Hepatology International (2024) 18:63–72
https://doi.org/10.1007/s12072-023-10618-6

ORGINAL ARTICLE

Interferon therapy improves survival in patients with hepatitis B virus-related hepatocellular carcinoma after curative surgery: a meta-analysis

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Received: 2 May 2023 / Accepted: 16 November 2023 / Published online: 2 January 2024

Abstract

Background and aim A novel study found interferon enhanced antitumor activity of anti-PD-1-based immunotherapy and played a crucial role in improving efficacy on HCC, but the opposite results about the efficacy of interferon on HBV-related HCC were obtained from previous clinical studies and meta-analyses. Thus, this meta-analysis aimed to re-evaluate whether interferon could improve survival and reduce recurrence of patients with HBV-related HCC after curative surgery.

Methods MEDLINE/PubMed, Cochrane Library, EMBASE, Web of Science and CNKI were searched for eligible studies from inception to November 2022 and a meta-analysis was done.

Results 10 trials with a total of 2062 subjects were screened. Interferon significantly improved 1-, 2-, 3- and 5-year OS and 1-, 2- and 3-year DFS, and reduced 2-, 3- and 5-year recurrence rates of patients with HBV-related HCC after curative surgery. However, interferon did not improve 8-year OS and 5-year DFS, did not reduce 1-year recurrence rate.

Conclusions Interferon may significantly reduce recurrence and improve DFS of patients with HBV-related HCC after curative surgery, and finally improve the OS. However, the efficacy advantage may gradually weaken as time goes on. The clinical application of interferon combined with NAs recommended in this meta-analysis is needed to be further studied.

Keywords Overall survival rates · Recurrence · Disease-free survival rates · Nucleoside analogues · Clinical study · Resection · TACE · IFN · Liver cancer · Liver tumor

Abbreviations

IFN	Interferon
HCC	Hepatocellular carcinoma
NAs	Nucleoside analogues
HBV	Hepatitis B virus
SVR	Sustained virological response

Introduction

Hepatocellular carcinoma (HCC) is the world's third common cause of cancer-related deaths [1]. Hepatitis B virus (HBV) infection is the most common etiology of HCC [2]. At present, there are few radical therapies for HBV-related HCC, including liver transplantation, resection and ablation [3–5]. Among them, liver transplantation is the most effective treatment for HCC, but it is severely limited by high costs and donor shortage [6]. Therefore, the most effective treatments are still resection and ablation [7, 8]. Unfortunately, the 3-year recurrence rate after resection or ablation

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is more than 50%, and the 5-year overall survival (OS) rate after resection ranges from 40% to 60% [9–11].

Fortunately, with the deepening of research on tumor immune microenvironment, researches have confirmed that anti-PD-1 could remove the immunosuppression of antitumor T cells and increase the sensitivity of its mediated killing effect, finally activate the antitumor immune response [12]. Anti-PD-1 has achieved unprecedented success in treating HCC, but it still faces major challenges. Encouragingly, a novel study found that IFN enhanced antitumor activity of anti-PD-1-based immunotherapy in patients with unresectable HCC [12]. Authors further built immunocompetent orthotopic and spontaneous HCC models and found IFN synergized with anti-PD-1 led to significant enrichment of cytotoxic CD27+ CD8+ T cells. Mechanistically, IFN suppressed HIF1α signaling by inhibiting FosB transcription in HCC cells, resulting in reduced glucose consumption capacity and consequentially establishing a high-glucose microenvironment that fostered transcription of the T-cell costimulatory molecule Cd27 via mTOR–FOXM1 signaling in infiltrating CD8+ T cells, thereby potentiating the PD-1 blockade-induced immune response [12]. Therefore, IFN may play a crucial role in preventing recurrence and improving OS of patients with HBV-related HCC after curative surgery.

However, it was found that different clinical trials had different results through literature search, and even the opposite results were obtained from several previous meta-analyses [10, 11, 13]. Therefore, there is always a question that whether IFN can improve survival and reduce recurrence of patients with HBV-related HCC after curative surgery. Encouragingly, new randomized controlled trial (RCT) and retrospective cohort study (RCS) have been published in recent years, and the previous analytical results need to be updated now. Hence, we conducted this comprehensive meta-analysis to re-evaluate the efficacy of IFN on recurrence and OS of patients with HBV-related HCC after curative surgery.

Materials and methods

The protocol of this meta-analysis was registered in PROSPERO (CRD42022381867).

Search strategy

We searched MEDLINE/PubMed, Cochrane Library, EMBASE, Web of Science and CNKI databases from inception to November 2022. The terms were "hepatocellular carcinoma OR liver cancer OR liver neoplasm OR hepatic carcinoma OR HCC", "resection OR surgery OR hepatectomy OR ablation OR TACE OR transcatheter arterial chemoembolization", "HBV OR hepatitis B" and "interferon OR IFN" in English or Chinese. Conference proceedings at the International Liver Congress and the Liver Meeting were also searched manually. Two authors independently evaluated the retrieved studies. If there was any disagreement, we would consult a third author for quality assurance.

Inclusion and exclusion criteria

The inclusion criteria included the following: a. all eligible patients had HBV-related HCC; b. the outcomes included at least one of OS and recurrence; c. curative surgery included surgical resection or ablation or transcatheter arterial chemoembolization (TACE). d. the sample size of each group > 30; e. the follow-up time > 12 months.

Exclusion criteria: (a) metastatic liver cancer or recurrent liver cancer; (b) the follow-up time < 12 months; (c) repetitive articles written in different languages; (d) HCC not associated with HBV; (e) single-arm studies.

Outcomes

The OS and recurrence rate were the primary outcomes. The secondary outcome was disease-free survival (DFS).

Data extraction and quality assessment

Two reviewers independently extracted the data and assessed the quality of each study. The following data were extracted: author names, study type, dates, follow-up period, setting of study, interventions, characteristics of patients and outcomes. The number of survivors or patients with recurrence was computed from the Kaplan–Meier curves, if not reported in the text. The risk of bias tool suggested by the Cochrane Handbook for Systematic Reviews of Interventions was used to adjudicate the methodological quality of RCTs [14]. The Newcastle–Ottawa Scale was used to assess the methodological quality of non-RCTs [15].

Statistical analysis

Stata software ver.12 was used to conduct statistical analysis. The Q test and I^2 statistic were used to assess the heterogeneity of the effects. Significant heterogeneity was defined as $p < 0.1$ and $I^2 > 50\%$, and the random effect model was used, otherwise, the fixed effect model was used. When significant heterogeneity existed, a subgroup analysis was carried out according to operation selection and whether to use NAs or not. The relative risk and their 95% confidence interval were calculated. Publication bias was assessed qualitatively by Funnel plot, and statistically using Egger's and Begg's test. Sensitivity analysis was conducted by excluding a single

Fig. 1 Flow diagram

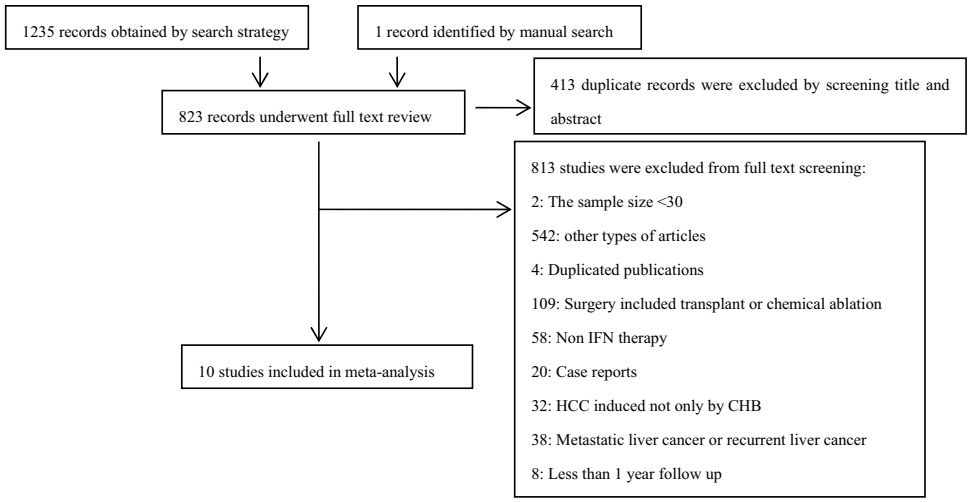

Table 1 Characteristics of studies

First author, year	Country	Patients, *n* (T/C)	Study design	Age, years (T/C)	Male, % (T/C)	Follow-up, months	Therapy (T/C)	Outcomes
Xin, 2018 [16]	China	70/68	RCT	NA	70/68	> 24	TACE + IFN/TACE	①②
Qu, 2010 [17]	China	101/467	RCS	50.98 ± 9.88/52.65 ± 10.32	85/87	53.3[a]	Resection + IFN/resection	①③
Du, 2022 [18]	China	30/30	RCS	NA	NA	12–60[b]	Resection or other + IFN/resection or other	①②
Qi, 2020 [19]	China	108/151	RCT	53.6 ± 5.1/53.9 ± 6.8	79/70	T: 6.4 ± 1.8 C: 6.9 ± 1.2	Resection or other + IFN + NAs/resection or other + NA	①
Sun, 2006 [20]	China	118/118	RCT	52.2[a]/50.4[a]	90/86	36.5[a]	Resection + IFN/resection	①②③
Zuo, 2015 [21]	China	102/126	RCS	20–79[b]/19–78[b]	90/90	14[a]	Resection + TACE + IFN/resection + TACE	①②③
Gao, 2004 [22]	China	31/31	RCT	NA	NA	> 24	TACE + IFN/TACE	①②
Li, 2009 [23]	China	108/108	RCT	< 75	71/69	24.8[a]	TACE + IFN/TACE	①②③
Lo, 2007 [24]	China	40/40	RCT	18–75[b]	78/85	> 30	Resection + IFN/resection	①②③
Chen, 2012 [25]	China	106/109	RCT	< 70	NA	63.8[a]	Resection + IFN/resection	①

RCT: Randomized controlled trial; RCS: retrospective cohort study; ①: OS; ②: recurrence rate; ③: DFS; T: treatment group; C: control group; NA: not available or not-applicable

[a]Median

[b]Range

study and recalculating the pooled estimates. $p < 0.05$ was considered to be significant (p values were two-sided).

Results

Characteristics of studies

As shown in the flow diagram (Fig. 1), 1236 clinical studies were identified and finally a total of 10 studies were finalized based on the predefined inclusion and exclusion criteria.

There were 2062 patients in the 10 studies [16–25], which included 6 RCTs and 4 RCSs. Among them, 814 patients were treated with IFN and 1248 patients were treated without IFN. The length of follow-up ranged from

12 to 96 months. The ages of the patients ranged from 18 to 79 years. IFN combination with nucleoside analogues (NAs) were used in one study compared with NAs alone. The curative surgery included resection in 4 studies, TACE in 3 studies, resection combination with TACE in 1 study and resection or other in 2 studies. The Child–Pugh was A or B in 4 studies, while other 6 studies did not mention Child–Pugh Grade. Two articles reported the 8-year OS, and 8 years were the longest available follow-up time. Characteristics of studies is shown in Table 1.

Primary outcome

OS

There were 10 articles (2026 patients), 9 studies (1834 patients), 8 studies (1784 patients), 7 studies (1646

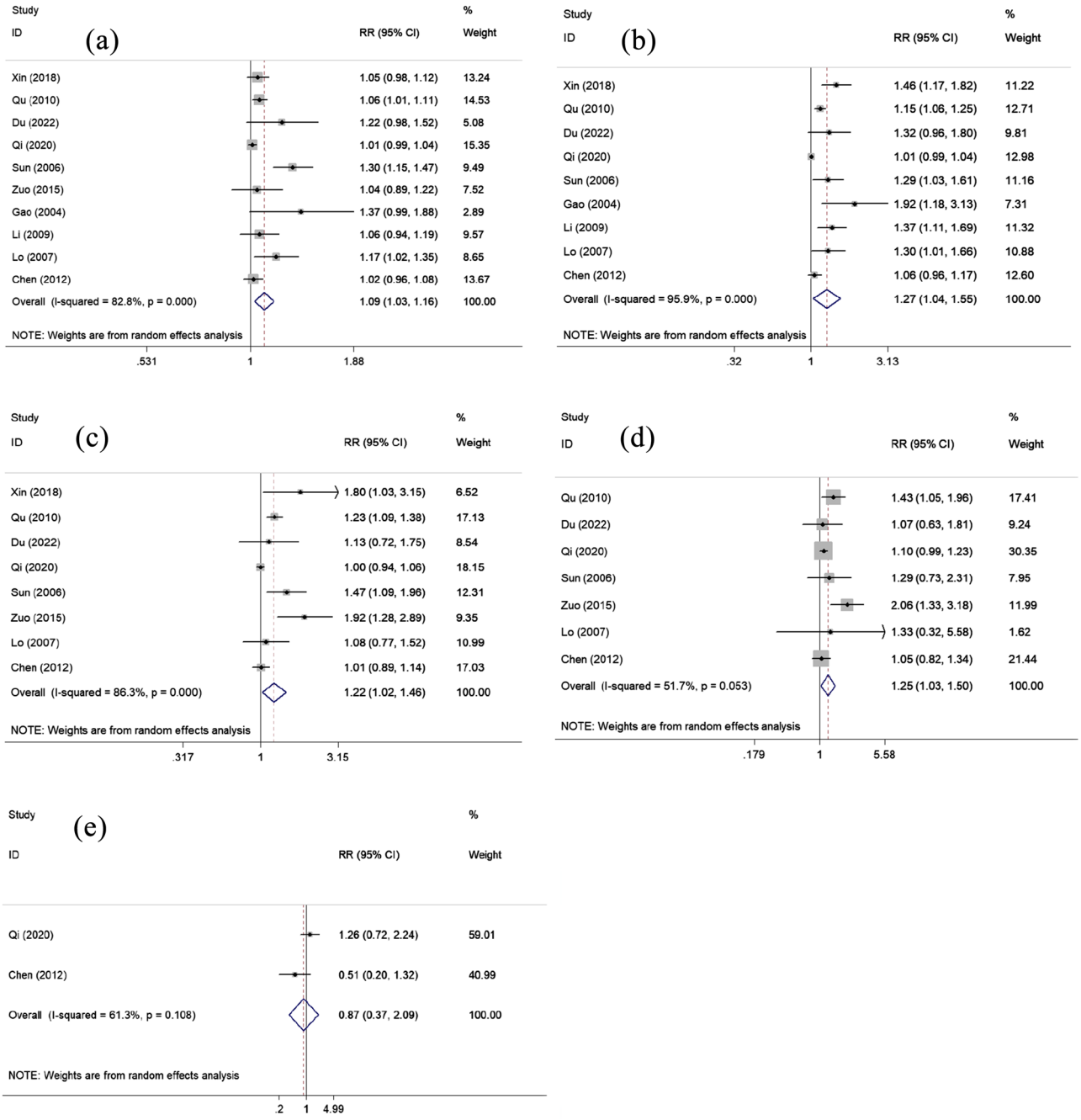

Fig. 2 Forest plots of OS. **a** 1-year OS. **b** 2-year OS. **c** 3-year OS. **d** 5-year OS. **e** 8-year OS

patients) and 2 studies (474 patients) compared the 1-, 2-, 3-, 5- and 8-year OS, respectively. Results showed that IFN significantly improved the 1-, 2-, 3- and 5-year OS (RR = 1.09, 95% CI, 1.03–1.16, $p = 0.006$, $I^2 = 82.8\%$; RR = 1.27, 95% CI, 1.04–1.55, $p = 0.021$, $I^2 = 95.9\%$; RR = 1.22, 95% CI, 1.02–1.46, $p = 0.026$, $I^2 = 86.3\%$; RR = 1.25, 95% CI, 1.03–1.50, $p = 0.021$, $I^2 = 51.7\%$, respectively) (Fig. 2a–d), but IFN could not improve the 8-year OS (RR = 0.87, 95% CI, 0.37–2.09, $p = 0.763$, $I^2 = 61.3\%$) (Fig. 2e).

Recurrence rate

There were 4 studies (438 patients), 4 studies (340 patients), 3 studies (356 patients) and 4 studies (604 patients) compared the 1-, 2-, 3- and 5-year recurrence rates, respectively. The result showed IFN could not reduce 1-year recurrence rate (RR = 0.73, 95% CI, 0.36–1.49, $p = 0.383$, $I^2 = 71.7\%$) (Fig. 3a), but it significantly reduced 2-, 3- and 5-year recurrence rates (RR = 0.72, 95% CI, 0.58–0.90, $p = 0.003$, $I^2 = 33.1\%$; RR = 0.82, 95% CI, 0.69–0.97, $p = 0.025$, $I^2 = 0.0\%$; RR = 0.83, 95% CI, 0.74–0.94, $p = 0.002$, $I^2 = 28.8\%$) (Fig. 3b–d).

Secondary outcome

DFS

There were 5 studies (1328 patients), 4 studies (1100 patients), 4 studies (1112 patients) and 4 studies (1112 patients) compared the 1-, 2-, 3- and 5-year DFS, respectively. The result showed IFN significantly improved 1-, 2- and 3-year DFS (RR = 1.13, 95% CI, 1.05–1.23, $p = 0.002$, $I^2 = 0.0\%$; RR = 1.27, 95% CI, 1.12–1.44, $p = 0.000$, $I^2 = 0.0\%$; RR = 1.20, 95% CI, 1.01–1.42, $p = 0.041$, $I^2 = 0.0\%$, respectively) (Fig. 4a–c), but it could not improve 5-year DFS (RR = 1.17, 95% CI, 0.85–1.60, $p = 0.336$, $I^2 = 0.0\%$) (Fig. 4d).

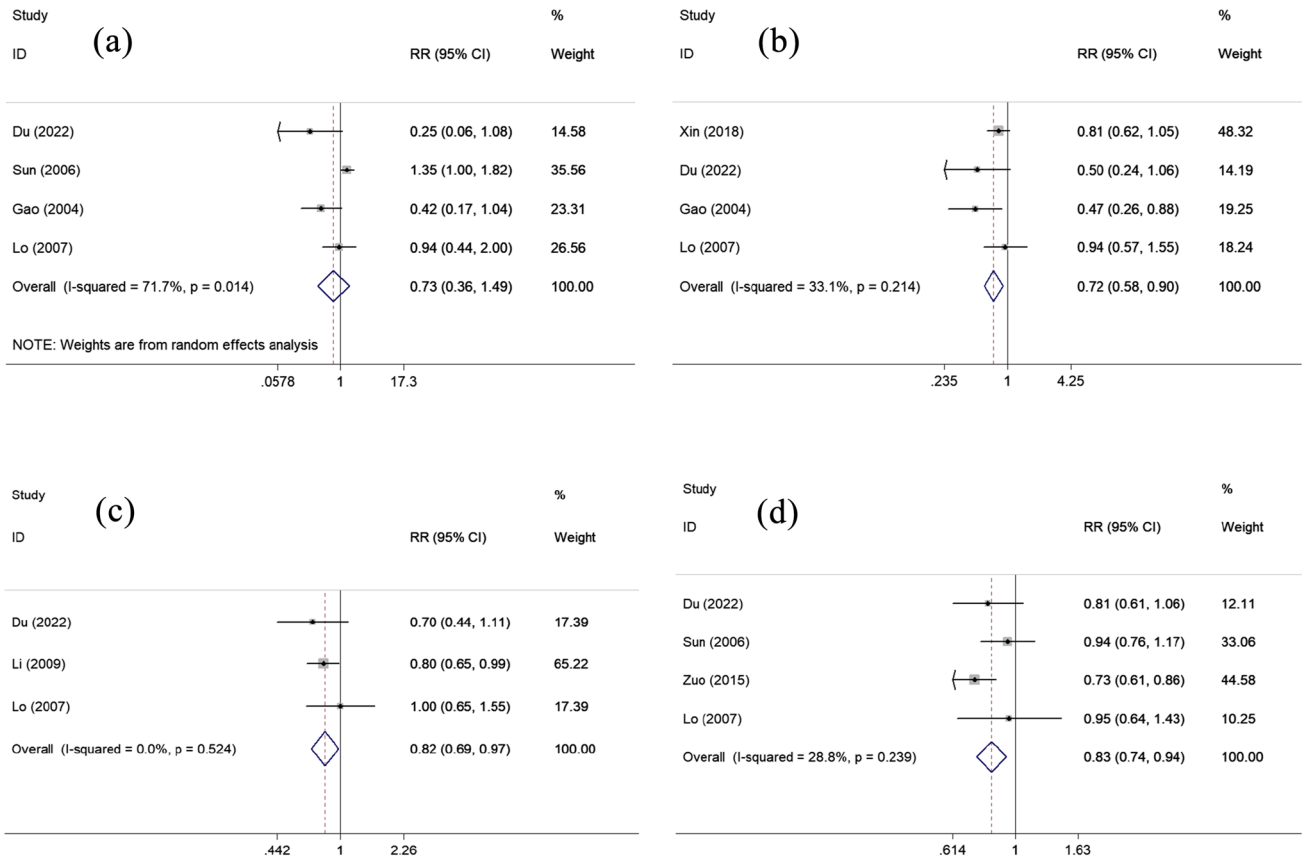

Fig. 3 Forest plots of recurrence rates. **a** 1-year recurrence rate. **b** 2-year recurrence rate. **c** 3-year recurrence rate. **d** 5-year recurrence rate

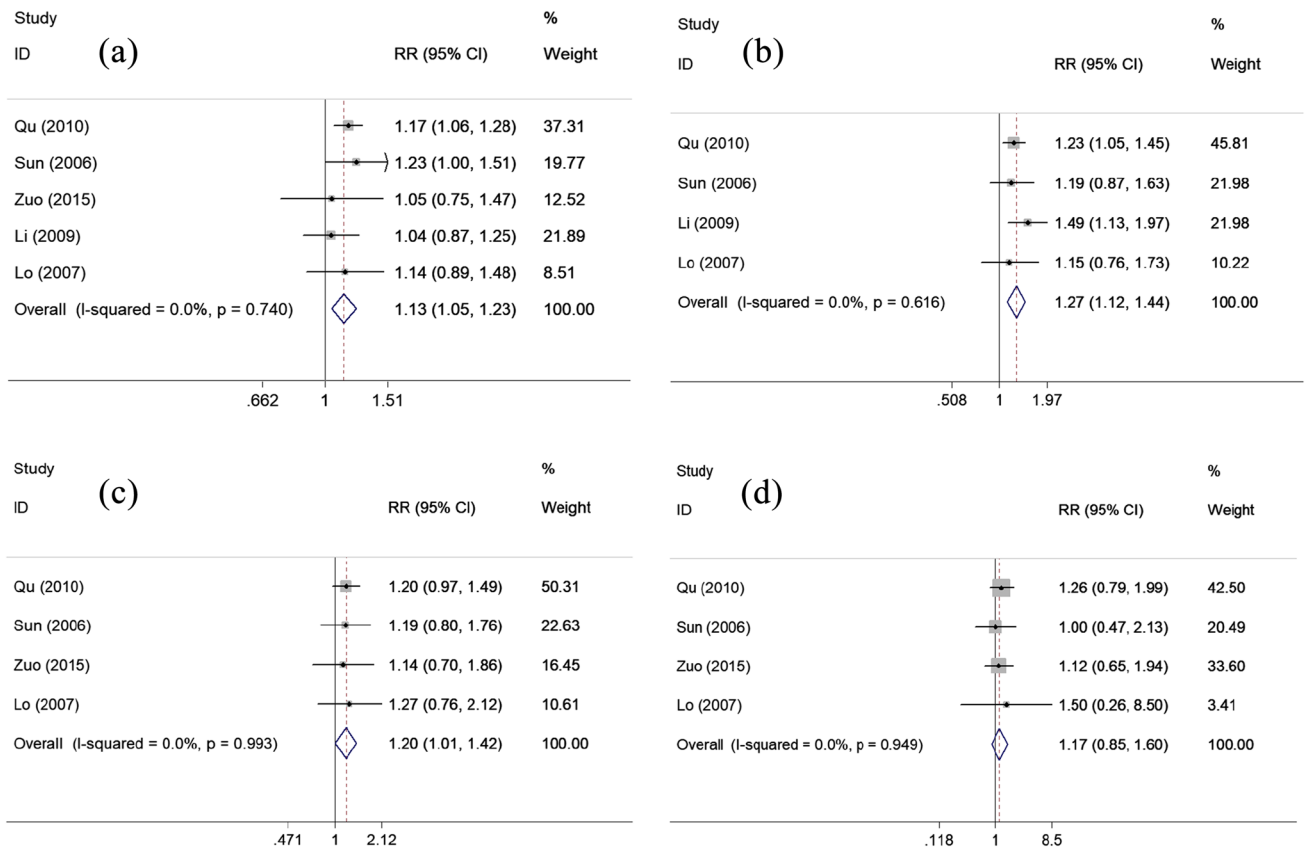

Fig. 4 Forest plots of DFS. **a** 1-year DFS. **b** 2-year DFS. **c** 3-year DFS. **d** 5-year DFS

Table 2 OS based on operation selection

Subgroup	Outcome	Studies, *n*	Effect estimate [RR (95% CI)]	Heterogeneity, I^2	*p* value	Favour group
Resection	1-year OS	4	1.12 [1.01, 1.23]	84.9%	0.030	IFN
	2-year OS	4	1.15 [1.05, 1.25]	38.4%	0.002	IFN
	3-year OS	4	1.16 [0.99, 1.37]	68.0%	0.070	None
	5-year OS	4	1.19 [0.99, 1.43]	0.0%	0.058	None
	8-year OS	1	0.51 [0.20, 1.32]	–	0.167	None
TACE	1-year OS	3	1.07 [0.97, 1.18]	42.7%	0.149	None
	2-year OS	3	1.45 [1.25, 1.68]	0.0%	0.000	IFN
	3-year OS	1	1.80 [1.03, 3.15]	–	0.002	IFN
	5-year OS	0	–	–	–	/
	8-year OS	0	–	–	–	/
Resection or other	1-year OS	2	1.10 [0.80, 1.50]	87.8%	0.560	None
	2-year OS	2	1.14 [0.66, 1.96]	91.6%	0.633	None
	3-year OS	2	1.00 [0.94, 1.06]	0.0%	0.984	None
	5-year OS	2	1.10 [0.99–1.23]	0.0%	0.075	None
	8-year OS	1	1.26 [0.72, 2.24]	–	0.418	None
Resection and TACE	1-year OS	1	1.04 [0.89, 1.22]	–	0.601	None
	2-year OS	0	–	–	–	/
	3-year OS	1	1.92 [1.28, 2.89]	–	0.002	IFN
	5-year OS	1	2.06 [1.33, 3.18]	–	0.001	IFN
	8-year OS	0	–	–	–	/

Table 3 Recurrence based on operation selection

Subgroup	Outcome	Studies, n	Effect estimate [RR (95% CI)]	Heterogeneity, I^2	*p* value	Favour group
Resection	1-year recurrence	2	1.28 [0.97, 1.70]	0.0%	0.080	None
	2-year recurrence	1	0.94 [0.57, 1.55]	–	0.822	None
	3-year recurrence	1	1.00 [0.65, 1.55]	–	1.000	None
	5-year recurrence	2	0.95 [0.78, 1.14]	0.0%	0.570	None
TACE	1-year recurrence	1	0.42 [0.17, 1.04]	–	0.061	None
	2-year recurrence	2	0.71 [0.56, 0.91]	60.6%	0.007	IFN
	3-year recurrence	1	0.80 [0.65, 0.99]	–	0.037	IFN
	5-year recurrence	0	–	–	–	–
Resection or other	1-year recurrence	1	0.25 [0.06, 1.08]	–	0.064	None
	2-year recurrence	1	0.50 [0.24, 1.06]	–	0.071	None
	3-year recurrence	1	0.70 [0.44, 1.11]	–	0.127	None
	5-year recurrence	1	0.81 [0.61, 1.06]	–	0.125	None
Resection and TACE	1-year recurrence	0	–	–	–	–
	2-year recurrence	0	–	–	–	–
	3-year OS	0	–	–	–	–
	5-year recurrence	1	0.73 [0.61, 0.86]	–	0.000	IFN

Subgroup analysis

Stratified analyses by operation selection

Studies were further grouped according to operation selection. Long-term OS was defined as the survival time exceeded 2 years, short-term OS was defined as the survival time < 2 years, early recurrence meant the tumor recurred within 2 years and late recurrence meant the tumor recurred after 2 years [26, 27]. In this meta-analysis, patients receiving IFN showed higher long-term OS and lower late recurrence rate in resection combined with TACE subgroup, higher long-term OS and lower early and late recurrence rates in TACE subgroup, higher short-term OS in resection subgroup (Tables 2, 3).

Stratified analyses based on whether to use NAs or not

Studies were grouped according to whether to use NAs or not. Results showed that IFN significantly improved the 1-, 2-, 3- and 5-year OS in the subgroup without NAs, but there were no statistical significances in the subgroups with NAs. IFN could not significantly improve the 8-year OS in both subgroups (Table 4).

Publication bias and sensitivity analysis

No evidence of publication bias was detected by funnel plots and Begg's and Egger's test. The statistical significances were not altered by removing one study and re-analysing

Table 4 OS based on whether to use NAs or not

Subgroup	Outcome	Studies, *n*	Effect estimate [RR (95% CI)]	Heterogeneity, I^2	*p* value	Favour group
With NAs	1-year OS	1	1.01 [0.99,1.04]	–	0.331	None
	2-year OS	1	1.01 [0.99,1.04]	–	0.331	None
	3-year OS	1	1.00 [0.94,1.06]	–	0.928	None
	5-year OS	1	1.10 [0.99,1.23]	–	0.077	None
	8-year OS	1	1.26 [0.72,2.24]	–	0.418	None
Without NAs	1-year OS	9	1.10 [1.04,1.16]	65.3%	0.001	IFN
	2-year OS	8	1.26 [1.13,1.41]	63.9%	0.000	IFN
	3-year OS	7	1.27 [1.06,1.52]	71.6%	0.009	IFN
	5-year OS	6	1.32 [1.04,1.66]	40.7%	0.020	IFN
	8-year OS	1	0.51 [0.20,1.32]	–	0.167	None

the data of the remaining studies, which meant the data were comparatively stable and credible.

Discussion

Postoperative recurrence significantly affect the outcome of patients with HBV-related HCC [28, 29], IFN is hopeful to solve this problem, however, there is a controversy in the application of IFN [30, 31]. Hence, we conducted this meta-analysis and obtained valuable data that should provide valuable references and recommendations for the clinical application of IFN.

In this meta-analysis, IFN statistically reduced recurrence rates of patients with HBV-related HCC at 2, 3 and 5 years, and significantly improved the DFS at 1, 2 and 3 years, finally improved the OS at 1, 2, 3 and 5 years. However, the result showed IFN did not improve the OS at 8 years. Therefore, we suppose that the efficacy advantage of IFN may gradually weaken as time goes on. However, only two studies reported the 8-year OS, more clinical researches with longer observation time are needed to further support our hypothesis. On the other hand, researches were mainly conducted in Asia, there were only few studies including non-Asian population but not met the criteria. A study from Italy showed IFN could reduce late recurrence in patients with HCC after resection [32], which was consistent with our conclusions. Another study from Italy showed the time to recurrence was lower in patients with SVR by IFN compared with those with active HCV infection, but there was no difference in patients with SVR by IFN-free or IFN-based strategies [33], which was also consistent with our subgroup analysis.

To further understand the comprehensive efficacy of IFN on HCC, subgroup analysis was conducted. First, some studies have shown that NAs could improve the survival rate of patients with HCC after surgery [34]. To observe whether NAs affected the outcome, studies were grouped according to whether to use NAs or not. Results showed IFN significantly improved the 1-, 2- and 3-year OS in the subgroup without NAs, but there were no statistical significances in the subgroup with NAs. Did this mean that NAs had the same efficacy with IFN? As all we know, researches have shown that sustained virological response (SVR) might be the most important factor affecting the prognosis of patients with hepatitis virus-related HCC [35–38]. Previous studies have shown that NAs could significantly reduce the risk of recurrence in patients with HBV-related HCC and improve OS after curative surgery [39, 40]. However, there was only 1 study compared IFN combined with NAs therapy vs NAs therapy, the data available in this meta-analysis could not completely support this conclusion. More importantly, persistence of cccDNA is the main reason for recurrence of HBV in patients, even years after using NAs [2]. In fact, NAs have no effects of antitumor or immunomodulatory [41], in contrast, IFN can control angiogenesis and tumor immunoregulation, enhance the immunogenicity of tumor, finally directly inhibit the proliferation of tumor cells [16, 42]. Two studies have shown that the prognosis of naive HCC after hepatectomy might be improved through achieving SVR by additional INF [30, 43]. Some other studies even have shown that IFN was superior to NAs in reducing HCC development of CHB patients [44, 45]. Recent research found that IFN liberated T-cell cytotoxic capacities and enhanced antitumor activity of anti-PD-1-based immunotherapy in patients with unresectable HCC [12]. In addition, IFN appeared to be more effective in preventing HCC in Asia [46]. Some reports have demonstrated that even the patients with HCC undergoing INF-free therapy obtained SVR, the rates of early tumor occurrence and recurrence still remained high [30]. Therefore, IFN may have more advantages than NAs in preventing recurrence and improving survival rate of patients with HCC. In recent years, more and more studies have shown that IFN combined with NAs might be a better choice [47, 48]. Therefore, we recommend the clinical application of IFN combined with NAs therapy in reducing recurrence rate and improving OS in patients with HBV-related HCC after curative surgery.

Second, studies were further grouped according to different operation selection. The result showed the clinical application of IFN in resection combined with TACE subgroup and TACE subgroup had more efficacy advantage, which had higher long-term OS and lower recurrence rate.

At the same time, subgroup analysis indicated that operation selection and whether to use NAs or not were not significant factors affecting heterogeneity. We believe that heterogeneity may be related to the following factors. First, study design. Although the well-designed RCS can achieve the similar effect with RCT, not all RCSs had high quality in this meta-analysis. Second, differences in patient characteristics. The application time of IFN, follow-up time, whether the patients accompanied with cirrhosis and the basic characteristics of tumors, such as the number, size, and location, were not exactly the same, which might influence clinical prognosis of HCC. Third, no study focused on whether IFN and NAs had the same efficacy when all patients reached SVR by IFN or NAs. Due to sample size limitation and incomplete data, we could not further perform subgroup analysis. They were also limitations of this study.

Hence, what should we do next? Our results should further encourage well-designed studies to address these limitations. High quality RCTs with large multicenter which contain appropriate application time of IFN, longer follow-up time, fixed characteristics of patient and tumor should be conducted. More importantly, we should focus on RCTs which contain the comparison between IFN and NAs. In

addition, the clinical application of IFN combined with NAs recommended in this meta-analysis is also needed to be further studied. The well-designed RCTs will help us to understand the efficacy of IFN on HCC more accurately and comprehensively, finally guiding clinical application of IFN on treating HCC.

Conclusion

This meta-analysis may provide valuable data to re-evaluate the efficacy of IFN on HBV-related HCC. The results indicated that IFN might significantly reduce recurrence and improve DFS of patients with HBV-related HCC after curative surgery, and finally improve the survival. However, the efficacy advantage of IFN might gradually weaken as time goes on. The clinical application of IFN combined with NAs recommended in this meta-analysis is also needed to be further studied.

Acknowledgements The authors are particularly grateful for the excellent professional assistance from their colleagues in the Department of Infectious Diseases, Hospital of Chengdu University of Traditional Chinese Medicine.

Author contributions X-YH and J-XL designed the study. Screening, review, data extraction and interpretation were done by J-XL, X-YH, YZ and NX. Data analysis was done by YZ and NX. J-XL and NX wrote the manuscript. All authors made contributions to the editing and revision of the manuscript. All authors read and approved the final manuscript for publication. J-XL and YZ contributed equally to this work.

Funding This work was supported by grant from the Science and Technology Project of hospital of Chengdu University of Traditional Chinese Medicine (No. 21YY03).

Data availability The data used to support the findings of this study is included within the article.

Declarations

Conflict of interest Jian-Xing Luo, Yang Zhang, Xiao-Yu Hu and Ne Xiang have declare no conflict of interest.

References

1. Murai H, Kodama T, Maesaka K, et al. Multiomics identifies the link between intratumor steatosis and the exhausted tumor immune microenvironment in hepatocellular carcinoma. Hepatology. 2023;77(1):77–91
2. Mani SKK, Andrisani O. Interferon signaling during Hepatitis B Virus (HBV) infection and HBV-associated hepatocellular carcinoma. Cytokine. 2019;124: 154518
3. Tran NH, Muñoz S, Thompson S, et al. Hepatocellular carcinoma downstaging for liver transplantation in the era of systemic combined therapy with anti-VEGF/TKI and immunotherapy. Hepatology. 2022;76(4):1203–1218
4. Choi J, Jo C, Lim YS. Tenofovir versus entecavir on recurrence of hepatitis B virus-related hepatocellular carcinoma after surgical resection. Hepatology. 2021;73(2):661–673
5. Zeng X, Liao G, Li S, et al. Eliminating METTL1-mediated accumulation of PMN-MDSCs prevents hepatocellular carcinoma recurrence after radiofrequency ablation. Hepatology. 2023;77(4):1122–1138
6. Kardashian A, Florman SS, Haydel B, et al. Liver transplantation outcomes in a U.S. multicenter cohort of 789 patients with hepatocellular carcinoma presenting beyond Milan criteria. Hepatology. 2020;72(6):2014–2028
7. Zhu P, Liao W, Zhang WG, et al. A prospective study using propensity score matching to compare long-term survival outcomes after robotic-assisted, laparoscopic, or open liver resection for patients with BCLC stage 0—a hepatocellular carcinoma. Ann Surg. 2023;277(1):e103–e111
8. Hara K, Takeda A, Tsurugai Y, et al. Radiotherapy for hepatocellular carcinoma results in comparable survival to radiofrequency ablation: a propensity score analysis. Hepatology. 2019;69(6):2533–2545
9. Rasic G, de Geus SWL, Beaulieu-Jones B, et al. A nationwide propensity score analysis comparing ablation and resection for hepatocellular carcinoma. J Surg Oncol. 2023;127(7):1125–1134
10. Xu JB, Qi FZ, Xu G, et al. Adjuvant interferon therapy after surgical treatment for hepatitis B/C virus-related hepatocellular carcinoma: a meta-analysis. Hepatol Res. 2014;44(2):209–217
11. Yang S, Lin Q, Lin W, et al. Effect of adjuvant interferon therapy on hepatitis B virus-related hepatocellular carcinoma: a systematic review. World J Surg Oncol. 2016;14(1):159
12. Wei CY, Zhu MX, Zhang PF, et al. IFNα potentiates anti-PD-1 efficacy by remodeling glucose metabolism in the hepatocellular carcinoma microenvironment. Cancer Discov. 2022;12(7):1718–1741
13. Huang TS, Shyu YC, Chen HY, et al. A systematic review and meta-analysis of adjuvant interferon therapy after curative treatment for patients with viral hepatitis-related hepatocellular carcinoma. J Viral Hepat. 2013;20(10):729–743
14. Higgins J, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions Version 6.3. 2022. http://training.cochrane.org/handbook/current
15. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
16. Xin M, Feng D, Yin B, et al. Efficacy of interferon therapy in patients with hepatitis B virus-related primary hepatic carcinoma after transcatheter arterial chemoembolization. Prec Radiat Oncol. 2018;2:76–84
17. Qu LS, Jin F, Huang XW, et al. Interferon-α therapy after curative resection prevents early recurrence and improves survival in patients with hepatitis B virus-related hepatocellular carcinoma. J Surg Oncol. 2010;102(7):796–801
18. Du J, Zhang Y. Clinical application of Peg-IFN in anti-relapse after resection and/or intervention for HBV-related HCC. China Mod Dr. 2022;60(3):1–3, 20
19. Qi W, Zhang Q, Xu Y, et al. Peg-interferon and nucleos(t)ide analogue combination at inception of antiviral therapy improves both anti-HBV efficacy and long-term survival among HBV DNA-positive hepatocellular carcinoma patients after hepatectomy/ablation. J Viral Hepat. 2020;27:387–396
20. Sun HC, Tang ZY, Wang L, et al. Postoperative interferon alpha treatment postponed recurrence and improved overall survival in patients after curative resection of HBV-related hepatocellular carcinoma: a randomized clinical trial. J Cancer Res Clin Oncol. 2006;132(7):458–465
21. Zuo CH, Xia M, Liu JS, et al. Transcatheter arterial chemoembolization combined with interferon-α is safe and effective for patients

with hepatocellular carcinoma after curative resection. Asian Pac J Cancer Prev. 2015;16(1):245–251
22. Gao J, Li XS, Shen W, et al. Therapeutic effect and prognosis of interferon therapy after transcatheter arterial chemoembolization in patients with hepatocellular carcinoma associated with hepatitis B virus. Zhonghua Gan Zang Bing Za Zhi. 2004;12(8):460–462
23. Li M, Lu C, Cheng J, et al. Combination therapy with transarterial chemoembolization and interferon-alpha compared with transarterial chemoembolization alone for hepatitis B virus related unresectable hepatocellular carcinoma. J Gastroenterol Hepatol. 2009;24(8):1437–1444
24. Lo CM, Liu CL, Chan SC, et al. A randomized, controlled trial of postoperative adjuvant interferon therapy after resection of hepatocellular carcinoma. Ann Surg. 2007;245(6):831–842
25. Chen LT, Chen MF, Li LA, et al. 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(1):8–17
26. Wang WQ, Lv X, Li J, et al. Repeat hepatectomy versus microwave ablation for solitary and small (≤3 cm) recurrent hepatocellular carcinoma with early or late recurrence: a propensity score matched study. Eur J Surg Oncol. 2023;49(5):1001–1008
27. Li N, Wan X, Zhang H, et al. Tumor and peritumor radiomics analysis based on contrast-enhanced CT for predicting early and late recurrence of hepatocellular carcinoma after liver resection. BMC Cancer. 2022;22(1):664
28. Xie L, Yin J, Xia R, et al. Cost-effectiveness of antiviral treatment after resection in hepatitis B virus-related hepatocellular carcinoma patients with compensated cirrhosis. Hepatology. 2018;68(4):1476–1486
29. Li Q, Wei Y, Zhang T, et al. Predictive models and early postoperative recurrence evaluation for hepatocellular carcinoma based on gadoxetic acid-enhanced MR imaging. Insights Imaging. 2023;14(1):4
30. Muroya D, Nishimura T, Kanno H, et al. Impact of interferon on the prognosis of hepatitis C virus-related hepatocellular carcinoma patients with a sustained virological response—an additional comparison between preoperative and postoperative sustained virological response. Kurume Med J. 2023;68(1):9–18
31. Dang H, Yeo YH, Yasuda S, et al. Cure with interferon-free direct-acting antiviral is associated with increased survival in patients with hepatitis C virus-related hepatocellular carcinoma from both East and West. Hepatology. 2020;71(6):1910–1922
32. Mazzaferro V, Romito R, Schiavo M, et al. Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. Hepatology. 2006;44(6):1543–1554
33. Petta S, Cabibbo G, Barbara M, et al. Hepatocellular carcinoma recurrence in patients with curative resection or ablation: impact of HCV eradication does not depend on the use of interferon. Aliment Pharmacol Ther. 2017;45(1):160–168
34. Zhang X, Li C, Wen T, et al. The different effects of nucleotide and nucleoside analogues on the prognosis of HBV-related HCC after curative resection. J Gastrointest Surg. 2021;25(6):1419–1429
35. Liu S, Deng R, Zhou B, et al. Association of serum hepatitis B virus RNA with hepatocellular carcinoma risk in chronic hepatitis B patients under nucleos(t)ide analogues therapy. J Infect Dis. 2022;226(5):881–890
36. Nan Y, Zhao S, Zhang X, et al. Machine learning-based predictive and risk analysis using real-world data with blood biomarkers for hepatitis B patients in the malignant progression of hepatocellular carcinoma. Front Immunol. 2022;13:1031400
37. Borgia M, Dal Bo M, Toffoli G. Role of virus-related chronic inflammation and mechanisms of cancer immune-suppression in pathogenesis and progression of hepatocellular carcinoma. Cancers (Basel). 2021;13(17):4387
38. Nakajima M, Kobayashi S, Wada H, et al. Viral elimination is essential for improving surgical outcomes of hepatitis C virus-related hepatocellular carcinoma: multicenter retrospective analysis. Ann Gastroenterol Surg. 2020;4(6):710–720
39. Qi W, Shen J, Dai J, et al. Comparison of nucleoside and nucleotide analogs in the recurrence of hepatitis B virus-related hepatocellular carcinoma after surgical resection: a multicenter study. Cancer Med. 2021;10(23):8421–8431
40. Gan W, Chen X, Wu Z, et al. The relationship between serum exosome HBV-miR-3 and current virological markers and its dynamics in chronic hepatitis B patients on antiviral treatment. Ann Transl Med. 2022;10(10):536
41. Pockros PJ, Mulgaonkar A. Cessation of nucleoside/nucleotide analogue therapy in chronic hepatitis B HBeAg-negative patients. Gastroenterol Hepatol (N Y). 2022;18(6):320–325
42. Ding WB, Wang MC, Yu J, et al. HBV/pregenomic RNA increases the stemness and promotes the development of HBV-related HCC through reciprocal regulation with insulin-like growth factor 2 mRNA-binding protein 3. Hepatology. 2021;74(3):1480–1495
43. Tsujita E, Maeda T, Kayashima H, et al. Effect of sustained virological response to interferon therapy for hepatitis C to the hepatectomy for primary hepatocellular carcinoma. Hepatogastroenterology. 2015;62(137):157–163
44. Ren P, Cao Z, Mo R, et al. Interferon-based treatment is superior to nucleos(t)ide analog in reducing HBV-related hepatocellular carcinoma for chronic hepatitis B patients at high risk. Expert Opin Biol Ther. 2018;18(10):1085–1094
45. Mao QG, Liang HQ, Yin YL, et al. Comparison of Interferon-α-based therapy and nucleos(t)ide analogs in preventing adverse outcomes in patients with chronic hepatitis B. Clin Res Hepatol Gastroenterol. 2022;46(1): 101758
46. Michielsen P, Ho E. Viral hepatitis B and hepatocellular carcinoma. Acta Gastroenterol Belg. 2011;74(1):4–8
47. Xu Y, Wang X, Liu Z, et al. Addition of nucleoside analogues to peg-IFNα-2a enhances virological response in chronic hepatitis B patients without early response to peg-IFNα-2a: a randomized controlled trial. BMC Gastroenterol. 2017;17(1):102
48. Qi WQ, Zhang Q, Wang X, et al. Long-term clinical benefit of Peg-IFNα and NAs sequential anti-viral therapy on HBV related HCC. Neoplasma. 2021;68(1):200–207