Meta-analysis of the performance of 18F-FDG PET in primary tumor detection in unknown primary tumors

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CRD summary
This review aimed to determine the usefulness of 18-fluorine fluorodeoxyglucose positron emission tomography (18F-FDG PET) in detecting primary tumours whose location is unknown. It concluded that 18F-FDG PET may be useful for this purpose and would miss few tumours that subsequently prove locatable by other available tests. However, further research is required to determine the effect of this imaging technique on patient management.

Authors' objectives
To assess the accuracy of 18-fluorine fluorodeoxyglucose positron emission tomography (18F-FDG PET) for the detection of primary tumours in patients with an unknown primary tumour (UPT).

Searching
MEDLINE and Cancerlit were searched for studies published from January 1994 to May 2001; the search terms were reported. The reference lists of retrieved articles and abstracts from recent conference proceedings were manually reviewed. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
No inclusion criteria were specified for the study design. The included studies were of two types: in type I, 18F-FDG PET was performed when all diagnostic procedures performed did not detect the primary tumour; in type II, 18F-FDG PET was compared with computed tomography (CT) or magnetic resonance imaging in a double-blinded study that included UPT participants with negative results in other tests.

Specific interventions included in the review
Studies assessing the diagnostic performance of 18F-FDG PET were eligible for inclusion. The included studies were of 18F-FDG PET of the whole body or of the head-neck-thorax region only.

Reference standard test against which the new test was compared
No inclusion criteria were specified for the reference standard. The included studies used histology of biopsy or surgical samples, other imaging procedures, or clinical follow-up to confirm diagnosis.

Participants included in the review
The included studies were required to contain a minimum of 4 participants with UPT. The site of localisation of metastases of UPT varied in the included studies.

Outcomes assessed in the review
Studies were included if there were sufficient data for calculation of the sensitivity and specificity for primary tumour detection.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed titles, abstracts, or complete articles for inclusion. Any disagreements were resolved by consensus. The reviewers were not blinded to the journal, author, institution, or date of publication.

Assessment of study quality
The methodological quality of the included studies was evaluated using an adaptation of a published guideline (see Other Publications of Related Interest no.1). Description of study design, description of study population, indications...
leading to 18F-FDG PET use, technical and image interpretation issues, final confirmation, sensitivity and specificity data, and change in management information were graded ('adequate', 'partial', 'not addressed', or 'not applicable') for adherence to the guidelines. Contribution to patient management was assessed according to the efficacy model of Fryback and Thornbury (see Other Publications of Related Interest no.2). A grade of evidence was assigned based on methodological quality, generalisability and contribution to patient management. One reviewer evaluated methodological quality evaluation, while two reviewers independently assigned the grade of evidence. Any disagreements were resolved by consensus. The reviewers were not blinded to the study title, results, authors, institution, or journal of publication.

Data extraction
One reviewer abstracted the following data from the included studies: number and demographic characteristics of the participants; inclusion criteria for the participants; study design; UPT characteristics; and results, i.e. numbers of true positives, false positives, true negatives and false negatives. True positive was defined as 'location suggested by 18F-FDG PET confirmed'; false positive was considered when this location was not confirmed. True negative was considered if no other lesions were detected when 18F-FDG PET did not suggest the location of the primary tumour, or when other lesions were detected but the primary tumour remained unknown. False negative was considered if the primary tumour was identified subsequent to a negative 18F-FDG PET.

Methods of synthesis
How were the studies combined?
The sensitivity, specificity, diagnostic accuracy and odds ratio (OR) were calculated for each included study. The natural logarithm (ln) of the OR and variance for individual studies, as well as a pooled estimate with 95% confidence intervals (CIs), were presented on a forest plot. A summary receiver operating characteristic curve was constructed using the method of Moses et al. (see Other Publications of Related Interest no.3). Summary positive and negative likelihood ratios were also estimated.

How were differences between studies investigated?
Subgroup analyses, which compared the pooled sensitivity and specificity values, were conducted: for type I and type II studies; and for studies of 18F-FDG PET of the whole body compared with those of the head-neck-thorax region only. Homogeneity in the 95% CIs was analysed, using the Q statistic, to assess the possibility of determining summary estimates. A multiple linear regression model was used to assess variation in test performance due to study characteristics.

Results of the review
Fifteen studies (9 type I and 6 type II) were included in the meta-analysis. These studies included 302 participants, of whom 298 had confirmed diagnoses and were included in the meta-analysis.

The assessment of methodological quality classified all included studies as evidence grade C (weak evidence in studies with several methodological defects, small sample sizes of incomplete description). For the assessment of contribution to patient management, 8 studies reached level two (diagnostic accuracy efficacy), 6 studies reached level 4 (therapeutic efficacy), and one study reached level five (patient outcome efficacy).

The sensitivity of 18F-FDG PET was 0.87 (95% CI: 0.81, 0.92) and the specificity was 0.71 (95% CI: 0.64, 0.78). The pooled estimate for ln OR was 2.50 (95% CI: 1.97, 3.03), indicating that 18F-FDG PET produced statistically significant changes. The pooled positive likelihood ratio was 3.05 (95% CI: 2.39, 3.88) and the pooled negative likelihood ratio was 0.17 (95% CI: 0.11, 0.27).

The subgroup analyses did not indicate any significant heterogeneity in results between the types of studies examined. The regression analysis found no significant variation in diagnostic performance due to any of the study characteristics assessed.

A funnel plot of sensitivity did not suggest publication bias. However, a funnel plot of specificity showed an asymmetric distribution, suggesting publication bias.
Authors' conclusions
18F-FDG PET could be useful in patients with UPT. The high sensitivity (few false negatives) calculated indicates potential utility in the initial stages of the management of oncologic patients. Further research is required to assess the clinical utility and role of 18F-FDG PET in patient management.

CRD commentary
The article reported a generally good-quality systematic review. The research question was clearly stated and defined by appropriate inclusion criteria. The limitation of the electronic literature search to two databases might have resulted in the omission of some relevant data. Despite some attempts to identify grey literature, a visual assessment indicated a possible presence of publication bias. A quality assessment, which included some methodological criteria relevant to diagnostic accuracy studies, was conducted. However, these data do not appear to have been utilised in the analyses.

The details of the included studies were adequately reported, thus enabling the reader to assess the relevance of the results. The methods used to pool diagnostic performance parameters and to investigate sources of heterogeneity were appropriate and clearly described. The authors’ conclusions follow broadly from the data presented.

Implications of the review for practice and research
Practice: The authors made no specific recommendations for practice.

Research: The authors stated that more data, from methodologically rigorous studies, are required to assess the clinical utility and role of 18F-FDG PET in patient management. Future studies will need to assess whether diagnostic performance will be improved significantly by the introduction of CT or PET systems and new software fusion approaches. A cost-effectiveness study is recommended. If diagnostic performance improves significantly in the future, owing to technical advances, the role of 18F-FDG PET in UPT will need to be re-assessed.

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