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Effect of Adjuvant Interferon Therapy on Hepatitis B/C Virus-Related Hepatocellular Carcinoma After Curative Therapy – Meta-Analysis*

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Background. Hepatocellular carcinoma is the fifth most common malignant cancer in the world. Liver resection and local ablation are the most effective therapeutic approaches for most HCC patients. Recurrence after curative therapy is very common. Some studies reveal that IFNs have an effect on recurrence. While the opinion is disagreement.

Objectives. The aim of this meta-analysis was to evaluate whether interferon therapy could reduce the recurrence of patients of hepatitis B/C virus-related hepatocellular carcinoma after curative therapy.

Material and Methods. All randomized controlled trials about interferon on recurrence of hepatitis B/C virus-related hepatocellular carcinoma patients after curative surgery treatment were searched from PubMed, Embase, Cochrane library (all from 1977 to January 2014). Two reviewers independently assessed the quality of each included study and extracted data. RevMan 5.1 was used for meta-analysis.

Results. Pooled data analysis revealed that the interferon group had no statistical significance on the recurrence of hepatitis-related hepatocellular carcinoma compared to the control group (RR = 0.91, 95% CI, 0.82 to 1.00); p = 0.11). While from the subgroup analysis of adjuvant interferon can reduce the recurrence of the median tumor size below 3 cm (RR 0.50, 95% CI 0.35–0.72; p = 0.00002).

Conclusions. Adjuvant IFN after curative treatment of hepatitis-related HCC can improve the survival of HCC patients. In addition, IFN could decrease the recurrence rate of HCC patient with median tumor size below 3 cm but not exceeding 3 cm (**Adv Clin Exp Med 2015, 24, 2, 331–340**).

Key words: interferon, hepatocellular carcinoma, recurrence, survival.

Hepatocellular carcinoma (HCC) is the 5th most common malignant cancer and the 2nd most common cause of cancer-related deaths in the world [1]. Population-based studies show that the incidence rate continues to approximate the death rate, indicating that most of the patients who develop HCC die of it [1]. HBV and HCV are considered the main etiology of HCC, which accounts for about 70–80% [2]. Plenty of therapies have been tested for the treatment of HCC, only a few are curative, such as liver transplantation, surgical resection, radiofrequency ablation. Among these curative therapies, only liver transplantation is the most promising. However, shortage of donors, high cost and strict selection criteria are the reasons why transplantation can only be available to a small portion of patients [3, 4]. So liver resection and local ablation are commonly used by clinicians as the most effective therapeutic approaches for most HCC patients [5–9]. However,

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the recurrence after resection or ablation is very common. Tumor recurrence appears in about half of HCC patients after resection or ablation within 3 years [10–12].

It has been studied that transarterial chemoembolization [13–15], acyclic retinoid [16], interferon (IFN) therapy [17] can reduce the recurrence. Among these, IFN is one of the most potential therapies, owing the antiviral properties of interferons (that can clear or suppress HBV or HCV), antiproliferative, immunomodulatory and antiangiogenesis against human cancers [18–20].

In recent years, several randomized controlled trials [8, 10, 21–28] have revealed that IFN can have some influence on the recurrence of HCC. Some of them give a promising conclusion that the adjuvant IFN can reduce recurrence, while the others hold the opposite opinion. In our study, we conducted a meta-analysis to evaluate whether adjuvant IFN after curative treatment of hepatitis-related HCC can reduce the recurrence.

Material and Methods

Inclusion and Exclusion Criteria

The selected studies were included based on the following set of inclusion criteria: (1) patients older than 18 years without gender restrictions who had primary HBV or HCV-related HCC; (2) all patients received IFN therapy after curative surgical treatment no matter whether they had received previous IFN treatment; (3) the included studies were randomized controlled trials (RCTs); (4) each included trial assessed at least one of the following outcomes by comparing IFN therapy to placebo or no treatment: overall survival rates at 5 years and HCC recurrence (local recurrence or a new focus) on follow-up (5) when similar studies were reported by the same institution, either the better-quality study or the more recent publication was included.

Exclusion criteria are as follows: (1) patients were primarily treated by percutaneous ethanol injection (PEI), percutaneous microwave coagulation therapy, or liver transplantation rather than surgery; (2) non-comparative studies were excluded; (3) studies assessing liver metastases, recurrence after hepatectomy or unresectable HCC and studies with no outcome measure of probability of survival, mortality or recurrence reported.

Search Strategy

We performed a comprehensive literature strategic search to identify studies about IFN on the recurrence of HCC patients after curative surgery treatment. The electronic search included PubMed, Embase and the Cochrane Library from 1977 to February 2014. In addition, the reference articles of the retrieved studies were also searched. We used the terms in "IFN OR interferon", "liver carcinoma", "hepatocellular", "hepatocellular carcinoma", "HCC", "liver neoplasm", "liver cancer" in English.

Data Extraction and Methodology Quality Assessment

We screened the studies according to the inclusion and exclusion criteria. Two reviewers independently extracted the following data from the selected studies: first author, year of publication, design, number of patients (IFN/control), patient characteristics, tumor characteristics and so on. Extracted data was entered into a standardized form and was checked by another author. Any disagreements were resolved by discussion and consensus.

The outcome of interest was the survival and the recurrence of hepatitis B/C virus-related hepatocellular carcinoma after curative surgical treatment. The number of recurrences and death in patients was computed from the Kaplan-Meier curves, if there was no additional description.

We evaluated the methodological quality of each trial using the Jadad scale. This scale consists of 3 items describing randomization (0–2 points), blinding (0–2 points), and dropouts and withdrawals (0–1 point) in the report of a RCT. A score of 1 was given for each of the points described. A further point was obtained where the method of randomization and/or blinding was given and was appropriate; where it was inappropriate, a point was deducted. The quality scale ranges from 0 to 5 points. Higher scores indicated better reporting. The studies were said to be of low quality if the Jadad score was ≤ 2 and of high quality if the score was ≥ 3.

Statistical Analysis

Review Manager Software version 5.1 was used for all analysis. All outcomes were expressed as RR with 95% CI. The Cochrane Q test was used to detect heterogeneity of the effects; significant heterogeneity was defined as a p value < 0.1. A fixed--effects model or random-effects model was used depending on the absence or presence of heterogeneity. I2 statistic was estimated to describe the percentage of the variability attributable to heterogeneity rather than sampling error. Studies with

an I2 statistic of < 25 % are considered to have no heterogeneity, those with an I2 statistic of 25% to 50% are considered to have low heterogeneity, those with an I2 statistic of 50% to 75% are considered to have moderate heterogeneity, and those with an I2 statistic of > 75% are considered to have high heterogeneity. Whenever heterogeneity was present, sensitivity analyses based on the sample size, study quality, and the process of omitting one study in each turn were performed to identify potential sources.

Results

Study Description

The search strategy initially identified 133 relevant studies. Two reviewers screened the studies according to the inclusion and exclusion criteria. After an initial screening of titles and abstracts, 114 studies of reviews, letters, editorials, comments, case reports and irrelevant clinical comparative studies were excluded. The remaining 19 articles were then retrieved for full text. Nine articles were excluded, of which 4 applied non-curative treatments for HCC, 4 did not undergo IFN therapy and 1 was a Chinese article. Ten articles studies were thought to meet the inclusion criteria, of which 3 were published from the same institution and the most recent one was selected in our analysis [28]. Finally, 8 articles [8, 10, 21–24, 27, 28] were eligible for this meta-analysis (Fig. 1).

The studies' basic characteristics and outcome measures are shown in Table 1. There were 888 patients, of which 461 patients underwent adjuvant IFN, and 427 underwent placebo or nothing.

Meta-Analysis Recurrence

All 8 studies reported the recurrence of IFN therapy for the HBV/HCV related HCC after curative surgical treatment. The pooled analysis showed no significant statistical difference between IFN and the control group (RR, 0.91; 95%CI, 0.82–1.00; p = 0.06) (Fig. 2).

We also performed some subgroup analysis (Table 2). When the trials were divided by the type of hepatitis virus and tumor size, we found that the pooled analysis showed no significant difference (RR 0.94, 95% CI 0.82–1.09; p = 0.41) in HCV-related HCC patients. Meanwhile, no statistical recurrence decrease of IFN therapy in HBV-related HCC patients was observed (RR 0.95, 95% CI 0.82–1.11; p = 0.55) (Fig. 3). On the median tumor size of < 3 cm, IFN therapy resulted in a significant reduction in HBV/HCV-related HCC recurrence after curative treatment (RR 0.50, 95% CI 0.35–0.72; p = 0.00002) (Fig. 4). Conversely, when the median tumor size was > 3 cm, there was no statistical positive effect of IFN therapy.

Survival

For the survival of IFN therapy for the HBV/HCV related HCC after curative surgical treatment, 6 studies were included. The pooled ana-

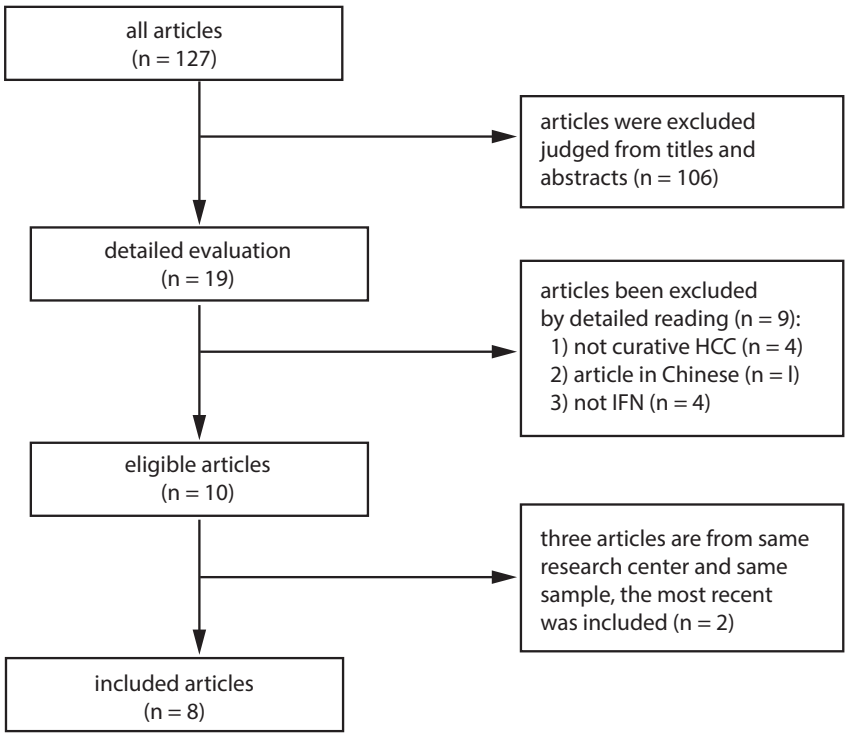

Fig. 1. The process of selecting the articles included in meta-analysis

Table 1. The basic characteristic of trials

Reference (year)	Intervetion	Type (IFN)	Total dose (Miu)		Patients (n)	Male (n)	HCV (n)	HBV (n)	HBV + HCV (n)	Median age (year)	Median tumor size (mm)	AFP (ng/L)	JADAD
Ikeda (2000)	surgical resection/ ethanol injection	IFN-β	824	IFN	10	7	20	0	0	60 (54–70)	22 (12–45)	/	3
				control	10	6				64.5 (51–69)	20 (12–40)	/	
Shiratori (2003)	PEI	IFN-α	864	IFN	49	35	74	0	0	61 (37–70)	22 (17–29)	18 (8–45)	4
				control	20	17				63 (51–69)	23 (19–30)	23 (13–54)	
Lin (2003)	PAI/PAI + TACE	IFN-α	864/360	IFN	20	16	13	16	1	60 (26–70)/63 (31–65)	20 (10–69)/23 (12–37)	16/18	3
				control	10	7				59 (49–72)	25 (20–36)	20	
Nishiguchi (2005)	surgical resection	IFN-α	1572	IFN	15	15	30	0	0	61.9 ± 5.8	25 (29–35)	/	4
				control	15	15				60 ± 4.8	26 (24–39)	/	
Sun (2006)	surgical resection	IFN-α	1092	IFN	118	106	0	236	0	52,2	43 ± 2.7	/	4
				control	118	102				50,4	49 ± 3.0	/	
Mezzaferro (2006)	surgical resection /TACE/RFA/PEI	IFN-α	432	IFN	76	61	80	0	70	65 (61–74)	33.7 ± 27.5	/	4
				control	74	51				67 (36–73)	31.9 ± 22.6	/	
Lo (2007)	surgical resection	IFN-α	1920	IFN	40	31	2	77	1	49 (26–75)	55 (18–220)	23 (3–103)	4
				control	40	34				54 (24–74)	57 (12–180)	126 (2–182)	
Chen (2012)	surgical resection	IFN-α	835	IFN	133	108	53	215	0	50 (48–54)	35 (3–4)	/	4
				control	135	112				49 (46–51)	30 (25–35)	/	

IFN – interferon; PAI – percutaneous acetic acid injection; TACE – transchatheter arterial chemoembolization; RFA – radiofrequency ablation; PEI – percutaneous ethanol injection; Miu – million.

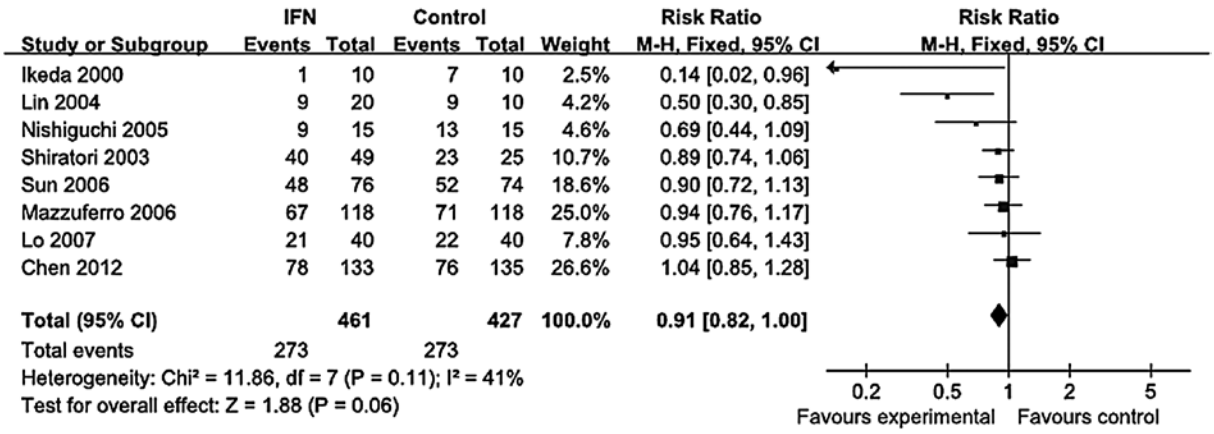

Fig. 2. Forest plot of the effect of adjuvant IFN on recurrence after curative treatment of hepatitis-related HCC

Table 2. The subgroups analyses of recurrence and survival

Subgroup		RR (95% CI)	I^2 %	P
(Recurrence)				
Types of hepatitis	HBV	0.95 (0.82–1.11)	62	0.55
	HCV	0.94 (0.82–1.09)	34	0.41
Median tumor size	< 3 cm	0.50 (0.35–0.72)	44	0.0002
	> 3 cm	0.97 (0.86–1.09)	0	0.59
(Survival)				
Median tumor size	< 3 cm	0.49 (0.32–0.74)	0	0.0008
	> 3 cm	0.77 (0.61–0.96)	67	0.02

lysis showed a significant difference between IFN and control group (RR, 0.70; 95% CI, 0.58–0.86; p = 0.0004) (Fig. 5).

A subgroup analysis was conducted (Table 2). Taking the median tumor size of 3 cm as a threshold, we found that the pooled analysis showed a significant difference in both the median tumor size of < 3 cm and > 3 cm (Fig. 6).

Sensitivity Analysis

When studies with large sample size (> 100) or those published before 2005 studies were assessed, the result changed on recurrence. And studies with a small sample size (< 100) or total dose of IFN < 1000 miu, the result of survival changed. A further sensitivity analysis of studies with IFN-α, sample size less than 100, total dose of IFN more than 1000 miu, published before 2005, surgical resection or after we deleted studies with highest and lowest HR, or by applying random-effects model, still showed the same result of recurrence and survival between IFN group and control group (Table 3).

Adverse Effects

A statistical assessment comparing adverse effects of IFN therapy was not applicable due to lack of data. Common adverse effects after initial IFN injection were flu-like symptoms, including chills, fever, myalgia and headache. These affected almost every patient in all of the studies. A dose reduction was needed in 237 of 461 patients (51.4%) due to such side effects as neutropenia, thrombocytopenia and leucocytopenia. Of 461 patients treated with IFN, 35 (7.6%) developed intolerable adverse effects requiring discontinuation of IFN therapy.

Discussion

This meta-analysis indicates no statistical significance of adjuvant IFN on the recurrence of HBV/HCV-related HCC. The result is contrary to the meta-analyses or systematic reviews published before [29, 30]. One of the meta-analysis reported by S. Breitenstein [29] included one trial less than ours. And this trial [28] was published recently by

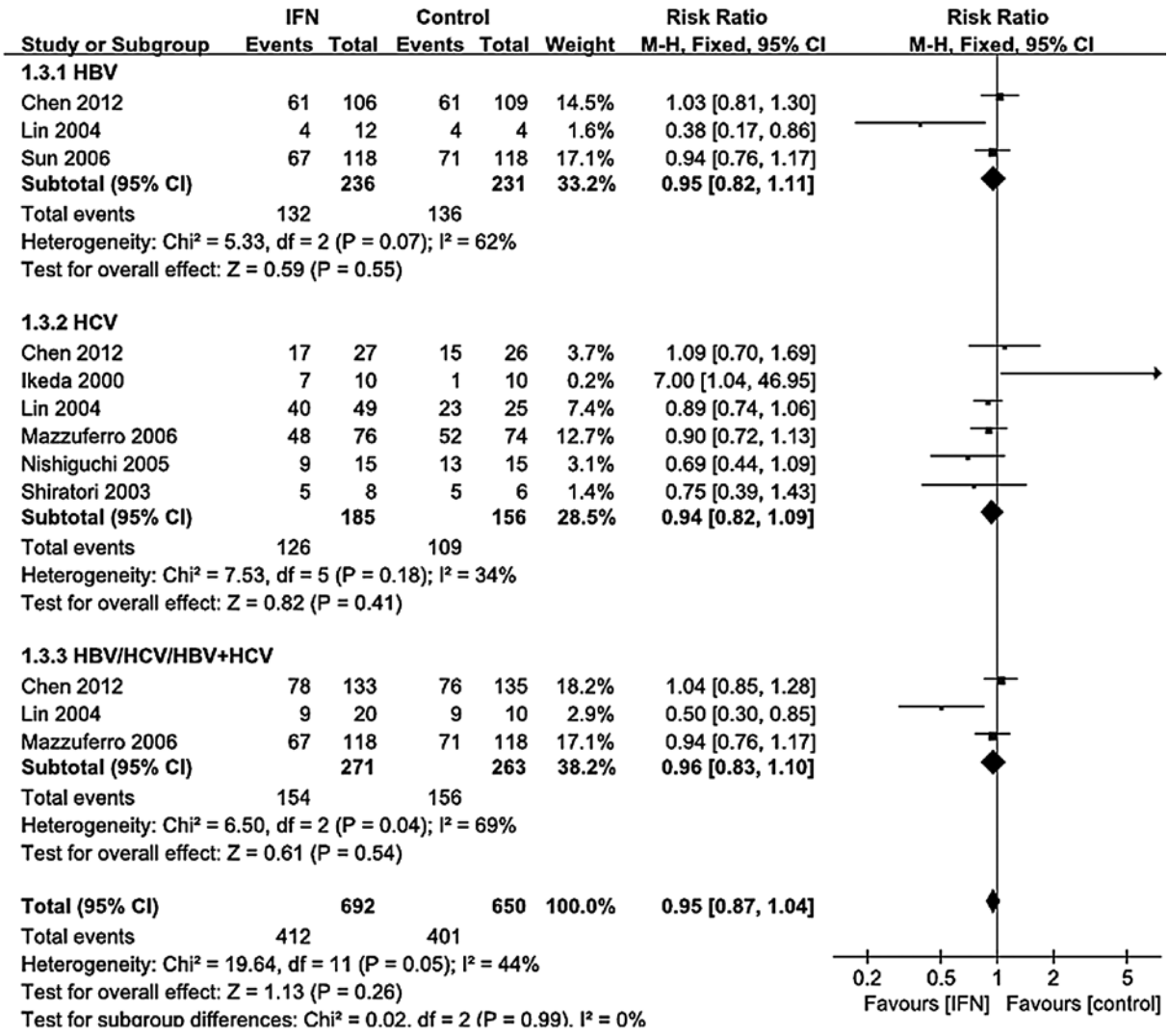

Fig. 3. Forest plot of adjuvant IFN on recurrence of different types of hepatitis-related HCC

LT Chen and its conclusion was contrary to the trials which were included in Breitenstein's report [29]. Meanwhile, samples in Chen's [28] report were much larger than any other RCTs [8, 10, 21–24, 27], which were all included in our meta-analysis. So the weight of the trial largely affected the final results, different conclusion achieved is reasonable. Though the other meta-analysis [30] of larger samples was published before, its data was extracted from both RCTs and nonrandomized trials. Nonrandomized trials may encounter many problems that could reduce their internal and external validity, and the lack of precision and reliability of these trials can lead to significant inherent biases toward false positive results of meta-analysis report [31, 32]. So results of this meta-analysis may be unreliable. Our meta-analysis not only includes all RCTs but also possesses a larger sample. So the disadvantages appeared before were avoided. Still, more studies are needed to evaluate the effect of IFN on recurrence.

IFN could improve the survival according to our meta-analysis. However, contradiction was found between the improved survival and unimproved recurrence. Beyond all doubts, the recurrence of postoperative HCC had become one of the most serious obstacles of improving the prognosis of patients [32–34]. It is evident that the survival of hepatitis-related HCC after curative therapy was related to not only tumor recurrence but also other reasons, such as biological characteristics of tumor, liver function, progress of hepatitis or HCC, the status of individual patient and so on [35]. Obviously, these other reasons or composite effects played a more important role in the influence of survival than recurrence alone. As a result, it is not enough for improving the prognosis of curative treatment of hepatitis-related HCC with monotherapy of IFN. The combination of IFN and other therapies would be a promising therapy and may not only improve the survival but also reduce the recurrence.

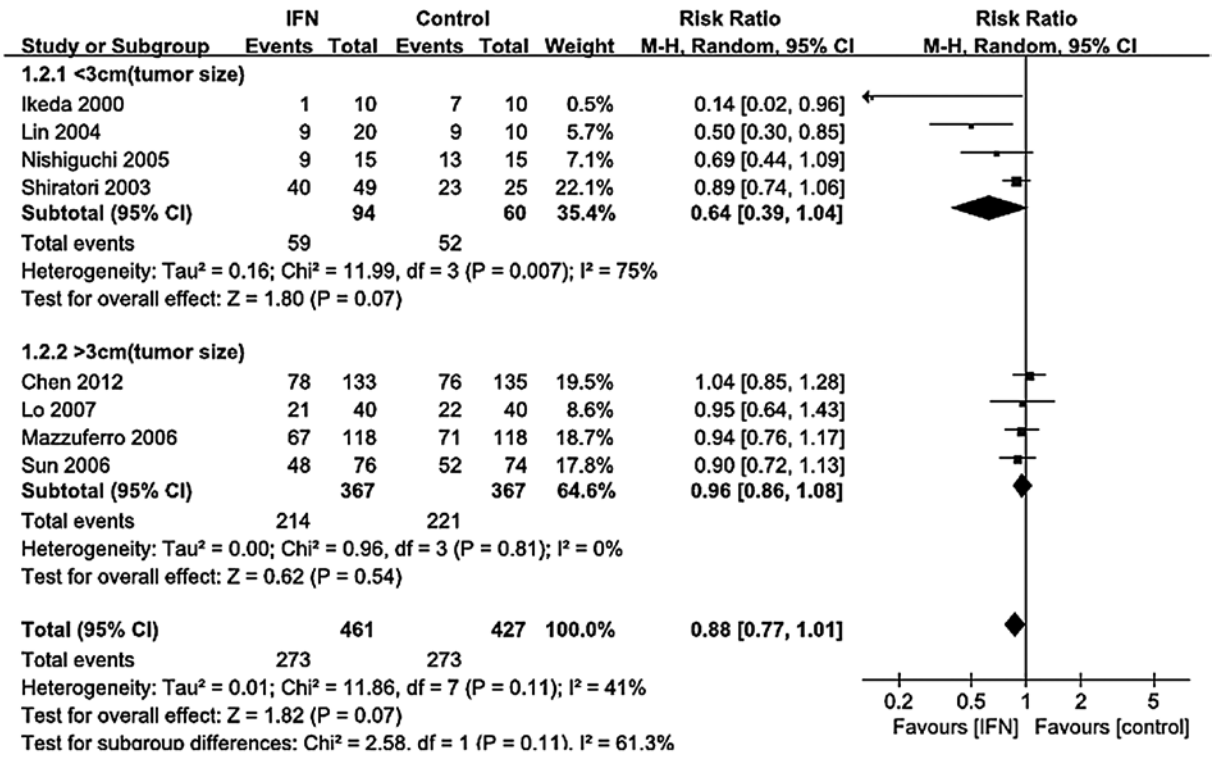

Fig. 4. Forest plot of adjuvant IFN on recurrence of different size of HCC

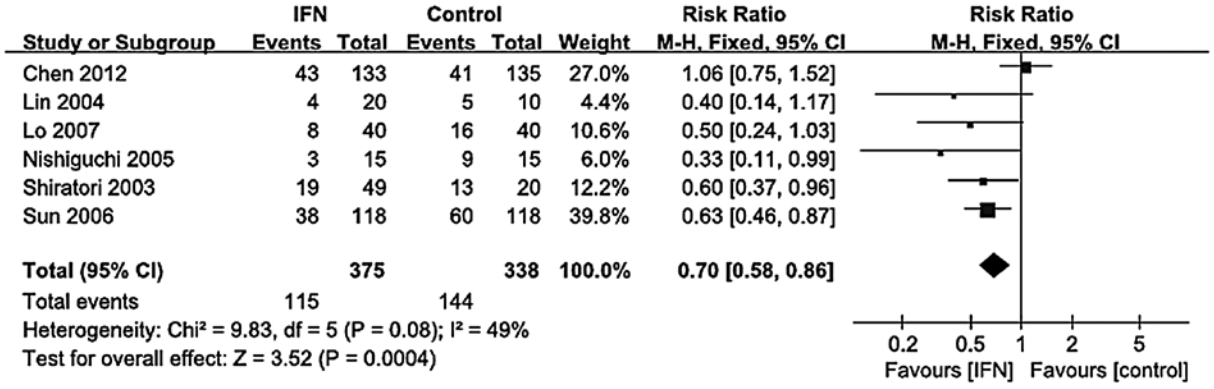

Fig. 5. Forest plot of adjuvant IFN on survival of hepatitis-related HCC after curative therapy

In subgroup analysis of HCV and HBV-related HCC, there is also no statistical significance in both HCV and HBV-related HCC. However, high heterogeneity existed in subgroup analysis of HBV-related HCC. After we removed the study of Lin SM's [24] which heterogeneity may come from, the heterogeneity disappeared and the result did not change. Meanwhile, we took median tumor size of 3 cm as a threshold, the subgroup analysis indicated that IFN can reduce the recurrence of HCC where the median tumor size was smaller than 3 cm, while the result is opposite to the group where the tumor size was larger than 3 cm. We reasoned this difference as follows: firstly, median tumor size less than 3 cm is common in an earlier stage of development; secondly, it has fewer metastases than the tumor size larger than 3 cm; thirdly, the larger size of the tumor is difficult to be ablated or resected absolutely. As a consequence, we can speculate adjuvant IFN is more suitable for the median size which is less than 3 cm and more studies are needed to explore this speculation.

For the survival of HCC after curative therapies analysis, IFN has an advantage compared to control group (RR = 0.70; 95% CI (0.58, 0.86); p = 0.08). Subgroup analysis of both the median tumor size less than 3 cm and more than 3 cm groups showed the same result in survival. The result is in accord with other meta-analyses before [29, 30, 36, 37]. We reasoned this phenomenon as follows: firstly, IFN can relieve active-hepatitis and improving hepatic fibrosis and liver function; to

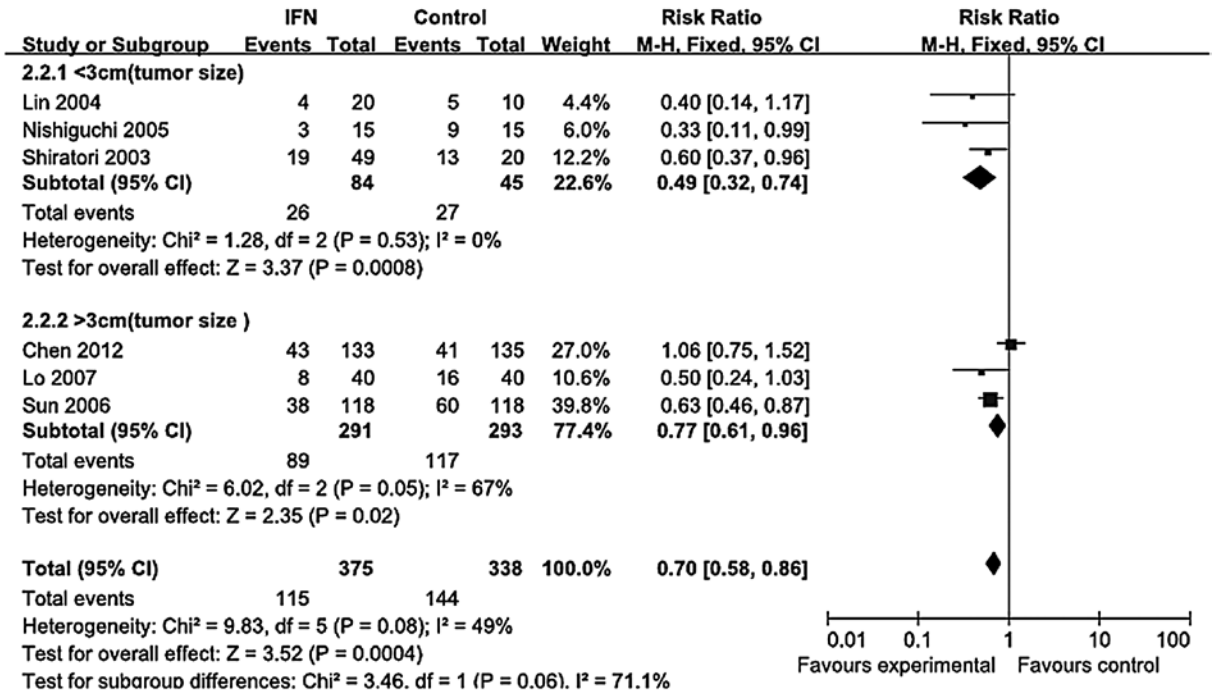

Fig. 6. Forest plot of adjuvant IFN on survival of different size of hepatitis-related HCC

Table 3. Sensitivity analysis of comparing IFN vs control

Subgroup		RR (95%CI)	I^2 %	P
(Recurrence)				
Years	< 2005	0.50 (0.35,0.72)	44	0.0002
	> 2005	0.97 (0.86,1.09)	0	0.59
Types of IFN	IFN-β	0.14 (0.02,1.09)	/	0.05
	IFN-α	0.93 (0.84,1.03)	29	0.14
Surgical resection	no	0.70 (0.38,1.28)	79	0.24
	yes	0.93 (0.80,1.07)	24	0.28
Dose of IFN	< 1000 miu	0.92 (0.81,1.09)	62	0.17
	> 1000 miu	0.88 (0.73,1.04)	0	0.18
Sample size	large	0.76 (0.63,0.91)	59	0.02
	small	0.97 (0.86,1.10)	0	0.62
(Survival)				
Years	< 2005	0.49 (0.32,0.74)	0	0.0008
	> 2005	0.77 (0.61,0.96)	67	0.02
Types of IFN	IFN-β	/	/	/
	IFN-α	0.70 (0.58,0.86)	49	0.0004
Surgical resection	no	0.54 (0.35,0.85)	0	0.007
	yes	0.73 (0.59,0.91)	63	0.005
Dose of IFN	< 1000 miu	0.87 (0.66,1.14)	65	0.31
	> 1000 miu	0.58 (0.44,0.76)	0	0.0001
Sample size	large	0.49 (0.34,0.71)	0	0.0002
	small	0.81 (0.64,1.02)	78	0.07

be next, decrease the severity of a recurrent tumor and thus be amenable to secondary curative ablation or resection.

Our meta-analysis also has many limitations which are described as follows. First of all, positive results were more likely to be published than negative. Despite all the hard work in trying our best to search the related trials as comprehensively as possible, the published bias cannot be avoided. Next, even with access to advanced radiologic technology, some shortcomings also exist in the assessment of whether the tumor is completely resected when using CT or MRI. It is impossible to avoid the impact on result brought by the drawbacks of radiologic technology. Last, most of the patients in our meta-analysis were treated by surgical resection, RFA and PEI, but TACE as a palliative treatment which was treated as a curative therapy in some trials [10, 24]. Although the number of patients which were treated by TACE made up a very small percentage of the total, heterogeneity was inevitable.

Adjuvant IFN after curative treatment of hepatitis-related HCC can improve the survival of HCC patients. In addition, IFN could decrease the recurrence rate of HCC patient with median tumor size below 3 cm but not exceed 3 cm.

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