Diagnostic performance of integrated positron emission tomography/computed tomography for mediastinal lymph node staging in non-small cell lung cancer: a bivariate systematic review and meta-analysis

Lv YL, Yuan DM, Wang K, Miao XH, Qian Q, Wei SZ, Zhu XX, Song Y

CRD summary
This review concluded that fludeoxyglucose-positron emission tomography/computed tomography was a relatively accurate imaging technique with high specificity for the staging of mediastinal lymph nodes in patients with non-small cell lung cancer. The authors’ conclusions reflected the data presented but it was possible that some studies were missed.

Authors’ objectives
To assess the accuracy of positron emission tomography/computed tomography (PET/CT) for the staging of mediastinal lymph nodes in patients with non-small cell lung cancer.

Searching
MEDLINE, EMBASE and SpringerLink were searched to December 2010 for articles published in English or Chinese. Search terms were reported. Bibliographies of included studies and review articles were screened for additional studies. Abstracts and conference proceedings were excluded.

Study selection
Studies that assessed fludeoxyglucose (FDG)-PET/CT for the staging of mediastinal lymph nodes in patients with non-small cell lung cancer were eligible for inclusion. Studies were required to use histological examination of the lymph nodes following surgery or biopsy as the reference standard to confirm staging and report clear diagnostic criteria and sufficient data to derive the absolute numbers of true positive, false negative, false positive and true negative FDG-PET/CT results. Studies of re-staging following chemotherapy were excluded.

Half of the included studies used a maximum standardised uptake value of at least 2.5 as the FDG-PET/CT diagnostic threshold for lymph node metastases. Other studies used qualitative visual criteria or maximum standardised uptake values of at least 3.0 or at least 5.2. Histological confirmation followed mediastinoscopy, pulmonary resection or both.

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

Assessment of study quality
The methodological quality of the included studies was assessed using 13 items of the 14-item QUADAS tool (the item on clinical review bias was considered not relevant to this study and was omitted). Overall quality scores were calculated and expressed as a percentage of the maximum.

Two reviewers independently assessed study quality. Any disagreements were resolved by consensus.

Data extraction
Data were extracted on numbers of true positive, false negative, false positive and true negative FDG-PET/CT results. These data were used to calculate the per patient or per lymph node sensitivity and specificity of FDG-PET/CT, with 95% confidence intervals (CIs).

Two reviewers independently extracted data. Any disagreements were resolved by consensus.

Methods of synthesis
Pooled estimates of sensitivity and specificity, with 95% CIs, were calculated using a bivariate model. These estimates were used to derive summary positive and negative likelihood ratios and diagnostic odds ratios (DOR). Separate summary estimates were calculated for per patient and per lymph node data.

Hierarchical summary receiver operating characteristic (HSROC) curves and associated area under the curve estimates
Between-study heterogeneity was assessed using the $I^2$ statistic. Subgroup analyses were used to explore potential sources of heterogeneity. These included: prospective versus retrospective study design; per patient versus per lymph node analysis; quantitative versus qualitative FDG-PET/CT diagnostic criteria; English versus Chinese language; adequate reporting of selection criteria; and adequate reporting of FDG-PET/CT methods. Publication bias was assessed using Deeks' funnel plots.

Results of the review
Fourteen studies (2,550 participants, range 46 to 674) were included in the review. Seven studies were prospective and seven were retrospective. The median overall quality score was 69\% (range 54\% to 85\%). More than 60\% of the included studies were rated "no" for avoidance of verification bias, 40\% did not provide adequate details of selection criteria and approximately 30\% did not report sufficient detail of the FDG-PET/CT methods used.

The pooled estimate of per patient sensitivity was 76\% (95\% CI 65 to 84) and the pooled estimate of specificity was 88\% (95\% CI 82 to 92). The summary positive likelihood ratio was 6.1 (95\% CI 4.3 to 8.7) and the summary negative likelihood ratio was 0.28 (95\% CI 0.19 to 0.40). Estimates were based on data from 11 studies and the $I^2$ values for both sensitivity and specificity were more than 75\%, which indicated substantial between-study heterogeneity.

The pooled estimate of per lymph node sensitivity was 65\% (95\% CI 62 to 68) and the pooled estimate of specificity was 95\% (95\% CI 94 to 95). The summary positive likelihood ratio was 11.5 (95\% CI 7.6 to 17.6) and the summary negative likelihood ratio was 0.34 (95\% CI 0.24 to 0.48). Estimates were based on data from nine studies and the $I^2$ values for both sensitivity and specificity were more than 75\%, which indicated substantial between-study heterogeneity.

Subgroup analysis indicated that use of a quantitative diagnostic threshold and publication in English significantly affected sensitivity but not specificity and the method of data collection affected specificity but not sensitivity.

Deeks' funnel plots indicated some evidence for publication bias.

Authors' conclusions
FDG-PET/CT was a relatively accurate imaging technique with high specificity for the staging of mediastinal lymph nodes in patients with non-small cell lung cancer.

CRD commentary
The review reported a clear objective and defined appropriate inclusion criteria. Several sources were searched for relevant studies. The restriction to published studies in English or Chinese raised the possibility of language and publication biases and the omission of relevant studies. Some evidence for publication bias was identified. The methodological quality of included studies was assessed and the results of this assessment were reported and included in the evidence synthesis. The data extraction and quality assessment processes included measures to minimise error and bias; it was not clear whether similar measures were used during study selection. The meta-analytic methods used were appropriate and clearly reported.

The authors' conclusions reflected the data presented but it was possible that some studies were missed.

Implications of the review for practice and research
Practice: The authors stated that FDG-PET/CT alone was not adequate to confirm the presence or absence of mediastinal lymph node metastases. They recommended that biopsies should be performed on all suspicious mediastinal lymph nodes.

Research: The authors stated that future studies should directly compare CT, PET, PET/CT, EBUS-TBNA (endobronchial ultrasound-guided transbronchial needle aspiration) and mediastinoscopy to better define where PET/CT might fit into the diagnostic algorithm.

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