Noninvasive staging of non-small cell lung cancer: a review of the current evidence

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CRD summary
This review assessed the performance of noninvasive techniques used to stage non-small cell lung cancer. Positron emission tomography was more accurate than computed tomography or endoscopic ultrasound for detecting mediastinal metastases. The review has a number of methodological limitations meaning that the authors’ conclusions should be interpreted with caution.

Authors’ objectives
The review was in two parts. The objective of question 1 was to determine the test performance characteristics of computed tomography (CT) scanning, positron emission tomography (PET) scanning, magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) for staging the mediastinum. The objective of question 2 was to evaluate the accuracy of clinical evaluation for predicting metastatic disease in suspected lung cancer patients.

Searching
MEDLINE (from January 1991 to July 2001), HealthSTAR and the Cochrane Library. The keywords used were reported. In addition, the authors searched the reference lists from a number of sources. Only English language articles were included.

Study selection
Study designs of evaluations included in the review
Inclusion and exclusion were not reported in terms of the study design. The studies had to include at least 20 patients, while studies of CT scanning had to include at least 50 patients.

Specific interventions included in the review
Question 1: studies that examined CT scanning, MRI, EUS and PET scanning for detecting malignant mediastinal lymph node involvement were eligible.

Question 2: studies that examined the accuracy of clinical evaluation for predicting metastatic disease were eligible.

Reference standard test against which the new test was compared
Question 1: the reference standard was either tissue histologic confirmation or, if that was unavailable, the long-term (at least 1 year) clinical outcome.

Question 2: positive findings on neuroimaging studies, abdominal CT scans and radionucleotide bone scans were used as the reference standards.

Participants included in the review
Studies that included patients with suspected lung cancer (non-small cell or small cell) were eligible. The studies had to include histologic or cytologic confirmation of mediastinal nodes or extrathoracic sites in addition to the primary tumour. The authors considered only mediastinal nodal involvement (stages N2 and N3) as being ‘disease-positive’. Patients with clinical or histopathologic stage IV disease were excluded from the analyses if the nodal stage was not described.

Outcomes assessed in the review
Question 1: studies that reported the raw data required to calculate the sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) were eligible.

Question 2: studies that reported the data needed to calculate the NPV were eligible.
How were decisions on the relevance of primary studies made?
At least two reviewers independently evaluated all titles, abstracts and full text articles for inclusion.

**Assessment of study quality**
The authors did not state that they assessed validity.

**Data extraction**
Question 1: data were extracted from the included studies and tabulated separately according to the type of noninvasive test. The data were tabulated under the following headings: study/year, number of patients, sensitivity, specificity, PPV, NPV and prevalence.

Question 2: data were extracted from the included studies and tabulated separately according to the site of metastatic disease.

**Methods of synthesis**
How were the studies combined?
The summary sensitivity and specificity were calculated, along with corresponding confidence intervals (CIs). For studies that included patients with a positive and negative clinical evaluation, the sensitivity, specificity and PPV of the evaluation of metastatic disease were calculated. The NPV was calculated for studies that included only asymptomatic patients. Summary receiver operating characteristic (ROC) curves were produced for studies that included patients with positive and negative clinical evaluation results and for studies with tissue conformation of disease. Summary ROC curves were compared using Student's t-test.

How were differences between studies investigated?
Question 1: the studies were grouped according to the type of noninvasive test.

Question 2: the studies were grouped according to the site of metastatic disease. Studies including patients with a positive and negative clinical evaluation were analysed separately.

**Results of the review**
Forty-seven studies were identified for question 1 and 41 studies for question 2.

Question 1: Mediastinal staging.

CT scan (20 studies, n=3,438): the pooled sensitivity was 0.57 (95% CI: 0.49, 0.66) and the pooled specificity was 0.82 (95% CI: 0.77, 0.86). The authors found evidence of marked heterogeneity between the pooled studies. The overall PPV and NPV were 0.56 (range: 0.26, 0.84) and 0.83 (range: 0.63, 0.93), respectively. The overall prevalence of mediastinal disease was 28% (range: 18 to 50%).

PET scan (18 studies, n=1,045): the pooled sensitivity was 0.84 (95% CI: 0.78, 0.89) and the pooled specificity was 0.89 (95% CI: 0.83, 0.93). The overall PPV and NPV were 0.79 (range: 0.40, 1.00) and 0.93 (range: 0.75, 1.00), respectively. The overall prevalence of mediastinal disease was 32% (range: 5 to 56%).

Combined CT and PET scan (3 studies, n=152): the sensitivity ranged from 0.78 to 0.93, and the specificity ranged from 0.82 to 0.95. The PPV and NPV ranged from 83 to 93% and from 88 to 95%, respectively. The prevalence of mediastinal disease ranged from 32 to 50%.

MRI scan (1 study, n=20): with gadolinium, the sensitivity was 1.0, the specificity was 0.91, and the PPV and NPV were 0.96 and 1.0, respectively. Without gadolinium, the sensitivity was 0.63, the specificity was 1.0, and the PPV and NPV were 1.0 and 0.55, respectively.

EUS (5 studies, n=163): the pooled sensitivity was 0.78 (95% CI: 0.61, 0.89) and the pooled specificity was 0.71 (95%
CI: 0.56, 0.82). The overall PPV and NPV were 75% and 79%, respectively. The overall prevalence of mediastinal involvement was 50% (range: 25 to 76%).

Question 2: Clinical evaluation.

Detection of brain metastases (17 studies, n=1,784): the NPV ranged from 0.79 to 1.00; the authors stated that there was significant heterogeneity between the included studies in the pooled estimate (0.94, 95% CI: 0.91, 0.96). For 8 studies that evaluated patients with positive and negative clinical evaluation, the pooled sensitivity was 0.76 (95% CI: 0.64, 0.84) and the pooled specificity was 0.87 (95% CI: 0.74, 0.94). The PPV was 0.54 and the overall prevalence of brain metastases was 13% (range: 0 to 32%).

Detection of abdominal metastases (12 studies, n=1,201): the NPV ranged from 0.82 to 1.0; the authors stated that there was heterogeneity between the included studies in the summary estimate (0.95, 95% CI: 0.93, 0.96). For 3 studies that evaluated patients who had a negative and a positive clinical evaluation, the pooled sensitivity was 0.92 (95% CI: 0.83, 0.97) and the pooled specificity was 0.49 (95% CI: 0.25, 0.74). The PPV ranged from 0.20 to 0.59, and the overall prevalence of abdominal metastases was 10% (range: 0 to 40%).

Detection of bone metastases (7 studies, n=633): the pooled sensitivity was 0.87 (95% CI: 0.79, 0.93) and the pooled specificity was 0.67 (95% CI: 0.40, 0.88). The NPV ranged from 0.70 to 1.0; the authors stated that heterogeneity was detected between the included studies in the summary estimate (0.90, 95% CI: 0.86, 0.93). The PPV ranged from 0.16 to 0.90, and the overall prevalence of bone metastases was 20% (range: 8 to 34%).

Authors' conclusions
PET scanning is more accurate than CT scanning or EUS for detecting mediastinal metastases. The authors also concluded that the NPVs of the clinical evaluation for brain, abdominal and bone metastases suggested that the routine imaging of asymptomatic lung cancer patients may not be necessary, but that more definitive prospective studies are required.

CRD commentary
The authors set out clear questions for the review and included comprehensive inclusion criteria. The search appeared to be relatively thorough and the search terms were reported; however, only English language publications were included. The process of selecting the studies was well described and some details on the data extraction were reported. The authors did not report a method for assessing the validity of the included studies, nor was the quality of the studies discussed in the text. Only a few study details were tabulated and no patient characteristics were reported. The authors chose to pool the sensitivity and specificity and, as it is rarely appropriate to pool these, the review would have benefited from a further discussion of heterogeneity and the potential differences between the included studies. The authors' conclusions should be interpreted with caution given the methodological limitations outlined.

Implications of the review for practice and research
Practice: The authors stated that PET scanning is more accurate for detecting mediastinal metastases in newly diagnosed lung cancer patients than standard assessment with CT chest scanning.

Research: The authors stated that future studies should be undertaken to determine the role of combined PET and CT scanning, to further define which types of patients should undergo PET after CT scanning.

Bibliographic details

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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.