



The efficacy and adverse reactions of DCF and FOLFOXs regimens for patients with advanced gastric cancer in China: a meta-analysis

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Background: Gastric cancer is a malignant tumor originating from the gastric mucosal epithelium, ranking fourth in the incidence of male malignant tumors and third in mortality rate. The aim of this study is to investigate the efficacy and adverse reactions of DCF and FOLFOXs regimens in the treatment of advanced gastric cancer.

Methods: Relevant prospective clinical controlled studies were retrieved from WanFang Data, CBM, CNKI, PubMed, The Cochrane Library and Embase databases and meta-analysis was performed using RevMan 5.3 software.

Results: The effective rates of DCF group and FOLFOXs group were basically the same (RR 1.06, 95% CI: 0.92–1.23, P=0.41). The incidence of nausea and vomiting (RR 1.36, 95% CI: 1.15–1.60), anemia (RR 2.04, 95% CI: 1.55–2.68), thrombocytopenia (RR 1.52, 95% CI: 1.15–2.01) and leukopenia (RR 1.70, 95% CI: 1.44–2.01) with FOLFOXs regimen were significantly lower than DCF regimen, while the incidence of sensory neurotoxicity was significantly higher than DCF regimen (RR 0.53, 95% CI: 0.38–0.74). There were no significant differences in efficacy, ORR and DCR between different doses in the FOLFOXs group (P=0.233).

Conclusions: The efficacy of FOLFOXs regimen was comparable to that of DCF regimen in the treatment of advanced gastric cancer, but the incidence of adverse reactions was significantly lower, and there were no significant differences between different therapeutic doses.

Keywords: Advanced gastric cancer; DCF regimen; FOLFOXs regimen; efficacy; adverse reactions

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Introduction

Gastric cancer is a malignant tumor originating from the gastric mucosal epithelium, ranking fourth in the incidence of male malignant tumors and third in mortality rate, and seventh in the incidence of female malignant tumors and

fifth in mortality rate (1), imposing serious damages to the people's health. Early gastric cancer often manifests as upper abdominal discomfort, non-specific symptoms such as fullness and nausea after eating, and it is difficult to differentiate early from other gastric diseases. Some

Table 1 PubMed search strategy

Steps	Search strategy
#1	Docetaxel
#2	Cisplatin
#3	Fluorouracil
#4	#1 OR #2 OR #3
#5	Oxaliplatin
#6	Fluorouracil
#7	Leucovorin
#8	#4 OR #5 OR#6
#9	Advanced gastric cancer
#10	#4 AND #8 AND #10

patients with gastric cancer have progressed to advanced stage and are difficult to undergo radical resection. DCF regimen [docetaxel (TXT) + cisplatin (DDP) + fluorouracil (FU)] and FOLFOXs regimen [oxaliplatin (L-OHP) + fluorouracil (FU) + leucovorin (LV)] are the currently used chemotherapy for gastric cancer. However, due to its many adverse reactions and uncertainties in efficacy, selecting an appropriate chemotherapy regimen is another important issue in our clinical work. Therefore, this study intends to conduct a meta-analysis of the efficacy and adverse effects of DCF and FOLFOXs regimens in patients with advanced gastric cancer, and systematically evaluate the clinical value of the two chemotherapy regimens from the perspective of evidence-based medicine. We present the following article in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/tcr-19-2564>).

Methods

Search strategy

WanFang Data, CNKI, PubMed, The Cochrane Library, Embase databases were retrieved using computer according to the “PICOS” search principle, combined keywords and free words for related documents published since the establishment of the databases. The Chinese search terms were: “晚期胃癌” “奥沙利铂” “顺铂” “多西他赛” “亚叶酸钙” “氟尿嘧啶”. The English search terms were: “advanced gastric cancer” “Oxaliplatin” “Cisplatin” “Docetaxel” “Leucovorin” “Fluorouracil”. At the same time, the

references of the articles included and related meta-analysis were traced. Take PubMed as an example, the specific search strategy was as shown in *Table 1*.

Study inclusion and exclusion

Type of study: randomized controlled study.

Inclusion criteria: (I) pathological diagnosis of advanced gastric cancer; (II) KPS score ≥ 60 points; (III) imaging and laboratory tests showed that the heart, liver, kidney and hematopoietic function were basically normal, and the expected survival time >3 months.

Exclusion criteria: (I) old literature; (II) incomplete data due to loss of follow-up or other reasons (and not stated in the text); (III) similar or identical repeated reports; (IV) single-center repeated studies; (V) single protocol sample size $n < 20$; (VI) combined with other treatments (add other chemotherapy or radiotherapy).

The basic characteristics of the experimental group and control group were comparable.

Outcome indicators: (I) chemotherapy efficacy (using Response Evaluation Criteria in Solid Tumors (RECIST) to evaluate the efficacy of tumor chemotherapy); (II) adverse reactions such as anemia, leukopenia, thrombocytopenia, nausea and vomiting.

Literature screening

Two evaluators independently selected the literature according to the pre-determined inclusion criteria, first read the literature title and abstracts, followed by the full text of the literature for those that might meet the inclusion criteria, to determine whether it met the inclusion criteria. After cross checking the results, the data of research that met the requirements were extracted in the Excel data extraction table, and in case of disagreement, it is solved through discussion with a third party.

Literature quality evaluation

The Cochrane Handbook for RCT bias risk assessment tools was used to evaluate the literature including random sequence generation, allocation concealment, participant and investigator blinding, assessor blinding, outcome indicator integrity, selective reporting, and other sources of bias. Each item was rated as “low risk of bias” “unclear” and “high risk of bias” according to the evaluation criteria.

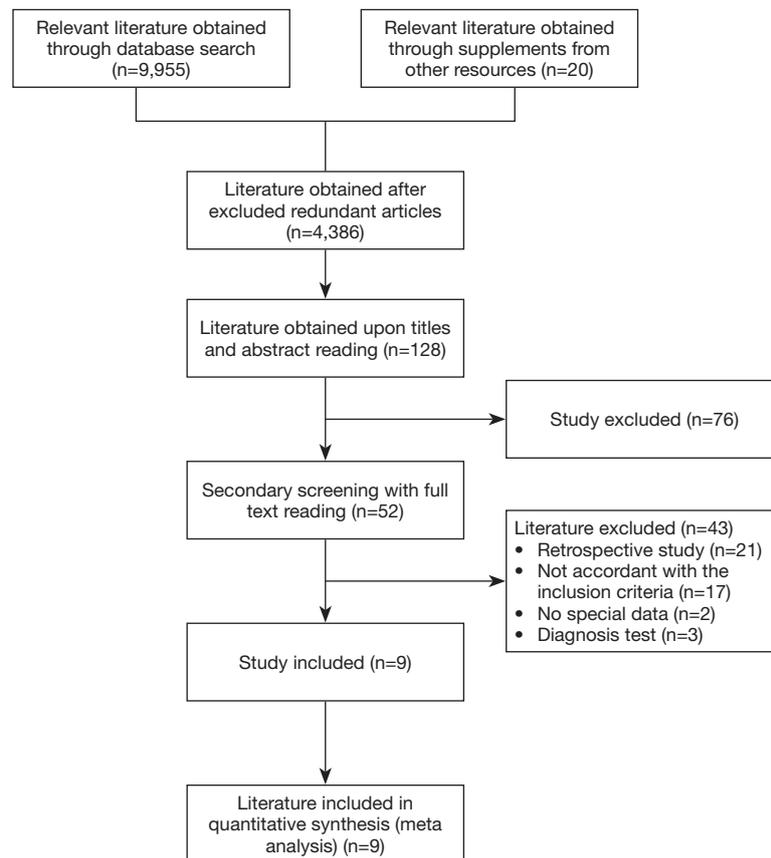


Figure 1 Flow chart of study for identification, inclusion, and exclusion. The number of specific search databases and literature: PubMed (n=3,219), The Cochrane Library (n=537), CNKI (n=1,064), Embase (n=3,325), Wanfang data (n=1,198), CBM (n=710).

Data statistics indicators and analysis methods

RECIST was used to describe changes in tumors after chemotherapy, including: complete response (CR), partial response (PR), disease stable (no change, NC) and progressive disease (PD) in all articles included objective response rate (ORR) and disease control rate (DCR). Data statistics were analyzed using Review Manager 5.3 software, with relative risk (RR) as analytical statistic for the counting data, and 95% confidence interval (CI) for each effect quantity. Before data analysis, χ^2 test was used to test for heterogeneity. If $P > 0.05$, $I^2 \leq 50\%$, fixed effect model was used for analysis. Otherwise, random effect model was used. The final result was presented in the form of forest map, and $P < 0.05$ was considered to be statistically significant. Publication bias was evaluated by funnel plot.

Results

Document search process and results

A total of 52 Chinese literatures were initially screened. After reviewing the full text, 9 articles were obtained according to the inclusion and exclusion criteria of the study. A total of 715 patients were enrolled, including 360 in the DCF group and 355 in the FOLFOXs group. The flow chart of study was as shown in *Figure 1*.

Basic information of the included studies and quality evaluation

The basic characteristics of the literature of the included studies were shown in *Table 2*. There was a total of 9 RCTs,

Table 2 Basic characteristics and methodological quality evaluation of the included studies

Included studies	Case collection period	Grouping method	Research object of DCF regime		Research object of FOLFOXs regime		Observation indicator	Methodology quality evaluation						
			Gender (male/female)	Age (year)	Gender (male/female)	Age (year)		Random method	Allocation concealment	Completeness of the outcome data	Selective reporting of the research findings	Blind method		Other sources of bias
												Patients and investigator	Outcome assessor	
Zhikuan Wang, 2009 (2)	2006.1 to 2008.12	RCT	32/12	55.78±10.24	30/12	55.78±10.24	①②	Computer random selection	Sealed envelope	Complete	No	No	Unclear	Unclear
Meiqing Luo, 2011 (3)	2004.1 to 2008.4	RCT	26/9	57.3±8.1	26/8	57.3±8.3	①②③	Unclear	Unclear	Complete	No	No	Unclear	Unclear
Guohua Han, 2011 (4)	2004.3 to 2010.3	RCT	20/8	50.3±4.2	19/9	50.3±4.1	①②④	Unclear	Unclear	Complete	No	No	Unclear	Unclear
Lu Bai, 2012 (5)	2008.7 to 2011.6	RCT	17/16	57.35±10.52	18/15	57.35±10.52	①②⑤	Computer random selection	Sealed envelope	Complete	No	No	Unclear	Unclear
Huiqiong Sun, 2016 (6)	2010.1 to 2016.1	RCT	37/29	57.39±10.55	36/30	57.36±10.53	①②⑤	Computer random selection	Sealed envelope	Complete	No	No	Unclear	Unclear
Lihua Fang, 2017 (7)	2015.9 to 2016.12	RCT	19/11	56.2±4.2	18/12	57.5±4.1	①②⑥	Computer random selection	Sealed envelope	Complete	No	No	Unclear	Unclear
Jianhuang Li, 2009 (8)	2005.1 to 2008.1	RCT	32/20	55.7±4.7	31/21	55.7±4.5	①②⑤	Unclear	Unclear	Complete	No	No	Unclear	Unclear
Xiaohui Yang, 2012 (9)	2007.1 to 2008.6	RCT	22/10	50.2±4.2	19/11	50.2±4.2	①②⑥⑦	Computer random selection	Sealed envelope	Complete	No	No	Unclear	Unclear
Defu Wu, 2016 (10)	2010.5 to 2015.6	RCT	26/14	58.3±9.1	25/15	58.1±9.2	①②⑤	Computer random selection	Sealed envelope	Complete	No	No	Unclear	Unclear

① : short-term efficacy; ② : adverse reactions; ③ : survival condition; ④ : quality of life improvement rate; ⑤ : clinical efficacy; ⑥ : survival period; ⑦ : quality of life.

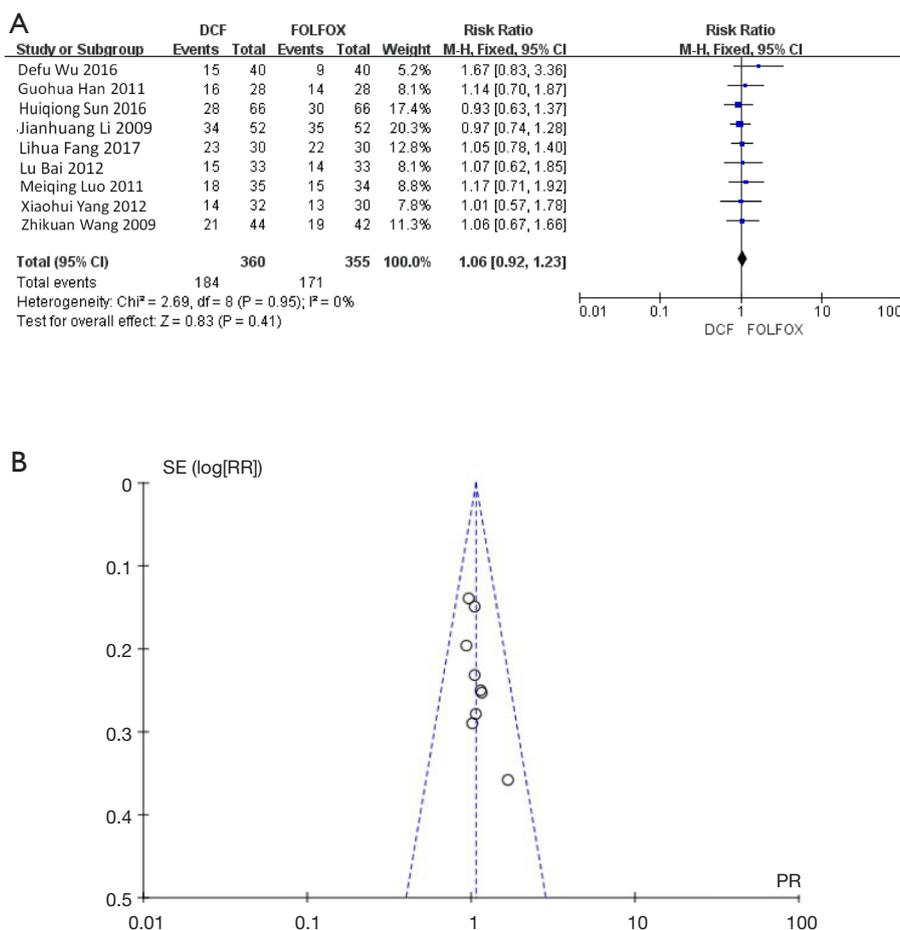


Figure 2 The effective rate of chemotherapy DCF and FOLFOXs regimens in patients with advanced gastric cancer. (A) Forest chart. The response rate of chemotherapy of the included studies was calculated by CR + PR; (B) The publication bias was shown in funnel plot. DCF, docetaxel (TXT) + cisplatin (DDP) + fluorouracil (FU); FOLFOXs, oxaliplatin (L-OHP) + fluorouracil (FU) + Leucovorin (LV); CR, complete response; PR, partial response.

all of which were multicenter clinical studies. Age, gender and other data were described in detail in each study, and there were no significant differences between the two treatment regimens ($P > 0.05$).

Efficacy of the two chemotherapy regimens

The response rate of chemotherapy of the included studies was calculated by CR + PR. The heterogeneity of the included studies was $P = 0.95$, $I^2 = 0\%$, thus fixed effect model was used. Statistical analysis by Review Manager 5.3 software the effective rates of DCF group and FOLFOX group were 51.11% and 48.17%, respectively (RR 1.06, 95% CI: 0.92–1.23). There was no statistical significance between the two groups ($P = 0.41$), as shown in *Figure 2A*.

Then we analyzed the publication bias. The small sample studies were distributed at the bottom of the funnel plot, while large sample studies were distributed at the top of the funnel plot, and basically arranged symmetrically around the center baseline, suggesting that publication bias of the literature of the included studies was relatively small, as shown in *Figure 2B*.

ORR and DCR of the two chemotherapy regimens

The ORR and DCR of the DCF and FOLFOXs regimens were evaluated. All ORR evaluation showed no significant differences between the DCF and FOLFOXs regimens (RR 1.06, 95% CI: 0.92–1.23; $P = 0.41$) (*Figure 3A*). All DCR evaluation showed no significant differences between the

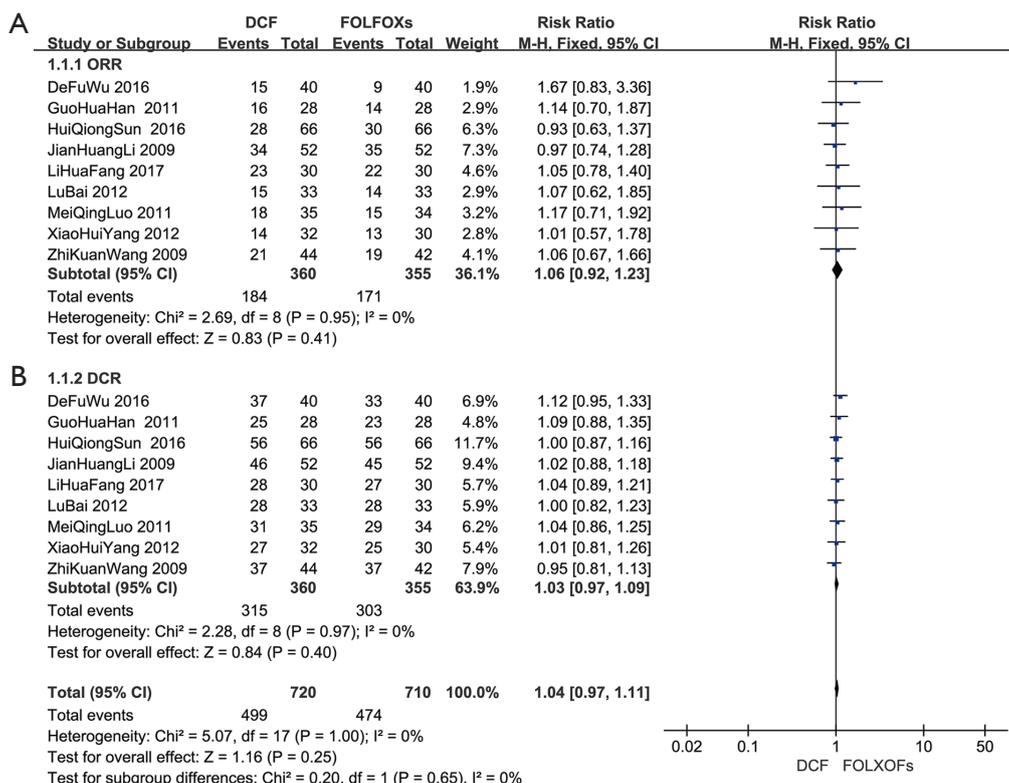


Figure 3 ORR and DCR of the two chemotherapy regimens. (A) ORR evaluation showed no significant differences between the DCF and FOLFOXs regimens. (B) DCR evaluation showed no significant differences between the DCF and FOLFOXs regimens. ORR, objective response rate; DCR, disease control rate.

DCF and FOLFOXs regimens (RR 1.03, 95% CI: 0.97–1.09; P=0.40) (Figure 3B).

Adverse reactions of the two chemotherapy regimens

The types of adverse reactions in the DCF regimen and the FOLFOXs regimen were statistically analyzed and the results were shown in Table 3. The common adverse reactions of DCF regimen and FOLFOXs regimen were mainly found in the blood system (anemia, leukopenia and thrombocytopenia), digestive system (diarrhea, nausea and vomiting), and other systems (oral mucositis, sensory neurotoxicity and hepatic insufficiency). Statistical analysis was performed using Review Manager 5.3 software. The results showed that the incidence of nausea and vomiting (RR 1.36, 95% CI: 1.15–1.60), anemia (RR 2.04, 95% CI: 1.55–2.68), thrombocytopenia (RR 1.52, 95% CI: 1.15–2.01) and leukopenia (RR 1.70, 95% CI: 1.44–2.01) of the FOLFOXs regimen was significantly lower (P<0.05), while the incidence of

sensory neurotoxicity (RR 0.53, 95% CI: 0.38–0.74) was significantly higher (P=0.0002) in the FOLFOXs regimen than the DCF regimen (Table 3, Figure 4).

Analysis of the efficacy and adverse reactions of different cumulative therapeutic doses in the FOLFOXs regimen

The 7 included studies were grouped according to the cumulative therapeutic doses of FOLFOXs regimen, which were mainly divided into FOLFOX4 regimen group and FOLFOX6 regimen group (group III). FOLFOX4 regimen group can be divided into groups I and II according to the doses of fluorouracil used (Table 4). The differences in efficacy and adverse effects of each cumulative therapeutic dose in the FOLFOXs regimens were analyzed. There were no significant differences in efficacy between the three groups (P=0.233). Analysis of the adverse reactions showed no significant differences in the incidence of diarrhea, hepatorenal dysfunction, and oral mucositis between the groups.

Table 3 Statistical table of chemotherapy adverse reactions in patients with advanced gastric cancer with DCF and FOLFOXs

Adverse reactions	Numbers of included studies	DCF group (n/N)	FOLFOXs group (n/N)	Heterogeneity		RR	95%CI	Test for overall effect	
				I ² (%)	P			Z value	P
Anemia	5 (3-6,8)	94/214	46/213	0	0.90	2.04	1.55–2.68	5.05	<0.00001
Leukopenia	7 (3-6,8-10)	172/286	100/283	51	0.06	1.70	1.44–2.01	6.19	<0.00001
Thrombocytopenia	6 (3-6,8,9)	85/246	55/243	83	<0.0001	1.52	1.15–2.01	2.90	0.004
Diarrhea	3 (3,5,6)	28/134	20/133	0	0.40	1.38	0.85–2.25	1.30	0.19
Nausea and vomiting	5 (3-5,8,10)	132/188	97/187	51	0.09	1.36	1.15–1.60	3.61	0.0003
Hepatic insufficiency	3 (3,5,9)	26/100	23/97	19	0.29	1.08	0.69–1.67	0.32	0.75
Peripheral neurotoxicity	6 (3-5,8-10)	41/220	76/217	74	0.002	0.53	0.38–0.74	3.72	0.0002
Oral mucositis	2 (3,5)	13/68	11/67	0	0.87	1.17	0.57–2.39	0.44	0.66

Discussion

Gastric cancer is the fifth largest cancer in the world. Clinical research shows that surgical treatment, such as expanded regional lymph node dissection and combined with multiple organ resection, cannot bring more survival benefits to patients with advanced gastric cancer (11). Therefore, chemotherapy is essential to improve the quality of life of patients with advanced gastric cancer, but there is no “gold standard” for the selection of chemotherapy regimen in the world. At the same time, with more in depth into “individualized treatment” and “targeted therapy”, higher requirements were proposed for selection of chemotherapy regimens for advanced gastric cancer (12).

From neoadjuvant chemotherapy to adjuvant chemotherapy, there are numerous chemotherapy regimens for gastric cancer. Currently, for palliative chemotherapy for advanced gastric cancer, the treatment option for first-line chemotherapy is still fluorouracil (5-Fu, Tegafur, Capecitabine) (13-17), platinum-based (cisplatin, oxaliplatin) (18), taxanes (Docétaxel, Paclitaxel) (19), Epirubicin (20) and Irinotecan (20,21). Although there are support from multiple clinical studies, the most commonly used adjuvant therapy is XELOX and SOX (22-24), but its efficacy and adverse effects with DCF and FOLFOXs regimens are still controversial (25-27), and there is no meta-analysis of big data to indicate the clinical advantages and disadvantages between them. Therefore, the DCF and FOLFOX regimens, as the classic treatment of advanced gastric cancer, still have their unique clinical application value. At present, there is no meta-analysis to indicate the efficacy and adverse reactions of DCF and FOLFOXs

regimens in the treatment of advanced gastric cancer. In this study, we collected the local research literature on the treatment of advanced gastric cancer with DCF and FOLFOXs regimens in recent years, and compared their efficacy and adverse reactions.

Efficacy analysis

Hacibekiroglu *et al.* (28) retrospectively analyzed the efficacy and safety of modified FOLFOX6 regimen and DCF regimen as the first-line treatment for advanced gastric cancer, and it showed that the efficacy of modified FOLFOX6 was comparable to that of DCF regimen, while toxicity analysis showed that the adverse reactions of DCF in the blood system were significantly higher than that of modified FOLFOX6, however, as it was a retrospective analysis, the number of studies of the two regimens was quite different. Only the FOLFOX6 regimen was studied. Besides, it was unable to include all FOLFOXs regimen within the FOLFOX4 regimen, making it less precise in evidence-based medicine. In this study, through meta-analysis of 9 included studies, it showed that in the treatment of advanced gastric cancer, the efficacy of DCF regimen was similar to that of FOLFOXs regimen and the ORR and DCR were not statistically significant, but the adverse effects of the FOLFOXs regimen were significantly lower than that of the DCF regimen. This result can more comprehensively demonstrate the advantages and disadvantages of the clinical application of the two regimens. At present, the studies on long-term effects of chemotherapy for advanced gastric cancer such as surgical resection rate, disease-free survival, disease-bearing survival,

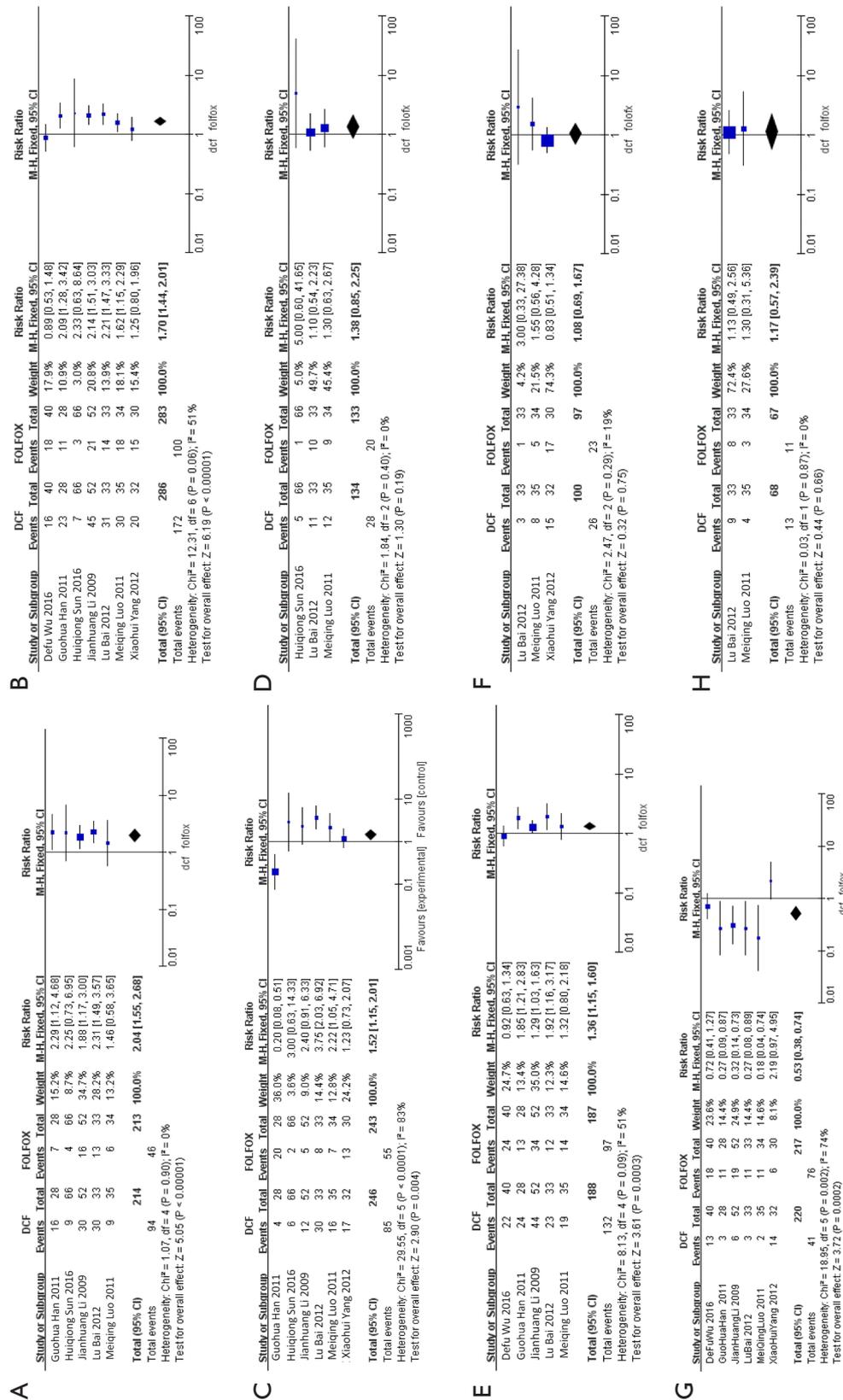


Figure 4 Incidence of adverse reactions of the two chemotherapy regimens. (A) Anemia of the two chemotherapy regimens; (B) leukopenia of the two chemotherapy regimens; (C) thrombocytopenia of the two chemotherapy regimens; (D) diarrhea of the two chemotherapy regimens; (E) nausea and vomiting of the two chemotherapy regimens; (F) hepatic insufficiency of the two chemotherapy regimens; (G) sensory neurotoxicity of the two chemotherapy regimens; (H) oral mucositis of the two chemotherapy regimens.

Table 4 Condition of the 7 included studies of FOLFOXs regimens grouping by different therapeutic doses

Investigator	Grouping and treatment	Number of participants, N	CR+PR	Effective rate (%) (CR+PR)/N
Meiqing Luo (3), Guohua Han (4), Jianhuang Li (8)	Group I: L-OHP 85 mg/m ² , d1; LV 200 mg/m ² , d1–2; FU 400 mg/m ² intravenous infusion, d1–2; followed by FU 400 mg/m ² intravenous pump 22 h, d1–2; 2 courses of treatment	114	64	56.14
Lihua Fang (7), Defu Wu (10)	Group II: L-OHP 85 mg/m ² , d1; LV 200 mg/m ² , d1–2; FU 400 mg/m ² intravenous infusion, d1; followed by FU 600 mg/m ² intravenous pump 22 h, d1–2; 3 courses of treatment	70	35	50.00
Lu Bai (5), Huiqiong Sun (6)	Group III: L-OHP 80–100 mg/m ² , d1; LV 200 mg/m ² , d1; FU 400 mg/m ² , d1; followed by 2,400–3,000 mg/m ² 46 h; 2 courses of treatment	99	44	44.44

The other two studies were not suitable for statistical analysis due to large differences in treatment doses. $\chi^2=2.910$, $P=0.233$

and overall survival time was relatively scarce, thus it is impossible to make a more systematic and accurate analysis on the chemotherapy regimens. At the same time, as the 9 included studies did not give a more detailed description of TNM stage, thus it was impossible to perform a subgroup analysis based on the TNM staging of the patients between the two groups to provide a more individualized efficacy evaluation.

Adverse reaction analysis

The common adverse reactions of DCF and FOLFOXs regimens mainly include anemia, leukopenia, thrombocytopenia, and nausea and vomiting, but the overall incidence of adverse reactions of FOLFOXs was significantly lower than that of DCF. FOLFOXs regimen has significant advantages. The incidence of hepatorenal dysfunction and oral mucositis was not statistically significant, but the incidence of sensory neurotoxicity and diarrhea was significantly higher than that of DCF. This result suggested that in the clinical work of chemotherapy for patients with advanced gastric cancer, the FOLFOXs regimen should be used first. If the patient has sensory neurotoxicity and diarrhea symptoms, with no or mild other adverse reactions, it can be replaced with DCF regimen as appropriate.

For the low incidence of adverse reactions of the FOLFOXs regimen, further analysis of different treatment doses of the regimen was performed and it showed no significant differences in the effective rate among the three different cumulative treatment doses. With the increase of treatment doses, there were no significant differences in the incidence of diarrhea, hepatorenal dysfunction, and oral mucositis among the groups, but the statistical

difference of the incidence of adverse reactions such as anemia, leukopenia, thrombocytopenia, and nausea and vomiting was large in each study, making it inconvenient to analyze. This provides us an idea to further study the relationship between the therapeutic doses, course of treatment and adverse reactions of the FOLFOXs regimen, and at the same time, the adverse reactions of different treatment doses, and clarify the relationship between them and the incidence of various adverse reactions, which is helpful to select a better therapeutic doses for patients with corresponding underlying diseases in clinical applications.

Conclusions

In conclusion, the results of this meta-analysis showed that the efficacy of FOLFOXs regimen was comparable to that of DCF regimen in the treatment of advanced gastric cancer, but the incidence of adverse reactions was significantly lower, and there was no difference in efficacy between different treatment doses. Due to the limitations in the study area and quality of the included studies, the conclusions of this study still need to be further verified by more large-scale clinical studies.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr-19-2564>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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