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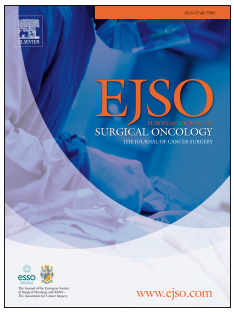

Survival benefit and additional value of preoperative chemoradiotherapy in resectable gastric and gastro-oesophageal junction cancer: A direct and adjusted indirect comparison meta-analysis

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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 a HR of 0.71 (95% CI 0.45–1.12, $P=0.146$). Combination of direct and adjusted indirect comparisons yielded a 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.

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 criticized 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 analyze 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 esophagus) 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 respective publication. Data not available upon database closure, either because IPD had not been provided or because full manuscripts had not been published, were not included in the final meta-analysis.

Data collection processes and clinical endpoint

Data were extracted by the first author (KK). Any discrepancies were dealt with by discussion among the authors and a consensus was reached. The following general information was extracted from each study: first author, year of publication, the number of patients who were randomised, and those who received surgery. Hazard ratios (HRs) for overall mortality were extracted as the summary statistic directly from the original studies or provided IPD. If they were not available, HRs were estimated indirectly by either using the number of randomised patients, the number of events occurred during observation period and *P* values for the log-rank test or, if no other information was available, by reading off survival curves as suggested by Parmar et al.[10] The 95% confidence interval (CI) for each HR was extracted directly from the original report or from IPD if available. Otherwise these variables were estimated indirectly by using the information available; e.g. data from earlier published meta-analyses. Risk ratios (RRs) for postoperative morbidity and mortality were also extracted directly from the original studies or provided IPD. In the analyses of morbidity rate, the incidences of the following postoperative complications were extracted: any complication, cardiac complication, respiratory complication, anastomotic leakage, and pancreatitis/pancreatic

fistula. Respiratory complications included pneumonia, acute respiratory distress syndrome (ARDS), pulmonary embolism, and respiratory failure. Diagnosis of postoperative pancreatic fistula was based on the International Study Group of Pancreatic Fistula (ISGPF) definition.[11] However, cases where the pancreatic fistula was diagnosed solely on clinical grounds by the primary investigators were also included. The following mortality related information was extracted: 30-day postoperative mortality and total postoperative mortality and treatment-related mortality. Total postoperative mortality was defined as any in-hospital death or any post-discharge death that could be related to a postoperative complication. Treatment-related mortality was defined as the sum of total postoperative mortality and death before surgery caused by adverse side effects of neoadjuvant treatment.

Statistical analysis

The meta-analysis was performed according to the recommendations specified in the PRISMA guidelines using STATA ver. 11.2 (StataCorp, Texas, USA).[12] Statistical analysis was carried out using the HR for survival analyses and the RR for postoperative morbidity and mortality as the summary statistics. Random-effects models were used to estimate the summary statistics and confidence intervals because

preoperative treatment regimens and surgical procedures used in the trials were heterogenic and thus heterogeneity of the effect across different regimens could not be excluded a priori. Locational subgroup analysis was performed and no other subgroups were examined. Higgins' I squared was the statistic used to test for heterogeneity, and the inverse of variance method was selected to combine results and calculate the heterogeneity among subgroups. The pooled HRs and RRs were reported with 95 per cent confidence intervals (CIs). In the analysis comparing preoperative therapy plus surgery with surgery alone, the HRs represented the relative risk of overall mortality and RRs represented the relative risk of postoperative morbidities and mortalities when preoperative chemoradiotherapy or chemotherapy was followed by surgery compared with surgery alone. A summary statistic (HR or RR) greater than 1 indicated a higher overall mortality or postoperative morbidity/mortality rate in patients who received preoperative treatments and the point estimate of the HR or RR was considered statistically significant at a 95% confidence level if the 95% CI did not include 1.

In the direct comparison analysis between preoperative chemoradiotherapy plus surgery and preoperative chemotherapy plus surgery, HRs represented the relative risk of overall mortality and RRs represented the relative risk of postoperative morbidities and mortalities for a patient who received preoperative chemoradiotherapy followed by

surgery compared with a patient who received preoperative chemotherapy followed by surgery. A summary statistic (HR or RR) greater than 1 indicated a higher overall mortality or postoperative morbidity/mortality rate in patients who received preoperative chemoradiotherapy and the point estimate of the HR or RR was considered significant at a 95% confidence level if the 95% CI did not include 1. An adjusted indirect comparison method was applied for indirect comparison of preoperative chemoradiotherapy plus surgery and preoperative chemotherapy plus surgery using a common control group (surgery alone). The results from adjusted indirect comparisons were combined with the results from direct comparison of preoperative chemoradiotherapy plus surgery versus preoperative chemotherapy plus surgery. A weighted combination ($_c$) of the results from adjusted indirect comparison ($_i$) and the direct comparison ($_d$) was computed as an inverse variance weighted average. The weighted average and variance (Var) of the combination were calculated as:

$$Weight_i=1 / Var(lnHR_i),\ Weight_d=1 / Var(lnHR_d)$$

$$lnHR_c=(Weight_i * lnHR_i + Weight_d * lnHR_d) / (Weight_i + Weight_d)$$

$$Var(lnHR_c)=1 / (Weight_i + Weight_d)$$

To examine the consistency between the adjusted indirect comparison and the direct comparison, the discrepancy between the adjusted indirect comparison and the

direct comparison was evaluated by dividing the difference in the lnHR ($lnHR_i$ - $lnHR_d$) by the standard error of the difference ($\sqrt{[Var(lnHR_i) + Var(lnHR_d)]}$), and comparing the resulting number with a standard normal distribution to obtain a *P*-value.[13]

Funnel plots were used to assess publication bias, where asymmetry implied that results were subject to reporting or publication bias. Begg's test was also used to assess the bias, where an absolute z value over 1.96 implied that results were significantly subject to bias.[14]

Results

Study selection

In total 18 studies[7,15-31] were eligible (Fig 1). Eight were randomised comparisons of preoperative (chemo)radiotherapy versus surgery alone[21-27,30], 8 were randomised comparisons of preoperative chemotherapy versus surgery alone [15,17-20,28,29,31], and 2 were randomised comparisons of preoperative chemoradiotherapy versus preoperative chemotherapy.[7,16] One study was a 3-arm study that compared preoperative chemotherapy using oral 5'-DFUR versus preoperative chemotherapy using intravenous 5-FU plus cisplatin versus surgery alone.[31] This study was treated as a 2-arm study that compared preoperative chemotherapy versus surgery alone and the patients in two groups of preoperative chemotherapy were combined. In three studies, patients in the preoperative chemotherapy group received postoperative chemotherapy if they were fit.[17,19,29] One study included intraoperative radiotherapy in addition to preoperative radiotherapy.[23]

Individual patient data (IPD)

Requests for IPD were sent to the corresponding authors of primary investigators of all 18 eligible studies by either air mail or email on October 3, 2013 and

data analyses were started on February 6, 2014. Seven authors gave replies by the time analyses started. [7,16-18,20,24,26] IPD were provided by two authors[16,20] and complementary data were provided by one author.[7] The numbers of patients contained in IPD data sets were identical with the intention-to-treat population reported in the publications. Any extreme and implausible outliers were not identified in the provided IPD.

Risk of bias within studies

All studies were randomised clinical trials. The randomisation method used was specified in 14 out of 18 trials.[7,15-19,21-26,29,30] Seven studies applied stratification for some factors.[7,17-19,24,25,29] The minimisation method was used in three[15,17,29] and the block randomisation was used in three.[16,18,26] Blinding patients and clinicians to interventions was not evaluated because it was not possible given the design of the trials. No dropouts were observed in 3 trials[21,28,30] and detailed information of dropouts was available in 14 trials.[7,15-20,22-27,29] Average Jadad's score, based on only three evaluation items (randomisation, description and adequacy of randomisation method, and dropouts), was 2.5.

Surgical procedures

The details of the surgical procedures were mentioned in 11 trials. [7,16,17,19-23,27,29,31] Gastrectomy was the most common surgical procedure in 6 trials. [17,20-23,31] In the other 5 trials oesophagectomy was the most common procedure in their original report.[7,16,19,27,29] The extent of lymphadenectomy was described in 8 trials. [7,16-18,20,22,23,29] D2 and D1 lymphadenectomy was mostly performed in 4[7,17,20,29] and in 3 [18,22,23] trials, respectively. Oesophagectomy with the dissection of the lymph nodes in the lower mediastinum, at the origin of the left gastric artery and the splenic artery to the hilum of the spleen was performed in one trial.[16] Survival data or postoperative morbidity and mortality for each surgical procedure or lymphadenectomy were not separately reported in any of the trials.

Overall survival

Overall survival was reported in all 18 trials, while 4 trials among them were excluded from the meta-analysis because they included oesophageal cancer patients without any possibility to extract tumour site specific results from the original reports and IPDs were not provided.[15,24-26] Therefore the meta-analysis was performed with 14 trials [7,16-23,27-31] (Fig.1, Table 1). This was also true of the following meta-analysis on progression free survival, morbidity, and mortality. In 5 trials data were obtained from

earlier published meta-analyses by Ronellenfitsch, which was performed by combining IPD and aggregate data.[2,17,19,27,29,31] The current meta-analysis yielded a pooled HR of 0.75 (95% CI 0.65–0.86, *P*<0.001) for preoperative (chemo)radiotherapy compared to surgery alone (Fig. 2a) and a HR of 0.83 (95% CI 0.67-1.01, *P*=0.065) for preoperative chemotherapy compared to surgery alone (Fig. 2b). Direct comparison of preoperative chemoradiotherapy versus preoperative chemotherapy was performed including 2 trials, which showed a pooled HR of 0.71 (95% CI 0.45–1.12, *P*=0.146) for preoperative chemoradiotherapy compared to preoperative chemotherapy (Fig. 2c). Overall, adjusted indirect comparison yielded a HR of 0.91 (95% CI 0.71-1.16, *P*=0.445) for preoperative (chemo)radiotherapy compared to preoperative chemotherapy (Table 2). Combination of direct comparisons and adjusted indirect comparisons of all patients yielded a HR of 0.86 (95% CI 0.69-1.07, *P*=0.171) for preoperative (chemo)radiotherapy compared to preoperative chemotherapy (Table 2).

Tumour site specific subgroup analysis was possible only in GOJ cancer, which showed a HR of 0.74 (95% CI 0.50-1.09, *P*=0.131) for preoperative (chemo)radiotherapy compared to preoperative chemotherapy (Table 2).

Progression free survival

Progression free survival was available for GOJ cancer in 2 trials which compared preoperative chemoradiotherapy to preoperative chemotherapy (7;16. Direct comparison meta-analysis yielded a HR of 0.70 (95% CI 0.45-1.07. *P*=0.101) for preoperative chemoradiotherapy compared to preoperative chemotherapy (data not shown).

Morbidity and mortality

There was considerable variation in morbidity between the single studies with rates in the single arms ranging from 2.9% (Zhao[31], preoperative chemotherapy group) to 98.0% (Stahl[7], preoperative chemoradiotherapy group). We were unable to demonstrate that (chemo)radiotherapy or chemotherapy given preoperatively increased the risk of any type of postoperative complication, cardiac complication, respiratory complication, anastomotic leak, pancreatitis/pancreatic fistula, 30-day mortality or total postoperative mortality as compared to surgery alone (Table 3). Adjusted indirect comparison showed no significant risk enhancement for any morbidity or mortality when preoperative (chemo)radiotherapy and chemotherapies were given (Table 3). Direct comparison between preoperative chemoradiotherapy and chemotherapy again revealed the same risk for morbidity as well as mortality (Table 3). Combination of

direct comparisons and adjusted indirect comparisons gave basically the same outcome (Table 3). Only one preoperative death was reported; a patient in chemotherapy group died preoperatively presumably due to chemotherapy induced toxicity in the direct comparison between preoperative chemoradiotherapy and chemotherapy.[7] Therefore, it seemed not to be significant to evaluate treatment-related mortality besides total postoperative mortality. Furthermore, tumour site specific subgroup analysis was not feasible regarding morbidity or mortality. Any discrepancies in the findings of the adjusted indirect comparisons and the direct comparisons were assessed and no such impact was revealed on any type of morbidity or mortality.

Risk of bias across studies

There was no noticeable asymmetry in the funnel plots and absolute z values in Begg's test were less than 1.96 in all analyses (data not shown). Therefore, no publication bias seemed to be present.

Differences in interventions might also introduce bias. Four out of 5 trials comparing preoperative (chemo)radiotherapy to surgery alone used only radiotherapy as a preoperative therapy in the treatment arm, while another trial used cisplatinum-fluorouracil based chemotherapy which is the most common regimen in the trials

comparing preoperative chemotherapy to surgery alone or preoperative chemoradiotherapy to chemotherapy. The total amount of cisplatin and fluorouracil varied from 150 mg/m^2 to 600 mg/m^2 and 500 mg/body to 30000 mg/m^2, respectively. Cunningham et al. used epirubicin in combination with cisplatin and fluorouracil.[17] Hartgrink et al. used methotrexate and doxorubicin instead of cisplatin in combination with fluorouracil.[18] The median total dose of radiation was 40 (range 20-40) Gy, and the median dose fraction was 2.7 (2–5 Gy. Skoropad et al. used 20 Gy of intraoperative radiotherapy in combination with 20 Gy of preoperative radiotherapy.[23] Preoperative radiation therapy was given concurrently with chemotherapy in all 3 trials that used the combination.[7,16,27]

Discussion

In total 18 studies were eligible when we scrutinized the relevant literature and among these data were available from 14 of them. The subsequent meta-analysis on overall survival yielded a HR of 0.75 for preoperative (chemo)radiotherapy compared to surgery alone in resectable gastric and GOJ cancer, suggesting an important therapeutic effect. We also found that preoperative chemotherapy in resectable gastric and GOJ cancer showed a strong trend towards better long-term survival compared to surgery alone, although not statistically significant. It should be noted that four out of five studies on (chemo)radiotherapy in the analysis were comparisons between preoperative radiotherapy without any chemotherapy and surgery alone.[21-23,30] Our results basically accord those from a previously completed meta-analysis by Fiorica et al. suggesting that preoperative radiotherapy for resectable stomach cancer improves survival compared to surgery alone.[3] These results suggest a quite promising potential of preoperative radiotherapy for resectable stomach cancer, although preoperative radiotherapy without any chemotherapy is currently not a reasonable option, given the established evidence for the efficacy of preoperative multidrug chemotherapy.[2] Moreover, using an adjusted indirect method it was possible to compare preoperative (chemo)radiotherapy and preoperative chemotherapy more comprehensively regarding the same outcome

variables. Combination of direct comparisons and adjusted indirect comparisons of overall patients provided evidence to suggest that preoperative (chemo)radiotherapy does show a tendency towards improving long-term survival compared to preoperative chemotherapy for resectable stomach cancer. These combined results are reliable because no statistically significant differences were observed between the results from direct and adjusted indirect comparisons. While four out of five studies on preoperative (chemo)radiotherapy used radiotherapy only, three out of eight studies on preoperative chemotherapy included postoperative chemotherapy as well.[17,29,32] Despite these disadvantages, preoperative (chemo)radiotherapy showed a trend towards better long-term survival compared to chemotherapy alone highlighting the need for dedicated clinical studies.

Neither the direct nor the adjusted indirect comparisons demonstrated data to suggest that preoperative (chemo)radiotherapy increased the risk of postoperative morbidity or perioperative mortality neither when compared to preoperative chemotherapy alone nor to surgery alone. These combined results are also reliable since no differences were observed between the results from direct and adjusted indirect comparisons. These results are consistent with our previously published meta-analysis comparing postoperative morbidity and perioperative mortality between neoadjuvant

chemoradiotherapy and chemotherapy for oesophageal cancer.[33] Accordingly, there are no additional concerns that have to be incorporated into the delicate balance between the tumour target and micrometastases issue for the cytotoxic therapy and its capability for enhanced surgical risks.

Recently, three different designs of adjuvant therapies for localized gastric cancer have shown improvement in survival based on large-scale, randomised clinical trials originating in three different regions in the world. The SWOG 9008/INT 0116 trial investigating postoperative chemoradiation in the United States[34], the MAGIC trial of perioperative three-agent chemotherapy in Europe[17], and postoperative chemotherapy regimens in Japan (the ACTS-GC trial)[35] and in three Asian countries (the CLASSIC trial)[36] have launched a multimodality therapeutic concept in gastric and GOJ cancers.

There are some drawbacks confined to postoperative adjuvant therapy for stomach cancer connected with the high morbidity and mortality rate after gastrectomy with radical lymphadenectomy, often delaying and even precluding postoperative treatment. The Dutch trial comparing D1 and D2 lymphadenectomy, without adjuvant therapy, showed 10 % of postoperative mortality and 43 % of postoperative morbidity in the D2 group.[37] This high morbidity and mortality may have discouraged from the use of postoperative adjuvant therapy, especially in the West. This makes comparisons

between preoperative and postoperative treatment difficult, as postoperative therapy can only be given to the selected group of patients fit enough to tolerate it after surgery and surgical complications.

Not unexpectedly, a variety of surgical procedures and pre-and perioperative treatment regimens were used in both chemotherapy and radiotherapy currently reviewed, which introduces a risk of bias and, at the same time, represents a limitation of this meta-analytical approach.

There are also some methodological drawbacks in the present meta-analysis. It was mandated to use AIC because of the lack of studies comparing preoperative chemotherapy and chemoradiotherapy for non-cardia stomach (corpus and antrum) cancer, which was the reason for the invalidity of a tumour site specific subgroup analysis. The result of the AIC may be subject to greater bias (especially selection bias) than head-to-head randomised comparisons because the AIC is based on the transitivity assumption. If there are differences in selection criteria or distribution of effect modifiers between trials for chemoradiotherapy and for chemotherapy the transitivity assumption is violated and the result of the adjusted indirect effect may be biased. In our study, a possible modifier may be the tumour site since the overall I^2=43 % and *P*=0.081 in the preoperative chemotherapy versus surgery alone comparison is suggestive of a

moderate heterogeneity between the subgroups. If treatment-by-tumour site interaction exists, we must be very cautious before drawing conclusions on the findings from the AIC because the distribution of tumour site varied between trials for chemoradiotherapy and for chemotherapy. Furthermore, the increase in precision due to the combination of indirect and direct comparisons is valuable only when bias is absent. This condition once again relies on the similarity of the participants and interventions in the different trials. Two randomised clinical trials addressing this issue are ongoing in Australia (ClinicalTrials.gov Identifier: NCT01924819) and in China (NCT01815853). The results from these pivotal studies are awaited.

The present meta-analysis is an aggregation of tabulated data and IPD, which might jeopardize the robustness of the meta-analysis. Despite our effort to get IPD from all eligible RCTs, IPD were provided from only 2 primary investigators and compensatory tabulated data was provided from one investigator. In 6 studies, estimates were calculated from the data reported in original studies. In 5 studies, data were extracted from the meta-analysis by Ronellenfitsch.[2] However the results from all the reviewed trials seemed consistent with the results from the IPD.

In conclusion, preoperative (chemo)radiotherapy for resectable gastric and GOJ cancer is associated to a significant survival benefit over surgery alone. Preoperative

chemotherapy alone seemed to act in the same direction. In adjusted indirect and direct comparisons between preoperative chemotherapy and chemoradiotherapy, the latter showed a trend towards better long-term survival, which could not be fully substantiated statistically. Neither of these neoadjuvant therapies increased the risk for postoperative morbidity or perioperative mortality. Although the results were not conclusive because of some methodological drawbacks, they raise an issue regarding a possible role for preoperative radiotherapy in the curatively intended treatment for stomach and GOJ cancer.

Conflict of interest statement

The authors state they have no conflict of interest to disclose regarding current manuscript.

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Author	Year published	Preoperative radiotherapy and chemotherapy regimens	Tumour site			No. of pts included in the MA	Information source
			O	GOJ	S		
Preoperative radio(chemo)therapy plus surgery vs. surgery alone							
Shchepotin	1994	20 Gy of RT in 4 fractions	0	0	198	198	5- and 3-year survival, date of trial started and published
Zhang	1998	40 Gy of RT in 20 fractions	0	370	0	370	Number of randomised pts and overall mortality and p-value
Skoropad	2000	20 Gy of RT in 5 fractions plus 20 Gy as an IORT	0	78		78	Number of eligible pts and overall mortality and p-value
Urba	2001	45 Gy of RT in 30 fractions; Two cycles of CT: Cis 20 mg/m² days 1–5; FU 300 mg/m² days 1–21; vinblastine 1 mg/m² days 1–4	100		0	0	Excluded
Skoropad	2002	20 Gy of RT in 5 fractions	0	102		102	10- and 5-year survival, date of trial started and published
Walsh	2002	40 Gy of RT in 15 fractions; Two cycles of CT: Cis 75 mg/m² on day 7; FU 15 mg/kg on days 1–5	74	39	0	39	lnHR, selnHR from MA by Ronellenfitsch
Tepper (CALGB 9781)	2008	50.4 Gy of RT in 28 fractions; Two cycles of CT: Cis 60 mg/m² day 1; FU 1000 mg/m² days 3–5	56		0	0	Excluded
van Hagen (CROSS)	2012	41.4 Gy of RT in 23 fractions; 5 weeks concurrent CT: carboplatin area under curve=2 mg/ml/min and paclitaxel 50 mg/m² on day 1 weekly	366		0	0	Excluded
Preoperative chemotherapy plus surgery vs. surgery alone							
Wang	2000	Orally FPLC over 12.5 days (5-FU 160 mg/day)	0	60	0	60	Number of randomised pts, death during 5 years and p-value
Hartgrink (FAMTX)	2004	Two to four cycles: methotrexate 1500 mg/m² on day 2; 5-FU 1500 mg/m² on day 2; leucovorin 240 or 480 mg cumulative dose on days 3 to 4; doxorubicin 30 mg/m² on day 15	0	0	56	56	Number of eligible patients and overall mortality and p-value
Cunningham (MAGIC)	2006	Three cycles: epirubicin 50 mg/m² on day 1; Cis: 60 mg/m² on day 1; 5-FU 4200 mg/m² cumulative dose on days 1 to 21) preop.; surgery 3 to 6 weeks after last chemotherapy dose; 3 cycles (see above) postop. starting 6 to 12 weeks after surgery	73	58	372	430	lnHR, selnHR from MA by Ronellenfitsch
Zhao	2006	Group 1: 800-1200 mg/day 5`-DFUR for 3-5 days, Group 2: 500 mg 5-FU + 200mg/day CF for 3-5 days	0	0	54	54	lnHR, selnHR from MA by Ronellenfitsch
Kelsen (RTOG 8911)	2007	Three cycles preoperatively: Cis 100 mg/m² day 1; FU 1000 mg/m² days 1–5; two cycles postoperatively: Cis 75 mg/m² day 1; FU 1000 mg/m² days 1–5	143	93	0	93	lnHR, selnHR from MA by Ronellenfitsch
Allum (OE02)	2009	Two cycles: Cis 80 mg/m² day 1; FU 1000 mg/m² days 1–4	720	82	0	0	Excluded
Schuhmacher (EORTC 40954)	2010	Two cycles: Cis 50 mg/m² day 1, 15 and 29; FU 2000 mg/m² and folinic acid 500mg/m² days 1, 8, 15, 22, 29 and 36	0	144		144	IPD
Ychou (ACCORD07)	2011	Planned six perioperatively: (two or three cycles before surgery plus four or three cycles after surgery) of intravenous Cis (100 mg/m²) on day 1 and every 28 days continuous intravenous infusion of FU (800 mg/m² per day) for 5 consecutive days (days 1-5)	25	144	55	199	lnHR, selnHR from MA by Ronellenfitsch
Preoperative chemoradiotherapy vs. preoperative chemotherapy							
Stahl (POET)	2009	30 Gy of RT in 15 fractions, commencing 2 weeks after last day of induction CT, (CT group) 15 weeks: Cis 50 mg/m² biweekly; FU 2000 mg/m²/day weekly; folinic acid 500 mg/m²/weekly (CRT group) 12 weeks (induction): Cis 50 mg/m² biweekly; FU 2000 mg/m²/day weekly; folinic acid 500 mg/m²/day weekly. Followed by Cis 50 mg/m² on day 1 and day 8 and etoposide 80 mg/m² on days 3–5, concurrent with RT	0	119	0	119	HR and CI for OS and PFS provided by the original trialist
Burmeister	2011	35 Gy of RT in 15 fractions commencing day 22, (CT group) Cis 80 mg/m² day 1 and 21; FU 1000 mg/m²/day infusion over 96 h day 1 and 21 (CRT group) 1 cycle induction: Cis 80 mg/m² day 1 and FU 1000 mg/m²/day infusion over 96 h day 1. Followed by Cis 80 mg/m² day 1 and FU 800 mg/m²/day infusion over 96 h on day 1; concurrent with RT	60	15	0	14*	IPD

*One patient with unknown histology tumour was excluded; O,oesophagus; GOJ, gastro-oesophageal junction (including cardia); S, stomach (corpus and antrum); No., number; pts, patients; MA, meta-analysis; HR, hazard ratio; CI, confidence interval; OS, overall survival; PFS, progression free survival; IPD, individual patient data; RT, radiotherapy; IORT, intraoperative radiotherapy; CT, chemotherapy; NA, not available; Cis, cisplatin; FU, fluorouracil

Table 1 Treatment regimens, sample size and information source for survival analyses in randomised trials eligible for the meta-analysis

Tumour site		HR	95 % CI		*z*	*P*
			Lower	Upper		
Overall	Pre-op chemoradio vs. chemo (AIC)	0.91	0.71	1.16	-0.76	0.445
	Pre-op chemoradio vs. chemo (combination of DC and AIC)	0.86	0.69	1.07	-1.37	0.171
	Difference between DC and AIC				-0.91	0.363
GOJ	Pre-op chemoradio vs. chemo (AIC)	0.82	0.38	1.78	-0.51	0.613
	Pre-op chemoradio vs. chemo (combination of DC and AIC)	0.74	0.50	1.09	-1.51	0.131
	Difference between DC and AIC				-0.30	0.768
Stomach	Pre-op chemoradio vs. chemo (AIC)	0.77	0.53	1.10	-1.46	0.145
	Pre-op chemoradio vs. chemo (combination of DC and AIC)	NA	NA	NA	NA	NA
	Difference between DC and AIC				NA	NA

HR, hazard ratio; CI, confidence interval; GOJ, gastro-oesophageal junction; CRTx, chemoradiotherapy; CTx, chemotherapy; DC, direct comparison; AIC, adjusted indirect comparison; NA, not available

Table 2 Combination of direct and adjusted indirect comparisons of preoperative chemoradiotherapy with preoperative chemotherapy (overall survival)

			Events	Total	RR	95 % CI Lower	Upper	*z*	*P*
Any complication	Pre-op chemoradio vs. surgery alone	chemoradio	44	91	0.97	0.64	1.48	0.15	0.881
		surgery alone	44	89	1				
	Pre-op chemo vs. surgery alone	chemo	20	102	1.87	0.96	3.65	1.83	0.067
		surgery alone	11	92	1				
	Pre-op chemoradio vs. chemo (DC)	chemoradio	49	52	1.17	0.69	1.98	0.59	0.557
		chemo	46	61	1				
	Pre-op chemoradio vs. chemo (AIC)	chemoradio	44	91	0.52	0.24	1.14	-1.63	0.104
		chemo	20	102	1				
	Pre-op chemoradio vs. chemo (combined)	chemoradio	93	143	0.91	0.59	1.41	-0.41	0.679
		chemo	66	163	1				
	Difference between DC and AIC							1.68	0.093
Cardiac complication	Pre-op chemoradio vs. surgery alone	chemoradio	2	91	2.93	0.31	27.60	0.94	0.348
		surgery alone	0	89	1				
	Pre-op chemo vs. surgery alone	chemo	2	102	0.36	0.07	1.96	1.18	0.238
		surgery alone	5	92	1				
	Pre-op chemoradio vs. chemo (DC)	chemoradio	8	52	1.06	0.23	5.03	0.08	0.937
		chemo	9	61	1				
	Pre-op chemoradio vs. chemo (AIC)	chemoradio	2	91	8.10	0.49	134.82	1.46	0.145
		chemo	2	102	1				
	Pre-op chemoradio vs. chemo (combined)	chemoradio	10	143	1.71	0.44	6.67	0.78	0.438
		chemo	11	163	1				
	Difference between DC and AIC							-1.24	0.216
Respiratory complication	Pre-op chemoradio vs. surgery alone	chemoradio	23	91	1.52	0.86	2.68	1.43	0.153
		surgery alone	15	89	1				
	Pre-op chemo vs. surgery alone	chemo	8	102	2.82	0.78	10.20	1.58	0.113
		surgery alone	3	92	1				
	Pre-op chemoradio vs. chemo (DC)	chemoradio	9	52	1.56	0.60	4.06	0.92	0.359
		chemo	8	61	1				
	Pre-op chemoradio vs. chemo (AIC)	chemoradio	23	91	0.54	0.13	2.19	-0.87	0.386
		chemo	8	102	1				
	Pre-op chemoradio vs. chemo (combined)	chemoradio	32	143	1.12	0.51	2.46	0.27	0.785
		chemo	16	163	1				
	Difference between DC and AIC							1.23	0.218
	Pre-op chemoradio vs. surgery alone	chemoradio	11	262	0.69	0.21	2.20	0.64	0.525
		surgery alone	16	288	1				
	Pre-op chemo vs. surgery	chemo	4	102	2.12	0.40	11.19	0.88	0.377

	alone	surgery alone	2	92	1				
	Pre-op chemoradio vs.	chemoradio	8	52	0.71	0.32	1.58	0.84	0.399
Anastomotic leak	chemo (DC)	chemo	12	61	1				
	Pre-op chemoradio vs.	chemoradio	11	262	0.32	0.04	2.47	-1.09	0.277
	chemo (AIC)	chemo	4	102	1				
	Pre-op chemoradio vs.	chemoradio	19	314	0.64	0.30	1.34	-1.19	0.236
	chemo (combined)	chemo	16	163	1				
	Difference between DC and AIC							0.70	0.483
	Pre-op chemoradio vs.	chemoradio	18	91	0.56	0.05	5.88	0.48	0.629
	surgery alone	surgery alone	18	89	1				
	Pre-op chemo vs. surgery	chemo	3	102	7.41	0.39	140.77	1.13	0.183
	alone	surgery alone	0	92					
	Pre-op chemoradio vs.	chemoradio	0	52					
Pancreatitis /Pancreatic fistula	chemo (DC)	chemo	0	61	NA	NA	NA	NA	NA
	Pre-op chemoradio vs.	chemoradio	18	91	0.08	0.00	3.28	-1.34	0.179
	chemo (AIC)	chemo	3	102	1				
	Pre-op chemoradio vs.	chemoradio	18	143					
	chemo (combined)	chemo	3	163	NA	NA	NA	NA	NA
	Difference between DC and AIC							NA	NA
	Pre-op chemoradio vs.	chemoradio	1	171	0.23	0.03	1.97	1.34	0.181
	surgery alone	surgery alone	5	199	1				
	Pre-op chemo vs. surgery	chemo	3	102	7.41	0.39	140.77	1.33	0.183
	alone	surgery alone	0	92	1				
	Pre-op chemoradio vs.	chemoradio	3	52	1.59	0.28	9.12	0.52	0.602
30-day mortality	chemo (DC)	chemo	2	61	1				
	Pre-op chemoradio vs.	chemoradio	1	171	0.03	0.00	1.20	-1.86	0.062
	chemo (AIC)	chemo	3	102	1				
	Pre-op chemoradio vs.	chemoradio	4	223	0.76	0.16	3.69	-0.34	0.734
	chemo (combined)	chemo	5	163	1				
	Difference between DC and AIC							1.90	0.057
	Pre-op chemoradio vs.	chemoradio	7	262	0.72	0.28	1.87	0.67	0.504
	surgery alone	surgery alone	11	288	1				
	Pre-op chemo vs. surgery	chemo	5	129	2.64	0.52	13.30	1.17	0.241
	alone	surgery alone	2	121	1				
	Pre-op chemoradio vs.	chemoradio	5	52	2.65	0.54	13.05	1.20	0.230
	chemo (DC)	chemo	2	61	1				
Total postoperative mortality	Pre-op chemoradio vs.	chemoradio	7	262	0.27	0.02	2.94	-1.08	0.280
	chemo (AIC)	chemo	5	129	1				
	Pre-op chemoradio vs.	chemoradio	12	314	1.32	0.35	4.96	0.40	0.687
	chemo (combined)	chemo	7	190	1				

Difference between DC and AIC	1.56	0.118

RR, risk ratio; confidence interval; DC, direct comparison; AIC, adjusted indirect comparison; NA, not available

Table 3 Combination of direct and adjusted indirect comparisons of preoperative chemoradiotherapy with preoperative chemotherapy (morbidity and mortality)

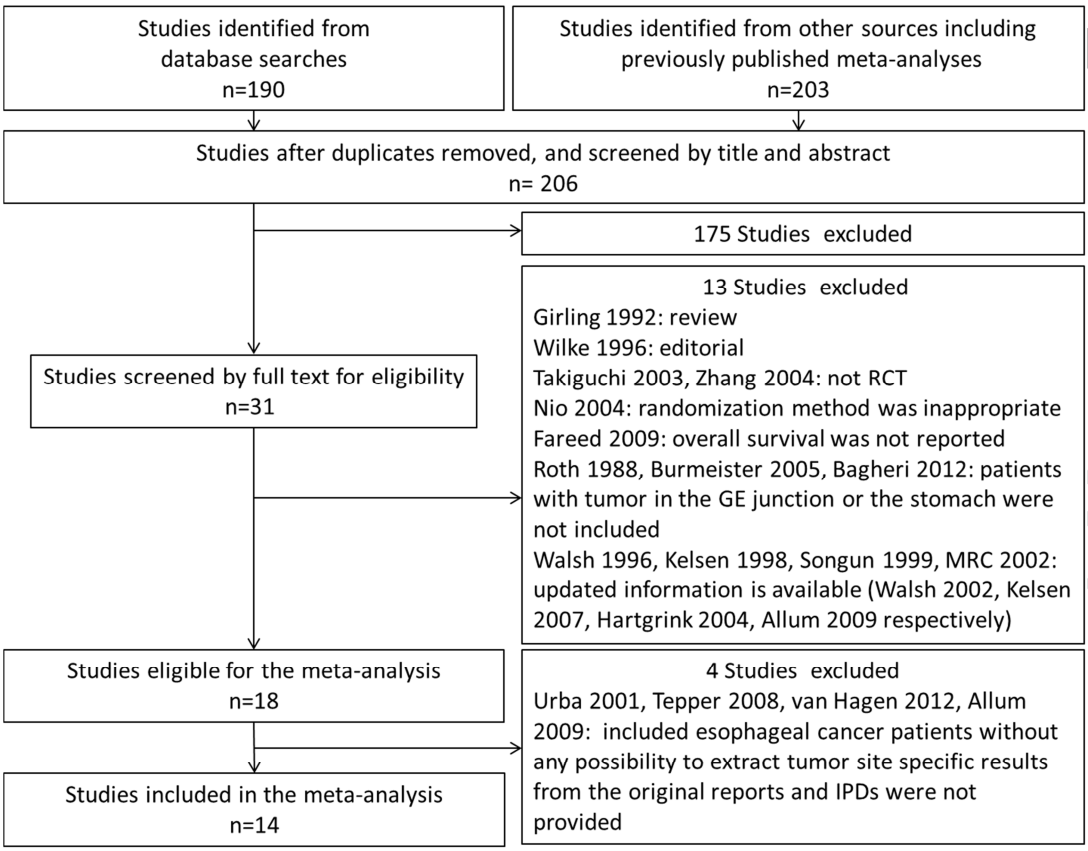
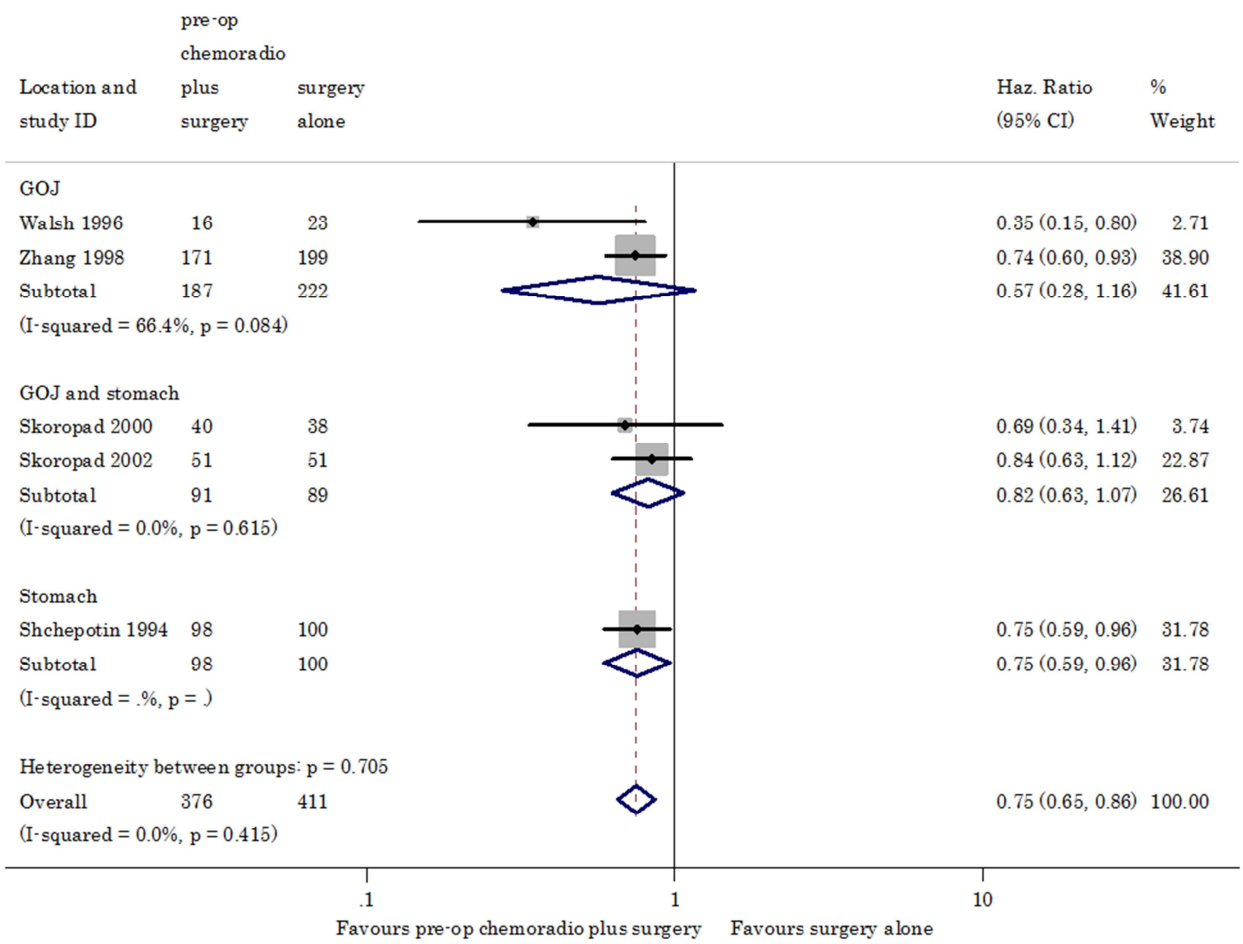
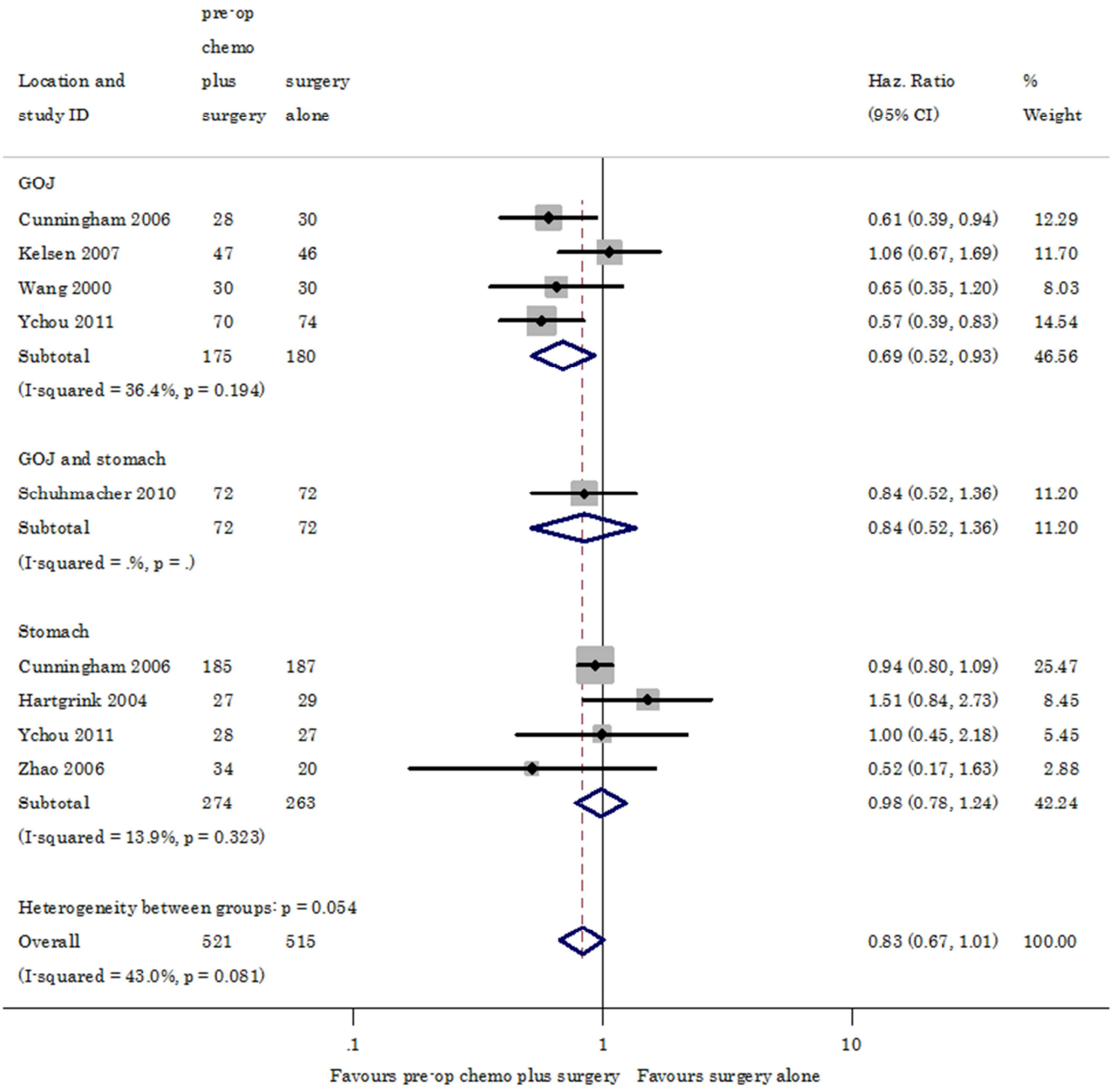


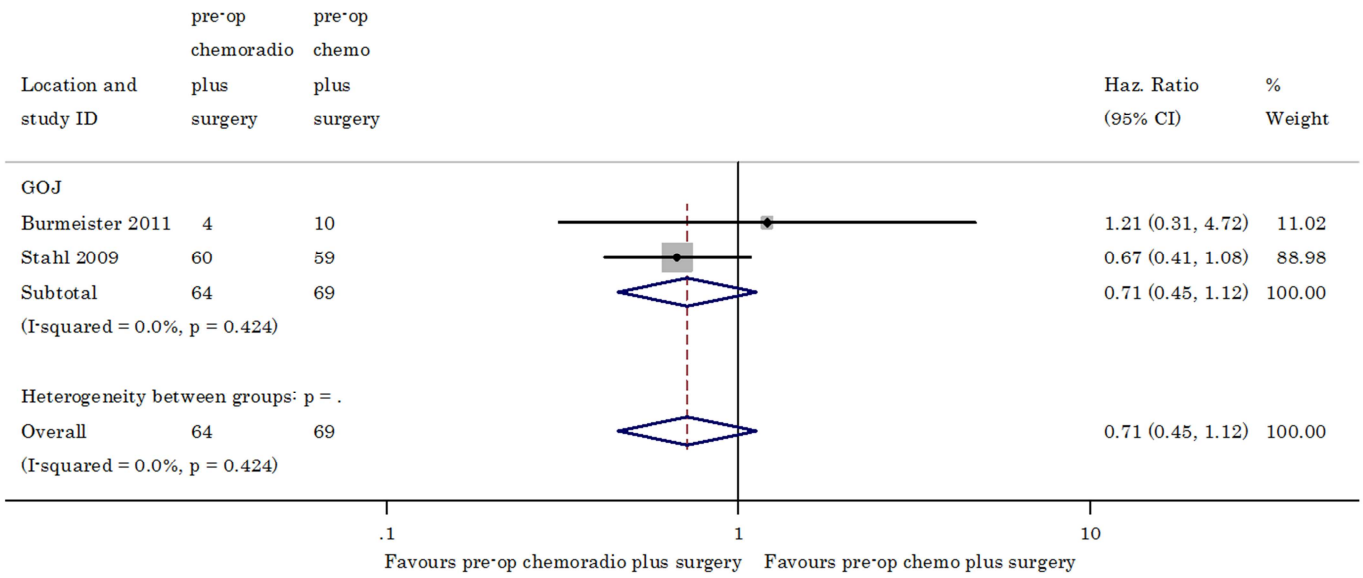
Fig. 1 Flow diagram showing inclusion and exclusion of studies



a Preoperative chemoradiotherapy plus surgery vs. surgery alone



b Preoperative chemotherapy plus surgery vs. surgery alone



c Preoperative chemoradiotherapy plus surgery vs. preoperative chemotherapy plus surgery

Fig. 2 Overall survival comparing **a** Preoperative chemoradiotherapy plus surgery to surgery alone, **b** Preoperative chemotherapy plus surgery to surgery alone and **c** Preoperative chemoradiotherapy plus surgery to preoperative chemotherapy plus surgery. GOJ, gastroesophageal junction; Haz. Ratio, hazard ratio; CI, confidence interval