Assessment of response to neoadjuvant therapy in esophageal cancer: an updated systematic review of diagnostic accuracy of endoscopic ultrasonography and fluorodeoxyglucose positron emission tomography

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CRD summary
This review concluded that endoscopic ultrasonography and fluorodeoxyglucose positron emission tomography (FDG-PET) had the same accuracy for assessing patient response to oesophageal cancer neoadjuvant therapy; the timing of FDG-PET (before/after completion of therapy) did not affect accuracy. These conclusions reflect the data, but should be interpreted cautiously due to varied studies included and limitations in the search strategy and analysis.

Authors' objectives
To compare the diagnostic performance of endoscopic ultrasonography and fluorodeoxyglucose positron emission tomography (FDG-PET) in reassessing the response of patients with oesophageal cancer to neoadjuvant therapy.

Searching
MEDLINE, EMBASE, and the Cochrane Library were searched (January 1980 to February 2008); search terms were reported. Bibliographies of included studies and review articles were screened for additional studies. Only studies published in full and in English were included.

Study selection
Studies that used endoscopic ultrasonography and fluorodeoxyglucose positron emission tomography (FDG-PET) to assess the response to neoadjuvant therapy with histopathologically confirmed cancer of the oesophagus were eligible for inclusion. Included studies were required to use pathological findings as the reference standard, include at least 10 patients, and report sufficient information to construct 2x2 contingency tables (numbers of true positive, false negative, false positive, and true negative test results) on a per-patient basis. Authors were contacted for clarification of information about inclusion criteria where necessary.

In the included studies, the age of participants ranged from 29 to 84 years; most had adenocarcinoma or squamous cell carcinoma. Most included studies assessed tumour response using FDG-PET standardized uptake value or maximal cross-sectional area; a variety of definitions of response were reported. Pathological response was mostly defined using the criteria of Mandard et al 1994.

Two reviewers independently assessed studies for inclusion; any disagreements were resolved by consensus.

Assessment of study quality
The methodological quality of included studies was independently assessed by two reviewers using the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) tool.

Data extraction
Two reviewers independently extracted the numbers of patients who responded to treatment, based on the results of endoscopic ultrasonography and fluorodeoxyglucose positron emission tomography. The final outcomes (response or non-response) confirmed by histopathologic findings were also extracted. The data were used to construct 2x2 tables. Values of zero in the 2 x 2 tables were adjusted by adding 0.5 to all cells. Sensitivity and specificity, with 95% confidence intervals (CIs), were calculated from the extracted 2x2 data.

Methods of synthesis
Summary receiver-operating characteristic curves were constructed for each imaging modality, using the Moses and Littenberg model; the area under the summary receiver-operating characteristic curve (AUC) and $Q^*$ index (that summarized maximum test performance where sensitivity and specificity were equal) were also calculated. Differences in AUC and $Q^*$ index between imaging modalities were assessed using the z-test.
Between study heterogeneity was explored using an inverse variance weighted meta-regression analysis, which included the following covariates: publication year (before 2000 versus after 2000); number of patients (under 50 patients versus 50 patients or more); method of data collection (prospective versus retrospective), and geographic origin of the study (e.g. USA versus other countries).

Subgroup analyses were also conducted for endoscopic ultrasonography subgroup analysis compared methods of assessment (restaging versus tumor size measurement), and for fluorodeoxyglucose positron emission tomography subgroup analyses compared timing of test (during the course of therapy versus after completion) and type of scanning (positron emission tomography only machine versus integrated positron emission tomography/computed tomography).

**Results of the review**

Nineteen studies (n=966 patients) were include in the review. Seven studies assessed endoscopic ultrasonography, 15 studies assessed fluorodeoxyglucose positron emission tomography (FDG-PET), and three studies assessed both imaging modalities. All studies met at least 10 of the 14 QUADAS criteria. Most studies (17) did not report uninterpretable/intermediate test results. Partial verification bias could not be excluded for eight studies. Interpretation of reference standard blind to index test results was absent or unclear in 13 studies. Participant selection criteria were unclear for 11 studies.

The diagnostic sensitivity of endoscopic ultrasonography ranged from 20 to 100%; the sensitivity of FDG-PET ranged from 42 to 100%. The specificity of endoscopic ultrasonography ranged from 36 to 100%; the specificity of FDG-PET ranged from 27% to 100%. The overall accuracy, as indicated by area under the summary receiver-operating characteristic curve, was similar for the two modalities (endoscopic ultrasonography 0.86, 95% CI 0.77 to 0.96; FDG-PET 0.80, 95% CI 0.72 to 0.89); Q* index values were also similar.

There were no significant differences in test performance for any of the subgroup analyses. Multi-variate regression modelling indicated that prospective studies gave higher diagnostic accuracy than retrospective studies (relative diagnostic odds ratio 8.51, 95% CI 1.2 to 60.2); no other co-variate was significant.

**Authors' conclusions**

There was no difference in accuracy for between early fluorodeoxyglucose positron emission tomography and fluorodeoxyglucose positron emission tomography after completion of neoadjuvant therapy. Endoscopic ultrasonography and fluorodeoxyglucose positron emission tomography have similar overall diagnostic accuracy for assessment of response to neoadjuvant therapy in patients with oesophageal cancer.

**CRD commentary**

The review provided a clear research objective and defined appropriate inclusion criteria. A number of sources were searched for relevant studies, although the restriction to published English language studies raised the possibility of language and publication biases. Measures to minimise error and/or bias were applied throughout the review process.

The methodological quality of included studies was assessed using an appropriate tool, with full results reported in an appendix. The use of an summary receiver-operating characteristic curve analysis, rather than pooling of sensitivity and specificity estimates, was appropriate given the apparent heterogeneity in definitions of 'response' used by included studies. However, bivariate or hierarchical summary receiver-operating characteristic curve models are generally recommended over the Moses and Littenberg model and may have been preferable as they would facilitate comparison of sensitivity and specificity between imaging modalities rather than limiting the comparison to measures of overall accuracy.

The authors conclusions reflect the data presented, but should be interpreted cautiously given the apparent heterogeneity of the included studies and some limitations in the search strategy and analysis.

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

**Practice:** The authors stated that endoscopic ultrasonography and FDG-PET have similar overall diagnostic accuracy for
assessment of response to neoadjuvant therapy in patients with oesophageal cancer. Therefore, as these imaging
techniques have different advantages and limitations, they should be considered as complimentary methods. The
performance of early FDG-PET assessment is comparable with FDG-PET after completion of neoadjuvant therapy, so
early assessment may aid early identification patients not responding to treatment and avoid unnecessary continuation
of the toxicity of chemoradiotherapeutic treatment.

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

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