

Postoperative therapy for local-advanced gastric cancer: A systematic review and meta-analysis

Zhuo Wang^{1,B–D,F}, Lihua Dong^{1,B,D,F}, Weiyan Shi^{1,B,D,F}, Ling Gao^{1,C,D,F}, Xin Jiang^{1,C,D,F}, Suyang Xue^{2,B,D,F}, Pengyu Chang^{1,A,E,F}

¹ Department of Radiation Oncology and Therapy, The First Hospital of Jilin University, Changchun, China

² Department of Interventional Therapy, The First Hospital of Jilin University, Changchun, China

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;

D – writing the article; E – critical revision of the article; F – final approval of the article

Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online)

Adv Clin Exp Med. 2024;33(7):669–678

Address for correspondence

Pengyu Chang

E-mail: radiojlu.edu@163.com

Funding sources

The study was supported by the National Natural Science Foundation of China (grant No. 82272738)

Conflict of interest

None declared

Acknowledgements

We would like to thank Yao Yan for her biostatistics services.

Received on February 28, 2023

Reviewed on April 24, 2023

Accepted on August 28, 2023

Published online on December 12, 2023

Abstract

Background. Adjuvant therapy after surgery is effective for the treatment of advanced gastric cancer (GC), but the regimens are not uniform, resulting in imbalanced benefits.

Objectives. To compare the overall survival (OS), relapse-free survival (RFS) and disease-free survival (DFS) of patients with local-advanced GC (LAGC) after surgery plus adjuvant therapy and with surgery alone based on meta-analysis.

Materials and methods. Literature search was performed among the articles published in the PubMed, Embase and Cochrane Library databases from January 2000 to December 2018. Study selection was conducted based on the following criteria: randomized clinical trials (RCTs) on surgery plus adjuvant therapy compared to surgery alone; studies compared OS and/or RFS/DFS; and cases medically confirmed with LAGC. Only articles in English were included.

Results. A total of 12 datasets from 11 randomized controlled trials (RCTs) involving 4606 patients were included in the meta-analysis. There was a significant improvement in OS of patients who underwent postoperative adjuvant therapy (HR 0.78; 95% CI: 0.72–0.84; $p < 0.001$). In the subgroup analysis, it showed a higher improvement in OS patients who received adjuvant chemotherapy plus immunotherapy or radiotherapy (HR 0.72; 95% CI: 0.61–0.85; $p < 0.001$).

Conclusions. Adjuvant therapy led to survival benefits in patients with LAGC.

Key words: chemotherapy, gastric cancer, radiotherapy, overall survival

Cite as

Wang Z, Dong L, Shi W, et al. Postoperative therapy for local-advanced gastric cancer: A systematic review and meta-analysis. *Adv Clin Exp Med.* 2024;33(7):669–678. doi:10.17219/acem/171616

DOI

10.17219/acem/171616

Copyright

Copyright by Author(s)

This is an article distributed under the terms of the Creative Commons Attribution 3.0 Unported (CC BY 3.0) (<https://creativecommons.org/licenses/by/3.0/>)

Background

Gastric cancer (GC) ranks as the 2nd leading cause of cancer-related mortality globally.¹ As revealed in GLOBOCAN 2012, the incidence of GC in East Asia populations is the highest.² Most patients are at an advanced stage at diagnosis, and surgery is their only chance of survival. In recent years, significant advances have been made in surgical techniques, and surgical concepts have been continuously updated. Although surgery for different extents of lymph node dissection, especially D2 lymphadenectomy, is well accepted as a standard for locally advanced GC (LAGC),³ many patients still present local-regional recurrence and distant metastasis. On this basis, the efficacy of single radical surgery for LAGC is not sufficient.

In the past decades, there have been many explorations into the treatment of LAGC, including preoperative neoadjuvant radiotherapy, neoadjuvant chemotherapy, neoadjuvant chemoradiotherapy, and combined immunotherapy. These treatment options can reduce the stage of tumor regression and eliminate micrometastases before surgery, thereby improving the R0 resection rate and reducing intraoperative spread and the recurrence rate. These indeed prolong patient survival. Although these studies^{4–6} have confirmed the efficacy and safety of neoadjuvant therapy in LAGC, there is still no treatment standard.

Postoperative chemotherapy has been considered an option for LAGC. Among these regimens, 5-fluorouracil (5-FU)-based chemotherapy combined with platinum and/or docetaxel is regarded as the standard.⁷ In the previous meta-analysis, postoperative chemotherapy contributed to the extension of overall survival (OS) in LAGC after radical surgery.⁸ In recent decades, several large-scale trials have continuously updated their data on treatment efficiency, such as CLASSIC⁹ and ACTS-GC.¹⁰ In recent years, with the development of radiation therapy and the gradual application of immunotherapy, many patients can benefit from radiotherapy and chemotherapy or combined immunotherapy. Meanwhile, other strategies (e.g., radiotherapy or immunotherapy) have been adopted for treating LAGC. However, the results of many studies are inconsistent, and there are disputes over therapeutic applications.

Objectives

This study aimed to investigate the effects of postoperative treatment on the prognosis of LAGC patients, especially those receiving chemotherapy plus radiotherapy or immunotherapy. This meta-analysis was designed to compare the OS, relapse-free survival (RFS), and disease-free survival (DFS) of patients with LAGC after surgery plus adjuvant therapy and those with surgery alone.

Materials and methods

Study design

Based on the guidelines of meta-analysis of observational studies in epidemiology and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), a protocol was designed by our team, including a search strategy, inclusion and exclusion criteria, primary and secondary outcomes, and statistical analysis. The study is consistent with the requirements of PRISMA and a measurement tool to assess systematic reviews (AMSTAR).

Criteria of eligibility

Two authors (WZ and DLH) independently searched articles published in PubMed, Embase and Cochrane Library between January 2000 and December 2018. The terms utilized included “gastric carcinoma”, or “adenocarcinoma of the stomach”, or “gastric cancer”, or “stomach tumors” and “radiotherapy”, or “radiation therapy”, or “chemotherapy”, or “external irradiation therapy”, or “adjuvant chemotherapy”, or “external radiation therapy”. Only randomized controlled trials (RCTs) published in English were included in this meta-analysis. The eligible studies should have met the following criteria: 1) involving patients histologically confirmed with advanced GC; 2) RCTs reporting the comparison between adjuvant therapy after radical surgery or surgery alone; 3) Reporting the hazard ratio (HR) and the corresponding 95% confidence interval (95% CI) for OS and RFS/DFS.

Data extraction

We extracted the following data from each eligible study: first author, study design, country, year of publication, patient age, number of patients (with/without postoperative adjuvant therapy), median survival, and HR of OS and/or RFS/DFS. In cases of missing data, we contacted the authors by e-mail to obtain the information. A comprehensive discussion was held among all investigators until reaching a consensus when there were any disputes on the data collection.

Hazard ratio was used to analyze the time-to-event data, including OS and RFS/DFS. The method by Tierney et al. was used to calculate the HR if it was not mentioned in the extracted articles.¹¹

Quality assessment

The risk of bias was evaluated using the domain-based Cochrane Collaboration’s tool as previously described.¹² Funnel plots were constructed to assess the risk of publication bias across the series for all outcome measures.

Statistical analysis

The χ^2 test Q-statistics evaluated the heterogeneity, and the degree of heterogeneity was estimated with the I^2 statistic. A random effects model was selected when $p < 0.10$ or the I^2 statistic was $>50\%$. Otherwise, a fixed-effects model was adopted. For the sensitivity analysis, we recalculated the pooled statistics after deleting the related study. Review Manager 5.3 (RevMan 5.3; Cochrane Collaboration, Copenhagen, Denmark) was used for the statistical analysis. A p-value of less than 0.05 was considered statistically significant.

Results

Characteristics of the eligible studies

Figure 1 shows the literature selection and screening flowchart, which resulted in 18 RCTs^{9,10,13–28} enrolling 7,919 patients into the meta-analysis. The basic characteristics of these studies are summarized in Table 1. In brief, the studies were published from 2001 to 2018, and the sample sizes ranged from 137 to 1,059 people. Six studies used 3 datasets, which were updated using 3 RCTs, and only 3 studies were included. Four studies were excluded as the HR could not be extracted due to the absence of OS, PFS, or DFS.^{13–16} Two datasets were selected from the 3-arm study.¹⁷

A total of 12 datasets were obtained from the RCTs comparing the OS of GC patients with or without postoperative therapy.^{9,10,17–24,27} All RCTs had undergone peer-review between 2001 and 2014. Herein, 3 trials were from Japan, South Korea, and China, respectively, 2 from France,

4 from Italy, 1 from Poland, and 1 from the USA. A total of 4,606 patients were included in the analysis, among which 2319 received postoperative therapy, and 2,287 underwent radical surgery.

The disease-stage classification of LAGC patients was mainly performed based on the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) tumor-node-metastasis (TNM) classification system, together with the classification system recommended by the Japanese Gastric Cancer Association (JGCA). Patients with at least a 70% lymph node-positive rate were recruited in 1 study.¹⁸ In addition, patients with N⁺ tumors with at least an 80% lymph node-positive rate were recruited in 7 studies.^{9,10,19–21,23,24} Three trials recruited patients with N⁺ tumors with a lymph node-positive rate of 100%.^{17,22,27} Meanwhile, D2 lymphadenectomy was performed in 4 trials^{9,10,22,27} and D1-plus and R0 resection was performed in 6 trials.^{9,10,18,21,22,27}

OS determination

All patients were followed up for more than 5 years. The OS rates were higher in most of adjuvant therapy groups than those of the surgery group in 5 of 11 trials^{9,10,17,22,24} (Fig. 2A). We present the pooled OS data in Supplementary Fig. 1. In the study by Nitti et al.,²¹ 2 datasets from the European Organization for Research and Treatment of Cancer (EORTC) trial and the International Collaborative Cancer Group (ICCG) were collected to be analyzed jointly. The OS rate in the adjuvant therapy group was higher than that in the surgery group in the EORTC trial.²¹ However, in the ICCG trial, the OS rate of patients receiving adjuvant therapy was lower than that of surgery-only cases.²¹

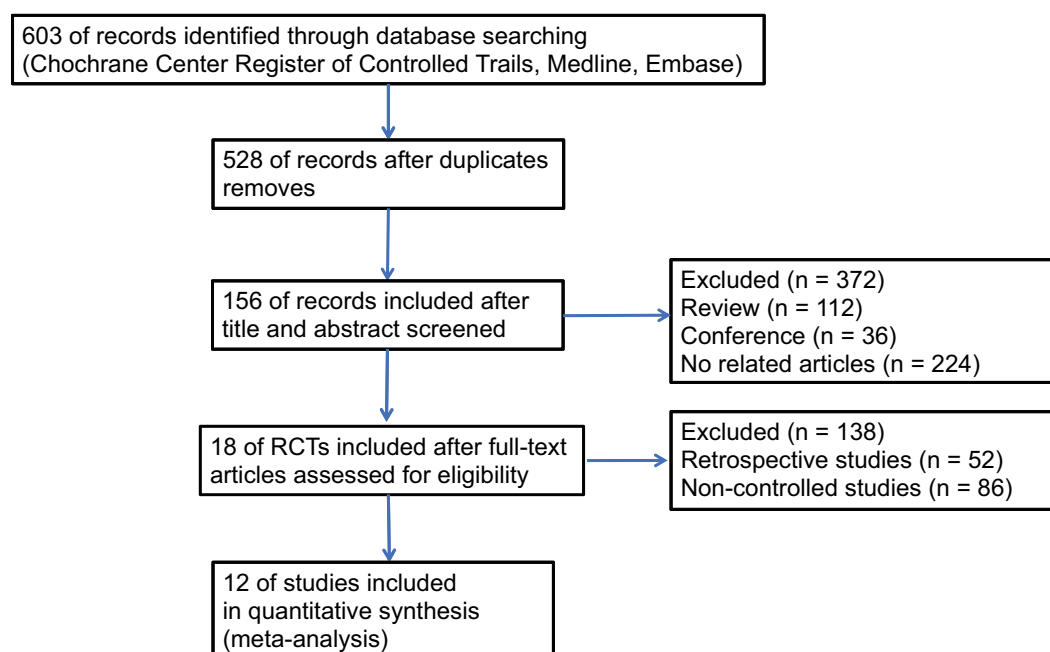


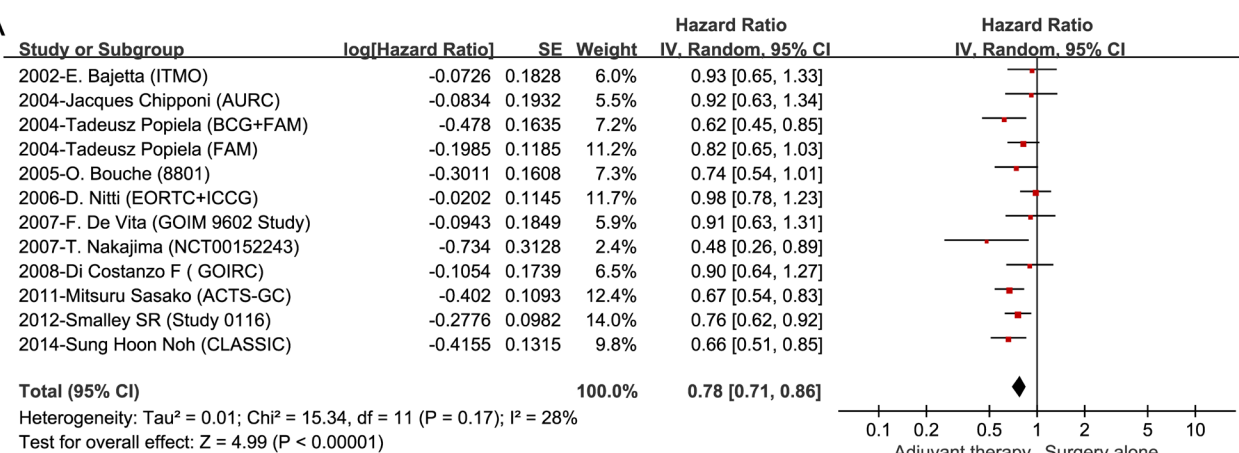
Fig. 1. Flow diagram of literature retrieval and screening

Table 1. The basic characteristics of included studies

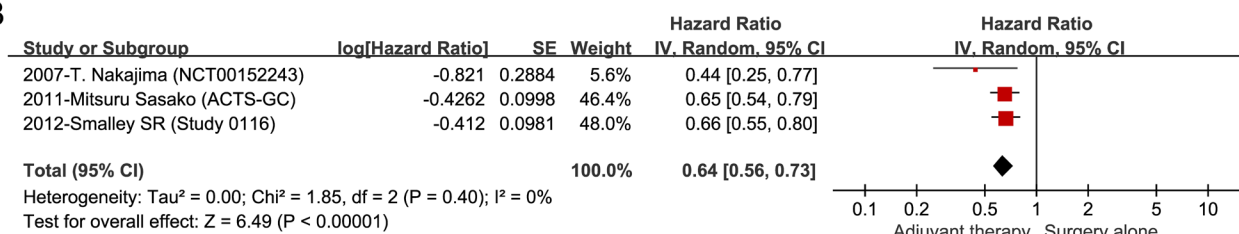
Year	Study	Country	Age [years]	Phase	Surgery	AT+S	S	AT regimens
2002	Bajetta et al. (ITMO) ²⁷	Italy	≤70	III–IVM0	D2 (R0)	135	136	EAP
2004	Chipponi et al. (AURC) ¹⁹	France	≤75	III–IVM0	D1/D2 (R0/R1)	93	103	LV+5FU+CDDP
2004	Popiela et al. (BCG+FAM) ¹⁷	Poland	<70	III–IVM0	D1/D2(R0/R1)	51	52	BCG+FAM
2004	Popiela et al. (FAM) ¹⁷	Poland	<70	III–IVM0	D1/D2(R0/R1)	53	52	FAM
2005	Bouché et al. (8801) ²⁰	France	31–83	II–IVM0	D0/D1/D2(R0)	127	133	5-FU+CDDP
2006	Nitti et al. (EORTC+ICCG) ²¹	Italy	<71	IB–IVM0	D1+(R0)	194	203	FAMTX or FEMTX
2007	De Vita et al. (GOIM 9602 Study) ¹⁸	Italy	<70	IB–IIIB	D1+ (R0)	112	113	ELFE
2007	Nakajima et al. (NCT00152243) ²²	Japan	20–75	III–IVM0	D2+ (R0)	93	95	UFT
2008	Di Costanzo et al. (GOIRC) ²³	Italy	<59	IB–IVM0	D1+	130	128	PELF
2011	Sasako et al. (ACTS-GC) ¹⁰	Japan	20–80	II–IIIB	D2 (R0)	529	530	S-1
2012	Smalley et al. (Study 0116) ²⁴	USA	23–87	IB–IVM0	D0/D1/D2 (R0)	282	227	FU + LV + RT
2014	Noh et al. (CLASSIC) ⁹	South Korea	≥18	II–IIIB	D2 (R0)	520	515	Cap+OXA

m – median; AT – adjuvant therapy; S – surgery; EAP – etoposide, adriamycin, cisplatin; BCG – bacille Calmette–Guérin; FAM – 5-FU, adriamycin, MMC; FAMTX – methotrexate, 5-FU, leucovorin, adriamycin; FEMTX – 5-FU, epirubicin, MTX, leucovorin; ELFE – epirubicin, leucovorin, 5-fluorouracil, etoposide; PELF – cisplatin, epirubicin, leucovorin, 5-fluorouracil; LV – leucovorin; Cap – capecitabine; OXA – oxaliplatin.

A



B



C

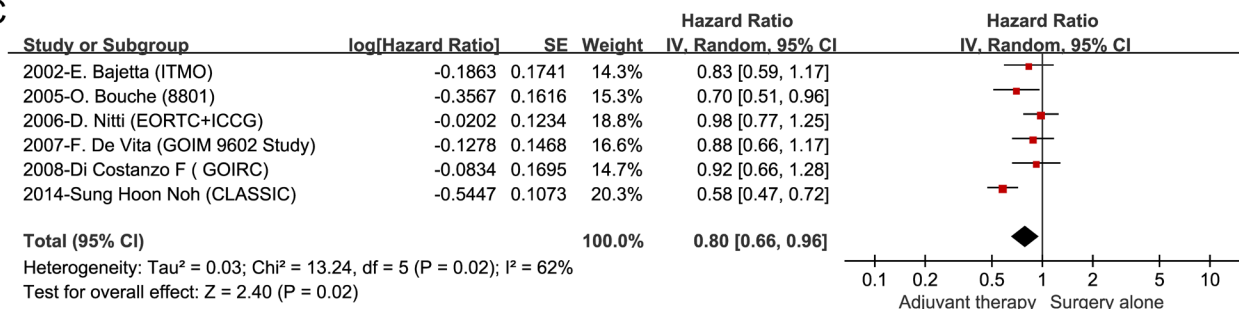


Fig. 2. A. Meta-analyses results for overall survival (OS); B. Relapse-free survival (RFS); C. Disease-free survival (DFS)

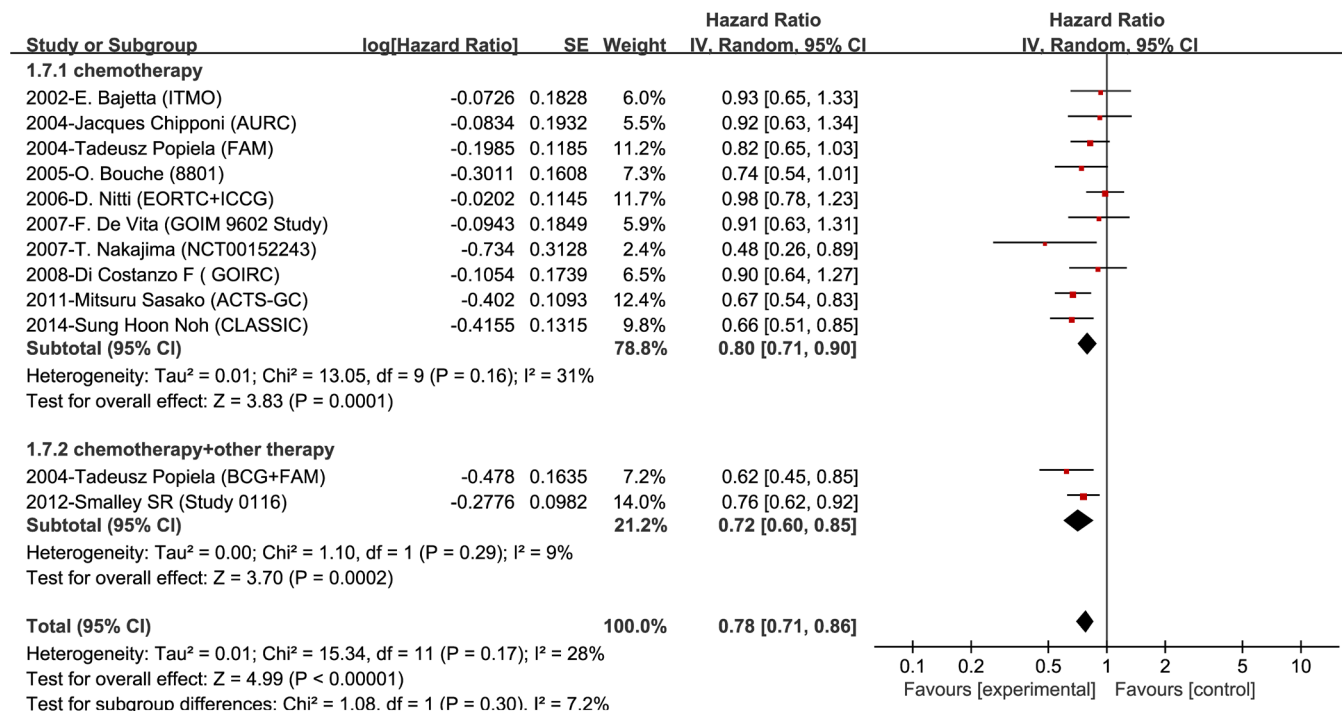


Fig. 3. Meta-analyses results for subgroup analysis of 5-year overall survival (OS)

RFS

Three RCTs reported the RFS with no heterogeneity ($p < 0.001$, $I^2 = 0\%$).^{10,22,24} Significant differences were observed between the patients receiving adjuvant therapy and those receiving just surgery ($HR = 0.64$; 95% CI: 0.56–0.73; $I^2 = 0\%$; Fig. 2B). We present the pooled RFS data in Supplementary Fig. 2.

DFS

Heterogeneity was observed in the DFS of 6 RCTs ($p = 0.02$; $I^2 = 62\%$).^{9,18,20,21,23,27} On this basis, the random-effects model was used, which indicated significant differences in DFS between the patients receiving adjuvant therapy and those only receiving surgery ($HR = 0.80$; 95% CI: 0.66–0.96; $p = 0.02$; $I^2 = 62\%$). There was no heterogeneity for these studies after omitting 1 study⁹ ($I^2 = 0\%$; Fig. 2C). We present the pooled DFS data in Supplementary Fig. 3.

Subgroup analysis

In addition to chemotherapy, we divided the 12 sets of data into 2 subgroups based on the combination of other adjuvant therapies (i.e., radiotherapy or immunotherapy). Subgroup analysis indicated that patients receiving postoperative chemotherapy plus radiotherapy or immunotherapy presented a significant increase in 5-year OS rate than those only receiving chemotherapy ($HR = 0.72$; 95% CI: 0.60–0.85; $p < 0.001$; Fig. 3).

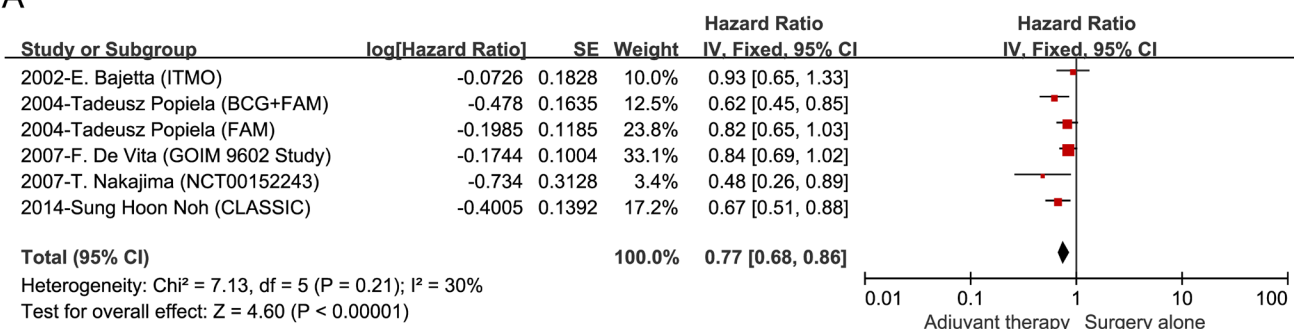
Different postoperative adjuvant regimens may affect the prognosis

All patients enrolled in the RCTs received chemotherapy with different regimens, with all studies applying 5-FU except for 1 study⁹ using capecitabine and oxaliplatin. Two studies involved the oral administration of fluorouracil agents, such as S-1 and tegafur–uracil (UFT).^{10,22} The rest of the regimens were carried out by iv. infusion of 5-FU. Among the included studies, 1 involved immunotherapy using the bacille Calmette–Guérin (BCG),¹⁷ and 1 involved radiotherapy.²⁴ The data supported that adjuvant chemotherapy combined with radiotherapy or immunotherapy contributed to the extension of OS (Fig. 3). The outcomes of OS for the patients with lymphatic metastasis are shown in Fig. 4.

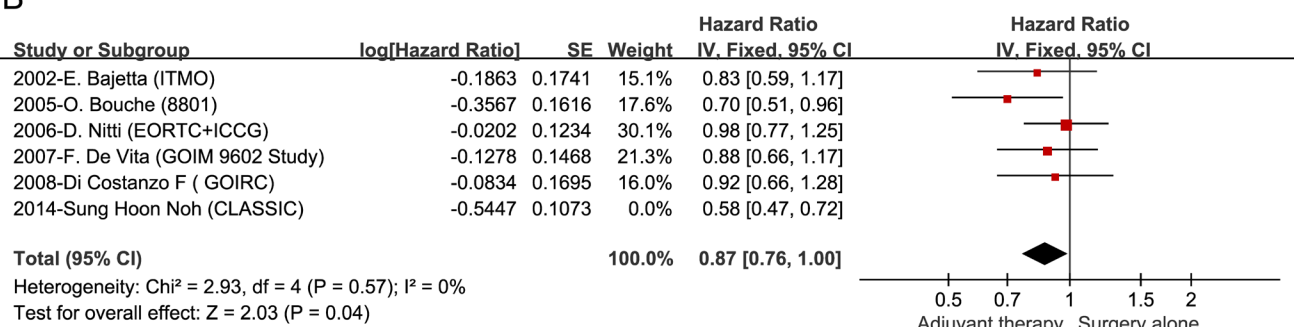
Publication bias

As shown in Fig. 5, together with the Egger's and Begg's tests, the publication bias in these studies was low. Egger's regression test determined the degree of asymmetry in the funnel plot by measuring the intercept of a standard normal regression that deviated from precision. The Begg's rank correlation test explained the correlation between the rank of the effect size and its variance. A p-value of more than 0.05 demonstrated statistical difference with a low risk of publication bias. In this study, the p-values for the Begg's test and Egger's test in most of the groups were more than 0.05. However, p-value for the Begg's test in the studies listed in Fig. 2B

A



B



C

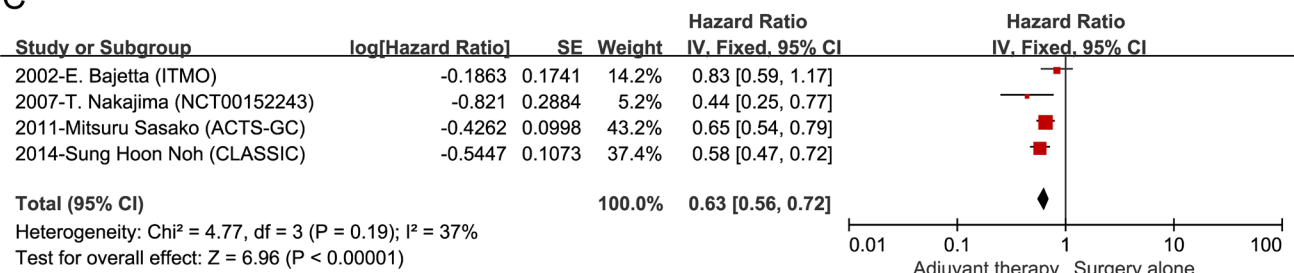


Fig. 4. A. Meta-analyses for the 5-year overall survival (OS) of patients with positive lymph nodes; B. Sensitivity analysis of disease-free survival (DFS) excluding the 2014 study by Noh et al.⁹; C. Meta-analyses for OS of patients receiving D2 gastrectomy showing no evidence of remaining tumor

was 0.1172, and p-value for the Egger's test was 0.0421 (Fig. 5B), which may be related to the minor trials in this group. The funnel plots of 12 trials listed in Fig. 2A were symmetric, and the p-values for the Begg's test and Egger's test were 0.885 and 0.680, respectively (Fig. 5A). Meanwhile, the p-values for the Begg's test and Egger's test for the studies listed in Fig. 2C were 0.851 and 0.359 (Fig. 5C), while those for the studies listed in Fig. 3 (chemotherapy and chemotherapy and other therapy) were 0.680 and 0.860 (Fig. 5D), respectively. The p-values for the Begg's test and Egger's test for chemotherapy of the study listed in Fig. 3 (chemotherapy only) were 0.531 and 0.927 (Fig. 5E), while those for the studies listed in Fig. 5A were 0.091 and 0.198 (Fig. 5F), those listed in Fig. 5B were 0.327 and 0.272 (Fig. 5G), and those listed in Fig. 5C were 0.497 and 0.858 (Fig. 5H), respectively. These data mostly indicated a low risk of publication bias.

Discussion

The prognosis of LAGC patients is usually poor, and many present with recurrences or metastases. In recent years, immunotherapy has been reported to be effective in the treatment of multiple malignancies.²⁹ However, the efficacy of immunotherapy alone is limited. Indeed, many studies confirmed that chemotherapy or radiotherapy combined with immunotherapy after surgery is more effective for solid tumors.^{30–32} This meta-analysis of 12 sets of data indicated that postoperative chemotherapy improved the prognosis of LAGC patients. Specifically, LAGC patients receiving adjuvant therapy showed an increase of about 22% in the 5-year OS rate compared to those only receiving radical surgery (Fig. 2A). Although there is a lack of statistical significance upon individual analysis, the OS data of 7 trials along with the DFS data from another 4 trials indicated that postoperative chemotherapy contributed

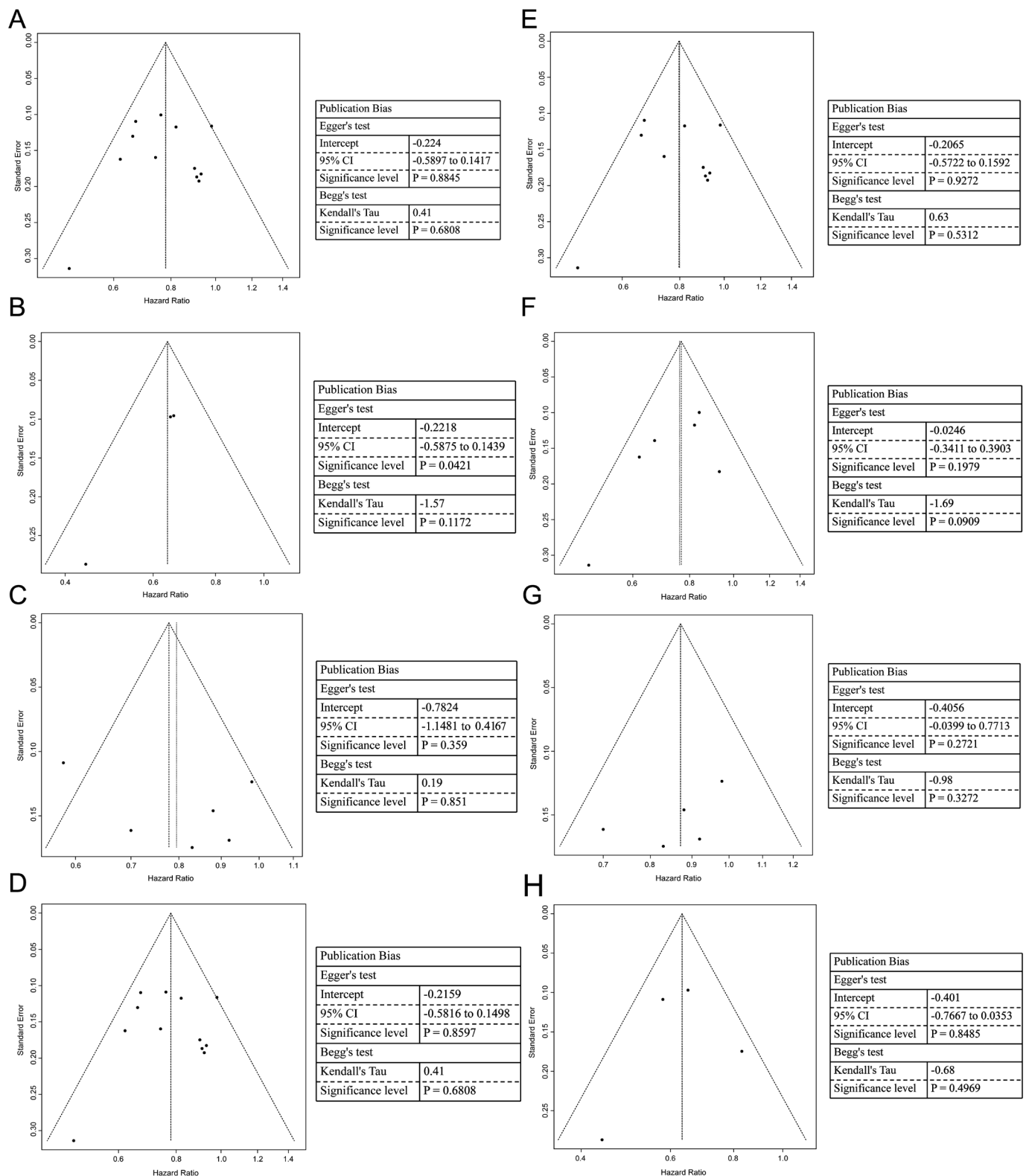


Fig. 5. Funnel plot for publication bias. A. The plot for the studies listed in Fig. 2A; B. The plot for the studies listed in Fig. 2B; C. The plot for the studies listed in Fig. 2C; D. The plot for the studies listed in Fig. 3 (chemotherapy and chemotherapy plus other therapy); E. The plot for the studies listed in Fig. 3 (chemotherapy only); F. The plot for the studies listed in Fig. 4A; G. The plot for the studies listed in Fig. 4B; H. The plot for the studies listed in Fig. 4C

to the survival of LAGC patients, though this is probably due to the small sample size enrolled in the trials. The survival benefits after postoperative chemotherapy were significant after pooling for the meta-analysis.

Six sets of data reported the OS outcomes for patients with lymphatic metastasis (Fig. 4A). The analysis of patients receiving postoperative chemotherapy showed increased OS by up to 23%. However, 3 trials supported

postoperative therapy with no statistically significant trends. Two RCTs mainly recruited patients with stage IIIA, IIIB, or IV (T4N1M0).^{17,27} Likewise, in another study,¹⁸ the ratio of patients with stage IIIA, IIIB, or IV (T4N1M0) exceeded 80% of all enrolled patients.

Nine studies considered RFS or DFS as their primary endpoint. Three RCTs compared the RFS of LAGC patients with and without postoperative chemotherapy,^{10,22,24} which indicated the survival benefits of postoperative chemotherapy. The pooled HR was 0.64 (95% CI: 0.56–0.73) after combining all the HRs in the selected trials, which significantly favored postoperative chemotherapy ($p < 0.001$, Fig. 2B). Six RCTs compared the DFS of GC patients receiving postoperative treatment compared with those who received no postoperative treatment.^{9,18,20,21,23,27} Almost all trials favored postoperative treatment except for 4 trials showing no statistical differences.^{18,21,23,27} When considering the study of Noh et al.,⁹ survival benefits were observed after postoperative therapy (HR = 0.80; 95% CI: 0.66–0.96; $p = 0.02$) with high heterogeneity ($I^2 = 62\%$; Fig. 2C). Upon removing the study, the survival benefits were significantly weaker (HR = 0.87; 95% CI: 0.76–1.0; $p = 0.04$) with a low heterogeneity ($I^2 = 0\%$; Fig. 4B). The high heterogeneity was mainly associated with higher weight and better survival benefits. In the study by Noh et al., 1,035 patients underwent curative D2 gastrectomy with no macroscopic or microscopic evidence of tumors. The radical surgical treatment produced a significant survival benefit, and the high heterogeneity might also be caused by the treatment design, including the chemotherapy regimen, the number of patients, and the surgeon's skills.

Four studies reported the outcomes of OS and RFS for patients who underwent D2 gastrectomy, with no evidence of remaining tumors noticed among these patients (Fig. 4C). The OS and RFS outcomes were consistent in the patients receiving combined therapy (OS: HR = 0.69; 95% CI: 0.58–0.83; $p < 0.001$; RFS: HR = 0.63; 95% CI: 0.53–0.76; $p < 0.001$). Patients enrolled in the Japanese trials showed higher postoperative survival rates than in trials carried out in Western Europe and the USA.⁸ Three trials were carried out in Japan, and the results showed statistically significant trends to support postoperative therapy. There was no statistical significance in the study by Bajetta et al.,²⁷ which was probably due to the advanced stage of the eligible patients.

Several studies reported that 40–60% of GC patients undergoing radical surgery at stage II or III showed a loco-regional recurrence before postoperative therapy. Loco-regional failure often occurred in the anastomosis, followed by the stomach bed and undissected regional nodes. Radiotherapy could improve postoperative local control of GC, but there were some disputes on survival

in the data from randomized trials. D2 loco-regional node resection was the standard method, and postoperative radiotherapy (PORT) combined with chemotherapy was still controversial for treating LAGC.³³ In this meta-analysis, 2 studies confirmed that LAGC patients showed longer OS after PORT combined with chemotherapy. In 2018, a network meta-analysis confirmed that the 5-year OS rate and the 2-year PFS of patients receiving chemoradiotherapy were higher than those only receiving surgery (HR = 0.80 and 0.58, respectively).⁸ However, the 5-year OS rate of patients who underwent PORT was poor, indicating that postoperative chemotherapy is important for advanced GC.

In this meta-analysis, there was a higher improvement in OS among patients receiving adjuvant chemotherapy plus immunotherapy or radiotherapy. Recently, malignant tumors have been confirmed to be immunogenic, and accumulating evidence demonstrates a potential link between cancer progression and anti-tumor immunity.³⁴ In 2018, a meta-analysis confirmed that chemotherapy combined with cytokine-induced killer cell (CIK)/dendritic cell-CIK (CIK/DC-CIK) therapy after surgery significantly increased OS rates (HR = 0.712; 95% CI: 0.594–0.854), DFS rates (HR = 0.66; 95% CI: 0.546–0.797), and T-lymphocyte responses in patients with GC.³⁵ In addition, a retrospective study reported a similar conclusion in epithelial ovarian cancer patients.³⁴ Another study confirmed that the immunotherapy group presented a higher 3-year OS rate and 5-year OS rate, respectively.²⁹ Meanwhile, patients receiving 3 or more cycles of immunotherapy showed a higher 5-year OS rate than those who received 2 cycles or less (82.10% compared to 69.90%; $p = 0.035$).²⁹

A study based on the National Cancer Database (NCDB) concluded that PORT conferred an additional OS advantage, which was higher than that of adjuvant chemotherapy alone for complete resection of N2 non-small cell lung cancer (NSCLC).³⁶ Similarly, another study reported that PORT was associated with improved OS in patients with incompletely resected stage II or III N0-2 NSCLC.³⁷ However, studies on PORT combined with immunotherapy are still limited for LAGC, and more clinical studies reporting the outcomes of LAGC are expected in the future.

Limitations

Indeed, there are limitations in this meta-analysis. First, the study designs of the trials differed. For example, the chemotherapy regimens and cycles were not totally consistent. Second, we only focused on the influence of postoperative treatment rather than complications and adverse effects, which may exaggerate the benefits of postoperative treatment. Finally, we could not eliminate the potential publication bias.

Conclusions

In conclusion, postoperative treatment plays a significant role in improving survival in patients with LAGC. We found that patients receiving adjuvant therapy after surgery showed a significant improvement in OS. Meanwhile, patients presented a higher improvement in OS after adjuvant chemotherapy plus immunotherapy or radiotherapy.

Supplementary data

The Supplementary materials are available at <https://doi.org/10.5281/zenodo.8294045>. The package consists of the following files:

- Supplementary Fig. 1. Pooled data of OS including 11 RCTs.
- Supplementary Fig. 2. Pooled data of RFS including 3 RCTs.
- Supplementary Fig. 3. Pooled data of DFS including 6 RCTs.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

ORCID iDs

Zhuo Wang  <https://orcid.org/0000-0001-8021-8146>
 Lihua Dong  <https://orcid.org/0000-0002-9454-3596>
 Weiyan Shi  <https://orcid.org/0009-0003-3290-678X>
 Ling Gao  <https://orcid.org/0000-0001-5313-1395>
 Xin Jiang  <https://orcid.org/0000-0002-4613-7438>
 Suyang Xue  <https://orcid.org/0009-0002-8144-5070>
 Pengyu Chang  <https://orcid.org/0000-0002-8916-3572>

References

- Wu DM, Wang S, Wen X, et al. Survival benefit of three different therapies in postoperative patients with advanced gastric cancer: A network meta-analysis. *Front Pharmacol*. 2018;9:929. doi:10.3389/fphar.2018.00929
- Ng CJ, Teo CH, Abdullah N, Tan WP, Tan HM. Relationships between cancer pattern, country income and geographical region in Asia. *BMC Cancer*. 2015;15(1):613. doi:10.1186/s12885-015-1615-0
- Mocellin S. The effect of lymph node dissection on the survival of patients with operable gastric carcinoma. *JAMA Oncol*. 2016;2(10):1363–1364. doi:10.1001/jamaoncol.2016.2044
- Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (v. 4). *Gastric Cancer*. 2017;20(1):1–19. doi:10.1007/s10120-016-0622-4
- Ychou M, Boige V, Pignon JP, 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(13):1715–1721. doi:10.1200/JCO.2010.33.0597
- Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. 2006;355(1):11–20. doi:10.1056/NEJMoa055531
- Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2016;27(Suppl 5):v38–v49. doi:10.1093/annonc/mdw350
- Sun P, Xiang JB, Chen ZY. Meta-analysis of adjuvant chemotherapy after radical surgery for advanced gastric cancer. *Br J Surg*. 2009;96(1):26–33. doi:10.1002/bjs.6408
- Noh SH, Park SR, Yang HK, et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomized phase 3 trial. *Lancet Oncol*. 2014;15(12):1389–1396. doi:10.1016/S1470-2045(14)70473-5
- Sasako M, Sakuramoto S, Katai H, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. *J Clin Oncol*. 2011;29(33):4387–4393. doi:10.1200/JCO.2011.36.5908
- Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials*. 2007;8(1):16. doi:10.1186/1745-6215-8-16
- Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd ed. Chichester, UK: Wiley & Sons; 2019. doi:10.1002/9781119536604
- Neri B, Cini G, Andreoli F, et al. Randomized trial of adjuvant chemotherapy versus control after curative resection for gastric cancer: 5-year follow-up. *Br J Cancer*. 2001;84(7):878–880. doi:10.1054/bjoc.2000.1472
- Nashimoto A, Nakajima T, Furukawa H, et al. Randomized trial of adjuvant chemotherapy with mitomycin, fluorouracil, and cytosine arabinoside followed by oral fluorouracil in serosa-negative gastric cancer: Japan Clinical Oncology Group 9206-1. *J Clin Oncol*. 2003;21(12):2282–2287. doi:10.1200/JCO.2003.06.103
- The Gastric Cancer Surgical Study Group in the Japan Clinical Oncology Group; Miyashiro I, Furukawa H, et al. Randomized clinical trial of adjuvant chemotherapy with intraperitoneal and intravenous cisplatin followed by oral fluorouracil (UFT) in serosa-positive gastric cancer versus curative resection alone: Final results of the Japan Clinical Oncology Group trial JCOG9206-2. *Gastric Cancer*. 2011;14(3):212–218. doi:10.1007/s10120-011-0027-3
- Mizutani T, Yamaguchi K, Mizusawa J, et al. A phase III trial to confirm modified S-1 adjuvant chemotherapy for pathological stage II/III vulnerable elderly gastric cancer patients who underwent gastric resection (JCOG1507, BIRDIE). *Jpn J Clin Oncol*. 2018;48(12):1101–1104. doi:10.1093/jjco/hyy152
- Popiela T, Kulig J, Czupryna A, Szczepanik AM, Zembala M. Efficiency of adjuvant immunochemotherapy following curative resection in patients with locally advanced gastric cancer. *Gastric Cancer*. 2004;7(4):240–245. doi:10.1007/s10120-004-0299-y
- De Vita F, Giuliani F, Orditura M, et al. Adjuvant chemotherapy with epirubicin, leucovorin, 5-fluorouracil and etoposide regimen in resected gastric cancer patients: A randomized phase III trial by the Gruppo Oncologico Italia Meridionale (GOIM 9602 Study). *Ann Oncol*. 2007;18(8):1354–1358. doi:10.1093/annonc/mdm128
- Chipponi J, Huguier M, Pezet D, et al. Randomized trial of adjuvant chemotherapy after curative resection for gastric cancer. *Am J Surg*. 2004;187(3):440–445. doi:10.1016/j.amjsurg.2003.12.014
- Bouché O, Ychou M, Burtin P, et al. Adjuvant chemotherapy with 5-fluorouracil and cisplatin compared with surgery alone for gastric cancer: 7-year results of the FFCD randomized phase III trial (8801). *Ann Oncol*. 2005;16(9):1488–1497. doi:10.1093/annonc/mdi270
- Nitti D, Wils J, Dos Santos JG, et al. Randomized phase III trials of adjuvant FAMTX or FEMTX compared with surgery alone in resected gastric cancer: A combined analysis of the EORTC GI Group and the ICCG. *Ann Oncol*. 2006;17(2):262–269. doi:10.1093/annonc/mdj077
- Nakajima T, Kinoshita T, Nashimoto A, et al. Randomized controlled trial of adjuvant uracil–tegafur versus surgery alone for serosa-negative, locally advanced gastric cancer. *Br J Surg*. 2007;94(12):1468–1476. doi:10.1002/bjs.5996
- Di Costanzo F, Gasperoni S, Manzione L, et al. Adjuvant chemotherapy in completely resected gastric cancer: A randomized phase III trial conducted by GOIRC. *J Natl Cancer Inst*. 2008;100(6):388–398. doi:10.1093/jnci/djn054
- Smalley SR, Benedetti JK, Haller DG, et al. Updated analysis of SWOG-directed intergroup study 0116: A phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. *J Clin Oncol*. 2012;30(19):2327–2333. doi:10.1200/JCO.2011.36.7136

25. Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): A phase 3 open-label, randomized controlled trial. *Lancet*. 2012;379(9813):315–321. doi:10.1016/S0140-6736(11)61873-4
26. Sakuramoto S, Sasako M, Yamaguchi T, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med*. 2007;357(18):1810–1820. doi:10.1056/NEJMoa072252
27. Bajetta E, Buzzoni R, Mariani L, et al. Adjuvant chemotherapy in gastric cancer: 5-year results of a randomised study by the Italian Trials in Medical Oncology (ITMO) Group. *Ann Oncol*. 2002;13(2):299–307. doi:10.1093/annonc/mdf040
28. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med*. 2001;345:725–730. doi:10.1056/NEJMoa010187
29. Du XH, Liu HL, Li L, et al. Clinical significance of immunotherapy with combined three kinds of cells for operable colorectal cancer. *Tumor Biol*. 2015;36(7):5679–5685. doi:10.1007/s13277-015-3242-4
30. DeVita VT, Rosenberg SA. Two hundred years of cancer research. *N Engl J Med*. 2012;366(23):2207–2214. doi:10.1056/NEJMr1204479
31. Cheever MA, Higano CS. PROVENGE (Sipuleucel-T) in prostate cancer: The first FDA-approved therapeutic cancer vaccine. *Clin Cancer Res*. 2011;17(11):3520–3526. doi:10.1158/1078-0432.CCR-10-3126
32. Zhao H, Fan Y, Li H, et al. Immunotherapy with cytokine-induced killer cells as an adjuvant treatment for advanced gastric carcinoma: A retrospective study of 165 patients. *Cancer Biother Radiopharm*. 2013;28(4):303–309. doi:10.1089/cbr.2012.1306
33. Agolli L. Adjuvant radiochemotherapy for gastric cancer: Should we use prognostic factors to select patients? *World J Gastroenterol*. 2016;22(3):1131–1138. doi:10.3748/wjg.v22.i3.1131
34. Zhou Y, Chen CL, Jiang SW, et al. Retrospective analysis of the efficacy of adjuvant CIK cell therapy in epithelial ovarian cancer patients who received postoperative chemotherapy. *Oncoimmunology*. 2019; 8(2):e1528411. doi:10.1080/2162402X.2018.1528411
35. Wang X, Tang S, Cui X, et al. Cytokine-induced killer cell/dendritic cell–cytokine-induced killer cell immunotherapy for the postoperative treatment of gastric cancer: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2018;97(36):e12230. doi:10.1097/MD.00000000000012230
36. Robinson CG, Patel AP, Bradley JD, et al. Postoperative radiotherapy for pathologic N2 non-small-cell lung cancer treated with adjuvant chemotherapy: A review of the National Cancer Data Base. *J Clin Oncol*. 2015;33(8):870–876. doi:10.1200/JCO.2014.58.5380
37. Wang EH, Corso CD, Rutter CE, et al. Postoperative radiation therapy is associated with improved overall survival in incompletely resected stage II and III non-small-cell lung cancer. *J Clin Oncol*. 2015; 33(25):2727–2734. doi:10.1200/JCO.2015.61.1517