Endoscopic ultrasound-guided fine-needle aspiration for non-small cell lung cancer staging: a systematic review and metaanalysis
Micames CG, McCrory DC, Pavey DA, Jowell PS, Gress FG

CRD summary
This review found the endoscopic ultrasound-guided fine-needle aspiration is safe and accurate for the staging of non-small-cell lung cancer. Although the authors' conclusions appear reliable, they should be interpreted with some degree of caution given the limitations in the literature search and possible limitations in the analysis.

Authors' objectives
To evaluate the accuracy of endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) for staging non-small-cell lung cancer (NSCLC).

Searching
PubMed and CINAHL were search from inception to November 2005; the search terms were reported. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Studies that included at least 10 patients were eligible for inclusion. Studies were both prospective and retrospective, and some studies enrolled consecutive patients.

Specific interventions included in the review
Studies of EUS-FNA used for the staging of mediastinal lymph nodes were eligible for inclusion. EUS-FNA was performed by 1 to 3 experienced operatives using either a 22- or 23-gauge needle. The studies used a curvilinear echoendoscope either alone or preceded by a radial echoendoscope.

Reference standard test against which the new test was compared
Studies in which the reference standard was histopathology or clinical follow-up after 6 months were eligible for inclusion.

Participants included in the review
Studies of adults with suspected or previously diagnosed NSCLC were eligible for inclusion. The mean age of the patients was 63 years, the median proportion of men was 63% (range: 53 to 86), and the median prevalence of malignant lymph nodes was 65% (range 33 to 85). The studies enrolled patients with proven lung cancer who had been referred for pre-operative staging; patients without enlarged mediastinal lymph nodes on computed tomography (CT) who were being considered for surgery; patients with enlarged mediastinal lymph nodes seen on CT or positive positron emission tomography (PET) scan, regardless of location; or patients referred for EUS-FNA based on prior imaging (CT or PET scanning) that showed lesions within easy reach of EUS.

Outcomes assessed in the review
Studies that reported sufficient data to enable the calculation of sensitivity and specificity were eligible for inclusion. The outcomes reported by the review were the sensitivity, specificity, and positive and negative predictive values.

How were decisions on the relevance of primary studies made?
Two reviewers independently screened studies for relevance.

Assessment of study quality
Studies were assessed for methodological quality using the following items from the STARD guidelines for reporting
diagnostic accuracy studies: prospective design; consecutive patient enrolment; reference standard; expertise of index test operators; blinding of index test operators to the results of prior tests; whether all participants underwent reference testing; and the reporting of adverse events relating to the index test and reference standard. The authors did not state how many reviewers performed the validity assessment.

Data extraction
Two reviewers independently extracted the data from the included studies. Any disagreements were resolved through consensus. The data extracted were used to construct 2x2 contingency tables for each study: patients were classified as having positive or negative EUS-FNA findings and as having malignant or benign mediastinal lymph nodes. Samples reported to be inconclusive were considered as true negatives if no malignancy was found or as false negatives if malignancy was confirmed. The sensitivity and specificity of EUS-FNA were calculated for its ability to distinguish mediastinal lymph node involvement (stations 1 to 9, or N2/N3 by TNM classification) from hilar, intrapulmonary (stations 10-14, or N1), or no lymph node involvement (N0). To account for zero cells a continuity correction was applied (details not reported). Diagnostic odds ratios (DORs) were also calculated.

Methods of synthesis
How were the studies combined?
A summary receiver operating curve meta-analysis, weighted on the inverse variance, was conducted and used to estimate the pooled sensitivity and specificity. Publication bias was investigated graphically using a funnel plot based on the DOR and its standard error.

How were differences between studies investigated?
DORs were compared between subgroups using analysis of variance.

Results of the review
Eighteen studies (1,201 patients) were included.

Sixteen studies were prospective, two were retrospective database reviews, and three enrolled consecutive patients. Only 1 study fulfilled all quality criteria. Ten studies used histopathology alone as the reference standard; other studies used a combined reference standard of histopathology or adequate clinical follow-up, and 1 study used surgery as the reference standard. All patients underwent the reference standard in 10 studies, at least 80% received it in 7 studies, and in 1 study only 51% of eligible patients received the reference standard.

Sensitivity ranged from 36 to 100% and the pooled sensitivity was 83% (95% confidence interval, CI: 78, 87%). Specificity was 100% in all but one of the studies; this was the only study to verify positive EUS-FNA findings by histopathology and it found two false-positive findings. For patients with abnormal mediastinal lymph nodes on CT scans, the pooled sensitivity was 90% (95% CI: 84, 94) based on 8 studies (560 patients). For patients without abnormal mediastinal lymph nodes on CT scans, the pooled sensitivity was 58% (95% CI: 39, 75) based on 4 studies (175 patients). Only one value for heterogeneity was given (no evidence of heterogeneity, p=0.77); it was unclear which measure of accuracy this referred to.

Studies that used a compound reference standard reported significantly higher pooled sensitivity (93%) than those that used histopathology exclusively (pooled sensitivity 79%)(p=0.01).

Minor adverse events relating to EUS-FNA were reported in 10 cases; there were no major adverse events.

The funnel plot showed no evidence of publication bias.

Authors' conclusions
EUS-FNA has high sensitivity for the detection of metastasis in patients in whom mediastinal lymph nodes have been seen on CT scans. Despite lower sensitivity in patients with normal mediastinal adenopathy on CT scans, it still has the potential to prevent unnecessary surgery in a large proportion of cases missed by CT screening.
CRD commentary
This review addressed a focused question that was supported by clearly defined inclusion criteria. The search was limited to two electronic databases and no additional attempts to identify studies. Relevant studies might therefore have been missed and the review may be subject to publication bias. Appropriate steps were taken to minimise bias and error in the study selection and data extraction processes, but it is unclear whether such steps were taken in the assessment of methodological quality. A detailed quality assessment was undertaken using appropriate criteria, and the results of this were discussed and considered in the synthesis of the results.

Generally, the methods used to pool the results seem appropriate but insufficient details were presented on the exact methods used. Given the fact that all but one of the studies reported a specificity of 100%, pooling of specificity appears inappropriate. The authors discussed why 1 study did not achieve a specificity of 100%; it appears that this study was more methodologically sound than the other studies, thus its estimate of a specificity of slightly less than 100% is more likely to be reliable than the estimates from the other studies. Heterogeneity was investigated statistically but it is unclear exactly what measure of diagnostic accuracy the reported statistic for heterogeneity related to. Whereas there was clearly an absence of heterogeneity in estimates of specificity, it would appear that estimates of sensitivity were highly heterogeneous. Reasons for this heterogeneity were investigated, although it is unclear exactly what measures of diagnostic accuracy the p-values for differences between the various subgroups related to. Publication bias was investigated but the methods used were not appropriate for test accuracy studies.

Overall, the authors’ conclusions appear reliable but should be interpreted with some degree of caution given the limitations in the literature search and some possible limitations in the analysis.

Implications of the review for practice and research
Practice: The authors stated that EUS-FNA may be the investigation of choice for staging NSCLC prior to surgery, even in patients without evidence of mediastinal lymphadenopathy on CT or PET scans.

Research: The authors did not state any implications for further research.

Bibliographic details

PubMedID
17296659

DOI
10.1378/chest.06-1437

Original Paper URL

Indexing Status
Subject indexing assigned by NLM

MeSH
Biopsy, Fine-Needle; Carcinoma, Non-Small-Cell Lung /pathology /ultrasonography; Endosonography; Humans; Lung Neoplasms /pathology /ultrasonography; Neoplasm Staging /methods; ROC Curve; Surgery, Computer-Assisted

AccessionNumber
12007005189

Date bibliographic record published
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.