18F-FDG PET for evaluation of bone marrow infiltration in staging of lymphoma: a meta-analysis
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CRD summary
This generally well conducted and reported review found that the agreement between 18F-fluorodeoxyglucose positron emission tomography and bone marrow biopsy for the detection of bone marrow infiltration in the staging of patients with lymphoma is good but not excellent. These conclusions are likely to be reliable.

Authors' objectives
To evaluate the diagnostic performance of 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) for the evaluation of bone marrow infiltration in patients with lymphoma.

Searching
MEDLINE and EMBASE were searched up to August 2004; the search terms were reported. References of retrieved articles were screened for additional relevant studies. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
The studies had to include at least 5 patients to be included.

Specific interventions included in the review
Studies of 18F-FDG PET in the evaluation of bone marrow infiltration in the initial staging or staging of recurrent disease before treatment were eligible for inclusion. Studies that evaluated PET for recurrences after treatment were excluded. Studies in which the decision to perform PET was based on the results of the bone marrow biopsy (BMB) were excluded. The 18F-FDG dose ranged from 200 to 300 MBq. PET results were analysed either quantitatively, based on standardised uptake values, or qualitatively.

Reference standard test against which the new test was compared
Studies that used BMB results as the reference standard were eligible for inclusion. Studies in which the decision to perform BMB was based on the results of the PET scan were excluded. Biopsy location was either the iliac crest, the sternum, or not reported.

Participants included in the review
Studies of patients with lymphoma, with and without bone marrow infiltration, were eligible for inclusion. Patients with both Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) were eligible for inclusion. The mean age of the participants ranged from 13 to 65 years. Some studies only included patients with primary disease; others included mixed populations with primary and recurrent lymphoma.

Outcomes assessed in the review
Studies that assessed diagnostic accuracy were eligible for inclusion.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
No formal validity assessment was undertaken. However, studies in which verification bias might have been a problem were excluded from the review, and data were extracted on relevant quality features such as study design, blinding of the PET measurements to the BMB results and vice versa, and data on inter-observer variability.
Data extraction
Two reviewers independently extracted the data from the included studies. Any discrepancies were resolved through discussion, or by referral to a third reviewer where necessary. Investigators of included studies were contacted and asked for additional data when key information relevant to the meta-analysis was missing. For each study, data on the number of true-positive, false-positive, true-negative and false-negative findings for PET in diagnosing bone marrow infiltration were extracted. Where possible, data were extracted separately for HD and NHL and for primary and recurrent lymphoma.

Methods of synthesis
How were the studies combined?
The sensitivity, specificity, and positive and negative likelihood ratios (LRs) were pooled using random-effects models. Summary receiver operating characteristic (SOC) curves were constructed. Both weighted and unweighted regressions were estimated.

How were differences between studies investigated?
Heterogeneity in sensitivity and specificity was assessed using the Fisher exact test. Heterogeneity in the LRs was assessed using the Q statistic. A sensitivity analysis were carried out to investigate whether the LRs differed between small and large studies. Subgroup analyses were carried out in which data were pooled separately according to definition of PET positivity, type of lymphoma (HD or NHL), disease status (primary or recurrent), type of biopsy (unilateral or bilateral), study design (prospective or retrospective), and blinding of each diagnostic test to the results of the other.

Results of the review
Thirteen studies (n=587) were included: 7 prospective studies (n=361), 4 retrospective studies (n=189) and 2 studies of unspecified design (n=37).

Nine studies reported blinding.

The sensitivity ranged from 0 to 100% and the specificity from 72 to 100%. There was significant heterogeneity in both sensitivity and specificity (P=0.014 and P<0.001, respectively). The pooled sensitivity was 51% (95% confidence interval, CI: 38, 64) and the pooled specificity was 91% (95% CI: 85, 95). Similar results were obtained based on the SOC curve.

The pooled positive LR was 5.75 (95% CI: 3.48, 9.48) and the pooled negative LR was 0.67 (95% CI: 0.55, 0.82). There was no statistical evidence of heterogeneity in either measure (P>0.10). There was no evidence that positive LRs differed between smaller and larger studies (correlation coefficient -0.03, P=0.90), although there was some evidence that negative LRs were less favourable in larger studies (correlation coefficient 0.69, P=0.001).

The subgroup analyses showed significantly better sensitivity in patients with HD (76%, 95% CI: 47, 92) than in those with NHL (43%, 95% CI: 28, 60). Sensitivity was also higher in studies restricted to patients with primary disease (72%, 95% CI: 57, 83) compared with those that included patients with both primary and recurrent disease (38%, 95% CI: 27, 50), and in studies that carried out unilateral biopsy (75%, 95% CI: 53, 89) compared with those with bilateral biopsy (46%, 95% CI: 32, 60). Estimates of specificity were similar across subgroups. No major differences were found for prospective versus retrospective studies, studies with and without blinding, and studies with qualitative compared with quantitative PET measurements.

Authors' conclusions
The concordance between 18F-FDG PET and BMB for the detection of bone marrow infiltration in the staging of patients with lymphoma is good but not excellent, but this may depend on the type of lymphoma.
CRD commentary
This was a generally well conducted and reported review. The review question was focused and was supported by clearly defined inclusion criteria. The literature search was limited to two databases and no attempts were made to identify unpublished studies, thus relevant studies might have been missed and the results may be subject to publication bias. Although a formal quality assessment was not undertaken, quality-related features were discussed and incorporated into the inclusion criteria and subgroup analysis. Some details of the review process were reported and these included appropriate steps to minimise bias. The methods used to synthesise the results were appropriate, and the interpretation of the results is helped by the inclusion of a summary ROC plot. The authors' conclusions are supported by the data presented.

Implications of the review for practice and research
Practice: The authors stated that PET cannot yet be recommended for replacing BMB routinely in the staging of lymphoma because many cases of bone marrow involvement would be missed. However, PET could complement BMB and could occasionally identify additional cases of focal bone marrow involvement that would be missed by the BMB.

Research: The authors stated that future research should focus on the complementary information that PET and BMB may provide and the impact that this may have on prognosis. They also stated that future studies should focus more on quantitative indices.

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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.