Role of PET in the initial staging of cutaneous malignant melanoma: systematic review

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CRD summary
This review assessed the accuracy of positron emission tomography with fluorine 18 fluorodeoxyglucose (FDG PET) for staging cutaneous malignant melanoma. It concluded that FDG PET was useful, particularly in higher stage disease and to detect deep soft tissue, lymph node and visceral metastases. Limitations in the analyses and reporting of the review mean that these conclusions may not be reliable.

Authors' objectives
To estimate the diagnostic accuracy (on a per patient and per lesion basis) of positron emission tomography with fluorine 18 fluorodeoxyglucose (FDG PET) for the initial staging of cutaneous malignant melanoma, using the new American Joint Committee on Cancer staging criteria.

Searching
MEDLINE, EMBASE, Web of Science and the Cochrane Database of Systematic Reviews were searched from inception to March 2007, without language restrictions. Search terms were based upon the test and target condition. The bibliographies of reviews and included studies were screened for additional articles.

Study selection
Prospective or retrospective studies that assessed the diagnostic accuracy of positron emission tomography with fluorine 18 fluorodeoxyglucose for initial staging, in patients with histologically proven cutaneous malignant melanoma, were eligible for inclusion. For studies without a histopathologic reference standard, clinical-radiologic follow-up was acceptable. Studies were required to report sufficient data for the construction of 2x2 contingency tables (numbers of true positives, false negatives, false positives and true negatives), on a per patient or per lesion basis, and to include a minimum of ten participants. Unpublished studies and conference proceedings were excluded.

The median age of study participants was 54 years (range 42 to 63 years) and the mean percentage of male participants was 60% (range 47 to 78%). The median post-test prevalence of active malignancy was 52% (range 15 to 93%). Further study details were available in supplementary tables on-line (see URL for Additional Data field).

Studies were assessed for inclusion by two reviewers, one of whom was an experienced clinical epidemiologist.

Assessment of study quality
The methodological quality of included studies was assessed using the QUADAS (Quality Assessment of Diagnostic Accuracy Studies Assessment) checklist.

Two reviewers independently assessed methodological quality and disagreements were resolved by consensus.

Data extraction
Data were extracted on positron emission tomography with fluorine 18 fluorodeoxyglucose characteristics (e.g. camera, fluorine 18 fluorodeoxyglucose dose and time between injection and scanning, attenuated or non-attenuated positron emission tomography), reference standard characteristics (pathologic methods, or length and intervals of follow-up), and the unit of observation (patient, lesion, lymph nodes, sentinel nodes).

Diagnostic accuracy data were presented as sensitivity and specificity, positive and negative likelihood ratio (LR) and diagnostic odds ratio (DOR).

Data were extracted by two reviewers independently and disagreements were resolved by consensus.
Methods of synthesis

Pooled estimates of sensitivity and specificity, positive and negative likelihood ratios and diagnostic odds ratios, with their 95% confidence intervals (CIs), were calculated. A summary receiver operating characteristic (SROC) curve was also presented. The presence of diagnostic threshold effect (variation in test performance with the diagnostic threshold used) was assessed by visual inspection of pairs of diagnostic odds ratios on a forest plot. Between study heterogeneity was assessed using the Cochrane Q and $\chi^2$ tests. Potential sources of between study heterogeneity were explored using regression analysis.

Results of the review

Twenty-eight studies, reporting 34 data sets (n=2,905 patients) were included in the meta-analyses. In 17 studies, patients were enrolled exclusively for initial staging; the remaining 11 studies were in mixed populations. Quality assessment indicated that most studies (70%) did not include an appropriate spectrum of patients. Potential review bias was frequently a problem; test results were not interpreted blind to reference standard in 13 studies, and vice versa in 11 studies. Only 21% of studies reported how indeterminate positron emission tomography with fluorine 18 fluorodeoxyglucose characteristics (FDG PET) results were handled.

The pooled estimates of FDG PET diagnostic sensitivity was 83% (95% CI 81 to 84) and specificity was 85% (95% CI 83 to 87). The pooled estimates of positive and negative likelihood ratios were 4.56 (95% CI 3.12 to 6.64) and 0.27 (95% CI 0.18 to 0.40) respectively. The overall diagnostic odds ratio was 19.8 (95% CI 10.8 to 36.4). A high level of between study heterogeneity was present (p<0.001). The unit of analysis (patient or lesion) did not effect estimates of accuracy.

Regression analyses suggested that the following were all positively associated with diagnostic accuracy (as indicated by diagnostic odds ratios): American Joint Committee on Cancer stage; post-test prevalence of active malignancy; disease status on referral for FDG PET; use of sentinel lymph node biopsy as the reference standard; reporting of the definition of a positive test result; reporting of details of the reference standard; and the presence of spectrum bias.

Four studies (n=309 patients) indicated that PET/CT (computed tomography; DOR 37.6, 95% CI 24 to 59) performed better than PET alone (DOR 10.6, 95% CI 6 to 20).

Data from eight studies suggested that FDG PET was associated with 33% (range 15 to 64%) changes in disease management.

Authors' conclusions

FDG PET showed moderate sensitivity and specificity for the detection of metastases in the initial staging of cutaneous malignant melanoma. PET/CT appeared to perform better than PET alone.

CRD commentary

The article presented a clearly stated research question, which was supported by appropriate inclusion criteria. The search strategy examined a number of sources and did not restrict by language. However, unpublished studies and conference abstracts were excluded, leaving open the possibility of publication bias. Appropriate measures to minimise error and bias in the review process were reported, and the methodological quality of included studies was assessed and incorporated in the analyses.

Reporting of the results of individual included studies was minimal and, in particular, no definitions of false-positive and false-negative results were provided (how were under and over staging treated in the analyses?). Given the significant between study heterogeneity identified, pooled estimates of accuracy measures were of limited value. Greater emphasis on the summary receiver operating characteristic curve, along side a more detailed description of the individual study results, may have been a more useful approach. The authors interpretation of the pooled accuracy estimates was reasonable, but these data should be viewed cautiously in light of the heterogeneity present. Data from the regression analyses appeared to support the assertion that FDG PET was more useful in higher American Joint Committee on Cancer stages, but detail was lacking and data on performance for the detection of metastases at different sites were not presented. The interpretation of the limited data on change in disease management induced by FDG PET and comparative performance of PET/CT and PET alone was reasonable, but these data were sparse, poorly
reported and addressed questions outside the stated objective of the review. Limitations in the available data, analyses and reporting of the review mean that the authors’ conclusions may not be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that, in American Joint Committee on Cancer stages III and IV, FDG PET is a useful adjunctive imaging technique, particularly for helping to detect deep soft tissue, lymph node and visceral metastases. Some early stage patients could also benefit from FDG PET.

**Research:** The authors stated that larger prospective studies are needed to assess the changes in disease management induced by routine use of FDG PET, and to determine the cost-effectiveness of including FDG PET in the imaging algorithm for cutaneous malignant melanoma.

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