Management of breast cancer in this growing patient population is challenging as breast cancer biology differs in some respects in older patients, treatment tolerance varies, and there are substantial competing risks of mortality [2,3]. Without definitive data demonstrating better survival with axillary lymph node dissection, the National Comprehensive Cancer Network (NCCN) recommends that axillary lymph node dissection *may be considered optional* in patients for whom the decision regarding adjuvant therapy is not affected by the results of the axillary dissection such as in the elderly [4].

Currently there is significant variability in managing elderly patients with breast cancer. A recently published study using the American Commission on Cancer's National Cancer Data Base, which captures approximately 80% of all newly diagnosed breast cancers, demonstrated significant variation in the use of axillary staging in T1N0 breast cancers in the elderly across the United States. Patients treated at academic facilities were 18.5% less likely to undergo axillary staging compared to community practices (OR 0.81, 95% CI 0.76–0.87) and there were also variations by geographic region [5]. Similarly, a study comparing breast cancer treatment in the elderly between the Netherlands and Ireland demonstrated variations in receipt of axillary surgery and concomitant variations in survival stage for stage [6].

Given the volume of breast cancer diagnoses and the non-centralized nature of its treatment, determination and dissemination of evidence-based practices are critical to avoid both the over-treatment and the under-treatment of elderly patients. Thus we undertook a systematic review and meta-analysis of randomized controlled trials in elderly women with early stage breast cancer to evaluate whether the omission of axillary staging impacts breast cancer outcomes.

2. Materials and Methods

2.1. Protocol

A systematic review protocol was developed using the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines for protocols (PRISMA-P) [7]. The protocol was registered on the PROSPERO register (Prospective Register Of Systematic Reviews) with registration number CRD42014010750.

2.2. Eligibility Criteria

The following criteria were used to select studies for inclusion:

Patients: Elderly (≥70 years of age) patients with early stage breast cancer (T1/T2, N0). Studies including a population with at least 50% of the patients over 70 years of age were included. Studies evaluating in-situ breast cancer or more advanced disease (T3/T4, clinically or biopsy proven positive nodes) were excluded.

Intervention: Axillary staging with a sentinel node biopsy, axillary sampling or axillary lymph node dissection.

Control: No axillary surgery. Studies comparing sentinel lymph node biopsy to axillary lymph node dissection or evaluating completion axillary dissection following a positive sentinel lymph node biopsy were excluded. Studies comparing axillary staging to axillary radiation were excluded.

Outcomes: Local, regional, and distant recurrence; breast cancer specific mortality and overall mortality.

Study design: Randomized controlled trials (RCTs).

Other: No other limitations were used (e.g. language of publication, publication status).

2.3. Information Sources

The electronic databases MEDLINE, Embase, and Cochrane Register of Controlled Trials were searched from inception until August, 2014. The MESH terms breast cancer and lymph node excision were used along with a validated filter for RCTs. The MEDLINE strategy was compiled by an expert librarian and peer reviewed by another using the Peer Review of Electronic Search Strategies (PRESS) checklist as a guide [8]. The final search strategies for MEDLINE and Embase can be found in Appendix 1. The reference lists of the eligible studies were searched. In order to ensure literature saturation, a PubMed Related Article search was conducted for the studies that were deemed relevant and included.

2.4. Study Selection

After pilot-testing the eligibility criteria, two independent reviewers assessed the relevance of the literature search results. This was conducted for level 1 screening of titles and abstracts and level 2 screening of potentially relevant full-text articles. Conflicts were resolved by discussion.

2.5. Data Collection Process

After a pilot-test of the data abstraction form, data was abstracted from the RCTs by two independent reviewers. Conflicts were resolved by discussion. Authors were contacted for data clarifications, as necessary.

2.6. Risk of Bias Appraisal

The risk of bias was assessed using the Cochrane Risk of Bias tool [9] by two reviewers, independently. Conflicts were resolved by discussion. Authors were contacted for further relevant information to assess risk of bias, as necessary. We planned to draw funnel plots for examining publication bias for outcomes with at least 10 RCTs contributing data [10].

2.7. Synthesis

The patient and study characteristics and risk of bias results were described narratively. For outcomes with at least two included RCTs, a fixed effect meta-analysis was conducted. A fixed effect was used, as the RCTs were clinically, methodologically, and statistically similar e.g., $I^2 < 75\%$) [11]. Statistical heterogeneity was assessed using the I^2 statistic [12]. Since all of the included outcomes were dichotomous, the relative risk (RRs) and corresponding 95% confidence intervals (CIs) were calculated. All analyses were conducted using Revman 5.1, the Cochrane Collaboration's software [11].

3. Results

3.1. Literature Search

A search of MEDLINE, Embase, and Cochrane Register of Controlled Trials resulted in 4640 titles and abstracts that were screened. Thirty-two full text articles were selected for full text screening. An additional 67 titles and abstracts were screened based on a related article search of the included RCTs. Subsequently, two RCTs [13,14] fulfilled the eligibility criteria and were included (Fig. 1). The characteristics of the included studies are shown in Table 1. All patients in Martelli et al. study received quadrantectomy and post-operative radiation to the residual breast using a conventional irradiation technique. A dosage regimen of 50 Gy over 25 fractions was used, and a boost of 10 Gy was administered to the tumor bed, with no irradiation aimed at the axillary, supraclavicular or internal mammary nodes. All patients were prescribed 20 mg per day tamoxifen for 5 years. In the Rudenstam et al. study, 45% of their patients received mastectomy, 33% of the patients underwent breast-conserving surgery and radiotherapy, and 23% underwent breast-conserving surgery without radiotherapy. Their patients in both arms received tamoxifen 20 mg per day for 5 years as well.

3.2. Patient and Study Characteristics

Martelli et al. [14] conducted a single-centre RCT of patients aged 65–80 with clinical T1N0 on mammographic measurement. The primary outcomes were overall survival and breast cancer-specific mortality in patients who had vs. who did not have axillary surgery as part of their initial breast cancer operation. The secondary outcomes were recurrence of ipsilateral breast cancer, contralateral breast cancer, distant metastasis, and overt axillary disease for those who did not undergo axillary surgery. This study had a calculated sample size of 642, for a power of 94% to exclude an increase of 10% in distant metastasis in the group who did not undergo axillary surgery as part of their primary operation.

Rudenstam et al. [13] conducted a multicentre RCT of patients older than the age of 60 with operable clinically node negative breast cancer. The primary outcome was quality of life in patients who had vs. who did not have axillary surgery. The secondary outcomes were overall survival, disease free survival, and breast cancer specific mortality. This study aimed for a sample size of 472 in order to have a power of 80% to detect a decrease of 13% in morbidity in the group who did not undergo axillary surgery as part of their primary operation.

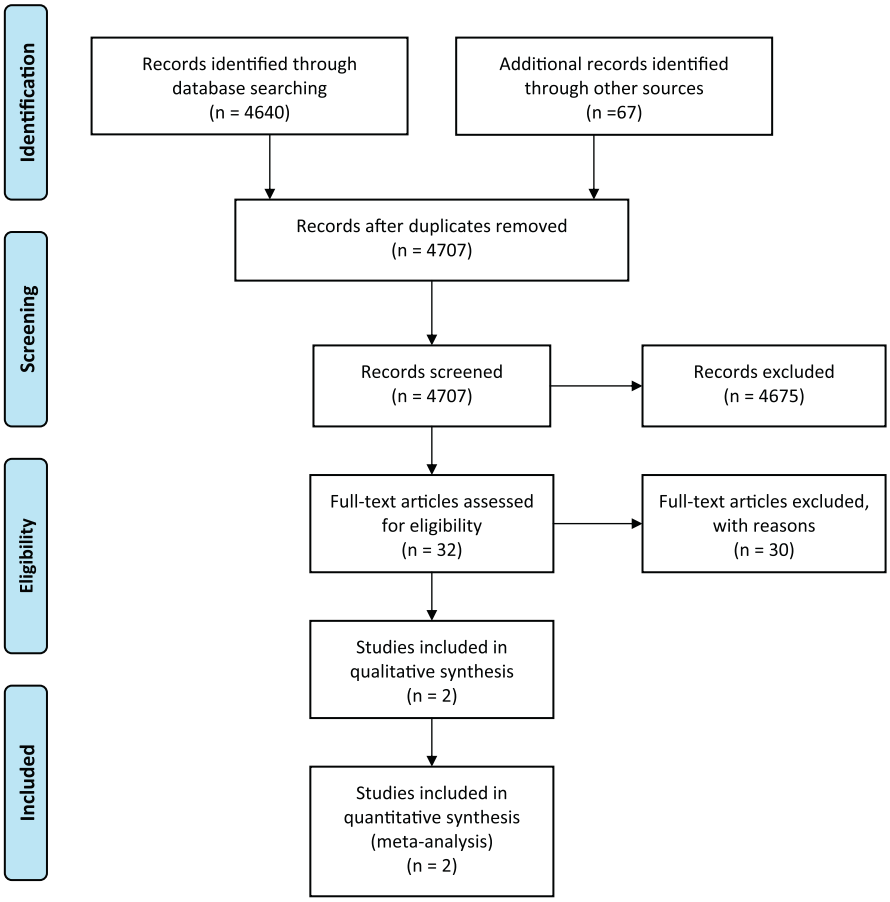


Fig. 1. Flow diagram of included and excluded studies.

Table 1
Summary of characteristics of the included studies.

Study	Accrual period	Single vs multicenter	Population	Sample size calculation	Follow-up, median (range), months	Axillary surgery/no axillary surgery	Primary outcome	Secondary outcome	Randomisation method	Adjuvant treatment
Martelli et al.	Jan 1996–June 2000	Single-center	Age 65–80, primary T1N0 2 cm or less, without clinical nodal disease. Median age 70, range 65–80.	Calculated sample size 642 Power of 94% to exclude an increase of 10% in distant metastasis within no AD group	50 (125–175)	109/110	Overall survival, and breast cancer mortality	Ipsilateral breast cancer, contralateral breast cancer, and distant metastasis. Overt axillary disease for patients who did not receive axillary dissection	Not reported	All patients received adjuvant radiotherapy to the residual breast, and tamoxifen 20 mg daily for 5 years
Rudenstam et al.	May 1993–December 2002	Multicenter	Age > 60, operable breast CA, without clinical nodal disease. Median age 74, range 60–91.	Calculated sample size 472 patients Power of 80% to detect a decrease of 13% in morbidity within no AD group	79	234/237	Quality of life	Overall survival, disease free-survival, breast cancer mortality	Permuted-blocks randomization schedule produced by use of pseudorandom numbers generated by a congruence method	Radiotherapy was recommended to patients who received breast-conserving surgery. All patients received tamoxifen 20 mg daily for 5 years.

3.3. Risk of Bias Results

Both studies used random sequence generation and allocation concealment. As shown in Table 2, neither study utilized blinding as part of their methodology. We were unable to draw funnel plots due to the dearth of studies included in the meta-analysis.

In Martelli et al.'s study, the risk of bias from incomplete outcome data is low as only 14 patients were excluded on the basis of protocol violations of the 238 patients who were randomized. The risk of selective reporting bias is low because all the outcomes were analyzed regardless of statistical significance.

Rudenstam et al.'s study also had a low risk of bias from incomplete outcome data: all 473 patients were analyzed, even though 10 patients did not meet the eligibility criteria (4%). An intent-to-treat analysis was used. The risk of selective reporting bias is low as all the outcomes were reported regardless of statistical significance.

3.4. Axillary Surgery Reduces Axillary Recurrences But Does Not Impact In-breast or Distant Recurrences

Axillary dissection reduced the risk of axillary recurrence compared to no axillary staging in a meta-analysis including 2 RCTs and 692 patients (RR 0.24, 95% CI: 0.06 to 0.95, $I^2 = 0\%$, $p = 0.04$) (Table 3A).

There were no differences observed in in-breast recurrence or distant recurrence between axillary staging and no axillary staging in a meta-analysis including 2 RCTs and 692 patients. (RR 1.20, 95% CI: 0.55 to 2.64, $I^2 = 62\%$, $p = 0.65$, RR 1.17, 95% CI: 0.75 to 1.82, $I^2 = 0\%$, $p = 0.48$, respectively) (Tables 3B & 3C).

3.5. Axillary Surgery Does Not Impact Overall or Disease-Specific Mortality

There were no differences in overall or breast-cancer specific mortality observed between axillary staging and no axillary staging in a meta-analysis including 2 RCTs and 692 patients. (RR 0.99, 95% CI: 0.79 to 1.24, $I^2 = 0\%$, $p = 0.92$, RR 1.07, 95% CI: 0.72 to 1.57, $I^2 = 0\%$, $p = 0.75$, respectively) (Tables 4A & 4B).

4. Discussion

Our systematic review provides a critical appraisal of the available randomized evidence; the pooled data suggests an increase in risk of regional recurrence with omission of axillary staging in the elderly. Our study also highlights the paucity of evidence available to direct the surgical management of elderly patients with early stage breast cancer. However, differences in overall or breast-cancer specific mortality were not observed between axillary staging and omission of axillary staging.

Until now, the lack of evidence to guide clinicians managing elderly patients with breast cancer has left chances for over and under treatment of many women. Evidence of variation in practice has been demonstrated in past studies [5,6]. In the United States, Pesce et al. found in patients older than 70, those treated at academic facilities were 18.5% less likely than community cancer programs to undergo axillary staging. There was significant regional variation as well, with patients treated in the Midwest 3.8 times more likely to undergo axillary staging than those in Northeast [5]. Truong and colleagues demonstrated significant variations in practice between age groups with a concomitant worsening in breast cancer outcomes [15]. With increasing age, axillary dissection was more frequently omitted (4% vs. 8% vs. 22% in the three groups respectively). Omission of axillary surgery was not associated with higher rates of regional recurrence for the entire cohort or any sub-cohort based on age. However, among women >75 years, there was a small benefit for overall survival with axillary dissection (adjusted HR 1.36, $p = 0.03$), but not for disease-specific survival (adjusted HR 1.26, $p = 0.38$). The finding of a small overall survival benefit and no disease-specific survival benefit in

Table 2
Assessment of the quality of the included randomized trials.

Study	Random sequence generation	Allocation concealment	Blinding	Blinding of outcome assessment	Incomplete outcome data bias	Selective reporting bias
Martelli et al.	Yes	Yes	No	No	Low risk	Low risk
Rudenstam et al.	Yes	Yes	No	No	Low risk	Low risk

women >75 years raises the concern of selection bias in observational studies, with healthier elderly patients more likely to undergo axillary surgery. Among patients included in the meta-analysis, 2 out of 343 patients (0.58%) with axillary surgery had a recurrence in the axilla, compared to 10 out of 349 patients (2.9%) had axillary recurrence without axillary surgery. Overall, the absolute number of patients that benefitted from the axillary recurrence remains small, and the vast majority of patients in the no axillary surgery group had no axillary recurrence (97%), or breast-cancer specific mortality (87.7%).

In both included studies, one of the inclusion criteria is clinically N0 disease. In Martelli et al.'s study, the ALND arm had a rate of 23% for occult positive axillary lymph node. In their no ALND arm, only 4 patients (3.6%) developed axillary disease, 2 of them remained alive and disease-free. The Rudenstam et al. study showed a similar pattern: 28% of patients in the ALND arm were found to have occult positive nodes. Among the no ALND arm, only 6 patients (2.5%) developed axillary recurrence. Rudenstam et al.'s study did modify their protocol in 1999 to allow SLNB in the ALND arm, but only two patients underwent the SLNB option. Taking both studies' findings together, there is little therapeutic benefit from getting rid of occult positive lymph nodes in patients with clinical N0 disease. Therefore, we speculate that similarly, SLNB would also have little therapeutic benefit.

Personalizing the care of elderly patients is difficult given the unclear oncologic benefit and the complicating comorbidities. What is clear, however, is the morbidity of axillary dissection and sentinel lymph node biopsy. Though sentinel lymph node biopsy is less morbid than axillary dissection, major randomized controlled trials such as ALMANAC and NSABP B-32 demonstrated persistent long-term problems with arm function, lymphedema, and paresthesia following a sentinel node biopsy [16,17]. In the ALMANAC trial, patients who underwent sentinel lymph node biopsy reported substantial arm swelling (7%) and numbness (8.7%) 18 months after surgery. In the NSABP B-32 trial, the sentinel lymph node biopsy group experienced residual arm numbness (8.1%) at 36 month follow-up and impaired should abduction (13.2%) at 6 month follow-up. Older patients (>70 years) had increased odds of long-term lymphedema (OR 1.41 $p = 0.006$). Given that many elderly patients have comorbidities and existing difficulty with independent activities of daily living, any additional morbidity after axillary surgery may have a greater impact on their daily function than their younger counterparts.

Few trials exist to guide clinicians in the management of early stage breast cancer specifically in elderly patients, leaving physicians to look for guidance from observational studies and treatment guidelines that have been validated in younger and healthier women. The more favorable tumor biology of breast cancer in the elderly is often cited as justification for a less aggressive approach. In this age group, primary breast tumors are more likely to express estrogen and progesterone receptors, have lower proliferative rates, a lower frequency of diploidy, have normal p53, and lack c-erbB2 [18,19].. Past studies have attempted to address the question of whether axillary staging impacts adjuvant therapy decision making in the elderly. A retrospective study from Milan identified that in women >65 years with clinically negative axillae, histologic nodal status did not change the treatment algorithm [20]. In the study by Truong et al., adjuvant chemotherapy was prescribed in only 1% of women older than 75 years of age who underwent axillary dissection [15]. Furthermore, Jackson et al. found that among patients with a clinically negative axilla, tumors <0.5 cm and without lymphovascular invasion, eliminating axillary dissection had an estimated mean difference in 5-year disease-free survival of <1% (5 year DFS 92.99% with axillary dissection vs 92.28% without axillary dissection) [21]. Overall, these studies among others have shown that axillary staging infrequently alters adjuvant treatment decisions as many elderly women are prescribed less toxic endocrine therapies regardless of nodal burden.

Table 3A
Forest plot of pooled effect of axillary dissection versus no axillary dissection on recurrence in the axilla.

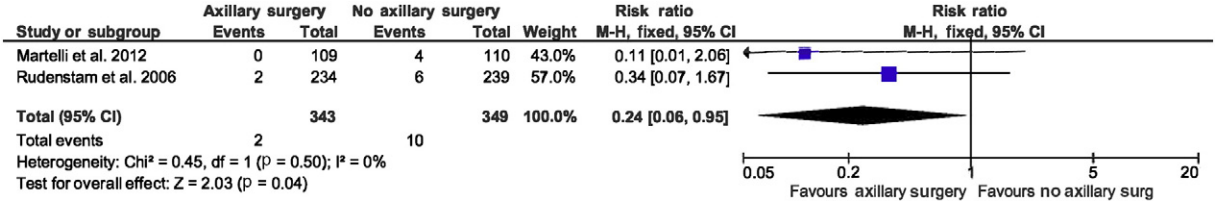


Table 3B
Forest plot of pooled effect of axillary dissection versus no axillary dissection on recurrence in the breast.

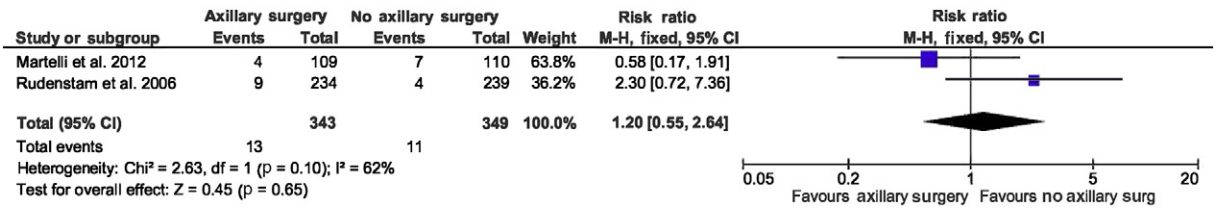


Table 3C
Forest plot of pooled effect of axillary dissection versus no axillary dissection on distant recurrence.

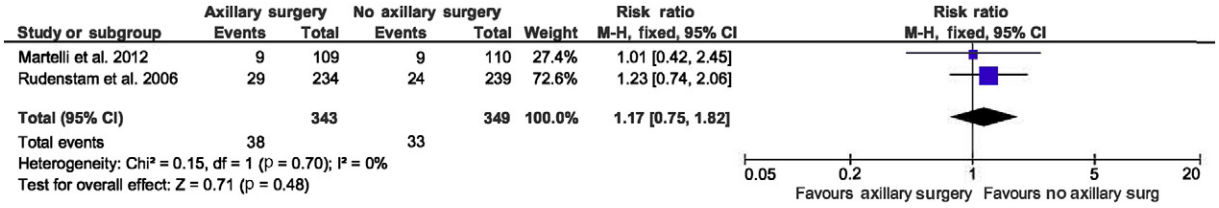
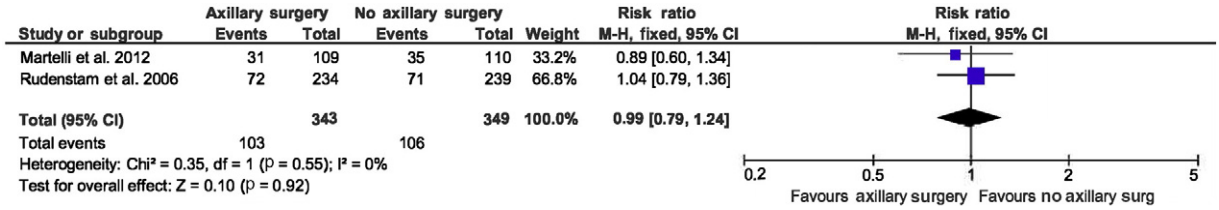


Table 4A
Forest plot of pooled effect of axillary dissection versus no axillary dissection on overall mortality.



The RCTs included in this systematic review had some limitations. Both of the included trials could not accrue the planned sample size and fewer than the expected number of deaths and disease events occurred. Past literature has highlighted the multiple barriers facing clinical trials recruiting the elderly. The main hurdles are the restrictions on enrolment due to comorbidities and functional status [22,23]. Many studies exclude patients with hypertension, cardiac, hematologic, renal or pulmonary diseases. In addition, more than 80% of clinical trials require participants to be ambulatory, capable of working, or carrying out their activities of daily living independently, and about 90% of the trials exclude patients with a history of previous cancer [23]. As a result, the elderly patients who are more likely to have multiple comorbidities, functional impairment and previous cancer are underrepresented in clinical trials. In similar settings where oncology clinical trials have failed to reach accrual, meta-analysis has been used to pool the data to achieve a larger sample [24,25]. Given the heterogeneity of the elderly population and barriers to recruiting them into studies, the external validity of trial data is limited, and as a result, the generalizability of this meta-analysis based on these trials should be considered carefully. Despite the limitations of the included studies, this meta-analysis strives to summarize the results from the RCTs in a transparent fashion, while highlighting the lack of high-level evidence on managing early breast cancer in the elderly.

There are a few limitations of our systematic review methods worth mentioning. For example, although an extensive search was performed for unpublished studies, the search strategy employed might have missed some trial protocols or conference abstracts reporting data relevant to this systematic review. In addition, publication bias could not be assessed since only two RCTs were included. Despite the limitations of the included studies and the limitations on the systematic review methods, this study strives to summarize the results from the RCTs in a transparent fashion, while highlighting the lack of high-level evidence on managing early breast cancer in the elderly.

The results of this meta-analysis indicate that omission of axillary staging in elderly patients with clinically negative axillae results in increased regional recurrence but does not appear to impact survival. Current research suggests that axillary staging infrequently impacts the management plan of elderly patients given the better tumor biology and increased rate of estrogen receptor overexpression. The role of axillary staging should be discussed on a case-by-case basis in a multidisciplinary setting to evaluate the potential impact of the results on adjuvant treatment decisions.

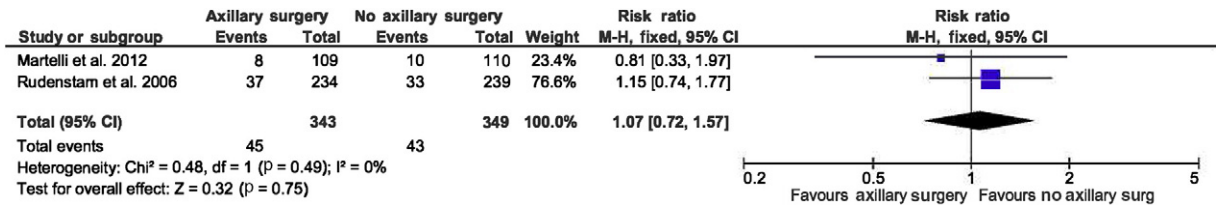
Disclosures and Conflict of Interest Statement

None of the authors have any conflict of interest or disclosures.

Author Contributions

Study Concept: S Liang, J Hallet, J Simpson, A Tricco, A Scheer.
Study Design: S Liang, J Hallet, J Simpson, A Tricco, A Scheer.
Data Acquisition: S Liang, A Scheer.
Quality Control of Data and Algorithms: S Liang, J Hallet, J Simpson, A Tricco, AScheer.

Table 4B
Forest plot of pooled effect of axillary dissection versus no axillary dissection on breast cancer-specific mortality.



Data Analysis and Interpretation: S Liang, J Hallet, J Simpson, A Tricco, A Scheer.
Statistical Analysis: S Liang, AScheer, A Tricco.
Manuscript Preparation: S Liang, J Hallet, J Simpson, A Tricco, A Scheer.
Manuscript Editing: S Liang, J Hallet, JSimpson, A Tricco, A Scheer.
Manuscript Review: S Liang, J Hallet, J Simpson, A Tricco, A Scheer.

Appendix 1. Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present & EBM Reviews — Cochrane Central Register of Controlled Trials July 2014

Search run on August 18, 2014
1 Carcinoma/
2 Lymphatic Metastasis/
3 exp breast neoplasms/
4 exp Breast/ or Breast Diseases/
5 neoplasms/ or Adenocarcinoma/ or Carcinoma/
6 4 and 5
7 (brca or (breast adj4 (adenocarcinoma* or cancer* or carcinoma* or metasta* or neoplasm* or neoplas* or tumo?r or malignan*))).ti,ab.
8 1 or 2 or 3 or 6 or 7
9 exp Lymph Node Excision/
10 Lymph Nodes/su
11 (axillary adj3 dissection).tw.
12 (Axillary adj (staging or clearance or surgery)).tw.
13 (Sentinel node adj (surgery or procedure or biopsy)).tw.
14 Neoplasm Staging/
15 ((stage or staging) adj2 (cancer* or neoplas* or tumo?r* or carcinoma* or malignan* or adenocarcinoma*)).tw.
16 Axilla/ or (axilla or lymph node*).tw.
17 (14 or 15) and 16
18 9 or 10 or 11 or 12 or 13 or 17
19 randomized controlled trial.pt.
20 controlled clinical trial.pt.
21 randomized.ab.
22 placebo.ab.
23 clinical trials as topic/
24 randomly.ab.
25 trial.ti.
26 19 or 20 or 21 or 22 or 23 or 24 or 25
27 8 and 18 and 26
28 27 not (exp "Animals"/not "Humans"/)

Embase Classic + Embase 1947 to 2014 Week 33

Search run on August 18, 2014
1 exp carcinoma/
2 exp lymph node metastasis/
3 exp breast tumor/
4 exp breast/ or breast disease/
5 Neoplasm/
6 4 and 5
7 (brca or (breast adj4 (adenocarcinoma* or cancer* or carcinoma* or metasta* or neoplasm* or neoplas* or tumo?r or malignan*))).ti,ab.
8 1 or 2 or 3 or 6 or 7
9 exp lymph node dissection/
10 exp lymph node/su
11 (axillary adj3 dissection).tw.
12 (Axillary adj (staging or clearance or surgery)).tw.
13 (Sentinel node adj (surgery or procedure or biopsy)).tw.
14 Neoplasm Staging/
15 ((stage or staging) adj2 (cancer* or neoplas* or tumo?r* or carcinoma* or malignan* or adenocarcinoma*)).tw.
16 Axilla/ or (axilla or lymph node*).tw.
17 (14 or 15) and 16
18 9 or 10 or 11 or 12 or 13 or 17
19 random*.tw.
20 factorial*.tw.
21 crossover*.tw.
22 cross over*.tw.
23 cross-over*.tw.
24 placebo*.tw.
25 (doubl* adj blind*).tw.
26 (singl* adj blind*).tw.
27 assign*.tw.
28 allocat*.tw.
29 volunteer*.tw.
30 crossover-procedure/
31 double-blind procedure/
32 randomized controlled trial/
33 single-blind procedure/
34 or/19-33
35 8 and 18 and 34

References

[1] SEER stat fact sheets: breast cancer. Available from: http://seer.cancer.gov/statfacts/html/breast.html; July 19 2016.
[2] Biganzoli L, Wildiers H, Oakman C, Marotti L, Loibl S, Kunkler I, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). Lancet Oncol 2012;13(4):e148–60.
[3] Mieog JS, de Kruijf EM, Bastiaannet E, Kuppen PJ, Sajet A, de Craen AJ, et al. Age determines the prognostic role of the cancer stem cell marker aldehyde dehydrogenase-1 in breast cancer. BMC Cancer 2012;12(42).
[4] NCCN. Available from: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf; July 19 2016.
[5] Pesce C, Czechura T, Winchester DJ, Huo D, Winchester DP, Yao K. Axillary surgery among estrogen receptor positive women 70 years of age or older with clinical stage I breast cancer, 2004–2010: a report from the National Cancer Data Base. Ann Surg Oncol 2013;20(10):3259–65.
[6] Kiderlen M, Walsh PM, Bastiaannet E, Kelly MB, Audisio RA, Boelens PG, et al. Treatment strategies and survival of older breast cancer patients — an international comparison between the Netherlands and Ireland. PLoS One 2015;10(2), e0118074.
[7] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6(7), e1000100.
[8] Sampson M, McGowan J, Cogo E, Grimshaw J, Moher D, Lefebvre C. An evidence-based practice guideline for the peer review of electronic search strategies. J Clin Epidemiol 2009;62(9):944–52.
[9] Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343, d5928.
[10] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315(7109):629–34.
[11] Collaboration TC. Cochrane Handbook for Systematic Reviews of Interventions. 5.1.0. ed; 2011.
[12] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21(11):1539–58.
[13] International Breast Cancer Study G, Rudenstam CM, Zahrieh D, Forbes JF, Crivellari D, Holmberg SB, et al. Randomized trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: first results of International Breast Cancer Study Group Trial 10-93. J Clin Oncol 2006;24(3):337–44.
[14] Martelli G, Boracchi P, Ardoino I, Lozza L, Bohm S, Vetrella G, et al. Axillary dissection versus no axillary dissection in older patients with T1N0 breast cancer: 15-year results of a randomized controlled trial. Ann Surg 2012;256(6):920–4.
[15] Truong PT, Bernstein V, Wai E, Chua B, Speers C, Olivotto IA. Age-related variations in the use of axillary dissection: a survival analysis of 8038 women with T1-ST2 breast cancer. Int J Radiat Oncol Biol Phys 2002;54(3):794–803.
[16] Mansel RE, Fallowfield L, Kissin M, Goyal A, Newcombe RG, Dixon JM, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC trial. J Natl Cancer Inst 2006;98(9):599–609.
[17] Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol 2010;11(10):927–33.
[18] Diab SG, Elledge RM, Clark GM. Tumor characteristics and clinical outcome of elderly women with breast cancer. J Natl Cancer Inst 2000;92(7):550–6.
[19] Cheung KL, Wong AW, Parker H, Li VW, Winterbottom L, Morgan DA, et al. Pathological features of primary breast cancer in the elderly based on needle core biopsies—a large series from a single centre. Crit Rev Oncol Hematol 2008;67(3):263–7.
[20] Greco M, Gennaro M, Valagussa P, Agresti R, Ferraris C, Ferrari B, et al. Impact of nodal status on indication for adjuvant treatment in clinically node negative breast cancer. Istituto Nazionale per lo Studio e las Cura dei Tumori. Ann Oncol 2000;11(9):1137–40.

[21] Jackson JS, Olivotto IA, Wai MDE, Grau C, Mates D, Ragaz JA. Decision analysis of the effect of avoiding axillary lymph node dissection in low risk women with invasive breast carcinoma. Cancer 2000;88(8):1852–62.
[22] Townsley CA, Selby R, Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. J Clin Oncol 2005;23(13):3112–24.
[23] Lewis JH, Kilgore ML, Goldman DP, Trimble EL, Kaplan R, Montello MJ, et al. Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol 2003;21(7):1383–9.
[24] Surgical oncology: a practical and comprehensive approach. New York: Springer; 2014.
[25] Bujko K, Glynne-Jones R, Bujko M. Does adjuvant fluoropyrimidine-based chemotherapy provide a benefit for patients with resected rectal cancer who have already received neoadjuvant radiochemotherapy? A systematic review of randomised trials. Ann Oncol 2010;21(9):1743–50.