ORIGINAL RESEARCH Cinobufotalin as an effective adjuvant therapy for advanced gastric cancer: a meta-analysis of randomized controlled trials

This article was published in the following Dove Press journal: OncoTargets and Therapy

Purpose: This study aimed to investigate the efficacy and safety of combining cinobufotalin and chemotherapy for advanced gastric cancer (GC).

Patients and methods: Literature retrieval was performed in Cochrane Library, Web of Science, PubMed, Embase, China National Knowledge Infrastructure (CNKI), Chinese Biological Medicine Database (CBM), Wanfang database and Chinese Scientific Journal Database (VIP) before September 2018. The primary reported outcomes including therapeutic efficacy, quality of life (QoL), and adverse events were systematically evaluated.

Results: Data from 27 trials including 1,939 advanced GC patients were included. The results indicated that, compared with chemotherapy alone, the combination of chemotherapy and cinobufotalin significantly improved patients' overall response rate (odds ratio [OR] =1.88, 95% confidence interval [CI] =1.54–2.31, P<0.00001) and disease control rate (OR =2.05, 95% CI =1.63-2.58, P<0.00001). The QoL of patients also evidently improved after chemotherapy and cinobufotalin combined treatment, as indicated by increased QoL improved rate (OR =2.39, 95% CI =1.81-3.15, P<0.00001), Karnofsky Performance Score (OR =7.00, 95% CI =2.25-11.75, P=0.004) and pain relief rate (OR =7.00, 95% CI =2.25-11.75, P=0.004). Adverse events including nausea and vomiting, diarrhea, leukopenia, handfoot syndrome, anemia, gastrointestinal side effects and peripheral neurotoxicity caused by chemotherapy were evidently alleviated (P<0.05) when cinobufotalin was administered to GC patients.

Conclusion: Evidence from the meta-analysis suggested that the combination of chemotherapy and cinobufotalin is more effective in treating GC than chemotherapy alone. It alleviates the adverse effects associated with chemotherapy and improves the QoL of GC patients.

Keywords: cinobufotalin, traditional Chinese medicine, chemotherapy, gastric cancer, metaanalysis

Introduction

Gastric cancer (GC) represents the second leading cause of death among all cancer types and caused 782,685 deaths worldwide in 2018.¹ Currently, the incidence of GC has significantly increased, with about 1,033,701 new cases every year.¹ China has a high risk for GC, and the new cases of GC in this region account for about 43% in the world.² Despite the improvement of diagnostic and therapeutic methods in the past decades,^{3,4} the prognosis of GC is still poor (5-year survival rate <20%) since it is mostly diagnosed at advanced stage.^{3,4} Therefore, effective therapeutic approaches should be developed.

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Traditional Chinese medicine has an extensive history and has been more widely used as an effective adjuvant drug for cancer treatment.⁵⁻¹⁰ Cinobufotalin is a cardiotonic steroid or bufotalin, which is extracted from the skin secretion of the giant toad.^{10–14} Many in vitro studies have shown that cinobufotalin has antitumor activity and enhanced chemotherapeutic effect.7,10,13,14 Cinobufotalin can inhibit the growth and metastasis of the tumor by inhibiting the expression of vascular endothelial growth growth receptor.15 factor and epidermal factor Additionally, it can also kill tumor cells by inducing nonapoptotic death possibly depending on cyclophilin-D involved pathway.12

Several studies have indicated that chemotherapy combined with cinobufotalin exhibits more prominent therapeutic effects than chemotherapy alone for advanced GC.^{16–42} Despite the intensive clinical studies using cinobufotalin and chemotherapy combined therapy in treating GC, its clinical efficacy and safety have not been systematically evaluated. In this study, we conducted a metaanalysis to investigate the treatment efficacy and safety of chemotherapy combined with cinobufotalin in comparison with chemotherapy alone for advanced GC to provide scientific reference for the design of future clinical trials.

Materials and methods

Search strategy and selection criteria

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and Cochrane Handbook. Original articles were searched across eight electronic databases, including Cochrane Library, Web of Science, PubMed, Embase, China National Knowledge Infrastructure (CNKI), Chinese Biological Medicine Database (CBM), Wanfang database and Chinese Scientific Journal Database (VIP) before September 2018, with key terms "huachansu" or "cinobufotalin," "cinobufacini," or "cinobufagin" combined with "gastric carcinoma" or "gastric cancer." No language limits were applied.

Selection Criteria: The inclusion criteria were as follows: (1) controlled trials concerning advanced GC patients, (2) literature comparing the clinical outcomes of chemotherapy plus cinobufotalin adjuvant therapy (experimental group) with chemotherapy treatments alone (control group) and (3) articles involving more than 40 GC patients. On the other hand, the exclusion criteria were as follows: (1) non-contrast articles, case studies and review papers and (2) patients with mixed malignancies.

Data extraction and quality assessment

Data were independently extracted by two investigators (Sun HL, and Bai MH) following the same inclusion criteria; disagreements were adjudicated by the third reviewer (Liu DL). The extracted characteristics were summarized as follows: (I) first author's names, (II) years of publication, (III) study locations, (IV) tumor stages, (V) Karnofsky Performance Score (KPS), (VI) number of cases, (VII) patient ages, (VIII) study parameter types, (IX) therapeutic regimens, (X) enrollment period and (XI) dosage of cinobufotalin. The included trial's quality was evaluated according to the Cochrane Handbook.⁴³

Outcome definition

Clinical responses include treatment efficacy, quality of life (QoL) and adverse events. Treatment efficacy was assessed in terms of the overall survival rates (OS rates, defined as the length of time from the start of treatment to death from any cause), complete response (CR) rates, partial response (PR) rates, stable disease (SD) rates, progressive disease (PD) rates, overall response rates (ORRs, ORR=CR + PR) and disease control rates (DCRs, DCR=CR + PR + SD). Patients' QoL was evaluated using QoL improved rate (QIR), KPS and pain relief rate (PRR). Adverse events including nausea and vomiting, diarrhea, leucopenia, thrombocytopenia, hepatotoxicity, nephrotoxicity, oral mucositis, alopecia, hand-foot syndrome, anemia, gastrointestinal adverse effects, peripheral neurotoxicity, neutropenia and myelosuppression were also assessed.

Statistical analysis

RevMan 5.3 (Nordic Cochran Centre, Copenhagen, Denmark) and Stata 13.0 (Stata Corp., College Station, TX, USA) software were the main statistical analysis tools in this study. P<0.05 was considered statistically significant. Analysis model was determined by heterogeneity among studies assessed using Cochran's Q test, and publication bias was analyzed using Begg's and Egger's regression asymmetry tests and presented using funnel plots.⁴⁴ I^2 <50% or P>0.1 indicated that the studies were homogenous. Treatment effects were mainly represented by odds ratio (OR) presented with a 95% confidence

interval (CI). Pooled analysis with publication bias determined that trim and fill method would be applied to coordinate the estimates of unpublished studies, and the adjusted results were compared with the original pooled OR.⁴⁵ Sensitivity analysis was performed to evaluate the impact of different therapeutic regimens, drug forms of cinobufotalin, sample sizes and research types on clinical efficacy.

Results

Search results

A total of 493 articles were identified and initially retrieved, and 275 papers were excluded due to duplication. After title and abstract review, 163 articles were further excluded because they did not include clinical trials (n=127) and were unrelated studies (n=34) or published before 2000 (n=2), leaving 55 studies as potentially relevant. After detailed assessment of full texts, articles without control group (n=8), studies with case reports (n=6), reviews or meta-analysis (n=5), and trials with insufficient data (n=9) were excluded. Finally, 27 trials^{16–42} involving 1,939 advanced GC patients were included in this analysis (Figure 1).

Patient characteristics

After selection, all included studies were performed in different medical centers of China since 2000. In total, 972 advanced GC patients were treated with chemotherapy in combination with cinobufotalin adjuvant therapy, while 967 patients were treated with chemotherapy alone. Detailed information of the involved studies and GC patients is shown in Tables 1 and 2.

Quality assessment

The assessment of bias risk is shown in Figure 2. A total of 24 studies were determined as having low risk, and the remaining 3 studies were not true randomized controlled



Figure I Flow diagram of the selection process.

Included studies	Nation	Tumor stage	KPS	Patients Con/Exp	Age (year)		Parameter types
					Con	Exp	
Cha XT (2016) ¹⁶	China	DN	>70	20/20	QN	ND	ORR, DCR, AE
Chen GF (2012) ¹⁷	China	≥	QN	86/62	71.8±18.6 (mean)	73.1±22.3 (mean)	ORR, DCR, QoL, AE
Chen HM(2009) ¹⁸	China	NI–IN	KPS≥60	33/34	49.6 (median)	50.6 (median)	ORR, DCR
Cui P (2009) ¹⁹	China	QN	65 (mean)	23/32	QN	DN	ORR, DCR, QoL, AE
Guo CJ (2011) ²⁰	China	≥	≥50	43/43	QN	DN	ORR, DCR, QoL
Guo XY (2013) ²¹	China	VI-II	≥65	38/42	64.8±3.7 (mean)	66.4±4.2 (mean)	ORR, DCR, QoL
Huang Q (2014) ²²	China	QN	≥60	20/26	55.8±4.9 (mean)	57.4±5.6 (mean)	ORR, DCR, QoL
Li W (2016) ²³	China	QN	Q	74/76	66.8±1.4 (mean)	66.6±1.5 (mean)	ORR, DCR, AE
Li YX (2012) ²⁴	China	QN	Q	74/74	QN	QN	ORR, DCR, QoL, AE
Lu B (2016) ²⁵	China	QN	>60	30/30	74.8±6.2 (mean)	73.7±5.1 (mean)	ORR, DCR, QoL, AE
Lu CH (2014) ²⁶	China	Q	71 (mean)	31/31	DN	QN	ORR, DCR
Tian B (2012) ²⁷	China	NI–IN	KPS>60	22/23	DN	QN	ORR, DCR, AE
Wang F (2014) ²⁸	China	Q	Q	58/58	58.8 (mean)	58.4 (mean)	ORR, DCR, QoL, AE
Wang WM (2010) ²⁹	China	QN	>60	23/20	QN	QN	ORR, DCR, AE
Wang YH (2009) ³⁰	China	N-III	>60	32/36	DN	DN	ORR, DCR, AE
Wang ZF (2012) ³¹	China	Q	>60	24/24	59.1 (median)	58.7 (median)	ORR, DCR, QoL
Xiao XN (2018) ³²	China	N-III	58 (mean)	31/34	DN	QN	ORR, DCR, QoL, AE
Xu DM (2015) ³³	China	QN	>60	30/30	65.0±3.9 (mean)	66.3±4.6 (mean)	ORR, DCR, QoL, AE
Xu YM (2016) ³⁴	China	Q	≥60	30/30	49.9 (median)	45.8 (median)	ORR, DCR, QoL, AE
Yang B (2017) ³⁵	China	Q	>60	34/34	53 (mean)	51 (mean)	ORR, DCR
Yang F (2018) ³⁶	China	Q	Q	25/25	50 (median)	54 (median)	ORR, DCR, QoL, AE
Zhang CW (2001) ³⁷	China	N-III	>70	32/35	66 (median)	64 (median)	ORR, DCR, AE
Zhang RG (2004) ³⁸	China	≥	≥40	43/43	48 (median)	49 (median)	OS, ORR, DCR, AE
Zhang Y (2005) ³⁹	China	≥	≥40	29/28	54 (median)	57 (median)	OS, ORR, AE
Zheng YL (2007) ⁴⁰	China	N-III	68 (mean)	20/20	DN	QN	OS, QoL
Zhu WK (2012) ⁴¹	China	N-III	≥70	32/32	62.8 (mean)	61.7 (mean)	ORR, DCR, QoL, AE
Zou HP (2012) ⁴²	China	N-III	Q	30/30	56.5 (median)	59.1 (median)	ORR, DCR, AE

Included studies	Therapeutic regimen		Enrollment Period	Dosage of cinobufotalin
	Experimental group	Control group		
Cha XT (2016) ¹⁶	Oxaliplatin+Tegafur+CF/SF+Cinobufotalin ^a	Oxaliplatin+Tegafur+CF/SF	January 2013–March 2016	750 mg/time, 3 times/day
Chen GF (2012) ¹⁷	Capecitabine+Cinobufotalin ^b	Capecitabine	October 2006–October 2010	10 ml/time, 3 times/day
Chen HM (2009) ¹⁸	Paclitaxel+Cisplatin+5-Fu+Cinobufotalin ^b	Paclitaxel+Cisplatin+5-Fu	October 2005–December 2007	30 ml/time, l time/day
Cui P (2009) ¹⁹	FOLFOX+Cinobufotalin ^b	FOLFOX	2004–2006	30 ml/time, l time/day
Guo CJ (2011) ²⁰	Docetaxel+Cinobufotalin ^b	Docetaxel	March 2005–March 2010	20 ml/time, l time/day
Guo XY (2013) ²¹	FOLFOX+Cinobufotalin ^c	FOLFOX	January 2009–May 2010	1200 mg/time, 4 times/day
Huang Q (2014) ²²	XELOX+Cinobufotalin ^b	XELOX	August 2009–August 2013	50 ml/time, I time/day
Li W (2016) ²³	Capecitabine+Cinobufotalin ^b	Capecitabine	January 2012–January 2015	10-20 ml/time, I time/day
Li YX (2012) ²⁴	Capecitabine+Cinobufotalin ^b	Capecitabine	January 2006–July 2011	10 ml/time, 1 time/day
Lu B (2016) ²⁵	Capecitabine+Cinobufotalin ^a	Capecitabine	January 2010–December 2012	500 mg/time, 3 times/day,
Lu CH (2014) ²⁶	FOLFOX+Cinobufotalin ^b	FOLFOX	2009–2013	20 ml/time, l time/day
Tian B (2012) ²⁷	FOLFOX+Cinobufotalin ^b	FOLFOX	2004–2006	30 ml/time, l time/day
Wang F (2014) ²⁸	Cisplatin+5-Fu+Cinobufotalin ^a	Cisplatin+5-Fu	ND	500 mg/time, 3 times/day,
Wang WM (2010) ²⁹	S-I+Cinobufotalin ^a	S-I	October 2011–October 2013	500 mg, 3 times/day
Wang YH (2009) ³⁰	FOLFOX+Cinobufotalin ^b	FOLFOX	December 2004–May 2008	10-20 ml/time, 1 time/day
Wang ZF (2012) ³¹	FOLFOX+Cinobufotalin ^b	FOLFOX	December 2003–May 2008	20 ml/time, I time/day
Xiao XN (2018) ³²	FOLFOX+Cinobufotalin ^b	FOLFOX	January 2008–December 2010	10-20 ml/time, 1 time/day
Xu DM (2015) ³³	Docetaxel+Cisplatin+Cinobufotalin ^b	Docetaxel+Cisplatin	2013-2016	20 ml/time, l time/day
Xu YM (2016) ³⁴	Capecitabine+Cinobufotalin ^b	Capecitabine	June 2010-June 2011	20 ml/time, l time/day
Yang B (2017) ³⁵	FOLFOX+Cinobufotalin ^a	FOLFOX	January 2014–April 2015	750 mg/time, 3 times/day,
Yang F (2018) ³⁶	XELOX+Cinobufotalin ^b	XELOX	January 2015–June 2017	20 ml/time, I time/day
Zhang CW (2001) ³⁷	EOF+Cinobufotalin ^a	EOF	May 2014–May 2015	200-500 mg/time, 3 times/day
Zhang RG (2004) ³⁸	Etoposide+Leucovorin+5-Fu+Cinobufotalin ^b	Etoposide+Leucovorin+5-Fu	March 1999–December 2000	20 ml/time, I time/day
Zhang Y (2005) ³⁹	HCPT+CF+5-Fu+Cinobufotalin ^b	HCPT+CF+5-Fu	July 1998–June 2003	20 ml/time, l time/day
Zheng YL (2007) ⁴⁰	FOLFOX+Cinobufotalin ^b	FOLFOX	March 2002–February 2003	50 ml/time, I time/day
Zhu WK (2012) ⁴¹	Oxaliplatin+Capecitabine+Cinobufotalin ^b	Oxaliplatin+Capecitabine	March 2010–MArch 2011	30 ml/time, l time/day
Zou HP (2012) ⁴²	EOF+Cinobufotalin ^b	EOF	May 2008–May 2011	20 ml/time, I time/day
Notes: Control group, chemothera Capsules. Abbreviations: ND non determit	Notes: Control group, chemotherapy alone group; Experimental group, chemotherapy and cinobufotalin combined group. a, cinobufotalin capsule; b, cinobufotalin tablet; S-1, Gimeracil and Oteracil Porassium Capsules. Abbreviations: ND non-determined: CE Calcium folinate: Et Elucorumacil: HCPT. Hodrowernerbecin: EOLEOX. Ovalindatin+CE+K.Etr. XELOX. Ovalindatin+Canacitabine: EOE Entimicit-Activitation-	talin combined group. a, cinobufotalin capsule CPT Hydrowramortherin: FOI FOX Ovali	s; b, cinobufotalin injection; c, cinobufotalin tablet; Ialarin+CE+5E.IV.X.Ovalialarin+Canacitahir	; S-I, Gimeracil and Oteracil Porassium
	ieu, Cr, Carriutti tollitare, Sr, Soututti tollitare, Fu, Fluorou acti, M		ріації т. Ст. т. Э. т. ц. Аст. Охапріації т. Саресісалії	

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Table 2 Information on cinobufotalin combined with chemotherapy

Α																											
Zou HP 2012	Zhu WK 2012	Zheng YL 2007	Zhang Y 2005	Zhang RG 2004	Zhang CW 2001	Yang F 2018	Yang B 2017	Xu YM 2016	Xu DM 2015	Xiao XN 2018	Wang ZF 2012	Wang YH 2009	Wang WM 2010	Wang F 2014	Tian B 2012	Lu CH 2014	Lu B 2016	LI YX 2012	Li W 2016	Huang Q 2014	Guo XY 2013	Guo CJ 2011	Cui P 2009	Chen HM 2009	Chen GF 2012	Cha XT 2016	
٠	•	•	•		٠	•	٠	•	•	•	•	٠	٠	•	•	٠	•	٠	•	٠	•	•	•	•	٠	•	Random sequence generation (selection bias)
٠	•	•	•	•	٠	٠	•	•	•	•	•	•	٠	•	•	•	•	•	٠	•	•	٠	•	•	•	•	Allocation concealment (selection bias)
~	~	~	•	~	••	~	~	~	~	~	•	••	~	•	~	~	•	•	~	~	~	~	?	~	~	~	Blinding of participants and personnel (performance bias)
~	•	~	~	~	••	~	••	•	~	<mark>∼</mark>	•	••	~	••	~	•	~	••	~	••	~	~	~	~	••	~	Blinding of outcome assessment (detection bias)
٠	•	•	•	•	٠	•	٠	÷	٠	٠	٠	٠	•	•	•	٠	٠	٠	•	٠	٠	•	٠	•	٠	•	Incomplete outcome data (attrition bias)
٠	•	~	~	•	٠	•	~	÷	٠	٠	~	•	•	•	•	~	٠	٠	•	••	~	~	•	~	•	•	Selective reporting (reporting bias)
•	•	<mark>~</mark> >	•	•	•	~	•	•	•	<mark>∼</mark> >	•	••	~	••	<mark>~</mark> >	••	•	•	•	•	•	<mark>∼</mark>	⊸	•	•	~	Other bias
B				R	anc	lon	nse	equ	ien	ce (ger	iera	atio	n (s	sele	ecti	ion	bia	ıs)								
							Allo	oca	tior	n co	onc	eal	me	nt (sel	ec	tior	i bia	as)								
BI	ind	ling) o	f pa	artic	cipa	ants	s a	nd j	per	sor	ne	l (p	erfo	orm	nan	ice	bia	s)								
			в	linc	ling	g of	ou	tcc	ome	as	se	ssn	nen	t (d	lete	ecti	on	bia	s)								
						1	nco	om	ple	te c	outo	om	ne c	lata	ı (a	ittri	tior	ı bi	as)							
									Sele																		
									Jere	JOU		cp	oru	ng	(10												
																	Oth	er	bia	S							
_																					0%	, D		25	5%		50% 75% 100%
		Lo	w	risl	< of	f bia	as							Ur	icle	ear	risl	k of	fbi	as						Hig	gh risk of bias

Figure 2 (A) Risk of bias summary: review of authors' judgments about each risk of bias item for included studies. (B) Risk of bias graph: review of authors' judgments about each risk of bias item presented as percentages across all included studies. Each color represents a different level of bias: red for high-risk, green for low-risk and yellow for unclear-risk of bias.

trials. All included trials did not provide clear description of performance and detection risks. The attrition risks of involved trials were low; 9 trials were considered as having unclear risk owing to selective reporting.

Therapeutic efficacy assessment

As shown in Figures 3 and 4, Figure S1 and Table 3, the pooled results showed that patients who underwent

combined therapy had significantly improved CR, PR, ORR and DCR (CR, OR =1.69, 95% CI =1.11–2.57, P=0.01; PR, OR =1.69, 95% CI =1.38–2.08, P<0.00001; ORR, OR =1.88, 95% CI =1.54–2.31, P<0.00001; DCR, OR =2.05, 95% CI =1.63–2.58, P<0.00001) and significantly decreased PD (OR =0.49, 95% CI =0.39–0.61, P<0.00001), whereas SD and 6- and 12-months OS rates had no significant



Figure 3 Forest plot of the comparison of 6-months (A) and 12-months (B) overall survival (OS) between the experimental and control group. Control group, chemotherapy alone group; Experimental group, chemotherapy and cinobufotalin combined group. The fixed-effects meta-analysis model (Mantel-Haenszel method) was used.

Α

	Experim	ental	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
Cha XT 2016	8	20	5	20	2.2%	2.00 [0.52, 7.72]	
Chen GF 2012	9	62	5	86	2.6%	2.75 [0.87, 8.66]	— <u> </u>
Chen HM 2009	25	34	19	33	3.7%	2.05 [0.73, 5.72]	
Cui P 2009	14	32	6	22	2.9%	2.07 [0.64, 6.68]	
Guo CJ 2011	29	43	26	43	6.2%	1.35 [0.56, 3.28]	
Guo XY 2013	27	42	20	38	5.5%	1.62 [0.66, 3.97]	
Huang Q 2014	18	26	11	20	2.8%	1.84 [0.55, 6.19]	
Li W 2016	48	76	34	74	9.2%	2.02 [1.05, 3.87]	
Li YX 2012	10	74	4	74	2.5%	2.73 [0.82, 9.15]	
Lu B 2016	7	30	5	30	2.8%	1.52 [0.42, 5.47]	
Lu CH 2014	23	31	18	31	3.4%	2.08 [0.71, 6.09]	
Tian B 2012	10	23	9	22	3.8%	1.11 [0.34, 3.63]	
Wang F 2014	17	58	3	58	1.5%	7.60 [2.09, 27.68]	· · · · ·
Wang WM 2010	7	20	7	23	3.1%	1.23 [0.34, 4.42]	
Wang YH 2009	25	36	17	32	4.0%	2.01 [0.74, 5.41]	
Wang ZF 2012	11	24	8	24	3.1%	1.69 [0.53, 5.44]	
Xiao XN 2018	9	34	7	31	3.9%	1.23 [0.40, 3.84]	
Xu DM 2015	13	30	11	30	4.5%	1.32 [0.47, 3.72]	
Xu YM 2016	17	30	11	30	3.5%	2.26 [0.80, 6.36]	
Yang B 2017	18	34	7	34	2.4%	4.34 [1.49, 12.65]	
Yang F 2018	15	25	8	25	2.3%	3.19 [1.00, 10.17]	
Zhang CW 2001	24	35	16	32	3.8%	2.18 [0.81, 5.90]	
Zhang RG 2004	17	43	16	43	7.0%	1.10 [0.46, 2.63]	.
Zhang Y 2005	12	28	11	29	4.5%	1.23 [0.43, 3.54]	
Zhu WK 2012	14	32	10	32	4.1%	1.71 [0.62, 4.76]	
Zou HP 2012	15	30	13	30	4.7%	1.31 [0.47, 3.61]	
Total (95% CI)		952		946	100.0%	1.88 [1.54, 2.31]	•
Total events	442		307				
Heterogeneity: Chi ² = 14	4.31, <i>df</i> =25	(P=0.96)	; /2=0%				
Test for overall effect:	Z = 6.13 (P<	0.00001)				0.01 0.1 1 10 100 Favors [Control] Favors [Experimental]
							Favors [Control] Favors [Experimental]

В

	Experime	ental	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
Cha XT 2016	13	20	8	20	2.7%	2.79 [0.77, 10.04]	
Chen GF 2012	23	62	18	86	9.2%	2.23 [1.07, 4.63]	
Chen HM 2009	29	34	27	33	3.9%	1.29 [0.35, 4.72]	
Cui P 2009	30	32	20	22	1.4%	1.50 [0.20, 11.54]	· · · · ·
Guo CJ 2011	39	43	37	43	3.3%	1.58 [0.41, 6.05]	
Guo XY 2013	39	42	33	38	2.4%	1.97 [0.44, 8.87]	
Huang Q 2014	23	26	18	20	2.3%	0.85 [0.13, 5.65]	
Li W 2016	62	76	58	74	10.5%	1.22 [0.55, 2.72]	
Li YX 2012	26	74	16	74	10.1%	1.96 [0.95, 4.08]	-
Lu B 2016	14	30	11	30	5.7%	1.51 [0.54, 4.24]	
Lu CH 2014	28	31	26	31	2.4%	1.79 [0.39, 8.27]	
Tian B 2012	18	23	15	22	3.2%	1.68 [0.44, 6.39]	
Wang F 2014	51	58	32	58	3.8%	5.92 [2.30, 15.22]	
Wang WM 2010	16	20	12	23	2.2%	3.67 [0.93, 14.39]	· · · · ·
Wang YH 2009	34	36	27	32	1.5%	3.15 [0.57, 17.51]	
Wang ZF 2012	19	24	17	24	3.4%	1.56 [0.42, 5.86]	
Xiao XN 2018	12	34	10	31	6.6%	1.15 [0.41, 3.21]	
Xu DM 2015	24	30	25	30	4.9%	0.80 [0.22, 2.97]	
Xu YM 2016	28	30	25	30	1.6%	2.80 [0.50, 15.73]	
Yang B 2017	29	34	20	34	2.9%	4.06 [1.26, 13.07]	
Yang F 2018	23	25	21	25	1.6%	2.19 [0.36, 13.22]	
Zhang CW 2001	32	35	21	32	1.8%	5.59 [1.39, 22.44]	
Zhang RG 2004	34	43	28	43	5.7%	2.02 [0.77, 5.32]	
Zhu WK 2012	25	32	19	32	4.0%	2.44 [0.82, 7.31]	
Zou HP 2012	27	30	26	30	2.5%	1.38 [0.28, 6.80]	
Total (95% CI)		924		917	100.0%	2.05 [1.63, 2.58]	•
Total events	698		570				
Heterogeneity: Chi2 = 1	6.80, <i>df</i> =24	(P=0.86)	; /2=0%				0.01 0.1 1 10 100
Test for overall effect:	Z=6.13 (P<	0.00001)				Favors [Control] Favors [Experimental]

Figure 4 Forest plot of the comparison of overall response rate (ORR, A) and disease control rate (DCR, B) between the experimental and control group. Control group, chemotherapy alone group; Experimental group, chemotherapy and cinobufotalin combined group. The fixed-effects meta-analysis model (Mantel-Haenszel method) was used.

differences in patients who received chemotherapy alone (SD, OR =0.94, 95% CI =0.76-1.15, P=0.53; 6months OS, OR =1.49, 95% CI =0.81-2.74, P=0.20; 12-months OS, OR =1.35, 95% CI =0.64-2.86, P=0.43). Fixed effect models were used to analyze OR rate because of low heterogeneity.

Table 3 Compari:	Table 3 Comparison of CR, PR, SD, PD, ORR and DCR between the experimental and control group	and DCR between the e	xperimental and control g	dnou				
Parameter	Experimental group	Control group	Analysis method	Heterogeneity	neity	Odds Ratio (OR)	95% CI	P-value
	No. patients (n)	No. patients (n)		l² (%)	P-value			
CR	924	617	Fixed	0	00.1	69.1	1.11 to 2.57	0.01
R	924	917	Fixed	0	0.95	1.69	1.38 to 2.08	<0.00001
SD	924	917	Fixed	0	0.62	0.94	0.76 to 1.15	0.53
Ð	924	917	Fixed	0	0.86	0.49	0.39 to 0.61	<0.00001
ORR	952	946	Fixed	0	0.96	1.88	I.54 to 2.31	<0.00001
DCR	924	917	Fixed	0	0.86	2.05	l.63 to 2.58	<0.00001
Notes: Control group,	Notes: Control group, chemotherapy alone group; Experimental group, chemotherapy and cinobufotalin combined group.	ntal group, chemotherapy and c	inobufotalin combined group.					

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate

Quality of life assessment

QoL was evaluated in this analysis. Result showed that QoL of patients in the combined group was significantly better than that of the control group, indicated by increased QIR, KPS and PRR (Figure 5, QIR, OR =2.39, 95% CI =1.81–3.15, *P*<0.00001; KPS, OR =7.00, 95% CI =2.25–11.75, *P*=0.004; PRR, OR =4.06, 95% CI =2.24–7.35, *P*<0.00001).

Adverse event assessment

As shown in Table 4 and Figure S2, patients treated with cinobufotalin and chemotherapy combined therapy showed lower incidences of nausea and vomiting, diarrhea, leucopenia, hand-foot syndrome, anemia, gastrointestinal side effects and peripheral neurotoxicity (nausea and vomiting, OR =0.55, 95% CI =0.41-0.74, P<0.0001; diarrhea, OR =0.65, 95% CI =0.46-0.90, P=0.010; leucopenia, OR =0.62, 95% CI =0.47-0.82, P=0.0008; hand-foot syndrome, OR =0.57, 95% CI =0.41-0.79, P=0.0007; anemia, OR =0.69, 95% CI =0.48-0.99, P=0.05; gastrointestinal side effects, OR =0.56, 95% CI =0.32-1.00, P=0.05; peripheral neurotoxicity, OR =0.32, 95% CI =0.20-0.50, P<0.00001), whereas analysis on thrombocytopenia, hepatotoxicity, nephrotoxicity, oral mucositis, alopecia, neutropenia and myelosuppression (thrombocytopenia, OR =0.69, 95% CI =0.44-1.11, P=0.13; hepatotoxicity, OR =0.53, 95% CI =0.24–1.16, P=0.11; nephrotoxicity, OR =0.56, 95% CI =0.16-1.95, P=0.36; oral mucositis, OR =0.62, 95% CI =0.28-1.34, P=0.22; alopecia, OR =0.61, 95% CI =0.24-1.56, P=0.30; neutropenia, OR =0.45, 95% CI =0.14 -1.42, P=0.17; myelosuppression, OR =0.38, 95% CI =0.08-1.84, P=0.23) did not differ significantly between the two groups.

Publication bias

Funnel plots drawn for the studies on primary outcomes (CR, PR, SD, PD, ORR, DCR and adverse events) were approximately symmetrical, which indicated generally controlled publication bias and reliability of our primary conclusions (Figure 6 and S3).

We also assessed publication bias using Begg's and Egger's regression asymmetry tests (Table 5), and PR and leucopenia were found with bias (PR, Begg, 0.038; Egger, 0.015; leucopenia, Begg, 0.003; Egger, <0.0001). To determine if the bias affects the pooled risk, we conducted a trim and fill analysis. The adjusted OR rate indicated the same trend with the result of the primary analysis (PR [before, P<0.0001; after, P<0.0001], leukopenia [before, P=0.0002; after. P=0.0002]), reflecting the

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	Experim	ental	Cont	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Chen GF 2012	32	62	31	86	19.1%	1.89 [0.97, 3.68]	
Cui P 2009	14	32	6	22	6.1%	2.07 [0.64, 6.68]	
Guo CJ 2011	10	43	4	43	4.7%	2.95 [0.85, 10.30]	
Huang Q 2014	12	26	9	20	8.3%	1.05 [0.32, 3.38]	
Li YX 2012	36	76	27	74	21.9%	1.57 [0.82, 3.01]	+
Lu B 2016	16	30	10	30	7.1%	2.29 [0.80, 6.50]	
Wang F 2014	28	58	11	58	8.6%	3.99 [1.73, 9.19]	
Wang ZF 2012	17	24	10	24	4.4%	3.40 [1.03, 11.26]	
Xiao XN 2018	12	34	3	31	3.1%	5.09 [1.28, 20.29]	
Xu DM 2015	11	30	7	30	6.7%	1.90 [0.62, 5.86]	
Yang F 2018	16	25	12		6.6%	1.93 [0.62, 5.98]	
Zhu WK 2012	23	32	8	32	3.4%	7.67 [2.52, 23.28]	
Total (95% CI)		472		475	100.0%	2.39 [1.81, 3.15]	•
Total events	227		138				
Heterogeneity: Chi2 = 1	1.61, <i>df</i> =11	(P=0.39);	I ² =5%				
Test for overall effect:	Z= 6.1 (P<	0.00001)					0.01 0.1 1 10 100
		,					Favors [Control] Favors [Experimental]
В							
	Experime	ental	Co	ntrol		Mean Difference	Mean Difference
Study or Subgroup	Mean SI	D Total	Mean	SD To	tal Weigh	t IV, Random, 95%	CI IV, Random, 95% CI
Guo XY 2013	80.4 6.1	7 42	77.5	6.2	38 37.49	6 2.90 [0.07, 5.73	
	78.23 6.9		70.45		30 35.39		
Yang F 2018	76.55 8.4	5 20	64.93	9.37	20 27.29	6.09, 17.15	5]
Total (95% CI)		92			88 100.09	% 7.00 [2.25, 11.75	a 🔶
Heterogeneity: Tau ² = 13			(P=0.008	3); <i>1</i> ²=79%	6		-100 -50 0 50 100
Test for overall effect: Z	= 2.89 (<i>P</i> =0	.004)					Favors [Control] Favors [Experimental]
							[[. +
-							
С							
	Experim		Cont			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total			Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Guo CJ 2011	34	43	14		26.9%	7.83 [2.96, 20.70]	
Xiao XN 2018	24	34	14		39.6%	2.91 [1.05, 8.10]	
Yang F 2018	18	25	13	25	33.5%	2.37 [0.73, 7.68]	
Total (95% CI)		102		99	100.0%	4.06 [2.24, 7.35]	•

Figure 5 Forest plot of the comparison of quality of life improved rate (QIR, A), karnofsky performance score (KPS, B) and pain relief rate (PRR, C) between the experimental and control group. Control group, chemotherapy alone group; Experimental group, chemotherapy and cinobufotalin combined group. The fixed-effects meta-analysis model (Mantel-Haenszel method) was used.

0.01

0.1

Favors [Control]

reliability of our primary conclusions, except those based on a few number of trials.

76

Heterogeneity: Chi² = 2.95, df =2 (P=0.23); l²=32%

Test for overall effect: Z = 4.62 (P<0.00001)

41

Total events

Sensitivity analysis

We performed subgroup analysis to explore the source of heterogeneity in ORR and DCR with respect to therapeutic regimens, drug forms of cinobufotalin, sample sizes and research types. As shown in Table 6, our analysis results showed that no significant difference was found between different forms of cinobufotalin, sample sizes and research types. Moreover, cinobufotalin combined with FOLFOX/ XELOX/capecitabine chemotherapy regimens was found to be more effective for GC treatment.

Discussion

In view of the limitations of the current chemotherapy for malignancies such as drug resistance and toxic side effects, clinicians have been exploring complementary and alternative medicine treatments to improve patients' survival time or QoL and reduce side effects caused by chemotherapy.^{6,10,46,47} Traditional Chinese medicine, particularly cinobufotalin, has been clinically applied as an adjuvant therapy for decades.^{7,10,11} Several studies have been reported that the addition of cinobufotalin could be beneficial to advanced GC patients.^{16–42} Even though there was a statistical analysis of published clinical trials, the exact therapeutic effects were still not systematically evaluated because of small sample sizes and different applied protocols in different studies. Therefore, in this analysis, we conducted a wide range of online search according to strict inclusion and exclusion criteria to provide clear and systematical conclusion.

10

Favors [Experimental]

100

Our meta-analysis revealed that cinobufotalin and chemotherapy combined therapy for GC patients achieved

No. of patients (r) No. of patients (r) No. of patients (r) Periode						•			
45 47 Freed 37 0.09 0.55 0.41 0.71 222 279 Freed 4 0.41 0.43 0.55	-	No. of patients (n)	No. of patients (n)		l² (%)	P-value			
22 279 Fixed 0 0.50 0.83 0.55 0.11 235 237 Fixed 0 0.61 0.41 0.23 0.45 0.77 235 221 Fixed 0 0.65 0.65 0.46 0.23 0.47 0.25 0.47 0.25 0.47 0.25 0.47 0.25 0.47 0.25 0.47 0.25 0.47 0.25 0.47 0.25 0.47 0.25 0.47 0.25 0.44 0.11 0.23 0.44 0.11 0.23 0.44 0.11 0.25 0.44 0.11 0.23 0.44 0.11 0.25 0.44 0.11 0.23 0.44 0.11 0.23 0.44 0.11 0.23 0.44 0.11 0.23 0.44 0.11 0.23 0.14 0.23 0.14 0.23 0.14 0.23 0.14 0.23 0.14 0.23 0.24 0.14 0.23 0.23 0.23 0.23		452	437	Fixed	37	0.09	0.55	t 2	<0.0001
22 279 Fixed 4 0.41 0.41 0.41 0.41 0.42 0.23 0.23 0.23 0.23 0.23 0.23 0.23 0.23 0.23 0.24 0.11 0.24 0.24 0.11 0.24 0.11 0.24 0.11 0.24 0.11 0.24 0.11 0.24 0.11 0.24 0.11 0.24 0.11 0.24 0.11 0.24 0.11 0.24 0.11 0.24 0.11 0.24 0.11 0.24 0.11 0.24 0.11 0.24 0.11 0.24 0.11		292	279	Fixed	0	0.50	0.83	0.59 to 1.16	0.27
355 379 Freed 0 0.88 0.65 0.64 co.97 235 221 Freed 0 0.09 0.27 0.04 co.97 236 238 Freed 0 0.09 0.27 0.04 co.073 230 238 Freed 0 0.05 0.77 0.06 0.77 0.06 co.77 230 Freed 0 0.05 0.07 0.05 0.47 co.075 240 178 Freed 0 0.07 0.05 0.47 co.075 178 Freed 0 0.07 0.05 0.47 co.075 178 Freed 0 0.07 0.06 0.47 co.075 178 Freed 0 0.07 0.04 0.70 177 107 Freed 0 0.77 0.26 0.47 co.075 117 107 Freed 0 0.77 0.26 0.17 co.017 173 Freed 0 0.77 0.26 0.74 co		292	279	Fixed	4	0.41	0.41	0.23 to 0.75	0.003
		395	379	Fixed	0	0.88	0.65	0.46 to 0.90	0.010
235 221 Freed 0 100 027 010 007 001 007 007 007 001 007 <td></td> <td>235</td> <td>221</td> <td>Fixed</td> <td>0</td> <td>0.69</td> <td>0.84</td> <td>0.56 to 1.27</td> <td>0.41</td>		235	221	Fixed	0	0.69	0.84	0.56 to 1.27	0.41
420 429 Freed 34 0.13 0.62 0.47 to 0.83 250 238 Freed 0 086 0.57 0.37 to 0.83 78 178 Freed 0 084 0.70 0.47 to 0.83 178 Freed 0 084 0.70 0.37 to 0.83 0.41 to 1.11 178 Freed 0 0.84 0.70 0.84 0.70 0.41 to 1.16 178 Freed 0 0.84 0.70 0.84 0.70 0.41 to 1.16 178 Freed 0 0.84 0.70 0.84 0.70 0.41 to 1.16 179 Freed 0 0.77 0.55 0.04 0.75 0.41 to 1.16 171 107 Freed 0 0.77 0.56 0.16 to 1.95 179 Freed 0 0.77 0.56 0.14 to 1.16 0.16 to 1.95 179 Freed 0 0.77 0.56 0.16 to 1.95 0.16 to		235	221	Fixed	0	1.00	0.27	0.10 to 0.75	0.01
20 238 Fixed 0 0.06 0.57 0.39 0.037 778 178 178 Fixed 0 0.77 0.36 0.17 0.39 0.017 778 178 Fixed 0 0.77 0.36 0.17 0.39 0.17 178 Fixed 0 0.81 0.69 0.41 0.17 0.39 0.11 178 Fixed 0 0.81 0.69 0.41 0.17 0.39 0.11 193 Fixed 0 0.83 0.91 0.39 0.24 0.16 0.36 117 107 Fixed 0 0.77 0.35 0.01 0.36 0.16 0.75 117 107 Fixed 0 0 0.77 0.36 0.016 0.36 0.16 0.75 117 107 Fixed 0 0 0.77 0.36 0.16 0.26 0.16 0.24 0.16		420	429	Fixed	34	0.13	0.62	0.47 to 0.82	0.0008
		250	238	Fixed	0	0.86	0.57	0.39 to 0.83	0.003
		250	238	Fixed	0	0.77	0.36	0.17 to 0.75	0.007
		178	178	Fixed	0	0.81	0.69	0.44 to 1.11	0.13
		178	178	Fixed	0	0.84	0.70	0.43 to 1.13	0.14
		178	178	Fixed	0	0.83	0.91	0.39 to 2.14	0.83
		193	193	Random	56	0.04	0.53	0.24 to 1.16	0.11
		193	193	Fixed	26	0.24	0.61	0.38 to 0.97	0.04
		193	193	Fixed	0	0.70	0.14	0.02 to 0.81	0.03
		117	107	Fixed	0	0.77	0.56	0.16 to 1.95	0.36
		117	107	Fixed	0	0.54	0.63	0.16 to 2.46	0.51
		117	107	Fixed			0.32	0.01 to 8.24	0.49
		235	233	Random	64	0.010	0.62	0.28 to 1.34	0.22
		179	178	Fixed	44	0.13	1.08	0.68 to 1.72	0.74
		179	178	Fixed	0	0.58	0.54	0.15 to 1.96	0.35
133 130 Fixed 0 0,93 0,93 0,48 to 181 133 130 Fixed 0 0,97 0.72 0.30 to 175 334 356 Fixed 0 0,97 0.57 0.41 to 0.79 334 356 Fixed 0 0,52 0.57 0.57 0.41 to 0.79 92 92 92 7 0.32 0.64 0.33 to 1.24 92 92 7 0.32 0.64 0.33 to 1.24 92 92 7 0.32 0.64 0.33 to 1.24 92 291 Fixed 0 0.91 0.69 0.33 to 1.24 186 187 Fixed 0 0.61 0.79 0.04 to 5.63 186 187 Fixed 0 0.65 0.32 to 1.00 0.12 to 0.96 186 187 71 72 72 0.71 0.32 to 1.00 17 71 72 72 0.74 0.71 </td <td></td> <td>133</td> <td>130</td> <td>Fixed</td> <td>0</td> <td>0.58</td> <td>0.61</td> <td>0.24 to 1.56</td> <td>0.30</td>		133	130	Fixed	0	0.58	0.61	0.24 to 1.56	0.30
133 130 Fixed 0 0.97 0.72 0.30 to 1.75 334 356 Fixed 0 0.52 0.57 0.41 to 0.79 92 356 Fixed 0 0.52 0.57 0.41 to 0.79 92 92 92 Fixed 12 0.32 0.64 0.33 to 1.24 92 92 92 Fixed 12 0.32 0.64 0.33 to 1.24 92 92 92 60 0.91 0.64 0.33 to 1.24 186 187 Fixed 0 0.91 0.69 0.48 to 0.99 186 187 Fixed 0 0.65 0.24 0.14 to 0.76 186 187 Fixed 0 0.65 0.79 0.78 to 0.96 186 187 Fixed 0 0.65 0.24 0.12 to 0.96 71 72 72 187 0.71 0.35 to 1.42 0.35 to 1.42 7 72 <td< td=""><td></td><td>133</td><td>130</td><td>Fixed</td><td>0</td><td>0.93</td><td>0.93</td><td>0.48 to 1.81</td><td>0.83</td></td<>		133	130	Fixed	0	0.93	0.93	0.48 to 1.81	0.83
334 356 Fixed 0 0.57 0.41 to 0.79 92 92 Fixed 12 0.32 0.57 0.41 to 0.79 92 92 Fixed 12 0.32 0.64 0.33 to 1.24 92 92 Fixed 12 0.32 0.64 0.33 to 1.24 92 92 Fixed 0 0.91 0.69 0.48 to 0.99 186 187 Fixed 0 0.91 0.69 0.48 to 0.99 186 187 Fixed 0 0.91 0.69 0.48 to 0.99 186 187 Fixed 0 0.65 0.32 0.12 to 0.96 186 187 Fixed 0 0.65 0.32 to 1.00 0.12 to 0.96 186 187 Fixed 0 0.67 0.32 to 1.00 0.12 to 0.96 17 71 72 Fixed 0 0.71 0.32 to 1.00 17 72 Fixed 0 0.79		133	130	Fixed	0	0.97	0.72	0.30 to 1.75	0.47
92 92 92 64 0.33 to 1.24 92 92 Fixed 12 0.32 0.64 0.33 to 1.24 92 92 Fixed 0 0 0 0 0 0 0 292 291 Fixed 0 0.91 0.69 0.04 to 5.63 0		334	356	Fixed	0	0.52	0.57	0.41 to 0.79	0.0007
92 92 92 Fixed 0.48 0.04 to 5.63 0.04 to 5.63 292 291 Fixed 0 0.91 0.69 0.48 to 0.99 186 187 Fixed 0 0.91 0.69 0.48 to 0.99 186 187 Fixed 0 0.65 0.92 0.48 to 0.99 186 187 Fixed 0 0.65 0.92 0.60 to 1.42 186 187 Fixed 0 0.65 0.34 0.12 to 0.96 7 295 Random 57 0.04 0.56 0.32 to 1.00 7 71 72 Fixed 0 0.75 0.71 0.35 to 1.42 1 72 Fixed 0 0.75 0.71 0.35 to 1.60 265 263 15 0 0.59 0.20 to 0.50		32	92	Fixed	12	0.32	0.64	0.33 to 1.24	0.18
292 291 Fixed 0 0.91 0.69 0.48 to 0.99 0 186 187 Fixed 0 0.65 0.92 0.60 to 1.42 186 187 Fixed 0 0.65 0.92 0.60 to 1.42 186 187 Fixed 0 0.65 0.34 0.12 to 0.96 1 277 295 Random 57 0.04 0.56 0.32 to 1.00 7 71 72 Fixed 0 0.75 0.71 0.35 to 1.42 1 71 72 Fixed 0 0.75 0.71 0.09 to 1.60 265 263 Fixed 0 0.59 0.32 0.00 to 1.60		22	92	Fixed			0.48	0.04 to 5.63	0.56
I86 I87 Fixed 0 0.65 0.92 0.60 to 142 I86 I87 Fixed 0 0.87 0.34 0.12 to 0.96 i 277 295 Random 57 0.04 0.56 0.32 to 1.00 i 71 72 Fixed 0 0.75 0.71 0.35 to 1.42 iv 71 72 Fixed 0 0.75 0.71 0.35 to 1.40 iv 71 72 Fixed 0 0.75 0.71 0.35 to 1.42 iv 71 72 Fixed 0 0.75 0.71 0.35 to 1.42 V 71 72 Fixed 0 0.75 0.71 0.70 to 0.50 265 263 Fixed 0 0.59 0.32 0.20 to 0.50		292	291	Fixed	0	0.91	0.69	0.48 to 0.99	0.05
I86 I87 Fixed 0 0.87 0.34 0.12 to 0.96 0.96 i 277 295 Random 57 0.04 0.56 0.32 to 1.00 i 71 72 Fixed 0 0.75 0.71 0.35 to 1.42 i 71 72 Fixed 0 0.75 0.71 0.35 to 1.42 i 71 72 Fixed 0 0.75 0.71 0.35 to 1.42 i 71 72 Fixed 0 0.75 0.71 0.09 to 1.60 265 263 Fixed 0 0.59 0.32 0.20 to 0.50		186	187	Fixed	0	0.65	0.92	0.60 to 1.42	0.71
s 277 295 Random 57 0.04 0.56 0.32 to 1.00 7 71 72 Fixed 0 0.75 0.71 0.35 to 1.42 IV 71 72 Fixed 0 0.75 0.71 0.35 to 1.42 IV 71 72 Fixed 0 0.75 0.71 0.09 to 1.60 265 263 Fixed 0 0.59 0.32 0.20 to 0.50		86	187	Fixed	0	0.87	0.34	0.12 to 0.96	0.04
71 72 Fixed 0 0.75 0.71 0.35 to 1.42 IV 71 72 Fixed 0 0.59 0.09 to 1.60 265 263 263 6.59 0.32 0.20 to 0.50		277	295	Random	57	0.04	0.56	0.32 to 1.00	0.05
71 72 Fixed 0.39 0.09 to 1.60 265 263 Fixed 0 0.59 0.32 0.20 to 0.50		71	72	Fixed	0	0.75	0.71	0.35 to 1.42	0.33
265 263 Fixed 0 0.59 0.32 0.20 to 0.50		71	72	Fixed			0.39	0.09 to 1.60	0.19
		265	263	Fixed	0	0.59	0.32	5	<0.00001

Table 4 Comparison of adverse events between the experimental and control group

No. of patients (n)No.Peripheral neurotoxicity I+II103Peripheral neurotoxicity III+IV103Neutropenia55S555	No. of patients (n) 104 104	Fixed	(%)	P-value			
103 103 55 55		Fixed					
103 55 55			29	0.24	0.52	0.26 to 1.03	0.06
55 55		Fixed	0	0.53	0.58	0.21 to 1.63	0.30
55		Fixed	0	0.98	0.45	0.14 to 1.42	0.17
_		Fixed	0	0.35	0.93	0.44 to 1.96	0.85
Neutropenia III+IV 55 55		Fixed	0	0.40	0.73	0.34 to 1.59	0.43
Myelosuppression 94 90		Random	80	0.03	0.38	0.08 to 1.84	0.23
Myelosuppression I+II 58 58		Fixed			1.09	0.48 to 2.49	0.83
Myelosuppression III+IV 58 58		Fixed			0.24	0.03 to 2.19	0.20

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more beneficial effects in comparison with those treated with chemotherapy alone. Combined therapy-treated patients broadly exhibited increased ORR and DCR (P<0.05) and also significantly improved their QoL. These results indicated that using cinobufotalin could improve the curative effects of chemotherapy.

Safety is the top priority of the clinical treatment. One trial⁷ that was conducted at Fudan University Cancer Hospital showed that cinobufotalin is well tolerated by hepatocellular carcinoma, non-small-cell lung cancer and pancreatic cancer patients (only mild adverse events were observed in cancer patients who received cinobufotalin therapy; no grade III and IV toxicities were observed). Our analysis showed that most of the adverse events caused by chemotherapy, including nausea and vomiting, diarrhea, leucopenia, hand-foot syndrome, anemia, gastrointestinal side effects and peripheral neurotoxicity, were alleviated with cinobufotalin is a safe auxiliary antitumor medicine for GC and can effectively alleviate the adverse events associated with chemotherapy.

The analysis on therapeutic effects may be influenced by several factors. In our study, no difference was found between different drug forms of cinobufotalin, sample sizes and research types. Cinobufotalin combined with FOLFOX/ XELOX/capecitabine chemotherapy regimens was more effective for GC treatment (Table 6). However, a comparative analysis of the above-mentioned individual chemotherapy regimens should be performed in the future to rule out the possibility that the therapeutic advantage of cinobufotalin combined with FOLFOX, XELOX or capecitabine is due to the better therapeutic effect of them alone compared to that of EOF. As a summary, recent studies on the impact of these factors on the curative effects of cinobufotalin adjuvant therapy remain insufficient, and hence, further investigations should be performed.

There are some limitations in our analysis. First, although traditional Chinese medicine has been exported to 185 countries and regions, its main markets still remained in Asia.⁴⁸ As a traditional medicine, cinobufotalin was mainly applied in China, which may bring the unavoidable regional bias and subsequently influence the clinical application of cinobufotalin worldwide. Second, according to the Cochrane Handbook for systematic reviews of interventions, the most appropriate way of summarizing survival outcomes is to use methods of survival analysis and express the intervention effect as a hazard ratio (HR) because this method takes into

Fable 4 (Continued)



Figure 6 Funnel plot of overall response rate (ORR, A), disease control rate (DCR, B), quality of life improved rate (QIR, C), Nausea and vomiting (D), Diarrhea (E), Leukopenia (F), Anemia (G) and neurotoxicity (H).

Table 5 Publication bias on therapeutic efficacy indexes (CR, PR, SD, PD, ORR, DCR and QIR) and adverse events indexes (Nausea and vomiting, Diarrhea, Leucopenia, Anemia and Neurotoxicity)

Publication	Thera	peutic e	fficacy					Adverse event	ts			
Bias	CR	PR	SD	PD	ORR	DCR	QIR	Nausea and vomiting	Diarrhea	Leucopenia	Anemia	Neurotoxicity
Begg Egger	0.742 0.833	0.038 0.015	0.513 0.721	0.870 0.905	0.280 0.331	0.870 0.905	0.304 0.235	0.161 0.069	0.755 0.623	0.003 <0.0001	0.454 0.528	1.000 0.894

Note: Parameters discussed in over 8 papers were conducted bias analyses.

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate; QIR, quality of life improved rate.

consideration the time factor and censored participants. However, the included articles that reported the OS rate only provided the survival number and the total number of patients at 6 months and 12 months, and none of them provided HR with 95% CI and Kaplan-Meier survival curves. Therefore, there were insufficient data to perform a statistical analysis using HR, which almost certainly will introduce bias. Third, treatment/medical history is very important in evaluating the efficacy of cinobufotalinmediated therapy. However, our data were partly extracted from published papers rather than from the original patient records; therefore, analytical bias would possibly exist. Moreover, the therapeutic effects of the combined therapy may be influenced by numerous variables such as dosage of cinobufotalin, tumor stage and patient's age. However, based on currently available literature, there are insufficient data to perform more statistical analysis to evaluate the correlation. We will keep following up with upcoming clinical trials to obtain relevant data when available. Finally, the follow-up durations of the included studies were short, and the long-term efficacy of cinobufotalin for advanced GC remains to be further evaluated.

Conclusion

In summary, this meta-analysis indicated that cinobufotalin and chemotherapy combined therapy was effective in treating advanced GC. Clinical application of cinobufotalin not only evidently improved the therapeutic effects of chemotherapy but also effectively alleviated most of the side effects caused by chemotherapy. However, the longterm efficacy of cinobufotalin-mediated adjuvant therapy for advanced GC still needs methodologically rigorous trials to verify its efficacy.

Acknowledgments

The risk bias assessment in this study was helped and guided by Dr. Ma J (Statistician, Department of Science and Education, Liaocheng People's Hospital). No funding was received for conducting out this study.

	rarameter ractors at study	Experimental group No. of	Control group No. of	Analysis	Heter	Heterogeneity	Odds Ratio	95%	P-value
	level	patients (n)	patients (n)	method	1 ² (%)	P. value	(OR)	Ū	
ORR	Therapeutic regimen	- ue							
	Cinobufotalin +FOI FOX	215	200	Fixed	0	66.0	I.84	1.23 to 2.76	0.003
	Cinobufotalin + XELOX	92	86	Fixed	0	0.41	2.43	1.30 to	0.005
	Cinobufotalin+EOF	55	55	Fixed	22	0.26	1.93	0.91 to	0.09
	Cinobufotalin + Capecitabine	272	294	Fixed	0	0.85	1.98	1.29 to 3.04	0.002
	Drug form of cinobufotalin	ufotalin							
	Cinobufotalin	186	185	Fixed	6	0.36	2.47	1.54 to 3 98	0.0002
	cinobufotalin injection	724	723	Fixed	0	0.98	1.78	2.25	<0.00001
	Study sample size								
	>60	634	641	Fixed	0	0.67	2.05	1.58 to 7 45	<0.00001
	≤60	318	305	Fixed	0	0.99	l.64	2.28 2.28	0.003
	Type of control trials	sli							
	RCT	833	829	Fixed	0	0.96	1.93	1.55 to	<0.0000
	Overall	952	946	Fixed	0	0.96	I.88	2.31 2.31	<0.00001
DCR	Therapeutic regimen	ua							

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Parameter	Factors at study	Experimental group No. of	Control group No. of	Analysis	Hetero	Heterogeneity	Odds Ratio	95%	P-value
	level	patients (n)	patients (n)	method	1 ²	P.	(OR)	Ū	
					(%)	value			
	Cinobufotalin	215	200	Fixed	0	0.97	2.26	1.26 to	0.006
	+FOLFOX							4.04	
	Cinobufotalin	92	86	Fixed	0	0.39	2.55	I.24 to	0.01
	+XELOX							5.23	
	Cinobufotalin+EOF	55	55	Fixed	0	0.71	1.70	0.52 to E E 7	0.38
				Ĩ	c		<u>,</u>	/0.0	
	-Cinopurotalin +Capecitabine	7/7	734	rixed	D	0.03	co. I	1.11 to 2.38	10:0
	Drug form of cinobufotalin	ufotalin							
	Cinobufotalin	186	185	Fixed	0	0.49	2.78	I.69 to	<0.0001
	capsule							4.58	
	Cinobufotalin	696	694	Fixed	0	0.87	I.88	I.45 to	<0.0000.0>
	injection							2.45	
	Study sample size								
	>60	634	641	Fixed	0	0.53	2.21	I.68 to	<0.0000
								2.90	
	≤60	290	276	Fixed	0	0.94	1.73	I.I3 to	0.01
								2.64	
	Type of control trials	sli							
	RCT	805	800	Fixed	0	0.86	2.16	l.69 to	<0.00001
								2.77	
	Overall	924	617	Fixed	0	0.86	2.05	l.63 to	<0.00001
								2.58	
Notes: Control gr	oup, chemotherapy alone gr	Notes: Control group, chemotherapy alone group; Experimental group, chemotherapy and cinobufotalin combined group.	nobufotalin combined group.						
Abbreviations: ORR, ove	DRR, overall response rate	; DCR, disease control rate; FOLFOX, Oxali	FOLFOX, Oxaliplatin+Calcium folinate+5-Fluorouracil; XELOX, oxaliplatin+capecitabine; EOF, epirubicin+oxaliplatin+calcium folate+fluorouracil; RCT,	XELOX, oxaliplatin+	apecitabine;	EOF, epirub	icin+oxaliplatin+calciu	m folate+fluo	rouracil; RCT,
נקוומסווווזפם כסות כ									

Table 6 (Continued).

Author contributions

All authors contributed to study design, data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials



Figure SI Forest plot of the comparison of complete response rates (CR, A), partial response rates (PR, B), stable disease rates (SD, C) and progressive disease rates (PD, D) between the experimental and control group. Control group, chemotherapy alone group; Experimental group, chemotherapy and cinobufotalin combined group. The fixed-effects meta-analysis model (Mantel–Haenszel method) was used.

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	Experimental Control		Odds Ratio		Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Cha XT 2016	7	20	16	20	8.3%	0.13 [0.03, 0.56]	
Cui P 2009	9	32	15	22	10.3%	0.18 [0.06, 0.60]	
Li W 2016	6	76	20	74	15.0%	0.23 [0.09, 0.62]	_
Lu B 2016	12	30	10	30	4.8%	1.33 [0.46, 3.82]	
Wang F 2014	39	58	40	58	10.5%	0.92 [0.42, 2.02]	_ _
Wang WM 2010	7	20	8	23	3.9%	1.01 [0.29, 3.55]	
Xiao XN 2018	12	34	12	31	6.5%	0.86 [0.32, 2.37]	
Xu DM 2015	3	30	10	30	7.2%	0.22 [0.05, 0.91]	
Xu YM 2016	10	30	13	30	7.0%	0.65 [0.23, 1.86]	
Yang F 2018	17	25	21	25	5.4%	0.40 [0.10, 1.58]	
Zhang CW 2001	12	35	12	32	6.6%	0.87 [0.32, 2.36]	
Zhu WK 2012	14	32	19	32	8.6%	0.53 [0.20, 1.44]	
Zou HP 2012	20	30	22	30	5.9%	0.73 [0.24, 2.21]	
Total (95% CI)		452		437	100.0%	0.55 [0.41, 0.74]	•
Total events	168		218				
Heterogeneity: Chi ² =		12 (P =		37%			
Test for overall effect:	,		,,	51.75			0.01 0.1 1 10 100
			,				Favors [Control] Favors [Experimental]
В	Experim	ental	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Cui P 2009	8	32	10	22	10.2%	0.40 [0.13, 1.28]	
Li W 2016	10	76	16	74	16.2%	0.55 [0.23, 1.30]	
Tian B 2012	4	23	11	22	10.7%	0.21 [0.05, 0.82]	
Wang F 2014	32	58	35	58	18.0%	0.81 [0.39, 1.69]	_ _
Wang WM 2010	3	20	4	23	3.6%	0.84 [0.16, 4.29]	
Xiao XN 2018	27	34	26	31	6.4%	0.74 [0.21, 2.64]	
Xu DM 2015	5	30	8	30	7.7%	0.55 [0.16, 1.93]	
Yang F 2018	11	25	14	25	9.0%	0.62 [0.20, 1.89]	
Zhang CW 2001	10	35	9	32	7.7%	1.02 [0.35, 2.96]	
Zhu WK 2012	6	32	7	32	6.5%	0.82 [0.24, 2.79]	
Zou HP 2012	4	30	4	30	4.0%	1.00 [0.23, 4.43]	
Total (95% CI)		395		379	100.0%	0.65 [0.46, 0.90]	•
Total events	120		144				
Heterogeneity: Chi ² =	5.15, <i>df</i> = 1	0 (P = 0	.88); /2 =	0%			
Test for overall effect:	Z = 2.58 (F	e 0.010)				0.01 0.1 1 10 100 Favors [Control] Favors [Experimental]
С							
	Experime		Contr			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events		-	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Cha XT 2016	6	20	13	20	7.3%	0.23 [0.06, 0.87]	
Chen GF 2012	32	62	41	86	13.3%	1.17 [0.61, 2.25]	
Cui P 2009	8	32	12	22	8.5%	0.28 [0.09, 0.89]	
Li YX 2012	34	74	35	74	15.1%	0.95 [0.50, 1.81]	
Lu B 2016	18	30	18	30	5.8%	1.00 [0.36, 2.81]	
Xiao XN 2018	16	34	17	31	7.5%	0.73 [0.28, 1.94]	
Xu YM 2016	21	30	28	30	6.7%	0.17 [0.03, 0.85]	
Zhang CW 2001	13	35	18	32	9.5%	0.46 [0.17, 1.22]	
Zhang RG 2004	25	43	31	43	10.4%	0.54 [0.22, 1.32]	
Zhang Y 2005	3	28	9	29	6.3%	0.27 [0.06, 1.12]	
Zhu WK 2012	13	32	20	32	9.5%	0.41 [0.15, 1.12]	

Total (95% CI)
420
429
100.0%
0.62 [0.47, 0.82]

Total events
189
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0.01 0.1 1 10 100 Favors [Control] Favors [Experimental]

Figure S2 Forest plot of the comparison of adverse effects including nausea and vomiting (\mathbf{A}) , diarrhea (\mathbf{B}) , leukopenia (\mathbf{C}) , thrombocytopenia (\mathbf{D}) , hepatotoxicity (\mathbf{E}) , nephrotoxicity (\mathbf{F}) , oral mucositis (\mathbf{G}) , alopecia (\mathbf{H}) , hand-foot syndrome (\mathbf{I}) , anemia (\mathbf{J}) , gastrointestinal adverse effects (\mathbf{K}) , peripheral neurotoxicity (\mathbf{L}) , neutropenia (\mathbf{M}) and myelosuppression (\mathbf{N}) between the experimental and control group. Control group, chemotherapy alone group; Experimental group, chemotherapy and cinobufotalin combined group.

П										
U	Experim	ental	Contr	ol		Odds Ratio	Odds Ratio			
Study or Subgroup	Events	Total	Events		Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI			
Cha XT 2016	6	20	10	20	16.4%	0.43 [0.12, 1.57]				
Lu B 2016	12	30	18	30		0.44 [0.16, 1.25]				
Xu YM 2016	7	30	8	30		0.84 [0.26, 2.70]				
Yang F 2018	15	25	15	25		1.00 [0.32, 3.10]				
Zhang RG 2004	4	43	6	43		0.63 [0.17, 2.42]				
Zou HP 2012	12	30	12	30		1.00 [0.36, 2.81]	_			
Total (95% CI)		178		178	100.0%	0.69 [0.44, 1.11]				
Total events	56		69							
Heterogeneity: Chi ² =		•		%			0.01 0.1 1 10 100			
Test for overall effect:	Z = 1.53 (F	P = 0.13)					Favors [Control] Favors [Experimental			
_										
E	Experime	antal	Contro	si.		Odds Ratio	Odds Ratio			
Study or Subgroup	Events	Total	Events		Weight	M-H, Random, 95% C				
Cha XT 2016	4	20	12	20	15.7%	0.17 [0.04, 0.69]				
Lu B 2016	14	30	11	30	20.5%	1.51 [0.54, 4.24]				
Wang F 2014	23	58	41	58	20.3%	0.27 [0.13, 0.59]				
Xu YM 2016	4	30	4	30	14.8%	1.00 [0.23, 4.43]				
Yang F 2018	5	25	4 5	25	16.0%	1.00 [0.25, 4.43]				
Zou HP 2012	1	30	4	30	8.8%	0.22 [0.02, 2.14]				
200 HF 2012		30	4	30	0.0%	0.22 [0.02, 2.14]				
Total (95% CI)		193		193	100.0%	0.53 [0.24, 1.16]	◆			
Total events	51		77							
Heterogeneity: Tau ² =			df = 5 (P:	= 0.04)	; /² = 56%		0.001 0.1 1 10 1000			
Test for overall effect:	Z = 1.60 (P	?= 0.11)					Favors [Control] Favors [Experimental			
-										
F	Experim	ontol	Contr	-		Odds Ratio	Odds Ratio			
Céudu an Cubanaun					Malaht					
Study or Subgroup	Events				-	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl			
Cui P 2009	2	32	3	22		0.42 [0.06, 2.76]				
Xu YM 2016	2	30	2	30		1.00 [0.13, 7.60]	T			
Yang F 2018	0	25	0	25		Not estimable				
Zou HP 2012	0	30	1	30	22.1%	0.32 [0.01, 8.24]				
Total (95% CI)		117		107	100.0%	0.56 [0.16, 1.95]				
Total events	4		6							
Heterogeneity: Chi 2 =	0.51, df = 2	2(P=0.)	77);/2 = 0	1%			0.01 0.1 1 10 100			
Test for overall effect:	Z = 0.91 (<i>I</i>	P= 0.36)				Favors [Control] Favors [Experimental			
-										
G	Even	mtal	Cantor			Odda Batia	Odda Batia			
Péudu es Pubas	Experime		Contro		Waight	Odds Ratio	Odds Ratio			
Study or Subgroup	Events	Total			Weight	M-H, Random, 95% C	I M-H, Random, 95% Cl			
Tian B 2012 Wang E 2014	2	23 58	7 32	22 58	11.0% 19.0%	0.20 [0.04, 1.12]	-			

Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% Cl
Tian B 2012	2	23	7	22	11.0%	0.20 [0.04, 1.12]	
Wang F 2014	40	58	32	58	19.0%	1.81 [0.84, 3.86]	+
Wang WM 2010	4	20	5	23	12.7%	0.90 [0.21, 3.94]	
Wang YH 2009	2	36	15	32	11.8%	0.07 [0.01, 0.33]	
Yang F 2018	14	25	15	25	15.6%	0.85 [0.28, 2.61]	
Zhang RG 2004	4	43	6	43	13.7%	0.63 [0.17, 2.42]	
Zou HP 2012	10	30	10	30	16.1%	1.00 [0.34, 2.93]	
Total (95% CI)		235		233	100.0%	0.62 [0.28, 1.34]	•
Total events	76		90				
Heterogeneity: Tau ² = 0	0.68; <i>Chi</i> ² =	0.01 0.1 1 10 100					
Test for overall effect: 2	Z = 1.22 (<i>P</i>	Favors [Control] Favors [Experimental]					

Figure S2 (Continued).

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	Experimental		Control		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
Xu YM 2016	26	30	29	30	33.9%	0.22 [0.02, 2.14]	
Yang F 2018	25	25	25	25		Not estimable	
Zhang CW 2001	28	35	27	32	49.4%	0.74 [0.21, 2.62]	
Zhang RG 2004	2	43	2	43	16.7%	1.00 [0.13, 7.44]	
Total (95% Cl)		133		130	100.0%	0.61 [0.24, 1.56]	-
Total events	81		83				
Heterogeneity: Chi ² = 2	1.08, <i>df</i> = 2	(P = 0.5)					
Test for overall effect:	Z = 1.03 (<i>F</i>	= 0.30)					0.01 0.1 1 10 100 Favors [Control] Favors [Experimental]

	Experimental		Control			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
Chen GF 2012	29	62	48	86	21.8%	0.70 [0.36, 1.34]	
Li W 2016	14	76	28	74	23.5%	0.37 [0.18, 0.78]	
Li YX 2012	39	74	44	74	21.2%	0.76 [0.40, 1.46]	
Lu B 2016	18	30	20	30	8.1%	0.75 [0.26, 2.15]	
Xu DM 2015	7	30	14	30	10.9%	0.35 [0.11, 1.05]	
Zhu WK 2012	5	32	5	32	4.3%	1.00 [0.26, 3.86]	
Zou HP 2012	5	30	12	30	10.2%	0.30 [0.09, 1.00]	
Total (95% CI)		334		356	100.0%	0.57 [0.41, 0.79]	•
Total events	117		171				
Heterogeneity: Chi ² = {	5.15, <i>df</i> = 6	(P = 0.5)	52); /² = 0	%			0.01 0.1 1 10 100
Test for overall effect:	Z = 3.40 (F	Favors [Control] Favors [Experimental]					

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	Experimental		Control		Odds Ratio		Odds Ratio
Study or Subgroup	Events Total		Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
Li W 2016	12	76	18	74	21.6%	0.58 [0.26, 1.32]	
Lu B 2016	15	30	13	30	9.1%	1.31 [0.47, 3.61]	
Xu DM 2015	6	30	9	30	10.1%	0.58 [0.18, 1.91]	
Xu YM 2016	6	30	7	30	7.9%	0.82 [0.24, 2.81]	
Yang F 2018	13	25	14	25	9.5%	0.85 [0.28, 2.59]	
Zhang RG 2004	9	43	15	43	16.7%	0.49 [0.19, 1.30]	
Zhang Y 2005	14	28	19	29	13.1%	0.53 [0.18, 1.53]	
Zou HP 2012	15	30	17	30	12.0%	0.76 [0.28, 2.11]	
Total (95% CI)		292		291	100.0%	0.69 [0.48, 0.99]	•
Total events	90		112				
Heterogeneity: Chi ² = 2	2.72, df = 7	(P = 0.9)	91); /² = 0	%			0.01 0.1 1 10 100
Test for overall effect:	Z = 1.99 (F	P = 0.05)					0.01 0.1 1 10 100 Favors [Control] Favors [Experimental]

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	Experimental		Control			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Chen GF 2012	24	62	35	86	21.7%	0.92 [0.47, 1.79]	
Li YX 2012	27	74	33	74	21.9%	0.71 [0.37, 1.38]	
Wang YH 2009	5	36	18	32	13.5%	0.13 [0.04, 0.41]	
Xiao XN 2018	10	34	9	31	14.9%	1.02 [0.35, 2.97]	
Zhang RG 2004	31	43	39	43	12.8%	0.26 [0.08, 0.90]	- _
Zhang Y 2005	12	28	14	29	15.3%	0.80 [0.28, 2.28]	
Total (95% Cl)		277		295	100.0%	0.56 [0.32, 1.00]	•
Total events	109		148				
Heterogeneity: Tau ² =	0.28; Chi ² :		0.01 0.1 1 10 100				
Test for overall effect:	Z = 1.95 (F	Favors [Control] Favors [Experimental]					

Figure S2 (Continued).

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	Experime	ental	Contr	Control		Odds Ratio	Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl			
Cha XT 2016	3	20	10	20	11.9%	0.18 [0.04, 0.80]				
Li W 2016	8	76	20	74	25.3%	0.32 [0.13, 0.78]				
Lu B 2016	5	30	7	30	8.1%	0.66 [0.18, 2.36]				
Wang WM 2010	5	20	7	23	6.8%	0.76 [0.20, 2.93]				
Wang YH 2009	13	36	25	32	23.6%	0.16 [0.05, 0.47]	_ _			
Xu DM 2015	4	30	10	30	12.1%	0.31 [0.08, 1.13]				
Yang F 2018	19	25	22	25	7.4%	0.43 [0.09, 1.97]				
Zhang Y 2005	25	28	29	29	4.9%	0.12 [0.01, 2.51]	•			
Total (95% CI)		265		263	100.0%	0.32 [0.20, 0.50]	•			
Total events	82		130							
Heterogeneity: Chi ² = 5	5.58, <i>df</i> = 7	(P = 0.8)	59); /² = 0'	%						
Test for overall effect: 2	Z = 5.02 (<i>F</i>	0.01 0.1 1 10 100 Favors [Control] Favors [Experimental]								

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	Experime	ental	Contr	ol		Odds Ratio	Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl			
Yang F 2018	21	25	23	25	40.5%	0.46 [0.08, 2.75]				
Zou HP 2012	24	30	27	30	59.5%	0.44 [0.10, 1.97]				
Total (95% CI)		55		55	100.0%	0.45 [0.14, 1.42]				
Total events	45		50							
Heterogeneity: $Chi^2 = 0.00, df = 1 (P = 0.98); I^2 = 0\%$										
Test for overall effect:	Z = 1.37 (<i>F</i>	9= 0.17)					0.01 0.1 1 10 100 Favors [Control] Favors [Experimental]			

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	Experimental		Contr	ol	Odds Ratio			Odds Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Rand	lom, 95%	% CI		
Wang F 2014	44	58	46	58	52.3%	0.82 [0.34, 1.97]			—			
Wang YH 2009	15	36	26	32	47.7%	0.16 [0.05, 0.50]						
Total (95% Cl)		94		90	100.0%	0.38 [0.08, 1.84]			-			
Total events	59		72									
Heterogeneity: Tau ² =	1.03; Chi2 =	= 4.97, a	df = 1 (P=	= 0.03);	/² = 80%		0.01	0.1	1	10	100	
Test for overall effect:	Z = 1.20 (F	? = 0.23))					avors [Control]	Favor		rimental]	

Figure S2 (Continued).



Figure S3 Funnel plot of percentage of complete response rates (CR, A), partial response rates (PR, B), stable disease rates (SD, C) and progressive disease rates (PD, D).

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