Breast cancer: sentinel node identification and classification after neoadjuvant chemotherapy; systematic review and meta analysis

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CRD summary
This review concluded that sentinel lymph node mapping and biopsy after neoadjuvant therapy was a reliable alternative to completion axillary lymph node dissection for planning treatment in patients with early-stage breast cancer. The authors’ conclusions appeared to reflect the evidence, but potential for bias in the review methods should be taken into consideration when interpreting the conclusions.

Authors' objectives
To assess the accuracy of sentinel node mapping in women with early-stage breast cancer after neoadjuvant chemotherapy.

Searching
MEDLINE, EMBASE, PubMed, Web of Science, Current Concepts Medicine and The Cochrane Library were searched between 1966 and December 2007 for studies in English, German, Spanish and Italian. Search terms were reported. References of identified articles and relevant journals were searched manually.

Study selection
Studies that evaluated the successful identification rate and false negative rate of sentinel lymph node mapping plus biopsy (dissection) in patients with breast cancer after chemotherapy were eligible for inclusion. Included studies were required to provide sufficient descriptions of the reference test (explicitly stating surgical open axillary lymph node dissection) and sentinel node mapping procedure and use established diagnostic criteria (finding malignant cells on histology of the axillary nodes and significant radioactivity in the sentinel lymph nodes) for an abnormal test result.

Most of the included studies were conducted in single institutions in USA between 2000 and 2004; others were conducted in Japan, Spain, Austria, Korea, Brazil and Taiwan. Studies were of patients with localised non-metastatic (Stage I to III) breast cancer who underwent sentinel lymph node mapping after neoadjuvant chemotherapy followed by axillary lymph node dissection. Where reported, mean age of patients ranged from 42.6 to 62 years. Included studies carried out sentinel lymph node mapping using blue dye and/or sulphur colloid. Most studies involved peritumoural injection of radiotracer. Most studies reported that mapping and axillary node dissection or surgical resection were performed on the same day. Approximately half of the studies used an intraoperative gamma probe. Studies used different immunohistochemistry staining techniques.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
It appeared that two reviewers assessed studies for quality in accordance with the QUADAS standard for reporting trials. Criteria included study size (>30), uniformity of reference tests, description of index and reference tests, adequate description of participants, point estimates and measures of variability for the primary outcome measure, whether patients were consecutive and whether the study could be generalised. The maximum quality score appeared to be 10.

Any discrepancies were resolved by consensus or referral to a third reviewer.

Data extraction
Two reviewers independently extracted data on the number of successful sentinel lymph node biopsies (successful identification) and the number of true positives and false negatives (classification performance) in women with successful sentinel lymph node biopsy. These data were used to calculate a summary successful identification rate and
false negative rate.

It appeared that discrepancies were resolved by consensus or referral to a third reviewer.

**Methods of synthesis**

A bivariate random-effects mixed model was used to calculate the summary successful identification rate and false negative rate, with 95% confidence intervals (CIs). Conditional localisation and classification probabilities were calculated to estimate the change in pre-test to post-test probabilities. Statistical heterogeneity was assessed using the $I^2$ statistic. Subgroup analyses and meta-regression analyses were performed to assess effects of study variables (use of dual mapping technique, peritumoural injection mapping technique, immunohistochemistry, same-day mapping and surgery, and intraoperative use of a gamma probe) and the effect of quality criteria on summary identification and false negative rates. Sensitivity analyses were conducted by removing each study one at a time.

Publication bias was assessed using funnel plots.

**Results of the review**

Twenty-four studies (n=1,799) were included in the review: 19 prospective and five retrospective studies. Sample sizes ranged from 14 to 428 patients. Study quality scores ranged from five to eight; no studies were blinded.

Successful sentinel node mapping ranged from 63% to 100%. The summary successful identification rate was 0.896 (95% CI 0.860 to 0.923) and the summary false negative rate was 0.084 (95% CI 0.064 to 0.109). There was significant statistical heterogeneity for studies that reported summary identification rate ($I^2$=78%), but not for studies that reported summary false negative rate.

Subgroup analyses showed no significant differences for identification rate, but there were some significant findings for false negative rate and these were reported in the review. Sensitivity analyses indicated that no one study had a greater effect on summary outcomes. Further exploratory analyses were reported in the review.

Inspection of funnel plots indicated some publication bias for studies that measured false negative rate.

**Authors' conclusions**

Sentinel lymph node mapping and biopsy after neoadjuvant therapy was a reliable alternative to completion axillary lymph node dissection for planning treatment in patients with early-stage breast cancer.

**CRD commentary**

The review question was clear and supported by appropriate inclusion criteria, although criteria were broad for study design. An adequate search of the literature was undertaken and included six electronic databases and other appropriate sources. The search was restricted by language, so language bias may have been introduced. There was no apparent search for unpublished data and assessment of funnel plots showed some evidence of publication bias. Validity was assessed using appropriate methods and, where possible, was taken into account in the analysis. Study quality appeared to be moderate, but as none of the studies were blinded there may have been some bias. The authors appeared to carry out validity assessment and data extraction in duplicate, but this was not clear for study selection and reviewer error and bias could not be ruled out. Appropriate statistical methods and tests for statistical heterogeneity were used, but there was some evidence of statistical heterogeneity for one outcome. The authors' conclusions appeared to reflect the evidence, but potential for bias should be taken into consideration when interpreting these conclusions.

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

**Practice:** The authors stated that the evidence suggested that this technique was effective across a wide variety of clinical practices.

**Research:** The authors stated that research (preferably a randomised trial) was needed to assess the effect of same-day mapping and surgical dissection on test performance.
Funding
Not stated.

Bibliographic details

PubMedID
19345896

DOI
10.1016/j.acra.2009.01.026

Original Paper URL
http://www.academicradiology.org/article/S1076-6332(09)00078-6/abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Antineoplastic Agents /therapeutic use; Breast Neoplasms /drug therapy /epidemiology /pathology; Female; Humans; Incidence; Lymphatic Metastasis; Neoadjuvant Therapy /utilization; Sentinel Lymph Node Biopsy /utilization

AccessionNumber
12009104678

Date bibliographic record published
19/08/2009

Date abstract record published
16/06/2010

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.