

World Journal of *Gastroenterology*

World J Gastroenterol 2019 July 21; 25(27): 3468-3663



OPINION REVIEW

- 3468** Stricter national standards are required for credentialing of endoscopic-retrograde-cholangiopancreatography in the United States
Cappell MS, Friedel DM
- 3484** Colorectal peritoneal metastases: Optimal management review
Sánchez-Hidalgo JM, Rodríguez-Ortiz L, Arjona-Sánchez Á, Rufián-Peña S, Casado-Adam Á, Cosano-Álvarez A, Briceño-Delgado J

REVIEW

- 3503** Eosinophils in the gastrointestinal tract and their role in the pathogenesis of major colorectal disorders
Loktionov A
- 3527** Immune suppression in chronic hepatitis B infection associated liver disease: A review
Li TY, Yang Y, Zhou G, Tu ZK

MINIREVIEWS

- 3538** Device-assisted enteroscopy: A review of available techniques and upcoming new technologies
Schneider M, Höllerich J, Beyna T
- 3546** Identifying high-risk individuals for gastric cancer surveillance from western and eastern perspectives: Lessons to learn and possibility to develop an integrated approach for daily practice
Quach DT, Hiyama T, Gotoda T
- 3563** Is the treatment outcome of hepatocellular carcinoma inferior in elderly patients?
Chu KKW, Chok KSH

ORIGINAL ARTICLE**Basic Study**

- 3572** Mucosal healing progression after acute colitis in mice
Vidal-Lletjós S, Andriamihaja M, Blais A, Grauso M, Lepage P, Davila AM, Gaudichon C, Leclerc M, Blachier F, Lan A
- 3590** Lingguizhugan decoction attenuates diet-induced obesity and hepatosteatosis *via* gut microbiota
Liu MT, Huang YJ, Zhang TY, Tan LB, Lu XF, Qin J

Retrospective Cohort Study

- 3607** Intermediate-advanced hepatocellular carcinoma in Argentina: Treatment and survival analysis
Piñero F, Marciano S, Fernández N, Silva J, Anders M, Zerega A, Ridruejo E, Romero G, Ameigeiras B, D'Amico C, Gaité L, Bermúdez C, Reggiardo V, Colombato L, Gadano A, Silva M

Retrospective Study

- 3619** Quantitative diffusion-weighted magnetic resonance enterography in ileal Crohn's disease: A systematic analysis of intra and interobserver reproducibility
Yu H, Shen YQ, Tan FQ, Zhou ZL, Li Z, Hu DY, Morelli JN

SYSTEMATIC REVIEWS

- 3634** Bioartificial liver support systems for acute liver failure: A systematic review and meta-analysis of the clinical and preclinical literature
He YT, Qi YN, Zhang BQ, Li JB, Bao J

META-ANALYSIS

- 3649** Immunotherapy with dendritic cells and cytokine-induced killer cells for hepatocellular carcinoma: A meta-analysis
Cao J, Kong FH, Liu X, Wang XB

ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Dar-In Tai, MD, PhD, Attending Doctor, Chief Doctor, Professor, Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, Taipei 105, Taiwan

AIMS AND SCOPE

World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. The *WJG* Editorial Board consists of 701 experts in gastroenterology and hepatology from 58 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, etc. The *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

INDEXING/ABSTRACTING

The *WJG* is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2019 edition of Journal Citation Report® cites the 2018 impact factor for *WJG* as 3.411 (5-year impact factor: 3.579), ranking *WJG* as 35th among 84 journals in gastroenterology and hepatology (quartile in category Q2). CiteScore (2018): 3.43.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yu-Jie Ma*
 Proofing Production Department Director: *Yun-Xiaojuan Wu*

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Subrata Ghosh, Andrzej S. Tarnawski

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

EDITORIAL OFFICE

Ze-Mao Gong, Director

PUBLICATION DATE

July 21, 2019

COPYRIGHT

© 2019 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Immunotherapy with dendritic cells and cytokine-induced killer cells for hepatocellular carcinoma: A meta-analysis

Jing Cao, Fan-Hua Kong, Xi Liu, Xiao-Bo Wang

ORCID number: Jing Cao (0000-0001-9302-4850); Fan-Hua Kong (0000-0003-3126-2508); Xi Liu (0000-0001-7349-8792); Xiao-Bo Wang (0000-0002-3603-3707).

Author contributions: Cao J performed the research; Cao J, Kong FH and Liu X analyzed the data; Cao J drafted the paper; Wang XB designed the research and revised the article.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Data sharing statement: No additional data are available.

PRISMA 2009 Checklist statement: The manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Received: March 18, 2019

Peer-review started: March 18, 2019

Jing Cao, Xiao-Bo Wang, Department of Surgery, Technical University of Munich, Munich 80333, Germany

Fan-Hua Kong, Xi Liu, Department of General Surgery, The Second Xiangya Hospital, Central South University, Changsha 410011, Hunan Province, China

Corresponding author: Xiao-Bo Wang, MD, Surgeon, Department of Surgery, Technical University of Munich, Arcisstrasse 21, Munich 80333, Germany. xiaobo.wang@tum.de
Telephone: +49-152-37359648

Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) has been revealed as the second most common cause of cancer-related deaths worldwide. The introduction of cell-based immunotherapy, including dendritic cells (DCs) and cytokine-induced killer cells (CIKs), has brought HCC patients an effective benefit. However, the efficacy and necessity of cellular immunotherapy after different interventional therapy remains to be further explored.

AIM

To investigate the efficacy of cellular immunotherapy, involving DCs and CIKs, combined with different conventional treatments of HCC.

METHODS

We performed a literature search on PubMed and Web of Science up to February 15, 2019. Long-term efficacy (overall survival and recurrence) and short-term adverse effects were investigated to assess the effectiveness of immunotherapy with DCs and/or CIKs. Review Manager 5.3 was used to perform the analysis.

RESULTS

A total of 22 studies involving 3756 patients selected by eligibility inclusion criteria were forwarded for meta-analysis. Combined with the conventional clinical treatment, immunotherapy with DCs and/or CIKs was demonstrated to significantly improve overall survival at 6 mo [risk ratio (RR) = 1.07; 95% confidence interval (CI): 1.01-1.13, $P = 0.02$], 1 year (RR = 1.12; 95% CI: 1.07-1.17, $P < 0.00001$), 3 years (RR = 1.23; 95% CI: 1.15-1.31, $P < 0.00001$) and 5 years (RR = 1.26; 95% CI: 1.15-1.37, $P < 0.00001$). Recurrence rate was significantly reduced by cellular immunotherapy at 6 mo (RR = 0.50; 95% CI: 0.36-0.69, $P < 0.0001$) and 1 year (RR = 0.82; 95% CI: 0.75-0.89, $P < 0.00001$). Adverse effect assessment addressed that immunotherapy with DCs and/or CIKs was accepted as a safe, feasible treatment.

First decision: April 11, 2019
Revised: April 18, 2019
Accepted: June 7, 2019
Article in press: June 8, 2019
Published online: July 21, 2019

P-Reviewer: Jiang YF, Tashiro H
S-Editor: Ma RY
L-Editor: Filipodia
E-Editor: Liu JH



CONCLUSION

Combination immunotherapy with DCs, CIKs and DC/CIK with various routine treatments for HCC was evidently suggested to improve patients' prognosis by increasing overall survival and reducing cancer recurrence.

Key words: Hepatocellular carcinoma; Immunotherapy; Dendritic cells; Cytokine-induced killer cells

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Hepatocellular carcinoma has been revealed as the second most common cause of cancer-related deaths worldwide. Though several analyses have supported the effective benefit of cellular immunotherapy when combined with specific hepatocellular carcinoma treatment, the efficacy and necessity of cellular immunotherapy after different interventional therapy remains to be interrogated. Our study suggested that the combination of immunotherapy with dendritic cells, cytokine-induced killer cells and a combination of the two with various routine hepatocellular carcinoma treatments could evidently improve patients' prognosis by increasing the overall survival and reduce the recurrence of the malignancy.

Citation: Cao J, Kong FH, Liu X, Wang XB. Immunotherapy with dendritic cells and cytokine-induced killer cells for hepatocellular carcinoma: A meta-analysis. *World J Gastroenterol* 2019; 25(27): 3649-3663

URL: <https://www.wjgnet.com/1007-9327/full/v25/i27/3649.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v25.i27.3649>

INTRODUCTION

Liver cancer, approximately 75% of which is ascribed to hepatocellular carcinoma (HCC), has been revealed as the second most common cause of cancer-related deaths worldwide with around 745000 deaths annually^[1]. Both the incidence and mortality are rising worldwide. Cirrhosis, hepatitis B virus and hepatitis C virus are commonly regarded as the main risk factors for HCC.

Curative treatment is achieved by surgical resection, orthotopic liver transplantation, transarterial chemoembolization (TACE) and local percutaneous tumor ablation. However, these curative approaches are only accessible to limited numbers of patients, as most are diagnosed at advanced stages with unresectable tumors. Although much progress has been made with promising phase II trial results, drug development has been disappointing with many failures in phase III trials^[2]; hence, few drugs have been approved so far by the United States Food and Drug Administration. A multitarget tyrosine kinase inhibitor, sorafenib, the only approved systemic therapy, achieves an increased survival of only up to 3 mo^[3,4].

Immunotherapy was introduced into the field as the ability to escape from immunological surveillance, which forms the basis for tumor progression. The underlying mechanism comprises of defective antigen presentation, dysfunction of effector T cells, cytokine disarray and alterations in immune checkpoints^[5]. While conventional chemotherapy exerts its effect by directly reducing tumor volume morphologically, immunotherapy works in an indirect way and takes longer to induce an effective immune response. However, it provides a more durable antitumor effect. Immune-based approaches include cytokines, vaccines, adoptive cell therapy [based on peripheral blood mononuclear cells or dendritic cells (DCs)]^[6-8], tumor-antibody-based immunotherapy^[9] and immune checkpoint inhibitors. Recombinant interferon- α was the first immunotherapeutic agent introduced into the field, although, even with its features of immunostimulation and antiangiogenesis, it failed to show a significant effect in clinical trials of patients with HCC^[10,11].

Vaccine strategies are carried out on different anti-cancer platforms, including RNA-, peptide- and protein-based vaccines, whole-tumor-cell vaccine, and most widely, DC-based vaccines. DC-based vaccines are adapted more for solid malignancies, including melanoma, renal cancer and prostate cancer, as well as HCC^[12,13]. As mature DCs prime T cells and boost memory T cells, induction of DC maturation by Toll-like receptor ligand or cytokines is often applied clinically. Cross-

presentation, the process of DCs presenting captured antigen to CD8⁺ cells via major histocompatibility complex class I, is regarded as a critical step in the efficient induction of antitumor cytotoxic response^[12]. An important subtype of DCs was identified in 2010 on account of its high capability in cross-presentation with high expression of CD141 and Toll-like receptor 3. These CD141⁺ DCs yielded high amounts of type I interferon under stimulation with polyinosinic-polycytidylic acid, which leads to a vigorous T helper 1 cell response; hence the effective anticancer response^[14]. Therefore, polyinosinic-polycytidylic acid and its derivatives are adopted as adjuvants for DC-based vaccines.

Adoptive cell therapy is commonly performed with cytokine-induced killer cells (CIKs), tumor-infiltrating lymphocytes and genetically modified T cells. Among these, CIKs have been used in more clinical trials. CIKs, consisting of NKG2D^{high} T cells, activated natural killer cells and natural killer T cells^[15], are generated *ex vivo* from peripheral blood mononuclear cells and stimulated with cytokines and antibodies targeting CD3. CIKs harbor high capacity of proliferation and have a cytolytic effect against cancer cells. Although several analyses have supported the beneficial effect of cellular immunotherapy when combined with specific HCC treatment^[16,17], the efficacy and necessity of cellular immunotherapy after different interventional therapy remains to be interrogated. In this study, a systematic review and meta-analysis was performed to investigate the efficacy of cellular immunotherapy, involving DCs, CIKs and DC/CIK combination therapy, combined with different treatments of HCC.

MATERIALS AND METHODS

Systematic literature search

We conducted a widespread literature search on PubMed and Web of Science Core Collection. Articles up to February 15, 2019 were filtered out by key words including hepatocellular OR liver AND cancer OR tumor OR tumour OR carcinoma OR neoplasm AND immunotherapy OR immune checkpoint OR immunotherapeutic. Study selection was conducted by two independent investigators. Discrepancies were resolved by discussion and consensus. Full text was retrieved for further decision if the abstract was insufficient to support the inclusion criteria. Three reviewers independently evaluated studies for eligibility.

Inclusion and exclusion criteria

Randomized controlled trials (RCTs) and controlled trials were taken into consideration, but trials with only safety data, animal studies and *in vitro* studies were excluded. Studies that met the following criteria were included: (1) Clinical trials on immunotherapy for HCC patients with full text and available data in English; and (2) Clinical trials providing survival data [disease-free survival, progression-free survival, and overall survival (OS)] and adverse effects.

Data extraction and quality assessment

The following information was extracted for each article: last name of first author, year of publication, phase of clinical trial, number of enrolled subjects, treatment arms, number of patients in control and conventional groups, OS, recurrence rate and adverse effects. The quality assessment was performed with Cochrane Collaboration's tool for RCT trails and MINORS^[18] for non-RCT cohort studies.

Statistical analysis

We conducted all the analysis with Review Manager 5.3 (Cochrane Collaboration). Risk ratio (RR) was calculated to assess the effect of interventions. Results were presented with 95% confidence interval (CI). We performed Cochrane's Q statistic (χ^2) to assess the heterogeneity of the trials and the I^2 statistic for inconsistency. $P < 0.05$ or $I^2 > 50\%$ was considered an invalid assumption of homogeneity. A random-effects model was applied for clinical trials of significant heterogeneity, otherwise a fixed-effects model was applied. Assessment of potential publication bias was evaluated by funnel plot, where two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Description of included trials

A total of 2643 citations were identified from the primary literature search. Among them, 2621 studies were excluded for the following reasons: overlapping studies, reviews, no access to full-text in English, letters, and individual case studies.

According to the inclusion criteria, 22 studies (Figure 1) including 3756 patients were adopted in the meta-analysis. Five of the included studies involving 390 patients were aligned for analyzing the effect of mono-immunotherapy with DC-based vaccines. A total of 3211 patients involved in 13 trials were assigned for comparative analysis of mono-immunotherapy with CIKs. The other four trials with 155 patients focused on the effect of combined approach with DC vaccines and CIKs (Table 1). Most of those trials evaluated the effect of immunotherapy based on interventions for primary tumor ablation by surgical resection, radiofrequency ablation and cryoablation. Five studies^[19,20,24,26,27] were conducted with patients receiving TACE treatment. A few studies assigned patients with chemotherapy^[32] or only supportive treatment^[21] as the control group.

Efficacy and prognosis assessment

Compared with the patients in the control group, regardless of original treatment arm, patients receiving monotherapy with DC-based vaccine had a higher 1-year OS (RR = 1.16; 95%CI: 1.03-1.30, $P = 0.01$), although there was no significant improvement in OS at 6 mo or 3 years. Monotherapy with CIKs demonstrated significant improvement in OS at 6 mo (RR = 1.09; 95%CI: 1.03-1.16, $P = 0.005$), 1 year (RR = 1.11; 95%CI: 1.06-1.16, $P < 0.00001$), 3 years (RR = 1.23; 95%CI: 1.15-1.31, $P < 0.00001$) and 5 years (RR = 1.25; 95%CI: 1.14-1.36, $P < 0.00001$). Unsurprisingly, combined therapy with DCs and CIKs also improved OS at 1 year (RR = 3.8; 95%CI: 1.29-11.22, $P = 0.02$) and 5 years (RR = 1.45; 95%CI: 0.99-2.12, $P = 0.05$). Taken together, immunotherapy based on DCs and/or CIKs significantly increased OS at 6 mo (RR = 1.07; 95%CI: 1.01-1.13, $P = 0.02$), 1 year (RR = 1.12; 95%CI: 1.07-1.17, $P < 0.00001$), 3 years (RR = 1.23; 95%CI: 1.15-1.31, $P < 0.00001$) and 5 years (RR = 1.26; 95%CI: 1.15-1.37, $P < 0.00001$) (Figure 2).

Besides the improved OS of patients, reduced tumor recurrence rate was achieved in most trials. DC-based vaccination alone addressed a declining shift in 1-year recurrence (RR = 0.64; 95%CI: 0.44-1.93, $P = 0.02$). Immunotherapy with CIKs showed similar effects on recurrence at 6 mo (RR = 0.45; 95%CI: 0.30-0.66, $P < 0.0001$), 1 year (RR = 0.83; 95%CI: 0.76-0.91, $P < 0.0001$) and 1.5 years (RR = 0.39; 95%CI: 0.18-0.85, $P = 0.02$). The data on recurrence with DC/CIK combined therapy were unfortunately not available. The retardation effect of recurrence was observed at 6 mo (RR = 0.50; 95%CI: 0.36-0.69, $P < 0.0001$) and 1 year (RR = 0.82; 95%CI: 0.75-0.89, $P < 0.00001$) (Figure 3).

Adverse effect analysis

None of the studies reported immunotherapy-related hospital mortality. Only 23 patients in four studies^[23,29,32,36] were reported with grade III or IV adverse events. Fever was addressed as the most common event after immunotherapy. Other adverse effects included shivering, vomiting, fatigue, abdominal pain and leukopenia. The overall adverse event rate was higher in immunotherapy groups, but symptomatic remissions were declared within 24 h. In brief, immunotherapy was accepted as a safe, feasible treatment, though with an increased incidence of adverse events.

Quality assessment of trials

Seven studies included in this systematic review were RCTs, including two with DC-based vaccine, three with mono-immunotherapy with CIKs and two with combination immunotherapies. Cochrane Collaboration's tool was used to assess the quality of the RCTs. All these RCTs were verified with high quality (Table 2), and 15 non-RCTs were validated as high quality by MINORS (Table 3).

Publication bias

Funnel plots and Egger's regression test were applied to OS and recurrence rate in order to guarantee the potency of this meta-analysis (Figure 4). Symmetrical distribution of individual studies indicated no evident publication bias.

DISCUSSION

Although surgical resection, transplantation, local tumor ablation and TACE are well accepted with proven survival benefit^[41], these clinical treatments of HCC have their limited scope of application according to the tumor progression of individual patients. Besides, tumor recurrence can occur within five years even with curative interventions^[42]. Unlike some other solid tumors, no effective neoadjuvant or adjuvant therapy has been validated to reduce the recurrence risk so far^[41]. The introduction of immunotherapy, however, brought new hope in this regard. In this meta-analysis, we found that immunotherapy could increase OS and decrease recurrence rate in HCC.

Table 1 Clinical information and characteristics of included studies

Author (year)	Country	Control	Immuno-therapy interventions	Patients		Child-Pugh score A/B/C		Immune cell regimens	Course
				Control	Trial	Control	Trial		
Nakamoto (2007) ^[19]	Japan	TACE	TACE + DC	11	10	4/7/0	8/2/0	5 × 10 ⁶	1
Nakamoto (2011) ^[20]	Japan	TACE	TACE + DC	22	13	NR	5/8/0	5 × 10 ⁶	1
El Ansary (2013) ^[21]	Egypt	Supportive treatment	DC	15	15	0/14/1	0/15/0	20 × 10 ⁶	1
Sun (2015) ^[22]	China	Resection + FOLFOX6	Resection + DC	80	80	NR	NR	8.9 × 10 ⁹	6
Lee (2017) ^[23]	South Korea	Resection/RF A/PEI	Resection/RF A/PEI + DC	75	69	NR	NR	3 × 10 ⁷	6
Weng (2007) ^[24]	China	TACE + RFA	TACE + RFA + CIK	40	45	33/7/0	36/9/0	1.0-1.5 × 10 ¹⁰	8/9
Dong (2008) ^[25]	China	Resection	Resection + CIK	43	84	34/9/0	68/16/0	1.0-2.0 × 10 ¹⁰	3/5
Hao (2010) ^[26]	China	TACE	TACE + RFA + CIK	74	72	66/8/0	65/7/0	1.0-5.0 × 10 ¹⁰	4
Pan (2010) ^[27]	China	TACE + RFA	TACE + RFA + CIK	39	42	NR	NR	1.0 × 10 ¹⁰	4
Pan (2013) ^[28]	China	Resection	Resection + CIK	206	204	206/0/0	204/0/0	1.0-1.5 × 10 ¹⁰	4
Lee (2015) ^[29]	South Korea	Resection/RF A/PEI	Resection/RF A/PEI + CIK	112	114	112/0/0	114/0/0	NR	16
Pan (2015) ^[30]	China	Resection	Resection + CIK	520	511	NR	NR	1.0-1.5 × 10 ¹⁰	4
Chen (2016) ^[31]	China	Resection	Resection + CIK	118	231	205/12/0	222/9/0	1.0-1.5 × 10 ¹⁰	4
Li (2016) ^[32]	China	Oxaliplatin + Capecitabine	CIK	37	37	33(A + B)/4(C)	27(A + B)/10(C)	NR	NR
Chang (2018) ^[33]	China	Resection	Resection + CIK	145	145	145/0/0	145/0/0	NR	NR
Lee (2018) ^[34]	South Korea	Resection/RF A/PEI	Resection/RF A/PEI + CIK	112	114	112/0/0	114/0/0	6.4 × 10 ⁹	16
Cui (2014) ^[35]	China	RFA	RFA + NK/γδT/CIK	32	30	14/18/0	18/12/0	1.2-2.0 × 10 ⁹	8
Qian (2016) ^[36]	China	RFA	RFA + NK/γδT/CIK	31	73	NR	NR	1.0-2.0 × 10 ⁹	8
Qiu (2011) ^[37]	China	Resection	Resection + DC/CIK	9	9	NR	NR	2.0-20.0 × 10 ⁹	NR
Niu (2013) ^[38]	China	Cryoablation	Cytotherapy + DC/CIK	12	21	NR	NR	6.0-10.0 × 10 ⁹	NR
Shimizu (2014) ^[39]	Japan	Resection	Resection + DC/CIK	40	35	44/8/0	34/8/0	NR	NR
Yu (2015) ^[40]	China	Microwave ablation	Microwave ablation + DC/CIK	15	14	15/0/0	13/1/0	NR	NR

TACE: Transcatheter arterial chemoembolization; RFA: Radiofrequency ablation; PEI: Percutaneous ethanol injection; DC: Dendritic cell; CIK: Cytokine-induced killer cell; NK: Nature killer cell; NR: Not reported.

We comprehensively analyzed 22 individual studies with 3756 HCC patients in this meta-analysis and illustrated a positive prognostic efficacy of immunotherapy with DC-based vaccine and/or CIK-based adoptive therapy. Our results demonstrated that an extended OS (6 mo, 1, 3 and 5 years) was achieved with the aforesaid immunotherapy based on different HCC interventional therapies. Similar benefits in OS were described in another meta-analysis^[43] of adjuvant adoptive immunotherapy, including CIKs, lymphokine-activated killer cells and lymphocytes in HCC patients after surgery. In that study, a significant reduction in mortality and recurrence was observed at 1, 2 and 3 years but not 5 years^[43]. However, compared to the slight

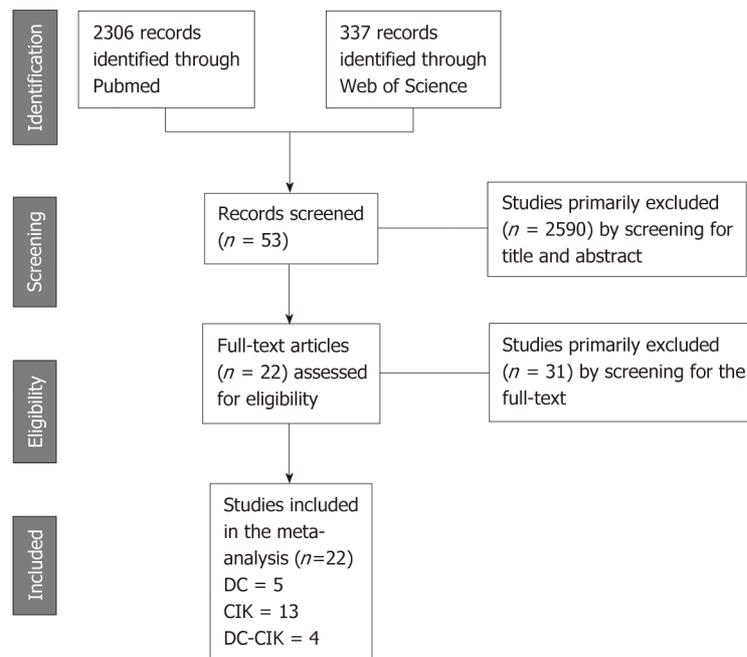


Figure 1 Flow diagram of the literature screening process. DC: Dendritic cell; CIK: Cytokine-induced killer cell.

increase in OS in our study, another systematic review demonstrated a more dramatic shift in OS in TACE-treated HCC patients^[16]. The smaller increase in OS in our analysis could have been ascribed to the heterogeneity of the patients included in the controlled trials. Yet, a significant benefit in OS was confirmed regardless of subgroup composition, and more intriguingly, our analysis indicated that short-term recurrence was intensely reduced with immunotherapy independent of the heterogeneity. The clinical benefit of the combined immunotherapy with DCs and CIKs has been demonstrated in many clinical studies^[17,44]. This combined approach was reported to have greater antitumor activity *in vitro* than CIK treatment alone^[45], while our analysis failed to find sufficient clinical data to support it.

One RCT^[22] and one non-RCT cohort study^[32] included in this meta-analysis were based on conventional chemotherapy as the control group. Cellular immunotherapy also resulted in improved outcomes, implying a critical role for immunotherapy in patients who have lost their chance for tumor ablation. The combination of chemotherapy and immunotherapy has accumulated positive efficacy in a number of unresectable malignancies^[46-48].

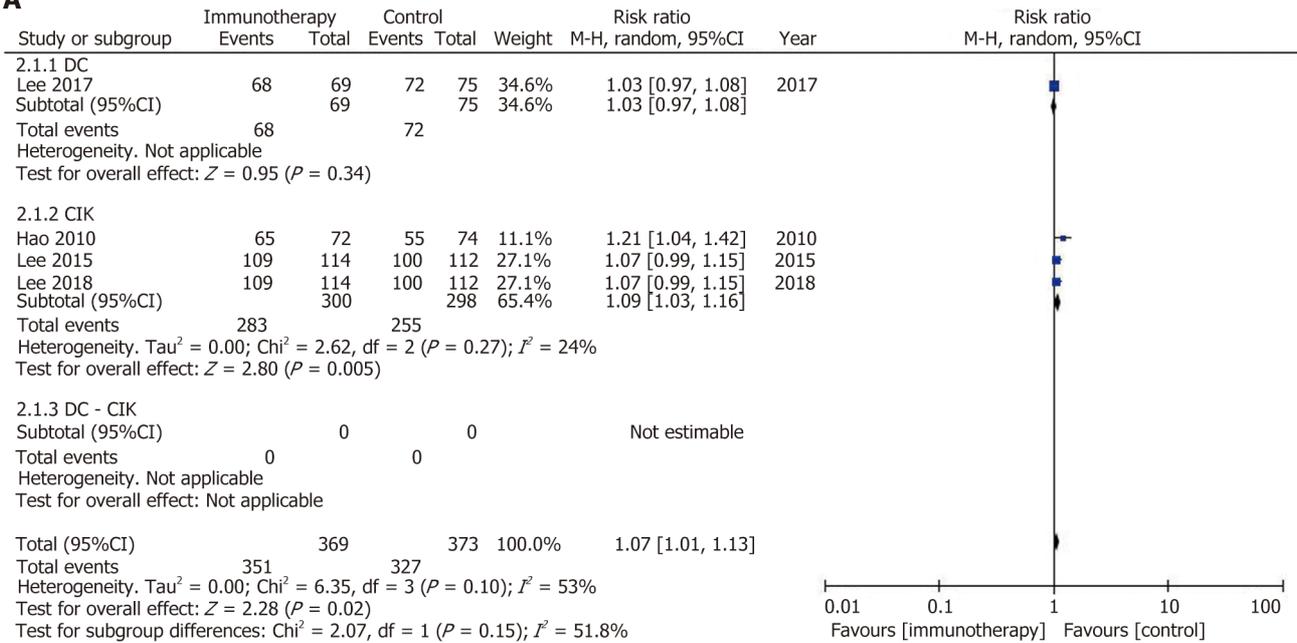
Recently, the introduction of immune checkpoint inhibitors has led to a clinical breakthrough in cancer treatment^[49]. Six immune checkpoint inhibitors for HCC treatment have been approved by the Food and Drug Administration, and even one (nivolumab) has been introduced as a second-line treatment^[50,51] due to its promising effect on immune checkpoints inhibitors in HCC patients. Although some clinical data have presented a good safety profile, disease control and time to progression^[50-52], clinical data concerning comparative trials with immune checkpoints in HCC patients are still insufficient for analysis.

A bias could have been raised due to the low number of available trials and the low number of included patients in the DC-based vaccine group and DC/CIK combination group, which comprised five trials with 390 patients and four trials with 155 patients, respectively. The quality of this meta-analysis was still assured as we have shown no evidence of publication bias.

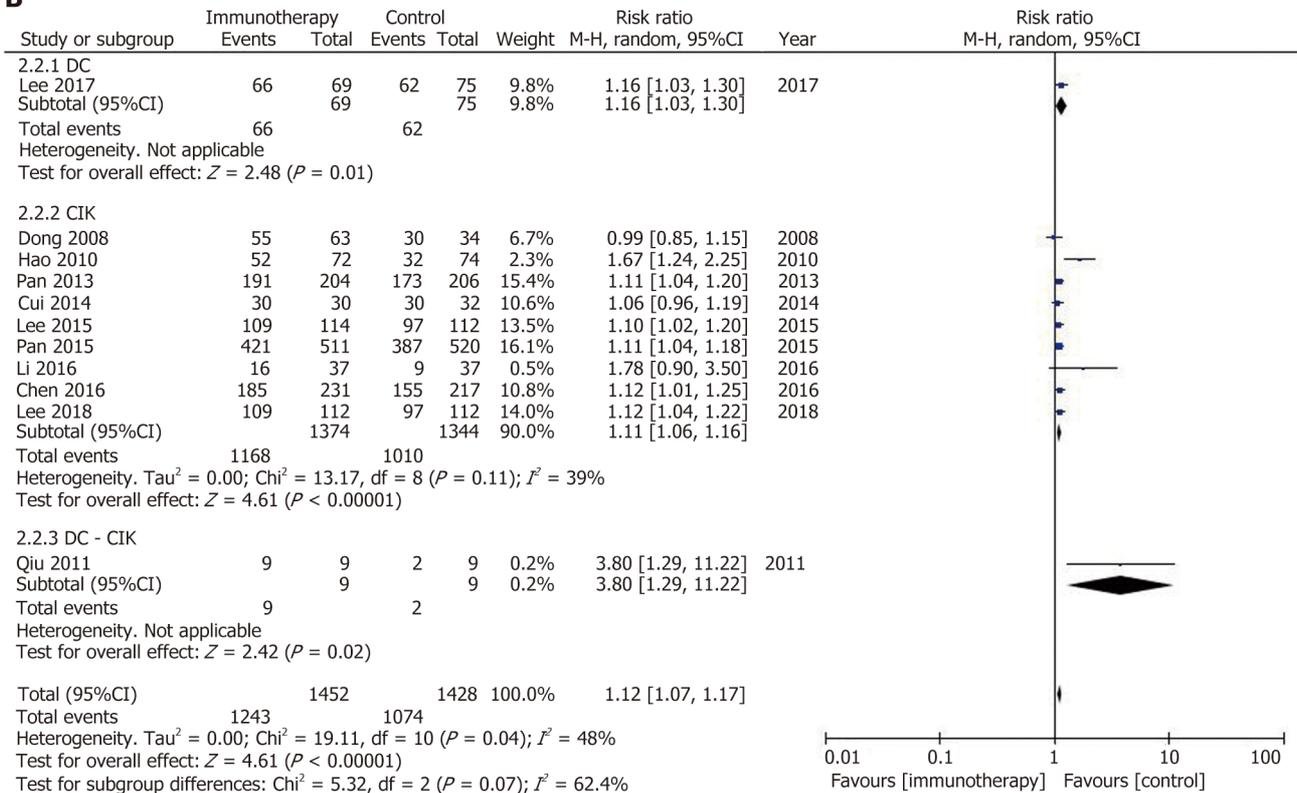
There were a few limitations to this systematic review and meta-analysis. First, although we included 22 trials in the analysis, the DC and DC/CIK groups comprised only five and four trials, respectively. Most of the trials were conducted in East Asian countries (China, Japan and South Korea); hence, they had less-sufficient statistical power due to the lack of multinational or multiracial clinical data. Second, heterogeneity was observed between the included studies. Factors, including stage of malignancy, different surgical method, number of immunotherapy fusion cycles, and duration of immunotherapy in different clinical centers could have contributed to the heterogeneity.

In conclusion, we demonstrated that the application of immunotherapy with DCs, CIKs and DCs/CIK in addition to various routine HCC treatments could evidently

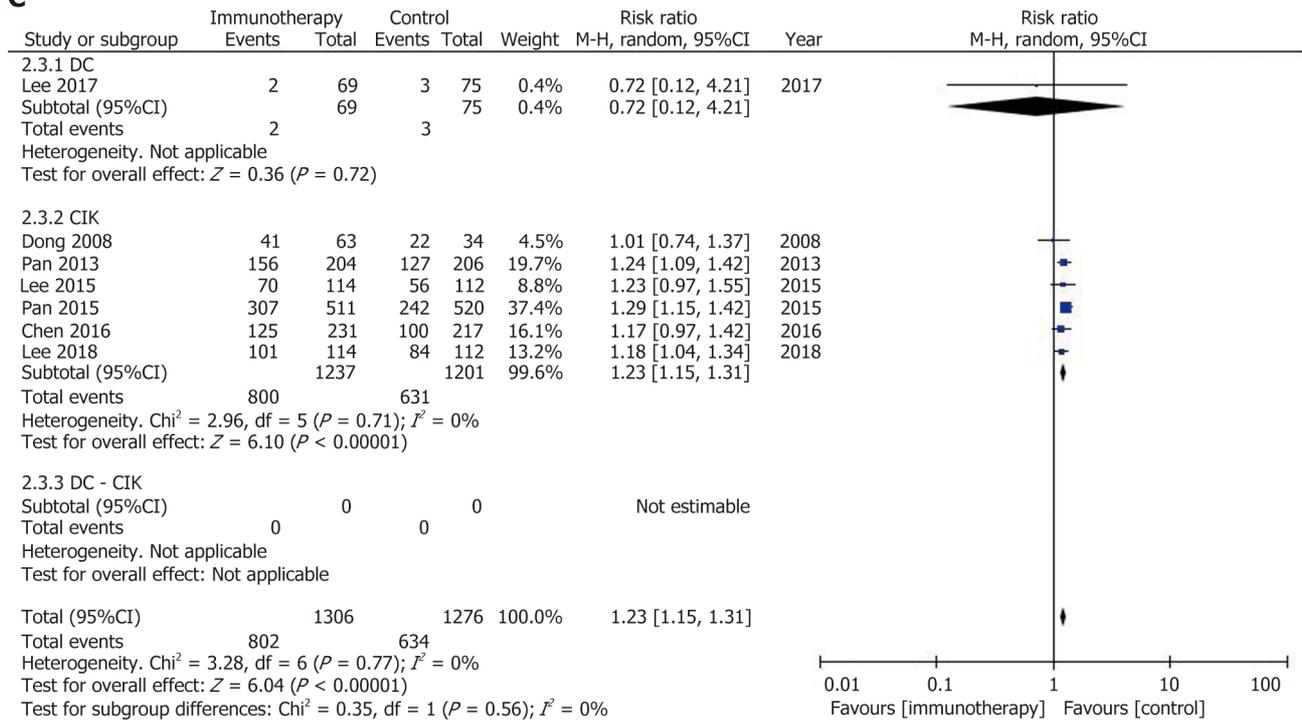
A



B



C



D

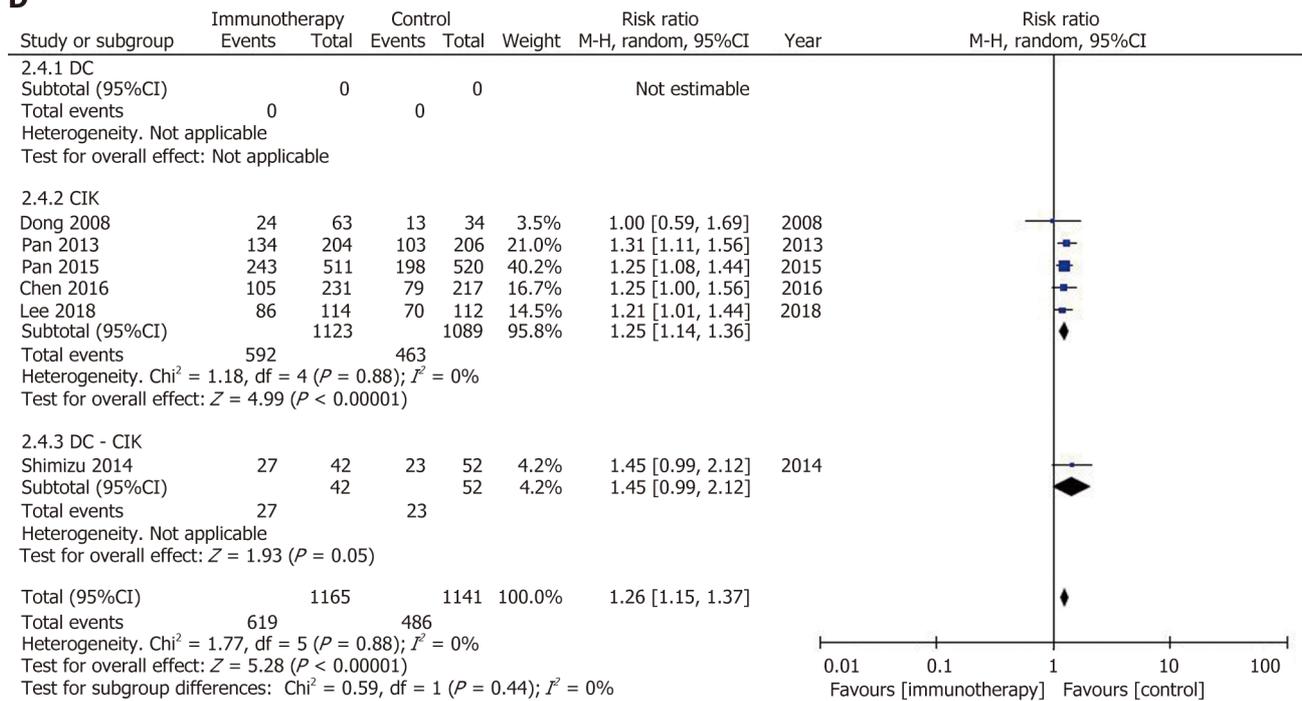


Figure 2 Comparison of 6-mo (A), 1- (B), 3- (C) and 5-yr (D) overall survival between immunotherapy groups and control groups. M-H: Mantel-Haenszel estimates; CI: Confidence interval.

improve patients' prognosis by increasing OS and reducing recurrence. The efficacy of novel immune checkpoint inhibitors based on clinical trials should be assessed in further studies when sufficient data are available. Due to the diverse mechanism behind the immune evasion of tumor cells, approaches combining different immunotherapies might lead to an appealing strategy to treat HCC.

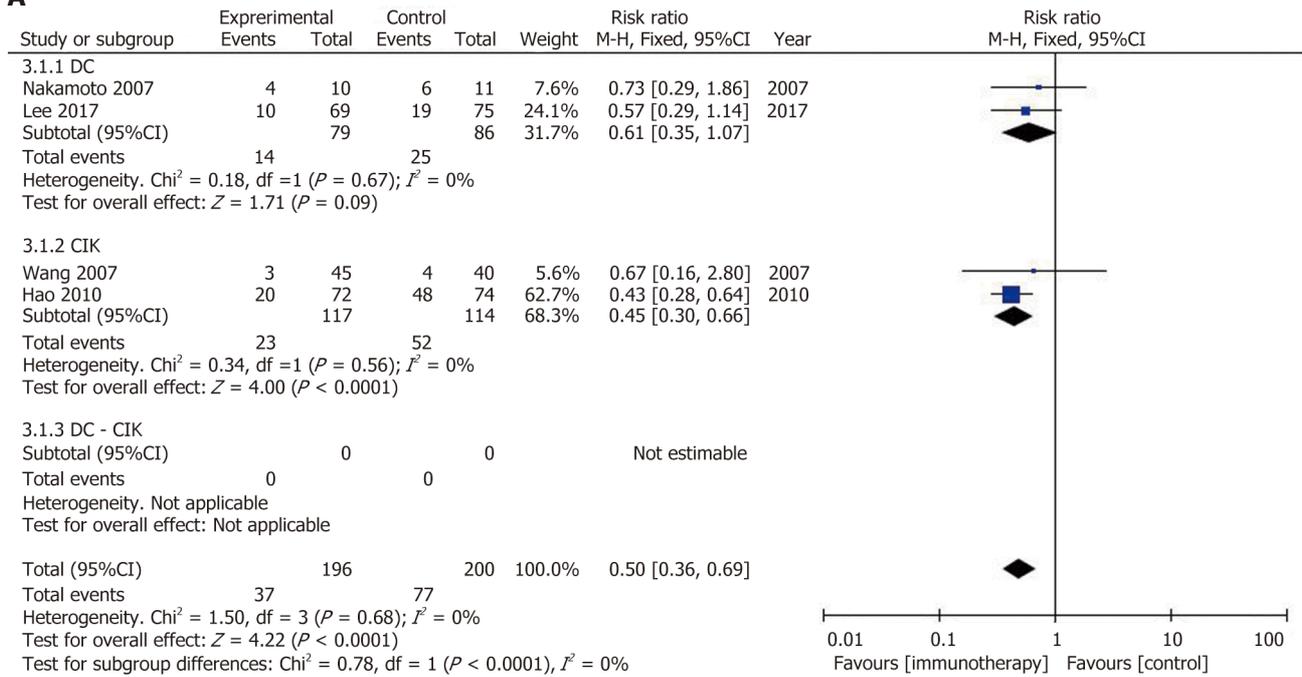
Table 2 Quality assessment of randomized controlled trials with Cochrane Collaboration's tool

Author (year)	Selection	Performance	Detection	Attrition	Reporting	Other
	Bias	Bias	Bias	Bias	Bias	Bias
El Ansary (2013)	Unclear	High	Unclear	Low	Low	Low
Sun (2015)	Unclear	High	Unclear	Low	Low	Low
Dong (2008)	Unclear	High	Unclear	Low	Low	Low
Lee (2015)	Unclear	High	Unclear	Low	Low	Low
Lee (2018)	Unclear	High	Unclear	Low	Low	Low
Qiu (2011)	Unclear	High	Unclear	Low	Low	Low
Yu (2015)	Unclear	High	Unclear	Low	Low	Low

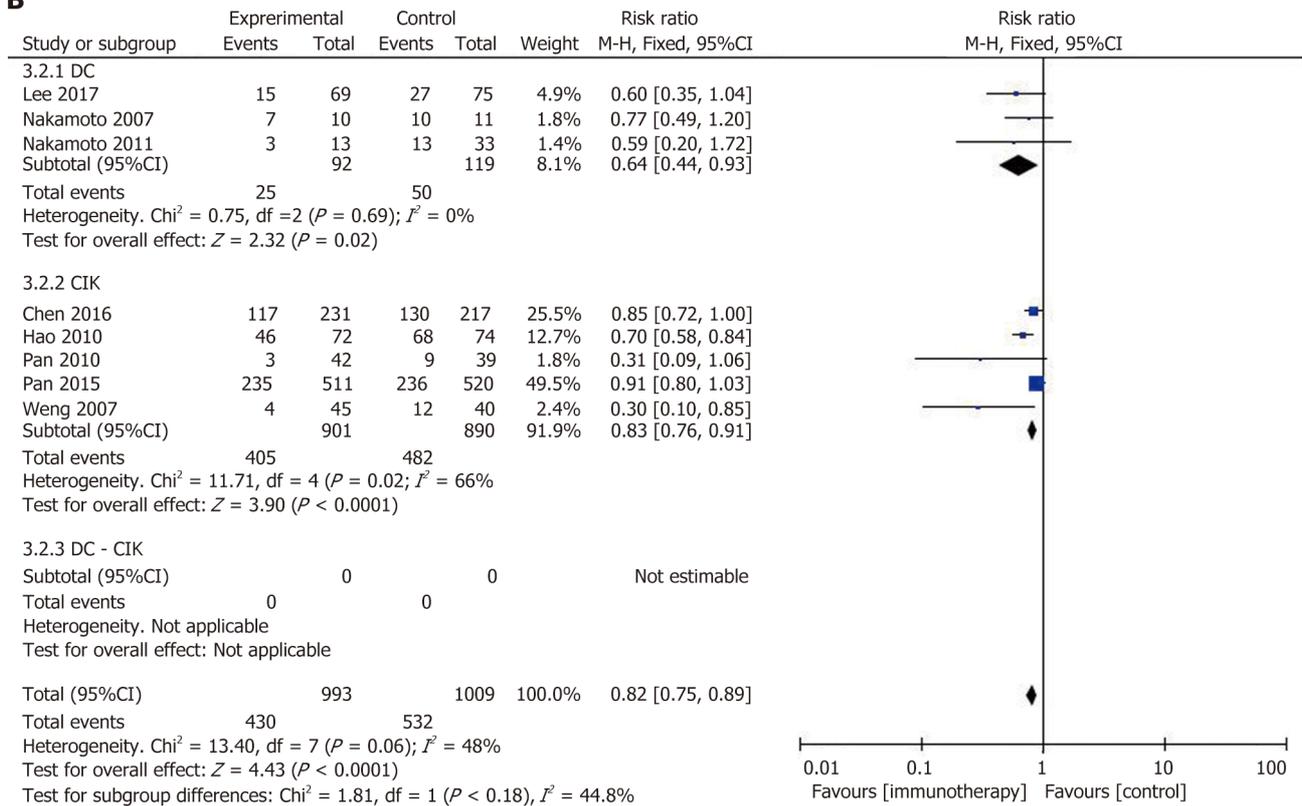
Table 3 Quality assessment of non-randomized controlled trials with MINORS

Author (year)	1	2	3	4	5	6	7	8	9	10	11	12
Nakamoto (2007)	2	2	2	0	0	1	2	0	2	2	2	2
Nakamoto (2011)	2	2	2	2	0	1	2	0	2	2	2	2
Lee (2017)	2	2	2	2	0	2	0	2	2	2	2	2
Weng (2007)	2	2	2	2	0	2	2	0	2	2	2	2
Hao (2010)	2	2	2	2	0	2	2	2	2	2	2	2
Pan (2010)	2	2	2	2	0	1	2	0	2	2	2	2
Pan (2013)	2	2	2	2	0	1	2	0	2	2	2	2
Pan (2015)	2	2	2	2	0	2	2	0	2	2	2	2
Chen (2016)	2	2	2	2	0	2	2	0	2	2	2	2
Li (2016)	2	2	2	2	0	1	2	2	2	2	2	2
Chang (2018)	2	2	2	2	0	2	2	2	2	2	2	2
Cui (2014)	2	2	2	0	0	1	2	0	2	2	2	2
Qian (2016)	2	2	2	1	0	2	0	0	2	2	2	2
Niu (2013)	2	2	2	0	0	2	2	0	2	2	2	2
Shimizu (2014)	2	2	2	0	0	2	2	2	2	2	2	2

A



B



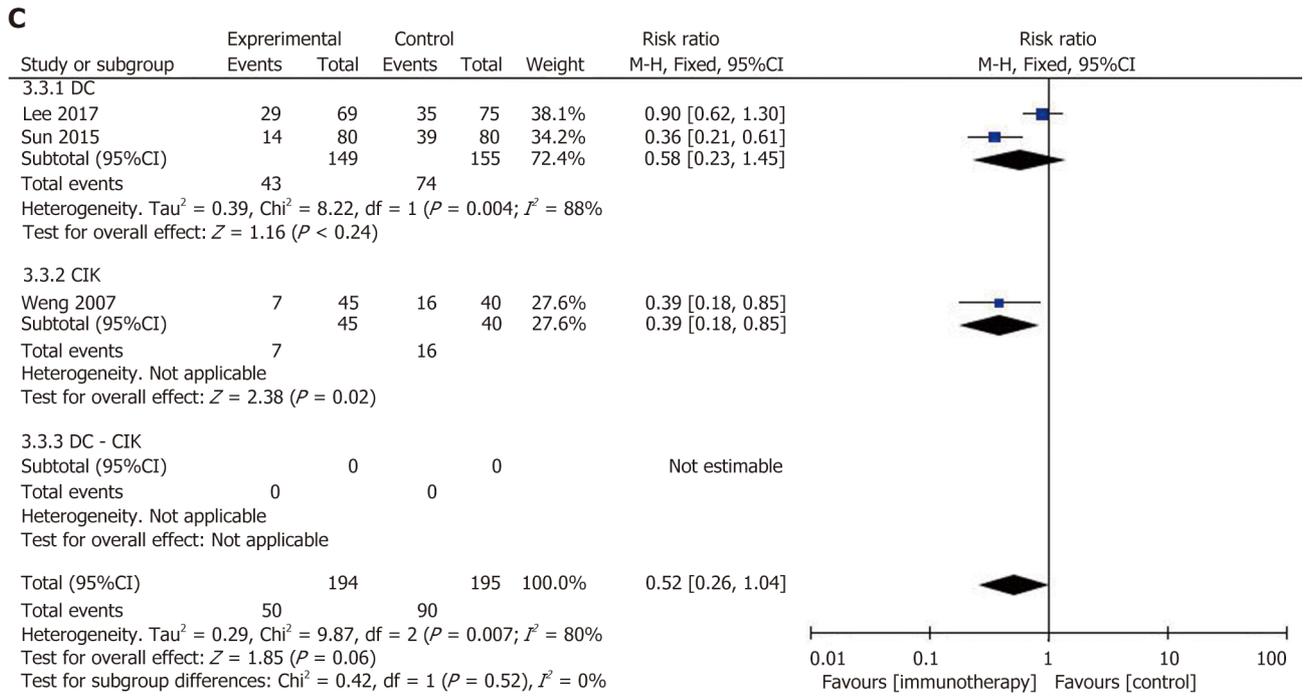


Figure 3 Comparison of 6-mo (A), 1- (B) and 1.5-yr (C) recurrence between immunotherapy groups and control groups. M-H: Mantel-Haenszel estimates; CI: Confidence interval.

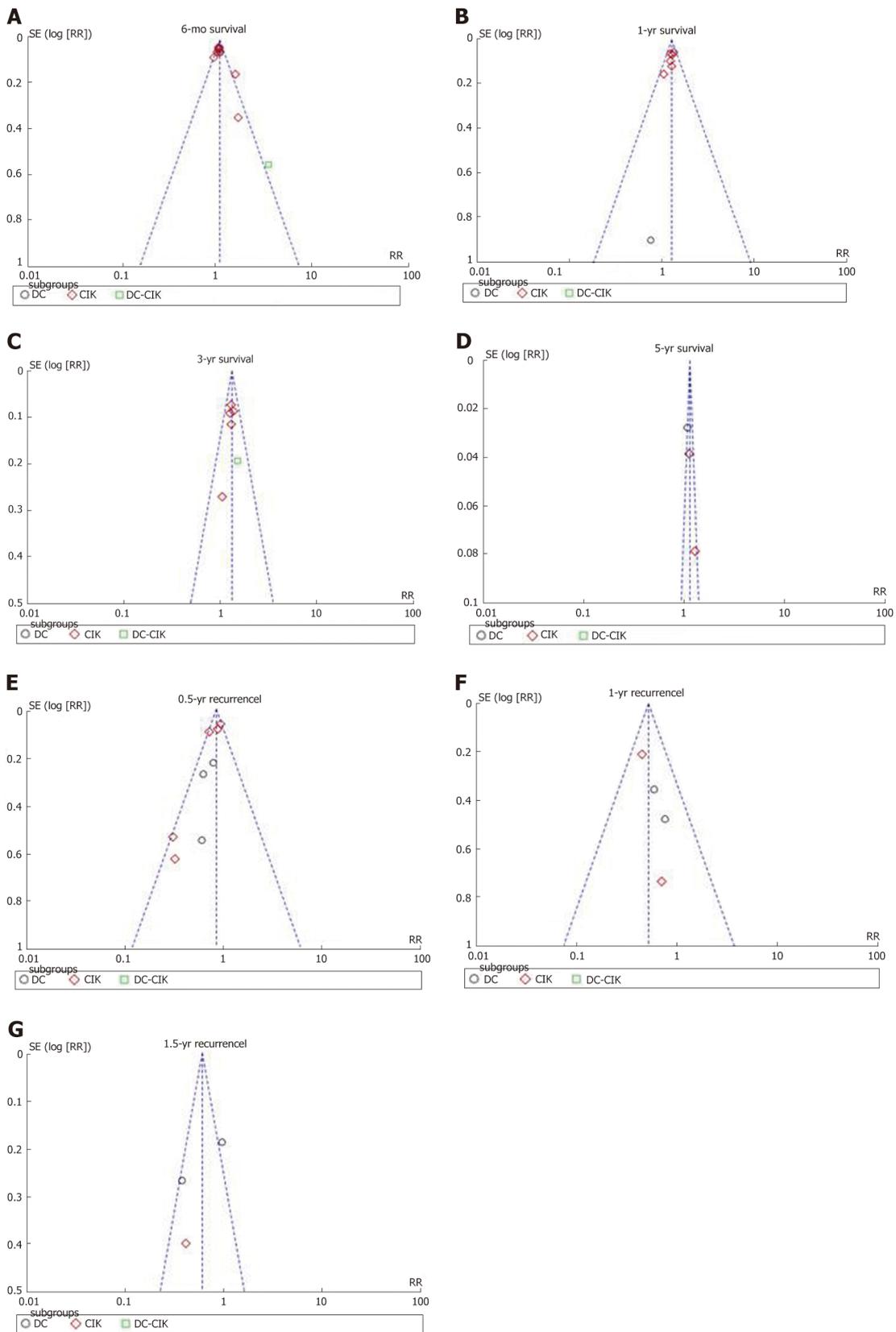


Figure 4 Funnel plots to detect publication bias. DC: Dendritic cell; CIK: Cytokine-induced killer cell.

ARTICLE HIGHLIGHTS

Research background

Hepatocellular carcinoma (HCC) has been revealed as the second most common cause of cancer-related deaths worldwide. The introduction of cell-based immunotherapy, including dendritic

cells (DCs) and cytokine-induced killer cells (CIKs), has brought HCC patients an effective benefit. However, the efficacy and necessity of cellular immunotherapy after different interventional therapy remain to be further explored.

Research motivation

Only patients with early to intermediate stage of HCC can benefit from curable interventions. Unfortunately, tumor recurrence within 5 years occurs even with curable treatment. As the introduction of immunotherapy has brought beneficial effects to HCC treatment, better strategies with combined interventions would help to improve the outcomes of HCC patients.

Research objectives

A systematic review and meta-analysis were performed in this study to investigate the efficacy of cellular immunotherapy, involving DCs, CIKs and DC/CIK combination therapy combined with different treatments of HCC.

Research methods

A literature search was performed on PubMed and Web of Science up to February 15, 2019. Long-term efficacy (overall survival and recurrence) and short-term adverse effects were investigated to assess the effectiveness of immunotherapy with DCs and/or CIKs. Review Manager 5.3 was used to perform the analysis.

Research results

A total of 22 studies involving 3756 patients selected by eligibility inclusion criteria were forwarded for meta-analysis. Combined with the conventional clinical treatment, immunotherapy with DCs and/or CIKs was demonstrated to significantly improve overall survival at 6 mo, 1 year, 3 years and 5 years. Recurrence rate was significantly reduced by cellular immunotherapy at 6 mo and 1 year. Adverse effect assessment addressed that immunotherapy with DCs and/or CIKs was accepted as a safe, feasible treatment.

Research conclusions

Combination immunotherapy with DCs, CIKs and DC/CIK with various routine treatments for HCC was evidently suggested to improve patients' prognosis by increasing overall survival and reducing cancer recurrence.

Research perspectives

This meta-analysis indicated that the combination of conventional therapy and the intervention of immunotherapy with DCs, CIK and DC/CIK could pave the way for a promising approach for HCC treatment. Further assessment of the efficacy of novel immune checkpoint inhibitors based on clinical trials will help us to better identify immunotherapy strategies to treat HCC.

REFERENCES

- 1 Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359-E386 [PMID: 25220842 DOI: 10.1002/ijc.29210]
- 2 Gretten TF, Sangro B. Targets for immunotherapy of liver cancer. *J Hepatol* 2017; pii: S0168-8278(17)32287-0 [PMID: 28923358 DOI: 10.1016/j.jhep.2017.09.007]
- 3 European Association For The Study Of The Liver. European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; **56**: 908-943 [PMID: 22424438 DOI: 10.1016/j.jhep.2011.12.001]
- 4 Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, Pracht M, Yokosuka O, Rosmorduc O, Breder V, Gerolami R, Masi G, Ross PJ, Song T, Bronowicki JP, Ollivier-Hourmand I, Kudo M, Cheng AL, Llovet JM, Finn RS, LeBerre MA, Baumhauer A, Meinhardt G, Han G; RESORCE Investigators. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; **389**: 56-66 [PMID: 27932229 DOI: 10.1016/S0140-6736(16)32453-9]
- 5 Tsuchiya N, Sawada Y, Endo I, Uemura Y, Nakatsura T. Potentiality of immunotherapy against hepatocellular carcinoma. *World J Gastroenterol* 2015; **21**: 10314-10326 [PMID: 26420958 DOI: 10.3748/wjg.v21.i36.10314]
- 6 Iwashita Y, Tahara K, Goto S, Sasaki A, Kai S, Seike M, Chen CL, Kawano K, Kitano S. A phase I study of autologous dendritic cell-based immunotherapy for patients with unresectable primary liver cancer. *Cancer Immunol Immunother* 2003; **52**: 155-161 [PMID: 12649744 DOI: 10.1007/s00262-002-0360-9]
- 7 Lee WC, Wang HC, Hung CF, Huang PF, Lia CR, Chen MF. Vaccination of advanced hepatocellular carcinoma patients with tumor lysate-pulsed dendritic cells: a clinical trial. *J Immunother* 2005; **28**: 496-504 [PMID: 16113606 DOI: 10.1097/01.cji.0000171291.72039.e2]
- 8 Takayama T, Sekine T, Makuuchi M, Yamasaki S, Kosuge T, Yamamoto J, Shimada K, Sakamoto M, Hirohashi S, Ohashi Y, Kakizoe T. Adoptive immunotherapy to lower postsurgical recurrence rates of hepatocellular carcinoma: a randomised trial. *Lancet* 2000; **356**: 802-807 [PMID: 11022927 DOI: 10.1016/S0140-6736(00)02654-4]
- 9 Zhu AX, Stuart K, Blaszkowsky LS, Muzikansky A, Reitberg DP, Clark JW, Enzinger PC, Bhargava P, Meyerhardt JA, Horgan K, Fuchs CS, Ryan DP. Phase 2 study of cetuximab in patients with advanced hepatocellular carcinoma. *Cancer* 2007; **110**: 581-589 [PMID: 17583545 DOI: 10.1002/ncr.22829]
- 10 Llovet JM, Sala M, Castells L, Suarez Y, Vilana R, Bianchi L, Ayuso C, Vargas V, Rodés J, Bruix J. Randomized controlled trial of interferon treatment for advanced hepatocellular carcinoma. *Hepatology* 2000; **31**: 54-58 [PMID: 10613728 DOI: 10.1002/hep.510310111]

- 11 **Chen LT**, Chen MF, Li LA, Lee PH, Jeng LB, Lin DY, Wu CC, Mok KT, Chen CL, Lee WC, Chau GY, Chen YS, Lui WY, Hsiao CF, Whang-Peng J, Chen PJ; Disease Committee of Adjuvant Therapy for Postoperative Hepatocellular Carcinoma, Taiwan Cooperative Oncology Group, National Health Research Institutes, Zhunan, Taiwan. Long-term results of a randomized, observation-controlled, phase III trial of adjuvant interferon Alfa-2b in hepatocellular carcinoma after curative resection. *Ann Surg* 2012; **255**: 8-17 [PMID: 22104564 DOI: 10.1097/SLA.0b013e3182363ff9]
- 12 **Radford KJ**, Tullett KM, Lahoud MH. Dendritic cells and cancer immunotherapy. *Curr Opin Immunol* 2014; **27**: 26-32 [PMID: 24513968 DOI: 10.1016/j.coi.2014.01.005]
- 13 **Quinn DI**, Shore ND, Egawa S, Gerritsen WR, Fizazi K. Immunotherapy for castration-resistant prostate cancer: Progress and new paradigms. *Urol Oncol* 2015; **33**: 245-260 [PMID: 25575714 DOI: 10.1016/j.urolonc.2014.10.009]
- 14 **Bachem A**, Güttler S, Hartung E, Ebstein F, Schaefer M, Tannert A, Salama A, Movassaghi K, Opitz C, Mages HW, Henn V, Kloetzel PM, Gurka S, Kroczeck RA. Superior antigen cross-presentation and XCR1 expression define human CD11c+CD141+ cells as homologues of mouse CD8+ dendritic cells. *J Exp Med* 2010; **207**: 1273-1281 [PMID: 20479115 DOI: 10.1084/jem.20100348]
- 15 **Prieto J**, Melero I, Sangro B. Immunological landscape and immunotherapy of hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol* 2015; **12**: 681-700 [PMID: 26484443 DOI: 10.1038/nrgastro.2015.173]
- 16 **Ding M**, Wang Y, Chi J, Wang T, Tang X, Cui D, Qian Q, Zhai B. Is Adjuvant Cellular Immunotherapy Essential after TACE-Predominant Minimally-Invasive Treatment for Hepatocellular Carcinoma? A Systematic Meta-Analysis of Studies Including 1774 Patients. *PLoS One* 2016; **11**: e0168798 [PMID: 28006010 DOI: 10.1371/journal.pone.0168798]
- 17 **He G**, Zheng C, Huo H, Zhang H, Zhu Z, Li J, Zhang H. TACE combined with dendritic cells and cytokine-induced killer cells in the treatment of hepatocellular carcinoma: A meta-analysis. *Int Immunopharmacol* 2016; **40**: 436-442 [PMID: 27716591 DOI: 10.1016/j.intimp.2016.09.015]
- 18 **Slim K**, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg* 2003; **73**: 712-716 [PMID: 12956787 DOI: 10.1046/j.1445-2197.2003.02748.x]
- 19 **Nakamoto Y**, Mizukoshi E, Tsuji H, Sakai Y, Kitahara M, Arai K, Yamashita T, Yokoyama K, Mukaida N, Matsushima K, Matsui O, Kaneko S. Combined therapy of transcatheter hepatic arterial embolization with intratumoral dendritic cell infusion for hepatocellular carcinoma: clinical safety. *Clin Exp Immunol* 2007; **147**: 296-305 [PMID: 17223971 DOI: 10.1111/j.1365-2249.2006.03290.x]
- 20 **Nakamoto Y**, Mizukoshi E, Kitahara M, Arihara F, Sakai Y, Kakinoki K, Fujita Y, Marukawa Y, Arai K, Yamashita T, Mukaida N, Matsushima K, Matsui O, Kaneko S. Prolonged recurrence-free survival following OK432-stimulated dendritic cell transfer into hepatocellular carcinoma during transarterial embolization. *Clin Exp Immunol* 2011; **163**: 165-177 [PMID: 21087443 DOI: 10.1111/j.1365-2249.2010.04246.x]
- 21 **El Ansary M**, Mogawer S, Elhamid SA, Alwakil S, Aboelkasem F, Sabaawy HE, Abdelhalim O. Immunotherapy by autologous dendritic cell vaccine in patients with advanced HCC. *J Cancer Res Clin Oncol* 2013; **139**: 39-48 [PMID: 22886490 DOI: 10.1007/s00432-012-1298-8]
- 22 **Sun TY**, Yan W, Yang CM, Zhang LF, Tang HL, Chen Y, Hu HX, Wei X. Clinical research on dendritic cell vaccines to prevent postoperative recurrence and metastasis of liver cancer. *Genet Mol Res* 2015; **14**: 16222-16232 [PMID: 26662415 DOI: 10.4238/2015.December.8.12]
- 23 **Lee JH**, Tak WY, Lee Y, Heo MK, Song JS, Kim HY, Park SY, Bae SH, Lee JH, Heo J, Kim KH, Bae YS, Kim YJ. Adjuvant immunotherapy with autologous dendritic cells for hepatocellular carcinoma, randomized phase II study. *Oncotarget* 2017; **6**: e1328335 [PMID: 28811965 DOI: 10.1080/2162402X.2017.1328335]
- 24 **Weng DS**, Zhou J, Zhou QM, Zhao M, Wang QJ, Huang LX, Li YQ, Chen SP, Wu PH, Xia JC. Minimally invasive treatment combined with cytokine-induced killer cells therapy lower the short-term recurrence rates of hepatocellular carcinomas. *J Immunother* 2008; **31**: 63-71 [PMID: 18157013 DOI: 10.1097/CJI.0b013e31815a121b]
- 25 **Hui D**, Qiang L, Jian W, Ti Z, Da-Lu K. A randomized, controlled trial of postoperative adjuvant cytokine-induced killer cells immunotherapy after radical resection of hepatocellular carcinoma. *Dig Liver Dis* 2009; **41**: 36-41 [PMID: 18818130 DOI: 10.1016/j.dld.2008.04.007]
- 26 **Hao MZ**, Lin HL, Chen Q, Ye YB, Chen QZ, Chen MS. Efficacy of transcatheter arterial chemoembolization combined with cytokine-induced killer cell therapy on hepatocellular carcinoma: a comparative study. *Chin J Cancer* 2010; **29**: 172-177 [PMID: 20109346 DOI: 10.5732/cjc.009.10410]
- 27 **Pan CC**, Huang ZL, Li W, Zhao M, Zhou QM, Xia JC, Wu PH. Serum alpha-fetoprotein measurement in predicting clinical outcome related to autologous cytokine-induced killer cells in patients with hepatocellular carcinoma undergone minimally invasive therapy. *Chin J Cancer* 2010; **29**: 596-602 [PMID: 20507732 DOI: 10.5732/cjc.009.10580]
- 28 **Pan K**, Li YQ, Wang W, Xu L, Zhang YJ, Zheng HX, Zhao JJ, Qiu HJ, Weng DS, Li JJ, Wang QJ, Huang LX, He J, Chen SP, Ke ML, Wu PH, Chen MS, Li SP, Xia JC, Zeng YX. The efficacy of cytokine-induced killer cell infusion as an adjuvant therapy for postoperative hepatocellular carcinoma patients. *Ann Surg Oncol* 2013; **20**: 4305-4311 [PMID: 23892527 DOI: 10.1245/s10434-013-3144-x]
- 29 **Lee JH**, Lee JH, Lim YS, Yeon JE, Song TJ, Yu SJ, Gwak GY, Kim KM, Kim YJ, Lee JW, Yoon JH. Adjuvant immunotherapy with autologous cytokine-induced killer cells for hepatocellular carcinoma. *Gastroenterology* 2015; **148**: 1383-1391.e6 [PMID: 25747273 DOI: 10.1053/j.gastro.2015.02.055]
- 30 **Pan QZ**, Wang QJ, Dan JQ, Pan K, Li YQ, Zhang YJ, Zhao JJ, Weng DS, Tang Y, Huang LX, He J, Chen SP, Ke ML, Chen MS, Wicha MS, Chang AE, Zeng YX, Li Q, Xia JC. A nomogram for predicting the benefit of adjuvant cytokine-induced killer cell immunotherapy in patients with hepatocellular carcinoma. *Sci Rep* 2015; **5**: 9202 [PMID: 25776856 DOI: 10.1038/srep09202]
- 31 **Chen CL**, Pan QZ, Zhao JJ, Wang Y, Li YQ, Wang QJ, Pan K, Weng DS, Jiang SS, Tang Y, Zhang XF, Zhang HX, Zhou ZQ, Zeng YX, Xia JC. PD-L1 expression as a predictive biomarker for cytokine-induced killer cell immunotherapy in patients with hepatocellular carcinoma. *Oncotarget* 2016; **5**: e1176653 [PMID: 27622026 DOI: 10.1080/2162402X.2016.1176653]
- 32 **Li W**, Wang Y, Kellner DB, Zhao L, Xu L, Gao Q. Efficacy of RetroNectin-activated cytokine-induced killer cell therapy in the treatment of advanced hepatocellular carcinoma. *Oncol Lett* 2016; **12**: 707-714 [PMID: 27347204 DOI: 10.3892/ol.2016.4629]
- 33 **Chang B**, Shen L, Wang K, Jin J, Huang T, Chen Q, Li W, Wu P. High number of PD-1 positive intratumoral lymphocytes predicts survival benefit of cytokine-induced killer cells for hepatocellular carcinoma patients. *Liver Int* 2018; **38**: 1449-1458 [PMID: 29356308 DOI: 10.1111/liv.13697]

- 34 **Lee JH**, Lee JH, Lim YS, Yeon JE, Song TJ, Yu SJ, Gwak GY, Kim KM, Kim YJ, Lee JW, Yoon JH. Sustained efficacy of adjuvant immunotherapy with cytokine-induced killer cells for hepatocellular carcinoma: an extended 5-year follow-up. *Cancer Immunol Immunother* 2019; **68**: 23-32 [PMID: 30232520 DOI: 10.1007/s00262-018-2247-4]
- 35 **Cui J**, Wang N, Zhao H, Jin H, Wang G, Niu C, Terunuma H, He H, Li W. Combination of radiofrequency ablation and sequential cellular immunotherapy improves progression-free survival for patients with hepatocellular carcinoma. *Int J Cancer* 2014; **134**: 342-351 [PMID: 23825037 DOI: 10.1002/ijc.28372]
- 36 **Qian L**, Wang N, Tian H, Jin H, Zhao H, Niu C, He H, Ge T, Han W, Hu J, Li D, Han F, Xu J, Ding X, Chen J, Li W, Cui J. Dual Effects of Cellular Immunotherapy in Inhibition of Virus Replication and Prolongation of Survival in HCV-Positive Hepatocellular Carcinoma Patients. *J Immunol Res* 2016; **2016**: 6837241 [PMID: 27069936 DOI: 10.1155/2016/6837241]
- 37 **Qiu Y**, Xu MB, Yun MM, Wang YZ, Zhang RM, Meng XK, Ou-Yang XH, Yun S. Hepatocellular carcinoma-specific immunotherapy with synthesized α 1,3- galactosyl epitope-pulsed dendritic cells and cytokine-induced killer cells. *World J Gastroenterol* 2011; **17**: 5260-5266 [PMID: 22219594 DOI: 10.3748/wjg.v17.i48.5260]
- 38 **Niu LZ**, Li JL, Zeng JY, Mu F, Liao MT, Yao F, Li L, Liu CY, Chen JB, Zuo JS, Xu KC. Combination treatment with comprehensive cryoablation and immunotherapy in metastatic hepatocellular cancer. *World J Gastroenterol* 2013; **19**: 3473-3480 [PMID: 23801841 DOI: 10.3748/wjg.v19.i22.3473]
- 39 **Shimizu K**, Kotera Y, Aruga A, Takeshita N, Katagiri S, Ariizumi S, Takahashi Y, Yoshitoshi K, Takasaki K, Yamamoto M. Postoperative dendritic cell vaccine plus activated T-cell transfer improves the survival of patients with invasive hepatocellular carcinoma. *Hum Vaccin Immunother* 2014; **10**: 970-976 [PMID: 24419174 DOI: 10.4161/hv.27678]
- 40 **Yu MA**, Liang P, Yu XL, Han ZY, Dong XJ, Wang YU, Cheng C, Li X. Multiple courses of immunotherapy with different immune cell types for patients with hepatocellular carcinoma after microwave ablation. *Exp Ther Med* 2015; **10**: 1460-1466 [PMID: 26622507 DOI: 10.3892/etm.2015.2681]
- 41 **Forner A**, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet* 2018; **391**: 1301-1314 [PMID: 29307467 DOI: 10.1016/S0140-6736(18)30010-2]
- 42 **Hasegawa K**, Kokudo N, Makuuchi M, Izumi N, Ichida T, Kudo M, Ku Y, Sakamoto M, Nakashima O, Matsui O, Matsuyama Y. Comparison of resection and ablation for hepatocellular carcinoma: a cohort study based on a Japanese nationwide survey. *J Hepatol* 2013; **58**: 724-729 [PMID: 23178708 DOI: 10.1016/j.jhep.2012.11.009]
- 43 **Yuan BH**, Li RH, Yuan WP, Yang T, Tong TJ, Peng NF, Li LQ, Zhong JH. Harms and benefits of adoptive immunotherapy for postoperative hepatocellular carcinoma: an updated review. *Oncotarget* 2017; **8**: 18537-18549 [PMID: 28061472 DOI: 10.18632/oncotarget.14507]
- 44 **Li XD**, Xu B, Wu J, Ji M, Xu BH, Jiang JT, Wu CP. Review of Chinese clinical trials on CIK cell treatment for malignancies. *Clin Transl Oncol* 2012; **14**: 102-108 [PMID: 22301398 DOI: 10.1007/s12094-012-0768-4]
- 45 **Pan Y**, Tao Q, Wang H, Xiong S, Zhang R, Chen T, Tao L, Zhai Z. Dendritic cells decreased the concomitant expanded Tregs and Tregs related IL-35 in cytokine-induced killer cells and increased their cytotoxicity against leukemia cells. *PLoS One* 2014; **9**: e93591 [PMID: 24705499 DOI: 10.1371/journal.pone.0093591]
- 46 **Rizvi NA**, Peters S. Immunotherapy for Unresectable Stage III Non-Small-Cell Lung Cancer. *N Engl J Med* 2017; **377**: 1986-1988 [PMID: 29141165 DOI: 10.1056/NEJMe1711430]
- 47 **Simon A**, Kourie HR, Kerger J. Is there still a role for cytotoxic chemotherapy after targeted therapy and immunotherapy in metastatic melanoma? A case report and literature review. *Chin J Cancer* 2017; **36**: 10 [PMID: 28086948 DOI: 10.1186/s40880-017-0179-6]
- 48 **Yang Y**, Lin H, Zhao L, Song Y, Gao Q. Combination of sorafenib and cytokine-induced killer cells in metastatic renal cell carcinoma: a potential regimen. *Immunotherapy* 2017; **9**: 629-635 [PMID: 28653574 DOI: 10.2217/imt-2016-0133]
- 49 **McNutt M**. Cancer immunotherapy. *Science* 2013; **342**: 1417 [PMID: 24357273 DOI: 10.1126/science.1249481]
- 50 **Duffy AG**, Ulahannan SV, Makorova-Rusher O, Rahma O, Wedemeyer H, Pratt D, Davis JL, Hughes MS, Heller T, ElGindi M, Uppala A, Korangy F, Kleiner DE, Figg WD, Venzon D, Steinberg SM, Venkatesan AM, Krishnasamy V, Abi-Jaoudeh N, Levy E, Wood BJ, Gretten TF. Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma. *J Hepatol* 2017; **66**: 545-551 [PMID: 27816492 DOI: 10.1016/j.jhep.2016.10.029]
- 51 **El-Khoueiry AB**, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, Kim TY, Choo SP, Trojan J, Welling TH Rd, Meyer T, Kang YK, Yeo W, Chopra A, Anderson J, Dela Cruz C, Lang L, Neely J, Tang H, Dastani HB, Melero I. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* 2017; **389**: 2492-2502 [PMID: 28434648 DOI: 10.1016/S0140-6736(17)31046-2]
- 52 **Sangro B**, Gomez-Martin C, de la Mata M, Iñarrairaegui M, Garralda E, Barrera P, Riezu-Boj JI, Larrea E, Alfaro C, Sarobe P, Lasarte JJ, Pérez-Gracia JL, Melero I, Prieto J. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. *J Hepatol* 2013; **59**: 81-88 [PMID: 23466307 DOI: 10.1016/j.jhep.2013.02.022]



Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

