Systematic Review and Meta-Analysis

Medicine®

OPEN

Postoperative morbidity and mortality in patients receiving neoadjuvant chemotherapy for locally advanced gastric cancers

A systematic review and meta-analysis

Huiyu Luo, BA[a], Liucheng Wu, MD[b,*], Mingwei Huang, MD[b], Qinwen Jin, MD[b], Yuzhou Qin, MD[b], Jiansi Chen, MD[b]

Abstract

Aim: To investigate the postoperative morbidity and mortality for neoadjuvant chemotherapy (NAC) plus surgery compared with surgery alone.

Methods: PubMed and Embase were searched to capture the incidence of any postoperative complications, pulmonary complications, anastomotic leakage, surgical site infections, and postoperative mortality in randomized clinical trials comparing NAC plus surgery with surgery alone. The meta-analyses were performed with a random effects model.

Results: Nine relevant studies were included. Comparing NAC with surgery alone, there were no increases in any postoperative complications, pulmonary complications, anastomotic leakage, surgical site infections, or postoperative mortality attributable to NAC. Sensitivity analysis suggested a possible increased risk of any postoperative complications compared with surgery alone: the risk difference 0.056 (95% confidence interval –0.032 to 0.145). Severe complications such as anastomotic leakage and pulmonary complications were similar in the 2 groups.

Conclusions: NAC for gastric cancer does not increase the risk of postoperative morbidity and mortality compared with surgery alone.

Abbreviations: CI = confidence interval, GC = gastric cancer, NAC = neoadjuvant chemotherapy, RD = risk difference.

Keywords: chemotherapy, gastric cancer, neoadjuvant, postoperative morbidity

1. Introduction

Gastric cancer (GC) is the fifth most common malignancy in the world, and it is also commonly diagnosed and identified as a leading cause of cancer death in China.[1] Unfortunately, 2/3 of GC patients are diagnosed in a locally advanced tumor stage, with poor overall survival rates between 20 and 60%.[2] Complete resection with lymph node dissection remains the primary treatment for resectable GC.[3] To improve survival, multimodal treatment has been used as an adjuvant to surgery in recent years.[4] Neo-adjuvant chemotherapy (NAC) has been shown to reduce the number of metastatic lymph nodes and to increase the rate of complete tumor resection, likely prolonging survival.[4] In addition, NAC is generally better tolerated than adjuvant chemotherapy, even when the same chemotherapy regimens are used.[5] NAC is currently used worldwide as an initial therapy for locally advanced GC.[6] Although there are few studies and meta-analyses comparing NAC followed by surgery with surgery alone, improved survival with NAC has been reported. One concern with NAC is the associated toxicity, possibly contributing to postoperative morbidity and mortality. However, this concern has not been thoroughly addressed in a number of aspects, including specific postoperative complications.[7] There are a few studies comparing postoperative morbidity and mortality; however, either the studies included patients with gastroesophageal squamous cell cancer or patients received neoadjuvant chemoradiation, all of which makes for conflicting evidence regarding postoperative complications.[8,9] Given that NAC was commonly used in Asian countries, it is necessary to conduct this comprehensive search of randomized clinical trials comparing NAC versus surgery alone. Data on postoperative morbidity and mortality were extracted and analyzed to clarify any differences in postoperative morbidity and mortality between groups of patients with locally advanced gastric cancer undergoing NAC and surgery alone.

2. Materials and methods

This meta-analysis was reported according to the preferred reporting items for systematic reviews and meta-analyses guidelines. All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

Editor: Neil Merrett.

The authors declare no conflicts of interest. Liucheng Wu orcid: 0000-0001-7969-3505.

[a] Affiliated Tumor Hospital of Guangxi Medical University, [b] Department of Gastrointestinal Surgery, Affiliated Tumor Hospital of Guangxi Medical University, Guangxi Autonomous Region, China.

[*] Correspondence: Liucheng Wu, Department of Gastrointestinal Surgery, Affiliated Tumor Hospital of Guangxi Medical University (e-mail: wuliucheng@gxmu.edu.cn)

Medicine (2018) 97:43(e12932)

Received: 6 May 2018 / Accepted: 25 September 2018

http://dx.doi.org/10.1097/MD.0000000000012932

2.1. Literature search

In April 2017, we performed a computerized literature search to identify all randomized controlled trials (RCT). Trials were identified by systematically searching PubMed and EMBASE. We limited our search to studies in humans. There were no language restrictions for either searching or trial inclusion. The search was conducted using the following key words: neoadjuvant chemotherapy, gastric cancer, esophagogastric cancer, surgery, and gastrectomy. In addition, an extensive manual search was carried out by using references from each retrieved study or review article.

2.2. Study selection

Trials were included using the following criteria: RCTs; trials needed to be conducted on patients with locally advanced histologically confirmed carcinoma of the stomach or gastrointestinal junction; and the intervention was defined as neoadjuvant chemotherapy with surgery, and the control intervention was surgery alone with curative intent. The study selection was performed by 2 authors (LW, QJ) independently, and any differences were settled by discussion. Publications identified as duplicates were excluded, and when one study had substantial overlap in terms of author, institution or study period with another study, the study with more available data was included.

Regarding surgery, patients with esophageal carcinomas or patients who had esophagectomy were excluded.

2.3. Assessment of risk of bias

Both independent authors assessed trial quality with regard to bias in the domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias according to criteria described in The Cochrane Handbook 5.0.1.[10] The reviewers determined the level of bias ('low'/'high'/'unclear') for each item, and then, a reviewer assigned an overall level of risk of existing bias to each trial ('low' if 'low' bias was determined for all items, 'moderate' if 'high' or 'unclear' bias was determined for 1 or 2 items, 'high' if 'high' or 'unclear' bias was determined for at least 3 items). This bias level was used as a measurement of the quality of each trial and was also used in sensitivity and subgroup analyses. A third reviewer was consulted, and a consensus was reached if the 2 reviewers came to different conclusions regarding the risk of bias in a single domain.

2.4. Assessment of heterogeneity

We assessed heterogeneity clinically (by judgment of the 2 independent reviewers) and statistically. Statistical heterogeneity was assessed by the calculation of the I^2 statistic, a measurement of the percentage of variability in effect estimates attributed to heterogeneity rather than to sampling error.

2.5. Assessment of publication bias

Publication bias was assessed by creating a funnel plot using the different outcomes and evaluating funnel asymmetry with Begg and Egger tests with respect to continuous data,[11,12] or Peters test with respect to binary data.[13]

2.6. Data extraction

Two reviewers independently extracted data using a dedicated form regarding relevant facts on general trial characteristics, trial quality, patient characteristics, interventions, and outcomes. The original papers were retrieved and jointly investigated to resolve any disagreement if there was inconsistency. The data extraction form compiled the following items: general information on the trial, trial design issue, baseline characteristics of participants, characteristics of the intervention, frequency of different types of surgery, and postoperative morbidity and mortality in each group. Our primary endpoint was postoperative mortality, and secondary endpoints included any complication, anastomotic leakage, pulmonary complications, and surgical site infection. Pneumonia, acute respiratory distress syndrome, pulmonary embolism, and respiratory failure were defined as respiratory complications. Postoperative mortality included 30-day mortality, 90-day mortality, in-hospital mortality, and surgery-related mortality. All analyses were carried out on the full analysis set population. Thus, we used the number of patients who actually underwent surgery as the denominator for each group in the meta-analysis of postoperative complications and mortality.

2.7. Statistical analysis

The meta-analysis was performed in line with PRISMA guidelines.[14] Statistical analysis was carried out using the risk difference (RD) as the summary statistic. We used a random-effects model to calculate RDs and confidence intervals (CIs) for all meta-analyses. The use of a random-effect model was preferred to that of a fixed model because the NAC regimens and surgical procedures used in the trials were heterogeneous.

In the first analysis comparing NAC plus surgery with surgery alone, RDs represented the risk of each event during the study interval in a patient who received NAC followed by surgery compared with the risk in a patient who received surgery alone. An RD greater than 1 indicated a higher mortality or morbidity rate in patients who received NAC, and the point estimate of the RD was considered significant at the $P < .05$ level if the 95% CI did not include 1.

All data analyses were performed using the statistical software Stata 10.0 (Stata Co., College Station, TX).

3. Results

Searches of the PubMed and Embase databases identified 564 and 99 abstracts, respectively. After removing 35 duplicate abstracts, 17 studies and their full texts were retrieved after screening the titles and the abstracts,[5,6,15–29] while 5 studies were found from a reference list.[30–34] Thus, a total of 10 studies were included in this systematic review.[16,21,23,24,26,29–32] Six studies were excluded because no adequate data were available,[15,17–19,27,33] 2 studies were excluded because the control group was not surgery alone,[20,22] 2 studies were excluded because they included patients who had esophagectomy,[5,6] 1 study was excluded because of duplicate data,[28] 1 study was excluded because it included stage gastric cancer patients,[34] 1 study was excluded because it performed short-term NAC, and it is not standard neoadjuvant regimen.[25] The flow chart of the literature search of this systematic review is shown in Figure 1. There were a 3-arm study that compared 2 different neoadjuvant chemotherapies versus surgery alone.[31] Data in different NAC groups from this study were combined and used in the analysis.

Patients were of European origin in 4 studies[16,23,26,29] and Asian in 5 studies.[21,24,30–32] Three of the included studies were in Chinese,[21,24,30] while the rest were in English.[16,23,26,29,31,32] Feng et al's study[30] included only Bormann's IV gastric cancer

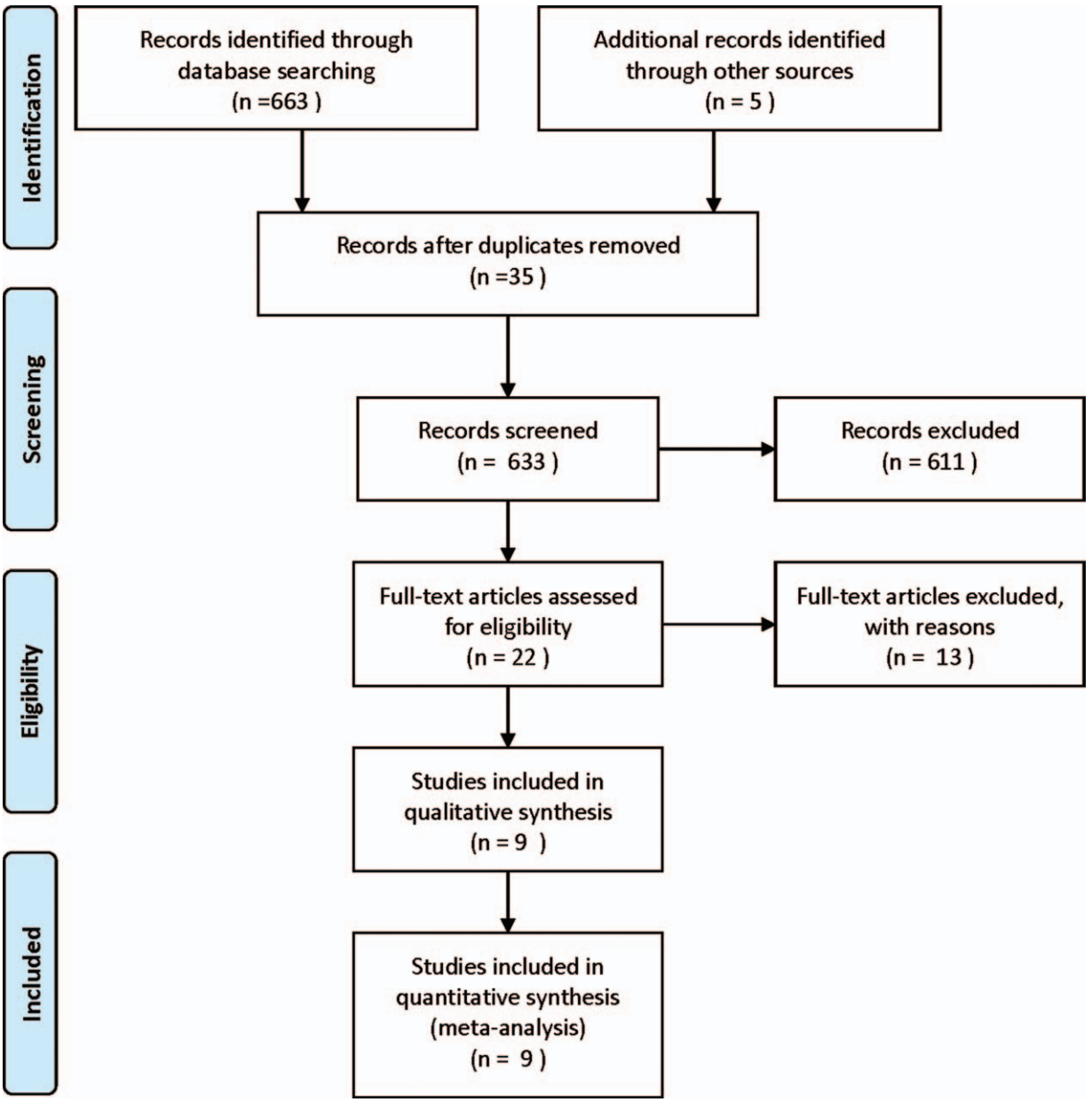

Figure 1. Flow chart shows the selection process.

patients. The NAC regimens of the included studies varied significantly. Details of lymphadenectomy were outlined in 4 studies.[16,23,26,29] There were no major differences in patient characteristics between groups, although no formal statistical comparison was done. Table 1[16,21,23,24,26,28–32] summarizes details of all trials included in the meta-analysis.

Risk of bias was low in 1 study,[24] moderate in 7 studies[16,23,26,29–32] and high in 1 study.[21] Both performance bias and detection bias were considered "low" across all studies because blinding of patients and clinicians to interventions was not possible, and bias is unlikely to be introduced during these 2 steps. Details of the risk of bias for each study are shown in Table 2,[16,21,23,24,26,28–32]Figures 2 and 3.

3.1. Postoperative mortality

All 9 included studies including 721 patients reported postoperative mortalities, 352 in the NAC group and 364 in the surgery alone group. The summary RD for postoperative mortality was 0.001 (95% CI –0.018 to 0.019), and there was no significant difference in postoperative mortality between the 2 groups (Fig. 4). The corresponding funnel plot did not suggest relevant publication bias. The sensitivity analysis excluding the trials did not report the extent of lymphadenectomy[21,24,30–32] showed a similar effect size to that in the analysis including all studies (data not shown). The subgroup analysis according to different regions did not indicate any difference in postoperative mortality in either European or Asian populations with NAC compared with

Table 1

Basic characteristics of studies included in this meta-analysis.

Author/Year	Region	Accural period	Patients(n)		Age, y		Sex (M/F)		Resectability rate (%)		Tumor type	Neoadjuvant chemotherapy schedule	Lymphadenectomy
			NAC	Control	NAC	Control	NAC	Control	NAC	Control			
Songun et al,[29] 1999	Europe	1993–1996	29	30	NR	NR	NR	NR	56%(15/27)	62%(18/29)	AC	MTX 1500 mg/m^2 on day 1; FU 1500 mg/m^2 on day 1; LV 30 mg/m^{2}days 2, 3; ADM 30 mg/m^2 on days 15	D1
Wang et al,[32] 2000	Asia	1987–1988	30	30	54 (37–65)	55 (33–67)	23/7	27/3	100%(30/30)	100%(30/30)	NR	FPLP 2×20 mL/d on days 1–12.5, total dose being 500 mL containing 2g of FU	NR
Zhao et al,[31] 2006	Asia	2001–2003	40	20	NR	NR	NR	NR	85%(34/40)	100%(20/20)	NR	Group 1:800–1200 mg/d on days 3–5. Group 2: FU 500 mg/d on days 3–5, CF 200 mg/d on days 3–5	NR
Feng et al,[30] 2008	Asia	2002–2004	29	26	50.4 (33–70)	54.8 (38–72)	19/10	17/9	82.8%(24/29)	76.9%(20/26)	AC + SRCC, Borrmann IV	DOC 75 mg/m^2 on day 1, CIS 30 mg/m^2 on days 1–3, FU 500 mg/m^2 on days 1–5, CF 200 mg/m^2 on days 1–5.	NR
Qu et al,[24] 2010	Asia	2005–2008	39	39	NR	NR	26/13	22/17	100%(39/39)	97.4%(38/39)	AC + SRCC	PTX 135 mg/m^2 on day 1, L-OHP 85 mg/m^2 on day 1, FU 400 mg/m^2 on days 1–2, FU 600 mg/m^2 CI on days 1–2, CF 200 mg/m^2 on days 1–2.	NR
Biffi et al,[26] 2010	Europe	1999–2005	34	35	57 (25–75)	59 (39–76)	23/11	25/10	96.9%(31/32)	97.1%(34/35)	AC	DOC 75 mg/m^2 on day 1, CIS 75 mg/m^2 on day 1, FU 300 mg/m^2 CI on days 1–14.	D2
Schuhmacher et al,[23] 2010	Europe	1999–2004	72	72	56 (38–72)	58 (26–69)	50/22	50/22	97.23%(70/72)	94.4%(68/72)	AC	CIS 50 mg/m^2 on days 1, 15, 29; FU 2000 mg/m^2 CI on days 1, 8, 15, 22, 29, 36; CF 500 mg/m^2 on days 1, 15, 22, 29, 36.	D2
Fan et al,[21] 2011	Asia	2009–2011	69	70	58.9±9.9	58.7±10.1	42/27	44/26	100%(69/69)	100%(70/70)	NR	FU 750 mg/m^2 on days 1–5; CF 200 mg/m^2 on days 1–5,34–38; L-OHP 150 mg/m^2, ADM 30 mg/m^2, VP16 100 mg/m^2 on days 6, 20, 39	NR
Hashemzadeh et al,[16] 2014	Europe	2011–2014	22	52	58.3±9.1	59.7±8.7	15/7	41/11	86.4%(19/22)	59.6%(31/52)	AC	DOC 75 mg/m^2 on day 1; CIS 75 mg/m^2 on day 1; FU 750 mg/ m^2/day CI on days 1–5.	D2 + D1

AC=adenocarcinoma, ADM=doxorubicin, CF=calcium folinate, CI=continuous intravenous infusion, CIS=cisplatin, DOC=docetaxel, FPLP=fluorouracili polyphase liposome composita pro orale, FU=fluorouracil, LV=leucovorin, MTX=methotrexate, n=The total number of the patients, NAC=neoadjuvant chemotherapy, NR=not reported, SRCC=signet ring cell carcinoma, VP16=etoposide.

Table 2

Risk of bias of included studies.

Author/Year	Selection bias	Attrition bias	Performance bias	Detection bias	Bias due to missing data	Reporting bias	Other bias	Overall risk of bias
Songun et al,[29] 1999	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Wang et al,[32] 2000	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Zhao et al,[31] 2006	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Feng et al,[30] 2008	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Qu et al,[24] 2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Biffi et al,[26] 2010	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Schuhmacher et al,[23] 2010	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Moderate risk
Fan et al,[21] 2011	Unclear risk	Low risk	Low risk	Low risk	High risk	High risk	High risk	High risk
Hashemzadeh et al,[16] 2014	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk

surgery alone. For European patients, the summary RD was 0.002 (95% CI –0.035 to 0.040), while for Asian patients, the summary RD was 0.000 (95% CI –0.021 to 0.021).

3.2. Any complication

Seven studies including 526 patients reported any complications, 256 in the NAC group and 270 in the surgery alone group.[16,23,24,26,30–32] The summary RD for any complication was 0.025 (95% CI –0.014 to 0.064), and there was no significant difference in any complication between the 2 groups (Fig. 5). The corresponding funnel plot did not suggest relevant publication bias. The sensitivity analysis excluding the trials that did not report the extent of lymphadenectomy[24,30–32] showed a similar effect size to that of the analysis including all studies (data not shown). The subgroup analysis according to different regions did not indicate any difference in any complication in either European or Asian populations with NAC compared with surgery alone. For European patients, the summary RD was 0.056 (95% CI –0.032 to 0.145), while for Asian patients, the summary RD was 0.018 (95% CI –0.026 to 0.061).

3.3. Anastomotic leakage

Seven studies including 526 patients reported anastomotic leakage, 256 in the NAC group and 270 in the surgery alone group.[16,23,24,26,30–32] The summary RD for anastomotic leakage was 0.007 (95% CI –0.019 to 0.032), not showing any significant differences in anastomotic leakage between the 2 groups (Fig. 6). There was no relevant heterogeneity between the results of each study, and all confidence intervals included equity ($I^2 = 0.0\%$, $P = .99$). The corresponding funnel plot did not suggest relevant publication bias. The sensitivity analysis excluding the trials that did not report the extent of lymphadenectomy[24,30–32] showed a similar effect size to that of the analysis including all studies (data not shown). The subgroup analysis according to different regions did not indicate any difference in anastomotic leakage in either European or Asian populations with NAC compared with surgery alone. For European patients, the summary RD was 0.011 (95% CI –0.030 to 0.051), while for Asian patients, the summary RD was 0.004 (95% CI –0.028 to 0.036).

3.4. Pulmonary complication

Seven studies including 527 patients reported pulmonary complications, 255 in the NAC group and 272 in the surgery alone group.[16,21,24,26,30–32] The summary RD for pulmonary complication was 0.002 (95% CI –0.029 to 0.033), and there was no significant difference in pulmonary complication between the 2 groups (Fig. 7). The corresponding funnel plot did not suggest relevant publication bias. The sensitivity analysis excluding the trials with high risk of bias,[21] and trials that did not report the extent of lymphadenectomy[21,24,30–32] showed a similar effect size to that of the analysis including all studies (data not shown). The subgroup analysis according to different regions did not indicate any difference in pulmonary complication in either European or Asian populations with NAC compared with surgery alone. For European patients, the summary RD was –0.020 (95% CI –0.084 to 0.044), while for Asian patients, the summary RD was 0.008 (95% CI –0.027 to 0.044).

3.5. Surgical site infection

Seven studies including 526 patients reported surgical site infection, 256 in the NAC group and 270 in the surgery alone group.[16,23,24,26,30–32] The summary RD for surgical site infection was 0.008 (95% CI –0.022 to 0.038), and there was no significant difference in pulmonary complication between the 2 groups (Fig. 8). The corresponding funnel plot did not suggest relevant publication bias. The sensitivity analysis excluding the trials that did not report the extent of lymphadenectomy[24,30–32] showed a similar effect size to that in the analysis including all studies (data not shown). The subgroup analysis according to different regions did not indicate any difference in pulmonary complication in either European or Asian populations with NAC compared with surgery alone. For European patients, the summary RD was 0.018 (95% CI –0.031 to 0.068), while for Asian patients, the summary RD was 0.002 (95% CI –0.037 to 0.040).

4. Discussion

The effectiveness of NAC for gastric cancer has been investigated thoroughly and is now recommended and used by many oncologists. However, only a few reports have been published regarding the morbidity and mortality of surgery after NAC.[16,23,29,31] This meta-analysis, based on 9 randomized clinical trials, compared NAC with surgery alone with regard to postoperative morbidity and mortality.

The first important finding of our meta-analysis was that the number of studies reporting postoperative morbidity and mortality was quite small, and most of them reported them as secondary endpoints. Most of the studies did not report the extent

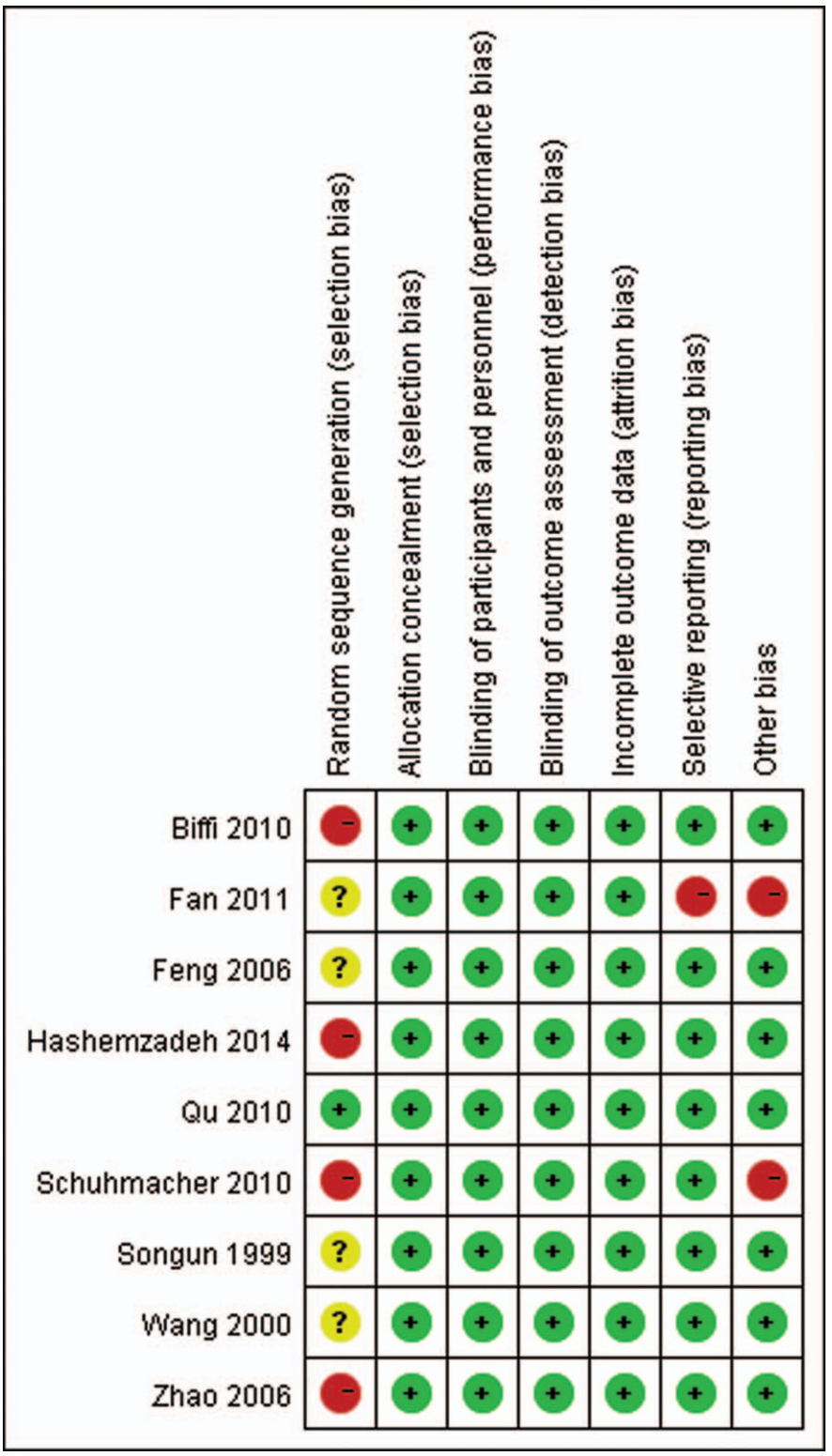

Figure 2. Risk of bias: each risk of bias item for each included study.

of lymphadenectomy of the surgery. Different NAC regimens were applied in the included studies, making it impossible to assess postoperative complications with regard to specific NAC regimens.

The comparison of NAC with surgery alone revealed no evidence of an increased risk of anastomotic leakage, any postoperative complication, pulmonary complication, surgical site infection or postoperative mortality compared with surgery alone. We should still be concerned about possible increased susceptibility to any postoperative complications after chemotherapy in Europe, although it did reach statistical significance. The observed trend of greater postoperative complications after

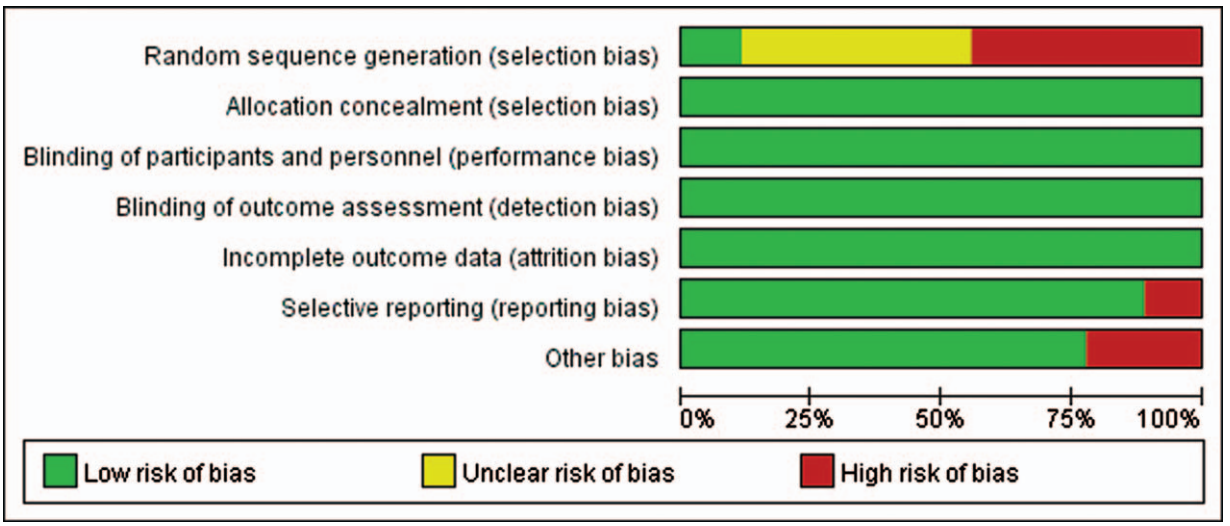

Figure 3. Risk of bias: each risk of bias item presented as percentages across all included studies.

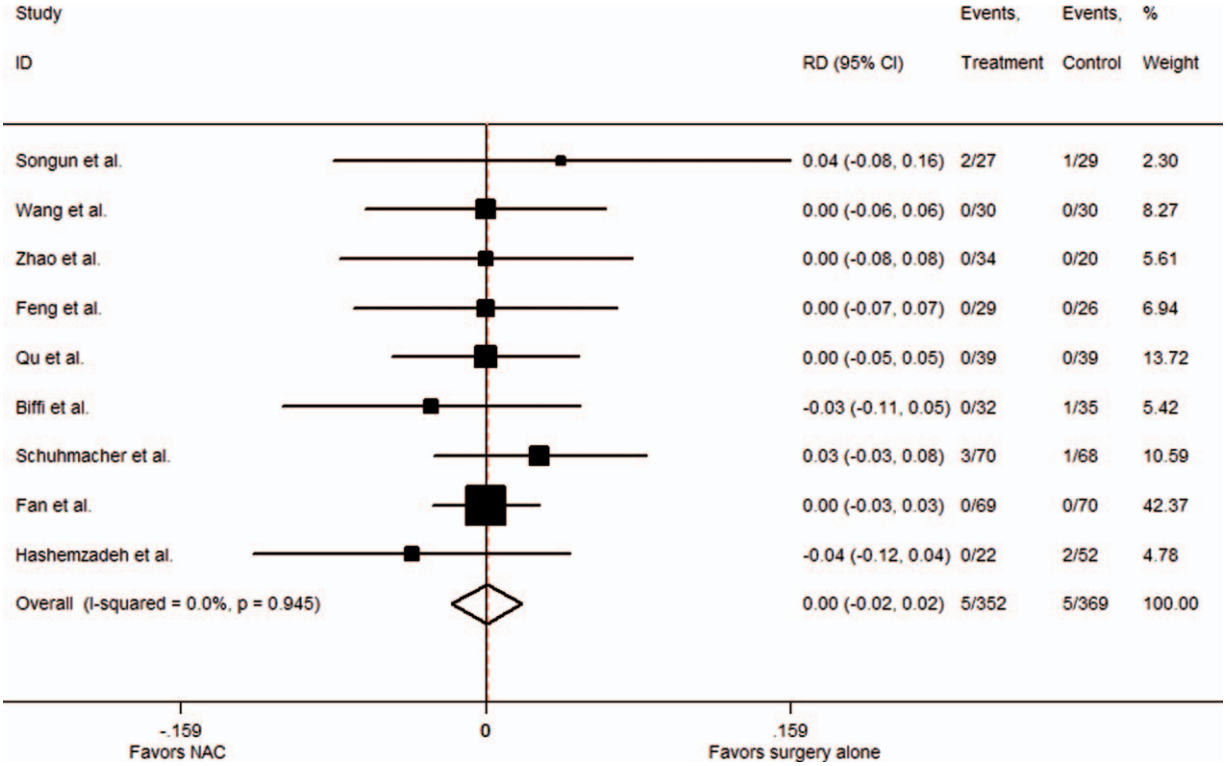

Figure 4. Postoperative mortality for neoadjuvant chemotherapy plus surgery compared with surgery alone.

NAC in Europe disappeared during sensitivity analysis after excluding Schuhmacher et al's study[23] which had a higher rate of postoperative complications after NAC. Two factors were identified as possible factors contributing to the greater postoperative complications in Schuhmacher et al's study.[23] The first factor was that 95.75% of patients with NAC had D2 lymph node dissection compared to only 43% of patients in the MAGIC trial. Since D2 is a complicated and challenging surgical technique, while NAC can lead to tissue fibrosis with a consequent more difficult feasibility of the procedure, then a higher rate of surgical complications might occur; the second factor was that patients in this study were operated in low-volume institutions where D2 lymphadenectomy may not be routinely carried out. Many studies have concluded that D2 can be considered safe in Western patients, at least when performed in experienced centers,[35] and D2 dissection should probably be

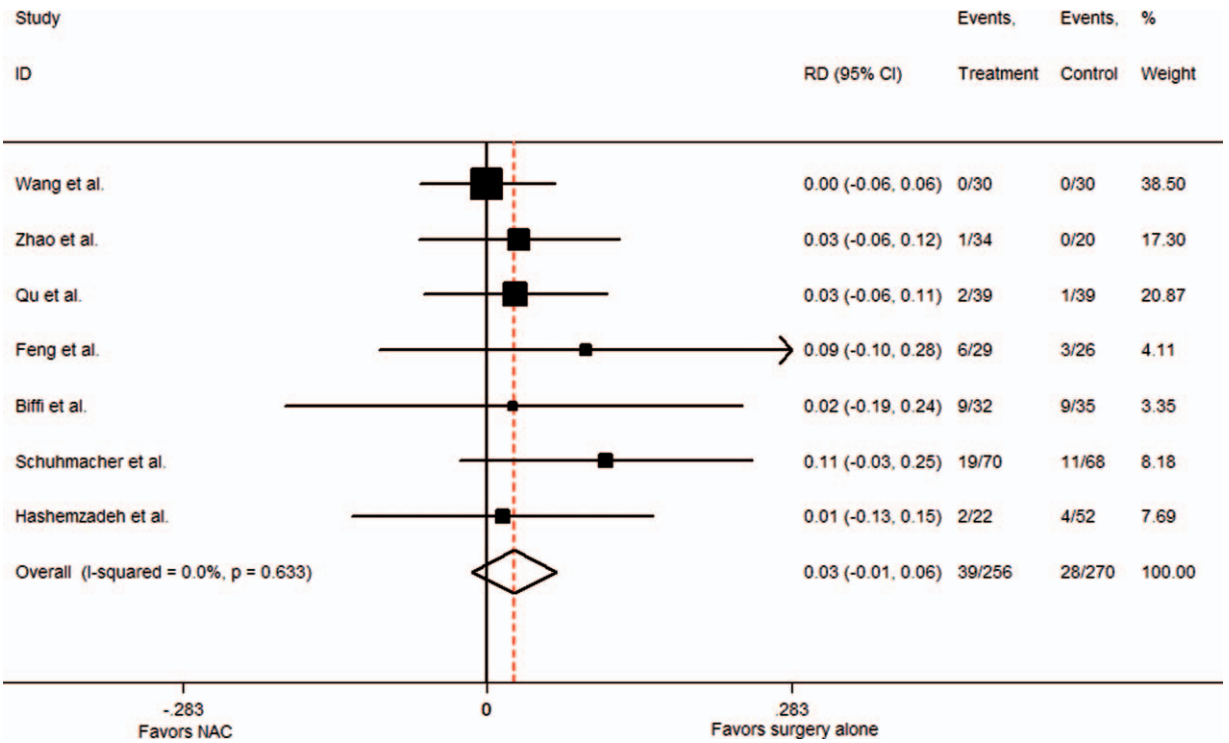

Figure 5. Any complication for neoadjuvant chemotherapy plus surgery compared with surgery alone.

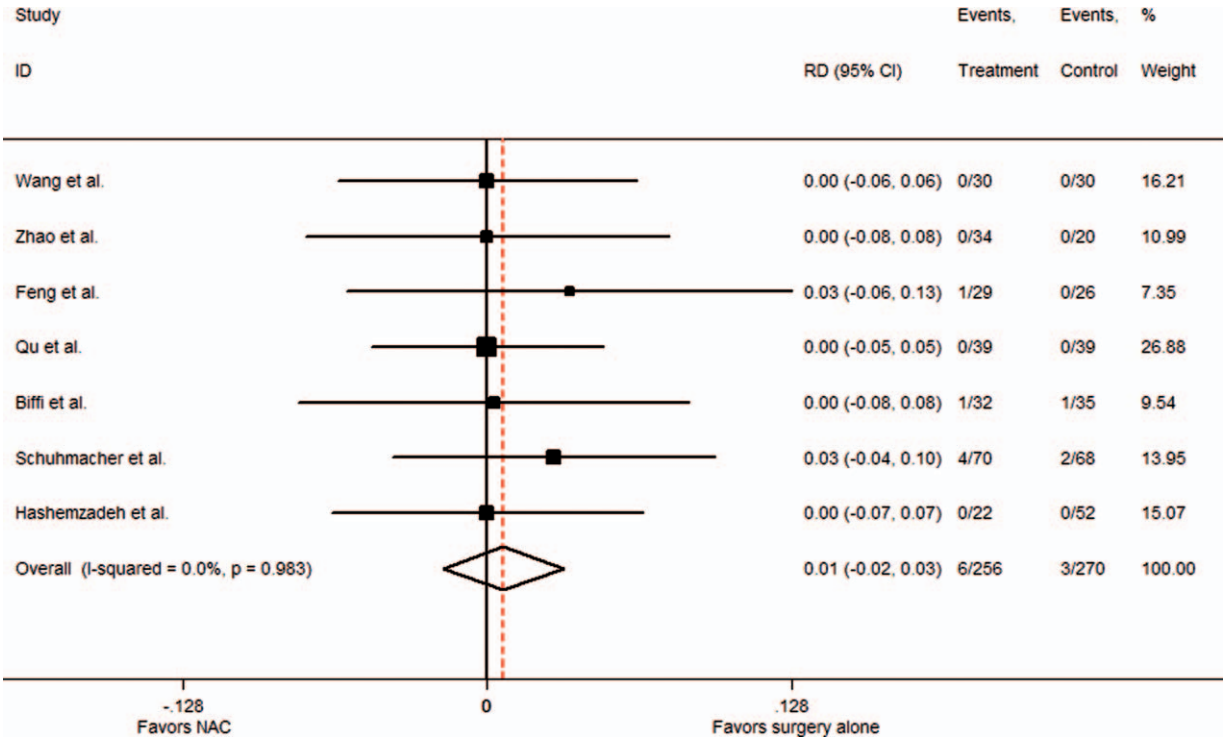

Figure 6. Anastomotic leakage for neoadjuvant chemotherapy plus surgery compared with surgery alone.

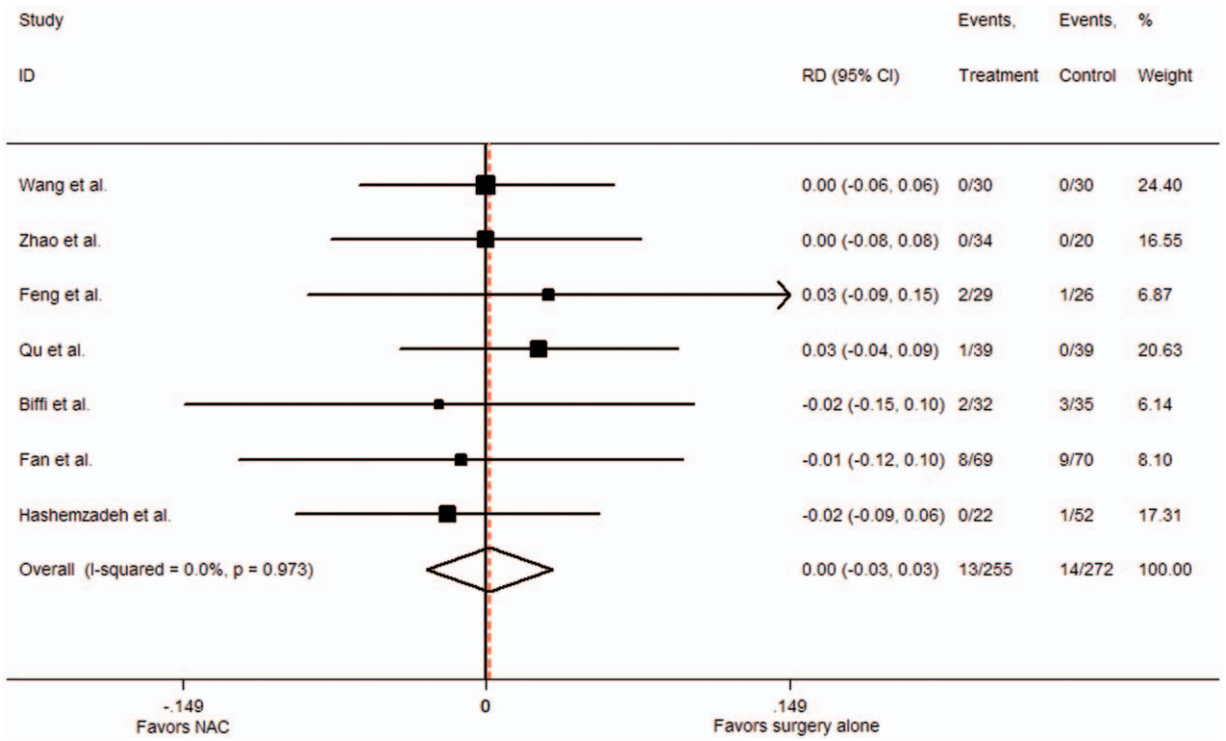

Figure 7. Pulmonary complication for neoadjuvant chemotherapy plus surgery compared with surgery alone.

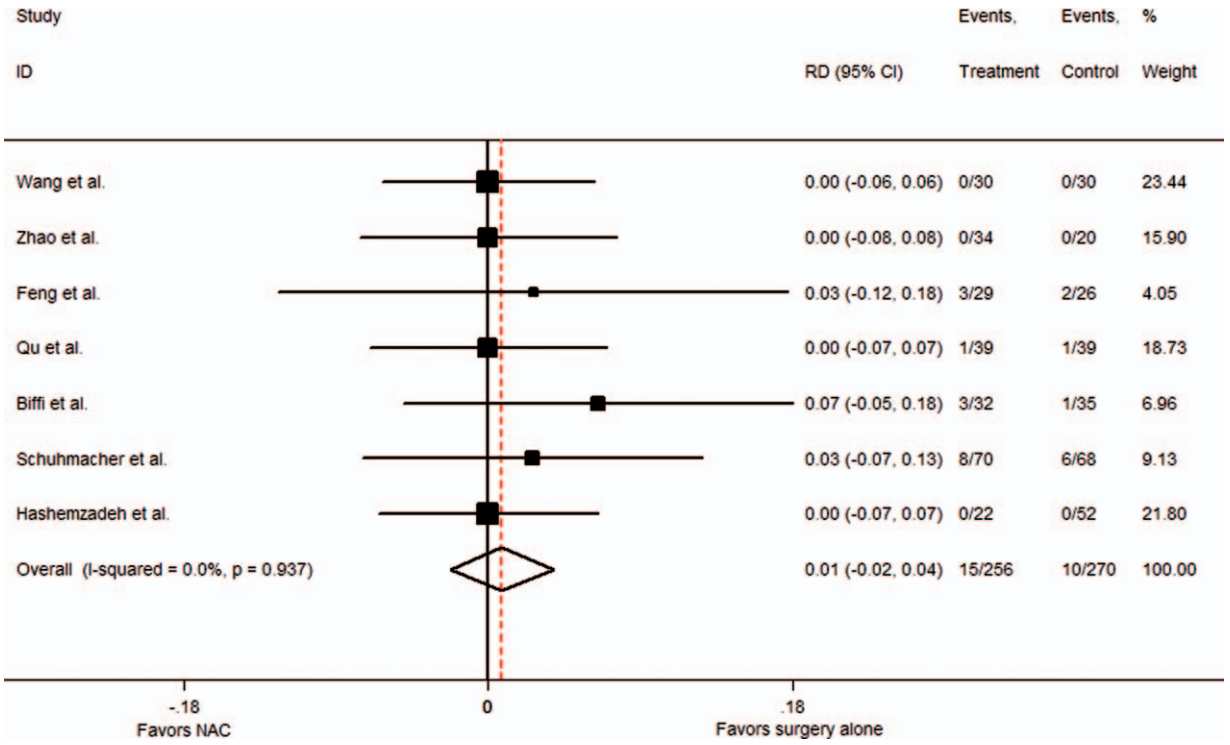

Figure 8. Surgical site infection for neoadjuvant chemotherapy plus surgery compared with surgery alone.

added to the growing list of procedures which are safer when performed in high-volume institutions.[36,37] The good news was that the risks of severe complications, including anastomotic leakage and pulmonary complications, were similar between the 2 groups for European patients.

This meta-analysis provided some additional insights into the feasibility of NAC in gastric cancer, although it also has some limitations. First, most studies reported postoperative morbidity and mortality as secondary endpoints; therefore, it was sometimes impossible to extract the outcomes required for this meta-analysis. Second, there were variations in the definitions and classifications of complications in the included studies. A standard classification system to describe complications and their severity in randomized clinical trials is critical to improve the quality of future meta-analyses. Third, this meta-analysis only included patients with tumors of the gastroesophageal junction (Siewert II, III) and stomach; it still bears a risk of heterogeneity, and this risk is augmented since surgical approaches vary between the stomach and gastroesophageal junction. In addition, the drugs used for NAC varied among trials. Therefore, although statistical heterogeneity was not evident for our outcomes, there might be relevant clinical heterogeneity.

Neoadjuvant chemotherapy can be administered for locally advanced gastric cancer patients without increasing anastomotic leakage, any postoperative complications, pulmonary complications, surgical site infections, and postoperative mortality. More investigations are warranted to clarify whether NAC will increase postoperative morbidity and mortality in Western patients compared with surgery alone.

Author contributions

Funding acquisition: Huiyu Luo.
Investigation: Huiyu Luo, Liucheng Wu.
Project administration: Huiyu Luo, Yuzhou Qin, Jiansi Chen.
Conceptualization: Liucheng Wu.
Methodology: Liucheng Wu, Yuzhou Qin.
Resources: Mingwei Huang.
Software: Mingwei Huang, Qinwen Jin.
Validation: Qinwen Jin, Jiansi Chen.
Supervision: Jiansi Chen.
Writing – original draft: Huiyu Luo.
Writing – review & editing: Huiyu Luo.

References

[1] Chen W, et al. Cancer statistics in China, 2015. CA: a cancer journal for clinicians 2016;66:115–32.
[2] Dong S, et al. Neoadjuvant chemotherapy in controlling lymph node metastasis for locally advanced gastric cancer in a Chinese population. J Chemother 2016;28:59–64.
[3] Sasako M. Principles of surgical treatment for curable gastric cancer. J Clin Oncol 2003;21:274s–5s.
[4] Proserpio I, et al. Multimodal treatment of gastric cancer. World J Gastrointest Surg 2014;6:55–8.
[5] Cunningham D, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11–20.
[6] Ychou M, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715–21.
[7] Xiong, BH, et al., An updated meta-analysis of randomized controlled trial assessing the effect of neoadjuvant chemotherapy in advanced gastric cancer 2014: Centre for Reviews and Dissemination (UK) 2014;32:272-284.
[8] Kumagai K, et al. Meta-analysis of postoperative morbidity and perioperative mortality in patients receiving neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal and gastro-oesophageal junctional cancers. Br J Surg 2014;101:321–38.
[9] Ronellenfitsch U, et al. Perioperative chemo (radio) therapy versus primary surgery for resectable adenocarcinoma of the stomach, gastroesophageal junction, and lower esophagus. Cochrane Database Syst Rev 2013;31:CD008107.
[10] Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions.Vol. 4. 2011;John Wiley & Sons,
[11] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;1088–101.
[12] Egger M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[13] Peters JL, et al. Comparison of two methods to detect publication bias in meta-analysis. JAMA 2006;295:676–80.
[14] Moher D, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
[15] Zhang GP, Wu Y, Chen HL. Neoadjuvant chemotherapy in treatment of patients with advanced distal gastric cancer. J Prac Oncol 2015;30:272–5.
[16] Hashemzadeh S, et al. The effects of neoadjuvant chemotherapy on resectability of locally-advanced gastric adenocarcinoma: a clinical trial. Int J Surg 2014;12:1061–9.
[17] Zhao Q, et al. Effects of XELOX regimen as neoadjuvant chemotherapy on radical resection rate and prognosis in patients with advanced gastric cancer. Zhonghua Zhong Liu Za Zhi 2013;35:773–7.
[18] Piessen G, et al. Phase II/III multicentre randomised controlled trial evaluating a strategy of primary surgery and adjuvant chemotherapy versus peri-operative chemotherapy for resectable gastric signet ring cell adenocarcinomas - PRODIGE 19 - FFCD1103 - ADCI002. BMC Cancer 2013;13:1471–2407.
[19] Basi A, et al. Comparing efficacy of preoperative neo-adjuvant chemotherapy and surgery versus surgery alone in patients with resectable gastroesophageal cancer. Int J Hematol Oncol Stem Cell Res 2013;7:24–8.
[20] Yoshikawa T, et al. A comparison of multimodality treatment: two and four courses of neoadjuvant chemotherapy using S-1/CDDP or S-1/CDDP/docetaxel followed by surgery and S-1 adjuvant chemotherapy for macroscopically resectable serosa-positive gastric cancer: a randomized phase II trial (COMPASS-D trial). Jpn J Clin Oncol 2012;42:74–7.
[21] Fan CG, Li GL. Effect of neoadjuvant chemotherapy on the postoperative pulmonary infection of patients with advanced gastric cancer. Zhonghua Wei Chang Wai Ke Za Zhi 2011;14:503–5.
[22] Dikken JL, et al. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS). BMC Cancer 2011;11:1471–2407.
[23] Schuhmacher C, et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. J Clin Oncol 2010;28:5210–8.
[24] Qu JJ, et al. A clinical study of paclitaxel combined with FOLFOX4 regimen as neoadjuvant chemotherapy for advanced gastric cancer. Zhonghua Wei Chang Wai Ke Za Zhi 2010;13:664–7.
[25] Imano M, et al. Prospective randomized trial of short-term neoadjuvant chemotherapy for advanced gastric cancer. Eur J Surg Oncol 2010;36:963–8.
[26] Biffi R, et al. Surgical outcome after docetaxel-based neoadjuvant chemotherapy in locally-advanced gastric cancer. World J Gastroenterol 2010;16:868–74.
[27] Nio Y, et al. A randomized consent design trial of neoadjuvant chemotherapy with tegafur plus uracil (UFT) for gastric cancer: a single institute study. Anticancer Res 2004;24:1879–87.
[28] Hartgrink HH, et al. Neo-adjuvant chemotherapy for operable gastric cancer: long term results of the Dutch randomised FAMTX trial. Eur J Surg Oncol 2004;30:643–9.
[29] Songun I, et al. Chemotherapy for operable gastric cancer: results of the Dutch randomised FAMTX trial. Eur J Cancer 1999;35:558–62.
[30] Feng L, et al. Treatment out come of neoadjuvant chemotherapy for Bormann's type IV gastric cancer. Chin J Cancer Prev Treat 2008;15:1022–4.
[31] Zhao W-H, et al. Apoptosis induced by preoperative oral 5'-DFUR administration in gastric adenocarcinoma and its mechanism of action. World J Gastroenterol 2006;12:1356–61.
[32] Wang X-L, et al. A favorable impact of preoperative FPLC chemotherapy on patients with gastric cardia cancer. Oncology Rep 2000;7:241–4.
[33] Kobayashi T, Kimura T. Long-term outcome of preoperative chemotherapy with 5'-deoxy-5-fluorouridine (5'-DFUR) for gastric cancer. Gan to kagaku ryoho. Gan To Kagaku Ryoho 2000;27:1521–6.

[34] Yonemura Y, et al. Neoadjuvant chemotherapy for high-grade advanced gastric cancer. World J Gastroenterol 1993;17:256–61.
[35] Biffi R, et al. Extended lymph node dissection without routine splenopancreatectomy for treatment of gastric cancer: low morbidity and mortality rates in a single center series of 250 patients. J Surg Oncol 2006;93:394–400.
[36] Degiuli M, et al. Morbidity and mortality after D1 and D2 gastrectomy for cancer: interim analysis of the Italian Gastric Cancer Study Group (IGCSG) randomised surgical trial. Eur J Surg Oncol 2004;30:303–8.
[37] Sierra A, et al. Role of the extended lymphadenectomy in gastric cancer surgery: experience in a single institution. Ann Surg Oncol 2003;10:219–26.