Int J Clin Exp Med 2016;9(2):1675-1683
www.ijcem.com /ISSN:1940-5901/IJCEM0017720

Original Article

Effect of interferon therapy on outcomes after hepatic resection for hepatitis C virus-related hepatocellular carcinoma: a meta-analysis

Yan-Jun Zhang[1], Yi-Ting Liu[1], Xiao-Song Yu[2]

[1]*Department of Physical Examination Center, The First Affiliated Hospital, China Medical University, Shenyang 110001, Liaoning, China;* [2]*Department of General Practice, The First Affiliated Hospital, China Medical University, Shenyang 110001, Liaoning, China*

Received October 12, 2015; Accepted January 27, 2016; Epub February 15, 2016; Published February 29, 2016

Abstract: Aim: To investigate the efficacy and safety of Interferon (IFN) therapy for hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC) after hepatic resection. Methods: A literature search of Pubmed, Embase and Cochrane Collaboration's database, were searched to identify eligible studies until July 2015. Randomized controlled trials (RCTs) and non-randomized controlled trials (NRCTs) were collected, if they evaluated the outcomes of IFN therapy after resection for HCV-related HCC. Major outcomes include early recurrence, overall mortality and 1-, 2-, 3-, 5-survival rates. A meta-analysis was conducted using risk ratio (RRs) and 95% confidence interval (95% *CI*s) as the effect sizes. Results: Overall, 658 papers were initially retrieved, of which 6 RCTs or NRCTs were included. They included a total of 959 subjects. Compared to patients without IFN therapy, the recurrence rates of HCC-related HCV in patients with IFN therapy were not significantly different [RR=0.94; 95% CI=0.71 to 1.24, *P*=0.66]. The overall mortality were significantly lower in patients with IFN therapy than in those without IFN therapy [RR=0.64; 95% CI=0.51 to 0.80; *P*=0.0001]. The 1- and 2-year survival rates were statistically similar between patients with and without IFN therapy after resection for HCV-related HCC [three trials, RR=1.01, 95% CI=0.92 to 1.09, *P*=0.90; three trials, RR=0.97, 95% CI=0.86 to 1.10, *P*=0.65]. By contrast, the 3- and 5-year survival rates were significantly higher in patients with IFN therapy than in those without IFN therapy [six trials, RR=1.09, 95% CI=1.00 to 1.18, *P*=0.04; six trials, RR=1.37, 95% CI=1.24 to 1.51, *P*<0.00001]. Conclusion: Adjuvant IFN therapy may significantly reduce the mortality of patients with HCV-related HCC and improve the 3- and 5- survival rates (>2 years) of patients after resection treatment.

Keywords: Interferon, hepatic resection, hepatitis C virus, hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver, which ranks the sixth among the malignant tumors in incidence [1]. The global incidence of HCC has continuously increased, with Asian countries accounting for almost 80% of victims worldwide [2, 3]. Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are the leading causes of HCC.

Current strategies for treating HCC include liver transplantation, liver resection and local ablative therapy [4]. Among these, liver resection is a potentially curative treatment option for HCC patients with preserved liver function [5]. With the advances in surgical techniques and perioperative management, the short-term outcome of surgery has dramatically improved over the last decade. However, the long-term outcome remains guarded because of the frequent locoregional tumor recurrence and concomitant hepatic decompensation [6].

Interferons (IFNs) are common antiviral drugs which not only have the property of suppressing the replication of HCV, but also possessing a variety of biological properties, including antiviral, immunomodulatory, antiproliferative, and antiangiogenic effects [7, 8]. IFNs might prevent from the tumor recurrence and improve the survival of HCV-related HCC. However, several clinical trials on the influence of IFNs in the

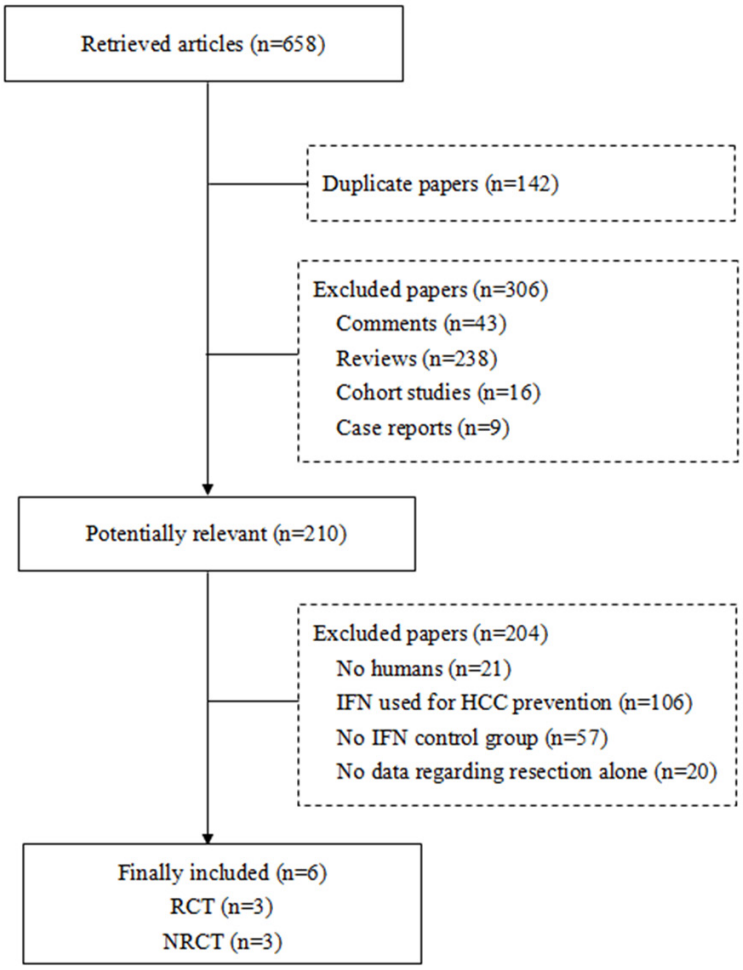

Figure 1. Flowchart of study selection.

management of HCC are still unclear. Additionally, a few meta-analyses have been conducted to evaluate the efficacy and safety of IFN therapy in patients with HCC. However, they were limited by selection bias of study population and treatment method and significant heterogeneity among studies [9-12].

The aim of our study was to confirm the potential effect of IFN therapy on HCV-related HCC after surgical resection by using currently available randomized controlled trials (RCTs) and non-randomized controlled trials (NRCTs).

Materials and methods

Selection of studies

A computerized literature search was conducted on the following databases up to June 19, 2015: Pubmed, Embase, Collaboration's database. The free text used for search purposes was 'hepatic resection OR liver resection OR surgery OR hepatectomy' AND 'interferon' AND 'hepatitis C virus OR HCV' AND 'hepatocellular carcinoma OR liver cancer'. The search was done without any restriction on language or publication year, and was conducted on human subject. All searched literatures were retrieved, and their references were checked as well for other relevant publications. Review papers were also searched to find additional eligible studies. For papers with overlapping data or on the same population, only the most recent or the ones with the largest group of subject data-set were included in this analysis. To identify potentially eligible articles, the title and abstract of each one identified by the literature search were assessed.

The following inclusion criteria were used for the paper selection: (1) the study design should be RCT or NRCT; (2) the participants should have primary HCC associated with HCV; (3) all eligible patients received IFN therapy after hepatic resection regardless of previous IFN treatment; (4) early recurrence rate, mortality and 1-, 2-, 3-, 5-survival rate and/or side effects were compared between patients with and without IFN therapy. Accordingly, the major reasons for exclusion were also used: (1) letters, reviews and duplicated literatures; (2) HBV-related HCC; (3) rather than surgery; (4) studies with no clear outcomes of recurrence, mortality and cumulative probability of survival.

Data extraction

From each of the eligible papers, the following data were extracted: publication data (first author, publication year, and country of population studied), design type, patients characteristics (patients number, mean age and sex ratio),

Table 1. Characteristics of included studies

Study	Years	Country	Design	Treatment	Patients	Mean age (years)	Sex ratio (male/female)	Tumor size (cm)	Tumor number (multiple)	Follow up (median, mo)
Kubo S et al.	2002	Japan	RCT	IFN	15	61.9	15/0	2.5	0	60.0
				Control	15	60.0	15/0	2.6	0	
Mazzaferro V et al.	2006	Italy	RCT	IFN	42	65.0	35/7	3.5	8	45.0
				Control	38	67.0	26/12	3.0	9	
Uenishi T et al.	2006	Japan	NRCT	IFN	50	62.0	43/7	2.2	10	70.0
				Control	262	65.0	214/48	3.0	81	
Ikeda K et al.	2010	Japan	NRCT	IFN	77	63.0	63/14	1.8	14	55.2
				Control	302	66.0	66/236	1.8	42	
Chen LT et al.	2012	China	RCT	IFN	133	50.0	108/25	3.5	30	63.8
		(Taiwan)		Control	135	49.0	112/23	3.0	20	
Tanimoto Y et al.	2012	Japan	NRCT	IFN	43	65.0	27/16	NA	37	84.0
				Control	76	71.0	47/29	NA	14	

tumor characteristics (tumor number, tumor size), therapy protocols (IFN type, median follow-up time).

Study quality assessment and level of evidence

The methodological qualities of the included trials were assessed independently by two investigators (Liu YT and Zhang YJ) in accordance with the Cochrane Collaboration's tool for assessing risk of bias [13].

Statistical analysis

Data were processed in accordance with the Cochrane Handbook. Intervention effects were expressed as risk ratios (RRs) with corresponding 95% confidence intervals (95% CIs). Z-test determined the significance of the pooled RRs and $P<0.05$ was considered as statistically significant. The random or fixed effects model was used for significantly heterogeneous or insignificantly heterogeneous data, respectively, as appropriate. Heterogeneity among studies was examined by chi-square test and I^2 test ($I^2>50\%$ and/or $P<0.1$, significant heterogeneity; $I^2<50\%$ insignificant heterogeneity) [14]. Subgroup analyses were used to examine the influence of various sources of patients and different study types. All the statistical analyses were performed using Review Manager 5.3 software (Cochrane collaboration, Oxford, UK).

Results

Search results and study characteristics

A total of 658 papers were initially searched, among which, six articles were selected for the present meta-analysis after reading the abstracts and full texts. The detailed steps of the literature search are shown in **Figure 1**.

In total, three RCTs [15, 16, 19] and three NRCTs [17, 18, 20] were eligible for this study. Sample sizes ranged from 30 to 379. The longest follow-up time was 45.0 months and the shortest follow-up time was 84.0 months. The characteristics of all included studies were listed in **Table 1**.

Risk of bias

All studies reported baseline circumstances of cases and showed a good comparability. Risk of bias evaluation was mainly from the following categories: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. The judgments about each risk of bias items for each included study are shown in **Figure 2**.

Recurrence rates for hepatocellular carcinoma

Six studies including 959 cases [15-20] compared the IFN group and the control group with regard to the recurrence rates of HCV-related HCC. The results was $P=0.002$ (<0.1), $I^2=73\%$, which indicated that there was a significant heterogeneity among studies. Therefore, we used a random-effect model. The results (RR=0.94; 95% CI=0.71 to 1.24, $P=0.66$) indicated that there was no difference between the IFN group after hepatic resection and the control group. The subgroup analysis suggested no significant associations in Japanese or in non-Japanese (**Figure 3**).

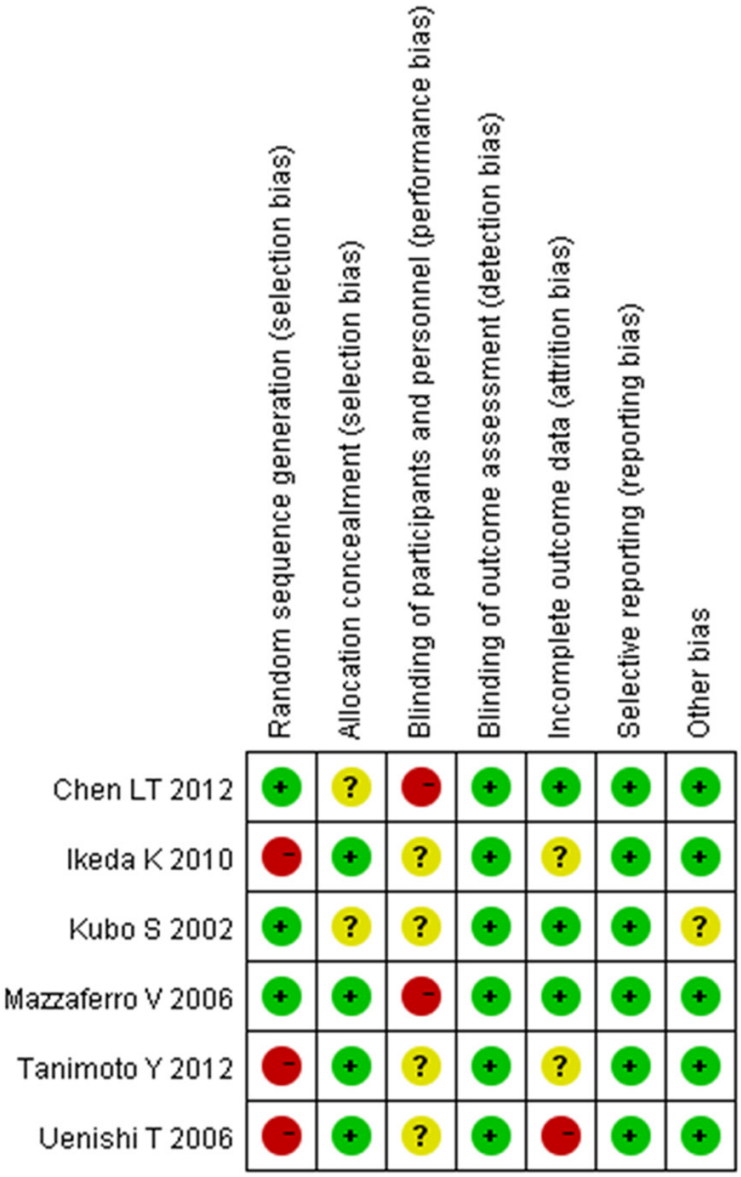

Figure 2. Risk of bias summary.

Overall mortality for hepatocellular carcinoma

Five studies including 910 patients [15-19] were performed in the comparison between IFN group and control group in the mortality of HCC. The results of heterogeneity was P=0.10, I^2=48% (<50%), which indicated there was no significant heterogeneity. So we conducted the present meta-analysis with a fixed-effect model. The results (RR=0.64; 95% CI=0.51 to 0.80; P=0.0001) suggested that IFN therapy might decrease the mortality of HCV-related HCC. The subgroup results with respect to ethnicity (RR=0.59; 95% CI=0.45 to 0.77; P< 0.0001 for Japanese; and RR=0.80; 95% CI=0.53 to 01.21; P=0.29 for non-Japanese) revealed that there was a significant difference between the IFN group and the control group for death rate of HCV-related HCC in Japanese. In the non-Japanese, there was no significant correlation (**Figure 4**). Overall survival rates for hepatocellular carcinoma. The meta-analysis showed that there was a significant difference in overall survival between two groups at 3 years (six trials; RR= 1.09; 95% *CI*=1.00 to 1.18; P=0.04), 5 years (six trials; RR=1.37; 95% *CI*=1.24 to 1.51; P<0.00001). For 1-, 2-, 4-year survival rate, pooled data didn't suggested a significant correlation (**Figure 5**).

Adverse effects of IFN

All included papers except one trial [17] reported data on adverse effects. The most common side effects of IFN therapy are high fever, depression, general fatigue and malaise, hepatotoxicity and hyperthyroidism, which occurred in almost every patient. Less common adverse effects include thrombocytopenia [16, 18-20], renal abscess [15], hyperthyroidism [16], hepatic encephalopathy [18] and skin eruption [20].

Sensitivity analysis

In order to compare the difference and confirm the stability and liability of the meta-analysis, we sequentially omitted individual eligible studies. Then, we reanalyzed the data of the remaining studies. The statistical significance of the results were not materially changed (data were not shown), indicating our results are comparatively stable and credible.

Discussion

The present meta-analysis evaluates the efficacy and safety of IFN therapy for HCV-related HCC who underwent surgical resection. The results indicate a significant benefit of IFN

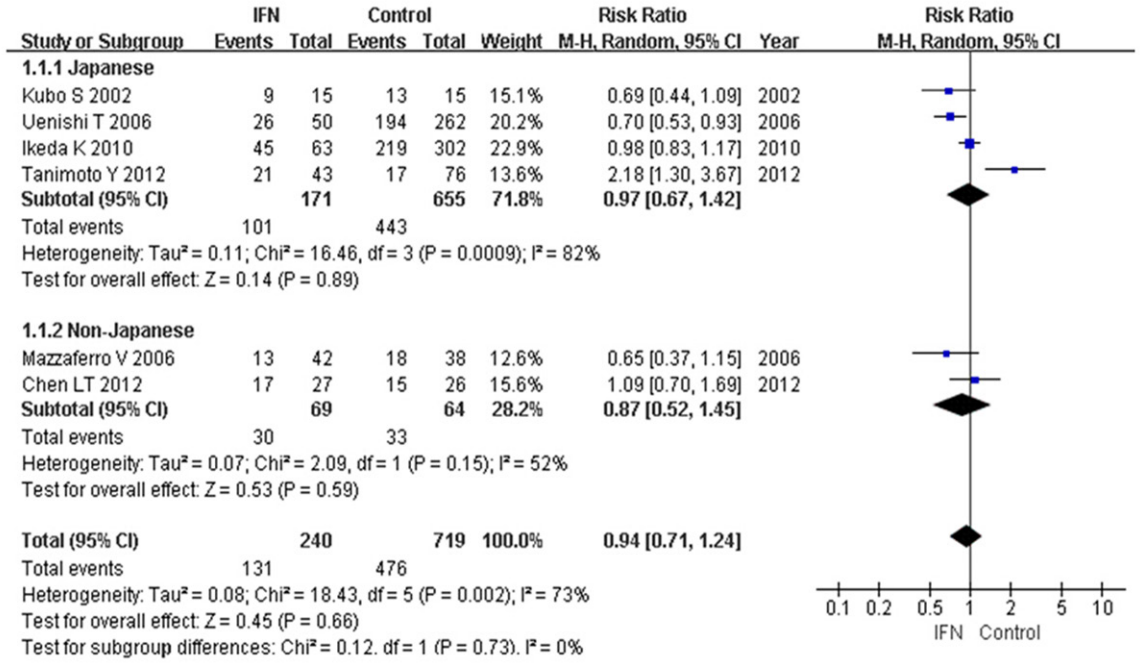

Figure 3. Forest plots describing the meta-analysis of recurrence rate of HCC.

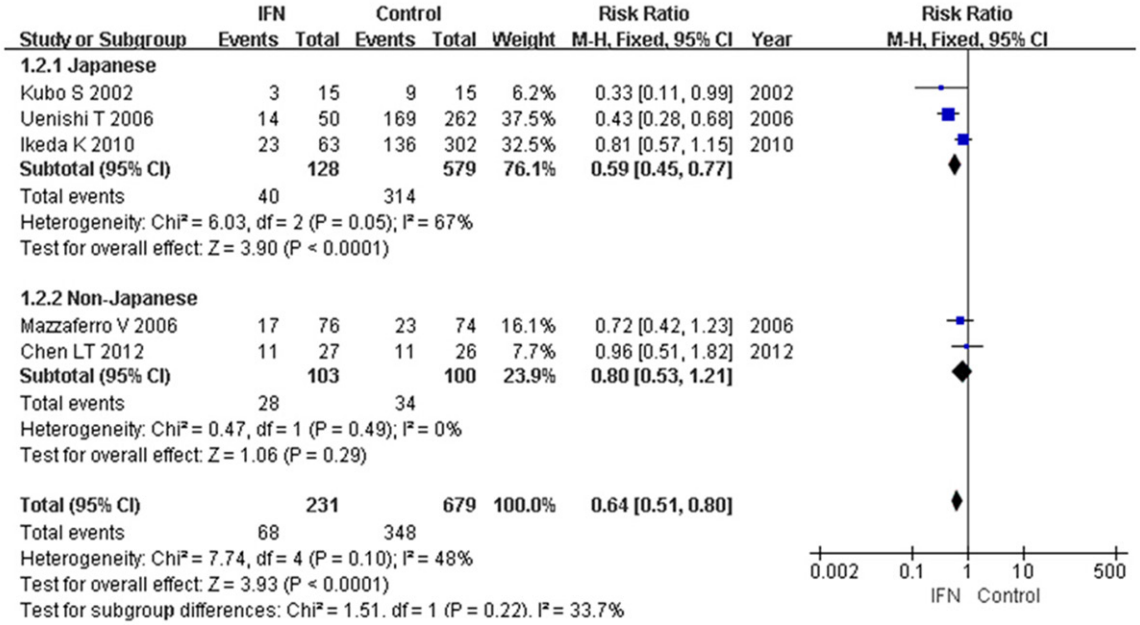

Figure 4. Forest plots describing the meta-analysis of mortality of HCC.

treatment on overall mortality and 3-, 5-year survival rate. But the effect of IFN on recurrence and 1, 2-year survival rate between IFN group and control group are not significant. In order to exclude bias stratified by the source of patients, we performed subgroup analysis on recurrence rate and mortality. Patients were divided into two groups including Japanese and non-Japanese. On recurrence rate aspect, both in Japanese and non-Japanese, the subgroup analysis results are similar to the overall results. On mortality, there is significant difference in Japanese but insignificant correlation in non-Japanese.

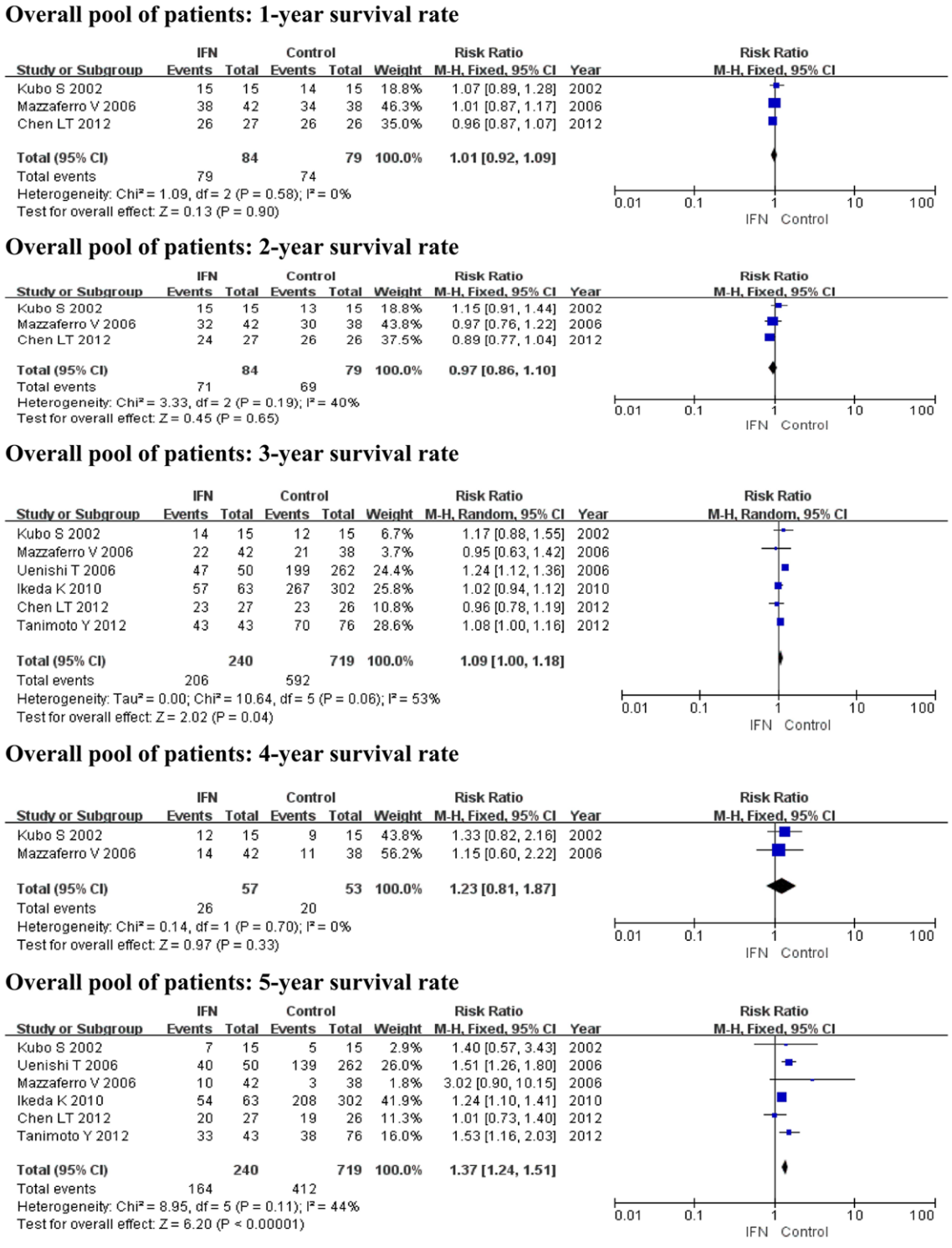

Figure 5. Forest plots describing the meta-analysis of overall survival rate.

The effects of IFN on HCC are affected by several factors, including antitumor, antiviral, antiangiogenic and modulatory inflammotory factors or hepatic stellate cells in the tumor microenviroment [21]. IFN is currently the standard therapy for HCV-infection and has also been proven to inhibit HCC development in HCV patients through clearance of HCV RNA, improv-

ing the degree of inflammation and preventing worsening of compensated cirrhosis [22]. Unquestionable, the recurrence of postoperative HCC has become the most important difficulty to improve the prognosis of patients [23, 24]. A meta-analysis of Singal AK et al. [25] found that patients underwent liver resection or ablation therapy for HCV-related HCC, the recurrence rate of sustaining virological responders who achieving IFN treatment was significantly lower than non-responders. Non-responders comparing to control groups without IFN treatment, the recurrence rate between the two groups was not statistically significant. In the report from China [26], there was no significant difference existing between IFN and control groups in a forest plot, which in consistent with our results. However, the meta-analyses conducting by Xu JB et al. [12] and Zhang W et al. [21] suggested a significant difference. Reportedly, the risk factors of tumor recurrence after surgical treatment include tumor location, tumor size, multi-nodular tumor and insufficient safety margin [27]. In contrast, Eastern Cooperative Oncology Group performance score, tumor size, microvascular invasion and tumor number were independent prognostic factors for overall survival [19]. Studies shown that, IFN therapy could reduce mortality in patients with HCC, and accordingly improving overall survival. Probably due to the following reasons: IFN helps relieve the inflammatory activity in the liver and improve liver function. Meanwhile, the improving of liver function provides a good condition for the following treatment of tumor recurrence. Though antiproliferative effect of IFN fails to prevent tumor recurrence, it suppresses tumor growth and reduce the severity of the tumor recurrence [28, 39].

Some limitations existing in this meta-analysis should be talked over. First of all, six trials included three NRCTs. In general, NRCTs are identified to result in incorrect associations because of the lack of reliability and precision. Second, the results failed to analyze the correlation between IFN therapy group and control group on early recurrence rate (≤2 years) and late recurrence rate (>2 years) of HCC proposed by Llovet et al [30]. Third, the treatment of most patients in this paper is surgery, but one study [19] did not list the curative treatments in detail and included ablation treatment, although making up a very small percentage of the total. Forth, the regimen of IFN therapy varied widely in the studies. The interval between previous therapies and IFN administration was not mentioned in most of the articles, which might be the potential factor that affects the efficacy. Lastly, four studies brought into Japanese populations, which might lead to bias. Further studies should include data from other ethnicities.

Acknowledgements

This study was funded by a grant form Science and Technology of Liaoning Province, China (No. 2013GS210102).

Disclosure of conflict of interest

None.

Authors' contributions

Zhang Yanjun and Liu Yiting contributed equally to this work including designing and drafting the manuscript, performing the literature search and selection, data extraction, quality assessment and statistical analyses. Yu Xiaosong gave the critical comments.

Address correspondence to: Dr. Xiao-Song Yu, Department of General Practice, The First Affiliated Hospital, China Medical University, No. 155, Nanjing North Street, Shenyang 110001, Liaoning, China. Tel: +86-024-83283089; Fax: +86-024-83283089; E-mail: xsyu@mail.cmu.edu.cn

References

[1] Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008. Int J Cancer 2010; 127: 2893-2897.

[2] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA cancer J Clin 2011; 61: 69-90.

[3] Lai EC, Lau WY. The continuing challenge of hepatic cancer in Asia. Surgeon 2005; 3: 210-215.

[4] Bruix J. Treatment of hepatocellular carcinoma. Hepatology 1997; 25: 259-262.

[5] Shindoh J, Hashimoto M, Watanabe G. Surgical approach for hepatitis C virus-related hepatocellular carcinoma. World J Hepatol 2015; 7: 70-77.

[6] Lo CM, Liu CL, Chan SC, Lam CM, Poon RT, Ng IO, Fan ST, Wong J. A randomized, controlled trial of postoperative adjuvant interferon therapy after resection of hepatocellular carcinoma. Ann Surg 2007; 245: 831-842.

[7] Marschall Z, Scholz A, Cramer T, Schäfer G, Schirner M, Oberg K, Wiedenmann B, Höcker

M, Rosewicz S. Effects of interferon alpha on vascular endothelial growth factor gene transcription a tumor angiogenesis. J Natl Cancer Inst 2003; 95: 437-448.
[8] Wang L, Wu WZ, Sun HC, Wu XF, Qin LX, Liu YK, Liu KD, Tang ZY. Mechanism of interferon alpha on inhibition of metastasis and angiogenesis of hepatocellular carcinoma after curative resection in nude mice. J Gastrointest Surg 2003; 7: 587-594.
[9] Jiang S, Liu Y, Wang L, Duan C, Liu M. A meta-analysis and systematic review: adjuvant interferon therapy for patients with viral hepatitis-related hepatocellular carcinoma. World J Surg Oncol 2013; 11: 240-247.
[10] Wang J, He XD, Yao N, Liang WJ, Zhang YC. A meta-analysis of adjuvant therapy after potentially curative treatment for hepatocellular carcinoma. Can J Gastroenterol 2013; 27: 351-363.
[11] Zhuang L, Zeng XT Yang Z, Meng Z. Effect and safety of interferon for hepatocellular carcinoma: A systematic review and meta-analysis. PLoS One 2013; 9: 1-5.
[12] Xu JB, Qi FZ, Xu G, Chen GF, Huang MD, Zhang JH. Adjuvant interferon therapy after surgical treatment for hepatitis B/C virus-related hepatocellular carcinoma: A meta-analysis. Hepatol Res 2014; 44: 209-217.
[13] Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available: www.Cochrane-handbook.org.
[14] Higgins JP, Thompson SG, Deek JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-560.
[15] Kubo S, Nishiguchi S, Hirohashi K, Tanaka H, Shuto T, Kinoshita H. Randomized clinical trial of long-term outcome after resection of hepatitis C virus-related hepatocellular carcinoma by postoperative interferon therapy. Br J Surg 2002; 89: 418-422.
[16] Mazzaferro V, Romito R, Schiavo M, Mariani L, Camerini T, Bhoori S, Capussotti L, Calise F, Pellicci R, Belli G, Tagger A, Colombo M, Bonino F, Majno P, Llovet JM; HCC Italian Task Force. Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. Hepatology 2006; 44: 1543-1556.
[17] Uenishi T, Nishiguchi S, Tamori A, Yamamoto T, Shuto T, Hirohashi K, Takemura S, Tanaka H, Kubo S. Influence of interferon therapy on outcome after surgery for hepatitis C virus-related hepatocellular carcinoma. Hepatol Res 2006; 36: 195-200.
[18] Ikeda K, Kobayashi M, Seko Y, Imai N, Hirakawa M, Kawamura Y, Sezaki H, Hosaka T, Akuta N, Saitoh S, Suzuki F, Suzuki Y, Arase Y, Kumada H. Administration of interferon for two or more years decreases early stage hepatocellular carcinoma recurrence rate after radical ablation: A retrospective study of hepatitis C virus-related liver cancer. Hepatol Res 2010; 40: 1168-1175.
[19] 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 randomized observation-controlled phase II trial of adjuvant interferon alfa-2b in hepatocellular carcinoma after curative resection. Ann Surg 2012; 255: 8-17.
[20] Tanimoto Y, Tashiro H, Aikata H, Amano H, Oshita A, Kobayashi T, Kuroda S, Tazawa H, Takahashi S, Itamoto T, Chayama K, Ohdan H. Impact of pegylated interferon therapy on outcomes of patients with hepatitis C virus-related hepatocellular carcinoma after curative hepatic resection. Ann Surg Oncol 2012; 19: 418-425.
[21] Zhang W, Song TQ, Zhang T, Wu Q, Kong DL, Li Q, Sun HC. Adjuvant interferon for early or late recurrence of hepatocellular carcinoma and mortality from hepatocellular carcinoma following curative treatment: A meta-analysis with comparison of different types of hepatitis. Mol Clin Oncol 2014; 2: 1125-1134.
[22] Nishiguchi S, Kuroki T, Nakatani S, Morimoto H, Takeda T, Nakajima S, Shiomi S, Seki S, Kobayashi K, Otani S. Randomised trial of effects of interferon-alpha on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. Lancet 1995; 346: 1051-1055.
[23] Kawano Y, Sasaki A, Kai S, Endo Y, Iwaki K, Uchida H, Shibata K, Ohta M, Kitano S. Prognosis of patients with intrahepatic recurrence after hepatic resection for hepatocellular carcinoma: a retrospective study. Eur J Surg Oncol 2009; 35: 174-179.
[24] Blum HE, Spangenberg HC. Hepatocellular carcinoma: an update. Arch Iran Med 2007; 10: 361-371.
[25] Singal AK, Freeman DH, Anand BS. Meta-analysis: interferon improves outcomes following ablation or resection of hepatocellular carcinoma. Aliment Pharmacol Ther 2010; 32: 851-858.
[26] Miao RY, Zhao HT, Yang HY, Mao YL, Lu X, Zhao Y, Liu CN, Zhong SX, Sang XT, Huang JF. Postoperative adjuvantantiviral therapy for hepatitis B/C virus-related hepatocellularcarci-

noma: a meta-analysis. World J Gastroenterol 2010; 21: 2931-2942.
[27] Liu L, Miao R, Yang H, Lu X, Zhao Y, Mao Y, Zhong S, Huang J, Sang X, Zhao H. Prognostic factors after liver resection for hepatocellular carcinoma: a single-center experience from China. Am J Surg 2012; 203: 741-750.
[28] Hagihara H, Nouso K, Kobayashi Y, Iwasaki Y, Nakamura S, Kuwaki K, Toshimori J, Miyatake H, Ohnishi H, Shiraha H, Yamamoto K. Effect of pegylated interferon therapy onintrahepatic recurrence after curative treatment of hepatic C virus-related hepatocellular carcinoma. Int J Oncol 2011; 16: 210-220.
[29] Murata M, Nabeshima S, Kikuchi K, Yamaji K, Furusyo N, Hayashi J. A comparison of the antitumor effects of interferon-alpha and beta on human hepatocellular carcinoma cell lines. Cytokine 2006; 33: 121-128.
[30] Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003; 362: 1907-1917.