Combined FDG-PET/CT for the detection of unknown primary tumors: systematic review and meta-analysis

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CRD summary
The review assessed the diagnostic performance of combined 18F-fluoro-2-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) in the detection of unknown primary tumours and concluded that FDG-PET/CT can be a useful method. Given the small size and heterogeneous nature of the data set, this conclusion may be optimistic.

Authors' objectives
To assess the diagnostic performance of combined 18F-fluoro-2-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) in the detection of primary tumors in patients with cancer of unknown primary (CUP).

Searching
PubMed (including MEDLINE) and EMBASE were searched from inception to March 2008. The search strategy was reported. Bibliographies of included studies were screened for additional articles.

English, German, French, Italian and Spanish studies were included.

Study selection
Studies that assessed the diagnostic performance of FDG-PET/CT for primary tumour detection in more than 10 patients with CUP were eligible for inclusion. Studies were excluded if metastases were not histologically confirmed. Included studies were required to report sufficient data for the construction of 2x2 contingency tables to calculate sensitivity and specificity for primary tumor detection in patients with CUP.

Study participants ranged in age from 29 to 95 years. The location of metastases of unknown primary was approximately evenly distributed between cervical and extra-cervical. Where reported, the FDG dose ranged from 222MBq to 555MBq. The technical details of CT were generally poorly reported; where reported, studies used two or 16 detector rows.

Two reviewers independently assessed the titles and abstracts of the retrieved articles, and full-text versions of those articles deemed relevant, for inclusion. Disagreements were resolved by consensus.

Assessment of study quality
The methodological quality of included studies was assessed using a modified 12-item review-specific version of the QUADAS tool that assessed elements of reporting quality, participant spectrum and selection, verification biases, comparator review bias, blinded interpretation of index test results and handling of indeterminate results and withdrawals. Items were rated as yes, no or unclear; both no and unclear were interpreted as item not being met. A total quality score was estimated as a percentage of the maximum score of 12.

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

Data extraction
Data were extracted on the numbers of true positives, false negatives, false positives and true negatives for each study. A true positive result was defined as location determined by FDG-PET/CT subsequently confirmed and a false-positive result was location not confirmed. A true negative result was defined as no location determined by either FDG-PET/CT or the reference standard. A false negative result was location determined by the reference standard at a site that was
negative on FGD-PET/CT. The reference standard was histopathological analysis of tissue obtained by biopsy or surgery; imaging procedures or clinical follow-up were accepted if no histology could be obtained.

Sensitivity and specificity, with 95% confidence intervals (CIs), were calculated for each included study.

The authors stated neither how data were extracted for the review nor how many reviewers performed the data extraction.

**Methods of synthesis**

Pooled estimates of sensitivity and specificity were calculated using a random-effects model.

A $\chi^2$ test was performed to test for heterogeneity between studies. Differences in test performance due to different diagnostic cut-offs used in different studies (threshold effect) were assessed using the Spearman correlation coefficient between the logit of sensitivity and logit of 1-specificity. Other potential sources of heterogeneity were explored by assessing whether predefined covariates significantly affected the relative diagnostic odds ratio.

Explanatory covariates assessed were: completeness of diagnostic workup prior to FDG-PET/CT (complete versus not complete); location of metastases of unknown primary (cervical versus extra-cervical); administration of CT contrast agents (both intravenous and oral contrast versus no intravenous or oral contrast agent, or not reported); type of FDGPET/CT images evaluated (both attenuation-corrected and non-attenuation-corrected images versus attenuation-corrected images only, or not reported); and method of FDG-PET/CT review (reported blinding to reference test versus no or unreported blinding to reference test).

**Results of the review**

Eleven studies (n=433 participants with CUP) were included in the review. The total methodological quality score ranged from 42% to 75% (median 50%).

Primary tumour detection rates ranged from 22% to 73%, with an overall detection rate of 37% (162 out of 433). The most common locations of false-positive FDG-PET/CT findings were lung and oropharynx (both 15%). The most common false-negative location was breast (27%). Sensitivity of FDG-PET/CT in primary tumor detection ranged from 55% to 100% and specificity ranged from 73% to 100%. The pooled estimates of sensitivity and specificity were 84% (95% CI 78% to 88%) for sensitivity and 84% (95% CI 78% to 89%) for specificity.

Significant between-study heterogeneity was identified for estimates of sensitivity. There was no evidence of a threshold effect. No significant changes in diagnostic odds ratio were observed for any of the covariates assessed.

**Authors' conclusions**

The authors concluded that although included studies were of moderate methodological quality and their results were heterogeneous, the results of their review and meta-analysis indicated that FDG-PET/CT can be a useful method for detecting unknown primary tumour.

**CRD commentary**

The review addressed a clearly stated objective to assess the utility of combined FDG-PET/CT in detecting the location of unknown primary tumours. Appropriate inclusion criteria were defined and a range of sources were searched to identify relevant studies. Language restrictions were applied, but studies in five European languages were included and so the impact of language bias was unlikely to be significant. The methodological quality of included studies was assessed. The results of quality assessment were reported in full and considered in the interpretation of results. Measures were taken to reduce error and bias during study selection and quality assessment; it was unclear whether similar measures were applied to the data extraction process. The value of pooled estimates of diagnostic performance generated from heterogeneous data sets was questionable; the bivariate summary receiver operating characteristic (SROC) model may have been more appropriate to these data. Given the heterogeneity of the summary performance estimates, methodological weaknesses in the included studies (most were retrospective) and the wide confidence intervals for individual study estimates, the authors' conclusion that FDG-PET/CT can be a useful method for detecting
unknown primary tumour appears optimistic.

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

**Practice:** The authors stated that FDG-PET/CT can be a useful method of detecting unknown primary tumors.

**Research:** The authors stated that future studies were required to prove the assumed advantage of FDG-PET/CT over FDG-PET alone and to further explore causes of heterogeneity.

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