



Review

Prognostic and predictive factors for overall survival in metastatic oesophagogastric cancer: A systematic review and meta-analysis



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Abstract Background: Consistent evidence on prognostic and predictive factors for advanced oesophagogastric cancer is lacking. Therefore, we performed a systematic review and meta-analysis.

Methods: We searched PubMed, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) databases for phase II/III randomised controlled trials (RCTs) until February 2017 on palliative systemic therapy for advanced oesophagogastric cancer that reported prognostic or predictive factors for overall survival (PROSPERO-CRD42014015177). Prognostic factors were identified from multivariate regression analyses in study reports. Factors were considered potentially clinically relevant if statistically significant ($P \leq 0.05$) in multivariate analysis in $\geq 50\%$ of the total number of patients in the pooled sample of the RCTs and were reported with a pooled sample size of ≥ 600 patients in the first-line or ≥ 300 patients in the beyond first-line setting. Predictive factors were identified from time-to-event stratified treatment comparisons and deemed potentially clinically relevant if the P-value for interaction between subgroups was ≤ 0.20 and the hazard ratio in one of the subgroups was significant ($P \leq 0.05$).

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Results: Forty-six original RCTs were included (n = 15,392 patients) reporting on first-line (n = 33) and beyond first-line therapy (n = 13). Seventeen prognostic factors for overall survival in the first-line and four in the beyond first-line treatment setting were potentially clinically relevant. Twenty-one predictive factors in first-line and nine in beyond first-line treatment setting were potentially relevant regarding treatment efficacy.

Conclusions: The prognostic and predictive factors identified in this systematic review can be used to characterise patients in clinical practice, be included in future trial designs, enrich prognostic tools and generate hypotheses to be tested in future research to promote patient-centred treatment.

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Research in context

Evidence before this study

Prognostic and predictive factors are important for estimation of prognosis, clinical decision making and trial design, and are key in a transition towards more personalised medicine. A variety of factors have been described in past trials on palliative treatment of oesophagogastric cancer, and available prognostic indexes use different sets of factors which are based on relatively small numbers of patients. Of predictive factors only HER-2 status is currently used in clinical practice. We therefore searched PubMed, EMBASE, and CENTRAL for phase II/III randomised controlled trials (RCTs) until February 2017 on palliative systemic therapy for advanced oesophagogastric cancer that reported prognostic or predictive factors for overall survival. Forty-six original RCTs were included, of which 33 were rated as having a low risk of bias. Adopting self-defined criteria for potential clinical relevance we identified 17 prognostic factors for first-line and four potential factors for beyond first-line palliative treatment, as well as 21 predictive factors for first-line and nine predictive factors for beyond first-line palliative treatment.

Added value of this study

In this systematic review we are the first to identify all prognostic and predictive factors that have been reported as statistically significant in previous RCTs. This review therefore reports more robust evidence on prognostic and predictive factors in the palliative treatment of advanced oesophagogastric cancer.

Implications of all the available evidence

Prognostic factors identified in this review can be used to better characterise patients in clinical practice, guide the development of better prognostic models, and be used in future trial design as stratification factors or to be included in regression analyses. The predictive factors we identified can generate hypotheses to be tested in future trials, and can in combination with prognostic factors eventually be used for more personalised medicine.

1. Introduction

Survival of patients with metastatic oesophagogastric cancer varies greatly among patient subpopulations [1]. There is no international consensus on standard first-line palliative treatment, but regimens usually consist of a fluoropyrimidine (e.g., 5-fluorouracil, capecitabine, S-1) and a platinum compound (e.g., cisplatin, oxaliplatin) [2–4]. Recently, targeted therapies such as monoclonal antibodies and tyrosine kinase inhibitors have been added as treatment options in both first- and beyond first-line treatment [2–4].

Identifying which patients have a dismal prognosis and which treatments they are most likely to benefit from would enable personalised treatment strategies and improve survival. Prognostic and predictive factors are key in this process. Prognostic factors are patient and tumour characteristics that can be used to estimate the prognosis of a patient, independent of a specific treatment regimen. Cohort studies or, preferably, well-conducted randomised controlled trials (RCTs) are suitable for evaluating the prognostic relevance of such patient and tumour characteristics [5]. In contrast, predictive factors indicate which patient (sub)populations may benefit more from a certain treatment over others [6]. Predictive factors, therefore, imply a differential treatment benefit that depends on the absence or presence of a particular patient or tumour characteristic. Predictive factors can be evaluated with stratified analyses in an RCT including a control group [5]. If there is evidence that a certain factor may have predictive value for the efficacy of the experimental intervention over the control treatment, the next step may be to repeat the RCT but with a selected patient group.

The tumour-node-metastasis (TNM) classification is an established combination of prognostic factors, which uses the following tumour characteristics: tumour size and invasion of surrounding structures, lymph node metastases and distant metastases [7]. Besides the TNM classification, other prognostic factors such as the performance status and peritoneal metastasis are also

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