

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7193-edited.doc).

Title: Impact of Antiviral Therapy on Post-Hepatectomy Outcome for Hepatitis B-Related Hepatocellular Carcinoma

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 7193

The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated

2. Revision has been made according to the suggestions of the reviewer

- (1) **“How many HCC patients will be really benefited from antiviral therapy? According to a prospective cohort study the authors cited, about 10 (6.1%) patients (of whom eight did not receive antiviral therapy prior to operation) among 164 developed HBV reactivation within one month of hepatic resection [16]. HBV reactivation was more common among those who were not receiving antiviral therapy (21%) compared with those who were (1.6%). Does this mean only a small part of HBV-related HCC patients will be benefited from antiviral therapy.”**

Answer:

The beneficial of roles of antiviral therapy may be more than reducing peri-operative HBV reactivation. From a recent meta-analysis, the potential beneficial effects of anti-viral therapy with nucleotide analogues after liver resection include lower tumor recurrence, HCC-related mortality, liver-related mortality and overall survival, in addition to the reduction in death secondary to liver failure, which is possibly secondary to HBV reactivation.

Reference:

Wong JS, Wong GL, Tsoi KK, Wong VW, Cheung SY, Chong CN, Wong J, Lee KF, Lai PB, Chan HL. Meta-analysis: the efficacy of anti-viral therapy in prevention of recurrence after curative treatment of chronic hepatitis B-related hepatocellular carcinoma. *Aliment Pharmacol Ther* 2011; **33**: 1104-1112 [PMID: 21488914]

- (2) **“Is there any difference on HCC recurrence and overall survival between the patients who receive prophylactic antiviral therapy and the patients who receive antiviral therapy after HBV reactivation within one month of hepatic resection. Considering the benefit-cost ratio, whether or not all HBV-related HCC patients need antiviral therapy before hepatectomy.”**

Answer:

Although the benefit of antiviral therapy on HCC recurrence and overall survival has been demonstrated by a number of studies including 2 meta-analyses, no subgroup analysis on prophylactic antiviral therapy vs early post-operative antiviral therapy has been performed. Our group is performing an analysis on this issue. Hopefully the results would be available in the near future. Concerning the routine prophylactic antiviral therapy, it is recommended from the currently available evidences. However, studies on the cost-effectiveness of routine prophylactic antiviral therapy are lacking.

References:

1. **Miao RY**, Zhao HT, Yang HY, Mao YL, Lu X, Zhao Y, Liu CN, Zhong SX, Sang XT, Huang JF. Postoperative adjuvant antiviral therapy for hepatitis B/C virus-related hepatocellular carcinoma: A meta-analysis. *World J Gastroenterol* 2010; **16**: 2931-2942 [PMID: ISI:000279034500014]
2. **Wong JS**, Wong GL, Tsoi KK, Wong VW, Cheung SY, Chong CN, Wong J, Lee KF, Lai PB, Chan HL. Meta-analysis: the efficacy of anti-viral therapy in prevention of recurrence after curative treatment of chronic hepatitis B-related hepatocellular carcinoma. *Aliment Pharmacol Ther* 2011; **33**: 1104-1112 [PMID: 21488914]
3. **Dan JQ**, Zhang YJ, Huang JT, Chen MS, Gao HJ, Peng ZW, Xu L, Lau WY. Hepatitis B virus reactivation after radiofrequency ablation or hepatic resection for HBV-related small hepatocellular carcinoma: a retrospective study. *Eur J Surg Oncol* 2013; **39**: 865-872. doi: 10.1016/j.ejso.2013.03.020. Epub 2013 Apr 15 [PMID: 23597497]
4. **Huang G**, Lai EC, Lau WY, Zhou WP, Shen F, Pan ZY, Fu SY, Wu MC. Posthepatectomy HBV reactivation in hepatitis B-related hepatocellular carcinoma influences postoperative survival in patients with preoperative low HBV-DNA levels. *Ann Surg* 2013; **257**: 490-505. doi: 10.1097/SLA.0b013e318262b218 [PMID: 22868358]

- (3) **“The mechanisms underlying perioperative reactivation should be highlighted.”**

Answer:

The mechanisms underlying perioperative reactivation is elaborated more under the section of “Impact of Antiviral Therapy on Perioperative HBV Reactivation”

- (4) **“Too much space is spent on "Antiviral therapy for chronic hepatitis B" that should be dismissed.”**

“Please comment on HBV treatment modalities (especially use of types nucleoside analogues and IFN) in cirrhotic patients (decompensation etc) who are a substantial part of this patient collective.”

Answer: The section of "Antiviral therapy for chronic hepatitis B" has been revised to cover comments from other reviewers.

- (5) **“It is not critical enough - there is not enough discussion of how Hepatitis B impact Post-Hepatectomy Outcome for HCC, which part should be included in this review.”**

Answer:

"How Hepatitis B impact Post-Hepatectomy Outcome for HCC" is elaborated more under the "Introduction".

- (6) **"How was the literature selected, referenced in this review? Please include a Methods section"**

Answer: "Method" section had been added.

- (7) **"The term "hepatectomy" might be misleading and could be understood in the context of liver transplantation. I suggest it may be changed to "liver resection"."**

Answer: To avoid confusion, "hepatectomy" has been changed to "liver resection" as much as possible, except in the keywords and title due to word limit.

- (8) **"Table 1 should include also information on the applied antiviral compounds."**

Answer: Table 1 has been revised.

3. References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



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