Diagnostic value of pro-gastrin-releasing peptide for small cell lung cancer: a meta-analysis
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CRD summary
This review concluded that pro-gastrin-releasing peptide appeared to be a promisingly consistent and accurate tumour marker for small cell lung cancer. Weaknesses in the meta-analyses, poor sensitivity and a wide range in reported estimates of sensitivity and specificity across studies, mean that these conclusions are not supported by the data.

Authors' objectives
To assess the performance of pro-gastrin-releasing peptide for the diagnosis of small cell lung cancer.

Searching
PubMed, EMBASE, CANCERLIT, The Cochrane Library, CBMdisc and CNKI were searched for studies published in Chinese or English, between January 1994 and April 2010; search terms were reported.

Study selection
Eligible studies measured pro-gastrin-releasing peptide, using commercial reagents, and using pathological diagnosis as the reference standard to confirm small cell lung cancer (case group) and non-small cell lung cancer (control group). Studies had to include more than 20 study samples and report sufficient data to calculate sensitivity and specificity.

Approximately half of the included studies were conducted in Japan or China and half in Europe; one study was conducted in Israel. All but two of the included studies used enzyme-linked immunosorbent assay techniques for pro-gastrin-releasing peptide; the remaining studies used radioimmunooassay and electrochemiluminescent immunoassay. Cut-offs for a positive pro-gastrin-releasing peptide test ranged from 29 to 87ng/L.

Where reported, data were also extracted for neuron specific enolase, an alternative tumour marker for small cell lung cancer. Most neuron specific enolase assays used enzyme-linked immunosorbent assay; two used radioimmunoassay. Cut-off values ranged from 7.5 to 25ng/L.

Retrieved studies were independently screened by two reviewers.

Assessment of study quality
Two reviewers independently assessed study quality using the QUADAS tool.

Data extraction
Data were extracted on the numbers of true positive, false negative, false positive and true negative test results for pro-gastrin-releasing peptide and neuron specific enolase. Sensitivity and specificity values, with 95% confidence intervals (CIs) were calculated for each study and tumour marker.

Two reviewers extracted data; no further details were reported.

Methods of synthesis
Pooled estimates of sensitivity and specificity, with 95% CIs, were calculated using a DerSimonian Laird random-effects model. Between-study heterogeneity was assessed using $X^2$ and quantified using $I^2$. A summary receiver operating characteristic curve was estimated using the Moses and Littenberg model.

Spearman correlation analysis was used to assess threshold effect, and other sources of heterogeneity were investigated using meta-regression.

Results of the review
Eleven studies, with a total of 5,146 participants (1,095 small cell lung cancer patients, 2,260 non-small cell lung cancer patients, 1,214 healthy controls, and 577 benign lung disease) were included in the review. All were case-control studies, six prospective and five retrospective. Most were described as "blind" (no further details reported).
Pro-gastrin-releasing peptide (11 studies): Reported sensitivities ranged from 54% to 100% and specificities ranged from 72% to 99%. The pooled estimate of sensitivity was 71.6% (95% CI 68.8 to 74.3%) and the pooled estimate of specificity was 92.1% (95% CI 90.9 to 93.2%); there was significant between-study heterogeneity in both estimates.

Neuron specific enolase (eight studies): Reported sensitivities ranged from 43% to 81% and specificities ranged from 66% to 93%. The pooled estimate of sensitivity was 60.2% (95% CI 56.3 to 63.9%) and the pooled estimate of specificity was 87.5% (95% CI 85.7 to 89.2%); there was significant between-study heterogeneity in both estimates.

There was evidence of a threshold effect for both pro-gastrin-releasing peptide and neuron specific enolase. The areas under the summary receiver operating characteristic curves were 0.94 and 0.82, respectively. Study size was the only significant variable in the pro-gastrin-releasing peptide meta-regression analysis.

Authors’ conclusions
Pro-gastrin-releasing peptide appeared to be a promisingly consistent and accurate tumour marker for small cell lung cancer, and may prove to be a rapid and less invasive method of diagnosis.

CRD commentary
The review stated a clear research question and defined inclusion criteria. Additional data (on the diagnostic performance of neuron specific enolase), which did not address the stated objective, were included in the article. Several sources were searched for relevant studies but the possibility of language bias remained as only Chinese and English studies were included. Measures to minimise error and/or bias were applied throughout the review process.

The methodological quality of included studies was assessed but results were not fully reported so it was not possible to assess the potential impact of study quality of the results of the review. There was considerable between-study heterogeneity for both pro-gastrin-releasing peptide and neuron specific enolase and both data sets showed evidence of threshold effect; the generation of pooled estimates of sensitivity and specificity using a random-effects model was of questionable value. The pooled estimates of sensitivity were poor and this, combined with the wide range of sensitivity and specificity estimates across studies and high degree of inconsistency, meant that the authors conclusions were not supported by the data.

Implications of the review for practice and research
Practice: The authors stated that it was advantageous to combine multiple tumour markers, such as pro-gastrin-releasing peptide and neuron specific enolase, for the diagnosis of small cell lung cancer. They further stated that the reference standard (pathology) may be more useful to confirm diagnosis in patients with advanced tumours, or to determine histological type.

Research: The authors did not specify any recommendations for future research.

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