The effects of pre-surgical antiviral therapy among patients with hepatitis B-related hepatocellular carcinoma: A meta-analysis

Canseco LML
Babaran HM
Cuaño CRG
Sunglao JCL
Salvaña AD

Section of Gastroenterology
Department of Medicine
University of the Philippines-Philippine General Hospital
Manila, Philippines

Correspondence:
Dr. Lariza Marie L. Canseco at lariza.canseco@gmail.com

Accepted for publication:
December 2019

Abstract

Significance: Liver cancer is the second most common cause of cancer-related deaths worldwide. Current guidelines recommend surgical resection for non-cirrhotic hepatitis B-related hepatocellular carcinoma (HCC) patients, with studies supporting the use of antiviral therapy post-surgery prior to anticancer treatment and immunosuppressive therapy. Data on pre-surgical antiviral therapy however, is less clear-cut. This study investigates the overall survival, disease-free survival and viral reactivation of early antiviral treatment prior to hepatectomy. Included studies were those hepatitis B-related HCC patients at least 18 years old with curative resection as primary form of treatment, comparing with and without pre-surgical antiviral therapy, and with data on viral recurrence or survival. Excluded were those positive for other viral hepatitis or HIV co-infection, and with HCC therapy other than hepatectomy. *Results:* Four studies selected had a pooled sample of 833 – 417 in the antiviral arm and 416 in the control arm. Patients given nucleoside analogues prior to liver resection have significantly reduced risk of viral reactivation compared to control subjects with relative risk of 0.12 (95% CI, 0.04-0.36). For the 1-, 3- and 5-year disease-free survival, treatment with nucleoside analogues prior to surgery shows a trend towards increased survival rate with risk ratios of 1.23, 1.18 and 1.13, respectively. There is significant increase in overall survival among those given nucleoside analogues prior to hepatectomy with risk ratios at 1.11, 1.26 and 1.17, respectively. *Conclusion:* For chronic hepatitis B-related HCC patients, giving nucleoside analogues prior to liver resection significantly decreases viral reactivation and improves disease-free and overall survival.

Keywords: chronic hepatitis B, hepatocellular carcinoma, meta-analysis, liver resection, nucleoside analogues

Introduction

In the study done by Akinyemiju et al., there was a 75% increase in the global incidence of liver cancer between 1990 and 2015.[1] Currently, liver cancer is the second most common cause of cancer-related deaths, majority of which is of the hepatocellular carcinoma (HCC) type and is seen predominantly in East Asia followed by the Asia Pacific region. Among the top contributory factors include the virus Hepatitis B and C.

The annual incidence of HCC from chronic hepatitis B is at one percent for non-cirrhotics and 2-3% for cirrhotics, based on the Asian Pacific Association for the Study of the Liver (APASL) Update 2015.[2] The latest European Association for the Study of the Liver (EASL) 2018 Guidelines recommends surgical resection as the treatment of choice for non-cirrhotic HCC patients. Five-year survival rate was estimated at 60-80% for well-selected candidates who will undergo surgical management.[3]

Significant mortality in patients with HCC is attributed to tumor recurrence; hence, maintaining remission of active hepatitis through nucleoside analogues may seem beneficial.[4] Several studies have shown favorable outcomes for hepatitis B-related HCC

patients given nucleoside analogues after surgery. Huang et al. noted a significantly lower incidence of HBV reactivation in the perioperative period among patients given anti-nucleosides after hepatectomy (2.9%) versus those who did not receive antivirals (31.8%).[5] In terms of overall survival, antivirals likewise showed a more favorable outcome compared to the non-antiviral group.[6] A meta-analysis by Sun et al. in 2014 showed that after curative treatment either through resection, radiofrequency ablation (RFA), percutaneous ethanol injection (PCEI) or cryoablation plus RFA, nucleoside analogues led to an increased recurrence-free survival and overall survival among patients with hepatitis B-related HCC.[7] This was likewise found in the meta-analysis of Zhou et al., which showed that patients given nucleoside analogues with resultant HBV DNA suppression had decreased recurrence of HCC among patients who underwent liver resection.[8] The American Association for the Study of Liver Diseases 2018 recommends prophylactic antiviral therapy, particularly entecavir and tenofovir, prior to anticancer treatment and immunosuppressive therapy for chronic hepatitis B, regardless of HBV DNA level, as this leads to mortality and reactivation reduction.[9]

The role of pre-surgical treatment of chronic hepatitis B is less clear-cut. This study investigates the benefits of early antiviral treatment prior to hepatectomy among patients with hepatitis-B related HCC in terms of overall survival, disease-free survival and viral reactivation.

Methods

Literature Search

A systematic literature search was done using electronic database (PubMed, Cochrane, and EMBASE) without language restrictions using the following terms: *nucleoside analogues*, *chronic hepatitis B*, *hepatocellular carcinoma*, *entecavir*, *tenofovir*, *adefovir*, *lamivudine*, *telbivudine*, *liver resection*, *hepatectomy*, *viral reactivation*, *overall survival*, and *disease-free survival*. Only studies on humans were included. Reference lists of associated papers were manually checked for additional articles.

Inclusion and Exclusion Criteria

Criteria for inclusion of researches were as follows: (1) studies dealing with 18-year-old patients diagnosed with hepatitis B-related HCC and curative resection as primary form of treatment; (2) with or without pre-surgical antiviral therapy; and (3) with data on viral recurrence or survival on follow-up. Exclusion criteria were as follows: (1) co-infection with other viral hepatitis or HIV; and (2) main form of therapy for HCC other than hepatectomy. **Figure 1** shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of this study.

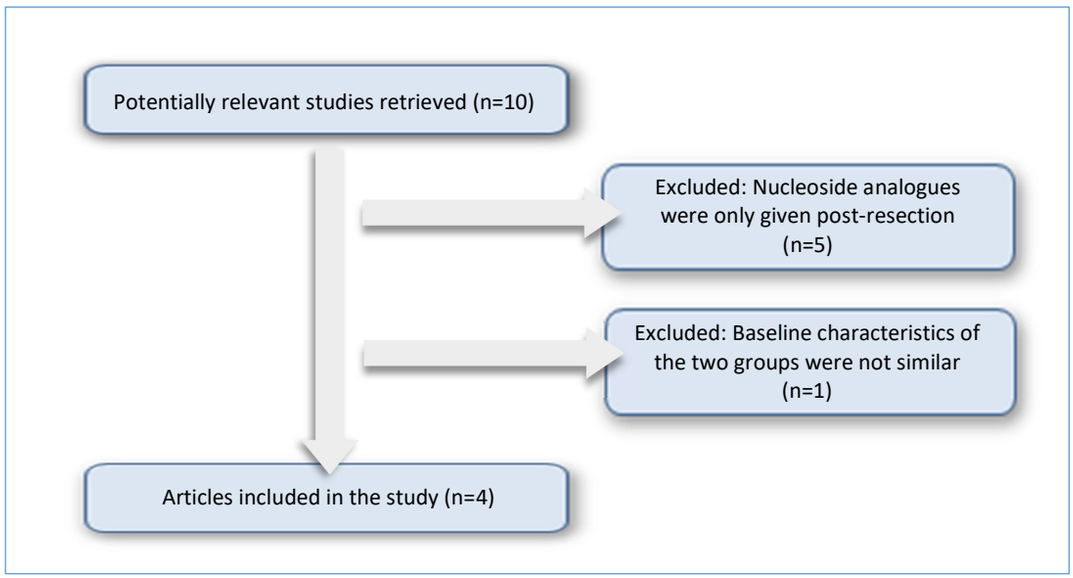


Figure 1. PRISMA flow diagram for selection of studies

Data extraction

Two authors independently screened the studies in accordance with the set inclusion and exclusion criteria. All studies were evaluated for methodological quality. Disagreements were resolved through a third author by consensus.

Statistical analysis and synthesis

Relevant data were compared and analyzed using Review Manager (RevMan) 5.3 software. Dichotomous outcomes were combined using risk ratios (RR). Chi-squared (Chi^2) test was used to detect heterogeneity ($P > 0.10$) and the I-squared (I^2) statistic was used to determine magnitude of heterogeneity, with $I^2 < 25\%$ indicating minimal heterogeneity, 25-50% moderate and > 50% substantial heterogeneity, respectively.

Results

Eligible Studies

Four studies met the inclusion and exclusion criteria, with a pooled sample population of 833 patients having 417 in the antiviral arm and 416 under the control arm. Overall survival was the primary outcome in the study by Chong[6] and Sakamoto[10], while HBV reactivation was analyzed by Dan[11] and Gong.[12] In the study by Chong and Sakamoto, data was available for both pre- and post-resection treatment arms. All studies used liver resection as primary curative intervention, with the study by Dan including RFA. All studies were assessed as low risk for bias. **Table 1** shows the characteristics of included studies.

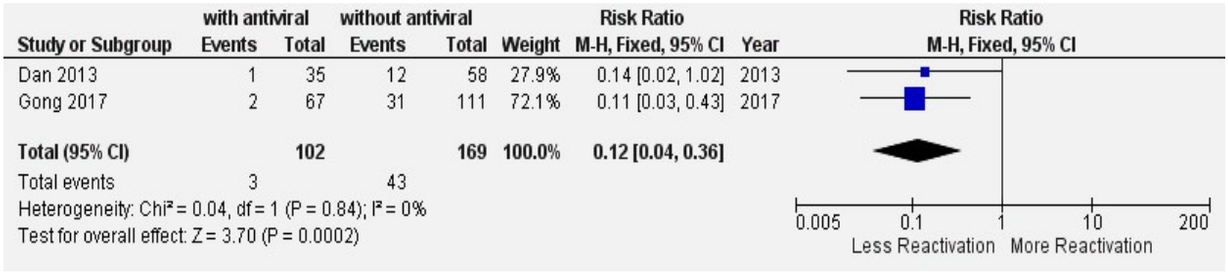
Table 1. Characteristics of studies included in the meta-analysis

Author Year	N	Population	Exposure	Outcome	Study Design
Dan 2013	93	HBV-related HCC	Lamivudine or Adefovir or Entecavir versus no antiviral	HBV reactivation	Retrospective August 2006 to August 2011
Chong 2015	404	HBV-related HCC; Antiviral = 254 (pre-resection 97, post-resection 157); No antiviral = 150	Entecavir or Lamivudine or Adefovir or Tenofovir or Telbivudine and a combination of Adefovir and Lamivudine versus no antiviral	1-, 3-, 5-year disease-free survival; 1-, 3-, 5-year overall survival	Prospective (February 2010 to June 2012); Retrospective (January 1999 to February 2010)
Sakamoto 2015	162	HBV-related HCC; Antiviral = 62 (pre-resection 24, post-resection 38); No antiviral = 100	Lamivudine or Lamivudine plus Adefovir or Lamivudine switched to Entecavir or Entecavir versus no antiviral	1-, 3-, 5-year disease-free survival; 1-, 3-, 5-year overall survival	Prospective cohort (January 2001 to March 2012)
Gong 2017	174	HBV-related HCC	Entecavir versus no antiviral	HBV reactivation	Prospective (July 2012 to June 2016)

Viral Reactivation

Patients who were given nucleoside analogues prior to liver resection had a significantly reduced risk of viral reactivation (RR 0.12, 95% CI 0.04-0.36), compared to the control group. Heterogeneity was absent in the two studies (I^2= 0%). The results are summarized in **Table 2**.

Table 2. Forest plot of studies involving viral reactivation



Disease-Free Survival

Treating with nucleoside analogues prior to surgery showed a trend towards increased disease-free survival rate with RR of 1.23, 1.18 and 1.13, respectively. Studies were homogeneous as well (I^2 = 0%). Studies by Sakamoto and Chong presented 1-, 3- and 5-year disease-free survival as shown in **Tables 3**, **4** and **5**.

Table 3. Forest plot of studies involving 1-year disease-free survival

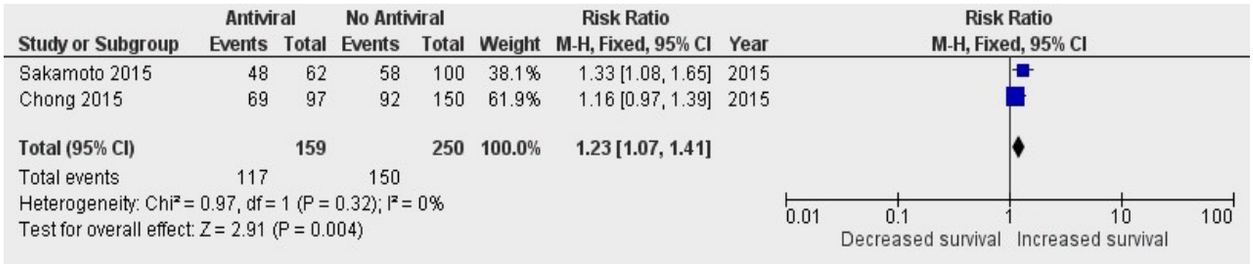


Table 4. Forest plot of studies involving 3-year disease-free survival

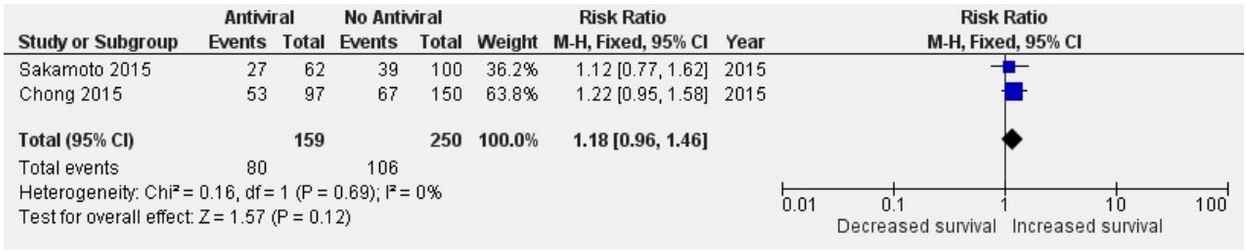
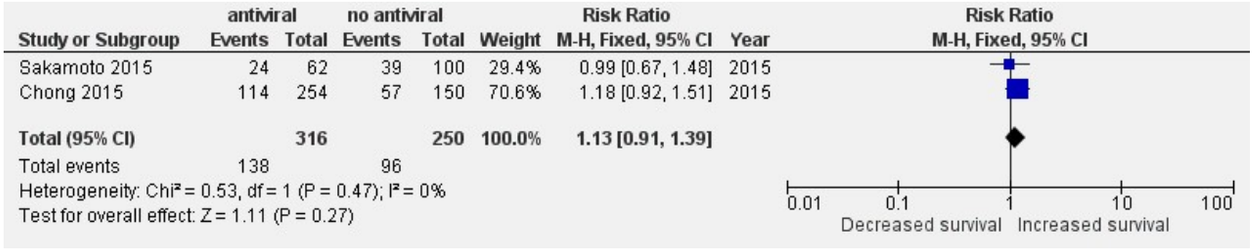


Table 5. Forest plot of studies involving 5-year disease-free survival



Overall Survival

Tables 6-**8** present increased overall survival at 1, 3, and 5 years, among patients given nucleoside analogues prior to hepatectomy with risk ratios at 1.11, 1.26 and 1.17, respectively. Studies did not show heterogeneity at five years (I^2= 0%) but were noted to be moderate and substantial at one year (I^2= 23%) and three years (I^2= 68%), respectively.

Table 6. Forest plot of studies involving 1-year overall survival

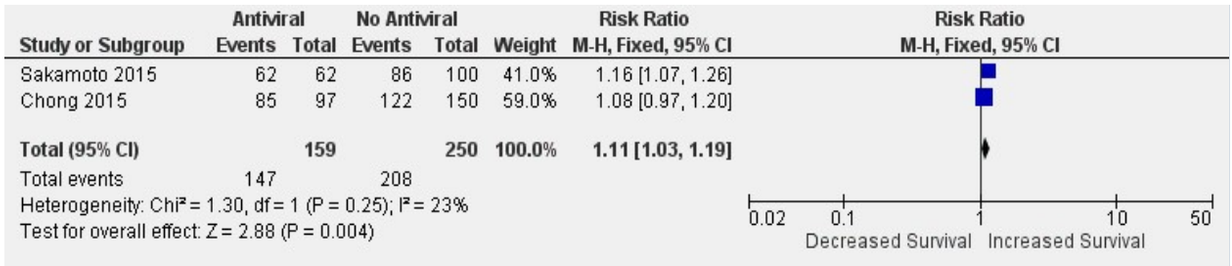


Table 7. Forest plot of studies involving 3-year overall survival

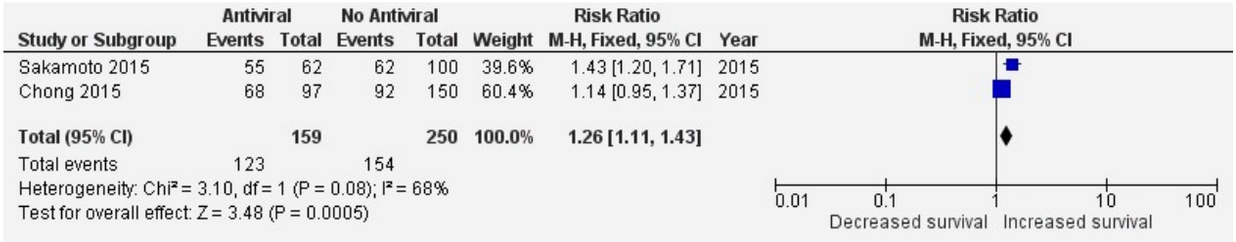
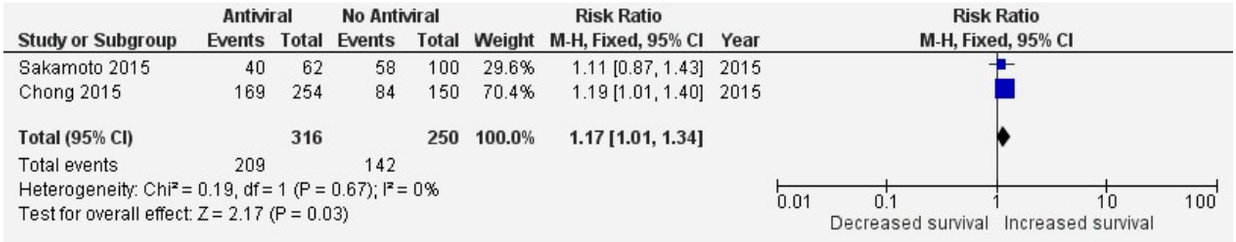


Table 8. Forest plot of studies involving 5-year overall survival



Discussion

Chronic hepatitis B can progress to hepatocellular carcinoma directly by modifying the expression of oncogenes and tumor suppressor genes through the incorporation of HBV DNA into the genome and indirectly by persistent hepatic injury leading to apoptosis and necroinflammation,[13] thus, targeting viral suppression can lead to HCC prevention. In addition, Huang et al. noted that undetectable HBV DNA by week 24 post-surgery is an important positive predictor of both disease-free and overall survival for hepatitis B-related HCC.[14]

HBV reactivation has been associated with pre-operative elevated levels of HBV DNA and alanine aminotransferase, hepatitis B core antigen and wild-type DNA, elements seen in the immune clearance phase of hepatitis B infection.[15] On the other hand, post-surgery reactivation is attributed to the augmented viral replication secondary to the

immunosuppression brought about by liver resection.[15,16] One article showed viral reactivation in up to 6.1% of hepatitis B-related HCC patients after partial hepatectomy.[4] In our study, we have shown a significant viral reactivation risk reduction by 88% for those given anti-nucleosides prior to surgery. Other studies have presented similar results. Dan et al. noted a reduction in incidence of viral reactivation among those who received antinucleosides prior to hepatectomy (2.9%) compared to those who did not (20.7%).[11] Even for patients with low viral load baseline, there was a marked difference in viral reactivation, with 2.9% in those who received pre-op antinucleosides, and 31.8% in those who did not.[4] Another study exhibited a nine-fold decrease in the occurrence of reactivation one month post-surgery; hence, they recommended the giving of prophylactic antivirals before and immediately after surgery.[12]

Our study likewise exhibits a significant 1-, 3-, and 5-year overall survival for chronic hepatitis B-related HCC patients given nucleoside analogues prior to liver resection. Though there is a favorable trend in terms of disease-free survival, it is not shown to be significant at 1, 3 and 5 years. These findings could be attributed to the nucleoside analogues' effect in improvement in liver function. Similarly, Chong et al. showed a significant higher overall survival in the antiviral group with no statistical difference in terms of disease-free survival. In addition, among those who developed recurrence, patients given antinucleosides were noted to have better liver function reserves and were more eligible to undergo curative therapy for the recurrence, such as re-hepatectomy, RFA or microwave ablation.[6] Aside from early tumor recurrence, microvascular invasion was likewise reduced for patients given antiviral treatment three months prior to surgery in Li's study.[17]

In our study, limitations include the non-uniformity of nucleoside analogues given prior to hepatic resection. Some of the cases received more than one nucleoside analogue while others were noted to shift to another antiviral during the study period. HBV genotyping which were not explicitly mentioned in the included studies might also affect the response of the patients to the antivirals given.

Conclusion

For chronic hepatitis B-related HCC patients, giving nucleoside analogues prior to liver resection significantly decreases viral reactivation and improves disease-free and overall survival. Given this evidence, the authors recommend that these should be given to such patients before hepatectomy. Furthermore, we recommend that this be included in the upcoming guidelines for managing HCC patients.

Acknowledgement

The authors would like to acknowledge the assistance of Dr. Janus Ong in the conceptualization of this research.

Conflicts of Interest

The authors declare no conflicts of interest or financial disclosures.

References

1. Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, Allen C, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level. JAMA Oncol. 2017; 3:1683–1691.
2. Asian-Pacific Clinical Practice Guidelines on the Management of Hepatitis B: A 2015 update. Hepatol Int. 2016; 10:1-98.
3. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. Journal of Hepatology. 2018; vol. 69 j: 182-236.
4. Wei Q, Xu X, Ling Q, Zhou B, and Zheng SS. Perioperative antiviral therapy for chronic hepatitis B-related hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int. 2013 Jun; 12(3):251-5.
5. Huang L, Li J, Yan J, Sun J, Zhang X, Wu M, and Yan Y. Antiviral therapy decreases viral reactivation in patients with hepatitis B virus-related hepatocellular carcinoma undergoing hepatectomy: A randomized controlled trial. Journal of Viral Hepatitis. 2013; 20:336-342.
6. Chong CC, Wong GL, Wong VW, Ip PC, Cheung YS, Wong J, Lee KF, Lai PB, and Chan HL. Antiviral therapy improves post-hepatectomy survival in patients with hepatitis B virus-related hepatocellular carcinoma: A prospective-retrospective study. Aliment Pharmacol Ther. 2015 Jan; 41(2): 199-208. doi: 1111/apt.13034. Epub 2014 Nov 21.
7. Sun P, Dong X, Cheng X, Hu Q, and 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. 2014; 9(7): e102761. doi:10.1371/journal.pone.0102761.
8. Zhou Y, Zhang Z, Zhao Y, Wu L, and Li B. Antiviral therapy decreases recurrence of hepatitis B virus-related hepatocellular carcinoma after curative resection: A meta-

analysis. World J Surg. 2014 Sept; 38(9):2395-402. doi: 10.1007/s00268-014-2586-z.

9. AASLD Guidelines for the Treatment of Hepatocellular Carcinoma. Hepatology. 2018; vol. 67 no. 1.
10. Sakamoto K, Beppu T, Hayashi H, Nakagawa S, Okabe H, Nitta H, et al. Antiviral Therapy and Long-term Outcome for Hepatitis B Virus-related Hepatocellular Carcinoma after Curative Liver Resection in a Japanese Cohort. Anticancer Research. 2015; 35: 1647-1656.
11. Dan JQ, Zhang YJ, Huang JT, Chen MS, Gao HJ, Peng ZW, et al. Hepatitis B virus reactivation after radiofrequency ablation or hepatic resection for HBV-related small hepatocellular carcinoma: A retrospective study. Eur J Surg Oncol. 2013 Aug; 39(8): 865-72.
12. Gong WF, Zhong JH, Lu SD,Wang XB, Zhang QMm Ma L, et al. Effects of antiviral therapy on post-hepatectomy HBV reactivation and liver function in HBV DNA-negative patients with HBV-related hepatocellular carcinoma. Oncotarget. 2017; vol. 8(9):15047-15056.
13. Fung, James and Kenneth S.H. Chok. The role of oral antiviral therapy in hepatitis B-related hepatocellular carcinoma. Hepatoma Res. 2017; 3:284-93.
14. Huang G, Yang Y, Shen F, Pan ZY, Fu SY, Lau WY, et al. Early viral suppression predicts good postoperative survivals in patients with hepatocellular carcinoma with a high baseline HBV-DNA load. Ann Surg Oncol. 2013; 20:1482-1490. doi 10.1245/s10434-012-2803-7.
15. Lalazar G, Rund D, and Shouval D. Screening, prevention and treatment of viral hepatitis B reactivation in patients with haematological malignancies. British Journal of Haematology. 2006; 136:699-712 doi:10.1111/j.1365-2141.2006.06465.
16. Kubo S, Nishiguchi S, Hamba H, Hirohashi K, Tanaka H, Shuto T, et al. Reactivation of viral replication after liver resection in patients infected with hepatitis B virus. Ann Surg. 2001; 233(1) 139-145.
17. Li Z, Lei Z, Xia Y, Li J, Wang K, Zhang H, et al. Association of preoperative antiviral treatment with incidences of microvascular invasion and early tumor recurrence in hepatitis B virus-related hepatocellular carcinoma. JAMA Surg. 2018 Oct 1; 153(10): e1882721. doi:10.1001/jamasurg.2018.2721.Epub 2018 Oct 17.