Meta-analysis of sentinel node imprint cytology in breast cancer

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CRD summary
This review assessed the accuracy of imprint cytology to diagnose axillary sentinel node breast cancer metastasis, intra-operatively. The authors concluded that imprint cytology has good sensitivity for macrometastasis. However, given limitations in the search strategy and review methodology, as well as apparent variation in the sensitivity estimates reported by different studies, the results should be treated with caution.

Authors' objectives
To assess the accuracy of imprint cytology to diagnose axillary sentinel node breast cancer metastasis, intra-operatively.

Searching
MEDLINE and EMBASE were searched from 1966 to June 2004; the search terms were presented. The references of the included articles were also checked for additional studies. Only papers available in English were included.

Study selection
Study designs of evaluations included in the review
No inclusion criteria for the study design were specified.

Specific interventions included in the review
Studies assessing the accuracy of imprint cytology to diagnose axillary sentinel node breast cancer intra-operatively were eligible for inclusion. Studies assessing imprint cytology in combination with another intra-operative method were also included. The included studies used a variety of section thicknesses and stains, full details of which were reported in the article.

Reference standard test against which the new test was compared
The studies needed to compare imprint cytology against paraffin section examination, the reference standard, to be included in the review.

Participants included in the review
Studies of participants undergoing sentinel node biopsy for breast cancer appeared to be eligible for inclusion. The study participants all had T stage 0-2 primary breast tumours with clinically involved axillary lymph nodes. The mean age of the participants, where reported, ranged from 46 to 60 years; the mean age across all studies was 56 years.

Outcomes assessed in the review
The included studies needed to present enough information to produce a cross-tabulation of the results. Data were assessed on a per patient, rather than per node, basis whenever possible. The outcome measures used were sensitivity and specificity.

How were decisions on the relevance of primary studies made?
A single reviewer selected the articles.

Assessment of study quality
The studies were assessed using the Cochrane Methods Group and the Standards for the Reporting of Diagnostic Accuracy Studies (STARD) committee guidelines.

Data extraction
A single reviewer extracted the data. Any inconsistencies in the data were clarified by contacting the authors of the study.

**Methods of synthesis**

How were the studies combined?
Pooled estimates of sensitivity and specificity were calculated, along with 95% confidence intervals (CIs), using a random-effects model. Summary receiver operator characteristic curves were constructed using the Moses and Littenberg model.

How were differences between studies investigated?
Heterogeneity was assessed using random-effects logistic regression modelling to perform a meta-regression analysis of sensitivity. Pre-selected predictors of between-study variation were included in this model if they were found to be significant predictors at the 10% level. Studies not presenting information on predictors were excluded from this analysis. Subgroup analyses were conducted to determine the diagnostic accuracy of imprint cytology for macrometastasis and micrometastasis.

**Results of the review**

Thirty-one studies (n=4,438) were included in the meta-analysis. Eleven studies were prospective and 14 did not report whether they were prospective or retrospective.

All included studies clearly reported the research question, the study population and the study setting. Nineteen studies enrolled consecutive patients and the majority of the remainder did not report the method of selection. Only 3 included studies reported that pathologists assessing paraffin sections were blinded to the results of the imprint cytology results.

The prevalence of sentinel node metastasis ranged from 17 to 50% (mean prevalence 34%).

The pooled sensitivity estimate for imprint cytology for all metastases was 63% (95% CI: 57, 69; 31 studies). The pooled sensitivity for imprint cytology for macrometastases was 81% (95% CI: 74, 86; 11 studies). The pooled sensitivity for imprint cytology for micrometastases was 22% (95% CI: 14, 33; 11 studies).

The pooled specificity estimate for imprint cytology for all metastases was 99% (95% CI: 98, 99; 31 studies).

The pooled estimates of sensitivity and specificity were similar (CIs overlapped) for imprint cytology and frozen section (3 studies).

From the multivariate analysis, sensitivity increased as mean tumour size increased, but decreased as the prevalence of metastases and proportion of micrometastases increased. Combining metastases and micrometastases in a multivariate model resulted in only micrometastases remaining significant. Similarly, when tumour size and micrometastases were combined, only micrometastases remained significant. Evidence of confounding was apparent for both models.

**Authors' conclusions**

Imprint cytology has good sensitivity for macrometastases but poor sensitivity for micrometastases.

**CRD commentary**

The review question was clear from the title and abstract, and there were inclusion criteria regarding the diagnostic intervention and reference standard. The search strategy was reasonable but only papers written in English were selected and there was no attempt to retrieve unpublished papers; this could lead to language and publication bias. Only one reviewer selected the papers and extracted the data, thereby introducing the potential for reviewer bias. The quality of the included studies was assessed using appropriate criteria, but the results from this assessment were not reported in detail.

Details of the included studies were well reported, allowing a clear overview of the existing primary studies. Statistical
heterogeneity between the studies was assessed using multivariate analysis but, since only predictors of heterogeneity that generated a significant result were presented, it was difficult to ascertain whether this assessment was comprehensive. The methods used to synthesise the results were appropriate, although pooling the data may be of limited value given the presence of heterogeneity. The authors’ conclusions are supported by the data presented but, given the limitations highlighted, the results should be treated with caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that future studies should aim for better study design and reporting of quality.

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