Usefulness of 18F-FDG PET, combined FDG-PET/CT and EUS in diagnosing primary pancreatic carcinoma: a meta-analysis

CRD summary
This review concluded that combined positron emission tomography/computed tomography (PET/CT) was highly sensitive and endoscopic ultrasonography was highly specific in diagnosing patients with pancreatic cancer. PET/CT and endoscopic ultrasonography could play different roles during different conditions in diagnosing pancreatic carcinoma. Limitations in the included studies and the analysis mean that the conclusion should be treated with caution.

Authors' objectives
To evaluate the diagnostic value of 18F-fluorodeoxyglucose positron emission tomography (PET), combined PET/computed tomography (CT) and endoscopic ultrasonography in diagnosis of patients with pancreatic carcinoma.

Searching
MEDLINE and EMBASE were searched for articles in English or Chinese from 1966 to April 2009; search terms were reported. Science Direct, SpringerLink, Scopus, The Cochrane Library and a database for Chinese technological journals were searched. CBMdisc databases were searched for Chinese articles. Reference lists of all retrieved articles were scanned.

Study selection
Studies with at least 10 patients that used PET, PET/CT or endoscopic ultrasonography to diagnose suspected pancreatic cancer were eligible for inclusion. Studies needed to use histopathologic analysis and/or close clinical and imaging follow-up for at least six months as the reference standard. Studies had to report sufficient data to construct 2x2 tables of test performance on a per patient basis. Studies that used a combination of tests where results of individual test could not be determined were excluded. Also excluded were studies of endoscopic ultrasonography-guided biopsy without information of endoscopic ultrasonography alone, studies that reported diagnosis for pancreatic neoplasms with other existing disease and could not be differentiated and studies that reported only cystic or neuroendocrine pancreatic tumours.

Most of the included studies used both histopathologic analysis and clinical or imaging follow-up as the reference standard. Other studies used histopathologic analysis only. Follow-up was at least six months in all studies. Most of the included participants were male. Most endoscopic ultrasonography studies used Doppler endoscopic ultrasound.

Two independent reviewers selected studies for the review; disagreements were resolved by consensus or referral to a third reviewer.

Assessment of study quality
Study quality was assessed using the 14-point QUADAS tool; studies that scored 9 or more were included.

The authors did not specifically state how many reviewers performed the quality assessment. It seemed that quality assessment was done as part of the data extraction process.

Data extraction
Data were extracted to produce 2x2 tables of test performance by two independent reviewers. Sensitivity, specificity and diagnostic odds ratio (DOR) were calculated from these data. Disagreements were resolved by consensus or referral to a third reviewer.

Methods of synthesis
Pooled estimates of sensitivity, specificity and diagnostic odds ratio were calculated for each modality using a fixed-effect model except for studies that were heterogeneous, where a random-effects model was used. Galbraith plots and X² were used to assess heterogeneity. Summary receiver operating characteristic curves (SROC) were produced using a
random-effects model for endoscopic ultrasonography and a fixed-effect model for PET and PET/CT. The *Q index (where sensitivity=specificity) and area under the curve were calculated. The Z test was used to detect significant differences in sensitivity, specificity, diagnostic odds ratio and *Q index between modalities. Multivariable regression with a backward stepwise algorithm was used to investigate heterogeneity in relation to modality category, published year, direction of data collection, sample size and QUADAS. Depending on the modality, subgroup analyses were undertaken based on patient spectrum, direction of data collection, use of contrast enhancement in endoscopic ultrasonography and blinding of interpreters.

Results of the review
Fifty-one studies met the inclusion criteria (n=3,857 participants; 28 studies had sample sizes over 50). Study quality was considered to be good. Six studies reported avoiding potential for progression bias. Fifteen studies avoided differential verification bias. Nineteen studies reported blinding of interpreters of tests. More than 80% of studies met the other QUADAS criteria.

PET: Pooled sensitivity was 88.4% (95% CI 86.3 to 90.3), specificity was 83.1% (95% CI 79.6 to 86.3) and DOR was 32.778 (95% CI 24.107 to 44.570).

PET/CT: Pooled sensitivity was 90.1% (95% CI 85.5 to 93.6), specificity was 80.1% (95% CI 73.1 to 86.0) and DOR was 27.105 (95% CI 15.307 to 47.998).

Endoscopic ultrasonography: Pooled sensitivity was 81.2% (95% CI 78.7 to 83.5), specificity was 93.2% (95% CI 91.7 to 94.5) and DOR was 49.774 (95% CI 25.756 to 96.189).

Sensitivity was significantly greater for PET/CT than for PET and endoscopic ultrasonography (p<0.001). Specificity was significantly greater for endoscopic ultrasonography than PET or PET/CT (p<0.001).

Significant heterogeneity was observed for all three measures for endoscopic ultrasonography and PET and for specificity of PET/CT. Patient spectrum was identified as the most important variable that explained the heterogeneity across studies.

The area under the curve was 0.9324 for PET, 0.9414 for PET/CT and 0.9387 for endoscopic ultrasonography; the *Q index for PET/CT and endoscopic ultrasonography were significantly higher than PET (p<0.05).

Results for a range of subgroup analyses were presented.

Authors' conclusions
PET/CT was a highly sensitive and endoscopic ultrasonography was a highly specific modality in diagnosing patients with pancreatic cancer. PET/CT and endoscopic ultrasonography could play different roles during different conditions in diagnosing pancreatic carcinoma.

CRD commentary
The authors addressed a clear research question supported by appropriate inclusion criteria. Several relevant sources were searched. Inclusion was restricted by language and unpublished studies were not sought specifically, so language and publication biases could not be ruled out. The search included diagnostic filters and so some studies may have been missed. Each stage of the review was conducted in duplicate; how disagreements were resolved was not reported.

Study quality was assessed using appropriate criteria, but a composite score was used to determine inclusion and did not account for the relative importance of different criteria. Study quality was considered good, but most of the included studies seemed subject to progression bias and blinding of interpreters was poor; these could have a large impact on estimates of sensitivity and specificity. This and the fact that the estimates of sensitivity and specificity were calculated separately using heterogeneous data made the reliability and generalisability of these estimates questionable. More robust SROC models take heterogeneity across studies into account and provide summary estimates of sensitivity and specificity while maintaining the within-study link of these measures.

Given the limitations of the included studies and the analysis, the conclusion should be treated with caution.
Implications of the review for practice and research

**Practice:** The authors stated that the high sensitivity of PET/CT meant this modality could be used to rule out pancreatic carcinoma and the high specificity of endoscopic ultrasonography used to rule it in. Compared with endoscopic ultrasonography, PET/CT would be more advantageous in managing, staging and evaluating the response to therapy for pancreatic cancer patients as PET/CT is a whole body imaging method.

**Research:** The authors stated a need for research that addressed cystic or neuroendocrine tumours.

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