Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis
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CRD summary
This review compared pre-operative (neoadjuvant) systemic therapy with post-operative (adjuvant) therapy for breast cancer using the same regimen. The authors concluded that neoadjuvant and adjuvant therapy appear equivalent in terms of survival and overall disease progression, but neoadjuvant therapy is associated with an increased risk of loco-regional recurrence when radiotherapy is used without surgery. The poor quality of the included studies may limit the reliability of these conclusions.

Authors' objectives
To compare the clinical end points of people with breast cancer treated pre-operatively with systemic therapy (neoadjuvant therapy) versus those treated post-operatively with the same regimen (adjuvant therapy).

Searching
MEDLINE, EMBASE, and the Cochrane CENTRAL Register were searched to October 2003; the search terms were reported. There were no language restrictions. The authors also handsearched oncology journals and the reference lists of retrieved papers, and contacted experts in the field for additional data. Abstracts from meetings were excluded.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included. Interim analyses were included if no final reports were available. Escalation dose studies and pseudo-randomised trials were excluded.

Specific interventions included in the review
Studies were eligible for inclusion in the review if they compared neoadjuvant systemic therapy with adjuvant therapy using the same regimen. Any chemotherapy or endocrine therapy was eligible, regardless of what additional therapy or radiation treatment was used, as long as additional treatments did not differ systematically between groups. Trials were also eligible if one arm received exclusive post-operative therapy while the other arm received some cycles of the same regimen pre-operatively and some post-operatively. Trials were included regardless of the specific drugs used. The number of adjuvant treatment courses ranged between four and eight. The number of neoadjuvant treatment courses ranged between one and six.

Participants included in the review
Studies of people with non metastatic breast cancer were included. The authors reported considerable variation between studies in the eligible stages of breast cancer, tumour size and lymph node status. The mean or median age of the participants was between 43 and 56 years across treatment arms. All but one trial included pre- and postmenopausal women. It was not explicitly stated that all participants were female.

Outcomes assessed in the review
The primary outcomes were death, disease progression, distant disease recurrence and loco-regional disease recurrence. Disease progression was defined as loco-regional or distant recurrence, the occurrence of contralateral cancer, or death. Loco-regional recurrence was defined as recurrence in the ipsilateral breast or in the ipsilateral regional lymph nodes or chest wall. The secondary outcomes were conservative local treatment and local response.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors assessed the following quality criteria: mode of randomisation, allocation concealment, withdrawals per group and blinding. Two authors extracted data relating to study quality. Any disagreements were resolved by consensus.

Data extraction
Two authors extracted data for the review, using consensus to address any disagreements. The data fields extracted were reported. The original investigators were contacted for missing data. The authors used the reported data to estimate risk ratios (RRs) and 95% confidence intervals (CIs) for each primary outcome, deriving estimates from survival curves or contact with the investigators where necessary.

Methods of synthesis
How were the studies combined?
The authors used fixed-effect and random-effects models to combine the data.

How were differences between studies investigated?
The authors used the Q statistic to assess heterogeneity in risk ratios between studies. They performed subgroup analyses for the primary outcomes based on the use of conservative local management (lumpectomy or quadrantectomy) and radiotherapy without surgery. They compared the outcomes of small and large studies using the Begg-Mazumdar test and assessed whether the summary effect size changed over time as more data accumulated, using the recursive cumulative meta-analysis.

Results of the review
Nine RCTs with 3,946 participants were included in the review.

Only one trial described the mode of randomisation, three described the mode of allocation concealment, seven fully described withdrawals, and none of the trials were blinded.

Neoadjuvant therapy was associated with a statistically significant increase in loco-regional disease recurrence (RR 1.22, 95% CI: 1.04, 1.43), especially when radiotherapy was used without surgery.

There were no statistically significant differences between adjuvant and neoadjuvant therapy in terms of death (RR 1.00, 95% CI: 0.90, 1.12), disease progression (RR 0.99, 95% CI: 0.91, 1.07) or distant disease recurrence (RR 0.94, 95% CI: 0.83, 1.06).

There was statistically significant heterogeneity between studies in terms of clinical response, pathological response and the use of conservative local treatment (p<0.001 for all).

Small trials did not differ from large trials in their results for death, distant disease recurrence or loco-regional recurrence. However, in smaller studies there was some indication that neoadjuvant treatment was associated with more favourable comparative overall disease progression. The summary effect size did not change over time as more data accumulated.

Authors’ conclusions
Neoadjuvant therapy appears equivalent to adjuvant therapy in terms of survival and overall disease progression, but neoadjuvant therapy is associated with an increased risk of loco-regional recurrence when radiotherapy is used without surgery.

CRD commentary
This review comprised a well-defined research question and specified inclusion and exclusion criteria. However, the review focused only on studies that were available as full reports; this may mean that not all relevant studies were included and publication bias might have been introduced. The authors provided some details about the characteristics
of the participants and the regimens used, but they did not explicitly report the gender of participants. This is important as some men have been included in previous breast cancer trials and the gender of the participants may impact on the outcome of treatment. In addition, the authors did not provide a great deal of detail about the exact treatment regimens used, including doses. The authors did not report the methods used to assess the relevance of studies for inclusion in the review. They described the data extraction procedures in some detail. The validity of the included studies was assessed using appropriate criteria. However, the quality of the included studies was poor with only one study describing the mode of randomisation.

The data analysis methods appear appropriate and the authors took steps to assess factors that might affect the results, such as heterogeneity between the studies. The authors acknowledged the limitations of the review and, overall, their conclusions appear to follow from the information reported. However, the poor quality of the included studies may reduce the overall validity of the conclusions.

**Implications of the review for practice and research**

Practice: The authors recommended avoiding the use of radiotherapy without any surgical treatment, regardless of response to chemotherapy.

Research: The authors stated that there is little research comparing neoadjuvant therapy with adjuvant therapy using taxanes and other agents with different modes of action. They also suggested that a meta-analysis comparing neoadjuvant therapy with adjuvant therapy using individual patient data may be worthwhile.

**Bibliographic details**


**PubMedID**

15687361

**DOI**

10.1093/jnci/dji021

**Original Paper URL**

http://jnci.oxfordjournals.org/content/97/3/188.abstract

**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Antineoplastic Agents /therapeutic use; Breast Neoplasms /drug therapy /pathology /surgery; Chemotherapy, Adjuvant; Disease Progression; Female; Humans; Neoadjuvant Therapy; Odds Ratio; Randomized Controlled Trials as Topic; Survival Analysis; Treatment Outcome

**AccessionNumber**

12005009581

**Date bibliographic record published**

30/11/2006

**Date abstract record published**

30/11/2006

**Record Status**

This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract
contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.