Contrast-enhanced EUS for differential diagnosis of pancreatic mass lesions: a meta-analysis
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CRD summary
This review concluded that contrast-enhanced endoscopic ultrasound, to identify hypoenhanced lesions, was a promising and reliable way to diagnose pancreatic adenocarcinoma in patients with pancreatic mass lesions. Limitations in the analysis and the methods of the included studies could have overestimated the accuracy and affected the generalisability of the results, and the conclusions seem too strong.

Authors' objectives
To assess the accuracy of contrast-enhanced endoscopic ultrasound, for diagnosing adenocarcinoma, in patients with pancreatic masses, by pooling the data from existing trials.

Searching
PubMed, Web of Science, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched; search terms were reported. References of retrieved articles were searched.

Study selection
Clinical trials investigating the accuracy of contrast-enhanced endoscopic ultrasound for the differential diagnosis of pancreatic solid masses were eligible for inclusion if they used histology or a follow-up period of at least six months as the reference standard. Trials had to report sufficient data to construct 2x2 tables of test performance. Case reports were excluded.

Where reported, for the included studies, the mean age ranged from 56.9 to 67 years, most participants were male, the size of the mass ranged from 3.56 to 42.5mm, and most lesions were in the head of the pancreas. Half of the included studies used Sonovue as the contrast agent, and over half used harmonic as the mode. Hypoenhancement was most commonly used as the diagnostic standard. All the included studies used histology as the reference standard, most with follow-up after six or 12 months.

Two reviewers independently searched for studies, but it was unclear if this included study selection.

Assessment of study quality
Study quality was assessed using the 14-point Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool. The authors did not state how many reviewers assessed quality.

Data extraction
Two reviewers independently extracted the data to produce 2x2 tables of test performance. Sensitivity, specificity, and positive and negative likelihood ratios were calculated. Disagreements were resolved by discussion and study authors were contacted for missing information.

Methods of synthesis
Pooled estimates of sensitivity, specificity, and positive and negative likelihood ratios, with 95% confidence intervals, were calculated, using a Mantel-Haenszel fixed-effect model, where there was no significant heterogeneity, or a DerSimonian and Laird random-effects model, where there was significant heterogeneity. Heterogeneity was assessed using Cochran Q and I², with 25% considered to be significant heterogeneity.

A summary receiver-operating characteristic curve was produced, using the Moses-Shapiro-Littenberg model, and the area under the curve was calculated. Meta-regression was used to investigate the impact of sample size; diagnostic standard; contrast medium, mode, and agents; and country. Subgroup analyses were performed by excluding the outliers. Publication bias was investigated in funnel plots, the Begg-Mazumdar test, and the Harbord-Egger test.
Results of the review

Twelve studies met the inclusion criteria, with 1,139 patients (range 10 to 277). All recruited a representative patient spectrum; used a suitable reference standard; reported on progression bias; avoided partial verification, incorporation and clinical review biases; clearly described the tests used; and blinded to allocation the interpreters of the reference standard. Most studies were open to differential verification bias and did not report blinding to allocation of the interpreters of the index test.

Contrast-enhanced endoscopic ultrasound had a sensitivity of 94% (95% CI 91 to 95; $I^2=0$), a specificity of 89% (95% CI 85 to 92; $I^2=70.2$), a positive likelihood ratio of 8.09 (95% CI 4.47 to 14.64; $I^2=73.2$), a negative likelihood ratio of 0.08 (95% CI 0.06 to 0.10; $I^2=0$), and an area under the curve of 0.9732, for the diagnosis of pancreatic adenocarcinomas.

When outliers were excluded, the sensitivity was 93% (95% CI 91 to 95), the specificity was 93% (95% CI 89 to 95), the area under the curve was 0.9745, and heterogeneity was eliminated. Meta-regression did not detect any relationship between the study characteristics and the diagnostic odds ratio. There was no evidence of publication bias.

Authors’ conclusions

Contrast-enhanced endoscopic ultrasound, to identify hypoenhanced lesions, was a promising and reliable way to diagnose pancreatic adenocarcinoma in patients with pancreatic mass lesions.

CRD commentary

The authors addressed a clear research question. The inclusion criteria for study design were unclear; only clinical trials were eligible, but diagnostic cohort studies were included. Relevant sources were searched. It was unclear whether language restrictions were applied, and there did not appear to be a specific search for unpublished studies, but abstracts were included. Data were extracted in duplicate, but it was unclear whether similar methods were used to reduce error and bias in study selection and quality assessment.

Study quality was assessed using appropriate criteria; the results were summarised and were not considered in the analysis. Differential verification bias and lack of blinding of interpreters of the index test could impact on the reliability of the estimates of diagnostic accuracy. Most of the included studies were small. The pooled estimates of sensitivity and specificity were derived separately, using standard frequentist meta-analysis, from clinically different studies, which might have overestimated the accuracy and affected the generalisability of the pooled results. More robust estimates could be derived from models that maintain the within-study relationship between sensitivity and specificity.

Given the limitations of the review and the included studies, the conclusions seem too strong.

Implications of the review for practice and research

Practice: The authors stated that contrast-enhanced endoscopic ultrasound seemed to be a useful tool for clinical practice.

Research: They did not state any implications for research.

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