Characterization of adrenal masses by using FDG PET: a systematic review and meta-analysis of diagnostic test performance

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CRD summary
This well-conducted review concluded that positron emission tomography was highly sensitive and specific for differentiating malignant from benign adrenal disease. These conclusions are likely to be reliable, although there is the possibility of missing studies.

Authors' objectives
To determine the diagnostic accuracy of adrenal fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) for distinguishing benign from malignant adrenal disease.

Searching
PubMed, EMBASE, Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to November 2009. Search terms were reported. Reference lists of retrieved studies and relevant journals were searched to identify additional relevant studies. The review was restricted to full-text peer-reviewed articles published in English.

Study selection
Studies that assessed the accuracy of FDG PET or PET/computed tomography (CT) for detection of benign and malignant adrenal lesions in at least 10 lesions were eligible for inclusion. Studies had to report results based on independent or consensual assessment of scans.

Most studies presented qualitative interpretation of PET scans: some presented only quantitative mean or maximal standardised uptake values; some only used standardised uptake ratio analysis; and some used combinations of quantitative and qualitative data. Reference standards consisted of histological diagnosis and/or established clinical and imaging follow-up (interval CT follow-up, lipid-sensitive and/or washout CT or lipid sensitivity magnetic resonance imaging). Studies used stand alone PET scanners or PET/CT scanners; scanner models and analysis methods varied across studies. Mean prevalence of malignant disease was 41%.

Two reviewers independently assessed studies for inclusion.

Assessment of study quality
Studies were assessed for methodological quality using 12 of the 14 QUADAS items; items for time between index test and reference standard and reporting of withdrawals were omitted.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Data were extracted to populate 2x2 tables of test performance. Sensitivity, specificity, positive and negative likelihood ratios and the diagnostic odds ratio (DOR) were calculated together with 95% confidence intervals (CIs). Data were extracted for patients who underwent PET; all other patients were excluded from the analysis. If data were reported for PET/CT only data for the PET component of the scan were included.

The authors did not state how many reviewers performed data extraction.

Methods of synthesis
Summary sensitivity and specificity together with 95% CIs were estimated using the bivariate random effects model.
Summary positive and negative likelihood ratios and diagnostic odds ratios were calculated from the summary estimates of sensitivity and specificity. Various pre-test probabilities of malignant lesions based on different clinical settings (multidisciplinary 5%, pulmonary 25% and oncologic 50%) were combined with likelihood ratios to give estimates of the post-test probability of disease. A hierarchical summary receiver operating characteristic (HSROC) curve was constructed and the area under the curve (AUC) was calculated. Heterogeneity was assessed graphically using forest plots and statistically using the I$^2$ statistic.

Subgroup analysis and meta-regression based on mode of data analysis (visual, standardised uptake ratio and standardised uptake values), QUADAS criteria and technical quality of the PET scan were performed. Publication bias was assessed using funnel plots and regression analysis.

**Results of the review**

Twenty-one studies were included in the review (1,217 patients, 1,391 adrenal lesions). All studies included an appropriate patient spectrum and avoided incorporation bias. One study fulfilled all criteria. Less than 20% of studies used an appropriate reference standard and less than 20% avoided verification bias. Blinding of was poorly reported.

Sensitivity ranged from 76% to 100% and specificity ranged from 73% to 100%. Summary sensitivity was 97% (95% CI 93% to 98%) and summary specificity was 91% (95% CI 87% to 94%). There was substantial heterogeneity in both sensitivity and specificity estimates (I$^2$=88%). The summary positive likelihood ratio was 11.1 (95% CI 7.5 to 16.3) and the summary negative likelihood ratio was 0.04 (95% CI 0.02 to 0.8). The AUC was 0.98. Summary estimates did not vary depending on method of image interpretation. The two variables to show an association with sensitivity in the regression analysis (p<0.05) were prospective design and full verification. Multi-observer interpretation, withdrawals, clinical data, blinding of the index test and clinical population were associated with specificity (p<0.05). At pre-test probabilities of 5%, 25% and 50% there were no significant differences in the post-test probability of a negative test results between the subgroups. A positive PET result increased the pre-test probabilities of 5%, 25% and 50% to 67.2%, 92.9% and 97.5% for patients with an adrenal mass with no known cancer. The authors stated that there was no evidence of publication bias.

**Authors' conclusions**

FDG PET was highly sensitive and specific for differentiating malignant from benign adrenal disease. Diagnostic accuracy was not influenced by the type of imaging device. Specificity was dependent on the clinical status (cancer versus no cancer).

**CRD commentary**

The review addressed a clear question and inclusion criteria were defined. Details on reference standard and population were not specified. An extensive literature search was conducted to locate published studies, but restriction of the review to published full-text studies in English raised the possibility of language and publication bias. This was assessed in the review, but methods used were not appropriate for diagnostic data. Appropriate steps were taken to minimise bias and errors when selecting studies; it was unclear whether such steps were taken when assessing quality and extracting data. Study quality was assessed using appropriate criteria and detailed results were presented as web appendices and considered in the analysis. Statistically robust models were used to pool data. Heterogeneity was appropriately assessed and investigated. The clinical context of the results was considered and clearly presented.

The authors' conclusions are likely to be reliable, although there is the possibility of missing studies.

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

**Practice:** The authors stated that PET alone can be used confidently to characterise adrenal masses, particularly those in patients with cancer. The specificity of PET for characterising adrenal lesions smaller than 10mm should be considered with caution.

**Research:** The authors did not state any implications for research.
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