



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

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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

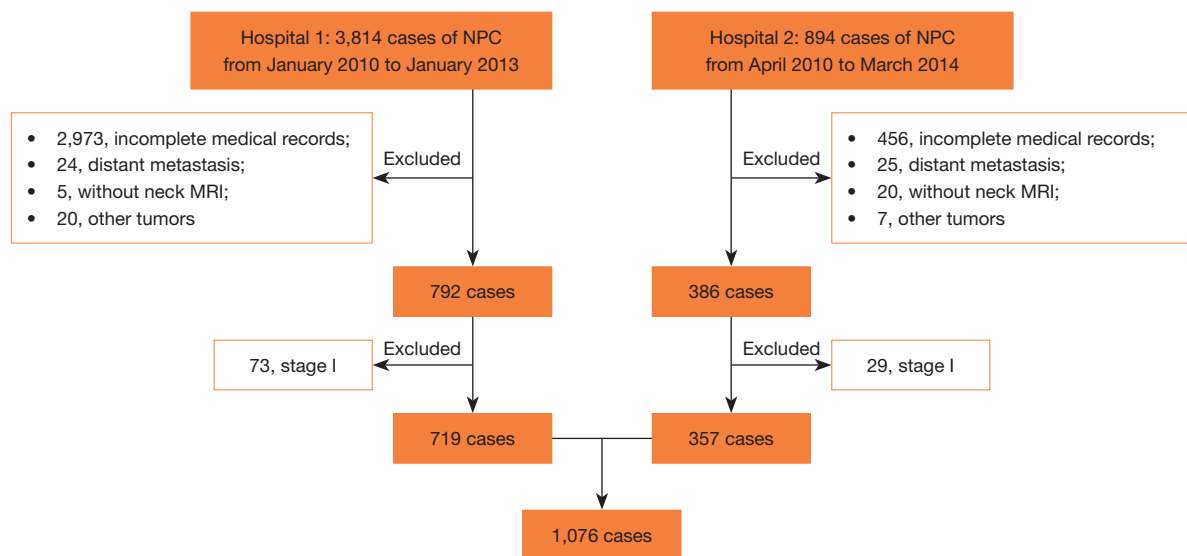


Figure 1 Flowchart of study enrollment. NPC, nasopharyngeal carcinoma; MRI, magnetic resonance imaging.

immunosorbent assay (ELLSA) 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 shown 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 aminotransferase (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				0.057
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)

Table 1 (continued)

Variables	Total patients (N=1,076)	HBsAg(-) (N=897)	HBsAg(+) (N=179)	P value [†]
Volume (cm ³)				0.892
Median (IQR)	31.4 (20.9–54.7)	30 (17.5–50.5)	29.7 (19.2–50.6)	
ALT				<0.001*
<50 U/L	997 (92.7%)	845 (94.2%)	152 (84.9%)	
≥50 U/L	79 (7.3%)	52 (5.8%)	27 (15.1%)	
AST				<0.001*
<40 U/L	1031 (95.8%)	871 (97.1%)	160 (89.4%)	
≥40 U/L	45 (4.2%)	26 (2.9%)	19 (10.6%)	

*, P<0.05; †, P values were calculated using Fisher's exact test or the Chi-square test for categorical variables and Student's *t*-test for continuous variables; ‡, according to the eighth edition of the AJCC/UICC staging system. HBsAg, hepatitis B surface antigen; +, positive; -, negative; IQR, interquartile range; WHO, World Health Organization; plasma EBV DNA level, plasma Epstein-Barr virus DNA level; CCRT, concurrent chemotherapy; IC, induction chemotherapy; IMRT, intensity-modulated radiotherapy; ALT, alanine aminotransferase; AST, aspartate transaminase.

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

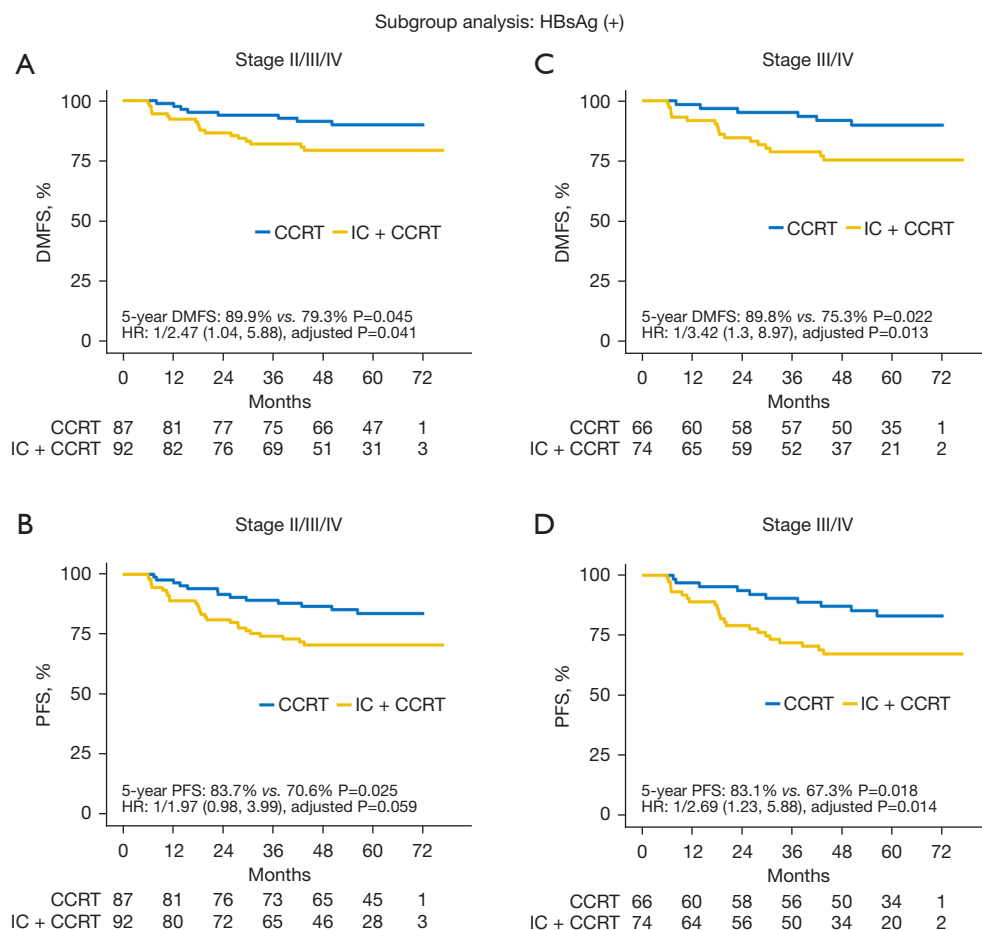


Figure 2 Stage-based subgroup analysis for DMFS and PFS between IC + CCRT and CCRT among HBsAg(+) NPC patients. In the stage II/III/IV subgroup, the DMFS (A) and PFS (B) in patients treated with IC + CCRT were significantly lower to those of patients treated with CCRT; IC + CCRT was an independent negative factor for DMFS (A) after adjusting for confounding factors, while its independence was weaker in PFS (B). In the stage III/IV subgroup, DMFS (C) and PFS (D) in patients treated with IC + CCRT were lower than those in patients treated with CCRT. After adjusting for confounding factors, IC + CCRT was an independent unfavorable factor for DMFS (C) and PFS (D). Kaplan-Meier survival with log-rank test was used to calculate the 5-year survival difference between the CCRT and IC + CCRT groups. The Y-axis represented survival probability. HRs and P values were calculated using multivariate Cox regression analysis. Detailed results are shown in Table S3. HBsAg, hepatitis B surface antigen; +, positive; CCRT, concurrent chemotherapy; IC, induction chemotherapy; HR, hazard ratio; DMFS, distant metastasis-free survival; PFS, progression-free survival.

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%

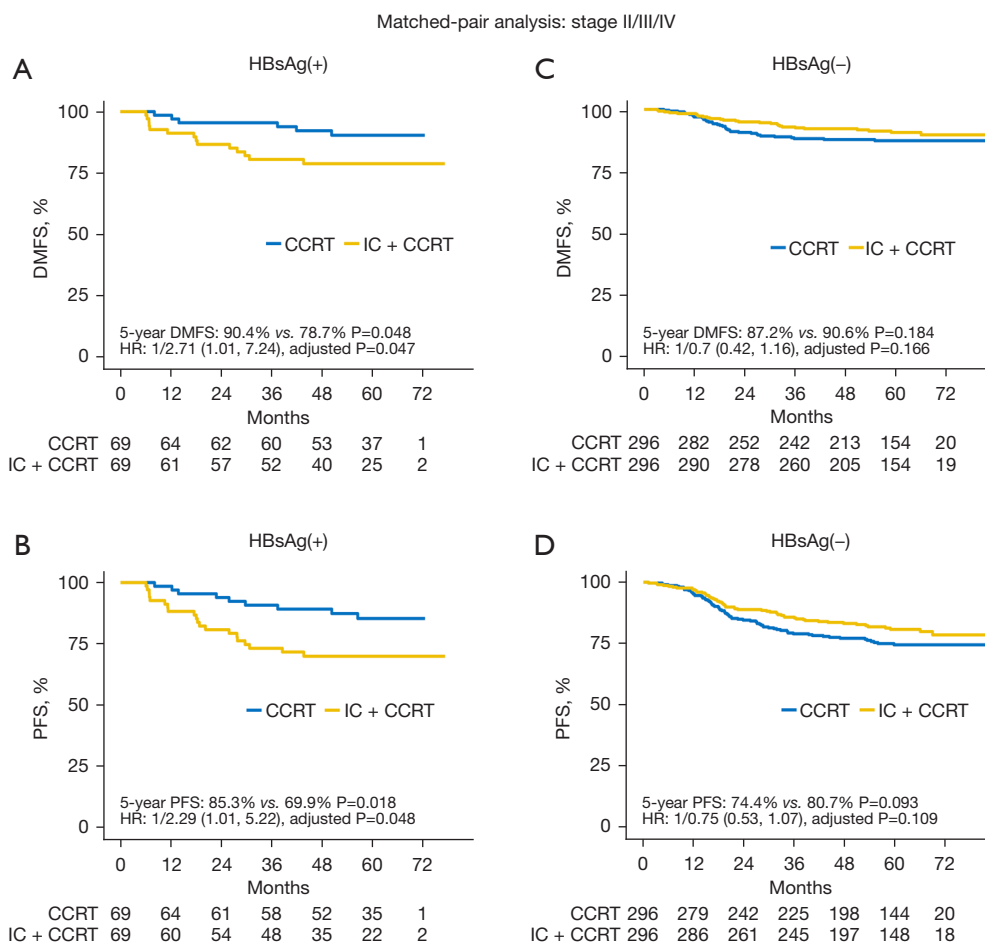


Figure 3 Matched-pair analysis for DMFS and PFS between IC + CCRT and CCRT in the stage II/III/IV subgroup. For 69 pairs of NPC patients with HBsAg(+), DMFS (A) and PFS (B) in patients treated with IC + CCRT were inferior to those in patients treated with CCRT, and IC + CCRT was proved as a negative prognostic factor in HBsAg(+) patients. For 296 pairs of NPC patients with HBsAg(-), the survival curve of DMFS (C) and PFS (D) in patients treated with IC + CCRT was higher than that in those treated with CCRT but was not significantly different. T and N classifications were used for 1:1 random pair matching, as shown in Table S4. Kaplan-Meier survival analysis with the log-rank test was used to calculate the 5-year survival difference between the CCRT and IC + CCRT groups. The Y-axis represented survival probability. HRs and P values were calculated using multivariate Cox regression. HBsAg, hepatitis B surface antigen; +, positive; -, negative; CCRT, concurrent chemotherapy; IC, induction chemotherapy; HR, hazard ratio; DMFS, distant metastasis-free survival; PFS, progression-free survival.

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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References

- Pfister DG, Spencer S, Adelstein D, et al. Head and Neck Cancers, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2020;18:873-98.
- Sun Y, Li WF, Chen NY, et al. Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial. *Lancet Oncol* 2016;17:1509-20.
- Zhang Y, Chen L, Hu GQ, et al. Gemcitabine and Cisplatin Induction Chemotherapy in Nasopharyngeal Carcinoma. *N Engl J Med* 2019;381:1124-35.
- Ribassin-Majed L, Marguet S, Lee AWM, et al. What Is the Best Treatment of Locally Advanced Nasopharyngeal Carcinoma? An Individual Patient Data Network Meta-Analysis. *J Clin Oncol* 2017;35:498-505.
- Hong RL, Hsiao CF, Ting LL, et al. Final results of a randomized phase III trial of induction chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in patients with stage IVA and IVB nasopharyngeal carcinoma-Taiwan Cooperative Oncology Group (TCOG) 1303 Study. *Ann Oncol* 2018;29:1972-9.
- Liu T, Liu LT, Lin JY, et al. Management of suboptimal response to induction chemotherapy in locoregionally advanced nasopharyngeal carcinoma: Re-induction therapy or direct to Radiotherapy? *Radiother Oncol* 2021;163:185-91.
- Li PJ, Mo HY, Luo DH, et al. The efficacy of induction chemotherapy in the treatment of stage II nasopharyngeal carcinoma in intensity modulated radiotherapy era. *Oral Oncol* 2018;85:95-100.
- Gabani P, Barnes J, Lin AJ, et al. Induction chemotherapy in the treatment of nasopharyngeal carcinoma: Clinical outcomes and patterns of care. *Cancer Med* 2018;7:3592-603.
- Yao JJ, Jin YN, Liu ZG, et al. Do all patients with advanced N-stage nasopharyngeal carcinoma benefit from the addition of induction chemotherapy to concurrent chemoradiotherapy? *Ther Adv Med Oncol* 2019;11:1758835919833863.
- Xie HJ, Yu YF, Sun XS, et al. Identifying optimal candidates for induction chemotherapy among stage II-IVa nasopharyngeal carcinoma based on pretreatment Epstein-Barr virus DNA and nodal maximal standard uptake values of 18 F-fluorodeoxyglucose positron emission tomography. *Cancer Med* 2020;9:8852-63.
- Xu C, Zhang S, Li WF, et al. Selection and Validation of Induction Chemotherapy Beneficiaries Among Patients With T3N0, T3N1, T4N0 Nasopharyngeal Carcinoma Using Epstein-Barr Virus DNA: A Joint Analysis of Real-World and Clinical Trial Data. *Front Oncol* 2019;9:1343.
- Xia WX, Ye YF, Lu X, et al. The impact of baseline serum C-reactive protein and C-reactive protein kinetics on the prognosis of metastatic nasopharyngeal carcinoma patients treated with palliative chemotherapy. *PLoS One* 2013;8:e76958.
- Xia WX, Zhang HB, Shi JL, et al. A prognostic model predicts the risk of distant metastasis and death for patients with nasopharyngeal carcinoma based on pre-treatment serum C-reactive protein and N-classification. *Eur J Cancer* 2013;49:2152-60.
- Zhou GQ, Tang LL, Mao YP, et al. Baseline serum lactate dehydrogenase levels for patients treated with intensity-modulated radiotherapy for nasopharyngeal carcinoma: a predictor of poor prognosis and subsequent liver metastasis. *Int J Radiat Oncol Biol Phys* 2012;82:e359-65.
- Chen S, Li J, Wang D, et al. The hepatitis B epidemic in China should receive more attention. *Lancet* 2018;391:1572.
- Wang H, Men P, Xiao Y, et al. Hepatitis B infection in the general population of China: a systematic review and meta-analysis. *BMC Infect Dis* 2019;19:811.
- Liu Z, Yang Q, Shi O, et al. The epidemiology of hepatitis B and hepatitis C infections in China from 2004 to 2014: An observational population-based study. *J Viral Hepat* 2018;25:1543-54.
- Ye YF, Xiang YQ, Fang F, et al. Hepatitis B virus infection and risk of nasopharyngeal carcinoma in southern China. *Cancer Epidemiol Biomarkers Prev* 2015;24:1766-73.
- Liu X, Li X, Jiang N, et al. Prognostic value of chronic hepatitis B virus infection in patients with nasopharyngeal carcinoma: analysis of 1301 patients from an endemic area in China. *Cancer* 2014;120:68-76.
- Xu T, Huang Z, Deng Y, et al. Clinical implications of hepatitis B viral infection in Epstein-Barr virus-associated nasopharyngeal carcinoma. *J Clin Virol* 2015;64:64-71.

21. Weng JJ, Wei JZ, Li M, et al. Effects of hepatitis B virus infection and antiviral therapy on the clinical prognosis of nasopharyngeal carcinoma. *Cancer Med* 2020;9:541-51.
22. Zhang LL, Zhou GQ, Li YC, et al. Induction Chemotherapy Has No Prognostic Value in Patients with Locoregionally Advanced Nasopharyngeal Carcinoma and Chronic Hepatitis B Infection in the IMRT Era. *Transl Oncol* 2017;10:800-5.
23. Lv JW, Chen YP, Huang XD, et al. Hepatitis B virus screening and reactivation and management of patients with nasopharyngeal carcinoma: A large-scale, big-data intelligence platform-based analysis from an endemic area. *Cancer* 2017;123:3540-9.
24. Voican CS, Mir O, Loulergue P, et al. Hepatitis B virus reactivation in patients with solid tumors receiving systemic anticancer treatment. *Ann Oncol* 2016;27:2172-84.
25. Lydiatt WM, Patel SG, O'Sullivan B, et al. Head and Neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual. *CA Cancer J Clin* 2017;67:122-37.
26. Chen J, Chen Y, Zheng D, et al. Pretreatment MR-based radiomics nomogram as potential imaging biomarker for individualized assessment of perineural invasion status in rectal cancer. *Abdom Radiol (NY)* 2021;46:847-57.
27. Tan T, Lim WT, Fong KW, et al. Concurrent chemoradiation with or without induction gemcitabine, Carboplatin, and Paclitaxel: a randomized, phase 2/3 trial in locally advanced nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2015;91:952-60.
28. Yang Q, Cao SM, Guo L, et al. Induction chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: long-term results of a phase III multicentre randomised controlled trial. *Eur J Cancer* 2019;119:87-96.
29. Li WF, Chen NY, Zhang N, et al. Concurrent chemoradiotherapy with/without induction chemotherapy in locoregionally advanced nasopharyngeal carcinoma: Long-term results of phase 3 randomized controlled trial. *Int J Cancer* 2019;145:295-305.
30. Chen YP, Wang YQ, Li WF, et al. Critical Evaluation of the Quality and Recommendations of Clinical Practice Guidelines for Nasopharyngeal Carcinoma. *J Natl Compr Canc Netw* 2017;15:336-44.
31. Chen YP, Tang LL, Yang Q, et al. Induction Chemotherapy plus Concurrent Chemoradiotherapy in Endemic Nasopharyngeal Carcinoma: Individual Patient Data Pooled Analysis of Four Randomized Trials. *Clin Cancer Res* 2018;24:1824-33.
32. OuYang PY, Zhang XM, Qiu XS, et al. A Pairwise Meta-Analysis of Induction Chemotherapy in Nasopharyngeal Carcinoma. *Oncologist* 2019;24:505-12.
33. Wang F, Xu RH, Luo HY, et al. Clinical and prognostic analysis of hepatitis B virus infection in diffuse large B-cell lymphoma. *BMC Cancer* 2008;8:115.
34. Fabrizi F, Cerutti R, Ridruejo E. Hepatitis B virus infection as a risk factor for chronic kidney disease. *Expert Rev Clin Pharmacol* 2019;12:867-74.
35. Oliviero B, Cerino A, Varchetta S, et al. Enhanced B-cell differentiation and reduced proliferative capacity in chronic hepatitis C and chronic hepatitis B virus infections. *J Hepatol* 2011;55:53-60.
36. Peng G, Li S, Wu W, et al. PD-1 upregulation is associated with HBV-specific T cell dysfunction in chronic hepatitis B patients. *Mol Immunol* 2008;45:963-70.
37. Gonzalez SA, Perrillo RP. Hepatitis B Virus Reactivation in the Setting of Cancer Chemotherapy and Other Immunosuppressive Drug Therapy. *Clin Infect Dis* 2016;62 Suppl 4:S306-13.
38. Perrillo RP, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 2015;148:221-244.e3.
39. Ma B, Yeo W, Hui P, et al. Acute toxicity of adjuvant doxorubicin and cyclophosphamide for early breast cancer -- a retrospective review of Chinese patients and comparison with an historic Western series. *Radiother Oncol* 2002;62:185-9.
40. Yeo W, Lam KC, Zee B, et al. Hepatitis B reactivation in patients with hepatocellular carcinoma undergoing systemic chemotherapy. *Ann Oncol* 2004;15:1661-6.
41. Jang JW, Kwon JH, You CR, et al. Risk of HBV reactivation according to viral status and treatment intensity in patients with hepatocellular carcinoma. *Antivir Ther* 2011;16:969-77.
42. Oksüzöğlü B, Kiliçkap S, Yalcin S. Reactivation of hepatitis B virus infection in pancreatic cancer: a case report. *Jpn J Clin Oncol* 2002;32:543-5.
43. Mok TS, Zee B, Chan AT, et al. A phase II study of gemcitabine plus oral etoposide in the treatment of patients with advanced nonsmall cell lung carcinoma.

- Cancer 2000;89:543-50.
44. Cheng JC, Liu MC, Tsai SY, et al. Unexpectedly frequent hepatitis B reactivation by chemoradiation in

- postgastrectomy patients. Cancer 2004;101:2126-33.
45. Cheong K, Li J, Karapetis CS. Gemcitabine and reactivation of hepatitis B. Med Oncol 2003;20:385-8.

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