Survival impact of additional induction chemotherapy in nasopharyngeal carcinoma with chronic hepatitis B infection: a retrospective, bi-center study

Haojiang Li¹#, Mingyang Chen²,³#, Shuqi Li¹#, Chao Luo¹#, Xuemin Qiu¹, Guangying Ruan¹, Yanping Mao⁴, Guoyi Zhang⁵, Lizhi Liu¹,⁶

¹Department of Medical Imaging, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Sun Yat-sen University Cancer Center, Guangzhou, China; ²Sun Yat-sen University, Guangzhou, China; ³School of Population Medicine and Public Health, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; ⁴Department of Radiation Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China; ⁵Department of Radiation Oncology, Foshan Academy of Medical Sciences, the First People’s Hospital of Foshan & Sun Yat-sen University Foshan Hospital, Foshan, China; ⁶Department of Radiology, The Third People’s Hospital of Shenzhen, Shenzhen, China

Contributions: (I) Conception and design: L Liu, G Zhang, H Li, Y Mao; (II) Administrative support: L Liu, G Zhang, G Ruan; (III) Provision of study materials or patients: H Li, M Chen, S Li, C Luo; (IV) Collection and assembly of data: H Li, M Chen, S Li, C Luo, G Ruan, X Qiu; (V) Data analysis and interpretation: H Li, M Chen, S Li, C Luo; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

# These authors contributed equally to this work.

Correspondence to: Lizhi Liu, PhD. Department of Radiology, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou, Guangdong 510060, China. Email: liulizh@sysucc.org.cn; Guoyi Zhang, PhD. Department of Radiation Oncology, Foshan Academy of Medical Sciences, the First People’s Hospital of Foshan & Sun Yat-sen University Foshan Hospital, Foshan 528000, China. Email: guoyizhf@163.com.

Background: Patients with nasopharyngeal carcinoma (NPC) who have hepatitis B virus (HBV) infection tend to be treated with induction chemotherapy (IC) due to a higher metastasis rate. However, additional IC may lead to immunosuppression and can negatively affect the prognosis. We evaluated whether receiving IC improved the prognosis of patients with NPC co-infected with HBV, on the basis of concurrent chemoradiotherapy (CCRT).

Methods: This large-scale retrospective cohort study included data of patients with pathologically confirmed NPC that were collected from two hospitals between January 2010 and March 2014. Patients were followed-up every 3 months during the first 2 years and once every 6 months thereafter. Univariate analysis identified confounding factors associated with prognosis. Stage-based subgroup analyses and 1:1 random-matched pair analyses were performed to compare the survival differences between patients treated with IC + CCRT and those treated with CCRT alone.

Results: Among the 1,076 enrolled patients, 16.6% were hepatitis B surface antigen (HBsAg)-positive. Among HBsAg-positive patients with stage II/III/IV NPC, distant metastasis-free survival (DMFS) (79.3% vs. 89.9%; P=0.045) and progression-free survival (PFS) (70.6% vs. 83.7%; P=0.025) were lower in patients who received IC + CCRT than in those who received CCRT alone. After adjusting for confounding factors, IC + CCRT was validated as a negative prognosticator for DMFS and PFS, while matched-pair analysis with HBsAg-negative patients showed a better overall survival (OS) for IC + CCRT (88.4% vs. 82.6%; P=0.04).

Conclusions: Compared with CCRT alone, IC + CCRT negatively affects DMFS and PFS in patients with NPC with chronic HBV infection. We advocate withholding IC but administering stronger initial treatment in NPC patients complicated with HBV infection.

Keywords: Nasopharyngeal carcinoma (NPC); hepatitis B virus (HBV); induction chemotherapy (IC); prognosis; retrospective cohort study

Submitted Jan 04, 2022. Accepted for publication May 16, 2022.
doi: 10.21037/atm-22-33

View this article at: https://dx.doi.org/10.21037/atm-22-33
Introduction

Radiotherapy is the main curative treatment for early-stage nasopharyngeal carcinoma (NPC), whereas concurrent chemoradiotherapy (CCRT) is crucial for treating locoregionally advanced NPC (LANPC) (1). Based on the survival benefit, especially in distant control as shown in several multicenter phase III trials (2-5), IC + CCRT is recommended as standard of care for the majority of NPC patients in the National Comprehensive Cancer Network (NCCN) guidelines and strongly recommended by Chinese Society of Clinical Oncology (CSCO) and American Society of Clinical Oncology (ASCO) guidelines (1,6). However, not all patients with NPC benefit from this therapy (7,8). Furthermore, considering the side effects, time, and economic cost of IC, many researchers have screened for biomarkers to optimize clinical decision-making (9-14). Serological hepatitis B surface antigen (HBsAg) is an important indicator of hepatitis B virus (HBV) infection, but whether HBsAg can be used as a reference factor in the choice of IC remains unclear.

China has the world's highest HBV infection rate (15-17), with a prevalence of more than 10% in eight cities, including Guangdong and Guangxi (18). The rate of HBsAg-positive [HBsAg(+)] in patients with NPC is 15.75%, which exceeds the infection rate in endemic areas (18). Thus, these patients may need more accurate treatment, but discouragingly, the NCCN guidelines on the management of these patients are incomplete. Chronic HBV infection is reportedly an independent adverse prognostic factor in patients with NPC (19-21). The distant metastasis risk is 3.7 times higher in HBV-positive than in HBV-negative patients (21). Per a clinical conjecture, IC should be administered in patients with a high risk of metastasis (3). However, whether IC benefits survival in patients with NPC co-infected with HBV is unclear and needs further investigation.

To date, only Zhang et al. have investigated the effectiveness of IC + CCRT in patients with both NPC and chronic HBV infection using propensity score matching (PSM); their results indicate no statistically significant survival differences between IC + CCRT and CCRT (22). Probable immunosuppression induced by additional chemotherapy may lead to HBV reactivation (HBVr) and cause liver damage, which may compromise the therapeutic effect and negatively affect the prognosis (23). HBVr is considered a clinical dilemma during chemotherapy in many tumor types (24). However, a small sample size, selection bias in patient enrollment, and residual confounding factors that cannot be eliminated by PSM may lead to negative results. NPC patients with HBV infection tend to receive IC due to a high metastasis rate; however, as IC also leads to immunosuppression and negatively affects the prognosis, in-depth studies are warranted to determine the value of IC therapy in these patients.

In this study, we retrospectively studied 1,076 pathologically confirmed NPC patients with HBsAg status. Subgroup analysis and random-matched pair experiment were used to study the relationship between additional IC and patients’ survival. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-33/rc).

Methods

Patients

This study enrolled 1,076 new pathologically confirmed NPC patients who were treated at the Sun Yat-sen University Cancer Center (SYSUCC) between January 2010 and January 2013, and at Foshan First People’s Hospital between April 2010 and March 2014. The study's inclusion criteria were: (I) pathology-based diagnosis of NPC; (II) complete clinical data and medical records; (III) complete magnetic resonance images of the nasopharynx and neck regions; and (IV) treatment with intensity-modulated radiation therapy. The exclusion criteria were: (I) distant metastasis and other tumor types at the first diagnosis and (II) incomplete data for plasma Epstein-Barr virus (EBV) DNA level and HBsAg status. All enrolled patients were followed-up every 3 months during the first 2 years and once every 6 months thereafter. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the committee of the Institutional Review Boards at the SYSUCC (Approval number: B2019-222) and individual consent for this retrospective analysis was waived.

Data Collection

All patients underwent a complete pretreatment evaluation and were restaged using the eighth American Joint Committee on Cancer TNM staging manual according to the clinical examinations, fiberoptic nasopharyngoscopy, and imaging technologies (25). All the patients in our study were tested for hepatitis B virus by enzyme-linked
immunosorbent assay (ELISA) at the first visit. Liver function tests were also performed before chemotherapy, including alanine transaminase (ALT) and aspartate aminotransferase (AST). Patients with HBsAg positive (>0.05 IU/mL) were considered as having HBV infection. For detailed HBV-related treatment and liver function information, the interested reader can find them in Appendix 1. Plasma EBV DNA level was detected using a quantitative polymerase chain reaction. Plasma EBV DNA level was classified as a categorical variable according to previously published articles (26). All patients were treated based on the treatment principle for NPC at the SYSUCC and Foshan First People’s Hospital (Appendix 1).

Statistical analyses

First, baseline characteristics between HBsAg(+) and HBsAg(−) patients were categorized. Differences between the two hospitals in baseline characteristics were calculated using Fisher’s exact test, Chi-square test, and Student’s t-test (Fisher’s exact test, Chi-square test are used for qualitative variables, Student’s t-test is for quantitative variables). Second, univariate analysis with a log-rank test identified confounding variables associated with prognosis. Thereafter, subgroup analysis for stages II/III/IV, III/IV, and II was performed in NPC patients with HBsAg(+) or HBsAg(−) status, and Kaplan–Meier survival curves with the log-rank test were used to calculate the 5-year survival differences between the CCRT and IC + CCRT groups. Hazard ratios (HRs) and P values were calculated using multivariate Cox regression analysis. Finally, a 1:1 random-matched pair experiment was performed using the T and N classification to further eliminate some unknown confounding variables. Kaplan–Meier survival curves, HRs, and adjusted P values were calculated for each pair.

All statistical analyses were performed using packages from R (version 3.2.5, https://www.r-project.org/), such as stats, survival, Hmisc, ggplot2, and survminer. Two-tailed P values ≤0.05 were considered statistically significant.

Results

Participants

A total of 1,076 patients were enrolled (the flowchart of study enrollment is showed in Figure 1), 179 patients (16.6%) had concurrent chronic HBV infection. HBsAg(+) patients were two years younger than HBsAg(−) patients (median, 46 vs. 44 years; P=0.032). Increased proportions of alanine transaminase (15.1% vs. 5.8%; P<0.001) and aspartate transaminase (10.6% vs. 2.9%; P<0.001) were observed in HBsAg(+) patients compared with HBsAg(−) patients. Other characteristics, such as sex, histologic type, plasma EBV DNA level, T classification, N classification, stage, tumor volume, and treatment modalities were well-balanced between the two groups (Table 1). There were significant differences in age, histologic type, plasma EBV DNA level,
Table 1 Clinical characteristics of HBsAg(+) patients versus HBsAg(−) patients with nasopharyngeal carcinoma

| Variables                  | Total patients (N=1,076) | HBsAg(−) (N=897) | HBsAg(+) (N=179) | P value‡ |
|---------------------------|--------------------------|------------------|------------------|----------|
| Age (years), median (IQR) | 46.0 (38.0–55.0)         | 46 (38.0–55.0)   | 44 (37–51.5)     | 0.032*   |
| Sex                       |                          |                  |                  |          |
| Male                      | 799 (74.3%)              | 656 (73.1%)      | 143 (79.9%)      |          |
| Female                    | 277 (25.7%)              | 241 (26.9%)      | 36 (20.1%)       |          |
| Histological type         |                          |                  |                  | 0.521    |
| WHO type 1/2              | 41 (3.8%)                | 36 (4%)          | 5 (2.8%)         |          |
| WHO type 3                | 1.035 (96.2%)            | 861 (96%)        | 174 (97.2%)      |          |
| Plasma EBV DNA level (10^3 copy/mL) |                  |                  |                  | 0.967    |
| <1                        | 482 (44.8%)              | 402 (44.8%)      | 80 (44.7%)       |          |
| <10                       | 337 (31.3%)              | 282 (31.4%)      | 55 (30.7%)       |          |
| ≥10                       | 257 (23.9%)              | 213 (23.7%)      | 44 (24.6%)       |          |
| T classification‡         |                          |                  |                  | 0.065    |
| T1                        | 205 (19.1%)              | 173 (19.3%)      | 32 (17.9%)       |          |
| T2                        | 150 (13.9%)              | 129 (14.4%)      | 21 (11.7%)       |          |
| T3                        | 429 (39.9%)              | 342 (38.1%)      | 87 (48.6%)       |          |
| T4                        | 292 (27.1%)              | 253 (28.2%)      | 39 (21.8%)       |          |
| N classification‡         |                          |                  |                  | 0.269    |
| N0                        | 143 (13.3%)              | 112 (12.5%)      | 31 (17.3%)       |          |
| N1                        | 655 (60.9%)              | 555 (61.9%)      | 100 (55.9%)      |          |
| N2                        | 189 (17.6%)              | 158 (17.6%)      | 31 (17.3%)       |          |
| N3                        | 89 (8.3%)                | 72 (8%)          | 17 (9.5%)        |          |
| Stage‡                    |                          |                  |                  | 0.115    |
| II                        | 264 (24.5%)              | 225 (25.1%)      | 39 (21.8%)       |          |
| III                       | 447 (41.5%)              | 360 (40.1%)      | 87 (48.6%)       |          |
| IV                        | 365 (33.9%)              | 312 (34.8%)      | 53 (29.6%)       |          |
| Chemotherapy              |                          |                  |                  | 0.242    |
| CCRT                      | 480 (44.6%)              | 393 (43.8%)      | 87 (48.6%)       |          |
| IC + CCRT                 | 596 (55.4%)              | 504 (56.2%)      | 92 (51.4%)       |          |
| IMRT times                |                          |                  |                  | 0.141    |
| Median (IQR)              | 32 (30.0–33.0)           | 32 (30.0–33.0)   | 32 (30.0–33.0)   |          |
| IC times                  |                          |                  |                  | 0.099    |
| 0                         | 480 (44.6%)              | 393 (43.8%)      | 87 (48.6%)       |          |
| 2                         | 318 (29.6%)              | 261 (29.1%)      | 57 (31.8%)       |          |
| 3                         | 251 (23.3%)              | 217 (24.2%)      | 34 (19%)         |          |
| 4                         | 27 (2.5%)                | 26 (2.9%)        | 1 (0.6%)         |          |

Table 1 (continued)
and N classification between patients from both hospitals, but no statistically significant differences were observed in terms of stage, treatment mode, and HBsAg(±) status (Table S1). In this study cohort of 1706 patients, the median age was 46 [interquartile range (IQR) 38–54] years and the median follow-up was 61.8 (IQR 1.3–99.1) months. During the follow-up period, 13.8% (235/1,706) of patients died within five years. The overall 5-year overall survival (OS), distant metastasis-free survival (DMFS), local recurrence-free survival (LRFS), and progression-free survival (PFS) were 85.5%, 86.3%, 89.9% and 76.8%, respectively.

The following results were obtained in the univariate analysis: stage was significantly associated with all endpoints; age was significantly associated with OS and PFS; plasma EBV DNA level was significantly associated with OS, DMFS, and PFS; and chemotherapy was significantly associated with DMFS and PFS (Table S2). No statistically significant prognostic difference was observed in the alanine aminotransferase and aspartate transaminase levels (all P>0.05). These statistically significant factors were subsequently studied in multivariate analysis. In the NPC patients, we found that stage and plasma EBV DNA level, independent factors for survival outcomes, had no statistical predictive value in patients with NPC that were HBsAg(+) (this table will be provided if necessary).

**HBsAg(+) patients failed to benefit from IC**

In cases of HBsAg(+) patients with stage II/III/IV NPC, IC + CCRT resulted in poorer DMFS (79.3% vs. 89.9%; P=0.045) and PFS (70.6% vs. 83.7%; P=0.025) than in those with CCRT alone (Figure 2A,2B), and a similar trend was observed for OS and LRFS, although not statistically significant (Figure S1A,S1B). After adjusting for confounding factors, IC + CCRT was an independent negative factor for DMFS (HR: 2.47; 95% CI: 1.04–5.88; P=0.041), and it was weakly independent for PFS (HR: 1.97; 95% CI: 0.98–3.99; P=0.059) (Table S3).

In the subgroup analysis, we analyzed the IC effectiveness in patients with stage III/IV NPC with HBsAg(+). The IC + CCRT group had poorer DMFS (75.3% vs. 89.8%; P=0.022) and PFS (67.3% vs. 83.1%; P=0.018) than that of the CCRT group (Figure 2C,2D). Similar trend was observed for OS and LRFS in III/IV NPC with HBsAg(+) (Figure S1C,S1D). After adjusting for covariates, IC + CCRT was found to be an independent negative factor for DMFS (HR: 3.42; 95% CI 1.30–8.97; P=0.013) and PFS (HR: 2.69; 95% CI: 1.23–5.88; P=0.014) (Table S3). In the subgroup analysis for stage II NPC patients with HBsAg(+), no statistically significant differences were observed in OS, DMFS, LRFS, and PFS when comparing IC + CCRT with CCRT alone (Figure S2).

**Matched-pair analysis**

T and N classifications were used for 1:1 random pair matching, and we identified 69 pairs of HBsAg(+) patients, 296 pairs of HBsAg(−) and 372 pairs of mixed groups. The
Chi-square test determined the distribution of patients receiving CCRT and IC + CCRT in these three groups. The plasma EBV DNA level was significantly higher in the IC + CCRT than in the CCRT group for all pairs [P<0.01 for HBsAg(+) and mixed groups; P=0.034 for HBsAg(−) group]. Patients treated with IC + CCRT were 2 years younger than those treated with CCRT in both HBsAg(−) pairs (median, 45 vs. 47 years; P=0.004) and mixed pairs (median, 45 vs. 47 years; P=0.006). No other difference in distribution was found between the two chemotherapy regimens (Table S4). The metastasis rate in HBsAg(+) patients was 14.5%, which was higher than that in HBsAg(−) patients (10.6%). In the Kaplan-Meier analysis, HBsAg(+) patients treated with IC + CCRT had poorer DMFS (78.7% vs. 90.4%; P=0.048) and PFS (69.9% vs. 85.3%; P=0.018) than HBsAg(−) patients. Furthermore, the multivariate analysis demonstrated that IC + CCRT was an independent adverse factor for DMFS (HR: 2.71; 95% CI: 1.01–7.24; P=0.047) and PFS (HR: 2.29; 95%
CI: 1.01–5.22; P=0.048) in the HBsAg(+) group (Figure 3).
Contrastingly, in HBsAg(−) patients, a statistically significant
difference in OS was observed between the IC + CCRT and
CCRT groups (88.4% vs. 82.6%; P=0.04); however, IC +
CCRT was not an independent positive prognostic factor
for OS in the multivariate analysis (Figure S3). In the mixed
group, no statistically significant difference in survival was
observed in the IC + CCRT and CCRT groups (all P>0.05)
(Figure S4).

Discussion
Here, HBsAg(+) patients with NPC accounted for 16.6%
of all patients, and the metastasis rate in HBsAg(+) patients
was 14.5%, higher than the 10.6% observed in HBsAg(−)
patients. Moreover, the multivariate and matched-pair
analyses indicated that IC + CCRT significantly reduced
the DMFS and PFS compared with CCRT alone in
HBsAg(+) patients with NPC. This trend also existed for
OS and LRFS; however, it was not statistically significant. Conversely, IC + CCRT was found to improve the OS in HBsAg(−) patients with NPC in the matched-paired analysis.

The analysis indicated no statistically significant difference between the two hospitals in the proportion of HBsAg(+) patients, 13.4% and 18.2%, similar to 15.75% reported previously (18). Moreover, the higher metastasis rate in HBsAg(+) patients compared with HBsAg(−) patients with NPC is also supported by previous studies (19,21).

Additionally, consistent with previous findings (19,20), the median age of HBsAg(+) patients was 2 years younger than that of HBsAg(−) patients. Chronic inflammation and cell proliferation promoted by the host immune response to persistent HBV infection may induce carcinogenic transformation of the infected cells, which partly explains the younger age of HBsAg(+) patients that present with NPC (18). Furthermore, we found no difference between HBsAg(+) and HBsAg(−) patients concerning tumor burden, T classification, N classification, stage, and tumor volume, consistent with the results of other studies (19,21), indicating that tumor load played little or no role in our findings. No statistically significant difference was found in CCRT or CCRT + IC between the two groups, suggesting that our results are independent of the treatment mode.

The randomized clinical trials have not reached a consensus regarding the efficacy of additional IC (2,3,5,7,8,27-30). A meta-analysis of 20 trials suggested that IC + CCRT achieved the highest effect on distant control of LANPC (HR: 0.44; 95% CI: 0.27–0.71). Another pooled analysis of four randomized trials also indicated that IC + CCRT improved OS, with the survival benefit mainly related to improved distant control (HR: 0.68; 95% CI: 0.51–0.90) (31,32). However, an increased overall incidence of acute adverse events was also found in patients treated with IC, especially of anemia, neutropenia, thrombocytopenia, nausea, and vomiting (3). Moreover, as a cycle of IC requires 21 days and two to four cycles are generally administered, IC prolongs hospital stay, increases hospitalization expenses, and aggravates the shortage of medical resources. Thus, recent studies emphasize selecting effective biomarkers to identify ideal candidates for IC. NPC patients with higher pre-treatment plasma EBV DNA level content reportedly benefit more from the IC administration (10), consistent with our data that the IC + CCRT group tended to have higher plasma EBV DNA loads. However, whether HBV infection is a prognostic factor for IC has not been widely investigated. Currently, the HBV infection impact on the NPC patient survival has been investigated with mixed results. According to Liu et al., HBV infection is an independent prognostic factor in patients with LANPC, but not in those with early-stage NPC (19). Conversely, Weng et al. found that HBV infection is an unfavorable factor for early-stage disease (21). However, Xu et al. observed that the HBsAg status did not independently affect survival outcomes (20). The above divergence may be attributed to the different chemotherapy modes followed in these studies, such as the IC administration.

Reportedly, only one study has investigated the efficacy of IC in HBsAg(+) patients with NPC and reported that IC + CCRT led to similar survival outcomes as did CCRT alone in patients with LANPC with chronic HBV infection (22). They found no benefits of IC as the immunosuppression caused by additional IC could negate its advantages. Here, HBsAg(+) patients with stage III/IV NPC had the worse DMFS and PFS, further suggesting the potential disadvantage of additional IC. However, despite these allusive results, generalizability should be carefully considered because of the small sample size. Additionally, selection bias was possible. Moreover, they failed to elaborate whether 140 pair-matched patients were balanced or adjusted in terms of plasma EBV DNA level, an important prognostic factor, and plasma EBV DNA level was not included in the multivariate analysis. Contrastingly, we recruited 1,076 patients from two hospitals, and univariate and multivariate analyses confirmed IC as an independent prognostic risk factor for HBsAg(+) patients with NPC. Similar results were obtained in our matched-pair analysis, which eliminated some known confounding factors, such as stage and plasma EBV DNA level, and may also eliminate some unknown confounding factors. After excluding HBsAg(+)/ patients in the matched-pair analysis, we observed that IC significantly improved OS in HBsAg(−) patients with NPC, consistent with the results of several multicenter, phase III trials (2,3). However, these trials did not address the HBsAg status in patients. Overall, our study and that by Zhang et al. (22) concluded that IC was not recommended for patients with NPC co-infected with HBV, but our study is superior concerning comprehensiveness and reliability.

The following explanations should be considered while explaining why IC is unsuitable in HBsAg(+) patients with NPC. First, HBV is associated with immune dysfunction, as indicated by its association with lymphoma (33) and hepatitis B-related kidney disease (34). The lower proliferative
capacity of activated B cells (35) and overexpression of programmed cell death protein 1 (PD-1) on CD8-positive T cells (36) demonstrate the immune system dysfunction in HBsAg(+) patients. Administration of IC may attack tumor and immune cells, thus, aggravating the immunity imbalance and compromising patients’ prognosis. Moreover, one of the triggering events for HBVr is cancer chemotherapy, and HBVr can lead to liver damage or fatal hepatic failure, disrupt the anti-cancer effects, and compromise patients’ prognosis (37). The frequency of HBVr is highest during chemotherapy for leukemia or lymphoma, with some reported rates exceeding 50% (38). HBVr also occurs during anticancer treatment of solid tumors, such as breast cancer (39), hepatocellular carcinoma (40,41), pancreatic cancer (42), lung cancer (43), gastric adenocarcinoma (44), and pleural carcinoma (45). Lv et al. indicated that the HBVr rate ranges from 0.0–21.4% for different treatments and regimens in patients with NPC, and patients treated with IC alone had a 3.8% risk for reactivation (23). However, these reasons need further immunological or pathway research, which is beyond the scope of this study.

Our study had some limitations. First, this was a retrospective analysis based on medical records; thus, not all data were completely documented. For example, hepatoprotective drugs received by patients during the antitumor period could not be obtained because the patients often undergo anti-hepatitis B treatment in other specialized hospitals. Second, we only tested serological HBsAg, and as HBV DNA loads were not routinely determined, HBVr rates could not be obtained; besides, purely HBsAg can be indicative of HBV infection, but cannot distinguish acute and chronic HBV infection. Third, plasma EBV DNA level was not balanced in the matched pair analysis as IC was more likely to be administered in patients with NPC who had higher plasma EBV DNA loads; however, plasma EBV DNA level was included in the multivariate analysis to adjust the results. Whether or not patients with subclinical hepatitis B with NPC will benefit from induction chemotherapy (IC) can only be answered by a randomized clinical trial. Hence, a randomized clinical trial and cytological experimentation are needed to further confirm our hypothesis and explain possible mechanism.

Conclusions

In conclusion, a high proportion of HBV infection and a higher metastasis rate in patients with NPC warrant a detailed study of this population. IC + CCRT negatively affects DMFS and PFS compared with CCRT alone in HBsAg(+) patients with NPC, but IC improves the OS in HBsAg(−) patients. Therefore, withholding IC in HBsAg(+) patients should help alleviate side effects, shorten hospitalization duration, and reduce hospitalization expenses. Our research provides improved guidelines for the IC administration in HBsAg(+) patients with NPC and the basis for their precise treatment.

Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing.

Funding: Lizhi Liu was supported by the Science and Technology Planning Project of Guangzhou City, China (grant number: 201907010043), and National Natural Science Foundation of China (No. 82171906).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-33/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-33/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-33/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the committee of the Institutional Review Boards at the SYSUCC (approval number: B2019-222) and individual consent for this retrospective analysis was waived.

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Cite this article as: Li H, Chen M, Li S, Luo C, Qiu X, Ruan G, Mao Y, Zhang G, Liu L. Survival impact of additional induction chemotherapy in nasopharyngeal carcinoma with chronic hepatitis B infection: a retrospective, bi-center study. Ann Transl Med 2022;10(13):731. doi: 10.21037/atm-22-33

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