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ORIGINAL RESEARCH

Clinical applications of dendritic cells–cytokine-induced killer cells mediated immunotherapy for pancreatic cancer: an up-to-date meta-analysis

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Purpose: This study aimed to systematically evaluate the efficacy and safety of dendritic cells–cytokine-induced killer (DC–CIK) cells immunotherapy in treating pancreatic cancer (PC) patients.

Methods: Data were collected from published articles of clinical trials. Databases including Web of Science, EMBASE, PubMed, Cochrane Library, Wanfang, and CNKI were searched. The main outcome measures in this research included the overall response rate (ORR), disease control rate (DCR), overall survival (OS), patients' quality of life (QoL), immune function, and adverse events. Comparative analysis was conducted between DC–CIK immunotherapy and chemotherapy (combined therapy) and chemotherapy alone.

Results: This analysis covered 14 trials with 1,088 PC patients involved. The combined therapy showed advantages over chemotherapy alone in ORR (odds ratio [OR] =1.69, 95% confidence interval [CI] =1.20–2.38, P=0.003), DCR (OR =2.33, 95% CI =1.63–3.33, $P<0.00001$), OS (1-year OS, OR =3.61, 95% CI =2.41–5.40, $P<0.00001$; 3-year OS, OR =2.65, 95% CI =1.56–4.50, P=0.0003) and patients' QoL ($P<0.01$) with statistical significance. After immunotherapy, lymphocyte subsets' percentages of $CD3^+$ ($P<0.00001$), $CD4^+$ (P=0.01), $CD3^+CD56^+$ ($P<0.00001$), and cytokine levels of IFN-γ ($P<0.00001$) were significantly increased, and the percentages of $CD4^+CD25^+CD127^{low}$ ($P<0.00001$) and levels of IL-4 ($P<0.0001$) were significantly decreased, whereas analysis on $CD8^+$ (P=0.59) and $CD4^+/CD8^+$ ratio (P=0.64) did not show a significant difference.

Conclusion: The combination of DC–CIK immunotherapy and chemotherapy is effective for PC treatment, indicated by prolonging the PC patients' survival time, which benefit from reconstructed immune function of patients.

Keywords: cytokine-induced killer cells, dendritic cells, pancreatic cancer, immunotherapy, meta-analysis

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Introduction

Pancreatic cancer (PC) is a fatal disease with high mortality and poor prognosis.[1] It is the twelfth most common cancer and is the seventh leading cause of cancer-related deaths in the world with 338,000 new cases per year.[2] In recent years, PC incidence has been significantly raised. The median overall survival (OS) of patients with advanced PC is 4–6 months,[3] and the 5-year OS rate is <10%.[4] Common therapeutic options for PC are surgery, radiotherapy, and chemotherapy,[3] but none of these strategies were able to thoroughly remove small residuals and metastatic cells, which is a main problem to be solved in tumor therapeutics. Therefore, effective therapeutic method should be developed.

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Adoptive cellular immunotherapy has demonstrated efficacy for the treatment of various malignant tumors, especially dendritic cells–cytokine-induced killer (DC–CIK) cells mediate immunotherapy.[5,6] Compared to immunotherapy using other types of cells, such as lymphokine-activated killer (LAK) cells,[7,8] natural killer (NK) cells,[9,10] and other immune cells,[11,12] DC–CIK-mediated immunotherapy exhibited a stronger antitumor ability and broader antitumor spectrum.[13,14] Cytokine-induced killer (CIK) cell is a heterogeneous subset of T lymphocytes, which primarily consist of $CD3^+CD56^+$ cells and is easy to be collected from human peripheral and umbilical cord blood, and subsequently induced by IFN-γ, anti-CD3 monoclonal antibodies (OKT-3), and IL-2 in vitro.[6] DC are the most potent antigen-presenting cells. DC have the capacity to enhance CIK's cytotoxicity by coculture with CIK cells, which is indicated by increased proportion of $CD3^+CD56^+$ cells and improved levels of cytokines such as IFN-γ and IL-2.[5,15]

Clinical application of DC–CIK immunotherapy for PC has been reported in several clinical trials.[16–19] In a meta-analysis comparing cellular immunotherapy combined with chemotherapy and chemotherapy alone, the former showed significantly prolonged OS,[3] while the discussed outcomes were not complete. Analysis considering overall response rate (ORR) and disease control rate (DCR), patients' quality of life (QoL) and safety were not involved in this analysis. Moreover, the immunotherapy regimens among studies were different (including DC, NK, and LAK), which may influence the analysis of clinical therapy. Our study focused on PC patients treated by DC–CIK immunotherapy and chemotherapy combined therapy or chemotherapy alone, and we performed an up-to-date meta-analysis to provide reliable evidence on the efficacy and safety of DC–CIK immunotherapy in treating PC patients.

Methods

Search strategy and selection criteria

Data were collected from Web of Science, EMBASE, PubMed, Cochrane Library, Wanfang, and CNKI databases using the key terms of "dendritic cells", "cytokine-induced killer cells" combined with "pancreatic cancer". No language limits were applied. Literature published before May 2017 was involved in our analysis.

The main selection criteria are that PC patients in the experimental group underwent DC–CIK immunotherapy combined with chemotherapy and patients in the control group were treated by chemotherapy alone.

Data collection and quality assessment

Literature screening and data extraction were carried out by two independent reviewers (YZ and XZ), and disagreements were eliminated upon discussing with a third researcher (AZ). Extracted information included first author's names, years of publication, study locations, tumor stages, number of cases, patient ages, therapeutic regimens, administration route, in vitro cell culture conditions, and dosages of utilized immune cells. The quality of the included trials was evaluated based on Cochrane Handbook.[20]

Treatment efficacy

Treatment efficacy was assessed in terms of the complete response (CR) rates, partial response (PR) rates, stable disease (SD) rates, progressive disease (PD) rates, ORR, (ORR = CR + PR) and DCR (DCR = CR + PR + SD). Prognosis was estimated by OS, which was defined as the length of time from the start of treatment to the death of patient from any cause,[21] patients' QoL, and adverse events. Immune function of PC patients before and after treatment was determined by lymphocyte subsets' percentages ($CD3^+$, $CD4^+$, $CD8^+$, $CD3^+CD56^+$, and $CD4^+CD25^+CD127^{low}$) and cytokines secretion levels (IFN-γ and IL-4).

Statistical analysis

This meta-analysis was performed using RevMan 5.2 (version 5.2, Nordic Cochran Centre, Copenhagen, Denmark). $P<0.05$ indicates the statistical significance of the difference. Heterogeneity among studies was assessed to determine suitable analysis model.[5,22] Cochran's Q test was performed to evaluate the homogeneity, and funnel plots were used to assess the publication bias of included studies. $I^2<50\%$ or $P>0.1$ indicated that the studies were homogenous. Odds ratio (OR) was the principal measurement for treatment efficacy and is presented with a 95% confidence interval (CI). Sensitivity analysis was conducted to evaluate the consistency of the results and evaluate the influence of single studies on overall risk estimate.[23]

Results

Search results

A total of 2,127 articles were identified upon initial retrieve; 2,082 articles were excluded because they lacked clinical trial (n=1,876), were unrelated studies (n=64), and were duplicated (n=142). After a detailed assessment of full texts, 14 reviews or meta-analyses, 10 articles without control

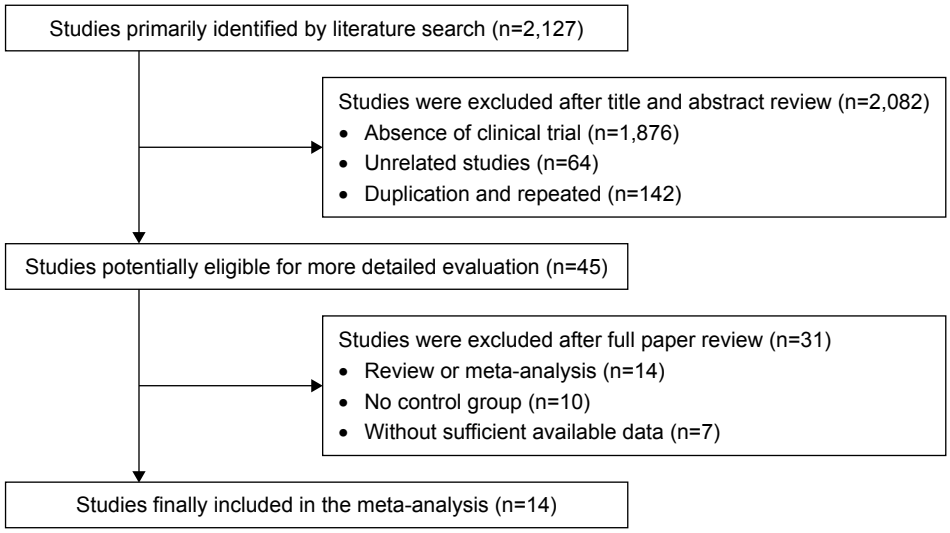

Figure 1 Flow diagram of the selection process.

group, and seven papers with insufficient data were excluded. Finally, 14 papers of clinical trials that included a total of 1,088 patients were eligible for inclusion in this meta-analysis (Figure 1).[16,17,24–35]

Patient's characteristics

All of the involved trials turn out to be conducted in China. In total, 513 PC patients in eight trials were treated by DC-CIK in combination with chemotherapy, while 575 patients in six trials were treatment by CIK alone. Detailed clinical information of the patients is presented in Table 1. DC and CIK cells were obtained from autologous peripheral blood, confirming free of bacterial and fungal contaminations before venous transfusion to the patients. Information of DC–CIK mediate immunotherapy is shown in Table 2.

Quality assessment

Bias risk assessment is shown in Figure 2. Seven studies were determined as low risk, four researches were not truly randomized controlled trials, and the remaining three studies lacked clear description of randomization process. Risks of allocation, performance, and detection were low. Two studies absent of follow-up, seven trials with selective

Table 1 Clinical information from the eligible trials in the meta-analysis

Included studies	Nation	Tumor stage	Patients, exp/con	Age (years)		Parameter types
				Exp	Con	
Ge and Ge (2016)[24]	China	I–IV	50/50	57.7±4.6 (mean)	57.5±4.7 (mean)	OS, LYM subsets
Kang and Zhang (2016)[25]	China	Kps >60	22/22	65.1±6.3 (mean)	66.1±6.3 (mean)	ORR, DCR, QoL
Li (2016)[26]	China	Kps ≥70	27/27	ND	ND	OS, ORR, DCR, QoL, AE
Liu (2012)[27]	China	I–IV	25/25	ND	ND	LYM subsets, cytokines
Mu et al (2016)[28]	China	III–IV	90/90	56.5±8.3 (mean)	57.8±7.3 (mean)	ORR, DCR, LYM subsets, AE
Shen et al (2015)[29]	China	III–IV	38/36	62 (median)	66 (median)	ORR, DCR
Wang (2015)[30]	China	I–IV	10/30	64.3±3.1 (mean)	63.8±3.4 (mean)	ORR, DCR
Wang et al (2013)[16]	China	Ps ≤2	28/30	ND	ND	ORR, DCR, AE
Wang et al (2016)[17]	China	Ps <3	25/5	<65 (14)	<65 (38)	OS, ORR, DCR, AE
Wen et al (2013)[31]	China	ND	30/30	63.5±13.2 (mean)	65.3±12.8 (mean)	OS, ORR, DCR
Zhang et al (2013)[32]	China	Kps >60	58/68	63 (median)	65 (median)	ORR, DCR, QoL
Zhang (2014)[33]	China	I–IV	30/30	ND	ND	OS, LYM subsets, cytokines
Zhang et al (2016)[34]	China	ND	40/40	55.9±8.7 (mean)	56.8±8.2 (mean)	OS
Zheng et al (2016)[35]	China	I–IV	40/40	39–82	35–83	OS, LYM subsets

Notes: Con, control group (chemotherapy alone group); Exp, experimental group (chemotherapy with DC–CIK immunotherapy).
Abbreviations: AE, adverse reaction; DC–CIK, dendritic cells–cytokine-induced killer; DCR, disease control rate; Kps, Karnofsky Performance Score; LYM, lymphocyte; ND, not determined; OS, overall survival; ORR, overall response rate; Ps, performance status score; QoL, quality of life.

Table 2 Information of DC–CIK immunotherapy

Included studies	Therapeutic regimen		Administration route	Culture conditions	Cell dose (cycles)
	Experimental group	Control group			
Ge and Ge (2016)[24]	Con Reg + DC–CIK	Gemcitabine + oxaliplatin +5-Fu	Intravenous infusion	ND	6×10^9 (2 cycles)
Kang and Zhang (2016)[25]	Con Reg + DC–CIK	Gemcitabine	ND	ND	ND
Li (2016)[26]	Con Reg + CIK	Gemcitabine + cisplatin + RT	Intravenous infusion	ND	$>1\times10^{10}$ ($\geq$2 cycles)
Liu (2012)[27]	Con Reg + DC–CIK	ND	Intravenous infusion	IFN-γ, IL-2, CD3, GM-CSF, IL-4	6×10^9 (2 cycles)
Mu et al (2016)[28]	Con Reg + DC–CIK	Gemcitabine + nab-paclitaxel	Intravenous infusion	ND	ND (4 cycles)
Shen et al (2015)[29]	Con Reg + CIK	Gemcitabine	Intravenous infusion	IFN-γ, IL-2, CD3	ND
Wang (2015)[30]	Con Reg + CIK	Gemcitabine	Intravenous infusion	ND	ND (2 cycles)
Wang et al (2013)[16]	Con Reg + CIK	S-1	Intravenous infusion	IFN-γ, IL-1α, IL-2, CD3	ND ($\geq$1 cycle)
Wang et al (2016)[17]	Con Reg + CIK	(gemcitabine + S-1)/other	Intravenous infusion	IFN-γ, IL-2, CD3	5×10^9 (2 cycles)
Wen et al (2013)[31]	Con Reg + DC–CIK	Mitomycin + adriamycin + Fu	Intravenous infusion	ND	ND
Zhang et al (2013)[32]	Con Reg + CIK	Gemcitabine	Intravenous infusion	ND	ND
Zhang (2014)[33]	Con Reg + DC–CIK	Gemcitabine + oxaliplatin +5-Fu	Intravenous infusion	GM-CSF, IL-4	ND
Zhang et al (2016)[34]	Con Reg + DC–CIK	Gemcitabine + oxaliplatin +5-Fu	Intravenous infusion	ND	$>1\times10^9$ (ND)
Zheng et al (2016)[35]	Con Reg + DC–CIK	Gemcitabine + oxaliplatin +5-Fu	Intravenous infusion	ND	6×10^9 (2 cycles)

Notes: Con, control group (chemotherapy alone group); exp, experimental group (chemotherapy with DC–CIK immunotherapy); RT, three-dimensional conformal radiotherapy.
Abbreviations: Con Reg, control group regimen; DC–CIK, dendritic cells–cytokine-induced killer; ND, not determined; 5-Fu, 5-fluorouracil; GM-CSF, granulocyte-macrophage colony-stimulating factor.

reporting were regarded as an unclear risk, and other two studies were considered as high risk for lacking primary outcome data.

Efficacy assessments

In our pooled analysis, patients treated by combined therapy showed higher PR (Figure S1A, OR =1.49, 95% CI =1.06–2.10, P=0.02), ORR (Figure 3A, OR =1.69, 95% CI =1.20–2.38, P=0.003), and DCR (Figure 3B, OR =2.33, 95% CI =1.63–3.33, $P<0.00001$) and lower PD rates (Figure S1B, OR =0.43, 95% CI =0.30–0.61, $P<0.00001$) with statistical significance, whereas CR and SD did not show obvious difference from chemo-alone group (Figure S1C and D, CR: OR =1.97, 95% CI =0.85–4.54, P=0.11; SD: OR =1.31, 95% CI =0.95–1.80, P=0.10). Fixed-effect models were used in this analysis because of low heterogeneity (Table 3).

Prognosis evaluation

In the 14 studies, patients treated by combined therapy had higher OS than those treated by chemotherapy alone (Figure 4,

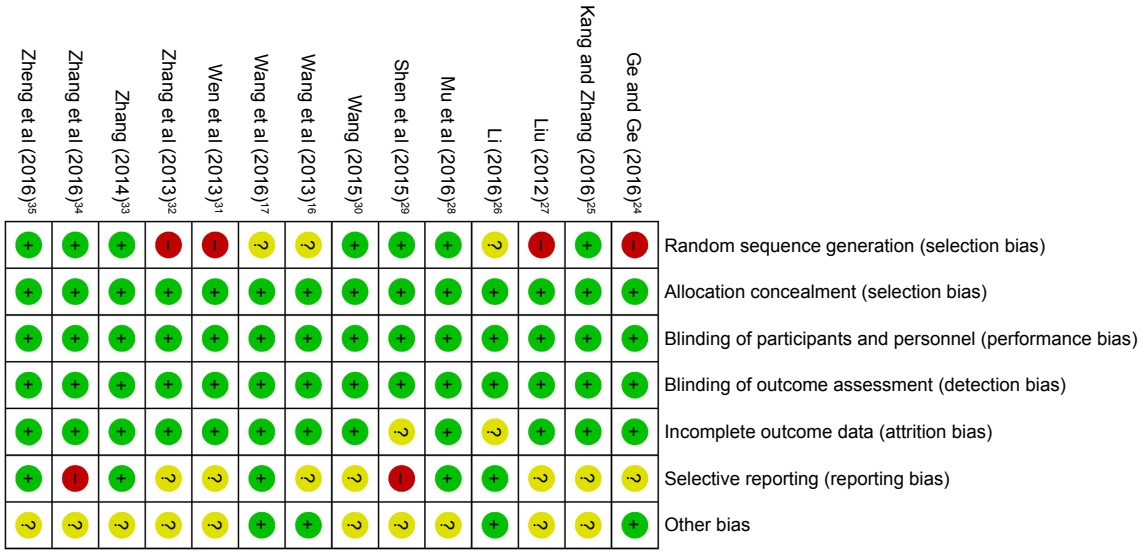

Figure 2 Risk of bias summary: review of authors' judgments about each risk of bias item for included studies.
Note: Each color represents a different level of bias: red for high-risk, green for low-risk, and yellow for unclear-risk of bias.

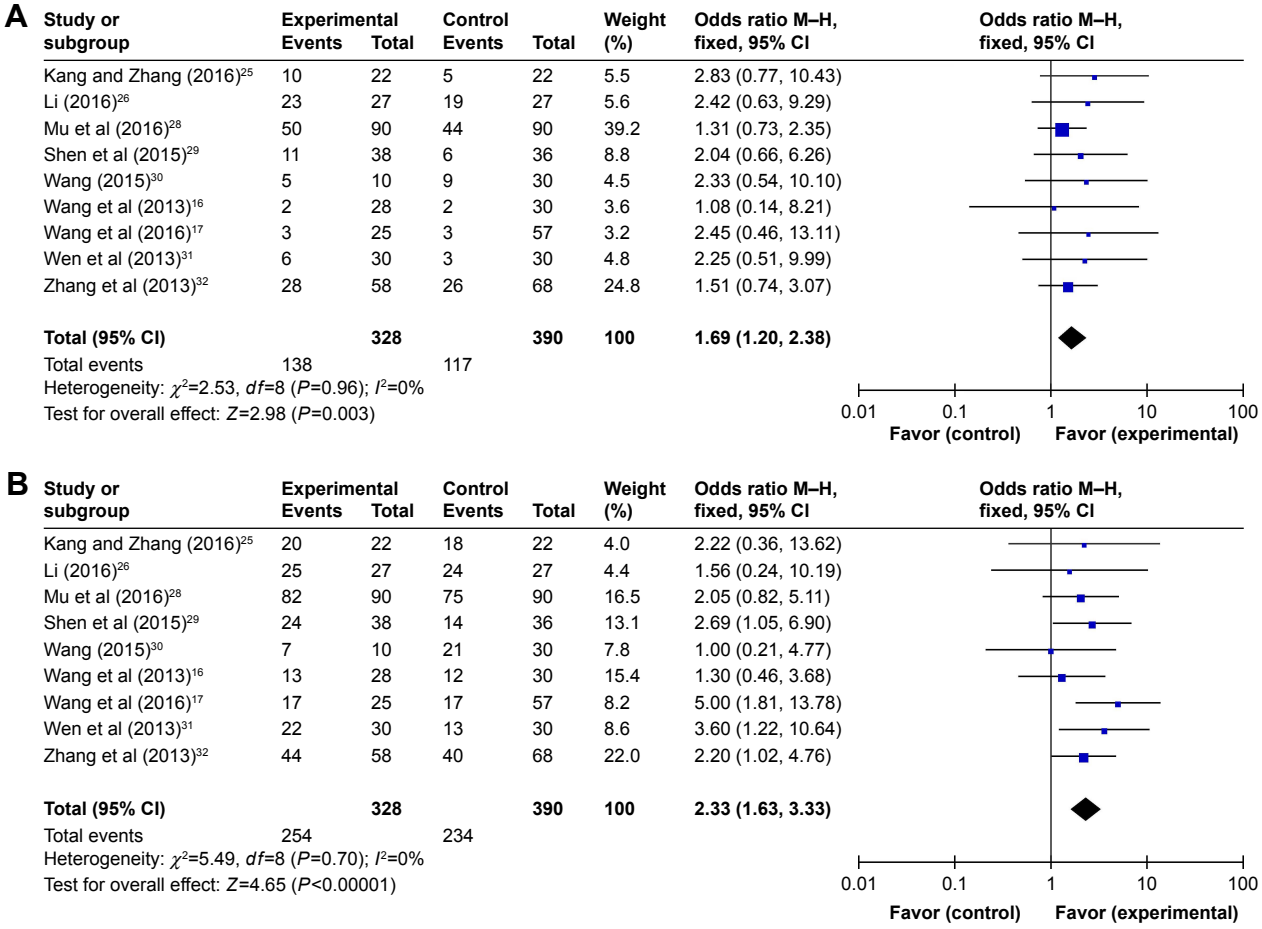

Figure 3 Forest plots of the comparison of ORR (**A**) and DCR (**B**) between the experimental and control groups.
Notes: Control group, chemotherapy alone group; experimental group, chemotherapy with DC–CIK immunotherapy. The fixed-effects meta-analysis model (M–H method) was used.
Abbreviations: CI, confidence interval; DC–CIK, dendritic cells–cytokine-induced killer; DCR, disease control rate; M–H, Mantel–Haenszel; ORR, overall response rate.

1-year OS: OR =3.61, 95% CI =2.41–5.40, $P<0.00001$; 3-year OS: OR =2.65, 95% CI =1.56–4.50, $P=0.0003$). Considering slightly significant heterogeneity, fixed-effects model were applied in this analysis. Compared to control group, patients in experimental group showed significantly improved QoL (Figure 5A, OR =3.04, CI =1.58–5.88, $P=0.0009$) and Karnofsky Performance Score (Kps) (Figure 5B, OR =9.06, 95% CI =7.27–10.84, $P<0.00001$), which also indicates the performance status of patients.

Immune function evaluation

The immune status of patients was examined before and after treatment. As shown in Figure 6, after DC–CIK treatment, percentages of $CD3^+$, $CD4^+$, and $CD3^+CD56^+$

Table 3 Comparison of CR, PR, SD, PD, ORR, and DCR between the experimental and control groups

Parameter	Number of patients (n)		Analysis method	Heterogeneity		OR	95% CI	*P*-value
	Experimental group	Control group		I^2 (%)	*P*-value			
CR	328	390	Fixed	0	0.84	1.97	0.85–4.54	0.11
PR	328	390	Fixed	0	0.96	1.49	1.06–2.10	0.02
SD	328	390	Fixed	35	0.14	1.31	0.95–1.80	0.10
PD	328	390	Fixed	0	0.74	0.43	0.30–0.61	<0.00001
ORR	328	390	Fixed	0	0.96	1.69	1.20–2.38	0.003
DCR	328	390	Fixed	0	0.70	2.33	1.63–3.33	<0.00001

Abbreviations: CI, confidence interval; CR, complete response; DCR, disease control rate; OR, odds ratio; ORR, overall response rate; PR, partial response; PD, progressive disease; SD, stable disease.

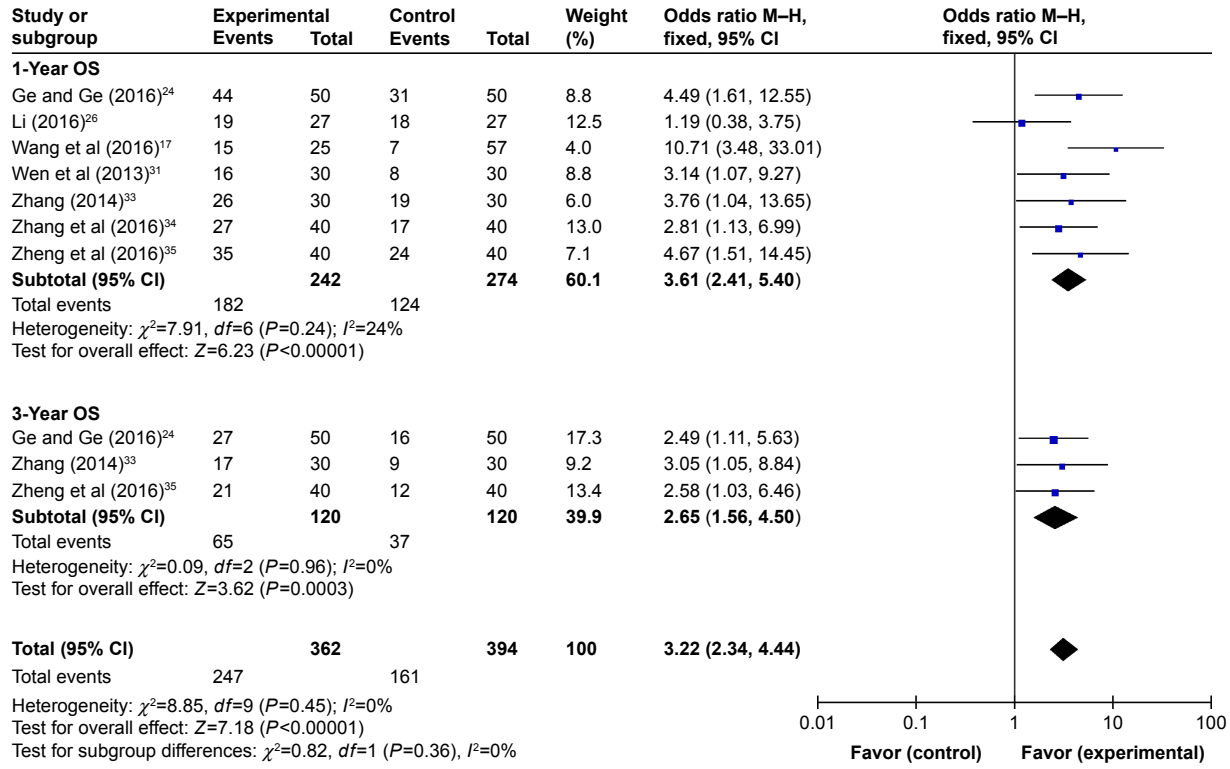

Figure 4 Forest plot of the comparison of OS between the experimental and control groups.
Notes: Control group, chemotherapy alone group; experimental group, chemotherapy with DC–CIK immunotherapy. The fixed-effects meta-analysis model (M–H method) was used.
Abbreviations: CI, confidence interval; DC–CIK, dendritic cells–cytokine-induced killer; M–H, Mantel–Haenszel; OS, overall survival.

were increased ($CD3^+$: OR =10.70, 95% CI =7.38–14.03, $P<0.00001$; $CD4^+$: OR =7.62, 95% CI =1.56–13.67, $P=0.01$; $CD3^+CD56^+$: OR =7.34, 95% CI =6.77–7.92, $P<0.00001$), and percentage of $CD4^+CD25^+CD127^{low}$ was decreased (OR =–3.52, 95% CI =–4.61 to –2.44, $P<0.00001$); the changes were statistically significant, whereas proportions of $CD8^+$ and $CD4^+/CD8^+$ ratio were not apparently changed ($CD8^+$: OR =–5.01, 95% CI =–23.14 to 13.12, $P=0.59$; $CD4^+/CD8^+$

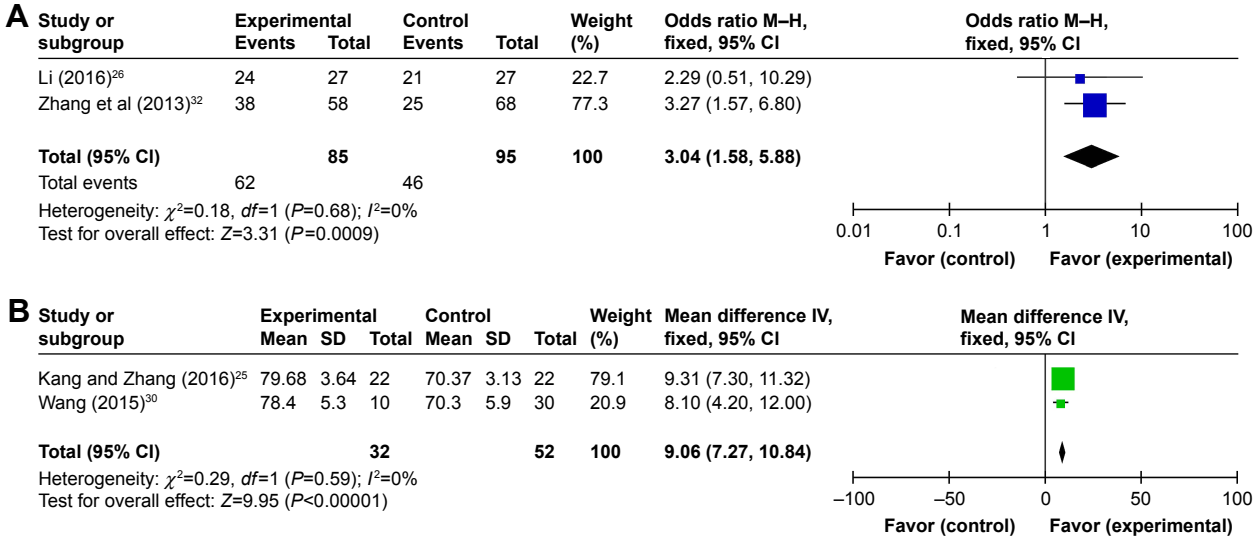

Figure 5 Forest plots of the comparison of QoL between the experimental and control groups.
Notes: (**A**) QoL improvement; (**B**) Kps. Control group, chemotherapy alone group; experimental group, chemotherapy with DC–CIK immunotherapy. The fixed-effects meta-analysis model was used.
Abbreviations: CI, confidence interval; DC–CIK, dendritic cells–cytokine-induced killer; Kps, Karnofsky Performance Score; M–H, Mantel–Haenszel; QoL, quality of life.

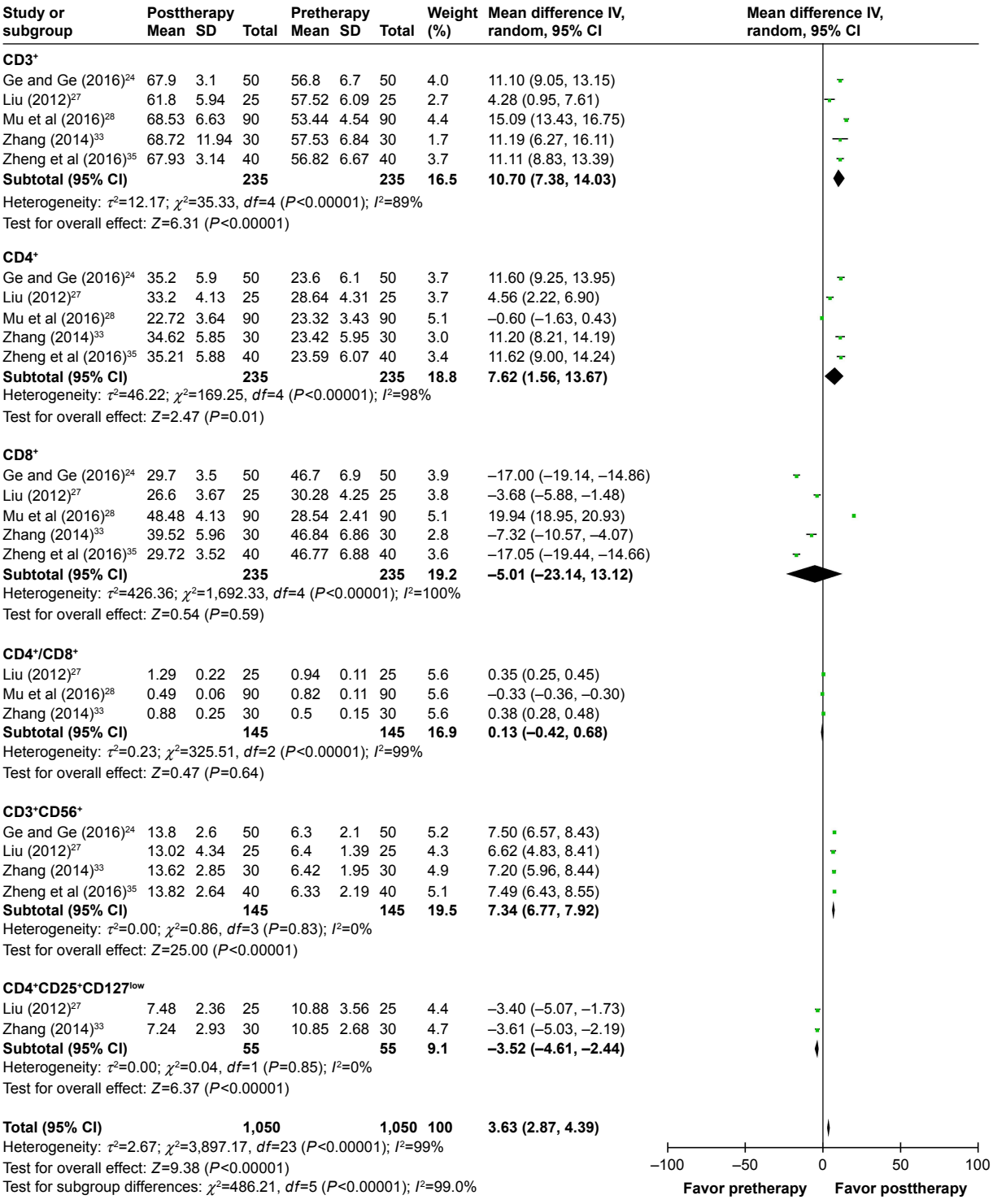

Figure 6 Forest plot of the comparison of immunophenotype in pre- and posttherapies.
Note: The random effects meta-analysis model (IV method) was used.
Abbreviations: CI, confidence interval; IV, inverse variance.

ratio: OR =0.13, 95% CI =–0.42 to 0.68, *P*=0.64). In contrast, IFN-γ level was increased distinctly after DC–CIK immunotherapy (IFN-γ: OR =2.28, 95% CI =1.33 to 3.22, *P*<0.00001), while IL-4 level was dramatically decreased (OR =–1.85, 95% CI =–2.69 to –1.01, *P*<0.0001) (Figure 7).

Adverse events' assessment

In the involved clinical trials, no serious adverse events or death occurrence was reported in patients receiving DC–CIK immunotherapy. As shown in Figures S2 and 3 and Table 4, no significant difference was found on adverse

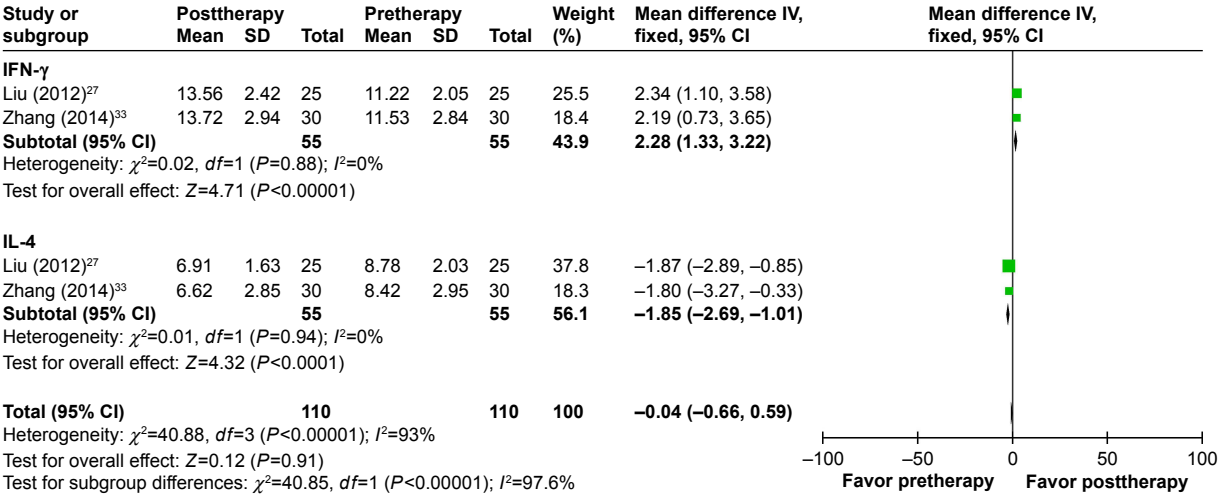

Figure 7 Forest plot of the comparison of IFN-γ and IL-4 in pre- and posttherapies.
Note: The fixed-effects meta-analysis model (IV method) was used.
Abbreviations: CI, confidence interval; IV, inverse variance; IFN-γ, interferon-γ; IL-4, interleukin-4.

events including fever, skin rash, leukopenia, thrombocytopenia, diarrhea, nausea and vomiting, gastrointestinal adverse reaction (AE), fatigue, neutropenia, and myelosuppression between the experimental and control groups (fever: OR =2.39, 95% CI =0.70–8.23, *P*=0.17 [Figure S3A, fever I + II: OR =4.34, 95% CI =1.35–13.89, *P*=0.01; fever III + IV: OR =3.11, 95% CI =0.12–79.87, *P*=0.49]; skin rash: OR =1.32, 95% CI =0.54–3.19, *P*=0.54 [Figure S3B, skin rash I + II: OR =2.21, 95% CI =0.52–9.36, *P*=0.28; skin rash III + IV: OR =3.33, 95% CI =0.13–85.11, *P*=0.47]; leukopenia: OR =0.56, 95% CI =0.22–1.47, *P*=0.24 [Figure S3C, leukopenia I + II: OR =0.86, 95% CI =0.36–2.06, *P*=0.73; leukopenia III + IV: OR =0.32, 95% CI =0.06–1.64, *P*=0.17]; thrombocytopenia: OR =0.54, 95%

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

Adverse events	Number of patients (n)		Analysis method	Heterogeneity		OR	95% CI	*P*-value
	Experimental group	Control group		I^2 (%)	*P*-value			
Fever	170	204	Random	67	0.03	2.39	0.70–8.23	0.17
Fever I + II	55	57	Random	57	0.13	4.34	1.35–13.89	0.01
Fever III + IV	55	57	Random			3.11	0.12–79.87	0.49
Skin rash	145	147	Random	0	0.46	1.32	0.54–3.19	0.54
Skin rash I + II	55	57	Random	0	0.66	2.21	0.52–9.36	0.28
Skin rash III + IV	55	57	Random			3.33	0.13–85.11	0.47
Leukopenia	55	57	Random	0	0.33	0.56	0.22–1.47	0.24
Leukopenia I + II	55	57	Random	0	0.92	0.86	0.36–2.06	0.73
Leukopenia III + IV	55	57	Random	0	0.62	0.32	0.06–1.64	0.17
Thrombocytopenia	55	57	Random	0	0.38	0.54	0.18–1.64	0.27
Thrombocytopenia I + II	55	57	Random	0	0.70	0.61	0.22–1.73	0.36
Thrombocytopenia III + IV	55	57	Random			0.32	0.01–8.24	0.49
Diarrhea	55	57	Random	0	0.48	1.52	0.57–4.03	0.40
Diarrhea I + II	55	57	Random	0	0.49	1.58	0.58–4.32	0.37
Diarrhea III + IV	55	57	Random			1.08	0.14–8.21	0.94
Nausea, vomiting	55	57	Random	0	0.42	0.83	0.30–2.28	0.72
Nausea, vomiting I + II	55	57	Random	0	0.49	0.95	0.35–2.60	0.92
Nausea, vomiting III + IV	55	57	Random			0.35	0.01–8.83	0.52
Gastrointestinal AE	52	84	Random	0	0.32	0.65	0.23–1.90	0.43
Fatigue	53	87	Random	72	0.06	0.66	0.08–5.80	0.71
Neutropenia	28	30	Random			1.09	0.28–4.25	0.90
Myelosuppression	25	57	Random			0.48	0.19–1.26	0.14

Abbreviations: AE, adverse reaction; CI, confidence interval; OR, odds ratio.

CI =0.18–1.64, *P*=0.27 [Figure S3D, thrombocytopenia I + II: OR =0.61, 95% CI =0.22–1.73, *P*=0.36; thrombocytopenia III + IV: OR =0.32, 95% CI =0.01–8.24, *P*=0.49]; diarrhea: OR =1.52, 95% CI =0.57–4.03, *P*=0.40 [Figure S3E, diarrhea I + II: OR =1.58, 95% CI =0.58–4.32, *P*=0.37; diarrhea III + IV: OR =1.08, 95% CI =0.14–8.21, *P*=0.94]; nausea and vomiting: OR =0.83, 95% CI =0.30–2.28, *P*=0.72 [Figure S3F, nausea and vomiting I + II: OR =0.95, 95% CI =0.35–2.60, *P*=0.92; nausea and vomiting III + IV: OR =0.35, 95% CI =0.01–8.83, *P*=0.52]; gastrointestinal AE: OR =0.65, 95% CI =0.23–1.90, *P*=0.43; fatigue: OR =0.66, 95% CI =0.08–5.80, *P*=0.71; neutropenia: OR =1.09, 95% CI =0.28–4.25, *P*=0.90; and myelosuppression: OR =0.48, 95% CI =0.19–1.26, *P*=0.14).

Sensitivity analysis

PC patients were treated by DC–CIK immunotherapy in eight trials[24,25,27,28,31,33–35] and by CIK alone in the other six trials.[16,17,26,29,30,32] Studies were grouped according to different immunotherapy strategies (CIK or DC–CIK), and pooled results were compared (Table 5). The comparison showed both CIK and DC–CIK were effective in treating PC, and no obvious difference between these two methods was observed in most pooled analyses including ORR (Figure S4A), DCR (Figure S4B), and 1-year OS (Figure S5).

Publication bias

Funnel plots drawn for the studies on primary outcomes (1- and 3-year OS, ORR, and DCR) were symmetrical approximately, which indicated generally controlled publication bias and reliability of our primary conclusions (Figure 8A, 1-year OS; Figure 8B, 3-year OS; Figure 8C, ORR; Figure 8D, DCR).

Discussion

In recent years, immunotherapy using DC–CIK was found effective in PC treatment.[16–18] Even though there was statistical analysis of published clinical trials, the exact therapeutic effects were not systematically evaluated and demonstrated because of sample sizes' variability among these trials. In addition, the different applied protocols in different clinical trials may lead to different clinical response. In this research, we performed an extensive online search followed by rigorous contrasting and combining data analysis in categorization, by which to provide clear and systematical conclusion.

Our analysis showed that DC–CIK immunotherapy enhanced the curative effect of chemotherapy for PC, which was supported by markedly increased ORR (*P*=0.0003) and DCR (*P*<0.00001) in PC patients treated by combined therapy. With the addition of DC–CIK immunotherapy, prognosis of PC patients was also improved, according to the significantly prolonged survival time (1-year OS, *P*<0.00001; 3-year OS, *P*<0.00001) and QoL (*P*=0.0009).

Previous study has reported the immunosuppressed status in cancer patient, and several researchers found that adjuvant immunotherapy of DC–CIK was able to enhance the efficacy of chemotherapy for various malignant tumors by reconstructing cancer patient's immune function.[5,6] Our analysis showed that DC–CIK treatment can significantly improve the percentages of $CD3^+$, $CD4^+$, and $CD3^+CD56^+$ T cells in PC patients. Moreover, $CD4^+CD25^+CD127^{low}$ regulatory T cells negatively regulate the antitumor activity of DC–CIK immune cells[36] and our analysis showed result that $CD4^+CD25^+CD127^{low}$ regulatory T-cell subset proportion decreased after DC–CIK immunotherapy. These results indicated that immune function of chemotherapy-treated PC patients was improved after DC–CIK immunotherapy. However, no significant difference was found in $CD8^+$ T cells' proportion and $CD4^+/CD8^+$ ratio between with and without immunotherapy, which may be caused by various choices of treatment opportunity and DC–CIK transfusion dosages in different clinical trials.[6] The balance between Th1 and Th2 cells is crucial in immunotherapy.[5] Our analysis showed that after DC–CIK immunotherapy, IFN-γ (Th1

Table 5 Meta-analysis of 1-year OS, ORR, and DCR in CIK and DC–CIK subgroups

Immunotherapy type (subgroup)	Parameters	Number of patients (n)		Analysis method	Heterogeneity		OR	95% CI	*P*-value
		Experimental group	Control group		I^2 (%)	*P*-value			
CIK	ORR	186	248	Fixed	0	0.96	1.80	1.12–2.90	0.01
	DCR	186	248	Fixed	0	0.44	2.25	1.47–3.44	0.0002
	1-Year OS	52	84	Random	86	0.007	3.58	0.41–30.95	0.25
DC–CIK	ORR	142	142	Fixed	0	0.50	1.57	0.95–2.58	0.08
	DCR	142	142	Fixed	0	0.73	2.53	1.32–4.85	0.005
	1-Year OS	190	190	Random	0	0.95	3.62	2.25–5.84	<0.00001

Abbreviations: DC–CIK, dendritic cells–cytokine-induced killer; DCR, disease control rate; OR, odds ratio; ORR, overall response rate; OS, overall survival.

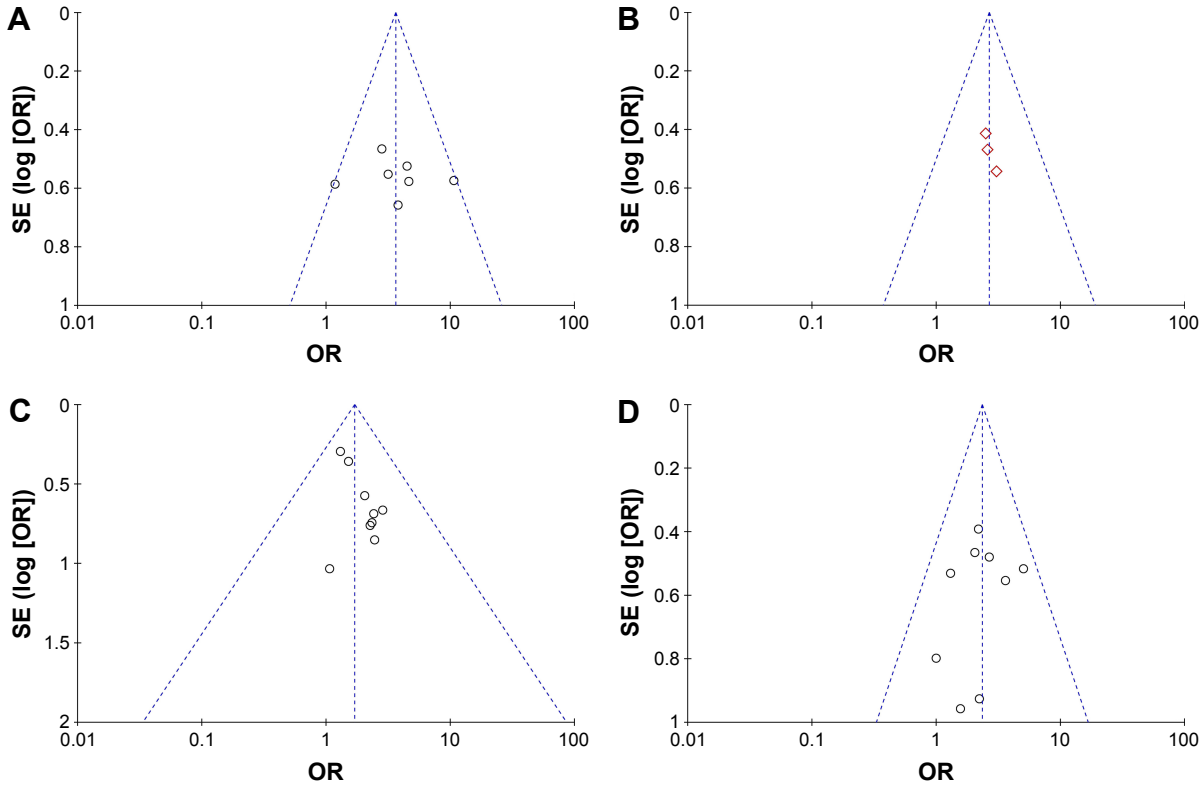

Figure 8 Funnel plot of each meta-analysis.
Notes: 1-Year OS (**A**); 3-year OS (**B**); ORR (**C**); and DCR (**D**).
Abbreviations: DCR, disease control rate; ORR, overall response rate; OS, overall survival; SE, standard error; OR, odds ratio.

cytokine) level in PC patients was significantly increased, whereas IL-4 (Th2 cytokine) level was obviously decreased, indicating a passably more important role of IFN-γ and IL-4 during the DC–CIK immunotherapy.

Safety is a crucial criterion for the popularization of clinical application of DC–CIK immunotherapy. Based on published literature up to May 2017, our meta-analysis shows that DC–CIK immunotherapy is a safe therapeutic strategy for PC, as no significant difference in adverse events was observed between with and without immunotherapy. Most side effects of DC–CIK immunotherapy were well tolerated by PC patients, and no serious adverse events or death occurred during DC–CIK therapy.

In this analysis, PC patients were treated by DC–CIK immunotherapy in eight trials and CIK alone in the other six trials. To provide evidence for making the choice of using CIK or DC–CIK, difference between their therapeutic effects was evaluated by sensitivity analysis, which showed that both CIK and DC–CIK were effective in treating PC without statistical difference. These results are inconsistent with in vitro study in which DC–CIK represented higher antitumor activity than CIK alone and need to be further explored. Moreover, we conducted publication bias to verify the reliability of our result and no obvious bias exists in our primary conclusions.

Limitations

A total of 14 included trials, which met our selection criteria, turned out to be conducted on Chinese population. One trial conducted in Korea was included in our research originally but was then excluded because it lacked insufficient data. Besides, data analyzed in this research were collected from published papers rather than original patient records, which may lead to overestimation of curative effects.

Conclusion

Our meta-analysis shows that the combination of DC–CIK immunotherapy and chemotherapy is a promising immune treatment for PC patients. It markedly prolongs PC patients' survival time passably by reconstructing patients' immune function.

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Author contributions

All authors contributed toward data analysis and drafting and critically revising the paper 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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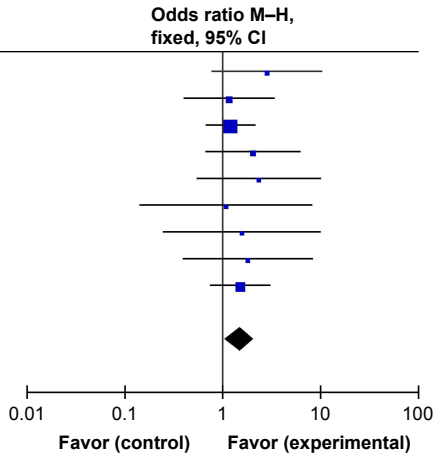
Supplementary materials

A

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Kang and Zhang (2016)[25]	10	22	5	22	5.0	2.83 (0.77, 10.43)
Li (2016)[26]	15	27	14	27	11.4	1.16 (0.40, 3.39)
Mu et al (2016)[28]	44	90	40	90	37.6	1.20 (0.67, 2.15)
Shen et al (2015)[29]	11	38	6	36	8.1	2.04 (0.66, 6.26)
Wang (2015)[30]	5	10	9	30	4.1	2.33 (0.54, 10.10)
Wang et al (2013)[16]	2	28	2	30	3.3	1.08 (0.14, 8.21)
Wang et al (2016)[17]	2	25	3	57	3.1	1.57 (0.24, 10.00)
Wen et al (2013)[31]	5	30	3	30	4.6	1.80 (0.39, 8.32)
Zhang et al (2013)[32]	28	58	26	68	22.8	1.51 (0.74, 3.07)
Total (95% CI)		**328**		**390**	**100**	**1.49 (1.06, 2.10)**
Total events	122		108			

Heterogeneity: χ^2=2.50, *df*=8 (*P*=0.96); I^2=0%
Test for overall effect: *Z*=2.32 (*P*=0.02)



B

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Kang and Zhang (2016)[25]	2	22	4	22	3.8	0.45 (0.07, 2.76)
Li (2016)[26]	2	27	3	27	2.9	0.64 (0.10, 4.17)
Mu et al (2016)[28]	8	90	15	90	14.5	0.49 (0.20, 1.22)
Shen et al (2015)[29]	14	38	22	36	15.1	0.37 (0.15, 0.95)
Wang (2015)[30]	3	10	10	30	3.7	0.86 (0.18, 4.04)
Wang et al (2013)[16]	15	28	18	30	8.5	0.77 (0.27, 2.18)
Wang et al (2016)[17]	8	25	40	57	17.5	0.20 (0.07, 0.55)
Wen et al (2013)[31]	8	30	17	30	13.2	0.28 (0.09, 0.82)
Zhang et al (2013)[32]	14	58	28	68	20.7	0.45 (0.21, 0.98)
Total (95% CI)		**328**		**390**	**100**	**0.43 (0.30, 0.61)**
Total events	74		157			

Heterogeneity: χ^2=5.13, *df*=8 (*P*=0.74); I^2=0%
Test for overall effect: *Z*=4.69 (*P*<0.00001)

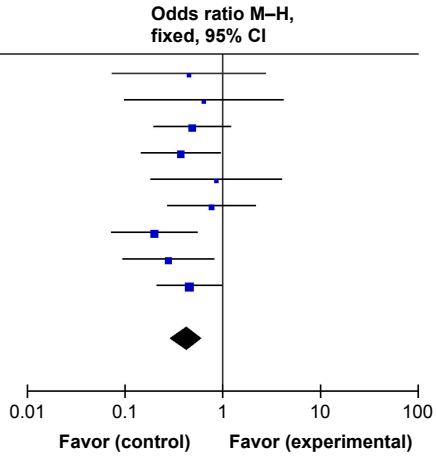
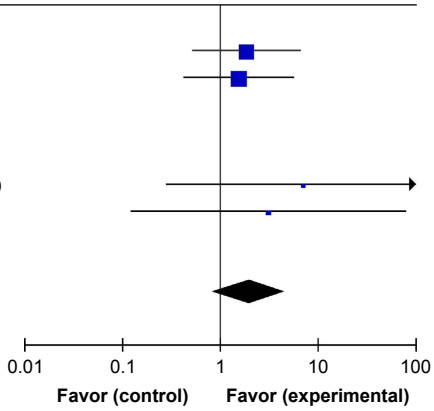


Figure S1 (*Continued*)

C

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Kang and Zhang (2016)[25]	0	22	0	22		Not estimable
Li (2016)[26]	8	27	5	27	43.9	1.85 (0.52, 6.63)
Mu et al (2016)[28]	6	90	4	90	46.6	1.54 (0.42, 5.64)
Shen et al (2015)[29]	0	38	0	36		Not estimable
Wang (2015)[30]	0	10	0	30		Not estimable
Wang et al (2013)[16]	0	28	0	30		Not estimable
Wang et al (2016)[17]	1	25	0	57	3.6	7.04 (0.28,178.94)
Wen et al (2013)[31]	1	30	0	30	5.9	3.10 (0.12, 79.23)
Zhang et al (2013)[32]	0	58	0	68		Not estimable
Total (95% CI)		**328**		**390**	**100**	**1.97 (0.85, 4.54)**
Total events	16		9			

Heterogeneity: χ^2=0.82, *df*=3 (*P*=0.84); I^2=0%
Test for overall effect: *Z*=1.59 (*P*=0.11)



D

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Kang and Zhang (2016)[25]	10	22	13	22	10.9	0.58 (0.17, 1.90)
Li (2016)[26]	2	27	5	27	7.1	0.35 (0.06, 2.00)
Mu et al (2016)[28]	32	90	31	90	30.7	1.05 (0.57, 1.94)
Shen et al (2015)[29]	13	38	8	36	8.3	1.82 (0.65, 5.11)
Wang (2015)[30]	2	10	11	30	6.8	0.43 (0.08, 2.41)
Wang et al (2013)[16]	11	28	10	30	9.0	1.29 (0.44, 3.78)
Wang et al (2016)[17]	14	25	14	57	5.8	3.91 (1.45, 10.56)
Wen et al (2013)[31]	16	30	10	30	7.2	2.29 (0.80, 6.50)
Zhang et al (2013)[32]	16	58	14	68	14.3	1.47 (0.65, 3.35)
Total (95% CI)		**328**		**390**	**100**	**1.31 (0.95, 1.80)**
Total events	116		116			

Heterogeneity: χ^2=12.32, *df*=8 (*P*=0.14); I^2=35%
Test for overall effect: *Z*=1.63 (*P*=0.10)

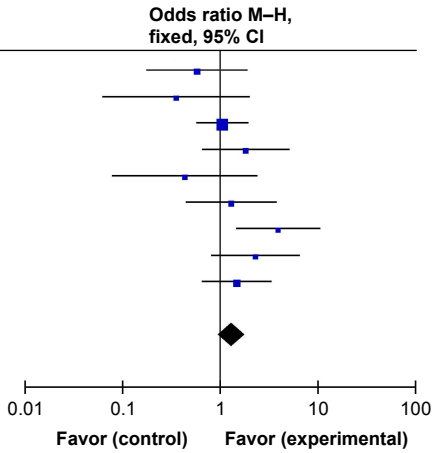


Figure S1 Forest plots of the comparison of PR (**A**), PD (**B**), CR (**C**), and SD (**D**) rates between the experimental and control groups.
Notes: Control group, chemotherapy alone group; experimental group, chemotherapy with DC–CIK immunotherapy. The fixed-effects meta-analysis model (M–H method) was used.
Abbreviations: CI, confidence interval; CR, complete response; CIK, cytokine-induced killer; DC–CIK, dendritic cells–CIK; M–H, Mantel–Haenszel; PD, progressive disease; PR, partial response; SD, stable disease.

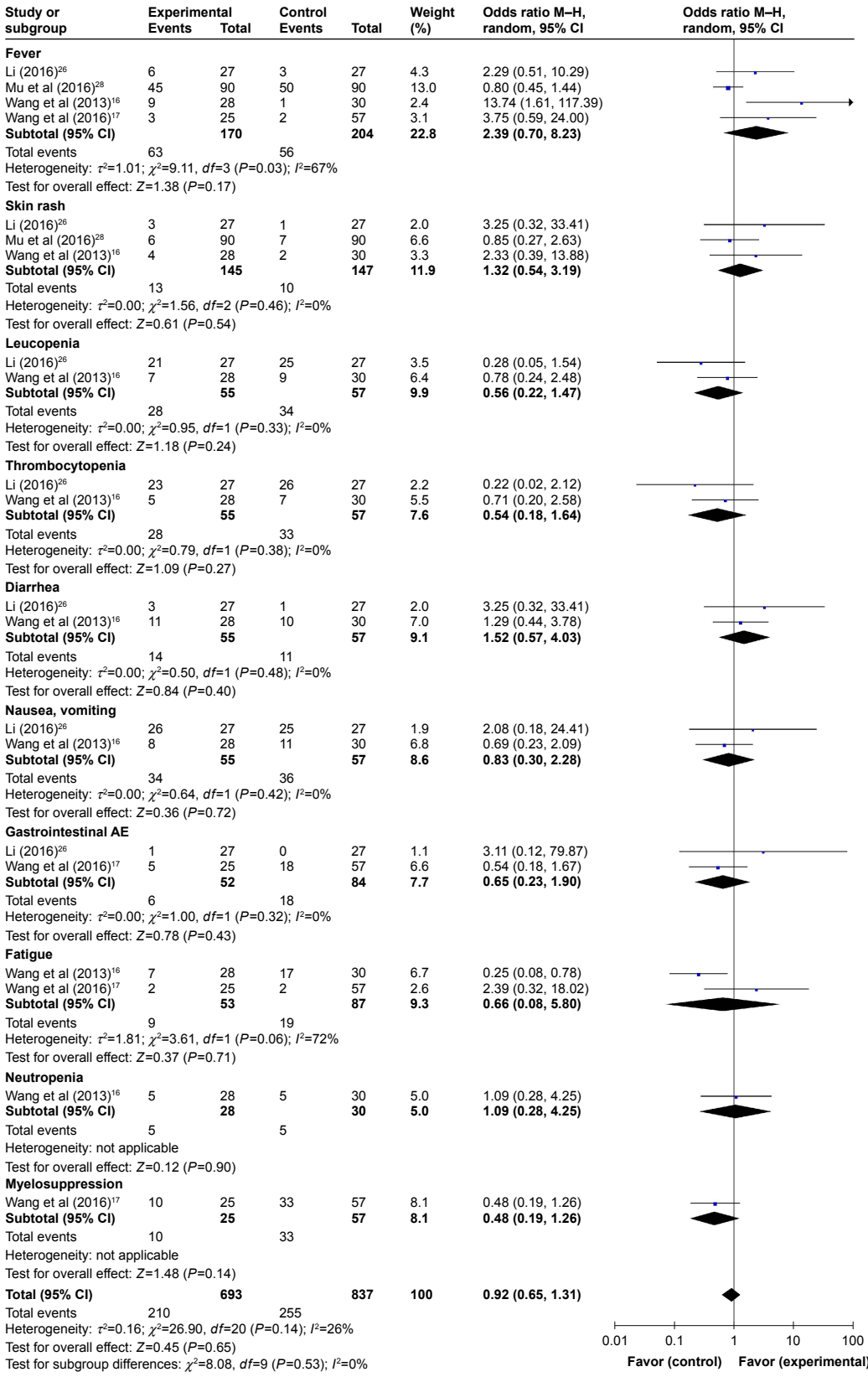


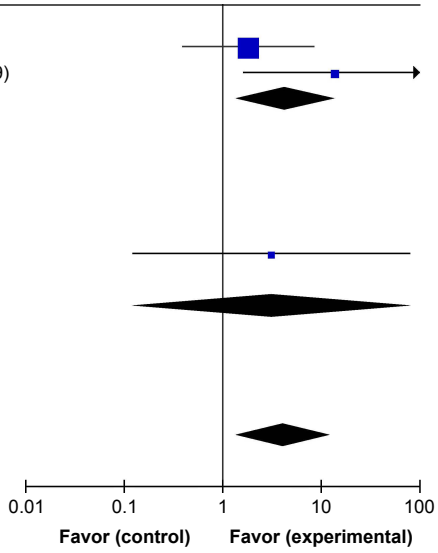
Figure S2 Forest plot of the comparison of adverse effects between the experimental and control groups.

Notes: Control group, chemotherapy alone group; experimental group, chemotherapy with DC–CIK immunotherapy. The random effects meta-analysis model (M–H method) was used.

Abbreviations: CI, confidence interval; DC–CIK, dendritic cells–cytokine-induced killer; M–H, Mantel–Haenszel.

A

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Fever I + II						
Li (2016)[26]	5	27	3	27	68.4	1.82 (0.39, 8.51)
Wang et al (2013)[16]	9	28	1	30	18.3	13.74 (1.61, 117.39)
Subtotal (95% CI)		**55**		**57**	**86.8**	**4.34 (1.35, 13.89)**
Total events	14		4			
Heterogeneity: χ^2=2.33, *df*=1 (*P*=0.13); I^2=57%						
Test for overall effect: *Z*=2.47 (*P*=0.01)						
Fever III + IV						
Li (2016)[26]	1	27	0	27	13.2	3.11 (0.12, 79.87)
Wang et al (2013)[16]	0	28	0	30		Not estimable
Subtotal (95% CI)		**55**		**57**	**13.2**	**3.11 (0.12, 79.87)**
Total events	1		0			
Heterogeneity: not applicable						
Test for overall effect: *Z*=0.69 (*P*=0.49)						
Total (95% CI)		**110**		**114**	**100**	**4.18 (1.40, 12.48)**
Total events	15		4			
Heterogeneity: χ^2=2.33, *df*=2 (*P*=0.31); I^2=14%						
Test for overall effect: *Z*=2.56 (*P*=0.01)						
Test for subgroup differences: χ^2=0.04, *df*=1 (*P*=0.85); I^2=0%						



B

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Skin rash I + II						
Li (2016)[26]	3	27	1	27	28.9	3.25 (0.32, 33.41)
Wang et al (2013)[16]	3	28	2	30	56.1	1.68 (0.26, 10.89)
Subtotal (95% CI)		**55**		**57**	**85.1**	**2.21 (0.52, 9.36)**
Total events	6		3			
Heterogeneity: χ^2=0.19, *df*=1 (*P*=0.66); I^2=0%						
Test for overall effect: *Z*=1.08 (*P*=0.28)						
Skin rash III + IV						
Li (2016)[26]	0	27	0	27		Not estimable
Wang et al (2013)[16]	1	28	0	30	14.9	3.33 (0.13, 85.11)
Subtotal (95% CI)		**55**		**57**	**14.9**	**3.33 (0.13, 85.11)**
Total events	1		0			
Heterogeneity: not applicable						
Test for overall effect: *Z*=0.73 (*P*=0.47)						
Total (95% CI)		**110**		**114**	**100**	**2.38 (0.64, 8.85)**
Total events	7		3			
Heterogeneity: χ^2=0.24, *df*=2 (*P*=0.89); I^2=0%						
Test for overall effect: *Z*=1.29 (*P*=0.20)						
Test for subgroup differences: χ^2=0.05, *df*=1 (*P*=0.82); I^2=0%						

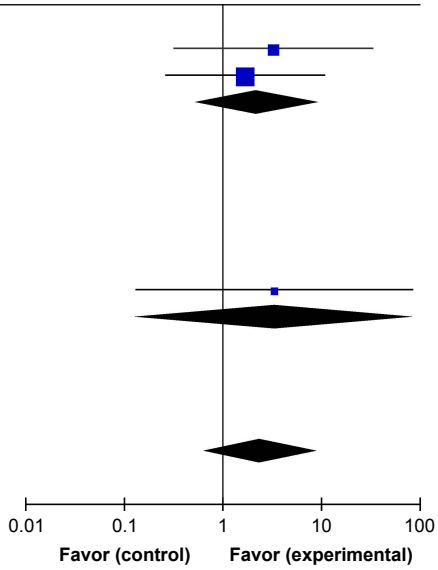
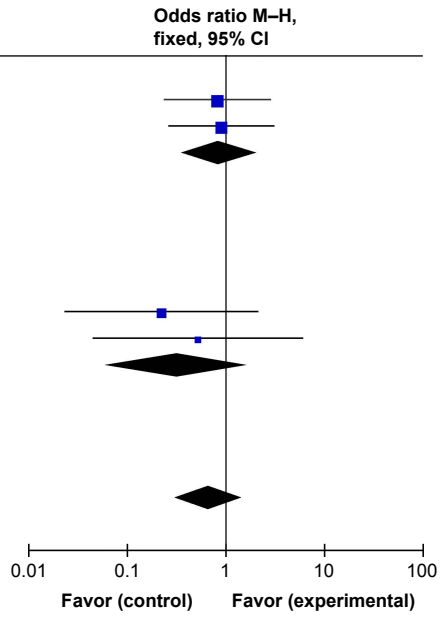


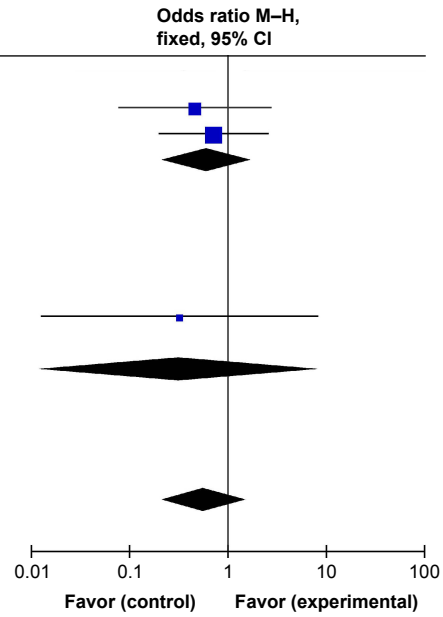
Figure S3 (*Continued*)

C



Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Leukopenia I + II						
Li (2016)[26]	20	27	21	27	33.1	0.82 (0.23, 2.85)
Wang et al (2013)[16]	6	28	7	30	32.2	0.90 (0.26, 3.09)
Subtotal (95% CI)		**55**		**57**	**65.3**	**0.86 (0.36, 2.06)**
Total events	26		28			
Heterogeneity: χ^2=0.01, *df*=1 (*P*=0.92); I^2=0%						
Test for overall effect: *Z*=0.35 (*P*=0.73)						
Leukopenia III + IV						
Li (2016)[26]	1	27	4	27	23.4	0.22 (0.02, 2.12)
Wang et al (2013)[16]	1	28	2	30	11.3	0.52 (0.04, 6.06)
Subtotal (95% CI)		**55**		**57**	**34.7**	**0.32 (0.06, 1.64)**
Total events	2		6			
Heterogeneity: χ^2=0.25, *df*=1 (*P*=0.62); I^2=0%						
Test for overall effect: *Z*=1.37 (*P*=0.17)						
Total (95% CI)		**110**		**114**	**100**	**0.67 (0.31, 1.43)**
Total events	28		34			
Heterogeneity: χ^2=1.27, *df*=3 (*P*=0.74); I^2=0%						
Test for overall effect: *Z*=1.04 (*P*=0.30)						
Test for subgroup differences: χ^2=1.08, *df*=1 (*P*=0.30); I^2=7.8%						

D

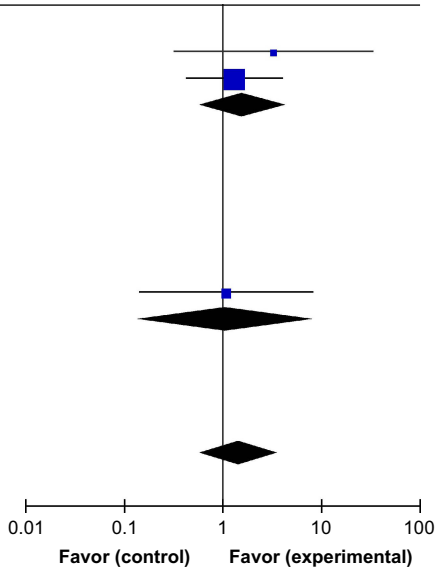


Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Thrombocytopenia I + II						
Li (2016)[26]	23	27	25	27	34.5	0.46 (0.08, 2.75)
Wang et al (2013)[16]	5	28	7	30	51.7	0.71 (0.20, 2.58)
Subtotal (95% CI)		**55**		**57**	**86.3**	**0.61 (0.22, 1.73)**
Total events	28		32			
Heterogeneity: χ^2=0.15, *df*=1 (*P*=0.70); I^2=0%						
Test for overall effect: *Z*=0.92 (*P*=0.36)						
Thrombocytopenia III + IV						
Li (2016)[26]	0	27	1	27	13.7	0.32 (0.01, 8.24)
Wang et al (2013)[16]	0	28	0	30		Not estimable
Subtotal (95% CI)		**55**		**57**	**13.7**	**0.32 (0.01, 8.24)**
Total events	0		1			
Heterogeneity: not applicable						
Test for overall effect: *Z*=0.69 (*P*=0.49)						
Total (95% CI)		**110**		**114**	**100**	**0.57 (0.21, 1.53)**
Total events	28		33			
Heterogeneity: χ^2=0.29, *df*=2 (*P*=0.86); I^2=0%						
Test for overall effect: *Z*=1.11 (*P*=0.27)						
Test for subgroup differences: χ^2=0.14, *df*=1 (*P*=0.71); I^2=0%						

Figure S3 (*Continued*)

E

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Diarrhea I + II						
Li (2016)[26]	3	27	1	27	11.2	3.25 (0.32, 33.41)
Wang et al (2013)[16]	9	28	8	30	66.2	1.30 (0.42, 4.04)
Subtotal (95% CI)		**55**		**57**	**77.4**	**1.58 (0.58, 4.32)**
Total events	12		9			
Heterogeneity: χ^2=0.48, *df*=1 (*P*=0.49); I^2=0%						
Test for overall effect: *Z*=0.90 (*P*=0.37)						
Diarrhea III + IV						
Li (2016)[26]	0	27	0	27		Not estimable
Wang et al (2013)[16]	2	28	2	30	22.6	1.08 (0.14, 8.21)
Subtotal (95% CI)		**55**		**57**	**22.6**	**1.08 (0.14, 8.21)**
Total events	2		2			
Heterogeneity: not applicable						
Test for overall effect: *Z*=0.07 (*P*=0.94)						
Total (95% CI)		**110**		**114**	**100**	**1.47 (0.60, 3.61)**
Total events	14		11			
Heterogeneity: χ^2=0.58, *df*=2 (*P*=0.75); I^2=0%						
Test for overall effect: *Z*=0.84 (*P*=0.40)						
Test for subgroup differences: χ^2=0.11, *df*=1 (*P*=0.74); I^2=0%						



F

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Nausea, vomiting I + II						
Li (2016)[26]	26	27	25	27	10.0	2.08 (0.18, 24.41)
Wang et al (2013)[16]	8	28	10	30	74.6	0.80 (0.26, 2.45)
Subtotal (95% CI)		**55**		**57**	**84.6**	**0.95 (0.35, 2.60)**
Total events	34		35			
Heterogeneity: χ^2=0.48, *df*=1 (*P*=0.49); I^2=0%						
Test for overall effect: *Z*=0.10 (*P*=0.92)						
Nausea, vomiting III + IV						
Li (2016)[26]	0	27	0	27		Not estimable
Wang et al (2013)[16]	0	28	1	30	15.4	0.35 (0.01, 8.83)
Subtotal (95% CI)		**55**		**57**	**15.4**	**0.35 (0.01, 8.83)**
Total events	0		1			
Heterogeneity: not applicable						
Test for overall effect: *Z*=0.64 (*P*=0.52)						
Total (95% CI)		**110**		**114**	**100**	**0.86 (0.33, 2.21)**
Total events	34		36			
Heterogeneity: χ^2=0.82, *df*=2 (*P*=0.67); I^2=0%						
Test for overall effect: *Z*=0.32 (*P*=0.75)						
Test for subgroup differences: χ^2=0.34, *df*=1 (*P*=0.56); I^2=0%						

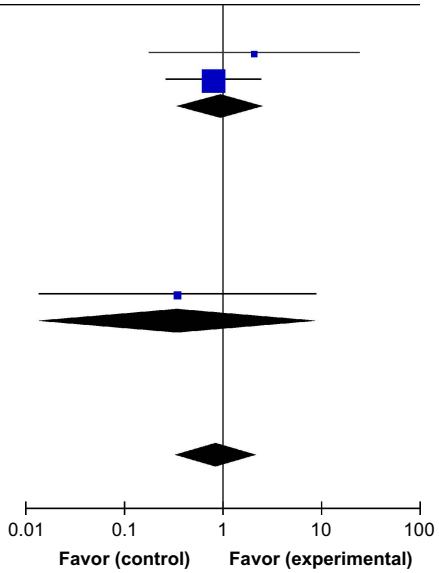


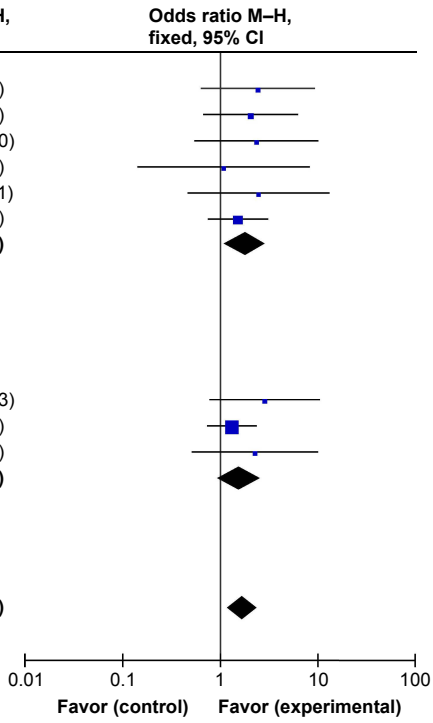
Figure S3 Forest plots of the comparison of all-grade adverse effects including fever (**A**), skin rash (**B**), leukopenia (**C**), thrombocytopenia (**D**), diarrhea (**E**), and nausea and vomiting (**F**).

Notes: Control group, chemotherapy alone group; experimental group, chemotherapy with DC–CIK immunotherapy. The fixed-effects meta-analysis model (M–H method) was used.

Abbreviations: CI, confidence interval; DC–CIK, dendritic cells–cytokine-induced killer; M–H, Mantel–Haenszel.

A

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
CIK						
Li (2016)[26]	23	27	19	27	5.6	2.42 (0.63, 9.29)
Shen et al (2015)[29]	11	38	6	36	8.8	2.04 (0.66, 6.26)
Wang (2015)[30]	5	10	9	30	4.5	2.33 (0.54, 10.10)
Wang et al (2013)[16]	2	28	2	30	3.6	1.08 (0.14, 8.21)
Wang et al (2016)[17]	3	25	3	57	3.2	2.45 (0.46, 13.11)
Zhang et al (2013)[32]	28	58	26	68	24.8	1.51 (0.74, 3.07)
Subtotal (95% CI)		**186**		**248**	**50.5**	**1.80 (1.12, 2.90)**
Total events	72		65			
Heterogeneity: χ^2=0.97, *df*=5 (*P*=0.96); I^2=0%						
Test for overall effect: *Z*=2.43 (*P*=0.01)						
DC–CIK						
Kang and Zhang (2016)[25]	10	22	5	22	5.5	2.83 (0.77, 10.43)
Mu et al (2016)[28]	50	90	44	90	39.2	1.31 (0.73, 2.35)
Wen et al (2013)[31]	6	30	3	30	4.8	2.25 (0.51, 9.99)
Subtotal (95% CI)		**142**		**142**	**49.5**	**1.57 (0.95, 2.58)**
Total events	66		52			
Heterogeneity: χ^2=1.39, *df*=2 (*P*=0.50); I^2=0%						
Test for overall effect: *Z*=1.76 (*P*=0.08)						
Total (95% CI)		**328**		**390**	**100**	**1.69 (1.20, 2.38)**
Total events	138		117			
Heterogeneity: χ^2=2.53, *df*=8 (*P*=0.96); I^2=0%						
Test for overall effect: *Z*=2.98 (*P*=0.003)						
Test for subgroup differences: χ^2=0.16, *df*=1 (*P*=0.69); I^2=0%						



B

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
CIK						
Li (2016)[26]	25	27	24	27	4.4	1.56 (0.24, 10.19)
Shen et al (2015)[29]	24	38	14	36	13.1	2.69 (1.05, 6.90)
Wang (2015)[30]	7	10	21	30	7.8	1.00 (0.21, 4.77)
Wang et al (2013)[16]	13	28	12	30	15.4	1.30 (0.46, 3.68)
Wang et al (2016)[17]	17	25	17	57	8.2	5.00 (1.81, 13.78)
Zhang et al (2013)[32]	44	58	40	68	22.0	2.20 (1.02, 4.76)
Subtotal (95% CI)		**186**		**248**	**70.9**	**2.25 (1.47, 3.44)**
Total events	130		128			
Heterogeneity: χ^2=4.77, *df*=5 (*P*=0.44); I^2=0%						
Test for overall effect: *Z*=3.73 (*P*=0.0002)						
DC–CIK						
Kang and Zhang (2016)[25]	20	22	18	22	4.0	2.22 (0.36, 13.62)
Mu et al (2016)[28]	82	90	75	90	16.5	2.05 (0.82, 5.11)
Wen et al (2013)[31]	22	30	13	30	8.6	3.60 (1.22, 10.64)
Subtotal (95% CI)		**142**		**142**	**29.1**	**2.53 (1.32, 4.85)**
Total events	124		106			
Heterogeneity: χ^2=0.63, *df*=2 (*P*=0.73); I^2=0%						
Test for overall effect: *Z*=2.79 (*P*=0.005)						
Total (95% CI)		**328**		**390**	**100**	**2.33 (1.63, 3.33)**
Total events	254		234			
Heterogeneity: χ^2=5.49, *df*=8 (*P*=0.70); I^2=0%						
Test for overall effect: *Z*=4.65 (*P*<0.00001)						
Test for subgroup differences: χ^2=0.09, *df*=1 (*P*=0.77); I^2=0%						

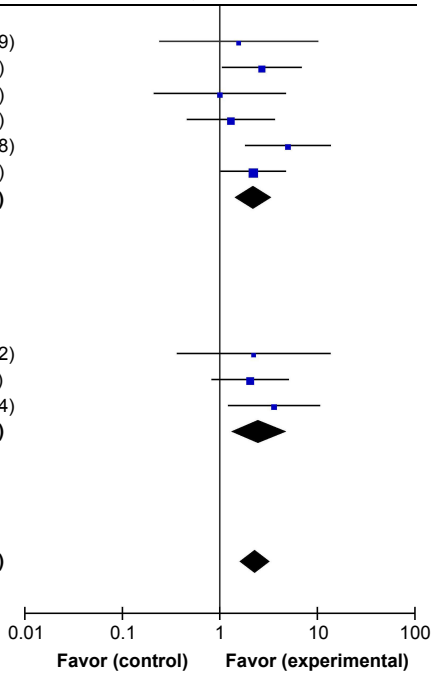


Figure S4 Forest plots of the comparison of ORR (**A**) and DCR (**B**) in CIK and DC–CIK subgroups.

Notes: Control group, chemotherapy alone group; experimental group, chemotherapy with DC–CIK immunotherapy. The fixed-effects meta-analysis model (M–H method) was used.

Abbreviations: CI, confidence interval; CIK, cytokine-induced killer; DC–CIK, dendritic cells–CIK; DCR, disease control rate; M–H, Mantel–Haenszel; ORR, overall response rate.

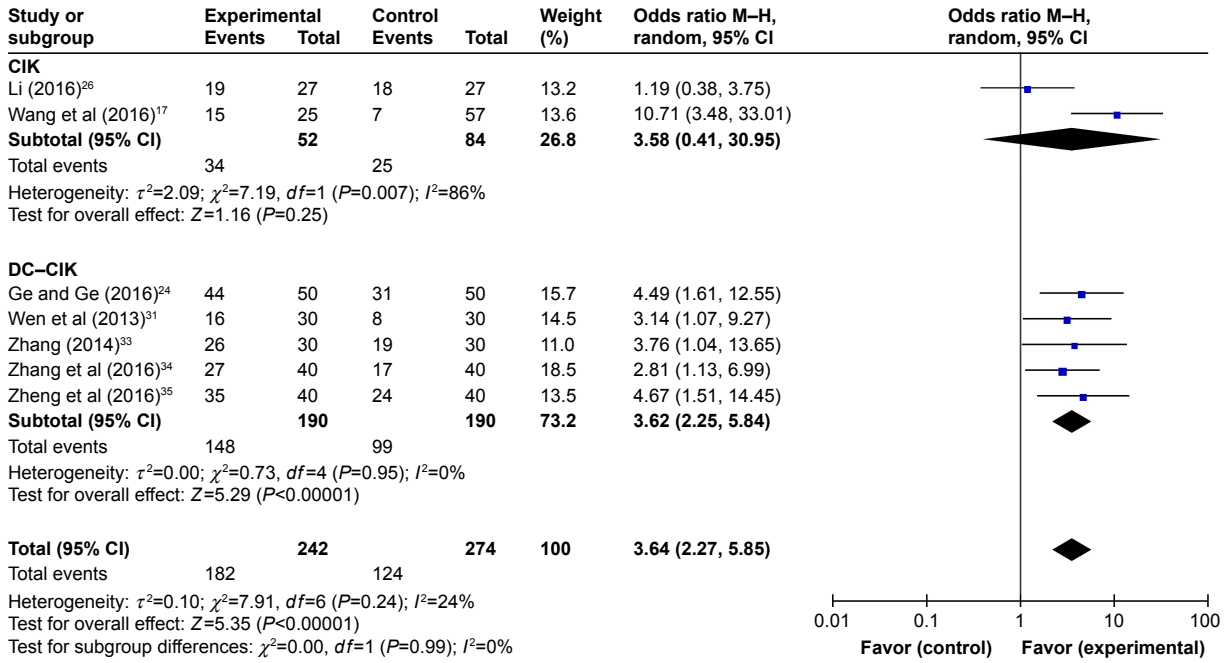


Figure S5 Forest plot of the comparison of 1-year OS in CIK and DC–CIK subgroups.

Notes: Control group, chemotherapy alone group; experimental group, chemotherapy with DC–CIK immunotherapy. The random effects meta-analysis model (M–H method) was used.

Abbreviations: CI, confidence interval; CIK, cytokine-induced killer; DC–CIK, dendritic cells–CIK; M–H, Mantel–Haenszel; OS, overall survival.