Criteria Grid
Best Practices and Interventions for the Diagnosis and Treatment of Hepatitis C

Best Practice/Intervention:	Singal AK. et al. (2010) Meta-analysis: interferon improves outcomes following ablation or resection of hepatocellular carcinoma. *Alimentary Pharmacology & Therapeutics*, 32(7):851-858.
Date of Review:	March 2, 2015
Reviewer(s):	Christine Hu

Part A

Category:

Basic Science ☐　Clinical Science ☐　Public Health/Epidemiology ☐

Social Science ☐　Programmatic Review ☒

Best Practice/Intervention:

Focus:　Hepatitis C ☒　Hepatitis C/HIV ☐　Other: Hepatocellular carcinoma, cirrhosis

Level:　Group ☒　Individual ☐　Other:

Target Population: HCV patients with hepatocellular carcinoma

Setting: Health care setting/Clinic ☒　Home ☐　Other:

Country of Origin: USA

Language:　English ☒　French ☐　Other:

Part B

	YES	NO	N/A	COMMENTS
Is the best practice/intervention a meta-analysis or primary research?	☒	☐	☐	Meta-analysis; to evaluate the efficacy of interferon therapy in the prevention of hepatocellular carcinoma (HCC) recurrence after curative treatment with surgical resection or ablation in HCV patient with cirrhosis
The best practice/intervention has utilized an evidence-based approach to assess:				
Efficacy	☒	☐	☐	Primary outcome: HCC recurrence on follow-up and the proportion of patients surviving at 5 years
Effectiveness	☐	☒	☐	
The best practice/intervention has been evaluated				

in more than one patient setting to assess:				
Efficacy	☒	☐	☐	10 studies with sample size varied from 13 to 150 were included in the analysis
Effectiveness	☐	☒	☐	
	YES	**NO**	**N/A**	**COMMENTS**
The best practice/intervention has been operationalized at a multi-country level:	☒	☐	☐	Literature performed through the use of online databases
There is evidence of capacity building to engage individuals to accept treatment/diagnosis	☐	☒	☐	
There is evidence of outreach models and case studies to improve access and availability	☐	☒	☐	
Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?	☒	☐	☐	Methodology was clearly stated
Are the best practices/methodology/results described applicable in developed countries?	☒	☐	☐	
Are the best practices/methodology/results described applicable in developing countries?	☒	☐	☐	Similar results can be found with analysis using the same criteria for study selection
Evidence of manpower requirements is indicated in the best practice/intervention	☐	☒	☐	
Juried journal reports of this treatment, intervention, or diagnostic test have occurred	☒	☐	☐	*Alimentary Pharmacology & Therapeutics*
International guideline or protocol has been established	☐	☒	☐	
The best practice/intervention is easily accessed/available electronically	☒	☐	☐	Open access for view at http://onlinelibrary.wiley.com/
Is there evidence of a cost effective analysis? If so, what does the evidence say? **Please go to Comments section**	☐	☒	☐	
How is the best practice/intervention funded? **Please got to Comments section**	☐	☒	☐	The study was no funded

Other relevant information: _____	☐	☐	☐	- IFN treatment reduces the risk of developing a new focus of HCC after curative treatment in HCV cirrhotics

Meta-analysis: interferon improves outcomes following ablation or resection of hepatocellular carcinoma

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SUMMARY

Background
Hepatocellular carcinoma (HCC) is third most common cause of tumour-related death in the US with hepatitis C virus (HCV) the most common aetiology. Surgical resection and tumour ablation are curative in patients who cannot be transplanted. With native liver having cirrhosis, HCC recurrence is a potential problem.

Aim
To perform a systematic review and meta-analysis of studies evaluating efficacy of IFN to prevent HCC recurrence after its curative treatment in HCV-related cirrhosis.

Methods
Ten studies ($n = 645$, 301 treated with IFN) on the use of IFN after resection or ablation of HCV-associated HCC were analysed.

Results
Pooled data showed benefit of IFN for HCC prevention with OR (95% CI) of 0.26 (0.15–0.45); $P < 0.00001$. The proportion of patients surviving at 5 years ($n = 505$ in 6 studies) was in favour of IFN with OR of 0.31 [(95% CI 0.21–0.46); $P < 0.00001$]. Data were homogeneous for HCC recurrence (χ^2 12.05, $P = 0.21$) and survival (χ^2 6.93, $P = 0.44$). The benefit of IFN was stronger with sustained virological response compared with nonresponders for HCC recurrence [0.19 (0.06–0.60); $P = 0.005$] and survival [0.31 (0.11–0.90); $P = 0.03$].

Conclusion
Interferon treatment after curative resection or ablation of HCC in HCV-related cirrhotics prevents HCC recurrence and improves survival.

INTRODUCTION

Hepatocelluar carcinoma (HCC) is a common tumour worldwide and its incidence has increased 2-fold in the US in the last 2 decades.[1–3] Cirrhosis is the strongest risk factor, with hepatitis C virus (HCV) being the most common aetiological agent.[4] Orthotopic liver transplantation (OLT) is the definitive treatment as it removes not only the HCC but also the cirrhotic liver. However, OLT cannot be offered to all patients due to shortage of organs and rigorous selection criteria.[5, 6] Curative surgical resection or ablation of HCC are other therapeutic options in patients with compensated cirrhosis.[7] However, local recurrence of the tumour, along with progression of the underlying cirrhosis, contributes to the long-term mortality after treatment.[8, 9]

Treatment of HCV in compensated cirrhotics is effective in eradicating the virus in about 50% of patients, using pegylated interferon and ribavirin (RBV) based regimens and 25–30% with interferon (IFN) alone.[10, 11] IFN has also been shown to have an inhibitory effect on carcinogenesis.[12] Studies on the efficacy of IFN in the prevention of recurrence of HCC and survival after curative resection of the HCC in HCV cirrhotics have provided conflicting data.[6, 13–21] The aim of the present study was to perform a systematic review and meta-analysis of studies evaluating the efficacy of IFN in the prevention of HCC after curative treatment of HCC with surgical resection or ablation in compensated HCV cirrhotics.

METHODS

Identification and selection of studies

Literature search was performed using electronic databases (Medline, Cochrane reviews, and EMBASE, ISI Web of science) for all publications between 1991 and 2009 including abstracts (reported at DDW, EASL, and AASLD) for studies employing the use of interferon after resection or ablation treatment of HCC in HCV cirrhosis. Search terms used were hepatitis C, HCV, cirrhosis, hepatocellular carcinoma, HCC, interferon, resection and ablation. Boolean logic was used to combine the words. In addition, a manual search was made for cross references from reviewed manuscripts.

Study quality

Criteria for study selection. The following selection criteria were used: (i) Study design – any design including randomized controlled trials (RCTs), retrospective, or open prospective studies; (ii) Study population – patients with compensated (Child Turcotte Pugh stage A or B) HCV cirrhosis; (iii) Treatment for HCC – curative surgical resection or ablation; (iv) Diagnosis of HCC: based on standard AASLD criteria; (v) anti-HCV treatment – use of IFN alone or IFN-RBV based regimens, used for a minimum duration of 6 months; (vi) Initiating IFN treatment within 6 months of resection or ablation; (vii) minimum follow-up of 2 years after starting IFN treatment; and (viii) follow-up data available on recurrence of HCC.

Outcome measure. The primary outcome measures were HCC recurrence (local recurrence or a new focus) on follow-up and the proportion of patients surviving at 5 years. The cause of death, if available, was analysed for assessment of disease-specific survival.

Assessment of study quality

All reports were assessed for quality of the study. Any conflict between the reviewers was resolved by consensus. Studies were graded using the following parameters: (i) study design: RCT or Non-RCT, (ii) study type for non-RCT studies: prospective or retrospective, (iii) defined inclusions/exclusions criteria, (iv) similarity between treated and control groups, (v) defined treatment response after ablation or resection, (vi) defined anti-HCV treatment intervention, (vii) follow-up of >3 years, (viii) analysis of results based on intention-to-treat model, (ix) details of drop outs or deaths, and (x) sample size calculation. Each parameter was given a numerical score of 0 or 1 and studies with a score of >5 were classified as good quality, otherwise the studies were rated as poor quality.

Data collection

Data were collected with respect to the study type, sample size, patient demographics and characteristics, treatment received for HCC (resection or ablation), characteristics of HCC (mean size, number, and vascular invasion), anti-HCV treatment regimen, interferon treatment details (type, schedule, timing, and duration), duration of follow-up, HCC recurrence (local recurrence and new focus), and proportion of patients surviving at 5 years (overall and disease specific). The data were recorded in a Microsoft Wiindows Excel sheet. The number of patients surviving at 5 years was computed from the Kaplan–Meier curves, if not reported in the text. HCC recurrence and survival data based on sustained virological response (SVR), if available, were also recorded.

Data analysis and statistical methods

Data on the total sample size and number with HCC recurrence and survival were entered by the study ID into a statistical software program, Revman 5. Odds ratio (OR) was used as the measure of association. After inclusion of data from all studies, the summary OR with 95% confidence interval (CI) and Forrest plot graphs were obtained using the DerSimonian-Laird method.[22] The Breslow Day test was used to assess whether the treatment effect varied across the studies. Publication bias was investigated by inspection of funnel plots and carrying out Egger's regression test.[23] Tests were considered significant at P-values <0.05.

The effect of IFN treatment was analysed in studies reporting data on HCC recurrence and survival in nonresponders and patients with SVR. Sensitivity analysis was performed after excluding studies with the highest and lowest OR and after excluding poor quality studies. Subgroup analyses were performed for the effect of variables across different studies on HCC recurrence and survival. Logistic regression analysis using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) was performed for these analyses. Variables studied were type of study (randomized or nonrandomized), patient characteristics (% males and % non-1 genotype), initial treatment for HCC (resection or ablation), Mean tumour size, IFN treatment details (duration of use in months and total dose) and follow-up in years. The report by Ikeda et al. was included in studies using resection for treatment of the initial HCC as 80% patients in both the treated and untreated groups were treated with resection.[13] Results were considered significant at $P < 0.05$ for the pooled and subgroup analyses.

RESULTS

Selection of studies

Ten studies comparing recurrence of HCC and mortality after curative resection ($n = 200$), ablation ($n = 321$), or ablation + resection ($n = 124$) for HCC in HCV cirrhotics were analysed (Figure 1). Two groups had produced duplicate reports and only the latest report from the respective group was included for the analysis. Amongst the studies on ablation treatment, two used multiple modalities. In one study, HCC was ablated by percutaneous ethanol injection (PEI), radiofrequency ablation or percutaneous microwave coagulation therapy,[18] while PEI and transarterial chemoembolization followed by PEI were used in another study.[16] Successful curative treatment after ablation was documented by CT scan within 1–3 months. Two studies ($n = 124$) included patients treated with either resection or ablation treatment for the initial HCC.[13, 14]

Study characteristics

The characteristics of the studies are shown in Table 1. The sample size varied from 13 to 150 (mean age: 60–69 years; males: 65–100%). Mean tumour size was ≤3 cm with ≤3 lesions in all the studies except in the study by Mazzaferro et al. in which the mean tumour size was 3.5 cm.[6] In patients undergoing surgical resection, vascular invasion in the resected specimen was present in 21% patients in one study. Patients were treated with IFN alone in all studies except one which used INF-ribavirin (RBV) combination regimen.[18] Interferon treatment schedule varied in different studies, and all studies except
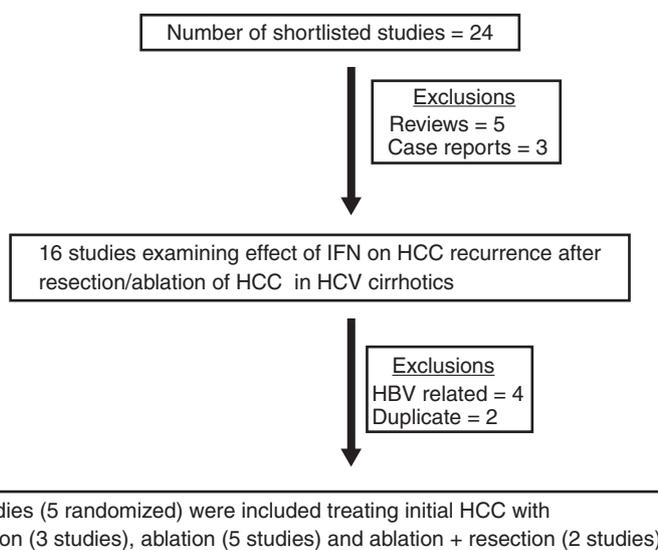
Figure 1 | Literature search and study selection process.

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┌─────────────────────────────────────────┐
│  Number of shortlisted studies = 24      │
└─────────────────────────────────────────┘
                 │
                 │        ┌──────────────────────┐
                 │        │ Exclusions           │
                 │        │ Reviews = 5          │
                 │        │ Case reports = 3     │
                 │        └──────────────────────┘
                 ▼
┌─────────────────────────────────────────────────────┐
│ 16 studies examining effect of IFN on HCC recurrence │
│ after resection/ablation of HCC in HCV cirrhotics    │
└─────────────────────────────────────────────────────┘
                 │
                 │        ┌──────────────────────┐
                 │        │ Exclusions           │
                 │        │ HBV related = 4      │
                 │        │ Duplicate = 2        │
                 │        └──────────────────────┘
                 ▼
┌─────────────────────────────────────────────────────┐
│ 10 studies (5 randomized) were included treating     │
│ initial HCC with resection (3 studies), ablation     │
│ (5 studies) and ablation + resection (2 studies)     │
└─────────────────────────────────────────────────────┘
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Table 1 | Characteristics of the studies included in the meta-analysis

	Ikeda 2000	Suou 2001	Kubo 2002	Lin 2003	Shiratori 2003	Hung 2005	Sakaguchi 2005	Mazzaferro 2006	Jeong 2007	Kudo 2007
Sample size (with IFN)	20 (10)	40 (18)	30 (15)	13 (8)	74 (49)	60 (20)	57 (24)	150 (76)	84 (42)	127 (43)
Study type	RCT	R-P	RCT	RCT	RCT	R-P	R-P	RCT	R-P	CC
Mean age in years	60	61	61	61	61	63	69	65	62	65
% Males	65	83	100	70	70	66	72	75	77	73
% Non-1 GT	0	15	20	NA	39	44	NA	21	33	0
% Low HCVRNA	NA	55 (<1 × 10⁶/mL)	50 (<1 × 10⁶/mL)	NA	100 (<2 × 10⁶/mL)	100 (<1 × 10⁶/mL)	NA	NA	52 (<100 kIU/mL)	0 (<100 kIU/mL)
Treatment for HCC	S 16 (8), A 4 (2)	S 25 (11), A 15 (7)	S	A*	A	A*	A	S§	S (24), A (18)	A
Mean HCC size (cm)	2.2	2.1	2.5	2.5	2.3	2.5	1.5	3.5	2.0	1.8
No. of HCC	≤3	1	1	≤2	≤3	≤3	≤3	≤3	≤3	≤3
Time to IFN (mo)	NA	3	4	4	3	4	NA	1.5	6	2
Treatment regimen	IFN alone	IFN alone	IFN alone	IFN alone	IFN alone	RBV based	IFN alone	IFN alone	IFN alone	IFN alone
IFN type	B	α-2b or α	A	α-2b	A	α-2b	α-2b	A	A	α-2b and PEGIFN†
IFN use (mo)	36	6	24	24	9.5	6-12	21	12	6	55
Total dose IFN (MU)	1728	480	1392	216 (4); 360 (4)‡	675	314	504¶	432	480	1320
Follow-up (yrs)	2.8	4	5	2.3	7	3	4	5	7	5
SVR %	NA	33	13	NA	29	50	4	7	69	5
Treatment >80% (%)	90	100	47	10 (continuous group)	69	35	100	54	33 (9/13 NR; 24/29 SR)	100
Discontinued treatment (%)	1 (10)	0 (0)	4 (26)	3 (38) (continuous group)	9 (21)	4 (20)	0 (0)	6 (8)	4 (10 – NR)	0 (0)
Study quality	7	5	8	7	8	6	6	9	6	6

RCT, randomized controlled study; R, retrospective; P, prospective; CC, case-control; S, resection; A, ablation; IFN, interferon; RBV, ribavirin; PEGIFN, pegylated interferon; MU, million units; SVR, sustained virological response; NR, nonresponse.

* Mixed ablation treatment.

† α-2b 1999–2004 and PEGIFN 2004–2007.

‡ Intermittent schedule of IFN in four patients.

§ Pre-resection ablation in 36 (21) patients.

¶ IFN given as continuous schedule and this is the mean dose based on mean follow-up.

one were of good quality (Table 1). The median follow-up ranged from 2.3 to 7 years.
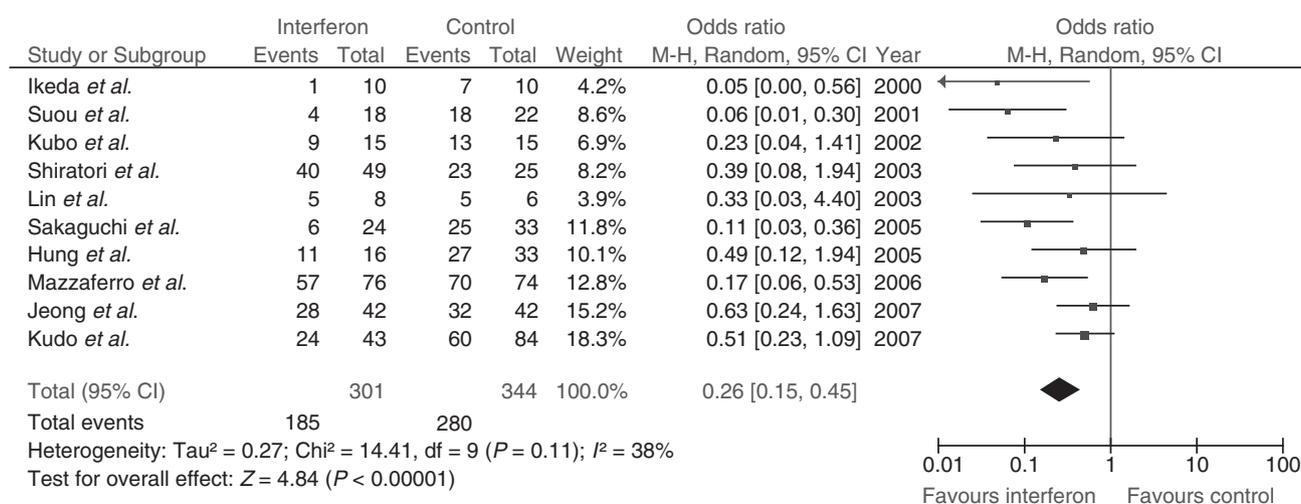
Quantitative analysis

HCC recurrence. Local HCC recurrence (at the site of initial HCC): Pooled data on four studies (*n* = 290) in which local recurrence was reported showed no difference between treated and untreated patients (12.6%; vs. 21.3%); *P* = 0.22 and the data were homogeneous (χ^2 = 0.36; *P* = 0.95).

New focus of HCC recurrence: A new focus was seen in 61% (185 of 301) in the treated group and 81% in the untreated group with the pooled OR in favour of IFN treatment (*P* < 0.00001). There was no statistical evidence of heterogeneity (Figure 2) or publication bias (*P* = 0.12). Sensitivity analysis after excluding the low quality study, as well as studies with the highest and lowest OR, and patients with anti-HBc positivity (in one study)[6] showed similar results [0.24 (0.12–0.45), *P* < 0.0001; 0.29 (0.19–0.43), *P* < 0.0001; and 0.26 (0.18–0.39), *P* < 0.0001], without losing homogeneity (*P* = 0.64; 0.39; and 0.18). In treated patients, sustained virological response occurred in 4–69% patients in the different studies (Table 1). Recurrence of HCC, based on SVR, was reported in three studies (*n* = 76). The HCC recurrence was lower in patients with SVR compared with nonresponders (35.6% vs. 61.3%) with pooled OR of 0.19 (0.06–0.60; *P* = 0.005). HCC recurrence rate among untreated patients was 79%. Pooled data were no different from the HCC recurrence rate among nonresponders with an OR of 0.42 (0.07–2.61; *P* = 0.35).

Overall survival: Five-year survival data reported in six studies showed that 76% patients survived 5 years or more in the IFN treated group (*n* = 243) compared with 60% in the untreated group (*n* = 263) with pooled effect in favour of IFN (Figure 3). There was no heterogeneity (χ^2 *P* = 0.57) or any publication bias (*P* = 0.08). Mortality was liver-related in all the patients with similar effect-size. Sensitivity analysis after excluding the low quality study and studies with the highest and lowest OR showed similar results [0.43 (0.26–0.73); *P* = 0.002 and 0.42 (0.26–0.70); *P* = 0.0008], without losing homogeneity (*P* = 0.31 and 0.46). In contrast, the effect of IFN on survival improved after excluding the study with anti-HBc positive patients[6] [0.33 (0.15–0.73); *P* = 0.006]; the data were again homogeneous (*P* = 0.21). Survival data based on SVR was reported in three studies (*n* = 107). Pooled data showed longer survival in patients with SVR compared with nonresponders (85% vs. 56%; *P* = 0.03).

Subgroup analyses were performed to assess the interaction of IFN treatment with the different variables (Table 2). The results showed that only the duration of follow-up had a significant (*P* = 0.03) effect on HCC recurrence (Table 2). Further analyses showed that this effect was seen only in nonrandomized studies (*P* = 0.03) and not among randomized studies (*P* = 0.55) (data not shown). Similar subgroup analyses for the overall survival did not show an interaction of IFN treatment with any of the variables. As the survival analysis was assessed at 5 years across the studies, follow-up duration variable was not assessed (Table 2).

Study or Subgroup	Interferon Events	Interferon Total	Control Events	Control Total	Weight	Odds ratio M-H, Random, 95% CI	Year
Ikeda *et al.*	1	10	7	10	4.2%	0.05 [0.00, 0.56]	2000
Suou *et al.*	4	18	18	22	8.6%	0.06 [0.01, 0.30]	2001
Kubo *et al.*	9	15	13	15	6.9%	0.23 [0.04, 1.41]	2002
Shiratori *et al.*	40	49	23	25	8.2%	0.39 [0.08, 1.94]	2003
Lin *et al.*	5	8	5	6	3.9%	0.33 [0.03, 4.40]	2003
Sakaguchi *et al.*	6	24	25	33	11.8%	0.11 [0.03, 0.36]	2005
Hung *et al.*	11	16	27	33	10.1%	0.49 [0.12, 1.94]	2005
Mazzaferro *et al.*	57	76	70	74	12.8%	0.17 [0.06, 0.53]	2006
Jeong *et al.*	28	42	32	42	15.2%	0.63 [0.24, 1.63]	2007
Kudo *et al.*	24	43	60	84	18.3%	0.51 [0.23, 1.09]	2007
Total (95% CI)		301		344	100.0%	0.26 [0.15, 0.45]	
Total events	185		280				

Heterogeneity: Tau² = 0.27; Chi² = 14.41, df = 9 (*P* = 0.11); I² = 38%
Test for overall effect: *Z* = 4.84 (*P* < 0.00001)

0.01 0.1 1 10 100
Favours interferon   Favours control

Figure 2 | Pooled data of studies on the use of interferon after curative treatment of HCC in hepatitis C virus-related cirrhosis on a new focus of HCC recurrence. The results show the benefit of IFN in reducing the risk of HCC compared with untreated patients.
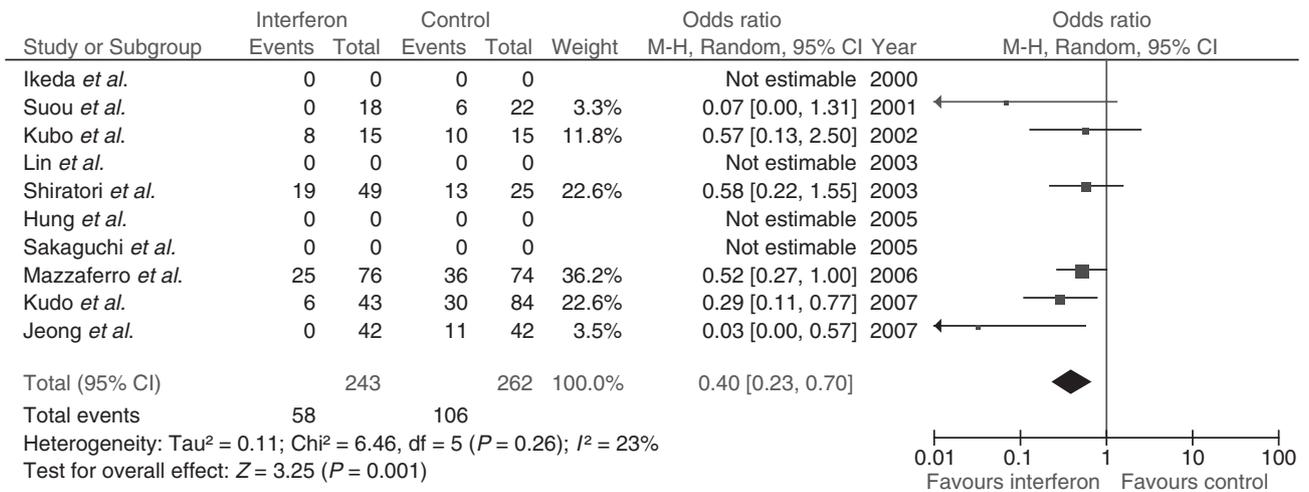
Figure 3 | Pooled data of studies on the use of interferon after curative treatment of HCC in hepatitis C virus-related cirrhosis on the overall survival. The results show a survival benefit with IFN compared with untreated patients.

Table 2 | Logistic regression for subgroup analyses of variables across different studies on the new focus of HCC recurrence and survival

	Recurrence HCC new focus			Survival		
	DF	Wald Chi-square	P	DF	Wald Chi-square	P
Study type	1	0.09	0.76	1	4.46	0.19
% Males	7	9.21	0.24	6	4.53	0.56
% non-1 GT	6	5.84	0.44	6	5.73	0.35
Tumour size	10	1.23	0.64	6	3.93	0.15
Initial HCC Rx	1	3.25	0.07	1	0.04	0.85
IFN use in months	6	7.17	0.31	5	6.19	0.47
Total IFN dose	8	8.51	0.39	6	7.21	0.49
Follow-up in years	5	12.41	0.03			

DISCUSSION

The present systematic review and meta-analysis was carried out to examine the effect of IFN on tumour recurrence and survival after curative treatment for HCC in HCV cirrhotics. A recently published meta-analysis included patients with both HCV and hepatitis B virus (HBV) infections.[24] It is known that HBV is associated with HCC in up to 40% cases without the presence of an underlying cirrhosis.[25, 26] Moreover, IFN is not the preferred treatment option in most patients with HBV infection.[27] Furthermore, IFN use after curative resection

of HCC in HBV patients has not been consistently shown to be effective.[6, 16] We therefore restricted our analysis to the efficacy of IFN after curative HCC treatment in HCV cirrhotics.

Patients with HCV-related cirrhosis even after curative treatment for HCC are at an increased risk for recurrent HCC due to factors such as persistent viraemia and presence of the underlying cirrhosis. Anti-viral therapy is known to reduce HCC occurrence in patients with HCV-related cirrhosis.[10] This information is the basis for the use of IFN in HCV cirrhotics after curative treatment of HCC with either resection or ablation of the tumour. In the present study, IFN had no impact on the occurrence of HCC at the initial site (local recurrence). Local recurrence was detected within 6–12 months amongst studies on ablation treatment for the initial HCC and is considered to be due to inadequate ablation treatment. In contrast, the use of IFN was associated with significant benefit in the development of a new focus of HCC (i.e. at a site different from the initial site) and survival (overall and disease specific) after curative treatment. The beneficial effects of IFN are perhaps related to its antifibrotic, antiproliferative, antiangiogenic and antitumour effects.[10, 28–32] With the availability of pegylated interferon (PEGIFN) and RBV, the current standard of care, the outlook for these patients may improve and studies assessing the effect of combination of PEGIFN and RBV are needed.

The beneficial effect of IFN was much more robust in patients who achieved an SVR. The SVR rate across different studies varied from 4% to 69% (Table 1). One of the important factors driving this is the study design

(RCT vs. Prospective-Retrospective studies). Among RCTs, the SVR data are, however, less heterogeneous with rates of 7–29%. These rates are similar to SVR rates with IFN reported in other studies among cirrhotics. RCTs in this population group are difficult to carry out, however. Nevertheless, the main point in our analysis was not the SVR rate in different studies, but the findings that patients who achieve an SVR have a reduced risk of HCC recurrence. However, despite obtaining an SVR, there was a 35% risk of HCC recurrence, with 16% mortality. Therefore, even patients who obtain an SVR should be kept under close surveillance for HCC recurrence. It has been shown that HCC occurs in 6% tumour-naïve HCV cirrhotics after SVR.[10] Aggressive biological behaviour of the HCV and the presence of micro-metastases are possible explanations for the high risk of HCC recurrence in patients with a history of HCC.

Subgroup analysis showed that the beneficial effect of IFN was greater with longer patient follow-up. The risk of HCC is known to increase with time in untreated patients, which may explain the beneficial effect of IFN as the patients are followed up longer.[33] This was also shown in the study by Mazzaferro et al. where the recurrence of HCC was significantly reduced for HCC after 2 years of follow-up compared with patients followed up for less than 2 years after starting IFN treatment.[6] However, this effect was observed only in nonrandomized studies which may suffer from incomplete data collection and selection bias. Future randomized studies are needed to assess the interaction of follow-up duration and IFN use on HCC recurrence after curative treatment of HCC in HCV cirrhotics. A trend towards lower recurrence of a new focus of HCC after resection as compared with ablation therapy was also noted. Resection of HCC offers a better chance of cure as the surgeon removes the lesion along with a margin of normal tissue under direct vision. In contrast, evaluation of the extent of ablation therapy depends on imaging studies which are not as precise as visual and histological assessment.

Five-year survival was not affected by any of the variables assessed. Post-operative liver failure is known to occur after resection, especially in patients with poor liver function.[34] Survival analysis amongst the studies did not take into account the post-operative mortality. It is interesting to note that despite this, survival was similar irrespective of the type of initial HCC treatment.

The adverse effects of IFN may play an important role because of the risk of dose reduction and treatment discontinuation. Adherence to treatment is critical. It has been shown that the best results are obtained in patients receiving ≥80% of the scheduled therapy. In the present analysis, 35–100% patients received ≥80% of the scheduled IFN dose, whereas 0–38% required treatment discontinuation (Table 1). In one study, an intermittent schedule of IFN was found to be tolerated better, with not a single treatment discontinuation compared with 38% discontinuation with the continuous schedule.[16] Although the total dose received with the intermittent schedule was only 360 μ (<50% of the dose with continuous schedule), better outcome with the former was perhaps due to better adherence to the treatment. Intermittent dosing of IFN is a potential treatment option for patients on long-term therapy, and needs to be evaluated in future studies. Maintenance IFN using one-half the recommended dose is another option, but data on its use are not promising.[10]

In summary, IFN treatment after curative treatment of HCC in HCV cirrhotics reduces the risk of developing a new focus of HCC and is associated with improvement in survival. The efficacy of IFN is clearly better in patients with an SVR. However, despite SVR, these patients carry a 35% risk of tumour recurrence and 16% mortality on long-term follow-up. Therefore, these patients need to be maintained under close follow-up for early detection of HCC recurrence.

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