
Cyst carcinoembryonic antigen in differentiating pancreatic cysts: a meta-analysis

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CRD summary

The authors concluded that the accuracy of carcinoembryonic antigen in differentiating benign and malignant pancreatic cysts was poor. Given the lack of clarity for reasons for high variation across the included studies, and therefore where the true values for accuracy lay, the authors' conclusion seems overly strong. The recommendations for practice and research seem justified.

Authors' objectives

To evaluate the diagnostic accuracy of cyst fluid carcinoembryonic antigen (CEA) in discriminating benign from malignant pancreatic neoplasms.

Searching

MEDLINE and EMBASE were searched for studies published in English prior to October 2012. Search terms were reported. Reference lists of identified studies and relevant reviews were screened.

Study selection

Eligible studies compared the diagnostic accuracy of cyst fluid CEA with histological diagnosis in differentiating benign from malignant pancreatic neoplasms. Malignant cysts were defined as either high grade dysplasia or invasive cancer. Studies had to provide sufficient data to construct 2x2 tables and had to apply a specific cut-off value of cyst fluid to determine diagnostic accuracy.

Most of the included studies were conducted in the USA followed by France and China. Where reported, there were generally more women than men and mean age ranged from 50 to 67 years. Cut-off values of cyst fluid CEA ranged from 109.9 to 6,000 ng/mL or more.

Two reviewers independently selected the studies for inclusion. Disagreements were resolved by consensus.

Assessment of study quality

Study quality was assessed using the 14-item QUADAS tool.

Two reviewers independently carried out the quality assessment. Disagreements were resolved by consensus.

Data extraction

Data were extracted to construct 2x2 tables of test performance from which sensitivity, specificity, likelihood ratios and diagnostic odds ratios were calculated. Study authors were contacted for additional information and data clarification.

It appeared that two reviewers were involved in the data extraction process.

Methods of synthesis

Pooled estimates of sensitivity, specificity, likelihood ratios, diagnostic odds ratios (DOR) and their 95% confidence intervals were calculated in a random-effects meta-analysis. A summary receiver operating characteristic curve (sROC) was presented and area under curve (AUC) was calculated. Statistical heterogeneity was assessed using Cochran Q and I^2 (where $p < 0.1$ and $I^2 > 50\%$ represented substantial heterogeneity).

A post-hoc analysis was conducted to explore the influence on heterogeneity and summary estimate of studies with overlapping populations. Subgroup analysis was performed to explore the effect on heterogeneity of including only high quality studies (QUADAS score ≥ 11) and for patients with mucinous cysts (mucinous cystic neoplasm and intraductal papillary mucinous neoplasm).

Results of the review

Eight studies were included in the analysis: two were prospective and six retrospective; total sample size appeared to be

523 patients (range 35 to 157). QUADAS scores ranged from 8 to 12 out of 14. Three areas of concern were unclear disease progression bias, whether assessors were blinded to the results of the reference test, and the existence of uninterpretable results.

Pooled sensitivity of cyst fluid CEA level in predicting malignant pancreatic cysts was 63% (95% CI 56% to 70%; $I^2=78%$); pooled specificity was also 63% (95% CI 58% to 69%; $I^2=89%$). The DOR was 3.84 (95% CI 1.37 to 10.75; $I^2=77%$) and the AUC was 0.70.

The post hoc analysis did not materially change the overall results and heterogeneity remained high.

In subgroup analysis including only patients with mucinous cysts, the DOR was 4.74 (95% CI 1.46 to 15.37; five studies). When only higher quality studies were included (QUADAS score ≥ 11), the DOR was 5.15 (95% CI 1.38 to 19.28; five studies) and heterogeneity was reported to remain high.

Sensitivity analysis revealed that type of pancreatic cyst and study quality did not have statistically significant effects on the overall DOR.

Authors' conclusions

The accuracy of carcinoembryonic antigen in differentiating benign and malignant pancreatic cysts was poor.

CRD commentary

The review question was clear and inclusion criteria were adequately specified. The search strategy was limited to two electronic databases which, together with language and publication restrictions, meant that relevant studies may have been missed. The review process included steps to minimise error and bias. Appropriate quality assessment criteria were applied and the full results of this were reported in an online appendix; this showed some areas of potential methodological bias in the included studies. A composite score was used to determine overall study quality with no consideration of the relative importance of individual criteria; it was unclear whether any of the studies blinded interpreters of the reference standard to the index test results (which could lead to an over-estimation of accuracy) and most of the studies were retrospective.

Study details were presented. There appeared to be some discrepancy between tables and text in relation to sample size. The sROC model used in the synthesis was not reported but appeared to be the Moses-Littenberg model, with pooled estimates of sensitivity and specificity produced in separate analyses. The high level of heterogeneity across the studies could impact on the reliability of these summary estimates. More robust sROC models are available that calculate summary estimates of sensitivity and specificity while maintaining the within-study association of these measures.

The authors acknowledged limitations of the review in relation to high heterogeneity and small sample sizes. There was substantial range in both sensitivity and specificity; the reason for this variability was unclear and therefore it was also unclear where on this range the true values of accuracy lay. Given this, the authors' conclusion seems overly strong. The recommendations for practice and research seem justified.

Implications of the review for practice and research

Practice: The authors stated that clinical decision-making, particularly to perform surgery, should not be based solely on carcinoembryonic antigen level and this supports current guidelines which do not recommend cyst fluid CEA to diagnose malignant pancreatic cysts.

Research: The authors stated that large multicentric well-designed trials were needed to characterise the role of cyst fluid tumour marker and molecular analysis in the evaluation of pancreatic cysts.

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