INPLASY PROTOCOL

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None declared.

Liquid biopsy in oesophageal cancer: a systematic review of blood biomarkers for early diagnosis

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Review question / Objective: **The authors are undertaking this systematic review to outline the developing blood biomarkers that have been described in the literature. What are the potential blood biomarkers that have been described with diagnostic potential?**
Condition being studied: **Oesophageal cancer (squamous cell carcinoma and adenocarcinoma). Oesophagogastric junction cancers are included.**
Eligibility criteria: **Included are any studies describing a blood test that shows possible discrimination between cancer and non-cancer patients. Primary studies included and meta-analysis, however reviews were not included (though references were searched to extract relevant primary papers). Excluded are animal model studies, rarer histological types. biomarkers utilised to prognosticate outcomes of therapy were excluded, as were markers of recurrence and "Pan-cancer" biomarkers.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 06 July 2022 and was last updated on 06 July 2022 (registration number INPLASY202270029).

INTRODUCTION

Review question / Objective: **The authors are undertaking this systematic review to outline the developing blood biomarkers that have been described in the literature. What are the potential blood biomarkers that have been described with diagnostic potential?**

Rationale: **The discovery and validation of blood biomarkers with a role in the diagnosis of oesophageal cancer may provide advantages of rapid, cost-effective testing and repeat evaluation and may**

facilitate non-invasive screening programmes with aim of reducing morbidity and mortality through earlier diagnosis. However, there is no such blood biomarker currently in clinical use. What are the potential markers described in the literature? We aim to summarise what has been previously described to guide further work on liquid biopsy and consider why none have come into clinical practice.

Condition being studied: Oesophageal cancer (squamous cell carcinoma and adenocarcinoma). Oesophagogastric junction cancers are included.

METHODS

Search strategy: A systematic search conducted on EMBASE (1974-), Medline (1947-), and Web of Science (1980-) from inception to 3rd November 2021. Exploded subject headings and combinations of keywords used. Search terms used: [oesophageal cancer or oesophageal ca or oesophageal malignancy or oesophageal neoplasm or Barrett's oesophagus or Barrett's metaplasia] AND [Tumour biomarkers or tumour markers or biological marker] AND [diagnosis or early diagnosis or screening or detection or discrimination] AND [adenocarcinoma or squamous cell carcinoma] AND [blood or serum or plasma] AND [esophagus or oesophagus].

Participant or population: Patients with adenocarcinoma or squamous cell carcinoma of the oesophagus, or oesophagogastric junction carcinoma.

Intervention: Blood tests that may discriminate between cancer and no cancer.

Comparator: N/A.

Study designs to be included: Papers describing blood biomarkers that hold potential in screening and diagnosing oesophageal cancer are included.

Eligibility criteria: Included are any studies describing a blood test that shows possible discrimination between cancer and non-cancer patients. Primary studies included and meta-analysis, however reviews were not included (though references were searched to extract relevant primary papers). Excluded are animal model studies, rarer histological types. biomarkers utilised to prognosticate outcomes of therapy were excluded, as were markers of recurrence and "Pan-cancer" biomarkers.

Information sources: Electronic databases (EMBASE, Medline, and Web of Science), manual search of reference lists.

Main outcome(s): Elevated/reduced or upregulated/downregulated levels of blood marker, sensitivity and specificity, positive predictive value/negative predictive value, area under receiver operating curve, and cut-off value.

Data management: Rayyan to facilitate screening of abstracts and full text review. Data extracted onto Excel sheet and biomarkers classified.

Quality assessment / Risk of bias analysis: Quality Assessment of Diagnostic Accuracy Study 2 (QUADAS-2) will be used to assess risk of bias and clinical applicability of primary diagnostic accuracy studies.

Strategy of data synthesis: Data will be extracted onto an Excel sheet, and will be summarised using descriptive statistics. Meta-analysis of the data is not anticipated. Studies will be summarised in tables, with author, country and year of publication. Biomarkers will be classified and grouped together into related markers (ie, microRNAs, classic tumour markers etc). Relevant diagnostic accuracy data will also be summarised in tables via spreadsheet.

Subgroup analysis: Data on diagnostic accuracy will also be divided between histological types where applicable.

Sensitivity analysis: No planned meta-analysis.

Country(ies) involved: UK.

Keywords: Oesophageal cancer; adenocarcinoma; squamous cell carcinoma; oesophagus; esophagus; liquid biospy; screening; diagnosis; blood; biomarker.

Dissemination plans: Presentation at conference and publication are planned on completion of review.

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