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Preoperative chemo(radio)therapy versus primary surgery for gastroesophageal adenocarcinoma: Systematic review with meta-analysis combining individual patient and aggregate data ☆

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Abstract ***Background:*** The prognosis of patients with gastroesophageal adenocarcinoma is poor. There is conflicting evidence regarding effects of preoperative chemotherapy on survival and other outcomes.
Methods: We conducted a meta-analysis with aggregate and individual patient data (IPD) to assess the effect of preoperative chemotherapy for gastroesophageal adenocarcinoma on survival and other outcomes. Two independent reviewers identified eligible randomised controlled trials (RCTs) comparing chemotherapy+/–radiotherapy followed by surgery with

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surgery alone for gastroesophageal adenocarcinoma. IPD was solicited from all trials. Meta-analyses were performed using the two stage method.

Results: We identified 14 RCTs (2422 patients). For eight RCTs (1049 patients; 43.3%) we obtained IPD. Preoperative chemotherapy was associated with longer overall survival (hazard ratio [HR] 0.81; 95% confidence interval [CI] 0.73–0.89; $p < 0.0001$). There were larger treatment effects in tumours of the gastroesophageal junction and for chemoradiotherapy compared to chemotherapy, but the tests for subgroup differences were not statistically significant. Preoperative chemotherapy was associated with longer disease-free survival, higher likelihood of R0 resection and more favourable post-treatment tumour stage, but not perioperative complications.

Conclusion: Preoperative chemotherapy for locoregional gastroesophageal adenocarcinoma increases survival compared to surgery alone. It should be offered to all eligible patients. There appear to be larger survival advantages in tumours of the gastroesophageal junction and for chemoradiotherapy, but these findings require prospective confirmation.

1. Introduction

Adenocarcinoma of the stomach, gastroesophageal junction and oesophagus ('gastroesophageal adenocarcinoma') ranks among the most common cancers.[1–4] Radical surgery is the most effective curative treatment modality. Despite improved surgical techniques and perioperative management,[1,4] five-year survival after resection is only 20–30% in patients with locoregionally advanced disease.[5,6] These poor survival rates provide a strong rationale for the design of new treatment modalities. Preoperative chemotherapy, defined as chemotherapy before and, optionally, after surgery, has been tested in randomised controlled trials (RCTs).[7–20] Results have been conflicting and inconclusive.

Systematic reviews and meta-analyses to date, that have summarised the evidence have either combined oesophageal squamous cell carcinoma and adenocarcinoma or failed to include all three tumour sites of GE adenocarcinoma.[21–24] Moreover, the analyses have been based on aggregate data, limiting their ability to sufficiently assess which patient and tumour characteristics might alter the treatment effect of preoperative chemotherapy. Therefore, we performed a new systematic comparison, based largely on individual patient data, of preoperative chemotherapy versus surgery alone for patients with locoregional resectable adenocarcinoma of the stomach, gastroesophageal junction and oesophagus.

2. Methods

The study was carried out according to Cochrane methodology and the previously published protocol.[25] The full publication in the Cochrane Library provides a more detailed description of the methods.[26]

2.1. Inclusion criteria

We included RCTs in which patients fulfilled the following criteria: adenocarcinoma of the stomach, gastroesophageal junction or oesophagus (for trials including other histologies we sought to obtain data for patients with adenocarcinoma only); no previous treatment; resectable and not metastasised. We included all trials comparing surgery alone with surgery combined with preoperative chemotherapy. To be regarded as preoperative, chemotherapy needed to be administered before, and, optionally, after surgery. We also included trials in which patients received chemoradiotherapy.

2.2. Outcome measures

The primary outcome was time to death from the date of randomisation, based on intention-to-treat analysis. Secondary outcomes were disease-free survival, defined as time from a landmark 6 months after randomisation until recurrence or death; tumour-free resection margin; tumour stage at resection according to the Union for International Cancer Control (UICC) tumor node metastasis (TNM) classification of malignant tumours[27]; perioperative morbidity and mortality; and frequency of non-administration of postoperatively planned chemotherapy for trials in which it was prescribed in the study protocol.

2.3. Identification of studies

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Review of Effectiveness (DARE), Cochrane Database of Systematic Reviews (CDSR), Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (EMBASE) and Literatura Latinoamericana y del Caribe en Ciencias de la Salud (LILACS). There were no language restrictions. We combined the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE[28] with pre-specified search terms. Moreover, we searched online databases and conference proceedings. We included data from published full articles until closure