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Review Article

Systematic evaluation of therapeutic efficacy and safety of traditional Chinese medicine injection (TCMI) combined with oxaliplatin-containing chemotherapy in the treatment of colorectal cancer

Wenqi Huang[1], Zhu Yang[2], Fengxi Long[3], Li Luo[4,6], Jinghui Wang[4], Bing Yang[1], Dongxin Tang[5]

Departments of [1]Clinical, [2]Principal Office, [3]Graduate School, Guiyang College of TCM, Guiyang 550002, Guizhou, China; Departments of [4]Oncology, [5]Science and Education Section, The First Affiliated Hospital of Guiyang College of TCM, Guiyang 550001, Guizhou, China; [6]Department of Oncology, Guihang Guiyang Hospital, Affiliated Guihang 300 Hospital of Zunyi Medical College, Guiyang 553009, Guizhou, China

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Abstract: Objective: This analysis was to evaluate the therapeutic efficacy and safety of traditional Chinese medicine injection (TCMI) combined with oxaliplatin-containing chemotherapy in the treatment of colorectal cancer. Methods: PubMed, Embase, Medline, Cochrane Library, Chinese Biomedical Literature Database, China National Knowledge Infrastructure (CNKI), China Knowledge Network, Weipu Chinese Journal Database, and Wanfang Database were searched, and randomized controlled trials (RCTs) concerning the combination treatment of TCMI and oxaliplatin chemotherapy were collected. Literature screening, data extraction, and methodology quality evaluation were performed. Meta-analysis was conducted with RevMan 5.3 software. Results: In total, 77 RCTs were included in this study, including 9 TCMI (i.e., ADI, BJOEI, CKSI, DLSI, KAI, KLTI, SQFZI, XAPI and XGDTI) and 6014 patients. Meta-analysis showed that, compared with the chemotherapy alone, the combination with the following 7 TCMI significantly elevated the efficacy rates: CKSI, ADI, SQFZI, BJOEI, DLSI, KAI and KLTI. In contrast, combination treatment with TCMIs of CKSI, ADI, SQFZI, BJOEI, DLSI, KAI, KLTI, or XAPI significantly improved quality of life for patients. Moreover, for treatment safety, compared with chemotherapy alone, the combination treatment with ADI, SQFZI, KAI, or KLTI significantly alleviated gastrointestinal reactions, and the combination treatment with CKSI, ADI, SQFZI, BJOEI, KAI, KLTI, or XAPI significantly ameliorated the bone marrow suppression. Notably, combination treatment with ADI also significantly reduced peripheral neurotoxicity. Conclusion: Oxaliplatin-containing chemotherapy combined with some TCMIs could exert therapeutic effects superior to chemotherapy alone in the treatment of colorectal cancer.

Keywords: Traditional Chinese medicine injection (TCMI), chemotherapy, colorectal cancer, systematic evaluation, meta-analysis

Introduction

Colorectal cancer (including colorectal cancer and rectal cancer) is a common malignant tumor. In China, the morbidity and mortality of colorectal cancers have been rising in recent years [1]. Early symptoms of colorectal cancer are always subtle, with a low diagnostic rate. In fact, 40% of the patients with colorectal cancer are diagnosed at the advanced stage, accompanied with poor prognosis and 5-year survival rate of less than 10% [2]. Chemotherapy is the main treatment option for advanced colorectal cancer, in which the FOLFOX, XELOX and FOLFIRI regimens are always used as first-line treatment, including oxaliplatin, 5-fluorouracil, and other drugs [3].

L-OHP is a third generation platinum-based anti-cancer drug, which has been currently used as the main drug for assistant and palliative chemotherapy for colorectal cancer. L-OHP inhibits DNA replication and transcription in tumor cells [4]. However, multi-cycle combination treatment with L-OHP is associated with unsatisfactory toxic side effects, including nausea and vomiting, altered hemogram, and neurotoxicity. The poor tolerance and serious toxicity of chemotherapy have limited its clinical application.

Studies have shown that traditional Chinese medicine can improve the clinical symptoms, quality of life, and immune status of patients with advanced colorectal cancer, attenuating the toxic effects and enhancing the synergistic effects of radiotherapy and chemotherapy. Moreover, combination treatments of radiotherapy/chemotherapy and traditional Chinese medicine injections (TCMIs; such as compound kushen injection and javanica oil injection) have been shown to exert the initial therapeutic effects [5]. There are a number of studies reporting that combination treatment of TCMI and L-OHP-containing chemotherapy regimen has good therapeutic effects in the treatment of colorectal cancer [6-8]. However, due to the small sample size and the lack of evidence from large-sample and multi-center clinical trials, reference values of these findings are limited.

In order to evaluate the effectiveness and safety of traditional Chinese medicine in the treatment of colorectal cancer, this study applied a systematic method to evaluate randomized controlled studies concerning treatment of colorectal cancer with traditional Chinese medicine. Moreover, combined with the clinical application, the advantages and disadvantages are also thoroughly assessed.

Materials and methods

Inclusion and exclusion criteria

Corresponding randomized and controlled trials (RCTs) were included in this study, regardless of whether they were blinded or not. The patients were diagnosed based on *the Criteria for Diagnosis and Treatment of Colorectal Cancer in China (2015)* [9], including colon cancer and rectal cancer, with no limitation regarding patient age and sex. For disease intervention, the application of oxaliplatin-containing regimens was clearly stated for the control groups, including various FOLFOX chemotherapy regimens consisting of oxaliplatin, fluorouracil, and tetrahydrofolate, as well as the combination treatment of oxaliplatin and other chemotherapy drugs [10]. For the test groups, in addition to the chemotherapy treatments used in the control groups, TCMI was administered.

Efficacy indicators were as follows: (1) recent efficiency = (CR + PR)/total cases × 100%, in which CR was complete remission and PR was partial remission, according to the WHO solid tumor efficacy or RECIST criteria [11]; (2) improvement rate of quality of life (KPS scoring) = increasing cases/total × 100%, in which elevating KPS scores ≥ 10 was regarded as increasing cases; and (3) safety evaluation, i.e., rate of adverse reactions, including gastrointestinal adverse reactions (nausea and vomiting), myelosuppression (leukopenia), and peripheral nerve toxicity.

Exclusion criteria were as follows: (1) Accompanied with other diseases and interventions, such as gastric cancer, radiotherapy, and other traditional Chinese medicine treatment; (2) Oxaliplatin not contained in the chemotherapy intervention; (3) Non-randomized studies, rigorously designed studies, or retrospective studies; (4) Animal experiments or literature reviews; (5) Studies without outcome indicators; and (6) Studies of suspected plagiarism.

Searching strategy

PubMed, Embase, Medline, Cochrane Library, Chinese Biomedical Literature Database, China National Knowledge Infrastructure (CNKI), China Knowledge Network, Weipu Chinese Journal Database, and Wanfang Database were subjected to the literature searches, covering from the date of database construction to May 20th, 2017. According to the PICOS (patients, intervention, comparator, outcomes, and study design) principles, the following key words and key word combinations were searched in Chinese: (Compound kushen injection, CKSI, sodium cantharidate injection, Aidi injection, ADI, astragalus injection, Shenqi Fuzheng injection, SQFZI, SF injection, SM injection, Delisheng injection, DLSI, Cinobufotalin injection, Kang'ai injection, KAI, Kanglaite injection, KLTI, Xiangguduotang injection, XGDTI, Xiaoaiping injection, Brucea javanica oil emulsion injection, BJOEI, Yanshu injection, Compound matrine injection) AND (Oxaliplatin, Eloxatin, L-OHP, FOLFOX) AND (colorectal cancer, colon cancer, rectal cancer) AND chemotherapy AND randomization; while the following keys were searched in English: (Compound cantharis, Disodium Cantharidinate, Aidi, Astragalus, Shenqi Fuzheng, Shenfu, Shenmai, Delisheng, Huachansu, Kang'ai, Kanglaite, Xianggu Duotang, Xiaoaiping, Brucea javanica oil emulsion, compound kushen) AND (colon cancer, rectal can-

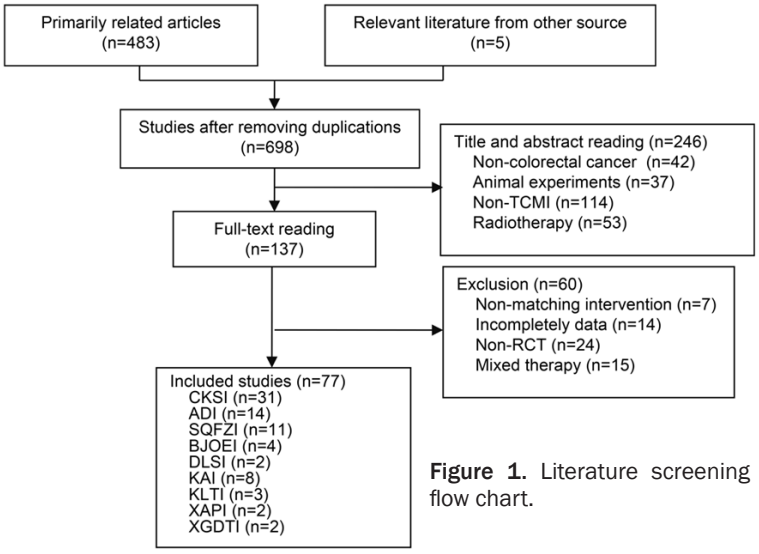

Figure 1. Literature screening flow chart.

cer, colorectal cancer, colorectal neoplasms) AND (Oxaliplatin, L-OHP) AND (clinical trials, random). Traditional Chinese medicine injection abbreviations and compositions are shown in Supplementary Table 1.

Evaluation methods

For data extraction, Endnote software was used for literature retrieval and management. Literature duplication was first removed, and then literature identification and screening were performed based on the title, abstract, and full text. Literature screening, data extraction, and quality evaluation of inclusion methodology were conducted by two independent reviewers. In cases of divergence, it was settled through discussion, or a third reviewer was introduced. Extracted data mainly included the clinical characteristics of study subjects (case numbers, average age, and cancer staging), the intervention characteristics (interventions, dosage, and treatment course), and the study outcomes (total effective rate, KPS scores, and adverse reaction rate).

Quality evaluation of included studies was conducted according to the Cochrane System Evaluator Manual (Version 5.2) [12]: (1) Whether the randomization was correct and sufficient; (2) Whether the allocation concealment was correct and sufficient; (3) Blinded or not; (4) Lost to follow-up: with or without whole-course follow-up, whether reporting the case number of followup was lost, and whether the proportion of follow-up loss was less than 20%; (5) Data completely or selectively reported. The bias risk of included studies was assessed by the Jadad scale [13]: 0-2, low-quality literature; and 3-5, high-quality literature.

Data analysis

Statistical analysis was performed using the Rev Man version 5.3 software. Clinical heterogeneity was analyzed, and the subgroups were defined based on the possible causes. Fixed effect model was used in case of no statistical heterogeneity between the studies within the subgroups ($P < 0.1$, $I^2 > 50\%$). Otherwise, in cases of statistical heterogeneity ($P > 0.1$, $I^2 < 50\%$), the source of heterogeneity was first analyzed, and the random effects model was used for cases of no obvious clinical heterogeneity when the source of statistical heterogeneity could not be determined. If there was significant clinical or methodological heterogeneity, or incomplete data were provided, when meta-analysis could not be available, descriptive analysis was performed. Continuous variables were expressed as WMD and 95% CI, while categorical variables were expressed as the relative risk (RR) and 95% CI. In cases of statistical heterogeneity due to varying qualities of inclusion methodologies, the sensitivity analysis was performed after removing low-quality studies. For those studies concerning more than nine major measurement indicators, publication bias was assessed with funnel plots.

Results

Literature retrieval results

A total of 488 related articles were retrieved according to the searching strategy and data extraction methods. After removing duplications and reading the titles and abstract, obviously irrelevant studies were excluded, leaving 383 clinical trials concerning the combination treatment (TCMI and FOLFOX chemotherapy regimen) for colorectal cancer. These studies were subjected to full-text reading, and after that, RCTs with multiple contributions from one manuscript, non-colorectal cancer, radiothera-

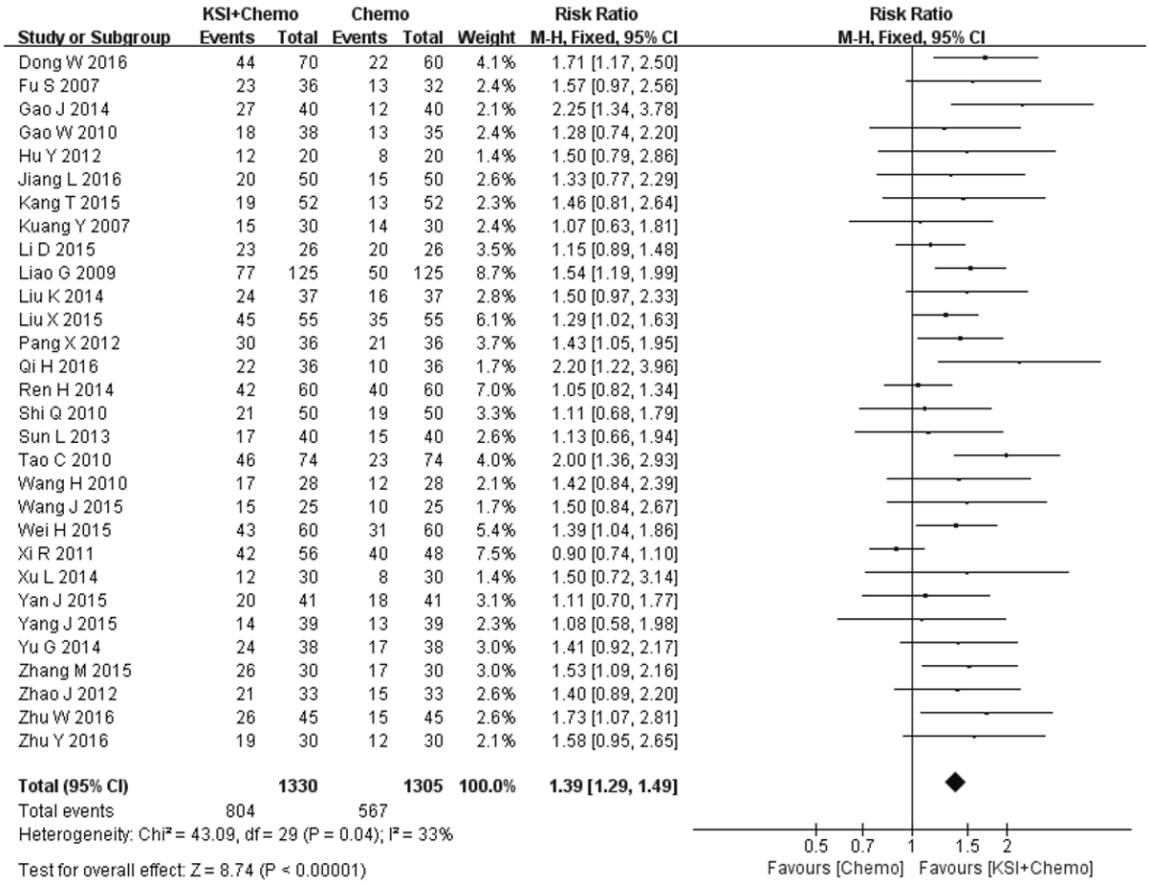

Figure 2. Forest map for total clinical effective rate of CKSI.

py, no control, unclear chemotherapy regimen, mixed chemotherapy, non-TCMI, unclear chemotherapy cycle, or unknown injection dose were excluded. Finally, 77 RCTs were included for the analysis [14-90], containing a total of 6014 subjects (**Figure 1**).

Basic information of included studies

In the included literature, 96.1% reported the age and KPS scores of the subjects. Colorectal cancer cases included colorectal cancer and rectal cancer, and most of the patients suffered from advanced colorectal cancer. Chinese medicine injection dosage was 15-250 mL, for 2-12 cycles. These 77 studies concerned totally 6014 patients, with an average sample size of 78.10 and a median of 68.3 (ranging from 36 to 250 cases). Interventions represented the combination treatment of TCMI and oxaliplatin-containing chemotherapy regimen, with the control group subjected to oxaliplatin chemotherapy alone. In total, 9 kinds of TCMI were involved, including compound Kushen injection (CKSI) [14-44], Aidi injection (ADI) [45-58], Shenqi Fuzheng injection (SQFZI) [59-69], Brucea javanica oil emulsion injection (BJOEI) [70-73], Delisheng injection (DLSI) [74, 75], Kang'ai injection (KAI) [76-83], Kanglaite injection (KLTI) [84-86], Xiaoaiping injection (XAPI) [87, 88], and Xiangguduotang injection (XGDTI) [89, 90]. No significant differences were observed in the subject cases, age, and sex between the corresponding groups in those included studies, indicating comparable data.

Methodology quality of included studies

The included 77 studies were all RCTs, with sufficient randomization grouping process, and the specific randomization methods and allocation concealment were clearly described in 26 RCTs. Moreover, there were 20 high-quality articles (with a Jadad score > 3), and the scores of these include studies ranged from 1 to 4, with the average score of 1.96. The basic char-

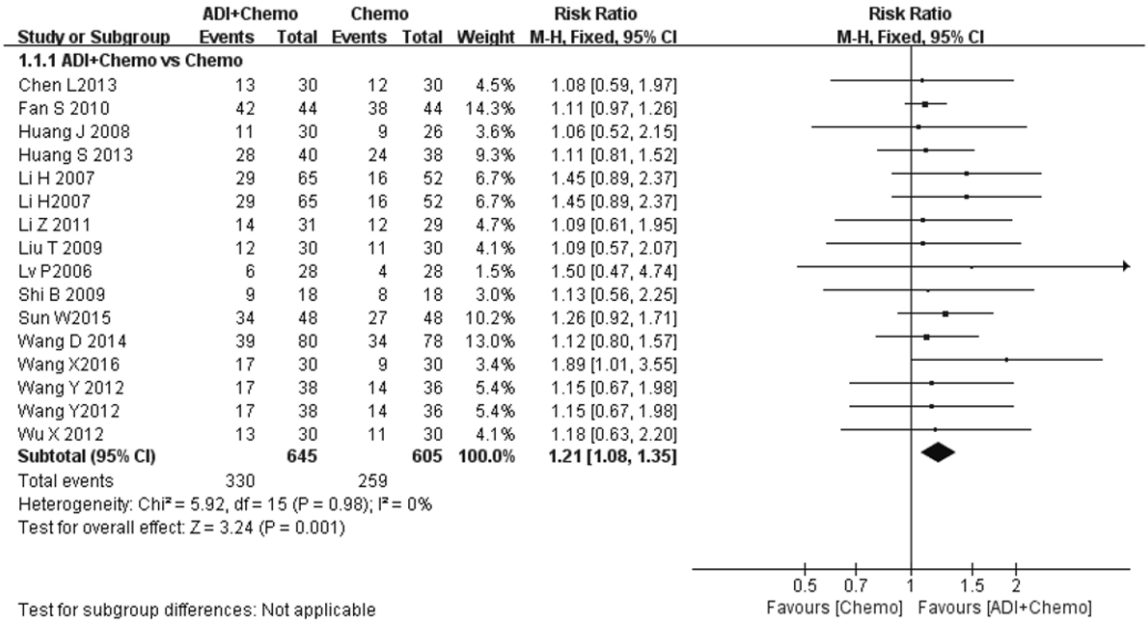

Figure 3. Forest map for total clinical effective rate of ADI.

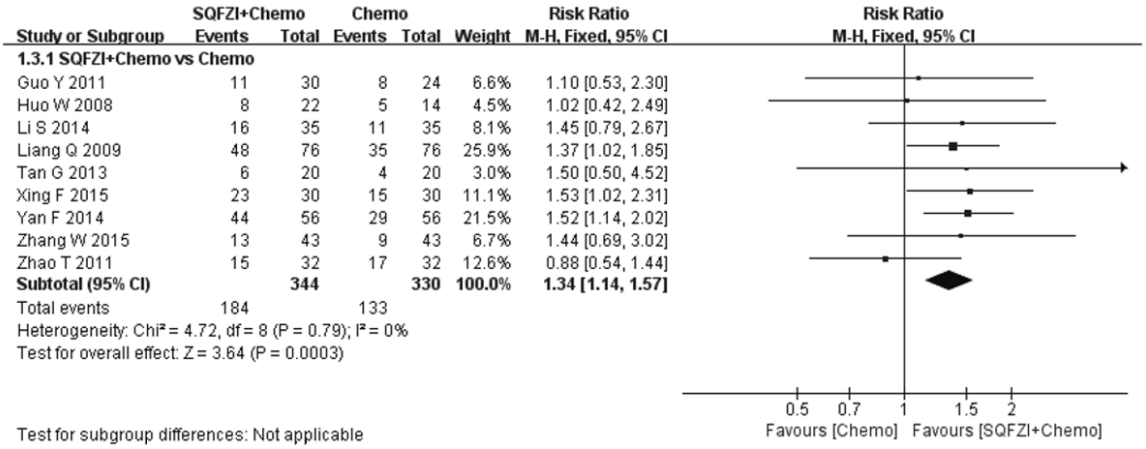

Figure 4. Forest maps for total clinical effective rate of SQFZI.

acteristics and methodological quality evaluation results are shown in Supplementary Tables 2 and 3.

Analysis of short-term effective rates

A total of 76 studies reported short-term effective rates, with no statistical heterogeneity among these studies (P = 0.79, I^2 = 0), and therefore the fixed effect model analysis was performed (**Figures 2-10**). Results from the Meta-analysis showed that, compared with the L-OHP chemotherapy regimen alone, the following 7 TCMIs combined with L-OHP-containing chemotherapy regimen reported significantly elevated short-term effect rates for the patients: CKSI [RR = 1.39, 95% CI (1.29, 1.49), P < 0.00001] (**Figure 2**), ADI [RR = 1.20, 95% CI (1.07, 1.35), P < 0.00001] (**Figure 3**), SQFZI [RR = 1.61, 95% CI (1.29, 2.02), P = 0.003] (**Figure 4**), BJOEI [RR = 1.27, 95% CI (1.03, 1.58), P = 0.03] (**Figure 5**), DLSI [RR = 1.53, 95% CI (1.02, 2.29), P = 0.04] (**Figure 6**), KAI [RR = 1.17, 95% CI (1.01, 1.36), P = 0.04] (**Figure 7**), and KLTI [RR = 1.59, 95% CI (1.20, 2.12), P = 0.001] (**Figure 8**); while the L-OHP-containing chemotherapy regimen combined with XAPI or XGDTI did not significantly elevate the clinical effects

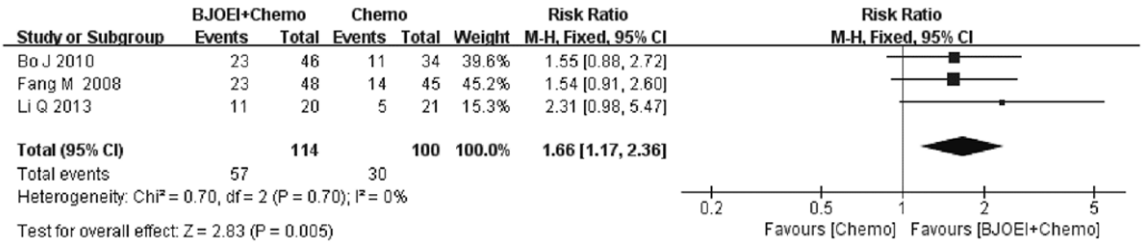

Figure 5. Forest map for total clinical effective rate of BJOEI.

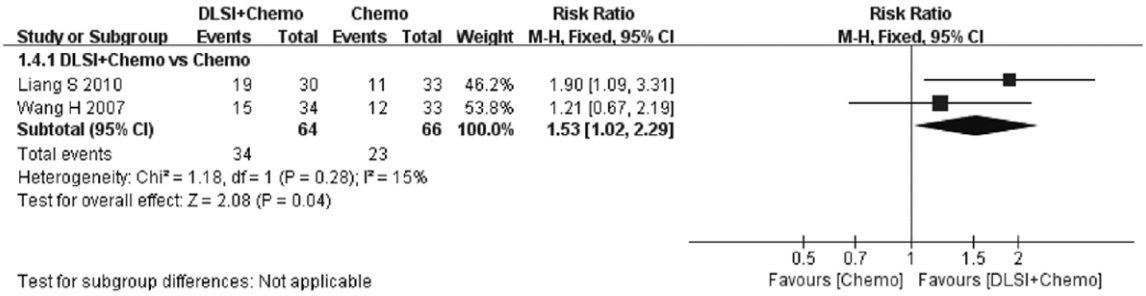

Figure 6. Forest map for total clinical effective rate of DLSI.

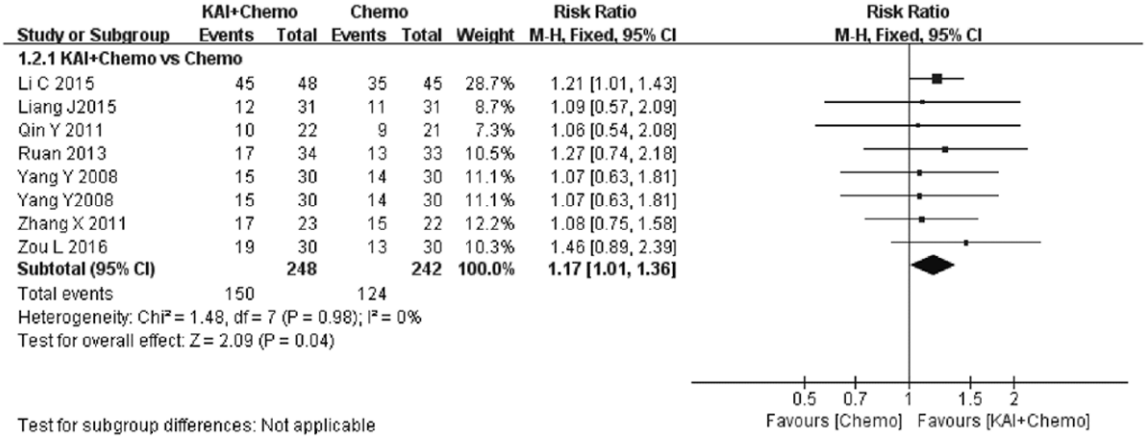

Figure 7. Forest map for total clinical effective rate of KLTI.

rates: XAPI [RR = 1.39, 95% CI (0.92, 2.11), P = 0.12] (**Figure 9**) and XGDTI [RR = 1.33, 95% CI (0.77, 2.30), P = 0.31] (**Figure 10**).

Analysis of KPS-score improvement rates

Within these 77 articles, 50 studies reported improved KPS scores, with statistical heterogeneity < 50%, and therefore the fixed-effect model analysis was performed (Supplementary Figures 1, 2, 3, 4, 5, 6, 7). Results from the Meta-analysis showed that, compared with the simple L-OHP chemotherapy regimen, the combination treatment with TCMIs of CKSI, ADI, SQFZI, BJOEI, DLSI, KAI, KLTI, or XAPI could significantly improve the patients' quality of life and elevated the KPS scores of these patients (P < 0.05) (**Table 1**).

Analysis of adverse reactions

In total, 63 studies reported chemotherapy-related adverse reactions, mainly including gastrointestinal reactions, bone marrow suppression, and peripheral neurotoxicity. Results from the Meta-analysis showed that, compared with the L-OHP chemotherapy regimen alone, the combination treatment with ADI, SQFZI, KAI, or

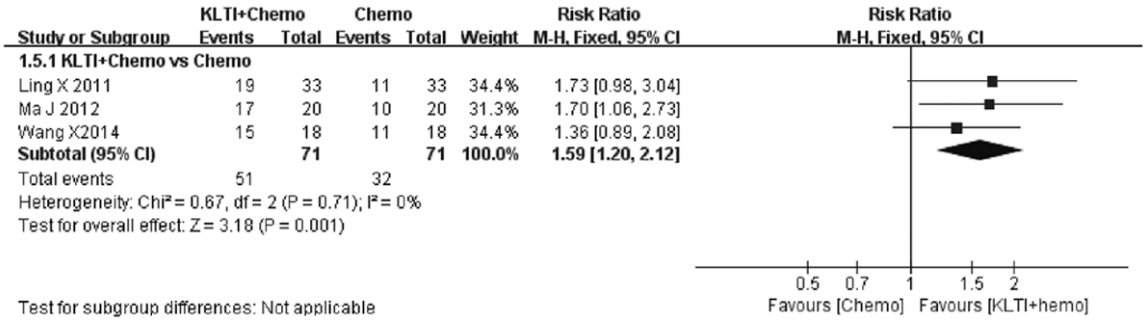

Figure 8. Forest map for total clinical effective rate of KAI.

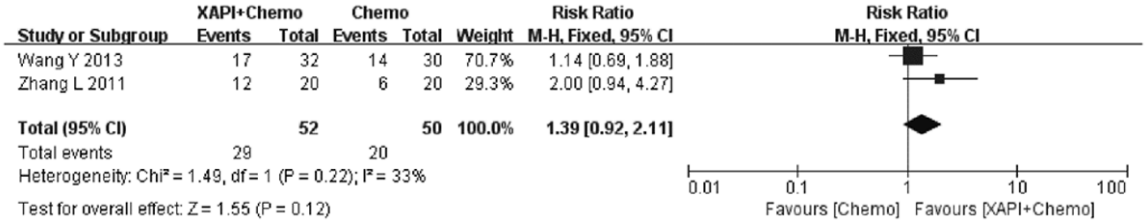

Figure 9. Forest map for total clinical effective rate of XAPI.

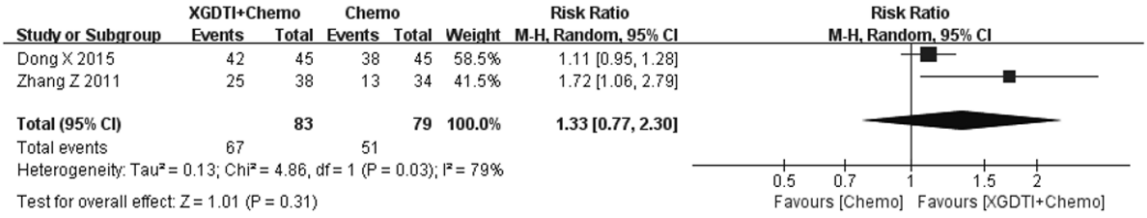

Figure 10. Forest map for total clinical effective rate of XGDTI.

KLTI significantly alleviated the gastrointestinal reactions, the combination treatment with CKSI, ADI, SQFZI, BJOEI, KAI, KLTI and XAPI significantly ameliorated the bone marrow suppression, and the combination treatment with ADI significantly reduced the peripheral neurotoxicity (all $P < 0.05$) (**Table 2**).

Analysis of publication bias

The risks of publication bias were analyzed with the funnel chart for the studies concerning the interventions of the CKSI and ADI (Supplementary Figures 8 and 9). Our funnel chart data suggest satisfactory symmetry on both sides and low risk of publication bias.

Discussion

Due to extensively changed lifestyles and increased work pressure, patients with colorectal cancer have been increasing over the past few years. There have been approximately 1,000,000 new cases of colorectal cancer and more than 500,000 cases of related death each year identified throughout the world [91]. Currently, surgery has been the major treatment option for colorectal cancer at early stage. However, at the diagnosis of colorectal cancer, metastasis would occur in about 25% patients, and up to 30%-50% of the patients diagnosed with colorectal cancer at early stage would develop metastasis during the clinical follow-up period [92]. In addition, surgical operation could not be performed during the metastasis period, and therefore other treatment methods such as chemotherapy, radiotherapy, and biological therapy are needed. However, these treatment methods, either alone or combined with other treatments, have various limitations and shortcomings, such as the disease

Table 1. Meta-analysis of KPS score improvement.

	Studies	Subjects (E/C)	RR	I^2	*P*
CKSI + Chemo vs Chemo	16	694/683	1.66 [1.46, 1.89]	22	< 0.00001
ADI + Chemo vs Chemo	11	420/395	1.96 [1.61, 2.39]	28	< 0.00001
SQFZI + Chemo vs Chemo	7	270/255	1.61 [1.29, 2.02]	0	< 0.0001
BJOEI + Chemo vs Chemo	3	114/100	1.66 [1.17, 2.36]	0	0.005
DLSI + Chemo vs Chemo	2	64/66	1.53 [1.11, 2.11]	0	0.01
KAI + Chemo vs Chemo	6	215/214	2.10 [1.65, 2.66]	4	< 0.00001
KLTI + Chemo vs Chemo	3	71/71	1.59 [1.20, 2.12]	3	0.001
XAPI + Chemo vs Chemo	2	52/50	1.61 [1.13, 2.29]	7	0.008

Abbreviations: CKSI, compound kushen injection; ADI, Aidi injection; SQFZI, Shenqi Fuzheng injection; BJOEI, Brucea javanica oil emulsion injection; DLSI, Delisheng injection; KAI, Kang'ai injection; KLTI, Kanglaite injection; XAPI, Xiaoaiping injection; Chemo, oxaliplatin-containing chemotherapy.

Table 2. Meta-analysis of adverse reactions of chemotherapy.

	Gastrointestinal reactions (RR)	Bone marrow suppression (RR)	Peripheral neurotoxicity (RR)
CKSI + Chemo vs Chemo	0.59 (0.34, 1.01)	0.31 (0.21, 0.39)	0.61 (0.31, 1.08)
ADI + Chemo vs Chemo	0.32 (0.21, 0.60)	0.22 (0.16, 0.35)	0.39 (0.25, 0.62)
SQFZI + Chemo vs Chemo	0.29 (0.14, 0.55)	0.35 (0.23, 0.54)	0.26 (0.08, 1.04)
BJOEI + Chemo vs Chemo	0.60 (0.34, 1.07)	0.28 (0.13, 0.61)	0.64 (0.13, 2.93)
DLSI + Chemo vs Chemo	-	0.40 (0.11, 1.34)	-
KAI + Chemo vs Chemo	0.43 (0.24, 0.85)	0.29 (0.19, 0.49)	0.60 (0.32, 1.12)
KLTI + Chemo vs Chemo	0.17 (0.04, 0.64)	0.33 (0.15, 0.77)	0.58 (0.21, 1.75)
XAPI + Chemo vs Chemo	0.77 (0.13, 4.41)	0.81 (0.21, 3.17)	-
XGDTI + Chemo vs Chemo	0.27 (0.09, 0.80)	0.36 (0.17, 0.79)	-

Abbreviations: CKSI, compound kushen injection; ADI, Aidi injection; SQFZI, Shenqi Fuzheng injection; BJOEI, Brucea javanica oil emulsion injection; DLSI, Delisheng injection; KAI, Kang'ai injection; KLTI, Kanglaite injection; XAPI, Xiaoaiping injection; XGDTI, Xiangguduotang injection; Chemo, oxaliplatin-containing chemotherapy.

recurrence, metastasis, and side effects (such as bone marrow suppression, gastrointestinal reactions, heart damage, liver and kidney dysfunction, and local radiation damage) [93]. Therefore, these treatments produce discomfort, either caused by cancer itself or treatment-related toxicities, which altogether impact the patients' quality of life.

The World Health Organization (WHO) has classified cancers as chronic diseases, just like hypertension and diabetes [93]. Therefore, the objective of treatment for tumors has switched from the simple biomedical model to the biological, physical, and social medical model, aiming at prolonging the patient's survival and improving the patients' quality of life. Modern studies have shown that TCM could induce apoptosis and reverse multidrug resistance, which has a comprehensive role in the angiogenesis, signal transduction pathways, and metastasis. In addition, TCM can regulate immune function, improve efficacy, and reduce toxicity, thus improving the patients' quality of life [94]. In China, TCM is involved throughout the process of prevention and treatment of tumors.

TCMIs originate from the combination of the traditional medicine theory and the modern technological procedures, which represents the important product of TCM modernization. Compared with other TCM formulations, TCMI is characterized by high bioavailability, exact efficiency, and rapid action onset. Most of the drug substance of TCMI on tumor is composed of more than two chemical components, which could play the multi-directional and -target roles in the human body, well targeting on the multi-factor and -link pathogenesis of tumors. Although direct anti-tumor effect might be weak compared with chemically synthesized drugs, clinical application of TCM is common due to its reduced side effects, less drug resistance, and

comprehensive anti-tumor effects. When combined with radiotherapy and chemotherapy, the TCMI could attenuate toxic effects and enhance synergistic effects, and regulate the immune responses [95]. However, because of the different administering route from the traditional sense, the adverse reactions of TCMI would involve multiple systems and organs, which might be rapid and induce serious responses. Most of the previous clinical trials have small sample sizes, resulting in limited reference value. Therefore, systematic evaluation was performed in the present study. Our results from the Meta-analysis showed that clinical treatment of oxaliplatin-containing chemotherapy combined with TCMI could play adjuvant roles in the treatment of colorectal cancer. Particularly, compared with the L-OHP chemotherapy regimen alone, the following 7 TCMI combined with L-OHP-containing chemotherapy regimen reported significantly elevated short-term effect rates: CKSI, ADI, SQFZI, BJOEI, DLSI, KAI and KLTI; while the combination treatment with TCMIs of CKSI, ADI, SQFZI, BJOEI, DLSI, KAI, KLTI, or XAPI could significantly improve the patients' quality of life. Moreover, for the analysis of safety, compared with the L-OHP chemotherapy regimen alone, the combination treatment with ADI, SQFZI, KAI, or KLTI significantly alleviated the gastrointestinal reactions, the combination treatment with CKSI, ADI, SQFZI, BJOEI, KAI, KLTI, or XAPI significantly ameliorated the bone marrow suppression, and the combination treatment with ADI significantly reduced the peripheral neurotoxicity. These findings suggest that the adjuvant therapy of TCMI in combination with oxaliplatin-containing chemotherapy can not only improve the overall clinical efficiency and improve the patients' quality of life, but also help to significantly alleviate the adverse reactions induced by chemotherapy, such as leucopenia, and nausea and vomiting. Our results are in line with the evaluation of the efficacy and safety of chemotherapy combined with TCMIs from previous reports, including the CKSI [96-100], ADI [101-103], and KAI [104, 105]. On the other hand, there have been few studies regarding systematic evaluation of the chemotherapy combined with SQFZI, BJOEI, DLSI, KLTI, or XAPI in the disease treatment.

In a previous study, Chen et al. [106] have analyzed 42 clinical trials and evaluated the therapeutic safety of the combination of traditional Chinese medicine and oxaliplatin-containing chemotherapy in the treatment of colorectal cancer, and subgroup analysis was performed based on the formulation. However, the control groups in the included literature were mainly associated with the herbal decoction, and only 11 studies concerning the TCMIs as the intervention measures were included. The present study provided the evidence of evidence-based medicine for the efficacy and safety of combination of the TCMI and chemotherapy. Most of these 77 RCTs herein applied the FOLFOX chemotherapy, i.e., combination of oxaliplatin, fluorouracil, and tetrahydrofolate, which is the clinically recommended and widely used chemotherapy regimen for colorectal cancer treatment. In addition, in this study, the interventions for the treatment groups are merely the TCMIs based on chemotherapy, and the randomized controlled trials with combination treatment concerning the TCM prescription or decoction, acupuncture, or radiotherapy were excluded, which avoid the possible bias due to different interventions.

There are also some limitations for this study. First, although there were 20 high-quality studies included, the average literature quality was not high. Some of these studies only described the random grouping, without any blindness. Second, there were only a few included studies concerning some TCMIs, including 2 studies of XAPI, 2 studies of DLEI, and 2 studies of XGDTI, and the results reliability might be influenced. Third, most of these included studies ignored the possibility of liver toxicity of the TCMI, and the safety observation should be improved. Fourth, due to the limited literature for each TCMI, further in-depth studies with subgroup analysis should be conducted in the future.

In conclusion, our results show that some TCMIs combined with oxaliplatin-containing chemotherapy regimen can exert good therapeutic effects in the treatment of colorectal cancer, which is superior to the chemotherapy alone. The ADI could significantly reduce the adverse reaction of peripheral nerve toxicity. These findings might provide clinical reference for the prevention and treatment of colorectal cancer.

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Disclosure of conflict of interest

None.

Address correspondence to: Dongxin Tang, Department of Science and Education Section, The First Affiliated Hospital of Guiyang College of TCM, No. 71, Baoshan North Road, Guiyang 550001, Guizhou, China. Tel: +86-851 8565 2079; E-mail: tangdongxin18@sina.com

References

[1] Zhu J, Tan Z, Hollis-Hansen K, Zhang Y, Yu C and Li Y. Epidemiological trends in colorectal cancer in China: an ecological study. 2017; 62: 235-243.

[2] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015; 65: 5-29.

[3] Moriarity A, O'Sullivan J, Kennedy J, Mehigan B and McCormick P. Current targeted therapies in the treatment of advanced colorectal cancer: a review. Ther Adv Med Oncol 2016; 8: 276-293.

[4] Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Pitot HC and Alberts SR. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2004; 22: 23-30.

[5] Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C and de Gramont A. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004; 22: 229-237.

[6] Cao H, Mu Y, Li X, Wang Y, Chen S and Liu JP. A systematic review of randomized controlled trials on oral Chinese herbal medicine for prostate cancer. PLoS One 2016; 11: e0160253.

[7] Nie J, Zhao C, Deng LI, Chen J, Bin YU, Xianlin WU, Pang P and Chen X. Efficacy of traditional Chinese medicine in treating cancer. Biomed Rep 2016; 4: 3-14.

[8] Chen M, May BH, Zhou IW, Xue CC and Zhang AL. Meta-analysis of oxaliplatin-based chemotherapy combined with traditional medicines for colorectal cancer: contributions of specific plants to tumor response. Integr Cancer Ther 2016; 15: 40-59.

[9] Medical and Health Administration NHaFPC and Oncology Branch CMA. Diagnosis and treatment guideline of colorectal cancer in China (2015). Chinese Journal of Digestive Surgery 2015; 14: 783-784.

[10] Douillard JY, Oliner KS, Siena S, Tabernero J, Burkes R, Barugel M, Humblet Y, Bodoky G, Cunningham D, Jassem J, Rivera F, Kocakova I, Ruff P, Blasinska-Morawiec M, Smakal M, Canon JL, Rother M, Williams R, Rong A, Wiezorek J, Sidhu R and Patterson SD. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med 2013; 369: 1023-1034.

[11] Shike M, Winawer SJ, Greenwald PH, Bloch A, Hill MJ and Swaroop SV. Primary prevention of colorectal cancer. The WHO collaborating centre for the prevention of colorectal cancer. Bull World Health Organ 1990; 68: 377-385.

[12] Higgins J and Green S. Cochrane handbook for systematic reviews of interventions the cochrane collaboration, 2011.

[13] Jadad AR, Cook DJ and Browman GP. A guide to interpreting discordant systematic reviews. CMAJ 1997; 156: 1411-1416.

[14] Dong W, Su Y, Chen J and Yu X. Clinical study on treatment of metastatic colon cancer with compound sophora flavescens combined with chemotherapy. Hebei Medicine 2016; 293-294.

[15] Fang X and Zhang K. Analysis on the clinic effects of compound sophora flavescens injection plus chemotherapy on terminal colorectal cancer. Anti-tumor Pharmacy 2012; 293-295.

[16] Fu S and Li S. Observation of curative efficacy of yanshu plus chemotherapy for advanced carcinoma of large intestine. Evaluation and Analysis of Drug-Use in Hospitals of China 2007; 7: 64-65.

[17] Gao J and Feng G. Treatment of advanced colon cancer with compound kushen injection combined with chemotherapy: 40 cases. China Pharmaceuticals 2014; 103-105.

[18] Gao W, Li H and Dang Q. Observation on effects of compound kushen injection combined with chemotherapy in treating metastatic colorectal cancer. Shandong Medical Journal 2010; 85-86.

[19] Ding X, Xiao XY, Yang XY and Zhu BH. Clinical observation of compound kushen injection combined with FOLFOX4 regime for patients with advanced colorectal cancer. China Oncology 2010; 20: 860-863.

[20] Jiang L. Observation on the curative effect of compound matrine injection combined with FOLFOX regimen in the treatment of colon cancer. Chinese Community Physician 2016; 103-104.
[21] Kang T, Liu M and Wei D. Effect of compound kushen injection combined with conventional chemotherapy on colon cancer. People's Military Surgeon 2015; 1336-1337.
[22] Kuang Y, Chen X, Luo S and Wang S. Compound kushen injection combined with chemotherapy in the treatment of sdvanced colorectal cancer. Clinical Medicine 2007; 36-37.
[23] Li D, Zhang Q, Wu S, Ruan W, Wu S, Zheng Q and Ao Y. Clinical study on compound kushen injection combined with chemotherapy in the treatment of advanced colon cancer. Liaoning Journal of Traditional Chinese Medicine 2015; 1021-1022.
[24] Liao G, QU Y, Liu P, Wang H and Xie G. Compound matrine injection in combination with FOLFOX-4 regimen for advanced colorectal cancer: a clinical study. Evaluation and Analysis of Drug-Use in Hospital of China 2009; 3: 207-208.
[25] Liu K and Wang Y. Clinical observation of compound kushen injection combined with FOLFOX4 chemotherapy in the treatment of gastric cancer. Chemotherapy in the Treatment of Gastric Cancer 2014; 20: 103-104.
[26] Liu X. Feasibility analysis of compound kushen injection combined with chemotherapy in the treatment of advanced colon cancer. Chinese Journal of Modern Drug Application 2014; 19: 150-151.
[27] Qi H. Clinical study on compound kushen injection combined with chemotherapy in the treatment of advanced colon cancer. Liaoning Journal of Traditional Chinese Medicine 2016; 3: 547-548.
[28] Ren H, Sun J and Zhang L. Observation on curative effect of compound kushen injection combined with chemotherapy on colon cancer. China Health Care Nutrition 2014; 24: 2468-2469.
[29] Yan Q, Liu Q and Yin Y. Observation on curative effect of compound kushen injection combined with oxaliplatin in the treatment of rectal cancer. Modern Journal of Integrated Traditional Chinese and Western Medicine 2015; 31: 3488-3489.
[30] Shi Q, Wang Z and Zhao Q. Treatment of metastatic or recurrent advanced colorectal carcinoma with compound kushen injection combined with FOLFIRI regimen: 50 cases. Chinese Journal of New Drugs 2010; 17: 1589-1592.
[31] Sun L. Clinical study on treatment of metastatic colorectal cancer with compound kushen injection combined with chemotherapy. Jilin Journal of Traditional Chinese Medicine 213; 1: 53-54.
[32] Tao C and Xu J. Clinical observation of advanced colon cancer treated by compound kushen injection combined with chemotherapy: 74 cases. Guiding Journal of Traditional Chinese Medicine and Pharmacology 2013; 11: 42-44.
[33] Wang J, Xu J and Zheng X. Observation of advanced colorectal cancer treated by compound kushen injection combined with chemotherapy: 25 cases. Zhejiang Journal of Traditional Chinese Medicine 2015; 3: 230.
[34] Wang H, Liu S and Liao G. Efficacy of compound radix sophorae flavescentis injection combined with chemotherapy for advanced colon carcinoma. Evaluation and Analysis of Drug-Use in Hospitals of China 2010; 5: 461-462.
[35] Wei H, Wang C and Ma D. Effect of compound kushen injection combined with chemotherapy on colorectal cancer and disease prognosis. Shaanxi Journal of Traditional Chinese Medicine 2015; 4: 446-448.
[36] Xi R. Clinical effect of compound kushen injection combined with chemotherapy on advanced colorectal cancer. Journal of Medical Forum 2011; 14: 52-53+55.
[37] Xu L. Efficacy observation of compound matrine injection and cisplatin for malignant pleural effusion. Contemporary Medicine Forum 2014; 3: 88-89.
[38] Yang J, Han L and Deng W. Clinical observation of compound sophora flavescens injection combined with chemotherapy in the treatment of advanced colorectal carcinoma. Chinese Journal of Practical Medicine 2015; 42: 76-77.
[39] Yu G, Jia Z and Chen X. Therapeutic effect of compound kushen injection combined with chemotherapy on advanced colorectal cancer: a report of 76 cases. China Practical Medicine 2014; 9: 154-155.
[40] Zhang M. Effect of compound kushen injection combined with chemotherapy on advanced colon cancer. Contemporary Medicine Forum 2015; 10: 241-242.
[41] Zhao J and Shu P. Clinical study on compound sophora flauescens Ait combined with chemotherapy for colorectal cancer. Journal of Clinical Medicine in Practice 2012; 11: 101-103.
[42] Zhu W. Clinical observation of compound kushen injection combined with FOLFOX in the treatment of colon cancer. The Journal of Medical Theory and Practice 2016; 22: 3093-3095.
[43] Zhu Y. Clinical study on treatment of metastatic colorectal cancer with compound kushen

injection combined with chemotherapy. Journal of Clinical Medicine (e-magazine) 2016; 3: 517-518.
[44] Ding X, Xiao X, Yang X and Zhu B. Clinical observation of compound kushen injection combined with FOLFOX4 regime for patients with advanced colorectal cancer. China Oncology 2010; 11: 860-863.
[45] Liu T and Ma T. Clinical observation of Aidi injection combined with chemotherapy in the treatment of advanced colorectal. Journal of China Tratitional Chinese Medicine Information 2009; 12: 2849-2850.
[46] Lv W, Qi H, Dong H and Xiao Y. Clinical observation of advanced colorectal cancer treated by Aidi injection: 28 cases. Shandong Medical Journal 2006; 28: 40.
[47] Wu X. Clinical observation of Aidi injection combined with FOLFIRI in the treatment of advanced colorectal. Modern Journal of Integrated Traditional Chinese and Western Medicine 2012; 9: 946-947.
[48] Sun W, Men Z and Guo S. Clinical study of Aidi injection combined with FOLFOX4 in the treatment of colon cancer. Pharmacology and Clinics of Chinese Materia Medica 2015; 4: 245-247.
[49] Shi B, Xu J and Zhang X. Clinical observation of Aidi injection combined with XELOX in the treatment of advanced colorectal cancer. Modern Journal of Integrated Traditional Chinese and Western Medicine 2009; 21.
[50] Li H, Dong L, Fu S and Li Y. Comparative study on treatment of advanced colorectal cancer by Aidi injection combined with FOLFOX4 regimen and by FOLFOX4 regimen alone. Chinese Journal of Integrated Traditional and Western Medicine on Liver Disease 2007; 12: 1086-1089.
[51] Li Z, Yu G, Li Q, Du H and Hu Z. Observation on the therapeutic effect of Aidi injection combined with chemotherapy on advanced colorectal cancer. Zhejiang Journal of Integrated Tradiyional Chinese and Western Medicine 2011; 6: 397-398.
[52] Fan S and Peng L. Clinical observation of Aidi injection combined with FOLFOX-4 regimen in the treatment of advanced colorectal cancer. China Modern Medicine 2010; 24: 76.
[53] Wang D, Wang P and Liu J. Clinical efficacy of Aidi injection combined with oxaliplatin in the treatment of advanced colorectal cancer. Journal of Clinical Medicine in Practice 2014; 11.
[54] Wang Y and Peng L. Clinical study on Aidi injection combined with FOLFOX4 regimen in the treatment of advanced colorectal cancer. Qingdao Medical Journal 2012; 3: 173-174.
[55] Wang X. Observation of curative effect of Aidi injection combined with FOLFOX-4 chemotherapy on colorectal cancer. Practical Clinical Journal of Integrated Traditional Chinese and Western Medicine 2016; 11: 37-38.
[56] Chen L. Efficacy of Aidi injection in chemotherapy of advanced colorectal cancer. Chinese Journal of Modern Drug Application 2013; 18: 166-167.
[57] Huang S, Lin J, Zhu J, Chen W and Shanming Chen S. Clinical observation on 40 cases of advanced colorectal cancer treated by Aidi injection combined with chemotherapy. Zhejiang Journal of Traditional Chinese Medicine 2013; 4: 311.
[58] Huang J, Shen H and Wang Y. Treatment of advanced colorectal cancer with Aidi injection combined with L-OHP + 5-Fu/LV: 30 cases. Henan Traditional Chinese Medicine 2008; 12: 65-66.
[59] Zhang W, Sun H and Zheng W. Effect of shenqi fuzheng injection on quality of life and immune function in patients with advanced colon cancer. Modern Practical Medicine 2015; 3: 358-359+391.
[60] Xing F and Feng G. Efficacy of shenqi fuzheng injection combined with FOLFOX4 in the treatment of advanced colorectal cancer. China Higher Medical Education 2015; 1: 140+144.
[61] Li S, Lv R, Wang J and Wang S. Clinical observation of shenqifuzheng injection and capectitabine in treatment of elderly patients with advanced carcinoma of large intestine. Medical Journal of Chinese People's Health 2014; 7: 6-7+9.
[62] Liang Q, Pan D, Xia J, Cai L, Li S and Yang Q. Effect of shenqi fuzheng injection combined with chemotherapy in treating advanced colorectal carcinoma. Chinese Journal of Integrated Traditional and Western Medicine 2009; 439-441.
[63] Yan F, Zhou Y and Jiang P. Effect of shenqifuzheng injection combined with chemotherapy on immune function in patients with colon cancer after operation. China Journal of Modern Medicine 2014; 72-74.
[64] Tan G, Liu L, Li J and Hu Y. Effects of shenqifuzheng injection on immunolologic function of patients with colon cancer. Journal of Hainan Medical University 2013; 627-629.
[65] Zhao T and Liu Y. Clinical observation of shenqi fuzheng injection combined with mFOLFOX6 regimen in treatment of advanced colon carcinoma. Chinese Journal of Modern Drug Application 2011; 16-17.
[66] Guo Y, Jia J, Zhao H and Chai B. Treatment of advanced colorectal cancer with shenqi fuzheng injection combined with oxaliplatin and 5-fluorouracil leucovorin: 30 cases. Chinese Remedies & Clinics 2011; 221-223.
[67] Huo W, Li Z, Pan X and Chen C. Observation on curative effect of shenqi fuzheng injection

combined with chemotherapy on advanced colorectal cancer. Chinese Journal of Clinical Oncology and Rehabilitation 2008; 454-456.
[68] Zou J, Li Z, Ye Y and Sun H. Effect of shenqi fuzheng injection combined with FOLFOX4 on immune function and quality of life in patients with stage II/III colorectal cancer. Chinese Journal of Modern Applied Pharmacy 2012; 755-758.
[69] Zhang W, Sun H and Zheng W. Clinical observation of shenqi fuzheng injection-induced toxicity and side effects in preventing and treating cancer chemotherapy. Journal of Practical Traditional Chinese Internal Medicine 2006; 666-667.
[70] Fan X, Zhuo X, Li X, Zhuo R, Tang X and Pan D. Study of brucea fruit water in oil emulsion combine with mFOLFOX regimen on old patients with advanced gastric cancer. Modern Journal of Integrated Traditional Chinese and Western Medicine 2008; 4229-4230.
[71] Liu M, Sun J, Huang X and Mao H. Clinical efficacy and possible mechanism of brucea javanica oil emulsion injection in the treatment of colorectal cancer Chinese Herbal Medicine 2016; 2640-2642.
[72] Bu J and Zhang C. Clinical evaluation of brucea javanica oil emulsion injection in the treatment of advanced colorectal cancer. Journal of Huaihai Medicine 2010; 63-64.
[73] Liu Q, Lin W and Huang K. FOLFOX6 regimen combined with bruceolic oil emulsion in the treatment of metastatic large intestine carcinoma. Journal of Basic and Clinical Oncology 2013; 16-18.
[74] Wang H, Gao Y and Zhang Y. Effect of delisheng injection plus OLF regimen in treatment of advanced colorectal carcinoma. Journal of Modern Oncology 2007; 5.
[75] Liang S. Observation on the therapeutic effect of deli sheng injection combined with chemotherapy in treating advanced colon cancer. Journal of Modern Oncology 2010; 974-975.
[76] Zhuo L. Kang'ai injection combined with chemotherapy in the treatment of advanced colorectal cancer for 30 cases. Chinese Medicine Modern Distance Education of China 2016; 91-92.
[77] Zhang X and Peng H. Efficacy observation of kang'ai injection combined with chemotherapy in treating advanced colorectal cancer. Modern Medicine & Health 2011; 1450-1451.
[78] Yang Y. A comparative study of kangai injection combined with FOLFOX4 regimen in the treatment of advanced colorectal. Fujian College of Traditional Chinese Medicine 2008.
[79] Liang J and Huang X. Clinical observation on toxicity attenuation and therapeutic efficiency of kangai injection in patients with colorectal cancer after surgery. Strait Pharmaceutical Journal 2015; 139-140.
[80] Ruan X, Liu C, Wei L and Wang F. Efficacy of kangai injection combined with XELOX in the treatment of advanced colorectal cancer. Modern Journal of Integrated Traditional Chinese and Western Medicine 2014; 18: 1983-1985.
[81] Lei Z and Li H. Clinical observation of combination Kang'ai injection and chemotherapy for patients after colorectal cancer surgery. Proceeding of Clinical Medicine 2012; 6: 403-405.
[82] Han H, Zhang L, Chen D and Wang Y. Clinical observation on 60 cases of colorectal cancer treated by kangai injection combined with chemotherapy. Journal of New Chinese Medicine 2010; 3: 42-43.
[83] Li C. Clinical observation of kangai injection combined with chemotherapy in the treatment of advanced colorectal cancer. Modern Diagnosis & Treatment 2015; 12: 2741-2742
[84] Ling X and Zhao D. Short term efficacy of combination of oxaliplatin,capecitabine and Kanglaite in the treatment of advanced colorectal carcinoma. Medical Information 2011; 2: 377-379.
[85] Wang X and Wang D. Clinical observation of Kanglaite injection combined with FOLFOX4 regimen in the treatment of advanced colorectal. Journal of Liaoning University of Traditional Chinese Medicine, 2014; 2: 175-177.
[86] Ma J. Clinical study of coix seed oil combined with FOLFOX4 in the treatment of colorectal cancer. Nanjing University of Chinese Medicine 2012.
[87] Wang Y. Clinical study on treatment of advanced colorectal cancer with xiaoyanping combined with XELOX regimen. Northern Pharmacy 2013; 7: 55.
[88] Zhang L. Treatment of advanced colon cancer with xiaoyanping injection combined with FOLFOX4 regimen: 40 cases. Traditional Chinese Medicinal Research 2012; 11: 14-16.
[89] Zhang Z, Ni B and Chen R. The effect of lentinan injection combined with FOLFOX chemotherapy in treatment of advanced colon cancer. Chinese and Foreign Medical Research 2011; 23: 11-13.
[90] Dong X and Li Q. Effect of lentinan injection combined FOLFOX for advanced colon cancer. The Practical Journal of Cancer 2015; 1: 136-138.
[91] de Vries NL, Swets M, Vahrmeijer AL, Hokland M and Kuppen PJ. The Immunogenicity of Colorectal cancer in relation to tumor development and treatment. Int J Mol Sci 2016; 17.
[92] Schmoll HJ, Van Cutsem E, Stein A, Valentini V, Glimelius B, Haustermans K, Nordlinger B, van de Velde CJ, Balmana J, Regula J, Nagtegaal

ID, Beets-Tan RG, Arnold D, Ciardiello F, Hoff P, Kerr D, Kohne CH, Labianca R, Price T, Scheithauer W, Sobrero A, Tabernero J, Aderka D, Barroso S, Bodoky G, Douillard JY, El Ghazaly H, Gallardo J, Garin A, Glynne-Jones R, Jordan K, Meshcheryakov A, Papamichail D, Pfeiffer P, Souglakos I, Turhal S and Cervantes A. ESMO consensus guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. Ann Oncol 2012; 23: 2479-2516.

[93] Qi F, Zhao L, Zhou A, Zhang B, Li A, Wang Z and Han J. The advantages of using traditional Chinese medicine as an adjunctive therapy in the whole course of cancer treatment instead of only terminal stage of cancer. Biosci Trends 2015; 9: 16-34.

[94] Nie J, Zhao C, Deng LI, Chen J, Yu B, Wu X, Pang P and Chen X. Efficacy of traditional Chinese medicine in treating cancer. Biomed Rep 2016; 4: 3-14.

[95] Li X, Yang G, Li X, Zhang Y, Yang J, Chang J, Sun X, Zhou X, Guo Y, Xu Y, Liu J and Bensoussan A. Traditional Chinese medicine in cancer care: a review of controlled clinical studies published in chinese. PLoS One 2013; 8: e60338.

[96] Zhuo X, Fan M and Lai L. Systematic evaluation of compound kushen injection combined with chemotherapy in treatment of colorectal cancer. Chinese Journal of Traditional Medical Science and Technology 2016; 23: 620-625.

[97] Ma J, Ailan T and Wu T. Systematic analysis of compound matrine injection combined with chemotherapy in treating advanced colorectal cancer. Journal of Guangzhou University of Traditional Chinese Medicine 2016; 33: 425-431.

[98] Wu Z, Tan W and Lian B. Efficacy and safety of compound kushen injection combined with oxaliplatin-based chemotherapy regimen in the treatment of colorectal cancer: a systematic review. China Pharmacy 2017; 28: 369-373.

[99] Zhang D, Wu J and Zhang B. Clinical evaluation of compound kushen injection combined with FOLFOX chemotherapy in the treatment of colorectal cancer: a meta-analysis. Chinese Journal of Pharmacoepidemiology 2016; 11: 685-690.

[100] Yu B, Zheng G and Zhu J. The effectiveness of compound matrine injection combined with chemotherapy or radiotherapy for colorectal cancer: a meta-analysis. Journal of Modern Oncology 2016; 24: 1767-1773.

[101] Ji B and Yuan J. Meta-analysis of efficacy and safety of Aidi injection combined with chemotherapy in treatment of colorectal cancer. China Pharmacy 2011; 40: 3797-3799.

[102] Li D and Lin F. Meta-analysis of the efficacy and safety of Aidi injection combined with chemotherapy in the treatment of advanced colorectal. Strait Pharmaceutical Journal 2016; 28: 113-116.

[103] Wang X, He W and Zhang H. Systematic evaluation of the efficacy and safety of kangyi injection combined with chemotherapy in the treatment of colorectal cancer. Journal of Chinese Medicine 2014; B12: 747-748.

[104] Zhang L, Wang Y and Qiu C. Meta analysis of kangai injection combined with FOLFIRI for the treatment of colorectal cancer. China Modern Medicine 2017; 24: 13.

[105] Liang L, Li L and Yang Q. Evaluation of the efficacy of Aidi injection combined with chemotherapy in the treatment of colorectal cancer. Journal of Medical Forum 2010; 22: 94-95.

[106] Chen M, May B and Zhou I. Meta-analysis of oxaliplatin-based chemotherapy combined With traditional medicines for colorectal cancer: contributions of specific plants to tumor response. Integrative Cancer Therapies 2016; 15: 40.

Supplementary Table 1. Traditional Chinese medicine injection ingredients

Injections	Ingredients
ADI	Mylabris, ginseng, astragalus, medofenoxate
KSI	Sophora flavescens, rhizoma heterosmilacis heterosmilar rhizome
SQFZI	Lanceolata, astragalus
DLSI	Red ginseng, astragalus, toad venom, mylabris
KAI	Astragalus, ginseng, oxymatrine
KLTI	Coix seed oil
XGDTI	Lentinan
XAPI	Marsdenia tenacissima

Supplementary Table 2. Baseline characteristics of the included literature

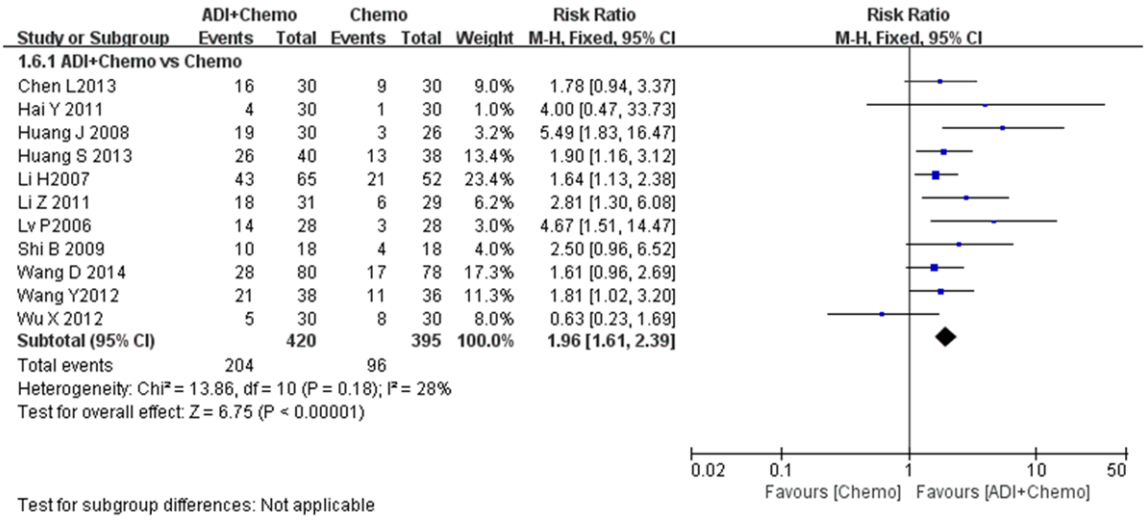
	Studies	Participants	Age (year)	Staging	KPS	Test group	Control group	Ref.
KSI	Dong W 2016	70/60	38-70/56	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[14]
	Fang X 2012	36/36	17-72	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[15]
	Fu S 2007	36/32	32-75/56	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[16]
	Gao J 2014	40/40	30-75/54.3±1.2	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[17]
	Gao W 2010	38/35	31-75/52	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[18]
	Hu Y 2012	20/20	28-73	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[19]
	Jiang L 2016	50/50	40-75/58.3±7.5	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[20]
	Kang T 2015	52/52	66.31±7.29	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[21]
	Kuang Y 2007	30/30	28-72	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[22]
	Li D 2015	26/26	45-70/55.8±7.3	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[23]
	Liao G 2009	125/125	26-80/58.6	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[24]
	Liu K 2014	37/37	44-76/60	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[25]
	Liu X 2015	55/55	36-78	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[26]
	Qi H 2016	36/36	42-70/53.26±6.59	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[27]
	Ren H 2014	60/60	33-76/56	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[28]
	Yan Q 2015	41/41	54.4±6.5	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[29]
	Shi Q 2010	50/50	57/56	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[30]
	Sun L 2013	40/40	61/60	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[31]
	Tao C 2013	74/74	49-74/60.2±8.9	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[32]
	Wang J 2015	25/25	58/60	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[33]
	Wang H 2010	28/28	58	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[34]
	Wei H 2015	60/60	41-78/55±4.8	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[35]
	Xi R 2011	56/48	26-75/52	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[36]
	Xu L 2014	30/30	45-78/56.8±1.2	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[37]
	Yang J 2015	39/39	55.1/53.8	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[38]
	Yu G 2014	38/38	47-75/62.8±6.3	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[39]
	Zhang M 2015	30/30	33-72/45.6±7.9	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[40]
	Zhao J 2012	33/33	35-75/52.3±6.7	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[41]
	Zhu W 2016	45/45	57.21±7.28/60.89±7.75	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[42]
	Zhu Y 2016	30/30	24-74/57.3±3.6	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[43]
	Ding X 2010	30/31	56-71/64	Advanced	≥60	CKSI + FOLFOX	FOLFOX	[44]
ADI	Liu T 2009	30/30	NR	Advanced	≥60	ADI + FOLFOX	FOLFOX	[45]
	Lv W 2006	28/28	63.2/61.2	Advanced	≥60	ADI + FOLFOX	FOLFOX	[46]
	Wu X 2012	30/30	63.6/64.1	Advanced	≥60	ADI + FOLFOX	FOLFOX	[47]
	Sun W 2015	48/48	55.82/55.67	Advanced	≥60	ADI + FOLFOX	FOLFOX	[48]
	Shi B 2009	18/18	52	Advanced	≥60	ADI + FOLFOX	FOLFOX	[49]

	Li H 2007	65/52	58/59	Advanced	≥60	ADI + FOLFOX	FOLFOX	[50]
	Li Z 2011	31/29	54/55	Advanced	≥60	ADI + FOLFOX	FOLFOX	[51]
	Fan S 2010	44/44	NR	Advanced	≥60	ADI + FOLFOX	FOLFOX	[52]
	Wang D 2014	80/78	69.8	Advanced	≥60	ADI + FOLFOX	FOLFOX	[53]
	Wang Y 2012	38/36	52	Advanced	≥60	ADI + FOLFOX	FOLFOX	[54]
	Wang X 2016	30/30	58.16±6.41/58.04±6.38	Advanced	≥60	ADI + FOLFOX	FOLFOX	[55]
	Chen L 2013	30/30	53.6/54.8	Advanced	≥60	ADI + FOLFOX	FOLFOX	[56]
	Huang S 2013	40/38	54/55	Advanced	≥60	ADI + FOLFOX	FOLFOX	[57]
	Huang J 2008	30/26	65/66	Advanced	≥60	ADI + FOLFOX	FOLFOX	[58]
SQFZI	Xing F 2015	30/30	32-74/52; 33-73/53	III, IV	≥60	SQFZI + FOLFOX	FOLFOX	[59]
	Zhang W 2015	43/43	63.5±6.7/64.3±7.2	Advanced	≥60	SQFZI + FOLFOX	FOLFOX	[60]
	Li S 2014	35/35	61-76/67	Advanced	≥60	SQFZI + FOLFOX	FOLFOX	[61]
	Liang Q 2009	76/76	53/52	Advanced	≥60	SQFZI + FOLFOX	FOLFOX	[62]
	Yan F 2014	56/56	56.2±11.3/56.9±10.8	Advanced	≥60	SQFZI + FOLFOX	FOLFOX	[63]
	Tan G 2013	20/20	52-72/64	Advanced	≥60	SQFZI + XELOX	XELOX	[64]
	Zhao T 2011	32/32	44-76	Advanced	≥70	SQFZI + FOLFOX	FOLFOX	[65]
	Guo Y 2011	30/24	38-68/65.4; 40-70/66.5	III, IV	≥60	SQFZI + FOLFOX	FOLFOX	[66]
	Huo W 2008	22/14	26-70/51	III, IV	≥70	SQFZI + FOLFOX	FOLFOX	[67]
	Zou J 2012	45/44	27-91/58.7	II, III	≥60	SQFZI + FOLFOX	FOLFOX	[68]
	Zhang W 2006	43/43	63.5±6.7/64.3±7.2	Advanced	≥60	SQFZI + XELOX	XELOX	[69]
BJOEI	Fan X 2008	48/45	59.5±11.3/56.4±10.3	IV	≥70	BJOEI + FOLFOX	FOLFOX	[70]
	Liu M 2016	50/50	54.89±12.34	Advanced	≥60	BJOEI + FOLFOX	FOLFOX	[71]
	Bu J 2010	46/34	46-80/58	Advanced	≥60	BJOEI + FOLFOX	FOLFOX	[72]
	Li Q 2013	20/21	56/57	Advanced	≥60	BJOEI + FOLFOX	FOLFOX	[73]
DLSI	Wang H 2007	34/33	55	Advanced	≥60	DLSI + FOLFOX	FOLFOX	[74]
	Liang Y 2010	30/33	45/47	Advanced	≥70	DLSI + FOLFOX	FOLFOX	[75]
KAI	Zhou L 2016	30/30	60.0±1.5/61.0±1.0	Advanced	NR	KAI + FOLFOX	FOLFOX	[76]
	Zhang X 2011	23/22	45-73/42-71	IV	≥60	KAI + FOLFOX	FOLFOX	[77]
	Yang Y 2008	30/30	51.07±10.44/51.33±10.95	Advanced	≥60	KAI + FOLFOX	FOLFOX	[78]
	Liang J 2015	31/31	53.8±6.4	Advanced	NR	KAI + FOLFOX	FOLFOX	[79]
	Ruan X 2014	30/30	35-63/34-67	Advanced	≥60	KAI + XELOX	XELOX	[80]
	Lei Z 2012	30/30	31-75	II, III	≥70	KAI + FOLFOX	FOLFOX	[81]
	Han H 2010	60/60	32-70/51; 35-70/52	Advanced	≥60	KAI + FOLFOX	FOLFOX	[82]
	Li C 2015	48/45	56.72±7.24/57.13±7.05	Advanced	≥60	KAI + FOLFOX	FOLFOX	[83]
KLTI	Ling X 2011	33/33	60-76	Advanced	≥60	KLTI + FOLFOX	FOLFOX	[84]
	Wang X 2014	18/18	67.19±2.48	Advanced	≥60	KLTI + FOLFOX	FOLFOX	[85]
	Ma J 2012	20/20	30-69	Advanced	≥60	KLTI + FOLFOX	FOLFOX	[86]
XAPI	Wang Y 2013	32/30	NS	Advanced	≥70	XAPI + XELOX	XELOX	[87]
XGDTI	Zhang Z 2011	38/34	27-76/58; 28-78/59	Advanced	>60	XGDTI + FOLFOX	FOLFOX	[88]
	Dong X 2015	45/45	63.5±1.0/63.0±1.0	Advanced	NR	XGDTI + FOLFOX	FOLFOX	[89]
	Zhang L 2011	20/20	59.24±20.37/61.56±21.53	Advanced	≥70	XAPI + FOLFOX	FOLFOX	[90]

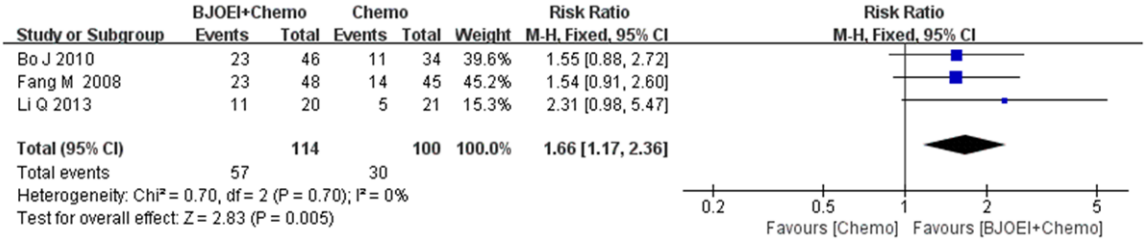
Supplementary Table 3. Quality analysis of the included studies

		Randomized	Allocation Concelment	Sequence Generation	Blinding of subjects	Selective reporting	Jadad scoring	Ref.
ADI	Liu T 2009	Yes	Unclear	Unclear	Yes	Unclear	1	[14]
	Lv W 2006	Yes	Unclear	Unclear	Yes	No	2	[15]
	Wu X 2012	Yes	Unclear	Unclear	Yes	Unclear	1	[16]
	Sun W 2015	Yes	Yes	Unclear	Yes	No	3	[17]
	Shi B 2009	Yes	Yes	Yes	Yes	No	4	[18]
	Li H 2007	Yes	Unclear	Unclear	Yes	Unclear	1	[19]
	Li Z 2011	Yes	Yes	Yes	Yes	No	4	[20]
	Fan S 2010	Yes	Unclear	Unclear	Yes	Unclear	1	[21]
	Wang D 2014	Yes	Unclear	Unclear	Yes	No	2	[22]
	Wang Y 2012	Yes	Unclear	Unclear	Yes	No	2	[23]
	Wang X 2016	Yes	Unclear	Unclear	Yes	Unclear	1	[24]
	Chen L 2013	Yes	Unclear	Unclear	Yes	No	1	[25]
	Huang S 2013	Yes	Unclear	Unclear	Yes	No	1	[26]
	Huang J 2008	Yes	Yes	Unclear	Yes	No	3	[27]
KAI	Zhou L 2016	Yes	Unclear	Unclear	Yes	No	1	[28]
	Zhang X 2011	Yes	Yes	Yes	Yes	No	3	[29]
	Yang Y 2008	Yes	Unclear	Unclear	Yes	Unclear	1	[30]
	Liang J 2015	Yes	Unclear	Unclear	Yes	No	1	[31]
	Ruan X	Yes	Unclear	Unclear	Yes	No	1	[32]
	Lei Z	Yes	Yes	Unclear	Yes	No	3	[33]
	Han H 2010	Yes	Yes	Yes	Yes	No	4	[34]
	Li C 2015	Yes	Unclear	Unclear	Yes	Unclear	1	[35]
SQFZI	Xing F 2015	Yes	Unclear	Unclear	Yes	No	1	[36]
	Zhang W 2015	Yes	Unclear	Unclear	Yes	No	2	[37]
	Li S 2014	Yes	Unclear	Unclear	Yes	No	2	[38]
	Liang Q 2009	Yes	Unclear	Unclear	Yes	No	1	[39]
	Yan F 2014	Yes	Unclear	Unclear	Yes	No	2	[40]
	Tan G 2013	Yes	Unclear	Unclear	Yes	Unclear	1	[41]
	Zhao T 2011	Yes	Yes	Unclear	Yes	No	3	[42]
	Guo Y 2011	Yes	Yes	Yes	Yes	No	3	[43]
	Huo W 2008	Yes	Unclear	Unclear	Yes	No	1	[44]
	Zou J 2012	Yes	Yes	Yes	Yes	No	3	[45]
	Zhang W 2014	Yes	Unclear	Unclear	Yes	Unclear	1	[46]
DLSI	Wang H 2007	Yes	Unclear	Unclear	Yes	No	2	[47]
	Liang S 2010	Yes	Yes	Unclear	Yes	No	3	[48]
KLTI	Ling X 2011	Yes	Yes	Yes	Yes	No	4	[49]
	Wang X 2014	Yes	Unclear	Unclear	Yes	Unclear	1	[50]
	Ma J 2012	Yes	Unclear	Unclear	Yes	No	2	[51]
KSI	Dong W 2016	Yes	Unclear	Unclear	Yes	No	1	[52]
	Fang X 2012	Yes	Unclear	Unclear	Yes	No	1	[53]
	Fu S 2007	Yes	Yes	Unclear	Yes	No	3	[54]
	Gao J 2014	Yes	Yes	Yes	Yes	Unclear	3	[55]
	Gao W 2010	Yes	Unclear	Unclear	Yes	No	1	[56]
	Hu Y 2012	Yes	Yes	Yes	Yes	No	3	[57]
	Jiang L 2016	Yes	Unclear	Unclear	Yes	Unclear	1	[57]
	Kang T 2015	Yes	Unclear	Unclear	Yes	No	2	[58]

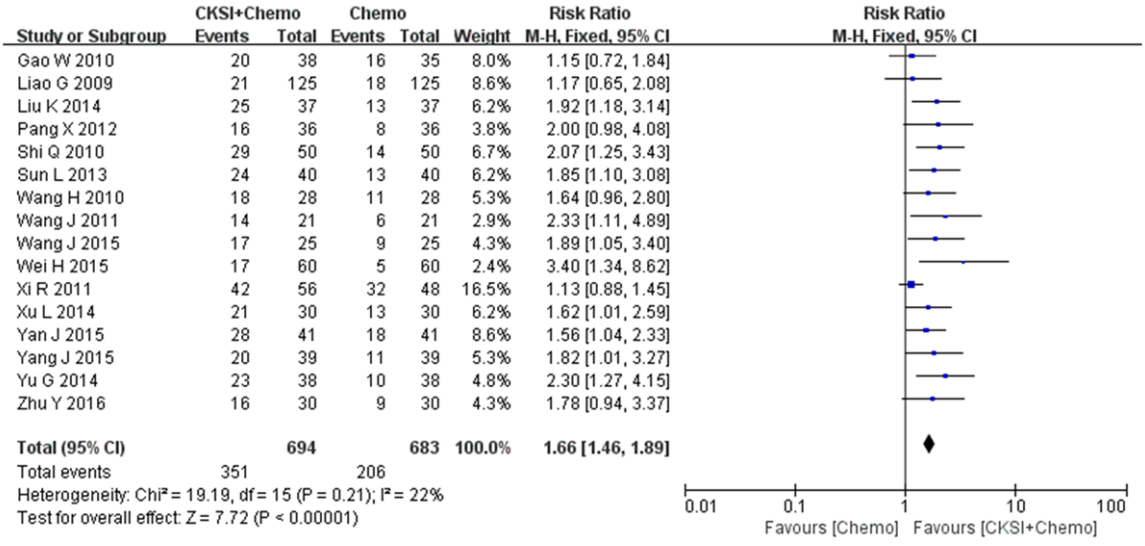
	Kuang Y 2007	Yes	Unclear	Unclear	Yes	No	1	[59]
	Li D 2015	Yes	Yes	Unclear	Yes	No	3	[60]
	Liao G 2009	Yes	Yes	Yes	Yes	No	4	[61]
	Liu K 2014	Yes	Unclear	Unclear	Yes	Unclear	1	[62]
	Liu X 2015	Yes	Yes	Yes	Yes	No	4	[63]
	Qi H 2016	Yes	Unclear	Unclear	Yes	No	1	[64]
	Ren H 2014	Yes	Unclear	Unclear	Yes	No	1	[65]
	Run H 2015	Yes	Unclear	Unclear	Yes	No	2	[66]
	Shi Q 2010	Yes	Unclear	Unclear	Yes	No	2	[67]
	Sun L 2013	Yes	Unclear	Unclear	Yes	No	1	[68]
	Tao C	Yes	Unclear	Unclear	Yes	No	1	[69]
	Wang J 2015	Yes	Yes	Unclear	Yes	No	3	[70]
	Wang H 2010	Yes	Yes	Yes	Yes	No	3	[71]
	Wei H 2015	Yes	Unclear	Unclear	Yes	No	1	[72]
	Xi R 2011	Yes	Yes	Yes	Yes	No	3	[73]
	Xu L 2014	Yes	Unclear	Unclear	Yes	No	1	[74]
	Yang J 2015	Yes	Unclear	Unclear	Yes	No	2	[75]
	Yu G 2014	Yes	Unclear	Unclear	Yes	No	1	[76]
	Zhang M 2015	Yes	Yes	Unclear	Yes	No	3	[77]
	Zhao J 2012	Yes	Yes	Yes	Yes	No	4	[78]
	Zhu W 2016	Yes	Unclear	Unclear	Yes	No	1	[79]
	Zhu Y 2016	Yes	Yes	Yes	Yes	No	4	[80]
	Ding X	Yes	Unclear	Unclear	Yes	No	1	[81]
BJOEI	Fang M2008	Yes	Unclear	Unclear	Yes	No	2	[82]
	Liu M 2016	Yes	Unclear	Unclear	Yes	No	1	[83]
	Bu J 2010	Yes	Unclear	Unclear	Yes	No	1	[84]
	Li Q 2013	Yes	Yes	Unclear	Yes	No	3	[85]
XGDTI	Zhang Z 2011	Yes	Unclear	Unclear	Yes	No	1	[86]
	Dong X 2015	Yes	Yes	Unclear	Yes	No	3	[87]
XAPI	Wang Y 2013	Yes	Unclear	Unclear	Yes	No	2	[88]
	Zhang L 2011	Yes	Unclear	Unclear	Yes	No	1	[89]



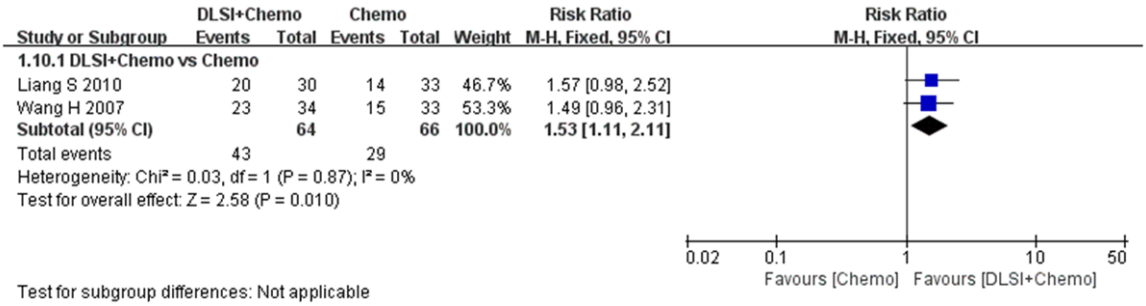
Supplementary Figure 1. Meta-analysis of ADI combined with oxaliplatin-containing chemotherapy for KPS score improvement in colorectal cancer.



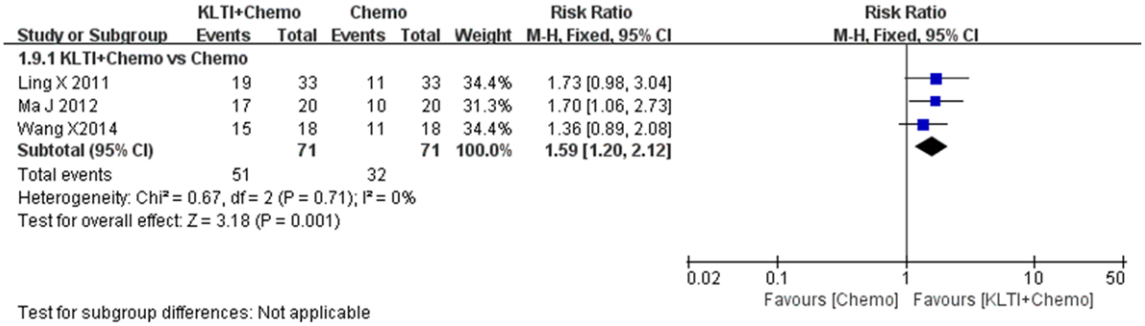
Supplementary Figure 2. Meta-analysis of BJOEI combined with oxaliplatin-containing chemotherapy for KPS score improvement in colorectal cancer.



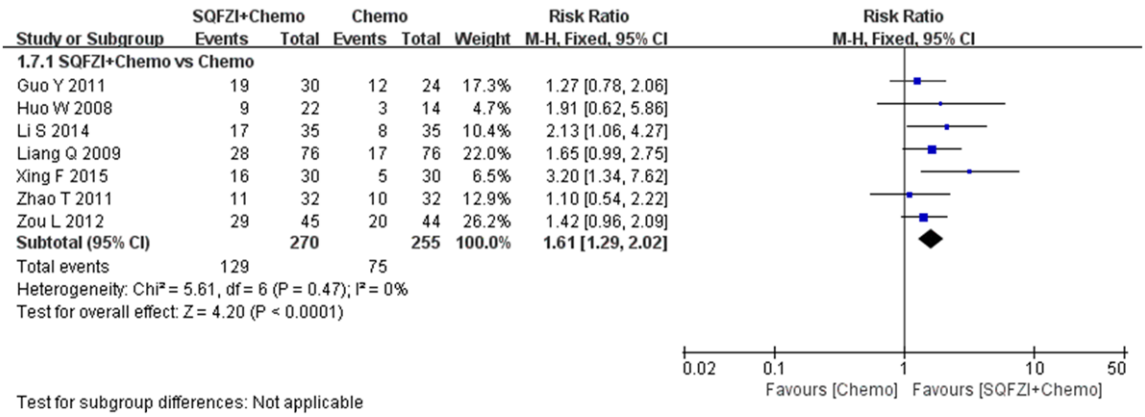
Supplementary Figure 3. Meta-analysis of KSI combined with oxaliplatin-containing chemotherapy for KPS score improvement in colorectal cancer.



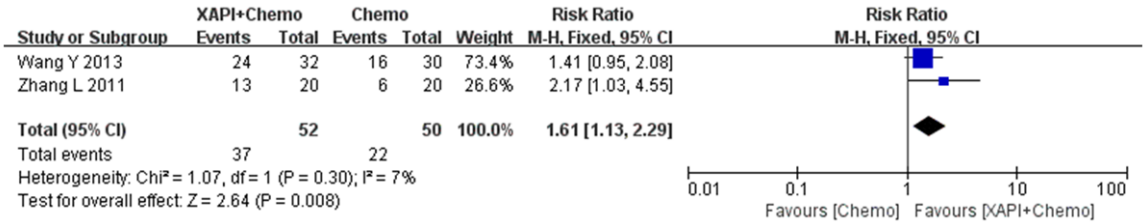
Supplementary Figure 4. Meta-analysis of DLSI combined with oxaliplatin-containing chemotherapy for KPS score improvement in colorectal cancer.



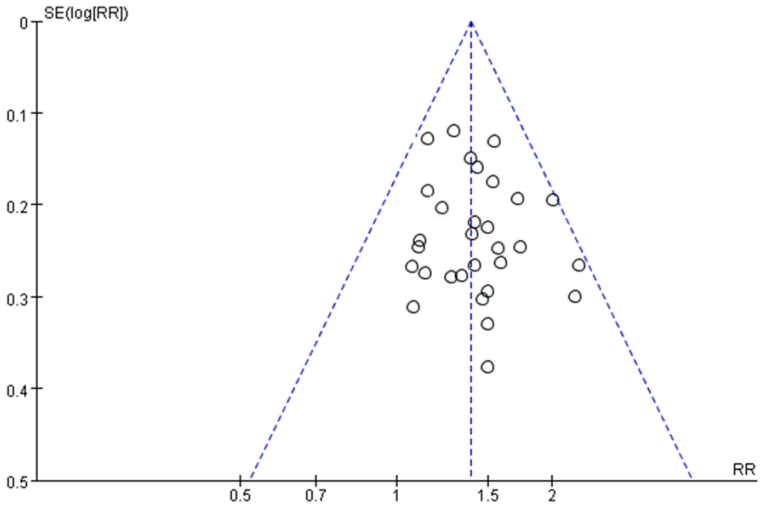
Supplementary Figure 5. Meta-analysis of KLTI combined with oxaliplatin-containing chemotherapy for KPS score improvement in colorectal cancer.



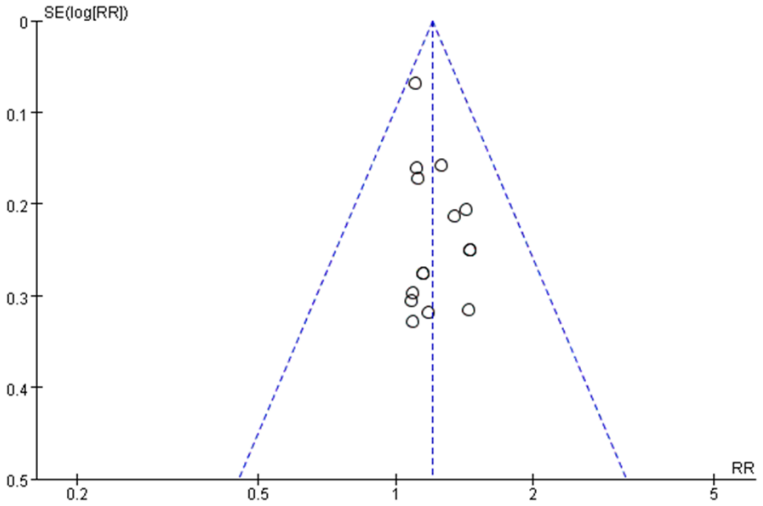
Supplementary Figure 6. Meta-analysis of SQFZI combined with oxaliplatin-containing chemotherapy for KPS score improvement in colorectal cancer.



Supplementary Figure 7. Meta-analysis of XAPI combined with oxaliplatin-containing chemotherapy for KPS score improvement in colorectal cancer.



Supplementary Figure 8. Funnel plot of KSI in the treatment of colorectal cancers.



Supplementary Figure 9. Funnel plot of ADI in the treatment of colorectal cancers.