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Comparison of neoadjuvant chemotherapy followed by surgery *vs.* surgery alone for locally advanced gastric cancer: a meta-analysis

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Abstract

Background: The neoadjuvant chemotherapy is increasingly used in advanced gastric cancer, but the effects on safety and survival are still controversial. The objective of this meta-analysis was to compare the overall survival and short-term surgical outcomes between neoadjuvant chemotherapy followed by surgery (NACS) and surgery alone (SA) for locally advanced gastric cancer.

Methods: Databases (PubMed, Embase, Web of Science, Cochrane Library, and Google Scholar) were explored for relative studies from January 2000 to January 2021. The quality of randomized controlled trials and cohort studies was evaluated using the modified Jadad scoring system and the Newcastle-Ottawa scale, respectively. The Review Manager software (version 5.3) was used to perform this meta-analysis. The overall survival was evaluated as the primary outcome, while perioperative indicators and post-operative complications were evaluated as the secondary outcomes.

Results: Twenty studies, including 1420 NACS cases and 1942 SA cases, were enrolled. The results showed that there were no significant differences in overall survival ($P = 0.240$), harvested lymph nodes ($P = 0.200$), total complications ($P = 0.080$), and 30-day post-operative mortality ($P = 0.490$) between the NACS and SA groups. However, the NACS group was associated with a longer operation time ($P < 0.0001$), a higher R0 resection rate ($P = 0.003$), less reoperation ($P = 0.030$), and less anastomotic leakage ($P = 0.007$) compared with SA group.

Conclusions: Compared with SA, NACS was considered safe and feasible for improved R0 resection rate as well as decreased reoperation and anastomotic leakage. While unbenefited overall survival indicated a less important effect of NACS on long-term oncological outcomes.

Keywords: Neoadjuvant chemotherapy followed by surgery; Surgery alone; Advanced gastric cancer; Gastrectomy; Overall survival; Meta-analysis

Introduction

Gastric cancer (GC) is one of the most common malignancies globally. In 2020, there were more than one million new cases of GC and 768,800 deaths worldwide.[1] According to the estimated number of new cases and cancer-related deaths in 2020, the GC ranked second and third among all tumors, respectively.[2] Due to the lack of typical clinical symptoms in early GC, most patients have progressed to the advanced stage at the initial treatment with poor prognosis. Only 40% to 50% cases of advanced gastric cancer (AGC) achieved radical resection (R0 resection). Even after that, the recurrence or death may occur in 50% to 90% of patients, and the 5-year overall survival rate is <30%.[3] At present, the treatment methods are diverse, including gastrectomy, post-operative chemotherapy, radiotherapy or chemoradiotherapy, targeted therapy, and immunotherapy.[4,5] The standard surgical procedure for AGC is radical gastrectomy with D2 lymph node dissection, and the second station lymph node is additionally removed for those with extensive lymph node metastasis; however, the prognosis remains poor, even after surgery and post-operative chemotherapy.[6,7]

In 1989, Wilke *et al*[8] first treated GC patients with neoadjuvant chemotherapy. The degraded tumor after treatment and successful radical resection of the focus with complete lymph node dissection indicated the effectiveness of neoadjuvant chemotherapy. Later, more researchers

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focused their attention to neoadjuvant therapy.[9] The multicenter phase III clinical trial of the Fédération Nationale des Centres de Lutte Contre le Cancer revealed that the neoadjuvant chemotherapy group showed a significantly better outcome than that in the surgery group in terms of R0 resection rate, overall survival, and disease-free survival.[10] The Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial found that the rate of post-operative complications and the number of deaths within 30 days after surgery were similar. The resected tumors were significantly smaller and less advanced in the neoadjuvant chemotherapy followed by surgery (NACS) group. In addition, compared with surgery alone (SA) group, patients in the NACS group had a higher likelihood of overall survival.[11] However, the reported downstaging of tumor in the MAGIC trial was based on incomplete data. The tumor size was not recorded in 35% of the perioperative chemotherapy group and 28% of the surgery group before treatment. Moreover, computed tomography was not precise enough in determining the local tumor stage and nodal status of AGC, compared with endoscopic ultrasonography.[12]

Pre-operative adjuvant chemotherapy combined with post-operative adjuvant therapy was included in the 2018 version of the National Comprehensive Cancer Network (NCCN) guideline as an optional treatment (category 2B) for prospective resectable AGC cases (≥cT2, any N).[13] However, neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy has not been recommended as a conventional treatment method by the Japanese Gastric Cancer Association (JGCA) guideline and is still defined as a research treatment.[14] Considering the current research status, it needs to be further confirmed whether neoadjuvant chemotherapy can bring benefits to patients with AGC.[15] This meta-analysis aimed to compare the surgical and oncological outcomes between NACS and SA for AGC.

Methods

Literature search

Literature published between January 2000 and January 2021 was searched from PubMed, Embase, Web of Science, Google Scholar, and Cochrane Library databases, with the following keywords: ("gastric neoplasm" OR "gastric cancer" OR "gastric adenocarcinoma" OR "stomach neoplasm") AND ("neoadjuvant chemotherapy" OR "neoadjuvant treatment" OR "neoadjuvant therapy") AND ("randomized controlled trial" OR "RCT" OR "controlled clinical trial" OR "cohort studies") AND ("gastric surgery" OR "gastrectomy") AND ("overall survival" OR "survival"). In addition, all references listed in this article were manually searched, and the language was limited to English. The flowchart is shown in Figure 1.

Inclusion criteria

All the included documents satisfied the following criteria: (1) the study was a randomized controlled trial (RCT) or a high-quality retrospective comparative non-randomized study (RCNT) published in the last 20 years; (2) patients with AGC underwent NACS or SA; (3) there were no limitations in surgical techniques, chemotherapy regimens, and cycles; and (4) the latest release was chosen when articles were published by the same institution or author.

Exclusion criteria

Case reports, literature reviews, and non-controlled studies were not involved. Studies enrolling patients with early GC, other stomach diseases, or simple gastroesophageal junction cancer were not included. Cases that underwent pre-operative neoadjuvant radiotherapy or studies that failed to provide valid data for meta-analysis were excluded.

Data collection and literature quality evaluation

Potential literature that complied with the above criteria was searched [Figure 1], and data were extracted with the standard data collection table. A total of 20 articles (six RCT and 14 RCNT studies) were included, with a total of 3362 patients with AGC. Among them, 1420 cases were in the NACS group and 1942 cases were in the SA group. The quality of RCTs and RCNTs was evaluated using the modified Jadad scoring system or the Newcastle-Ottawa scale (NOS) literature quality assessment scale, respectively.[16,17]

Data extraction

The following items were extracted from all enrolled studies: date of publication, author, country, literature type, sample size, age, gender, body mass index, surgical procedure and time, post-operative pathology, post-operative complications, mortality within 30 post-operative days, and overall survival.

Outcomes of interest and definitions

The primary outcome of interest in this meta-analysis was overall survival. The secondary outcomes included perioperative indicators and post-operative complications demonstrating surgical efficacy and safety. The perioperative indicators included operative time, number of harvested lymph nodes, and R0 resection rate. Moreover, the post-operative complications comprised of total complications, 30-day post-operative mortality, each grade of complications according to the Clavien-Dindo classification, reoperation, anastomotic leakage, intra-abdominal abscess, ileus, pneumonia, and wound infection.

Statistical analysis

The meta-analysis was performed using Review Manager version 5.3 (the Cochrane Collaboration, London, UK) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[18] The weighted mean differences (WMDs), risk ratios (RRs), and hazard ratios (HRs) were used to present the continuous, dichotomous, and survival outcomes, respectively. Furthermore, the heterogeneity of the included studies was

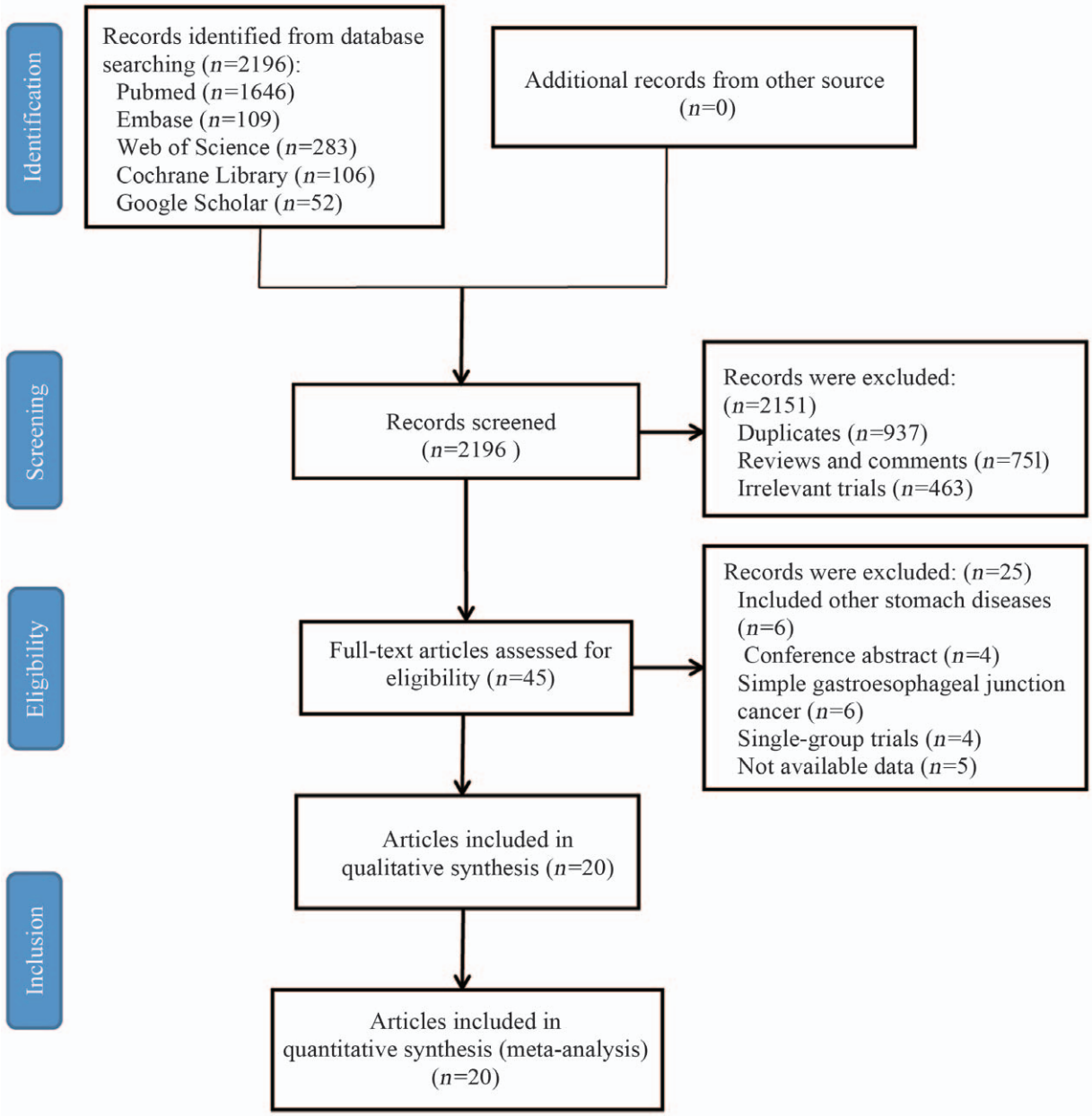

Figure 1: PRISMA flow diagram of literature search in this meta-analysis on comparison of surgical outcome of NACS *vs.* SA for locally advanced gastric cancer. NACS: Neoadjuvant chemotherapy followed by surgery; PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses; SA: Surgery alone.

evaluated using the Cochrane Q value and I^2 test. As a result of the I^2 value, the fixed-effects model was used when no obvious heterogeneity ($I^2 \leq 50\%$) was observed; otherwise, the random-effects model would be applied. Moreover, the overall survival was shown by the HRs and 95% confidence interval (CI). We directly extracted the raw data when the study provided or calculated the value by extracting the data from the Kaplan-Meier curves using Engauge Digitiser version 10.7 (free software foundation) according to Tierney *et al*[19]. $P < 0.050$ was considered statistically significant. Sensitivity analysis was performed using a one-at-a-time method to estimate the stability of results, which excluded one study from each combined analysis at one time and recalculated the HRs or RRs to compare the results before and after.[20] The publication bias was estimated using Egger and Begg tests in addition to the funnel plot for each outcome.[20,21]

Results

Characteristics of selected studies

The basic features of the 20 studies involved are shown in Table 1, six for RCT and 14 for RCNT studies, with 3362 GC patients, including 1420 in the NACS group and 1942 in the SA group.[10,22-39] All studies were published between January 2000 and January 2021. More specifically, Schuhmacher *et al*[32] and Fuentes *et al*[25] incorporated patients with gastroesophageal junction cancer, and the surgical procedure also included D1 dissection. Biffi

Table 1: Summary of basic characteristics of trials comparing neoadjuvant chemotherapy followed by surgery *vs.* surgery alone for locally advanced gastric cancer ($n = 20$) included.

Study, Year	Study type	Tumor type	CT regimens	Number of patients			Male/female		Mean age (years)		cTNM (7th): II		cTNM (7th): III		DG/TG		Lymphadenectomy
				Total	NACS	SA	NACS	SA	NACS	SA	NACS	SA	NACS	SA	NACS	SA	
Kochi, 2006	RCNT	GC	CF	39	14	25	12/2	20/5	64	69	0	0	6	25	2/12	10/15	D2
Schuhmacher, 2010	RCT	GC + EGJ	Cisplatin	144	72	72	50/22	50/22	58	58	NR	NR	NR	NR	NR	NR	D1 + D2
Biffi, 2010	RCT	GC	TCF	69	34	35	23/11	25/10	57	59	14	13	18	21	20/11	24/10	D2 + D3
Imano, 2010	RCT	GC	CF	63	47	16	32/15	9/7	60.5	59.5	NR	NR	NR	NR	34/13	11/5	D2
Ychou, 2011	RCT	EGJ	CF	224	113	111	96/17	82/29	63	63	NR	NR	NR	NR	15/23	14/26	D2
Li, 2011	RCNT	GC	mFOLFOX	377	110	260	83/27	194/66	55.5	59.7	NR	NR	NR	NR	36/47	156/66	D2
Ruf, 2014	RCNT	GC	PELF	64	26	38	20/6	23/15	64.5	73	NR	NR	NR	NR	1/25	7/31	D2
Ahn, 2014	RCNT	GC	mFOLFOX	140	48	92	42/6	59/33	53.8	58.9	NR	NR	NR	NR	26/20	47/9	D2
Téoule, 2015	RCNT	GC	ECF, ECX, FOLFIRI	135	30	105	21/9	62/43	61.7	65.6	8	18	9	31	3/27	8/95	D2
Feng, 2015	RCNT	GC	SOX	170	80	90	63/17	71/19	60	59	4	10	76	80	33/23	42/30	D2
Fuentes, 2016	RCNT	GC + EGJ	EOX, EOF, ECF, FOLFOX	453	145	308	104/41	199/109	63	71	52	112	46	78	26/45	146/80	D1 + D2
Ramachandra, 2019	RCT	GC	CF	60	30	30	22/8	18/12	50.7	51.8	NR	NR	NR	NR	20/7	19/5	D2
Wu, 2019	RCNT	GC	NR	172	86	86	68/18	71/15	54.8	55.0	5	81	5	81	36/36	37/37	D2
Wu, 2019	RCNT	GC	CF	460	230	230	167/63	164/66	56.5	57	49	44	181	186	156/74	163/67	D2
Kano, 2019	RCNT	GC	S-1 + Docetaxel	76	39	37	32/7	29/8	69.3	70.4	17	10	22	27	16/23	10/27	D2
Terashima, 2019	RCT	GC	SOX	300	151	149	87/64	89/60	64	62	48	43	60	65	16/117	21/123	D2
Charruf, 2019	RCNT	GC	CF	90	45	45	34/11	34/11	63.0	64.1	NR	NR	NR	NR	20/25	20/25	D2
Umeda, 2020	RCNT	GC	CF, DCS	192	64	128	50/14	110/18	NR	NR	0	0	64	128	21/43	46/82	D2
Li, 2020	RCNT	GC	SOX, DOS, FOLFOX	72	36	36	21/15	21/15	51.6	49.9	4	6	32	30	12/24	8/28	D2
Ma, 2020	RCNT	GC	EP, DOS, SOX	69	20	49	19/1	41/8	61.3	65.0	4	7	18	42	14/6	47/2	D2

CF: Cisplatin + fluorouracil; CT: Chemotherapy; D1: D1 lymph node dissection; D2: D2 lymph node dissection; D3: D3 lymph node dissection; DCS: Docetaxel + cisplatin + S-1; DG: Distal gastrectomy; EGJ: Esophagogastric junction; EOF: Epirubicin + oxaliplatin + fluorouracil; EP: Etoposide + cisplatin; EOX: Epirubicin + oxaliplatin; FOLFIRI: Folinic acid + fluorouracil + irinotecan; GC: Gastric cancer; mFOLFOX: Folinic acid + fluorouracil + oxaliplatin; NACS: Neoadjuvant chemotherapy followed by surgery; NR: Not reported; PELF: Cisplatin + epirubicin + leucovorin + fluorouracil; RCT: Randomized controlled trial; RCNT: Retrospective comparative non-randomized trial; SA: Surgery alone; SOX: S-1 + oxaliplatin; TCF: Docetaxel + cisplatin + fluorouracil; TG: Total gastrectomy.

Table 2: Quality assessment of randomized controlled trials ($n = 6$) included.

Study, year	Randomization	Allocation concealment	Blinding	Withdrawal and dropout	Jadad score*
Schuhmacher, 2010	Unclear	Unclear	Unclear	Well reported	4
Biffi, 2010	Unclear	Unclear	Unclear	Well reported	4
Imano, 2010	Unclear	Unclear	Unclear	Well reported	4
Ychou, 2011	Well reported	Unclear	Unclear	Well reported	4
Ramachandra, 2019	Well reported	Unclear	Unclear	Well reported	5
Terashima, 2019	Well reported	Unclear	Unclear	Well reported	5

* Based on modified Jadad risk assessment form.

Table 3: Quality assessment of retrospective comparative non-randomized trials ($n = 14$) included.

Study, year	Selection	Comparability	Outcome	NOS scores
Kochi, 2006	2	2	2	6
Li, 2011	2	2	2	6
Ruf, 2014	2	2	3	7
Ahn, 2014	2	2	2	6
Téoule, 2015	2	1	2	5
Feng, 2015	2	2	2	6
Fuentes, 2016	1	2	2	5
Wu, 2019	3	2	2	7
Wu, 2019	2	2	3	7
Kano, 2019	3	2	3	8
Charruf, 2019	2	3	2	7
Umeda, 2020	2	3	2	7
Li, 2020	2	3	3	8
Ma, 2020	2	1	2	5

NOS: Newcastle-Ottawa scale.

et al[23] performed D3 dissection in patients enrolled in the study. The pathological types of patients in Li *et al*'s[36] study and Ma *et al*'s[37] study were limited to gastric signet ring cell carcinoma and mixed adenoneuroendocrine carcinoma, respectively.

Literature quality of included studies

The qualities of the 20 papers included were evaluated. Among them, we used the improved Jadad risk assessment form to evaluate the literature quality of six RCT studies from four aspects: randomization, allocation concealment, blindness, and withdrawal and dropout. The specific evaluation results are shown in Table 2. All six RCT studies were of high quality, and the remaining RCNT studies were evaluated using the NOS literature quality assessment scale as shown in Table 3, which included three aspects: study population selection, inter-group comparability, and result measurement. All study scores were more than four points.

Meta-analysis of primary outcomes

Overall survival

Eight studies that reported overall survival matched the inclusion criteria.[10,27,28,31,32,36,37,39] No heterogeneity was found among the included studies ($P = 0.860$, $I^2 = 0\%$), and a fixed-effects model was used for meta-analysis. No publication bias was found using Egger ($t = 0.24$, $P = 0.820$) and Begg tests ($z_c = -0.25$, $P = 0.800$) [Supplementary Figure 1A, http://links.lww.com/CM9/A641]. The pooled HR for overall survival, based on these studies, showed no statistical difference in patients in the NACS group compared with those in the SA group (HR = 0.86, 95% CI: 0.67–1.11, $P = 0.240$) [Figure 2], which was robust according to the sensitivity analysis [Supplementary Figure 2A, http://links.lww.com/CM9/A641].

Meta-analysis of secondary outcomes

Operation time

In seven studies reporting the operation time, a fixed-effects model analysis ($P = 0.580$, $I^2 = 0\%$) was applied due to the absence of heterogeneity.[29,30,33,35-38] The funnel plot suggested there was no publication bias (Egger test, $t = -0.21$, $P = 0.840$; Begg test, $z_c = 0.30$, $P = 0.760$) [Supplementary Figure 1B, http://links.lww.com/CM9/A641]. The results showed that the operation time in the NACS group was significantly longer than that in the SA group (WMD = 14.27, 95% CI: 6.20–22.34, $P < 0.0001$). A statistically significant difference in operation time between the two groups could be observed [Figure 3A]. The result was reliable based on the sensitivity analysis [Supplementary Figure 2B, http://links.lww.com/CM9/A641].

Number of harvested lymph nodes

Six studies compared the number of lymph node dissection in both groups, and the random-effects model was chosen for relatively moderate heterogeneity ($P = 0.06$, $I^2 = 53\%$).[22,29,30,35,37,38] There was no obvious publication bias according to the funnel plot (Egger test, $t = -0.46$, $P = 0.670$; Begg test, $z_c = 0.00$, $P = 1.000$) [Supplementary Figure 1C, http://links.lww.com/CM9/A641]. The results showed that the number of harvested lymph nodes was not influenced by different treatments (WMD = −1.60, 95% CI: −4.06 to 0.87, $P = 0.200$) between the NACS and SA groups [Table 4]. The sensitivity analysis suggested that the result was credible [Supplementary Figure 2C, http://links.lww.com/CM9/A641].

R0 resection rate

Nine studies describing the R0 resection rate were involved in the analysis, including 590 patients in the NACS group

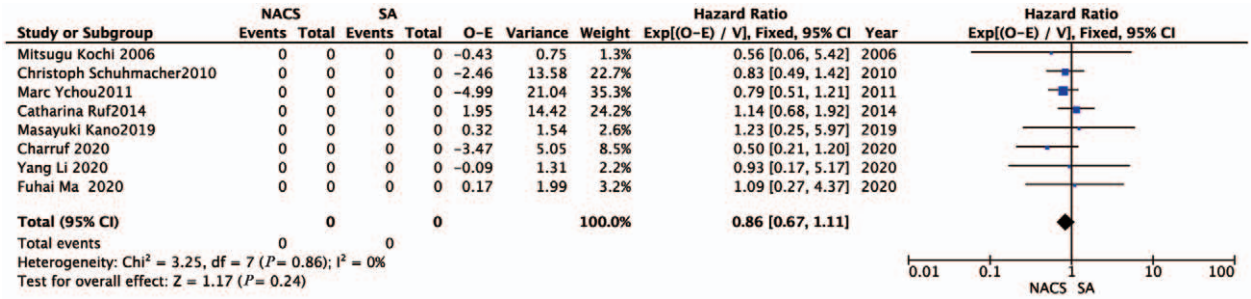

Figure 2: Forest plots of the overall survival of NACS *vs.* SA for locally advanced gastric cancer. CI: Confidence interval; HR: Hazard ratio; NACS: Neoadjuvant chemotherapy followed by surgery; SA: Surgery alone.

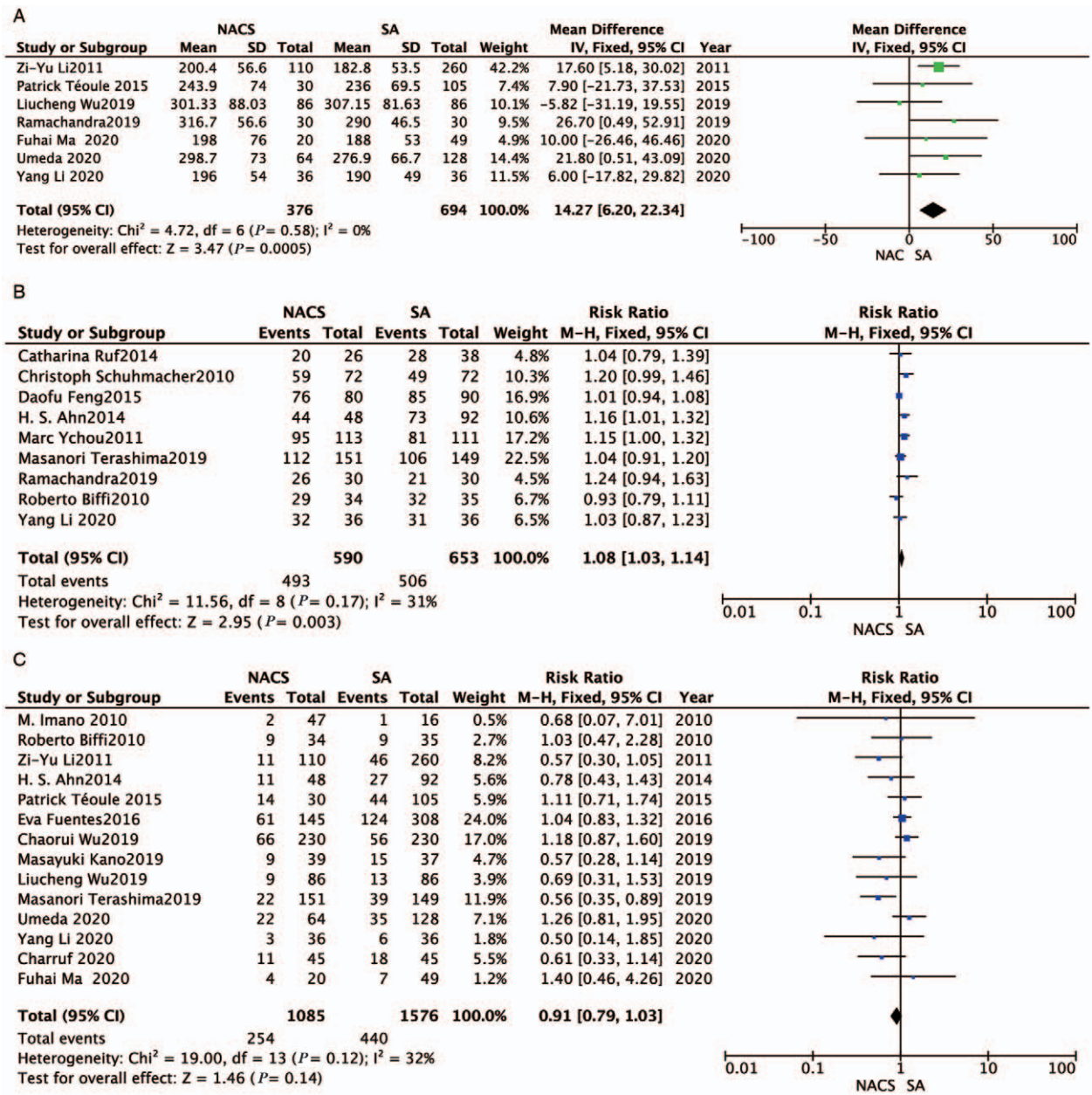

Figure 3: Forest plots of analysis on (A) operation time, (B) R0 resection rate, and (C) total complications of NACS *vs.* SA for locally advanced gastric cancer. CI: Confidence interval; NACS: Neoadjuvant chemotherapy followed by surgery; RR: risk ratio; SA: Surgery alone.

Table 4: Results of the meta-analysis in interested outcomes for locally advanced gastric cancer patients receiving NACS/SA treatment.

Outcome of interest	*N*	NACS/SA	Statistical method	WMD/RR/OR/HR (95% CI)	df	*P* value	I^2 (%)	*P* value
Overall survival	8	–	HR, Fixed, HR (95% CI)	0.86 (0.67, 1.11)	7	0.86	0	0.240
Operation time	7	376/694	IV, Fixed, WMD (95% CI)	14.27 (6.20, 22.34)	6	0.58	0	< 0.001
Number of harvested lymph nodes	6	358/645	IV, Random, WMD (95% CI)	−1.60 (−4.06, 0.87)	5	0.06	53	0.200
R0 resection rate	9	493/506	MH, Fixed, RR (95% CI)	1.08 (1.03, 1.14)	8	0.17	31	0.003
Total complications	14	254/440	MH, Fixed, RR (95% CI)	0.91 (0.79, 1.03)	13	0.12	32	0.140
30-day post-operative mortality	15	14/28	MH, Fixed, RR (95% CI)	0.80 (0.43, 1.50)	9	0.78	0	0.490
Grade II	10	148/224	MH, Fixed, RR (95% CI)	1.00 (0.83, 1.20)	9	0.33	12	0.980
Grade III	7	51/116	MH, Fixed, RR (95% CI)	0.79 (0.52, 1.04)	6	0.32	15	0.080
Grade IV	9	41/54	MH, Fixed, RR (95% CI)	0.95 (0.65, 1.40)	7	0.34	0	0.810
Reoperation	6	12/56	MH, Fixed, RR (95% CI)	0.52 (0.29, 0.93)	5	0.31	16	0.030
Anastomotic leakage	16	24/74	MH, Fixed, RR (95% CI)	0.53 (0.34, 0.84)	14	0.98	0	0.007
Intra-abdominal abscess	12	29/29	MH, Fixed, RR (95% CI)	1.50 (0.91, 2.48)	11	0.84	0	0.110
Ileus	11	16/38	MH, Fixed, RR (95% CI)	0.66 (0.38, 1.16)	9	0.48	0	0.150
Pneumonia	14	40/66	MH, Fixed, RR (95% CI)	0.91 (0.63, 1.32)	13	0.49	0	0.620
Wound infection	13	20/48	MH, Fixed, RR (95% CI)	0.76 (0.46, 1.25)	12	0.86	0	0.280

CI: Confidence interval; HR: Hazard ratio; IV: Inverse variance methods; MH: Mantel-Haenszel; NACS: Neoadjuvant chemotherapy followed by surgery; OR: Odds ratio; RR: Risk ratio; SA: Surgery alone; WMD: Weight mean difference.

and 653 in the SA group.[10,22-24,30-32,34,36] The funnel plot showed that the publication bias was ruled out (Egger test, $t = 1.38$, $P = 0.210$; Begg test, $z_c = 0.21$, $P = 0.840$) [Supplementary Figure 1D, http://links.lww.com/CM9/A641]. The fixed-effects model was used due to acceptable heterogeneity ($P = 0.170$, $I^2 = 31\%$). The results showed that the R0 resection rate in the NACS group was higher than that in the SA group, and the difference was statistically significant (RR = 1.08, 95% CI [1.03, 1.14], $P = 0.003$) [Figure 3B]. The result was reliable based on the sensitivity analysis [Supplementary Figure 2D, http://links.lww.com/CM9/A641].

Total complications

Data from 14 studies, which reported total complications after, were extracted, including 1085 patients in the NACS group and 1576 in the SA group.[22,23,25-27,29,33-40] A moderate heterogeneity was detected ($P = 0.120$, $I^2 = 32\%$), and a fixed-effects model was eligible in this analysis. No publication bias was found using Egger ($t = -1.92$, $P = 0.08$) and Begg tests ($z_c = -1.15$, $P = 0.25$) [Supplementary Figure 1E, http://links.lww.com/CM9/A641]. No significant difference in total post-operative complications could be observed between the two groups (RR = 0.91, 95% CI: 0.79–1.03, $P = 0.140$) [Figure 3C], which was robust according to the sensitivity analysis [Supplementary Figure 2E, http://links.lww.com/CM9/A641].

Thirty-day post-operative mortality

Data were extracted from 15 studies, which reported a 30-day post-operative mortality after gastrectomy in each group (NACS *vs.* SA: 14/1199 *vs.* 28/1730).[10,22,23,25,27,29,30,32-35,37-40] A fixed-effects model was used as a result of undetected heterogeneity ($P = 0.780$, $I^2 = 0\%$). The funnel plot suggested there was no publication bias (Egger test, $t = -1.01$, $P = 0.34$; Begg test, $z_c = -0.45$, $P = 0.66$) [Supplementary Figure 1F, http://links.lww.com/CM9/A641]. To conclude, there was no significant difference in the 30-day post-operative mortality between the two groups (RR = 0.80, 95% CI: 0.43–1.50, $P = 0.490$) [Figure 4A]. The result was reliable based on the sensitivity analysis [Supplementary Figure 2F, http://links.lww.com/CM9/A641].

Each grade of complications according to the Clavien-Dindo classification

Ten studies reported on the classification of post-operative complications,[23,25,27,30,33-35,38-40] which were divided into five grades using the Clavien-Dindo system.[41] Grades II to IV of post-operative complications were analyzed by a fixed-effects model because of undetected heterogeneity, and the results showed that there was no statistically significant difference between the NACS and SA groups in any degree of complications. The details were as follows: Grade II (RR = 1.00, 95% CI: 0.83–1.20, $P = 0.980$), Grade III (RR = 0.79, 95% CI: 0.52–1.04, $P = 0.080$), and Grade IV (RR = 0.95, 95% CI: 0.65–1.40, $P = 0.810$) [Table 4]. Grades I and V were not analyzed because no related data were provided. There was no obvious publication bias according to the funnel plot [Supplementary Figure 1G–I, http://links.lww.com/CM9/A641]. The sensitivity analysis suggested the results were credible [Supplementary Figure 2G–I, http://links.lww.com/CM9/A641].

Reoperation

A total of 12 patients in the NACS group and 56 patients in the SA group underwent reoperation in six studies with relevant information.[22,23,25,29,33,38] A fixed-effects model

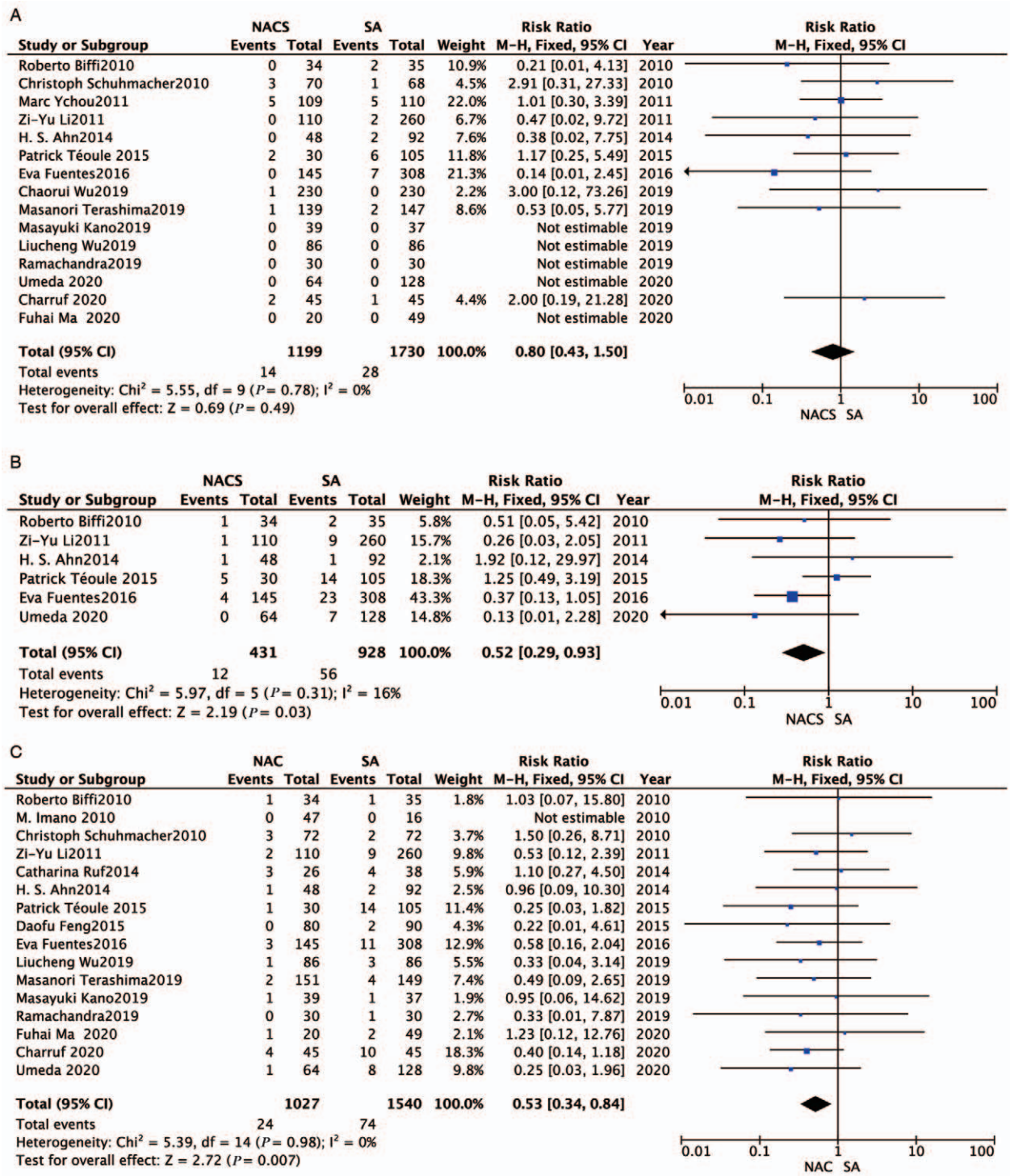

Figure 4: Forest plots of (A) 30-day post-operative mortality, (B) reoperation, and (C) anastomotic leakage of NACS *vs.* SA for locally advanced gastric cancer. CI: Confidence interval; NACS: Neoadjuvant chemotherapy followed by surgery; RR: risk ratio; SA: Surgery alone.

was used because of insignificant heterogeneity ($P = 0.310$, $I^2 = 16\%$). No publication bias was found by Egger ($t = -0.73$, $P = 0.510$) and Begg tests ($z_c = -0.19$, $P = 0.850$) [Supplementary Figure 1J, http://links.lww.com/CM9/A641]. Moreover, it was found that the reoperation rate was lower in the NACS group (RR = 0.52, 95% CI: 0.29–0.93, $P = 0.030$) [Figure 4B]. The result was reliable based on the sensitivity analysis [Supplementary Figure 2J, http://links.lww.com/CM9/A641].

Anastomotic leakage

Sixteen studies provided effective data for the incidence of anastomotic leakage after gastrectomy, including 1027 in

the NACS group and 1540 in the SA group, and a fixed-effects model was applied due to undetected heterogeneity ($P = 0.98$, $I^2 = 0\%$).[22-27,29-35,37-39] The funnel plot suggested no evidence of publication bias (Egger test, $t = 0.97$, $P = 0.100$; Begg test, $z_c = -0.25$, $P = 0.810$) [Supplementary Figure 1K, http://links.lww.com/CM9/A641]. The results showed that patients in the NACS group had a lower incidence of anastomotic leakage compared with that in the SA group (RR = 0.53, 95% CI: 0.34–0.84, $P = 0.007$) [Figure 4C], which was robust according to the sensitivity analysis [Supplementary Figure 2K, http://links.lww.com/CM9/A641].

Intra-abdominal abscess

Twenty-nine cases demonstrated post-operative abdominal infection in the NACS group, and the events that happened in the SA group were similar to those in the NACS group according to the 12 enrolled studies.[23-27,29,30,33,34,37,38] No heterogeneity ($P = 0.840$, $I^2 = 0\%$) could be observed between these two groups, but there was no obvious publication bias according to the funnel plot (Egger test, $t = 0.38$, $P = 0.71$; Begg test, $z_c = -0.82$, $P = 0.41$) [Supplementary Figure 1L, http://links.lww.com/CM9/A641]. Moreover, no statistical difference could be found after analysis using a fixed-effects model (RR = 1.50, 95% CI: 0.91–2.48, $P = 0.110$] [Table 4]. The sensitivity analysis suggested that the result was credible [Supplementary Figure 2L, http://links.lww.com/CM9/A641].

Ileus

We found 11 studies reporting intestinal obstruction after gastrectomy in both groups, with 16 out of 838 cases in the NACS group and 38 out of 1262 cases in the SA group.[24,25,27,29,31,32,34,37-39] A fixed-effects model was applied due to unfound heterogeneity ($P = 0.48$, $I^2 = 0\%$). The funnel plot suggested there was no publication bias (Egger test, $t = -0.36$, $P = 0.73$; Begg test, $z_c = -0.45$, $P = 0.66$) [Supplementary Figure 1M, http://links.lww.com/CM9/A641]. No significant difference in the occurrence of post-operative ileus could be observed between the two groups (RR = 0.66, 95% CI: 0.38–1.16, $P = 0.150$] [Table 4]. The result was reliable according to the sensitivity analysis [Supplementary Figure 2M, http://links.lww.com/CM9/A641].

Pneumonia

The occurrence of pneumonia after gastrectomy was observed in 14 studies (40/935 in the NACS group *vs.* 66/1419 in the SA group).[22-27,29-31,33-35,38,39] A fixed-effects model was used due to the low heterogeneity ($P = 0.49$, $I^2 = 0\%$), but no publication bias was found in Egger ($t = -2.99$, $P = 0.06$) and Begg tests ($z_c = -1.26$, $P = 0.21$) [Supplementary Figure 1N, http://links.lww.com/CM9/A641]. Furthermore, the results indicated that the incidence of pneumonia was similar in each group (RR = 0.91, 95% CI: 0.63–1.32, $P = 0.620$) [Table 4], which was robust according to the sensitivity analysis [Supplementary Figure 2N, http://links.lww.com/CM9/A641].

Wound infection

Thirteen studies reported wound infection after gastrectomy in both groups (20/907 in the NACS group *vs.* 48/1452 in the SA group). No heterogeneity ($P = 0.86$, $I^2 = 0\%$) was detected; therefore, a fixed-effects model was applied. The funnel plot suggested no evidence of publication bias (Egger test, $t = 0.06$, $P = 0.95$; Begg test, $z_c = 0.12$, $P = 0.90$) [Supplementary Figure 1O, http://links.lww.com/CM9/A641]. The incidence of wound infection in the NACS and SA groups was comparable (RR = 0.76, 95% CI: 0.46–1.25, $P = 0.28$) [Table 4].[22,24,29-35,37,38] The sensitivity analysis suggested the result was credible [Supplementary Figure 2O, http://links.lww.com/CM9/A641].

Discussion

Our research showed that compared with the SA group, the NACS group could improve the R0 resection rate and decrease reoperation and anastomotic leakage even though with clearly longer operation time. In addition, there were no significant differences in the long-term overall survival, the number of retrieved lymph nodes, post-operative complications, and short-term mortality. To a certain extent, neoadjuvant therapy was safe and feasible, which was consistent with published studies.[42-44] Nowadays, many studies have confirmed that NACS definitely downstaged the tumor and improved the R0 resection rate, and the safety was comparable with SA,[43,45-47] which was similar to our conclusion. However, there was no definite conclusion in whether neoadjuvant chemotherapy improved the overall survival and progression-free survival (PFS) in patients. Kano *et al*[27] concluded that the 3-year PFS rate for the NACS (docetaxel plus S-1) group was significantly higher than that for the surgery-first group (80.0% in the NACS group *vs.* 58.7% in the SA group; $P = 0.037$) using the log-rank test. In a published meta-analysis, Xiong *et al*,[43] Hu *et al*,[4] and Ma *et al*[37] proved that neoadjuvant chemotherapy was related to a significant survival benefit over SA.[11,48] However, the JCOG0002 trial and Charruf *et al*[39] showed a potential survival benefit than that of the historical controls at 2 years' follow-up, but without a statistically significant difference.[49] Furthermore, studies by Li *et al*,[36] Liao *et al*,[50] and Petrelli *et al*[51] did not demonstrate a survival benefit in combining neoadjuvant chemotherapy and surgery, which was consistent with the conclusion of Schuhmacher *et al*[32] and Ruf *et al*.[31] Given the current lack of high-quality studies, further RCTs are required to provide more credible evidence.

There are currently no unified standard indications for the application of neoadjuvant chemotherapy in AGC. The ambiguous matters of neoadjuvant chemotherapy in AGC treatment are not only related to the therapeutic dosage and cycles but also correlated with eligible patients. The JCOG1302A study in Japan suggested that AGC patients with "clinical T3/T4 and cN+" stage were more suitable to receive neoadjuvant chemotherapy than patients with only "clinical T3/T4" stage, since 12.3% of pathological T1 patients were overdiagnosed as "clinical T3/T4" stage before operation, which was far higher than expected (<5%) in this trial.[52] The recommended neoadjuvant

chemotherapy indications according to the JGCA guidelines are as follows: (1) R0 resection was expected but with a high risk of recurrence, such as clinical stages IIIA to IIIC (cT4, cN+, no peritoneal, and liver metastases), and (2) those who were dissected by R0/R1 had a poor prognosis, such as Borrmann type III or IV, extensive lymph node metastasis, and larger volume.[53] The indications of neoadjuvant chemotherapy for GC in the 2020 Chinese Society of Clinical Oncology (CSCO) guidelines were patients with gastroesophageal junction cancer with clinical staging (cT3-4aN + M0). However, the European Society for Medical Oncology (ESMO) clinical practice guidelines recommended a wider range of indications for neoadjuvant chemotherapy (>cT1N0).[54] The NCCN and ESMO guidelines had a wider range of indications, while the application range of the JGCA and CSCO guidelines was narrow. Benefits would be brought to patients in the condition of formulating suitable screening criteria, selecting the right people, and using individualized and precise treatment.

Currently, the most commonly used agents for neoadjuvant chemotherapy include fluorouracil, capecitabine, S-1, cisplatin, oxaliplatin, paclitaxel, and docetaxel. The drug regimens and treatment cycles of neoadjuvant chemotherapy remained inconclusive. Recently, German research indicated that perioperative fluorouracil plus leucovorin, oxaliplatin, and docetaxel brought overall survival benefits compared with perioperative epirubicin, cisplatin, and fluorouracil in locally advanced, resectable gastric, or gastroesophageal junction adenocarcinoma.[55] Another study found that oxaliplatin and capecitabine were effective and safe as perioperative chemotherapies in locally resectable GC.[56] Well-designed studies are required to explore effective chemotherapy regimens and cycles. There are few drug alternatives for targeted therapy of GC. Moreover, trastuzumab is still the only medicine with significantly confirmed effectiveness in the treatment of human epidermal growth factor receptor-2 positive AGC.[57] Related studies on trastuzumab, bevacizumab, and pembrolizumab combined with neoadjuvant chemotherapy are in progress.[58,59]

This study had some limitations. First, even though publication bias was not found by funnel plot as well as Egger and Begg tests for all outcomes, potential publication bias could not be avoided when the number of included studies was <10.[60] Second, not all studies included were RCT studies with high quality, and subjective bias may exist in retrospective studies due to the lack of a blinding. Third, the dosage and route of administration of neoadjuvant chemotherapy differed among trials. Additionally, different pre-operative staging methods for GC can also affect the accuracy of the results. Finally, in terms of treatment approaches, prognostic indicators should include recurrence and quality of life in addition to perioperative complications, which could not be analyzed in this study due to limited data.

Conclusions

Compared with SA, NACS was considered safe and feasible for improved R0 resection rate as well as decreased reoperation and anastomotic leakage, while unbenefited overall survival indicated a less important effect of NACS on long-term oncological outcomes.

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Conflicts of interest

None.

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