World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v20.i2.584

World J Gastroenterol 2014 January 14; 20(2): 584-592
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

META-ANALYSIS

Chemotherapy for patients with gastric cancer after complete resection: A network meta-analysis

Ya-Wu Zhang, Yu-Long Zhang, Hui Pan, Feng-Xian Wei, You-Cheng Zhang, Yuan Shao, Wei Han, Hai-Peng Liu, Zhe-Yuan Wang, Sun-Hu Yang

Ya-Wu Zhang, Yu-Long Zhang, Hui Pan, Feng-Xian Wei, You-Cheng Zhang, Yuan Shao, Wei Han, Hai-Peng Liu, Zhe-Yuan Wang, Sun-Hu Yang, Department of General Surgery, Lanzhou University Second Hospital, Lanzhou 730030, Gansu Province, China

Author contributions: Zhang YW, Zhang YL and Zhang YC designed the research; Wei FX, Han W and Wang ZY performed the research; Pan H, Shao Y, Liu HP and Yang SH analyzed the data; Zhang YW, Zhang YL and Zhang YC wrote the paper.

Correspondence to: Dr. You-Cheng Zhang, Department of General Surgery, Lanzhou University Second Hospital, Cuiying-men 82, Chengguan District, Lanzhou 730030, Gansu Province, China. zhangychmd@126.com
Telephone: +86-931-8942287 Fax: +86-931-8942287

Received: July 22, 2013 Revised: October 26, 2013
Accepted: November 1, 2013
Published online: January 14, 2014

Abstract

AIM: To conduct a network meta-analysis to evaluate the effectiveness of different chemotherapy regimens for patients with gastric cancer.

METHODS: PubMed (1966-2011.12), the Cochrane Library (2011 Issue 2) and EMBASE (1974-2011.12) were searched with the terms "gastric cancer" and "chemotherapy", as well as the medical subject headings. References from relevant articles and conferences were also included. Patients who had previous gastric surgery, radiation before or after surgery or chemotherapy before surgery were excluded. In this study, only randomized controlled trials (RCTs) were considered, and the end-point was the overall mortality. Direct comparisons were performed using traditional meta-analysis whereas indirect comparisons were performed using network meta-analysis.

RESULTS: In total, 31 RCTs with 7120 patients were included. Five chemotherapy regimens, fluorouracil (FU) + BCNU, FU + methyl-CCNU (mCCNU), FU + cisplatin, FU + anthracyclines and FU + mitomycin c (MMC) + cytarabine (Ara-c), were found to be less beneficial in terms of overall mortality. In contrast, four chemotherapy regimens were effective for the patients after surgery, including FU + MMC + adriamycin (FMA), FU + MMC (FM), Tegafur and MMC, There was no significant difference in terms of overall mortality among these regimens. The evidence for the FM regimen and MMC regimen was poor. Additionally, the FMA regimen, which includes a variety of chemotherapy drugs and causes many side effects, was not better than the Tegafur regimen.

CONCLUSION: Although the four chemotherapy regimens were effective in patients with gastric cancer after surgery and the overall mortality revealed no significant difference among them in the network meta-analysis, thorough analysis of the results recommends Tegafur as the first-line adjuvant chemotherapy regimen for patients after complete resection.

Key words: Gastric cancer; Chemotherapy; Randomized controlled trials; Indirect treatment comparison; Network meta-analysis

Core tip: Although adjuvant chemotherapy after complete resection of gastric cancer is therapeutically useful, which of the many regimens is most effective? To date, no regimen has been clearly recommended as the standard procedure post-operation; therefore, we performed a network meta-analysis, which is a useful tool to summarize the different clinical trials and to evaluate the effectiveness of different chemotherapy regimens for patients after complete resection of gastric cancer.

Based on our findings, the Tegafur regimen, especially S-1, is the first therapy that should be recommend to the patients to reduce overall mortality.

Zhang YW, Zhang YL, Pan H, Wei FX, Zhang YC, Shao Y, Han W, Liu HP, Wang ZY, Yang SH. Chemotherapy for patients with gastric cancer after complete resection: A network meta-analysis. *World J Gastroenterol* 2014; 20(2): 584-592 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i2/584.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i2.584

INTRODUCTION

Gastric cancer (GC) remains the second leading cause of cancer-related deaths in the world and is the most common malignancy in Asia, South America and Eastern Europe. The overall outcome for patients with GC has not significantly improved over recent decades[1-4]. GC remains a considerable threat to public health around the world. Currently, complete resection still has the highest potential for curatively treating GC[5]. However, approximately 20%-60% of GC patients who have already had curative surgery develop recurrent diseases[6] and will need to undergo adjuvant chemotherapy.

No network meta-analysis has been conducted to compare the efficacy of different chemotherapy protocols for patients with GC. Network meta-analysis is a useful tool for summarizing different clinical trials[7], especially when many different regimens are effective for the same clinical condition. In this type of analysis, all binary comparisons are shown with labels indicating superiority, inferiority or no difference in a summary graph[8-12]. Some recent meta-analyses have indicated that adjuvant chemotherapy after complete resection produces a small survival benefit[13-18]. Several additional trials have also been conducted in this setting. However, they did not indicate which chemotherapy protocol had the best efficacy for treating patients who have undergone complete resection. There is no clearly recommended protocol for the standard treatment of patients with GC after complete resection, and a 5-fluorouracil (5-FU) and platinum-based regimen is usually administered. Surgeons need empirical evidence to determine the best treatment for GC patients. Therefore, it was deemed important to assess the benefits of various adjuvant chemotherapy regimens through a network meta-analysis based on data from all relevant randomized controlled trials (RCTs).

The purpose of this network meta-analysis was to evaluate the effectiveness of different chemotherapy regimens for patients with GC who had undergone surgery.

MATERIALS AND METHODS

Study selection

PubMed (1966.01-2011.12), the Cochrane Library (2011 Issue 12) and EMBASE (1974.01-2011.12) were searched with the terms "gastric cancer" and "chemotherapy", as well as the medical subject headings. The relevant articles referenced in these publications were downloaded from the databases. The related article function was also used to widen the search results. All abstracts, comparative studies, non-randomized trials, and citations scanned were searched comprehensively. Additional searches were conducted by reviewing abstract booklets and review articles. Trials were included irrespective of the language in which they were reported.

Data extraction

Each article was critically reviewed by two researchers for eligibility in our network meta-analysis (Table 1). Only RCTs on palliative or adjuvant chemotherapy for treating GC patients who had undergone surgery were analyzed in this network meta-analysis. The two researchers extracted the data separately, which were then confirmed by a third researcher.

Inclusion criterion: Patients with GC after complete resection and age < 71 years.

Exclusion criteria: Patients who had previous gastric surgery, radiation before or after surgery, chemotherapy before surgery, a history of deep venous thrombosis or pulmonary embolism and severe cardiovascular, respiratory, hepatic or renal disease.

End point: Overall mortality was defined as the time from randomization to death from any cause, or to the last follow-up, which was used as the date of censoring.

Quality evaluation

The quality of the studies included was assessed using the Jadad score[19].

Statistical analysis

The traditional meta-analysis method was used for extracting the crude rates of our pre-specified clinical endpoint for each treatment group when the trials reported suitable information. We summarized the available data on overall survival from the reported results in all trials, computing pooled odd ratios and their respective 95% confidence intervals (95%CI) by means of a fixed-effects model. All statistical analyses were performed using Review Manager (RevMan version 5.0), the Cochrane Collaboration's software for preparing and maintaining Cochrane systematic reviews. We used the chi-square statistic to assess the heterogeneity between trials and the I^2 statistic to assess the extent of inconsistency. Subgroup analysis was used to explore important clinical differences among trials that might be expected to affect the magnitude of the treatment effect.

Network meta-analysis was used after traditional meta-analysis. When efficient chemotherapy regimens were compared through network meta-analysis, the head-to-head comparisons (in this case, indirect comparisons) were handled and consequently assigned a statistical result in terms of superiority/inferiority or no difference

Table 1 Characteristics of randomized trials included in the network meta-analysis

Trial	Year	Postoperative chemotherapy regimens	Sample size		Overall mortality		Follow-up (mo)	Jadad score
			Chemotherapy group	Control group	Chemotherapy group	Control group		
Lawton *et al*[20]	1981	FU + BCNU	13	12	11/13	10/12	60	2
Stablein *et al*[21]	1982	FU + MCCNU	71	71	29/71	40/71	48	3
Higgins *et al*[22]	1983	FU + MCCNU	156	156	121/156	117/156	36	3
Nakajima *et al*[23]	1984	FM + Ara-c	128	124	11/128	17/124	60	3
Engstrom *et al*[24]	1985	FU + MCCNU	91	89	57/91	51/89	24	3
Schlag *et al*[25]	1987	FU + BCNU	42	53	21/42	28/53	72	2
Bonfanti *et al*[26]	1988	FU + MCCNU	75	69	63/75	56/69	84	4
Coombes *et al*[27]	1990	FMA	131	148	101/133	123/148	68	3
Estape *et al*[28]	1991	MMC	33	37	16/33	31/37	120	2
Krook *et al*[29]	1991	FA	61	64	41/61	43/64	60	3
Kim *et al*[30]	1992	MMC + FU	77	94	54/77	71/94	60	2
Grau *et al*[31]	1993	MMC	68	66	40/68	49/66	105	2
Hallissey *et al*[32]	1994	FMA	138	145	101/138	110/145	60	3
Macdonald *et al*[33]	1995	FMA	93	100	59/93	68/100	114	2
Lise *et al*[34]	1995	FMA	155	159	88/155	99/159	78	3
Tsavaris *et al*[35]	1996	FMA	42	42	27/42	34/42	60	3
Cirera *et al*[36]	1999	MMC + Tegafur	76	76	33/ 76	44/72	37	3
Nakajima *et al*[37]	1999	MMC + FU + UFT	288	285	41/288	49/285	72	3
Neri *et al*[38]	2001	Epirubicin + FU	69	68	48/69	59/68	60	2
Bajetta *et al*[39]	2002	FU + Adriamycin etoposide + cisplatin	137	137	66/137	71/137	66	2
Nashimoto *et al*[40]	2003	MMC + FU + Ara C	128	124	11/128	23/124	69	2
Popiela *et al*[41]	2004	FAM	53	52	42/53	47/52	120	2
Chipponi *et al*[42]	2004	Cisplatin + FU	101	104	62/101	63/104	60	2
Bouché *et al*[43]	2005	Cisplatin + FU	127	133	68/127	77/133	97.8	3
Nitti *et al*[44]	2006	FU + Adriamycin + methotrexate + LV	103	103	54/103	49/103	60	3
Nitti *et al*[44]	2006	FU + Epirubicin + methotrexate + LV	91	100	63/91	64/100	60	3
De Vita *et al*[45]	2007	FU + Epirubicin + LV + etoposide	112	113	58/112	64/113	60	2
Nakajima *et al*[46]	2007	Uracil-Tegafur	95	95	18/95	30/95	60	4
Di Costanzo *et al*[47]	2008	FU + Epirubicin + cisplatin + LV	130	128	69/130	70/128	60	3
Miyashiro *et al*[48]	2011	Cisplatin + FU	132	132	50/132	52/132	60	4
Sasako *et al*[49]	2011	S-1	529	530	149/529	206/530	60	4

FU: Fluorouracil; MCCNU: Methyl-CCNU; MMC: Mitomycin c; LV: Leucovorin; Ara-c: Cytarabine; CDHP: 5-Chloro-2,4-dihydropyrimidine; Oxo: Potassium oxonate; FM: FU + MMC; FMA: FU + MMC + adriamycin; S-1: Tegafur + CDHP + Oxo.

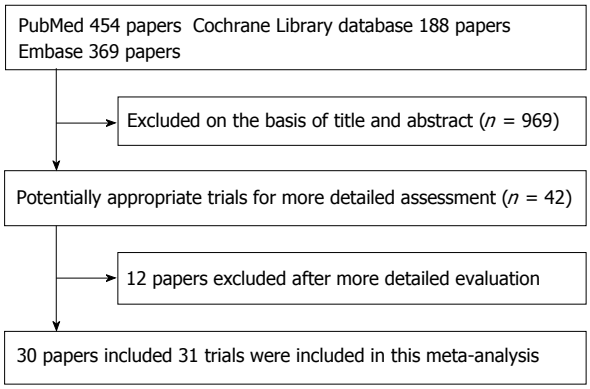

Figure 1 Flow diagram of trial selection.

along with the level of statistical significance. Statistical calculations and graph generation were carried out. The HR, with a 95%CI, for each indirect comparison was estimated according to the ITC software (Canadian Agency for Drugs and Technologies in Health, Indirect Treatment Comparison software, Ottawa, Ontario, Canada). This approach allows an indirect HR, with a 95%CI, to be estimated on the condition that both treatments included in the indirect comparison had been compared in actual trials against a common comparator.

Role of funding source

No sponsors were involved in the study design; during the collection, analysis, and interpretation of the data; in the writing of the report; or in the decision to submit the report for publication. All authors had access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit the report for publication.

RESULTS

Flow diagram of trial selection

In total, 31 RCTs, with a total of 7120 patients, were included (Figure 1) from the electronic databases. Figure

1 shows a flow chart of studies from the initial results of the publication searches to the final inclusion or exclusion. The RCTs that met the criteria for our analysis are described in Table 1. There were 12 RCTs that had a Jadad score of 2, 15 RCTs that had a Jadad score of 3 and 4 RCTs that had a Jadad score of 4.

Analysis of regimen groups

In terms of direct comparisons, this analysis divided the chemotherapy regimens into 9 subgroups, and 8 subgroups were assessed by the fixed effects models, while only 1 was assessed by the random effects models. In terms of overall mortality, at least 5 chemotherapy regimens were found to be of equal efficacy when compared to a blank control. The values of HR were as follows: 0.92 (95%CI: 0.43-1.96) for FU + BCNU regimen, 1.00 (95%CI: 0.76-1.32) for FU + methyl-CCNU (mCCNU) regimen, 0.93 (95%CI: 0.69-1.24) for FU + cisplatin regimen, 0.92 (95%CI: 0.74-1.14) for FU + anthracyclines regimen, and 0.67 (95%CI: 0.41-1.10) for FU + mitomycin c (MMC) + AraC regimen. In contrast, in terms of overall mortality, 4 chemotherapy regimens were found to be more effective than the blank control. The values of HR were as follows: 0.74 (95%CI: 0.58-0.94) for FAM regimen, 0.68 (95%CI: 0.49-0.94) for FM regimen, 0.60 (95%CI: 0.47-0.76) for Tegafur regimen, and 0.33 (95%CI: 0.13-0.86) for MMC regimen. These outcomes are described in Figures 2 and 3.

In terms of indirect comparisons, 4 chemotherapy regimens were found to be equal in terms of overall mortality. The values of HR were as follows: 1.09 (95%CI: 0.73-1.63) for 5-FU + adriamycin + MCC (FAM) regimen *vs* FM regimen; 1.23 (95%CI: 0.88-1.73) for 5-FU + MMC + adriamycin (FMA) regimen *vs* Tegafur regimen; 2.24 (95%CI: 0.85-5.95) for FMA regimen *vs* MMC regimen; 1.13 (95%CI: 0.76-1.70) for FM regimen *vs* Tegafur regimen; 2.06 (95%CI: 0.76-5.60) for FM regimen *vs* MMC regimen; and 1.82 (95%CI: 0.67-4.80) for Tegafur regimen *vs* MMC regimen. These outcomes are described in Figure 4.

DISCUSSION

In total, 31 RCTs, with a total of 7120 patients, were included in this analysis, and 12 RCTs had a Jadad score of 2, 15 RCTs had a Jadad score of 3, and 4 RCTs had a Jadad score of 4. This study divided these chemotherapy regimens into 9 subgroups. The result of this analysis indicated that 5 chemotherapy regimens had little benefit to the patients, including the FU + BCNU, FU + mCCNU, FU + cisplatin, FU + anthracyclines, and FU + MMC + AraC regimens. In contrast, 4 chemotherapy regimens were effective for patients after surgery, including the FMA, FM, Tegafur, and MMC regimens. In this study, Tegafur and the S-1 regimen were assigned to one regimen because S-1 was composed of Tegafur, CDHP and Oxo, as CDHP and Oxo reduced the side effects of Tegafur. As Tegafur is a fluorouracil derivative, the FM regimen was included in 3 RCTs. Additionally, anthracyclines, including adriamycin, epirubicin and doxorubicin, were part of the FMA regimen, which was included in 6 RCTs. Indirect comparisons were estimated according to the ITC software, and the results indicated that there was no difference among these four chemotherapy regimens in the terms of overall mortality.

Although this analysis indicated that MMC was effective for patients after surgery, the evidence for this result was poor because of the low quality of the 2 RCTs included. Specifically, one trial had a small sample size, and only 204 patients were contained in the subgroup analysis. Additionally, because there was also significant heterogeneity among the trials ($P = 0.14$, $I^2 = 54\%$), the analysis was carried out using the random effects models. The curative effect of MMC needs to be further validated. The evidence for the Tegafur regimen included 1249 patients, the RCTs were of high quality, and there was no significant heterogeneity among the trials ($P = 0.59$, $I^2 = 0\%$). Accordingly, the analysis was carried out using the fixed effects model, and we found strong evidence to confirm the efficacy of the Tegafur regimen. The joint application with 5-chloro-2,4-dihydropyrimidine (CDHP) and potassium oxonate (Oxo) reduced the side effects of Tegafur; therefore, the S-1 regimen (Tegafur + CDHP + Oxo) is recommended.

The combination of Tegafur and MMC in the FM regimen was similar to treatment with each component individually, as determined by indirect comparison, and further studies are needed to confirm which treatment is the primary effector. Additionally, if the side effects of Tegafur and MMC will reduce the overall efficacy, further studies are needed to identify an adjuvant that can reduce these side effects, as in the case of S-1. If the treatments have a mutual antagonist effect on each other, they should be used separately. As the evidence for the FM regimen is not very strong, larger sample sizes and multicenter RCTs are still needed. While the FMA regimen is available, surprisingly, it is not better than Tegafur or MMC. Traditional analysis indicated that the FU + anthracyclines regimen is not available, and thus, MMC may contribute to the efficacy of the FMA regimen to a great extent. Accordingly, based on these results, FMA is not recommended.

In summary, chemotherapy regimens, especially Tegafur, are available for GC. However, the efficacy of the FM regimen and MMC regimen needs to be further validated. The evidence for the Tegafur regimen is more credible, and S-1 may be the best current choice. Future studies should focus on identifying better adjuvants that can reduce the side effects of MMC as much as possible. Their combination could be a better regimen than S-1, and perhaps, the combination of MMC, Tegafur and adjuvant can achieve better outcomes than mono-chemotherapy alone. However, based on recent evidence, the Tegafur regimen, especially S-1, is most commonly recommended to patients after complete resection.

In conclusion, this analysis indicated that four che-

Study or subgroup	Adjuvant chemotherapy Events	Total	Control Events	Total	Weight	Odds ratio M-H, fixed, 95%CI
1.1.1 FU + BNCU						
Lawton *et al*[20] 1981	21	42	28	53	1.5%	0.89 [0.40, 2.01]
Schlag *et al*[25] 1987	11	13	10	12	0.2%	1.10 [0.13, 9.34]
Subtotal (95%CI)		55		65	1.7%	0.92 [0.43, 1.96]
Total events	32		38			
Heterogeneity: χ^2 = 0.03, *df* = 1 (*P* = 0.86); I^2 = 0%						
Test for overall effect: *Z* = 0.23 (*P* = 0.82)						
1.1.2 FU + mCCNU						
Bonfanti *et al*[26] 1988	47	75	40	69	1.9%	1.22 [0.62, 2.38]
Stablein *et al*[21] 1982	29	71	40	71	2.9%	0.54 [0.27, 1.04]
Engstrom *et al*[24] 1985	57	91	51	89	2.3%	1.25 [0.69, 2.27]
Higgins *et al*[22] 1983	121	156	117	156	3.2%	1.15 [0.68, 1.94]
Subtotal (95%CI)		393		385	10.3%	1.01 [0.75, 1.37]
Total events	254		248			
Heterogeneity: χ^2 = 4.52, *df* = 3 (*P* = 0.21); I^2 = 34%						
Test for overall effect: *Z* = 0.09 (*P* = 0.93)						
1.1.3 FU + Cisplatin						
Bouché *et al*[43] 2005	68	127	77	133	4.3%	0.84 [0.51, 1.37]
Chipponi *et al*[42] 2004	62	101	63	104	2.9%	1.03 [0.59, 1.81]
Miyashiro *et al*[48] 2011	50	132	52	132	3.9%	0.94 [0.57, 1.54]
Subtotal (95%CI)		360		369	11.1%	0.93 [0.69, 1.24]
Total events	180		192			
Heterogeneity: χ^2 = 0.31, *df* = 2 (*P* = 0.86); I^2 = 0%						
Test for overall effect: *Z* = 0.52 (*P* = 0.61)						
1.1.4 FU + Anthracyclines + others						
Bajetta *et al*[39] 2002	66	137	71	137	4.5%	0.86 [0.54, 1.39]
De Vita *et al*[45] 2007	58	112	64	113	3.7%	0.82 [0.49, 1.39]
Di Costanzo *et al*[47] 2008	69	130	70	128	4.0%	0.94 [0.57, 1.53]
Krook *et al*[47] 1991	41	61	43	64	1.7%	1.00 [0.47, 2.11]
Neri *et al*[38] 2001	48	69	59	68	2.2%	0.35 [0.15, 0.83]
Nitti *et al*[44] 2006a	54	103	49	103	2.8%	1.21 [0.70, 2.10]
Nitti *et al*[44] 2006b	63	91	64	100	2.3%	1.27 [0.69, 2.32]
Subtotal (95%CI)		703		713	21.3%	0.92 [0.74, 1.14]
Total events	399		420			
Heterogeneity: χ^2 = 7.15, *df* = 6 (*P* = 0.31); I^2 = 16%						
Test for overall effect: *Z* = 0.78 (*P* = 0.43)						
1.1.5 FU + MMC + AraC						
Nakajima *et al*[23] 1984	11	128	17	124	1.9%	0.59 [0.27, 1.32]
Nashimoto *et al*[40] 2003	102	156	52	72	3.0%	0.73 [0.39, 1.34]
Subtotal (95%CI)		284		196	4.9%	0.67 [0.41, 1.10]
Total events	113		69			
Heterogeneity: χ^2 = 0.16, *df* = 1 (*P* = 0.69); I^2 = 0%						
Test for overall effect: *Z* = 1.59 (*P* = 0.11)						
1.1.6 FU + MMC + Anthracyclines						
Coombers *et al*[27] 1990	73	133	91	148	4.7%	0.76 [0.47, 1.23]
Hallissey *et al*[32] 1994	101	138	110	145	3.5%	0.87 [0.51, 1.48]
Lise *et al*[34] 1995	88	152	99	154	5.0%	0.76 [0.48, 1.21]
Macdonald *et al*[33] 1995	59	93	68	100	2.9%	0.82 [0.45, 1.48]
Popiela *et al*[41] 2004	42	53	47	52	1.2%	0.41 [0.13, 1.27]
Tsavaris *et al*[35] 1996	27	42	34	42	1.5%	0.42 [0.16, 1.15]
Subtotal (95%CI)		611		641	18.9%	0.74 [0.58, 0.94]
Total events	390		449			
Heterogeneity: χ^2 = 2.76, *df* = 5 (*P* = 0.74); I^2 = 0%						
Test for overall effect: *Z* = 2.44 (*P* = 0.01)						
1.1.7 FD (fluorouracil derivative) + MMC						
Cirera *et al*[36] 1999	33	76	46	72	3.3%	0.43 [0.22, 0.84]
Kim *et al*[30] 1992	54	77	71	94	2.3%	0.76 [0.39, 1.50]
Nakajima *et al*[37] 1999	41	288	49	285	5.2%	0.80 [0.51, 1.26]
Subtotal (95%CI)		441		451	10.7%	0.68 [0.49, 0.94]
Total events	128		166			
Heterogeneity: χ^2 = 2.38, *df* = 2 (*P* = 0.30); I^2 = 16%						
Test for overall effect: *Z* = 2.32 (*P* = 0.02)						

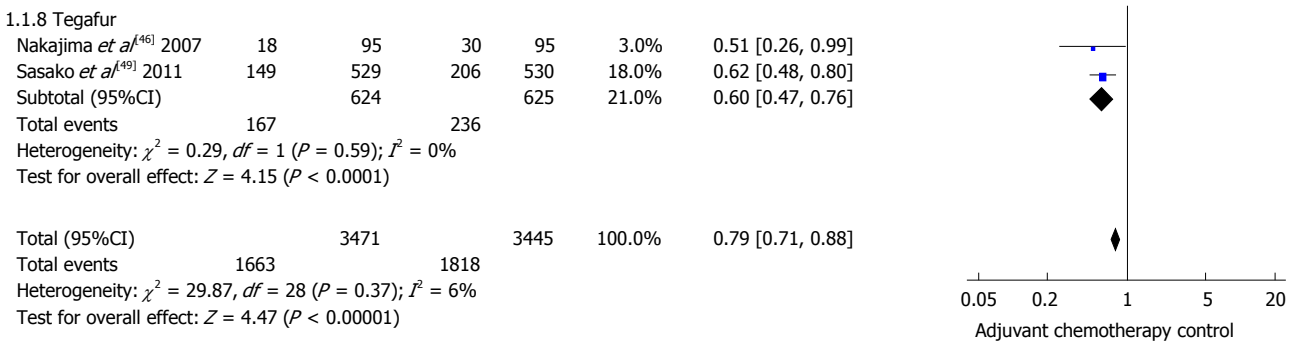

Figure 2 Eight subgroups in the fixed effects models.

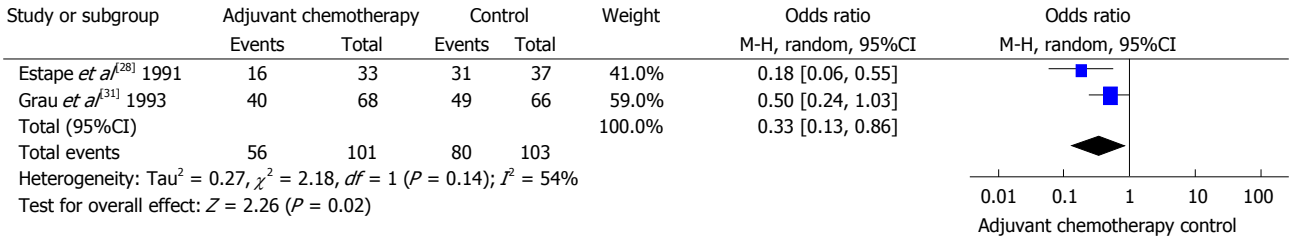

Figure 3 One subgroup in the random effects model. FU: Fluorouracil; mCCNU: Methyl-CCNU; MMC: Mitomycin c.

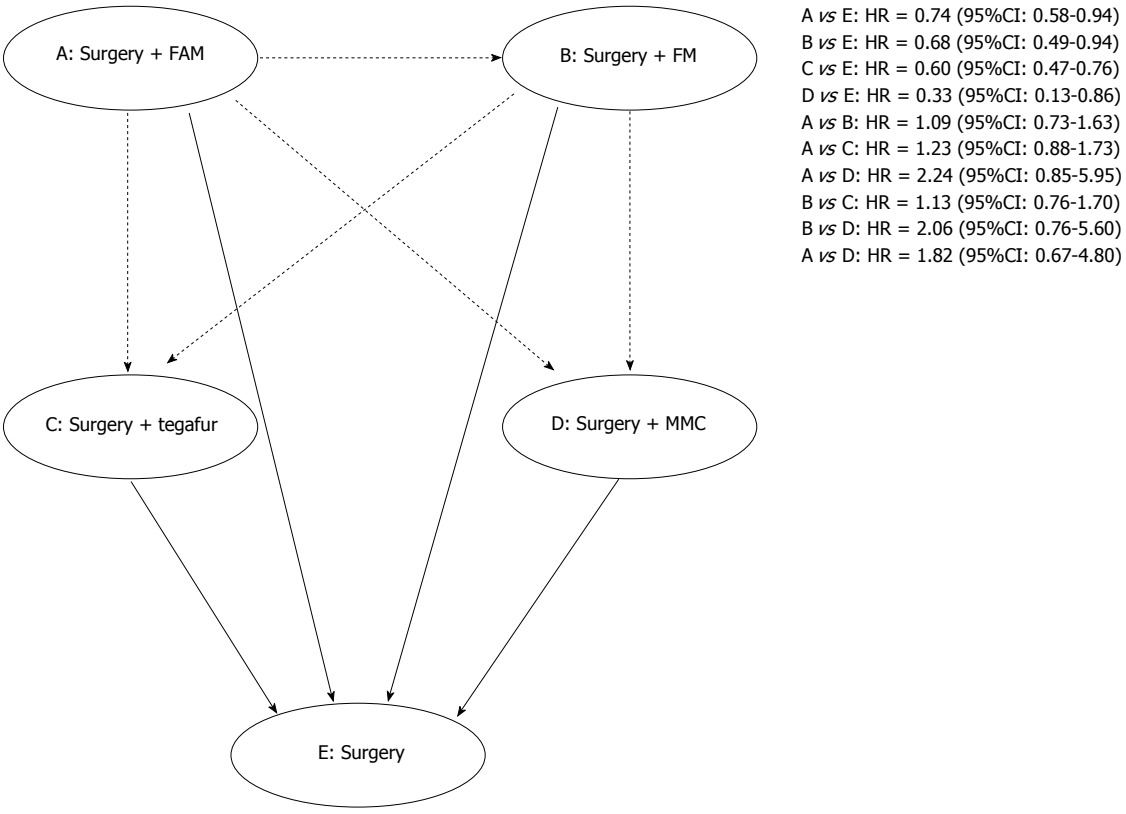

Figure 4 Network meta-analysis in terms of mortality. MMC: Mitomycin c; FAM: 5-fluorouracil, adriamycin, and mitomycin c.

motherapy regimens are effective for patients with GC after surgery, including the FMA regimen, FM regimen, Tegafur regimen and MMC regimen. However, the evidence for the FM regimen and MMC regimen was poor in terms of overall mortality. The FMA regimen, which includes many chemotherapy drugs and thus has many side effects, is not better than the Tegafur regimen. Based on this study, the Tegafur regimen is recommended as a better choice for doctors when dealing with GC patients after complete resection.

COMMENTS

Background

Gastric cancer is very common worldwide and, in most cases, will lead to serious health problems, even after complete resection. Currently, treatment with adjuvant and palliative chemotherapies are essential to prevent and treat recurrence disease. A standard chemotherapy regimen has not been established; therefore, the evaluation of which regimens may be better for gastric cancer patients is needed.

Research frontiers

This network meta-analysis was performed to evaluate the effectiveness of different chemotherapy regimens for patients with gastric cancer. The end point was overall mortality, which was defined as the time from randomization to death from any cause, or to the last follow-up.

Innovations and breakthroughs

The meta-analysis shows the following: four chemotherapy regimens [fluorouracil (FU) + mitomycin c + adriamycin, fluorouracil + mitomycin c (FM), tegafur and mitomycin c (MMC)] are effective for patients after surgery, whereas the other five regimens [fluorouracil + BCNU, FU + methyl-CCNU (mCCNU), FU + cisplatin, FU + anthracyclines and FU + mitomycin c + cytarabine] were found to be less beneficial.

Applications

From the analysis, Tegafur is recommended as the first-line adjuvant chemotherapy regimen for patients after complete resection. This recommendation is due to the high quality of the randomized controlled trials (RCTs), homogeneity among trials and fewer side effects.

Peer review

The current network meta-analysis evaluated the effectiveness of different chemotherapy regimens for gastric cancer patients after curative surgery, and we found that the outcomes and analysis were good. However, further RCTs are needed to study the FM regimen, MMC regimen and combination chemotherapy.

REFERENCES

1 **Akoh JA**, Macintyre IM. Improving survival in gastric cancer: review of 5-year survival rates in English language publications from 1970. *Br J Surg* 1992; **79**: 293-299 [PMID: 1576492 DOI: 10.1002/bjs.1800790404]

2 **Kim JP**, Lee JH, Kim SJ, Yu HJ, Yang HK. Clinicopathologic characteristics and prognostic factors in 10 783 patients with gastric cancer. *Gastric Cancer* 1998; **1**: 125-133 [PMID: 11957056 DOI: 10.1007/s101200050006]

3 **Nakamura K**, Ueyama T, Yao T, Xuan ZX, Ambe K, Adachi Y, Yakeishi Y, Matsukuma A, Enjoji M. Pathology and prognosis of gastric carcinoma. Findings in 10,000 patients who underwent primary gastrectomy. *Cancer* 1992; **70**: 1030-1037 [PMID: 1515980 DOI: 10.1002/1097-0142(19920901)70:5<1030::AID-CNCR2820700504>3.0.CO;2-C]

4 **Roder DM**. The epidemiology of gastric cancer. *Gastric Cancer* 2002; **5** Suppl 1: 5-11 [PMID: 12772880 DOI: 10.1007/s10120-002-0203-6]

5 **Sasako M**. Principles of surgical treatment for curable gastric cancer. *J Clin Oncol* 2003; **21**: 274s-275s [PMID: 14645409 DOI: 10.1200/JCO.2003.09.172]

6 **Yoo CH**, Noh SH, Shin DW, Choi SH, Min JS. Recurrence following curative resection for gastric carcinoma. *Br J Surg* 2000; **87**: 236-242 [PMID: 10671934 DOI: 10.1046/j.1365-2168.2000.01360]

7 **Caldwell DM**, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005; **331**: 897-900 [PMID: 16223826 DOI: 10.1136/bmj.331.7521.897]

8 **Fadda V**, Maratea D, Trippoli S, Messori A. Network meta-analysis. Results can be summarised in a simple figure. *BMJ* 2011; **342**: d1555 [PMID: 21430004]

9 **Fadda V**, Maratea D, Trippoli S, Messori A. Treatments for macular degeneration: summarising evidence using network meta-analysis. *Br J Ophthalmol* 2011; **95**: 1476-1477 [PMID: 21680571 DOI: 10.1136/bjophthalmol-2011-300316]

10 **Maratea D**, Fadda V, Trippoli S, Messori A. Prevention of venous thromboembolism after major orthopedic surgery: indirect comparison of three new oral anticoagulants. *J Thromb Haemost* 2011; **9**: 1868-1870 [PMID: 21711443 DOI: 10.1111/j.1538-7836.2011.04421]

11 **Messori A**, Del Santo F, Maratea D. First-line treatments for hepatitis C. *Aliment Pharmacol Ther* 2011; **33**: 1383-1385 [PMID: 21569068 DOI: 10.1111/j.1365-2036.2011.04672]

12 **Passaro D**, Fadda V, Maratea D, Messori A. Anti-platelet treatments in acute coronary syndrome: simplified network meta-analysis. *Int J Cardiol* 2011; **150**: 364-367 [PMID: 21652097 DOI: 10.1016/j.ijcard.2011.05.083]

13 **Janunger KG**, Hafström L, Glimelius B. Chemotherapy in gastric cancer: a review and updated meta-analysis. *Eur J Surg* 2002; **168**: 597-608 [PMID: 12699095 DOI: 10.1080/11024150201680005]

14 **Liu TS**, Wang Y, Chen SY, Sun YH. An updated meta-analysis of adjuvant chemotherapy after curative resection for gastric cancer. *Eur J Surg Oncol* 2008; **34**: 1208-1216 [PMID: 18353606 DOI: 10.1016/j.ejso.2008.02.002]

15 **Mari E**, Floriani I, Tinazzi A, Buda A, Belfiglio M, Valentini M, Cascinu S, Barni S, Labianca R, Torri V. Efficacy of adjuvant chemotherapy after curative resection for gastric cancer: a meta-analysis of published randomised trials. A study of the GISCAD (Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente). *Ann Oncol* 2000; **11**: 837-843 [PMID: 10997811 DOI: 10.1023/A:1008377101672]

16 **Oba K**, Morita S, Tsuburaya A, Kodera Y, Kobayashi M, Sakamoto J. Efficacy of adjuvant chemotherapy using oral fluorinated pyrimidines for curatively resected gastric cancer: a meta-analysis of centrally randomized controlled clinical trials in Japan. *J Chemother* 2006; **18**: 311-317 [PMID: 17129844]

17 **Paoletti X**, Oba K, Burzykowski T, Michiels S, Ohashi Y, Pignon JP, Rougier P, Sakamoto J, Sargent D, Sasako M, Van Cutsem E, Buyse M. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. *JAMA* 2010; **303**: 1729-1737 [PMID: 20442389 DOI: 10.1001/jama.2010.534]

18 **Zhao SL**, Fang JY. The role of postoperative adjuvant chemotherapy following curative resection for gastric cancer: a meta-analysis. *Cancer Invest* 2008; **26**: 317-325 [PMID: 18317973 DOI: 10.1080/07357900701834686]

19 **Jadad AR**, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1-12 [PMID: 8721797 DOI: 10.1016/0197-2456(95)00134-4]

20 **Lawton JO**, Giles GR, Hall R, Bird GG, Matheson T. Chemotherapy following palliative resection of gastric cancer. *Br J Surg* 1981; **68**: 397-399 [PMID: 6165425 DOI: 10.1002/bjs.1800680610]

21 **Stablein DM**, Douglass HO. Controlled trial of adjuvant chemotherapy following curative resection for gastric cancer[J]. *Cancer* 1982; **49**: 1116-1122 [PMID: 7037156 DOI: 10.1002/1097-0142(19820315)49:6<1116::AIDCNCR2820490609>3.0.CO;2-U]

22 **Higgins GA**, Amadeo JH, Smith DE, Humphrey EW, Keehn RJ. Efficacy of prolonged intermittent therapy with combined 5-FU and methyl-CCNU following resection for gastric carcinoma. A Veterans Administration Surgical Oncology, Group report. *Cancer* 1983; **52**: 1105-1112 [PMID: 6349780 DOI: 10.1002/1097-0142(19830915)52:6<1105::AID-CNCR2820520629>3.0.CO;2-Z]

23 **Nakajima T**, Takahashi T, Takagi K, Kuno K, Kajitani T. Comparison of 5-fluorouracil with ftorafur in adjuvant chemotherapies with combined inductive and maintenance therapies for gastric cancer. *J Clin Oncol* 1984; **2**: 1366-1371 [PMID: 6439835]

24 **Engstrom PF**, Lavin PT, Douglass HO, Brunner KW. Postop-

erative adjuvant 5-fluorouracil plus methyl-CCNU therapy for gastric cancer patients. Eastern Cooperative Oncology Group study (EST 3275). *Cancer* 1985; **55**: 1868-1873 [PMID: 3884131 DOI: 10.1002/1097-0142(19850501)55:9<1868::AID-CNCR2820550904>3.0.CO; 2-B]
25 **Schlag P**. Adjuvant chemotherapy in gastric cancer. *World J Surg* 1987; **11**: 473-477 [PMID: 3630192 DOI: 10.1007/BF01655812]
26 **Bonfanti G**. Adjuvant treatments following curative resection for gastric cancer[J]. *Br J Surg* 1988; **75**: 1100-1104 [PMID: 2905188]
27 **Coombes RC**, Schein PS, Chilvers CE, Wils J, Beretta G, Bliss JM, Rutten A, Amadori D, Cortes-Funes H, Villar-Grimalt A. A randomized trial comparing adjuvant fluorouracil, doxorubicin, and mitomycin with no treatment in operable gastric cancer. International Collaborative Cancer Group. *J Clin Oncol* 1990; **8**: 1362-1369 [PMID: 2199622]
28 **Estape J**, Grau JJ, Lcobendas F, Curto J, Daniels M, Viñolas N, Pera C. Mitomycin C as an adjuvant treatment to resected gastric cancer. A 10-year follow-up. *Ann Surg* 1991; **213**: 219-221 [PMID: 1900148 DOI: 10.1097/00000658-199103000-00006]
29 **Krook JE**, O'Connell MJ, Wieand HS, Beart RW, Leigh JE, Kugler JW, Foley JF, Pfeifle DM, Twito DI. A prospective, randomized evaluation of intensive-course 5-fluorouracil plus doxorubicin as surgical adjuvant chemotherapy for resected gastric cancer. *Cancer* 1991; **67**: 2454-2458 [PMID: 2015545 DOI: 10.1002/1097-0142(19910515)67:10<2454::AID-CNCR2820671010>3.0.CO; 2-2]
30 **Kim JP**, Kwon OJ, Oh ST, Yang HK. Results of surgery on 6589 gastric cancer patients and immunochemosurgery as the best treatment of advanced gastric cancer. *Ann Surg* 1992; **216**: 269-278; discussion 278-279 [PMID: 1417176]
31 **Grau JJ**, Estapé J, Alcobendas F, Pera C, Daniels M, Terés J. Positive results of adjuvant mitomycin-C in resected gastric cancer: a randomised trial on 134 patients. *Eur J Cancer* 1993; **29A**: 340-342 [PMID: 8398330]
32 **Hallissey MT**, Dunn JA, Ward LC, Allum WH. The second British Stomach Cancer Group trial of adjuvant radiotherapy or chemotherapy in resectable gastric cancer: five-year follow-up. *Lancet* 1994; **343**: 1309-1312 [PMID: 7910321 DOI: 10.1016/S0140-6736(94)92464-3]
33 **Macdonald JS**, Fleming TR, Peterson RF, Berenberg JL, McClure S, Chapman RA, Eyre HJ, Solanki D, Cruz AB, Gagliano R. Adjuvant chemotherapy with 5-FU, adriamycin, and mitomycin-C (FAM) versus surgery alone for patients with locally advanced gastric adenocarcinoma: A Southwest Oncology Group study. *Ann Surg Oncol* 1995; **2**: 488-494 [PMID: 8591078 DOI: 10.1007/BF02307081]
34 **Lise M**, Nitti D, Marchet A, Sahmoud T, Buyse M, Duez N, Fiorentino M, Dos Santos JG, Labianca R, Rougier P. Final results of a phase III clinical trial of adjuvant chemotherapy with the modified fluorouracil, doxorubicin, and mitomycin regimen in resectable gastric cancer. *J Clin Oncol* 1995; **13**: 2757-2763 [PMID: 7595735]
35 **Tsavaris N**, Tentas K, Kosmidis P, Mylonakis N, Sakelaropoulos N, Kosmas C, Lisaios B, Soumilas A, Mandrekas D, Tsetis A, Klonaris C. A randomized trial comparing adjuvant fluorouracil, epirubicin, and mitomycin with no treatment in operable gastric cancer. *Chemotherapy* 1996; **42**: 220-226 [PMID: 8983891 DOI: 10.1159/000239446]
36 **Cirera L**, Balil A, Batiste-Alentorn E, Tusquets I, Cardona T, Arcusa A, Jolis L, Saigí E, Guasch I, Badia A, Boleda M. Randomized clinical trial of adjuvant mitomycin plus tegafur in patients with resected stage III gastric cancer. *J Clin Oncol* 1999; **17**: 3810-3815 [PMID: 10577853]
37 **Nakajima T**, Nashimoto A, Kitamura M, Kito T, Iwanaga T, Okabayashi K, Goto M. Adjuvant mitomycin and fluorouracil followed by oral uracil plus tegafur in serosa-negative gastric cancer: a randomised trial. Gastric Cancer Surgical Study Group. *Lancet* 1999; **354**: 273-277 [PMID: 10440302 DOI: 10.1016/S0140-6736(99)01048-X]
38 **Neri B**, Cini G, Andreoli F, Boffi B, Francesconi D, Mazzanti R, Medi F, Mercatelli A, Romano S, Siliani L, Tarquini R, Moretti R. Randomized trial of adjuvant chemotherapy versus control after curative resection for gastric cancer: 5-year follow-up. *Br J Cancer* 2001; **84**: 878-880 [PMID: 11286464 DOI: 10.1054/bjoc.2000.1472]
39 **Bajetta E**, Buzzoni R, Mariani L, Beretta E, Bozzetti F, Bordogna G, Aitini E, Fava S, Schieppati G, Pinotti G, Visini M, Ianniello G, Di BM. 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**: 299-307 [PMID: 11886009]
40 **Nashimoto A**, Nakajima T, Furukawa H, Kitamura M, Kinoshita T, Yamamura Y, Sasako M, Kunii Y, Motohashi H, Yamamoto S; Gastric Cancer Surgical Study Group, Japan Clinical Oncology Group. 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**: 2282-2287 [PMID: 12805327]
41 **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**: 240-245 [PMID: 15616772]
42 **Chipponi J**, Huguier M, Pezet D, Basso N, Hay JM, Quandalle P, Jaeck D, Fagniez PL, Gainant A. Randomized trial of adjuvant chemotherapy after curative resection for gastric cancer. *Am J Surg* 2004; **187**: 440-445 [PMID: 15006580 DOI: 10.1016/j.amjsurg.2003.12.014]
43 **Bouché O**, Ychou M, Burtin P, Bedenne L, Ducreux M, Lebreton G, Baulieux J, Nordlinger B, Martin C, Seitz JF, Tigaud JM, Echinard E, Stremsdoerfer N, Milan C, Rougier P; Fédération Francophone de Cancérologie Digestive Group. 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**: 1488-1497 [PMID: 15939717]
44 **Nitti D**, Wils J, Dos Santos JG, Fountzilas G, Conte PF, Sava C, Tres A, Coombes RC, Crivellari D, Marchet A, Sanchez E, Bliss JM, Homewood J, Couvreur ML, Hall E, Baron B, Woods E, Emson M, Van Cutsem E, Lise M; EORTC GI Group; ICCG. 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**: 262-269 [PMID: 16293676 DOI: 10.1093/annonc/mdj077]
45 **De Vita F**, Giuliani F, Orditura M, Maiello E, Galizia G, Di Martino N, Montemurro F, Cartenì G, Manzione L, Romito S, Gebbia V, Ciardiello F, Catalano G, Colucci G; Gruppo Oncologico Italia Meridionale. 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**: 1354-1358 [PMID: 17525087]
46 **Nakajima T**, Kinoshita T, Nashimoto A, Sairenji M, Yamaguchi T, Sakamoto J, Fujiya T, Inada T, Sasako M, Ohashi Y; National Surgical Adjuvant Study of Gastric Cancer Group. Randomized controlled trial of adjuvant uracil-tegafur versus surgery alone for serosa-negative, locally advanced gastric cancer. *Br J Surg* 2007; **94**: 1468-1476 [PMID: 17948223 DOI: 10.1002/bjs.5996]
47 **Di Costanzo F**, Gasperoni S, Manzione L, Bisagni G, Labianca R, Bravi S, Cortesi E, Carlini P, Bracci R, Tomao S, Messerini L, Arcangeli A, Torri V, Bilancia D, Floriani I, Tonato M; Italian Oncology Group for Cancer Research, Dinota A, Strafiuso G, Corgna E, Porrozzi S, Boni C, Rondini E, Giunta A, Monzio Compagnoni B, Biagioni F, Cesari M, Fornarini G, Nelli F, Carboni M, Cognetti F, Enzo MR, Piga A, Romiti A, Olivetti A, Masoni L, De Stefanis M, Dalla Mola A, Camera S,

Recchia F, De Filippis S, Scipioni L, Zironi S, Luppi G, Italia M, Banducci S, Pisani Leretti A, Massidda B, Ionta MT, Nicolosi A, Canaletti R, Biscottini B, Grigniani F, Di Costanzo F, Rovei R, Croce E, Carroccio R, Gilli G, Cavalli C, Olgiati A, Pandolfi U, Rossetti R, Natalini G, Foa P, Oldani S, Bruno L, Cascinu S, Catalano G, Catalano V, Lungarotti F, Farris A, Sarobba MG, Trignano M, Muscogiuri A, Francavilla F, Figoli F, Leoni M, Papiani G, Orselli G, Antimi M, Bellini V, Cabassi A, Contu A, Pazzola A, Frignano M, Lastraioli E, Saggese M, Bianchini D, Antonuzzo L, Mela M, Camisa R. Adjuvant chemotherapy in completely resected gastric cancer: a randomized phase III trial conducted by GOIRC. *J Natl Cancer Inst* 2008; **100**: 388-398 [PMID: 18334706 DOI: 10.1093/jnci/djn054]

48 **Miyashiro I**, Furukawa H, Sasako M, Yamamoto S, Nashimoto A, Nakajima T, Kinoshita T, Kobayashi O, Arai K; Gastric Cancer Surgical Study Group in the Japan Clinical Oncology Group. 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**: 212-218 [PMID: 21336855 DOI: 10.1007/s10120-011-0027-3]

49 **Sasako M**, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, Nashimoto A, Fujii M, Nakajima T, Ohashi Y. 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**: 4387-4393 [PMID: 22010012]

P- Reviewers: Hahm KB, Tiberio GAM, Zaniboni A, Zoli W
S- Editor: Cui XM **L- Editor**: Wang TQ **E- Editor**: Wang CH

百世登
Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

ISSN 1007-9327
0 2>
9 771007 932045