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Review

Survival benefit and additional value of preoperative chemoradiotherapy in resectable gastric and gastro-oesophageal junction cancer: A direct and adjusted indirect comparison meta-analysis

K. Kumagai [a,*], I. Rouvelas [a], J.A. Tsai [a], D. Mariosa [b], P.A. Lind [c,d], M. Lindblad [a], W. Ye [b], L. Lundell [a], C. Schuhmacher [e], M. Mauer [f], B.H. Burmeister [g], J.M. Thomas [g], M. Stahl [h], M. Nilsson [a]

[a] *Center for Digestive Diseases, Karolinska University Hospital, Stockholm, Sweden*
[b] *Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden*
[c] *Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden*
[d] *Centre for Clinical Research Sörmland, Uppsala University, Uppsala, Sweden*
[e] *Department of Surgery, Klinikum rechts der Isar der Technischen Universitaet Muenchen, Muenchen, Germany*
[f] *EORTC Headquaters, Statistic Department, Brussels, Belgium*
[g] *Division of Cancer Services, University of Queensland, Princess Alexandra Hospital, Queensland, Australia*
[h] *Department of Medical Oncology and Hematology, Kliniken Essen-Mitte, Essen, Germany*

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Abstract

Several phase I/II studies of chemoradiotherapy for gastric cancer have reported promising results, but the significance of preoperative radiotherapy in addition to chemotherapy has not been proven. In this study, a systematic literature search was performed to capture survival and postoperative morbidity and mortality data in randomised clinical studies comparing preoperative (chemo)radiotherapy or chemotherapy versus surgery alone, or preoperative chemoradiotherapy versus chemotherapy for gastric and/or gastro-oesophageal junction (GOJ) cancer. Hazard ratios (HRs) for overall mortality were extracted from the original studies, individual patient data provided from the principal investigators of eligible studies or the earlier published meta-analysis. The incidences of postoperative morbidities and mortalities were also analysed. In total 18 studies were eligible and data were available from 14 of these. The meta-analysis on overall survival yielded HRs of 0.75 (95% CI 0.65–0.86, $P < 0.001$) for preoperative (chemo)radiotherapy and 0.83 (95% CI 0.67–1.01, $P = 0.065$) for preoperative chemotherapy when compared to surgery alone. Direct comparison between preoperative chemoradiotherapy and chemotherapy resulted in an HR of 0.71 (95% CI 0.45–1.12, $P = 0.146$). Combination of direct and adjusted indirect comparisons yielded an HR of 0.86 (95% CI 0.69–1.07, $P = 0.171$). No statistically significant differences were seen in the risk for postoperative morbidity or mortality between preoperative treatments and surgery alone, or preoperative (chemo)radiotherapy and chemotherapy. Preoperative (chemo)radiotherapy for gastric and GOJ cancer showed significant survival benefit over surgery alone. In comparisons between preoperative chemotherapy and (chemo)radiotherapy, there is a trend towards improved survival when adding radiotherapy, without increased postoperative morbidity or mortality.

Keywords: Stomach; Gastro-oesophageal junction; Adenocarcinoma; Preoperative chemotherapy; Preoperative chemoradiotherapy

* Corresponding author. Center for Digestive Diseases, K53, Karolinska University Hospital, 141 86 Stockholm, Sweden. Tel.: +46 8 58580000; fax: +46 8 58582340.
E-mail address: koshi.kumagai@gmail.com (K. Kumagai).

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Introduction

In Western countries, about two thirds of patients with gastric cancer have locally advanced disease at diagnosis and inevitably the R0 resection rate and prognosis after surgery alone are miserable in this clinical setting.[1]

In many new cases of gastric cancer, adequate locoregional and systemic disease control is difficult to obtain with resection alone, therefore surgery is frequently combined with preoperative cytoreductive treatment in contemporary clinical practice. A previous meta-analysis comparing the long-term survival between preoperative chemotherapy with or without radiotherapy and surgery alone in patients with adenocarcinoma of the stomach, gastro-oesophageal junction (GOJ) or lower oesophagus suggested a survival benefit of preoperative chemotherapy.[2] In this context, it should be noted that a corresponding survival benefit of preoperative radiotherapy alone has been alleged in a previous meta-analysis.[3]

Several phase I/II studies have presented promising results from the combination of preoperative chemotherapy and radiotherapy in patients with potentially resectable gastric cancer.[4–6] Given the established validity of chemoradiotherapy for gastric cancer, the significance of preoperative radiotherapy as an adjunct to chemotherapy in patients with potentially resectable gastric cancer warrants better scientific validation. To date, however, the sole direct randomised comparison between preoperative chemoradiotherapy versus chemotherapy alone focused on patients with GOJ cancer has been reported by Stahl et al.[7] This study showed a significantly higher pathologic complete response rate and a tendency toward an improved 3-year survival rate by the addition of radiotherapy.

Evidence from comparative head to head (direct) trials is often limited or unavailable, why indirect comparisons are mandated.[8] This is particularly the case with chemoradio- and chemotherapy when used preoperatively. A simple but inappropriate statistical method for indirect comparison is to compare the results of individual arms from different trials as if they were from the same randomised trial. This naive type of indirect comparison has been criticised for discarding the within trial comparison, and thereby increasing the liability to bias. In contrast, the adjusted indirect comparison can take advantage of the strength of randomised clinical trials in making unbiased comparisons. In the present study, the indirect comparison of different interventions is adjusted by comparing the results of their direct comparisons with a common control group.[8]

The objectives of the current study were threefold: firstly, to perform a careful literature survey to assess the feasibility of performing a meta-analysis concerning outcome after preoperative treatment added to surgery compared to surgery alone in patients with gastric cancer including GOJ adenocarcinoma. Secondly, we wanted to analyse the compiled database with regard to the main outcomes of interest: postoperative morbidity, perioperative mortality and long-term survival for preoperative chemotherapy and chemoradiotherapy, separately. Finally, we aimed to clarify the differences in endpoints mentioned above between preoperative chemotherapy and chemoradiotherapy by direct and adjusted indirect comparison analyses.

Patients and methods

Eligibility criteria

Eligible studies were randomised clinical trials in which patients fulfilled the following criteria: adenocarcinoma of the stomach and/or GOJ; no previous treatment; tumours clinically diagnosed as resectable. Trials comparing preoperative chemotherapy plus surgery with surgery alone, preoperative radiotherapy with or without chemotherapy [(chemo)radiotherapy] plus surgery with surgery alone, and preoperative chemoradiotherapy plus surgery with chemotherapy plus surgery were included. To be regarded as preoperative, chemotherapy had to be administered before surgery, but trials on perioperative therapy were also included. Articles for which the full text was not available in English were excluded.

Outcome measures

The primary outcome was overall survival defined as time from the date of randomisation until death. Secondary outcomes were progression free survival, defined as time from randomisation until tumour progression or death, postoperative morbidity and perioperative mortality.

Information sources, search, and study selection

Eligible trials were identified from earlier published meta-analyses and systematic electronic search. MEDLINE, Central (Cochrane clinical trials database) and EMBASE database were explored for studies published up to July 2013 using the following terms and search formula: (stomach OR oesophagus) AND cancer AND preoperative. The searches were limited to articles on randomised clinical trials and published in English. Furthermore, potentially relevant articles were identified by manually searching reference lists of all articles retrieved. Jadad's score was used to assess the risk of bias of individual studies.[9]

Individual patient data

For eligible studies, individual patient data (IPD) were solicited from the principal investigators of each study. Survival data were requested for the intention-to-treat population recruited from each trial. The investigators were asked to provide the most complete and updated follow-up data, even if the follow-up was longer than that used in the