Nucleot(s)ide Analogues for Hepatitis B Virus-Related Hepatocellular Carcinoma after Curative Treatment: A Systematic Review and Meta-Analysis

Ping Sun¹*, Xiaochuan Dong²*, Xiang Cheng¹*, Qinggang Hu¹, Qichang Zheng¹*

¹ Hepatobiliary Surgery Centre, Union hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, ² Department of Pathology, Union hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Abstract

Aim: The benefit of nucleot(s)ide analogues (NA) for hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) after curative treatment has been widely debated due to the relatively weak evidence. The objective of this systematic review was to evaluate the effect of NA on recurrence and survival after curative treatment of HBV-HCC.

Methods: A systematic electronic search was performed. All controlled trials comparing NA versus placebo or no treatment were considered for inclusion. Results were expressed as Hazard Ratio for recurrence and survival with 95% confidence intervals using RevMan 5.2.

Results: We included 13 trials with 6350 patients. There were significant improvements for recurrence-free survival (HR 0.66, 95% CI 0.54–0.80; p < 0.0001) and overall survival (HR 0.56, 95% CI 0.43–0.73; p < 0.0001) in the adjuvant NA group compared with the control group. Sensitivity analyses confirmed the robustness of the results. There were no serious adverse effects being reported. Lamivudine resistance was from 28.6% to 37.5% but could be rescued by other types of NA or combination therapy.

Conclusion: Our study suggested benefits of adjuvant NA therapy following curative treatment of HBV-HCC. Since the great proven efficacy of NA in improving clinical and viral parameters besides HCC, further studies should be focused on broadening the indications for NA therapy after curative treatment of HBV-HCC.

Citation: Sun P, Dong X, Cheng X, Hu Q, Zheng Q (2014) Nucleot(s)ide Analogues for Hepatitis B Virus-Related Hepatocellular Carcinoma after Curative Treatment: A Systematic Review and Meta-Analysis. PLoS ONE 9(7): e102761. doi:10.1371/journal.pone.0102761

Editor: Tetsuo Takehara, Osaka University Graduate School of Medicine, Japan

Received March 27, 2014; Accepted June 22, 2014; Published July 24, 2014

Copyright: © 2014 Sun et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: The authors report no current funding sources for this study.

Competing Interests: The authors have declared that no competing interests exist.

* Email: zqcmd1@163.com

These authors contributed equally to this work.

Introduction

Liver cancer is one of the most common cancers diagnosed worldwide [1]. Among primary liver cancers, hepatocellular carcinoma (HCC) represents the major histological subtype, accounting for 70% to 85% of the total liver cancer burden [2]. Hepatitis B virus (HBV) infection accounts for about 60% of the total liver cancer in developing countries and for about 23% in developed countries [3,4]. Liver transplantation is the definitive therapy for not only resecting the tumor but also replacing the cirrhotic liver. However, only a small proportion of patients can eventually get liver transplantation, most patients exceed rigorous selection criteria or die while waiting organs [5]. Therefore, ablation or resection is the only curative treatment for most patients [6]. More than 50% of cases suffered tumor recurrence within 3 years after curative resection or ablation, not to mention the progression of chronic liver disease, which are two main causes crippling long-term survival after treatment [5,7].

Nucleot(s)ide analogues (NA) can inhibit HBV replication, and have been shown to improve underlying liver disease and reduce the incidence of HBV-HCC [8,9]. Therefore, NA is supposed to be able to reduce recurrence rate and improve survival after curative treatment of HBV-HCC and have been investigated in several clinical trials [10-22]. Some trials failed to confirm the benefit of adjuvant NA therapy [12,16,18–20], but others [10,11,13–15,17,21,22], including one randomized controlled trial (RCT) [10], reported significant improvement of recurrence-free survival (RFS) or overall survival (OS).

This systematic review was implemented according to Cochrane handbook [23] and results were expressed as Hazard Ratio (HRs), which are most appropriate for survival data, taking into account not only the number but also the time of events, even further comprising the time until last follow-up for each patient who has not experienced an event [24].

Methods

Ethics Statement

This was a meta-analysis of published summary data and therefore did not require ethics approval.
Criteria for considering studies for this review

Inclusion criteria: (i) Study design: both randomized controlled trials (RCT) and nonrandomized studies were considered; (ii) Study population: >18 years old, without gender restrictions, diagnosed with HBV-HCC; (iii) Therapy for HCC: curative resection or ablation; (iv) Antiviral treatment: using NA as regular therapy compared with placebo or no treatment in control group after curative therapy of HCC; (v) Initiating NA therapy: within 6 months after curative treatment; (vi) Results available on RFS or OS. Exclusion criteria: (i) Primary HCC was treated with palliative therapy (transarterial chemoembolization, radiation, systemic chemotherapy); (ii) Trials including participants co-infected with hepatitis C virus or human immunodeficiency virus.

Search methods for identification of studies

We performed a systematic search of electronic databases (EMBASE, PubMed, Science Citation Index Expanded and Cochrane Library databases) for studies without language restriction (last literature search date: January 3, 2014). The search strategy was based on MeSH terms combining with free text words. The detailed search strategies are given in Table S1. Reference lists of all associated papers (relevant reviews and included studies) were checked as hand searching.

Data collection and assessment of bias

Studies was screened according to the inclusion and exclusion criteria and data was extracted using a predesigned data extraction form by two authors independently. For duplicated publications, only the most recent or the most complete report was included. All included studies were assessed for methodological quality by two independent authors, as recommended by the Cochrane Handbook for RCTs [23] and the Newcastle-Ottawa Scale (NOS) for observational studies [25]. Any disagreement between the two authors was resolved through discussion with a third author. RFS and OS were primary outcomes. Adverse effects was secondary outcome. We would contact and request the researchers to provide key missed information.

Statistical analysis

We performed this systematic review according to the recommendations of Cochrane Handbook [23] and reported in line with the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [26]. Hazard ratio (HR) between two arms was applied as a summary statistic for time-to-event outcomes like RFS and OS. HR and its standard error of each trial was calculated by a method described by Tierney and colleagues [24]. HR of individual trials were pooled into an overall HR by random-effects model. In accordance with customary, an overall HR<1 favored the NA group and the difference was considered statistically significant if the 95% CI of the HR didn’t overlap 1. Funnel plots and Beggs’s test would be used to evaluate the publication bias if there was sufficient studies. Sensitivity analyses were used to evaluate the reliability of the results.

Two authors input the data into RevMan 5.2 (Cochrane Collaboration, Oxford, UK) and Stata for Windows version 11.0 (StataCorp, College Station, Texas, USA), and performed all the analysis independently.
Results

Description of studies

The study screening process is shown in Figure 1. Twelve nonrandomized trials (including one large cohort) and one two-stage longitudinal study (including one RCT) were included for this systematic review (Table 1 [10–22]). The detailed information of the included trials was shown in Table S2. The reasons for excluding studies [27–35] were listed in Table S3.

All the included studies used lamivudine as adjuvant antiviral therapy, with adefovir or entecavir rescue. A total of 6350 patients were included in this systematic review, among which 1227 were in NA-group whereas 5123 in control-group. All the studies applied resection or radiofrequency ablation (RFA) as curative treatment for primary HCC except Hamm 2011 [15] and Nishikawa 2013 [22], which also used percutaneous ethanol injection (PCEI) and cryoablation besides RFA. The serum HBV-DNA levels ≥ 400 copies/mL-10, 000 copies/mL was an indication of adjuvant NA therapy in ten studies [10-12,14,16-22], in seven [10-12,17,19,20,22] of which the DNA levels in the treatment group were higher than the control group in different degrees. The risk of bias of included RCT was unclear and the NOS score was from 6 stars to 9 stars for nonrandomized trials (Table S2).

Effects of intervention

Pooling the data of twelve studies [10–18,20–22] that assessed RFS (Fig. 2A) in 6246 patients showed a significant difference favoring NA therapy (HR 0.66, 95% CI 0.54–0.80; p<0.0001), with significant between-study heterogeneity ($\chi^2$ = 28.43, degrees of freedom (df) 10; p = 0.005; I² = 50%). No significant publication bias was found by funnel plots (Fig. 3A) and Beggs’s test (p = 0.142). Besides, both the large cohort [13] and the RCT [10] showed significant benefit of RFS (HR 0.73, 95% CI 0.61–0.87; HR 0.44, 95% CI 0.30–0.64, respectively).

Ten studies [10–13,15–17,19,20,22] assessed OS (Fig. 2B) in 6246 patients, and showed a significant difference favoring NA therapy (HR 0.56, 95% CI 0.43–0.73; p<0.0001), with significant between-study heterogeneity ($\chi^2$ = 21.48, df 10; p = 0.02; I² = 53%). No significant publication bias was found by funnel plots (Fig. 3B) and Beggs’s test (p = 0.350). Similarly, both the large cohort [13] and the RCT [10] showed significant efficacy of OS (HR 0.76, 95% CI 0.63–0.90; HR 0.31, 95% CI 0.15–0.61, respectively).

Sensitivity analysis

Sensitivity analyses of studies with no less than 8 stars according to Newcastle Ottawa Scale, or studies with sample size greater than 50, or studies published after 2010, or after we deleted studies with lowest and highest HR or deleted studies with highest and lowest sample size, still showed significant difference between the NA group and the control group (table 2).

Adverse effects

Meta-analysis comparing adverse effects of NA therapy could not be achieved due to lack of enough data. Available data showed that no serious adverse effects attributable to NA therapy were recorded in nonrandomized cohort [10,19,20]. And in the RCT, no adverse effects caused by NA treatment were reported, except one patient who received adefovir dipivoxil plus lamivudine treatment had transient anorexia; None of the participants discontinued participation because of the adverse effects [10]. Lamivudine resistance or the emergence of YMDD mutants was from 28.6% to 37.5% but could be rescued by other types of NA or combination therapy [15,20,21].

Discussion

In this systematic review, twelve nonrandomized trials (including one large cohort) and one two-stage longitudinal study (including one RCT) fulfilled our criteria. The results showed the benefit of adjuvant NA therapy for both RFS and OS, which was similar to the results of large cohort and RCT. Sensitivity analysis also confirmed the robustness of the results. The DNA levels in the treatment group were higher than the control group in seven studies [10–12,17,19,20,22] and the levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) were higher than the control group in six studies [16–20,22] in different degrees. Many studies have confirmed that high HBV-DNA level was a risk factor of recurrence and poorer survival after primary treatment of HCC [36–38], and high levels of ALT or AST indicated persistent damage to liver parenchyma, the beneficial effect of NA therapy might be blunted by the development of lamivudine resistance and the relatively higher levels of HBV-DNA, ALT or AST. Statistical assessment of side effects of NA therapy failed because only part of included studies gave general description of the common side effects other than specifying the severity and incidence. No serious adverse effects attributable to NA therapy were recorded. Lamivudine resistance or the emergence of YMDD mutants was from 28.6% to 37.5% but could be rescued by other types of NA or combination therapy. Our results were also similar to Wong 2011 [39]. But four [30,33,34,40] of their nine included studies had been excluded due to our rigorous inclusion and exclusion criteria. Besides, eight more studies [10–16,22] published after 2010 were included. We also gave more detailed information of adverse effects of NA therapy. This systematic review would provide more evidence for researchers and clinicians.

Since many studies have demonstrated that antiviral therapy could reduce the incidence of hepatic decompensation and the risk of HCC [41–43], antiviral regimens are believed to be able to decrease recurrence rate and prolong survival after curative treatment of HBV-HCC. So far, all published RCTs applied interferon (IFN) as adjuvant antiviral regimen [44–52] except one [10] but obtained paradoxical results. Pooled-data meta-analyses found that only hepatitis C virus-related HCC patients could benefit from adjuvant IFN therapy but HBV-HCC patients could not. Meanwhile, dose reduction and discontinuation of IFN therapy happened in a large number of patients due to adverse effects [53]. However, in this study, NA, as the first-line treatment of patients with chronic HBV infection, reduced the risk of recurrence by 36% and the risk of death by 42% in patients after curative treatment of HBV-HCC despite lamivudine resistance happened in a large proportion of patients. Newer NA, such as entecavir, tenofovir, with higher potency and minimal risk of resistance development, are most likely to make patients benefit more from adjuvant NA treatment [8,9].

Theoretically, there is no one residual tumor cell after curative treatment of HCC. Such patients can be approximately treated as ordinary patients with chronic hepatitis B infection, except they have the highest risk of tumorigenesis. For these patients, clinicians should at least follow the indications for NA therapy in clinical practice guidelines [54]. Any trials published in the future concerning the prevention of HCC recurrence and the improvement of OS with the two current first-line agents, entecavir and tenofovir, is unlikely to be controlled, due to the great proven efficacy of them in improving viral, biochemical and pathological
**Table 1. Characteristics of the included studies.**

| Nature of Study | Sample size (T/C) | Male/Female | Age (T/C) | HCC size (cm) (T/C) | % with cirrhosis (T/C) | Curative treatment | Adjuvant treatment details | follow up (years) (T/C) | NOS (stars) | HBV-DNA (T) |
|-----------------|------------------|-------------|-----------|---------------------|------------------------|---------------------|-------------------------|--------------------------|-------------|-------------|
| Kubo 2007       | prospective cohort 14/10, 66.7% HBeAg+ | 17/7 | 55/55 | 2.4/2.8 | 43/40 | resection | LAM: 100 mg/day (with ADV rescue) | 3.06/0.61 | 7 | ≥ 5000 copies/mL |
| Kuzuya 2007     | retrospective cohort 16/33, 12.2% HBeAg+ | 41/8 | 59.8/61.1 | NA | NA | resection or RFA | LAM: 100 mg/day (with ADV rescue) | 3.2/2.7 | 7 | ≥ 400 copies/mL |
| Yoshida 2008    | retrospective cohort 33/71, 18.3% HBeAg+ | 78/26 | 57/59 | 2.6/2.8 | NA | RFA | LAM: 100 mg/day (with ADV rescue) | 2.75/3.92 | 8 | ≥ 5000 copies/mL |
| Chuma 2009      | retrospective cohort 20/30, 46% HBeAg+ | 36/14 | 55.6/55.7 | 2.1/1.7 | 70/83.3 | resection or RFA | LAM: 100 mg/day (with ADV rescue); OR ETV, 0.5 mg/day; | 2.96/4.1 | 8 | > 10³ copies/mL |
| Koda 2009       | cohort study 22/14 | NA | NA | NA | NA | resection or RFA | LAM, 100 mg/day; OR ETV, 0.5 mg/day; | NA | 7 | >5000 copies/mL |
| Chan 2011       | retrospective cohort 42/94 | 105/31 | 57/55 | 9.3/9.0 | 74/56 | resection | LAM, 100 mg/day; OR ETV, 0.5 mg/day; | NA | 7 | >10³ copies/mL |
| Hann 2011       | cohort study 8/5, 30.8% HBeAg+ | 12/1 | 57/55 | 2.5/3.0 | NA | Resection or ablation | LAM, tenofovir, ADV | 5.8/1.4 | 9 | NA |
| Wu 2012         | cohort study 518/4051 | 3770/799 | 54.4/54.6 | NA | 48.6/38.7 | resection | LAM, ETV, telbivudine | 2.64/2.18 | 8 | NA |
| Lee 2012        | retrospective cohort 12/16 | NA | NA | NA | 100/100 | resection | antiviral treatment | 4.2 | 8 | > 10³ copies/mL |
| Ke 2013         | retrospective cohort 141/141, 11% HBeAg+ | 256/26 | 48.9/49.7 | 4.5/5.0 | 81.6/81.6 | resection | LAM, 100 mg/day; | 2.1/9 | 6 | ≥ 200 IU/mL |
| Nishikawa 2013  | retrospective cohort 65/32, 26.8% HBeAg+ | 67/30 | 56.1/60.7 | 2.8/3.2 | 58.5/46.9 | resection or RFA | LAM or ADV OR ETV | 4.9/4.0 | 7 | NA |
| Su 2013         | retrospective cohort 40/142, 11% HBeAg+ | 158/24 | 52/58 | NA | 37.7/45.8 | resection | LAM OR ETV | 3.8 | 6 | > 2000 IU/mL |
| Yin 2013        | cohort study 215/402, 29% HBeAg+ | 530/87 | 50/50 | NA | 47.0/35.8 | resection | LAM: 100 mg/day (with ADV OR ETV rescue) | 1.99 | 8 | >500 copies/mL |
| Yin 2013        | RCT | 81/82, 41% HBeAg+ | 144/19 | 48/49 | NA | 24.7/28.0 | resection | LAM: 100 mg/day (with ADV OR ETV rescue) | 3.33 | Unclear bias | > 500 copies/mL |

Abbreviations: T, treated; C, control; HCC, hepatocellular carcinoma; NOS, Newcastle-Ottawa Scale; NA, not available; HBeAg+, hepatitis B virus e antigen positive; RFA, radiofrequency ablation; LAM, lamivudine; ADV, adefovir; ETV, entecavir; PCEI, percutaneous ethanol injection.

doi:10.1371/journal.pone.0102761.t001
parameters other than HCC. It would not be ethically approved to perform placebo-controlled studies, or even lamivudine and adefovir controlled studies [8]. HBV reactivation after hepatectomy influences postoperative survival in HBV-HCC patients with preoperative low HBV-DNA levels [55]. And antiviral therapy decreases HBV reactivation in patients with HBV-HCC undergoing hepatectomy in a randomized controlled trial [56]. Further

Figure 2. Forest plot of 13 studies on the use of NA after curative treatment of HBV-HCC. (A) Forest plot showing significant benefit of NA therapy for recurrence free survival. (B) Forest plot showing significant benefit of NA therapy for overall survival. doi:10.1371/journal.pone.0102761.g002

Figure 3. Funnel plot for assessing publication bias. (A) Funnel plot showing asymmetry indicative some extent of publication bias for recurrence free survival. (B) Funnel plot showing asymmetry indicative some extent of publication bias for overall survival. doi:10.1371/journal.pone.0102761.g003
### Table 2. Sensitivity analyses comparing nucleoside analogues versus control.

| Study Description                                      | No. of studies | No. of patients | HR (95% CI) | p-value | Study heterogeneity |
|--------------------------------------------------------|----------------|----------------|-------------|---------|---------------------|
|                                                        | NA Control Total |                 |             |         | χ² df I² p-value     |
| Studies with no less than 8 stars according to Newcastle Ottawa Scale* | 6              | 5440           | 0.56 (0.42, 0.76) | <0.001  | 18.84 5 73% 0.002  |
|                                                        | 5              | 5466           | 0.70 (0.52, 0.94) | 0.02    | 9.04 4 56% 0.06    |
| Excluding studies with highest and lowest HR            | 11             | 6197           | 0.66 (0.55, 0.80) | <0.001  | 22.35 10 55% 0.01  |
|                                                        | 9              | 6095           | 0.55 (0.42, 0.71) | <0.001  | 17.31 8 54% 0.03   |
| Excluding studies with highest and lowest sample size   | 11             | 1664           | 0.66 (0.52, 0.83) | <0.001  | 24.07 10 58% 0.007 |
|                                                        | 9              | 1666           | 0.50 (0.35, 0.72) | <0.001  | 18.49 8 57% 0.02   |
| Studies with sample size greater than 50               | 8              | 6096           | 0.71 (0.61, 0.83) | <0.001  | 11.37 7 38% 0.12   |
|                                                        | 8              | 6150           | 0.60 (0.46, 0.78) | <0.001  | 16.94 7 59% 0.02   |
| Studies published after 2010                           | 9              | 6087           | 0.66 (0.53, 0.81) | <0.001  | 21.36 8 63% 0.006  |
|                                                        | 8              | 6059           | 0.57 (0.43, 0.74) | <0.001  | 15.48 7 55% 0.03   |

Abbreviation: No., number; HR, hazard ratio; CI, confidence interval; df, degrees of freedom; RFS, recurrence free survival; OS, overall survival.

*Yin 2013 is a two-stage longitudinal clinical study and considered as 2 studies and the randomized controlled trial (RCT) is treated as high quality of non-RCT here.

doi:10.1371/journal.pone.0102761.t002
studies should be focused on broadening the indications for NA therapy after curative treatment of HBV-HCC.

Some limitations of this study should be discussed. First of all, all included studies were nonrandomized trials except one [10] and the NOS score of almost half trials was less than 8 stars. But the results showed obvious benefits of adjuvant NA therapy and were stable according to sensitivity analysis. Second, significant between-study heterogeneity existed because of the different patients (etiologies, virus activity, characteristics of tumors, et al), types of NA, treatment duration, as well as interval between HCC treatment and initiation of NA therapy. In this study, we conducted the pooled data neglecting the differences but applied random-effects model. Third, some extent of publication bias was existed despite without statistical significance by Beggs’s test, which might indicate some kinds of report bias unpredictable. Fourth, though the serum HBV-DNA levels might indicate some kinds of report bias unpredictable. Fourth, though the serum HBV-DNA levels were 400 copies/mL–10,000 copies/mL was an indication of adjuvant NA therapy in ten studies [10–12,14,16–21], most of the studies did not apply exactly the same indications, making it is impossible to figure out which kind of patients can benefit more from this adjuvant therapy.

In summary, despite these limitations listed above, our study still demonstrated obvious efficacy of adjuvant NA therapy after curative treatment of HBV-HCC. Since the great proven efficacy of NA in improving viral, biochemical and pathological parameters other than HCC. It would not be ethically approved to perform any other randomized trials. Further studies should be focused on broadening the indications for NA therapy after curative treatment of HBV-HCC besides indications in clinical practice guidelines for management of chronic HBV infection.

Supporting Information
Checklist S1 PRISMA checklist. (DOC)
Table S1 Search strategy. (DOC)
Table S2 Characteristics of included studies. (DOC)
Table S3 Characteristics of excluded studies. (DOC)

Author Contributions
Conceived and designed the experiments: PS XCD XC QGH. Wrote the paper: PS XCD XC QGH QCZ. Contributed some part of methodology: PS XCD XC QGH QCZ. Contributed reagents/materials/analysis tools: PS XCD XC QGH QCZ. Conceived and designed the experiments: PS XCD XC QCZ. Performed the experiments: PS XCD XC QCZ. Analyzed the data: PS XCD XC QGH QCZ. Contributed reagents/materials/analysis tools: PS XCD XC QGH QCZ. Wrote the paper: PS XCD XC QGH QCZ. Contributed additional data analysis: PS XCD XC QGH QCZ. Contributed some part of additional potentially eligible literature: QGH QCZ.

References
1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, et al. (2011) Global cancer statistics. CA Cancer J Clin 61: 69–90.
2. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP (2006) The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 45: 329–338.
3. Tsukuma H, Tanaka H, Akij W, Oshima A (2005) Liver cancer and its prevention. Asian Pac J Cancer Prev 6: 244–250.
4. Parkin DM (2006) The global health burden of infection-associated cancers in the year 2002. Int J Cancer 118: 3030–3047.
5. Mazzaferrro V, Regalia E, Doci R, Andreola S, Pulvirenti A, et al. (1996) Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 334: 693–699.
6. Bruix J, Sherman M (2005) Management of hepatocellular carcinoma. Hepatology 42: 1208–1236.
7. Llovet JM, Schwartz M, Mazzaferrro V (2005) Resection and liver transplantation for hepatocellular carcinoma. Semin Liver Dis 25: 181–200.
8. Shih KL, Yuen MF (2013) Prevention of hepatitis B virus-related hepatocellular carcinoma with antiviral therapy. Hepatology 57: 999–406.
9. Hosaka T, Suzuki K, Kobayashi M, Seko Y, Kawamura Y, et al. (2013) Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. Hepatology 50: 98–107.
10. Yin J, Li N, Han Y, Xue J, Deng Y (2013) Effect of antiviral treatment with nucleotide/nucleoside analogs on postoperative prognosis of hepatitis B virus-related hepatocellular carcinoma: a two-stage longitudinal clinical study. J Clin Oncol 31: 3647–3655.
11. Su CW, Chiao YW, Tsai YH, Teng RD, Chau GY, et al. (2013) The Influence of Hepatitis B Virus Load and Pre-S Deletion Mutations on Post-Operative Recurrence of Hepatocellular Carcinoma and the Tertiary Preventive Effects by Anti-Viral Therapy. PLoS One 8: e66457.
12. Ke Y, Ma L, You YM, Huang SX, Li YR, et al. (2013) Antiviral therapy for hepatitis B virus-related hepatocellular carcinoma after radical hepatectomy. Cancer Biol Med 10: 156–169.
13. Wu CY, Chen YJ, Ho-HJ, Hua YC, Kuo-KN, et al. (2012) Association between nucleoside-analogues and risk of hepatitis B virus-related hepatocellular carcinoma recurrence following liver resection. JAMA 308: 1906–1914.
14. Lee JW, Lee JI, Chung HJ, Kim YS, Lee DH (2012) Effect of antiviral therapy on late recurrence after curative resection of B-valvar hepatitis B-associated hepatocellular carcinoma (HCC). Journal of Hepatology 56: S389.
15. Hann HW, Bergin D, Cohen R, Dimarino AJ (2011) Prevention of new hepatocellular carcinoma with concomitant antiviral therapy in chronic hepatitis B patients whose initial tumor was successfully ablated. International Journal of Cancer 128: 740–743.
16. Chan ACY, Chok KSH, Yuen WK, Chan SC, Poon RTP, et al. (2011) Impact of antiviral therapy on the survival of patients after major hepatectomy for hepatitis B virus-related hepatocellular carcinoma. Archives of Surgery 146: 657–681.
17. Koda M, Nagahara T, Matono T, Sugihara T, Mandai M, et al. (2009) Nucleotide analogs for patients with HBV-related hepatocellular carcinoma increase the survival rate through improved liver function. Intern Med 48: 11–17.
18. Chuma M, Higa S, Kamiyama T, Meguro T, Nagasaki A, et al. (2009) The influence of hepatitis B DNA level and antiviral therapy on recurrence after initial curative treatment in patients with hepatocellular carcinoma. J Gastroenterol 44: 991–999.
19. Yoshida H, Goto E, Sato T, Ohki T, Masuzaki R, et al. (2008) Safety and efficacy of lamivudine after radiofrequency ablation in patients with hepatitis B virus-related hepatocellular carcinoma. Hepatol Int 2: 89–94.
20. Kuzuya T, Katano Y, Kumada T, Toyoda H, Nakano I, et al. (2007) Efficacy of antiviral therapy with lamivudine after initial treatment for hepatitis B virus-related hepatocellular carcinoma. J Gastroenterol Hepatol 22: 1929–1935.
21. Kubo S, Tanaka H, Takamura S, Yamamoto S, Hsai S, et al. (2007) Effects of lamivudine on outcome after liver resection for hepatocellular carcinoma in patients with active replication of hepatitis B virus. Hepatol Res 37: 94–100.
22. Nishikawa H, Nishijima N, Arimoto T, Inazuka T, Kina R, et al. (2013) Effect of nucleoside analog use in patients with hepatitis B virus-related hepatocellular carcinoma. Hepatol Res. 2013.
23. Higgins JPT, Green S, editors (2011) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration.
24. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR (2007) Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 8: 16.
25. Wells G, Shea B, O’Connell D, Peterson J, Welch V, et al. (2001) The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-analyses. Ottawa: Ottawa Hospital Research Institute. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 6 July 2014.
26. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 151: 264–269, W264.
27. Huang G, Yang Y, Shen F, Pan ZY, Fu SY, et al. (2013) Early Viral Suppression Predicts Good Postoperative Survivals in Patients with Hepatocellular Carcinoma with a High Baseline HBV-DNA Load. Annals of Surgical Oncology 20: 1492–1499.
28. Uzagai Y, Kubo S, Takemura S, Urushihara H, Kodai K, et al. (2012) Effects of antiviral therapy on long-term outcome after liver resection for hepatitis B virus-related hepatocellular carcinoma. J Hepatoonology 56: S150.
29. Mori T, Ikeda K, Ohno H, Tanigawa N, Ono T, et al. (2011) Antiviral therapy for recurrent hepatitis B virus (HBV) related hepatocellular carcinoma (HCC) improves the outcome in patients with high serum HBV DNA level. Hepatology 53: 1360A.
30. Li N, Liu L, Shi J, Guo WX, Xue J, et al. (2010) A comparative study of antiviral therapy after resection of hepatocellular carcinoma in the immune-active phase of hepatitis B virus infection. Annals of Surgical Oncology 17: 179–185.
31. Chan A, Chok SH, Yuen WK, Chan SC, Ng KKC, et al. (2010) Impact of antiviral therapy on the survival outcome after hepatectomy for hepatitis B-related hepatocellular carcinoma. HPB 12: 52.
32. Kim JH, Park JW, Koh JW, Lee WJ, Kim CM (2009) Efficacy of lamivudine on hepatitis B viral status and liver function in patients with hepatitis B virus-related hepatocellular carcinoma. Liver Int 29: 203–207.
33. Shuqan C, Mengchao W, Han C, Feng S, Jiahe Y, et al. (2006) Antiviral therapy using lamivudine and thymosin alpha1 for hepatocellular carcinoma coexisting with chronic hepatitis B infection. Hepatogastroenterology 53: 249–252.
34. Piao CY, Fujisaki S, Iwasaki Y, Fujio K, Kaneyoshi T, et al. (2005) Lamivudine treatment in patients with HBV-related hepatocellular carcinoma—using an untreated, matched control cohort. Acta Med Okayama 59: 217–224.
35. Inuzuka T (2010) Nucleoside analogues may prolong survival time without recurrence and overall survival time for HBV-related liver diseases after curative treatment of hepatocellular carcinoma. Hepatology 52: 525A.
36. Shin JH, Lee HC, Choi JG, Lee D, Kim KM, et al. (2011) Clinical implication of hepatitis B viral load in hepatitis B E antigen-negative chronic hepatitis B patients with hepatocellular carcinoma treated with curative resection. Journal of Hepatology 54: S301.
37. An HJ, Jung JW, Kwon JH, You CR, Kim JD, et al. (2010) Effect of hepatitis B viral status on cancer recurrence and long-term prognosis after surgical resection in patients with hepatocellular carcinoma. Hepatology International 4: 310.
38. Goto T, Yoshida H, Tateishi R, Enooku K, Goto E, et al. (2011) Influence of serum HBV DNA load on recurrence of hepatocellular carcinoma after treatment with percutaneous radiofrequency ablation. Hepatology International 5: 767–773.
39. Wang JSW, Wong GLH, Tsui KKF, Wong VWS, Cheung SYS, et al. (2011) Meta-analysis: The efficacy of anti-viral therapy in prevention of recurrence after curative treatment of chronic hepatitis B-related hepatocellular carcinoma. Gastroenterology and Hepatology 33: 1104–1112.
40. Hung IF, Poon RT, Lai CL, Fung J, Fan ST, et al. (2000) Recurrence of hepatitis B-related hepatocellular carcinoma is associated with high viral load at the time of resection. Am J Gastroenterol 103: 1663–1673.
41. Papaioannoudis GV, Lamperichtos P, Manolakopoulou S, Lek A (2010) Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos (ide) therapy: a systematic review. J Hepatol 53: 348–356.
42. Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, et al. (2004) Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 351: 1521–1531.
43. Shamiyani TA, MacDonald R, Shaukat A, Taylor BC, Yuan JM, et al. (2009) Antiviral therapy for adults with chronic hepatitis B: a systematic review for a National Institutes of Health Consensus Development Conference. Ann Intern Med 150: 111–124.
44. Chen LT, Chen MF, Li LA, Lee PH, Jeng LB, et al. (2012) Long-term results of a randomized, observation-controlled, phase III Trial of Adjuvant Interferon alfa-2b in hepatocellular carcinoma after curative resection. Annals of Surgery 255: 8–17.
45. Lo CM, Liu CL, Chan SC, Lam CM, Poon RTP, et al. (2007) A randomized, controlled trial of postoperative adjuvant interferon therapy after resection of hepatocellular carcinoma. Annals of Surgery 245: 831–842.
46. Sun HC, Tang ZY, Wang L, Qiu LX, Ma ZC, et al. (2006) 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 132: 456–465.
47. Mazzarotto V, Romito R, Schiavo M, Mariani L, Canevari T, et al. (2006) Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. Hepatology 44: 1543–1554.
48. Nishiguichi S, Tamori A, Kubo S (2005) Effect of long-term postoperative interferon therapy on intrahepatic recurrence and survival rate after resection of hepatitis C virus-related hepatocellular carcinoma. Intervirology 48: 71–75.
49. Lin SM, Lin CJ, Hsu GW, Tai DI, Sheen IS, et al. (2004) Prospective randomized controlled study of interferon-alpha in preventing hepatocellular carcinoma recurrence after medical ablation therapy for primary tumors. Cancer 106: 376–382.
50. Shiratori Y, Shinya S, Teratani T, Imamura M, Obi S, et al. (2003) Interferon therapy after tumor ablation improves prognosis in patients with hepatocellular carcinoma associated with hepatitis C virus. Ann Intern Med 138: 299–306.
51. Miyaguchi S, Watanabe T, Takashashi H, Nakamura M, Saito H, et al. (2002) Interferon therapy for hepatocellular carcinoma patients with low HCV-RNA levels. Hepatogastroenterology 49: 724–729.
52. Bedka K, Arase Y, Saitoh S, Kobayashi M, Suzuki Y, et al. (2000) Interferon beta prevents recurrence of hepatocellular carcinoma after complete resection or ablation of the primary tumor - A prospective randomized study of hepatitis C virus - Related liver cancer. Hepatology 32: 228–232.
53. Sun P, Yang X, He RQ, Hu QG, Song ZF, et al. (2013) Antiviral therapy after curative treatment of hepatitis B/C virus-related hepatocellular carcinoma: A systematic review of randomized trials. Hepatol Res.
54. (2012) EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 57: 167–185.
55. Huang L, Li J, Yan J, Sun J, Zhang X, et al. (2013) Antiviral therapy after tumor ablation improves prognosis in patients with hepatocellular carcinoma associated with hepatitis C virus. Ann Intern Med 138: 299–306.
56. Huang G, Lai ECH, Lau WY, Zhou WP, Shen F, et al. (2012) Posthepatectomy HBV reactivation in hepatitis B-Related hepatocellular carcinoma influences postoperative survival in patients with preoperative low HBV-DNA levels. Annals of Surgery 257: 490–505.
57. Huang L, Li J, Yan J, Sun J, Zhang X, et al. (2013) Antiviral therapy decreases viral reactivation in patients with hepatitis B virus-related hepatocellular carcinoma undergoing hepatectomy: a randomized controlled trial. Journal of Viral Hepatitis 20: 336–342.