A meta-analysis of 18FDG-PET-CT, 18FDG-PET, MRI and bone scintigraphy for diagnosis of bone metastases in patients with lung cancer

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CRD summary
This review concluded that 18F-fluoro-2-d-glucose positron emission tomography, with or without computed tomography, was the better imaging method for diagnosing bone metastasis from lung cancer than magnetic resonance imaging and bone scintigraphy. There are a number of limitations of the review and included studies that make the reliability and generalisability of the results and conclusions uncertain.

Authors' objectives
To evaluate 18F-fluoro-2-d-glucose positron emission tomography (FDG-PET) with or without computed tomography (CT), magnetic resonance imaging (MRI) and bone scintigraphy for the identification of bone metastases in patients with lung cancer.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched without language restrictions for published articles between 1990 and August 2010; search terms were reported. Bibliographies of eligible studies, reviews and textbooks were searched, and experts in diagnostic imaging contacted for additional studies.

Study selection
Studies that evaluated FDG-PET–CT, FDG-PET, MRI and bone scintigraphy to evaluate at least ten patients with suspected or previously diagnosed bone metastasis form lung cancer were eligible for inclusion. Studies had to use histopathological analysis and/or close clinical follow-up for at least three months as the reference standard, and report sufficient data to construct 2x2 tables of test performance on a per-patient or per-lesion basis for each imaging modality evaluated. Across the studies, the median age was 63.6 years. The median prevalence of bone metastasis was 21.65%. Where reported, the proportion of males ranged from 44.7% to 100%.

Two independent reviewers selected studies for the review; disagreements were resolved by discussion with a third reviewer.

Assessment of study quality
Study quality was assessed by two reviewers using the 14-point QUADAS tool.

Data extraction
Data were extracted to construct 2x2 tables of test performance, from which sensitivity, specificity and the diagnostic odds ratio (DOR) with 95% confidence intervals (CI) were calculate. Authors of potentially eligible studies that did not report sufficient data to construct 2x2 tables of test performance were contacted.

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

Methods of synthesis
Heterogeneity was assessed using the X² and I² statistics. Where heterogeneity was observed (X² p<0.05 and/or I²>50%), pooled estimates of sensitivity, specificity and the DOR with 95% confidence intervals were calculated using a random-effects model. Summary receiver operating characteristic (SROC) curves were produced using the Moses-Littenberg model, from which the area under the curve (AUC) was calculated. The authors stated that meta-regression and subgroup analyses were used to investigate potential sources of heterogeneity, but the variables investigated were not pre-specified. Publication bias was investigated using funnel plots.

Results of the review
Seventeen studies met the inclusion criteria (40 datasets; N=2,940; range 29 to 1,000 patients). Seven studies evaluated FDG-PET–CT, seven evaluated FDG-PET, four evaluated MRI and 13 evaluated bone scintigraphy. Five studies were
prospective, eight retrospective and the direction of data collection was unclear in four. Patient recruitment was consecutive in eight studies and not documented in nine. All studies scored over 8 out of 14 on the QUADAS tool and were considered moderate quality.

On a per-patient basis, pooled sensitivities for the detection of bone metastasis in lung cancer were 92% (95% CI, 88 to 95; seven studies) for FDG-PET–CT, 0.87% (95% CI, 81 to 92; five studies) for FDG-PET, 77% (95% CI, 65 to 87; three studies) for MRI and 86% (95% CI, 82 to 89; 12 studies) for bone scintigraphy. Pooled specificities were 98% (95% CI, 97 to 98) for FDG-PET–CT, 94% (95% CI, 92 to 96) for FDG-PET, 92% (95% CI, 88 to 95) for MRI and 88% (95% CI, 86 to 89) for bone scintigraphy.

Pooled DORs were 449.17 for FDG-PET–CT, 118.25 for FDG-PET, 38.27 for MRI and 63.37 for bone scintigraphy; the DOR for FDG PET-CT was statistically significantly higher than the other modalities.

Results were also presented for each diagnostic modality on a per-lesion basis. There was no evidence of publication bias. Results of meta-regression that explored the impact of study design, year of publication, sample size, histopathology analysis, prevalence of bone metastasis and study quality were also reported. The presence of differential verification bias resulted in significantly lower sensitivity and higher specificity.

**Authors’ conclusions**
Both FDG-PET–CT and FDG-PET were better imaging methods for diagnosing bone metastasis from lung cancer than MRI and bone scintigraphy. FDG-PET–CT has higher accuracy for diagnosing bone metastasis from lung cancer than any other imaging methods.

**CRD commentary**
The review addressed a clear research question with reproducible inclusion criteria. Several relevant sources were searched without language restrictions, and some attempts to identify unpublished studies were made. Diagnostic filters were used during the search, so studies could have been missed. Each stage of the review process was conducted in duplicate, which reduced the risk of error and bias. Study quality was assessed using relevant criteria, but the results were reported only in summary. Therefore, it was unclear which study suffered from which bias; however, the impact of each criterion was evaluated using meta-regression.

Summary estimates of sensitivity and specificity were derived using standard frequentist meta-analytic techniques for seemingly clinically heterogeneous studies. Most of the analyses showed moderate to substantial heterogeneity. The SROC curve was produced using the Moses-Littenberg model. More robust SROC models were available from which summary estimates of sensitivity and specificity could be derived whilst maintaining the within study relationship between these two variables. A number of relevant sensitivity analyses were conducted to investigate potential sources of heterogeneity.

Given the high degree of heterogeneity, and the lack of clarity regarding the biases individual included studies were prone to, the reliability and generalisability of the results and conclusions of the review is uncertain.

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

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