Original Article

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

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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

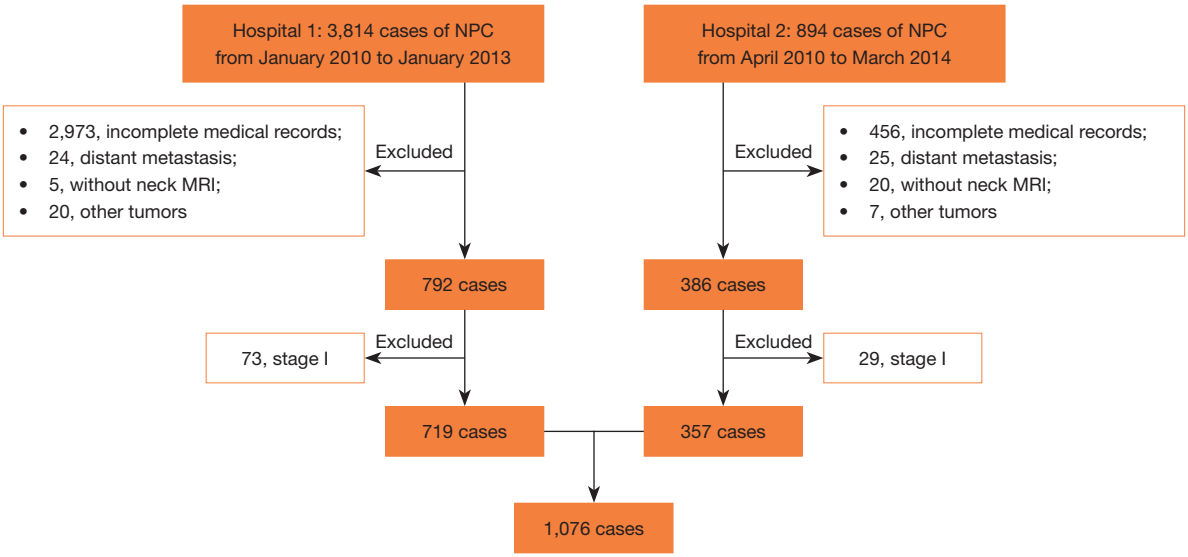

Figure 1 Flowchart of study enrollment. NPC, nasopharyngeal carcinoma; MRI, magnetic resonance imaging.

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 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 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*)

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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

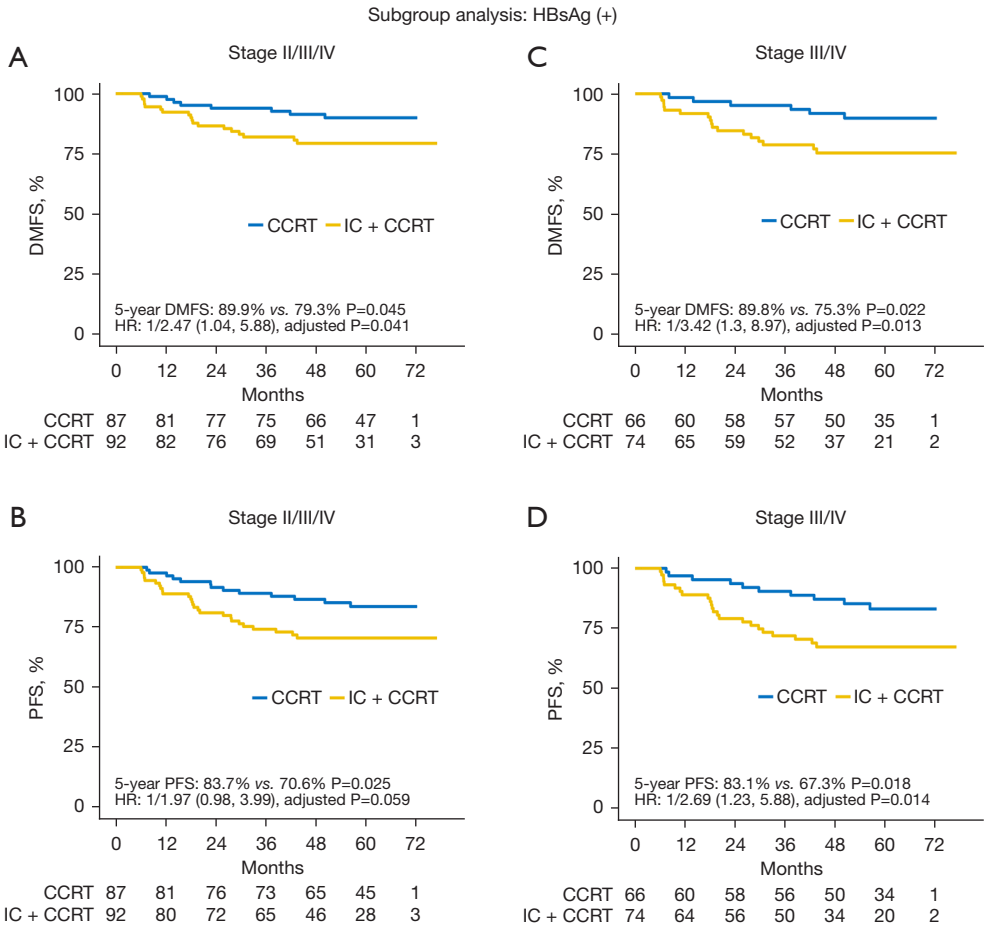

Figure 2 Stage-based subgroup analysis for DMFS and PFS between IC + CCRT and CCRT among HBsAg(+) NPC patients. In the stage II/III/IV subgroup, the DMFS (A) and PFS (B) in patients treated with IC + CCRT were significantly lower to those of patients treated with CCRT; IC + CCRT was an independent negative 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%

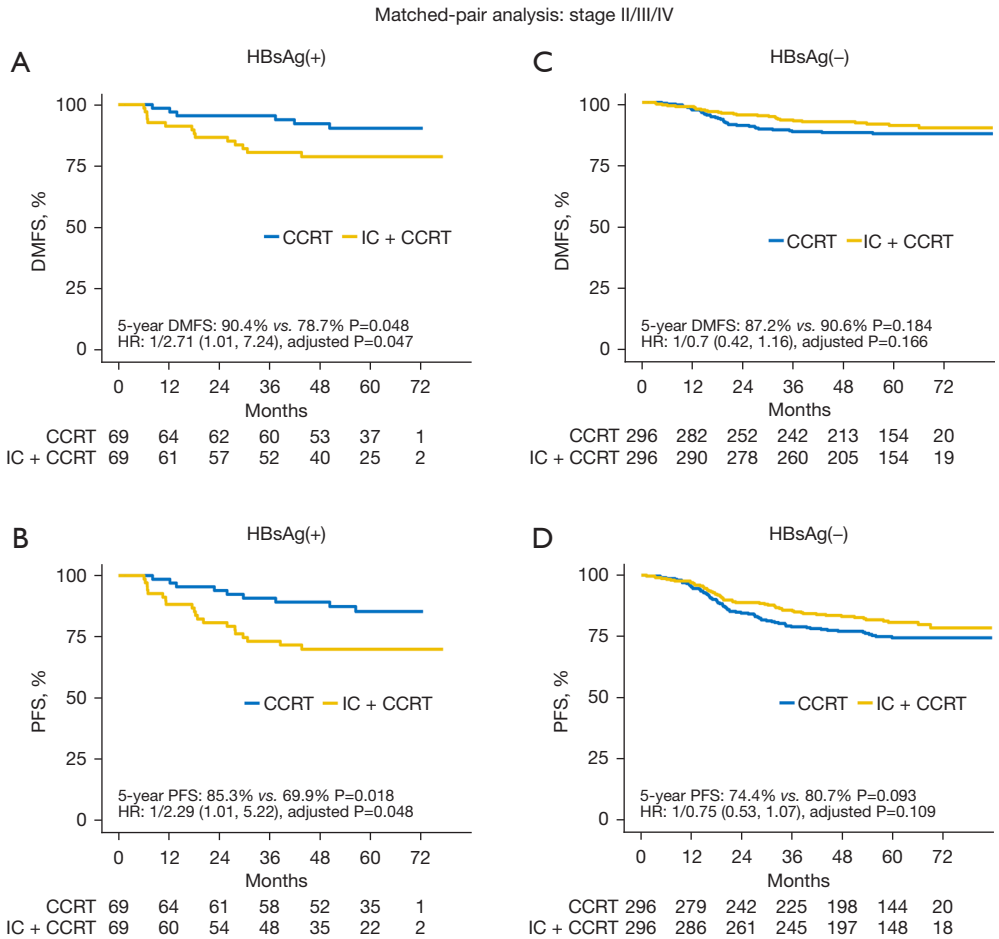

Figure 3 Matched-pair analysis for DMFS and PFS between IC + CCRT and CCRT in the stage II/III/IV subgroup. For 69 pairs of NPC patients with HBsAg(+), DMFS (A) and PFS (B) in patients treated with IC + CCRT were inferior to those in patients treated with CCRT, and IC + CCRT was proved as a negative 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.

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Footnote

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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.

References

1. 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.
2. 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.
3. Zhang Y, Chen L, Hu GQ, et al. Gemcitabine and Cisplatin Induction Chemotherapy in Nasopharyngeal Carcinoma. N Engl J Med 2019;381:1124-35.
4. 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.
5. 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.
6. 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.
7. 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.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.
15. Chen S, Li J, Wang D, et al. The hepatitis B epidemic in China should receive more attention. Lancet 2018;391:1572.
16. 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.
17. 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.
18. 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.
19. 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.
20. 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 chemo-radiation 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. Oksüzoğlu 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.

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Appendix 1 Supplementary methods

Treatment for HBV infection and liver function

Before receiving anti-cancer treatment, patients with active hepatitis were instructed to receive routine hepatitis and antiviral treatments. Only when HBV DNA is reduced to 1,000 copies/mL and approved by the infection specialist, can the patients commence anti-cancer treatment. NPC patients with HBsAg(+) received antiviral treatment at the same time or 1 week before chemotherapy, and until 6–12 months after chemotherapy, if necessary. In the interim, liver function was closely monitored.

In this study, the liver function data were relatively complete in one of hospitals, as shown in Table S5. Furthermore, in further univariable analysis (not supplied), during chemotherapy, all of the variables (ALT, AST, Antiviral treatment, and HBV DNA) showed no statistical significance (all P>0.05) for all endpoints (OS, DMFS, LRFS and PFS), suggesting that they may not be confounding variables. Even in the stratified analysis of patients with HBsAg(+), there was no statistical significance in those indicators of survival in NPC.

Treatment for NPC

Per the treatment principle for nasopharyngeal carcinoma (NPC) at the Sun Yat-sen University Cancer Center and First People's Hospital of Foshan, all included patients received intensity-modulated radiation therapy during the radiotherapy course. Target volumes were delineated slice-by-slice on treatment planning computed tomography (CT) scans using an individualized delineation protocol that complies with the International Commission on Radiation Units and Measurements Reports 50 and 62. The prescribed doses were 66–72 Gy at 2.12–2.43 Gy/fraction to the planning target volume (PTV) of the primary GTV (GTVnx), 64–70 Gy per 28–33 fractions to the PTV of the GTV of involved lymph nodes (GTVnd), 60–63 Gy per 28–33 fractions to the PTV of the high-risk clinical target volume (CTV1), and 54–56 Gy per 28–33 fractions to the PTV of the low-risk clinical target volume (CTV2). The median dose delivered was 72.77 ± 1.26 Gy to the PTV of the GTVnx. Neoadjuvant, concurrent, or adjuvant chemotherapy based on platinum was administered to patients with stage II–IV NPC. Patients who developed local recurrence or had persistent disease received salvage therapy, such as secondary radiation, surgery, and chemotherapy. Induction chemotherapy (IC) included docetaxel (60 mg/m^2 on day 1), cisplatin (60 mg/m^2 on day 1), fluorouracil (600 mg/m^2 per day for the first 5 days), or gemcitabine (1,000 mg/m^2 on days 1 and 8) and cisplatin (80 mg/m^2 on day 1), repeated every 3 weeks for two to four cycles. Concurrent chemotherapy included 30–40 mg/m^2 cisplatin per week, 80–100 mg/m^2 cisplatin on day 1, and 28–37 times of IMRT for radiotherapy.

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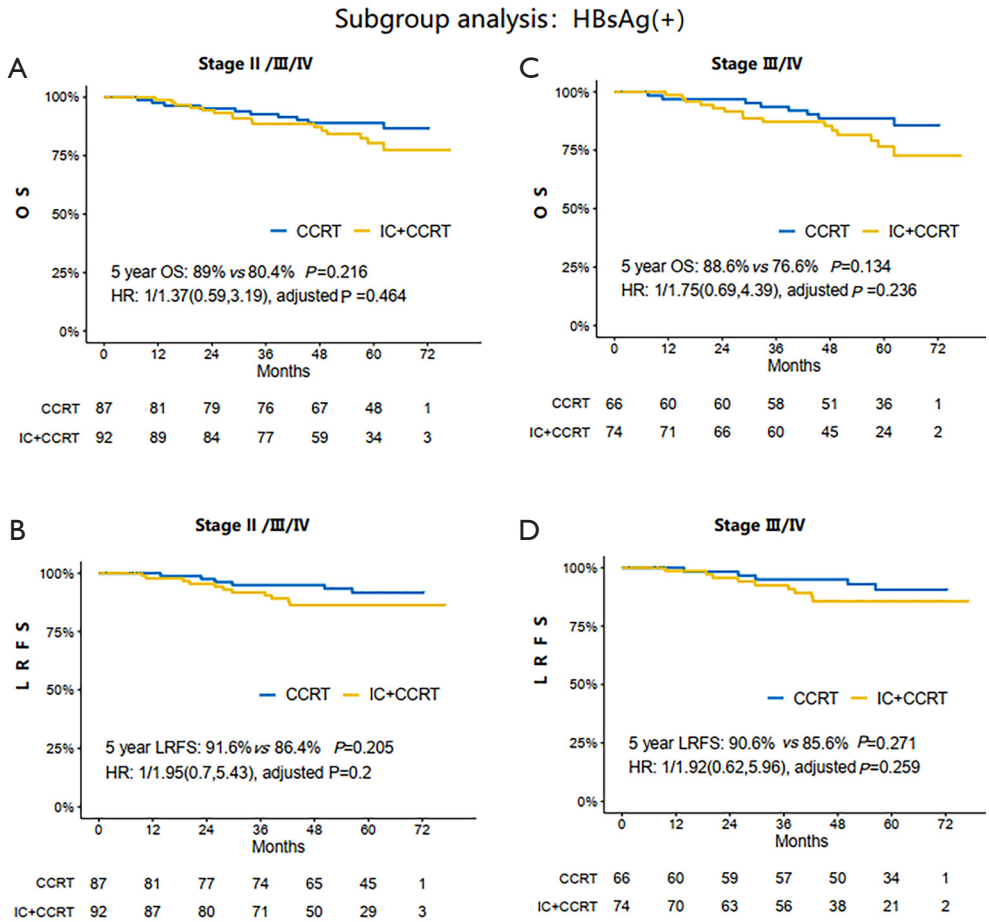

Figure S1 Subgroup analysis for OS and LRFS in NPC patients with HBsAg(+). In stage II/III/IV and stage III/IV subgroups, NPC patients with HBsAg(+) showed no significant differences in OS (A,C) or LRFS (B,D) between those treated with IC + CCRT or CCRT. Kaplan–Meier survival analysis with the log-rank 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 analysis. Detailed results are shown in Table S3. OS, overall survival; LRFS, local recurrence-free survival; NPC, Nasopharyngeal carcinoma; HBsAg, hepatitis B surface antigen; +, positive; CCRT, concurrent chemotherapy; IC, induction chemotherapy; HR, hazard ratio.

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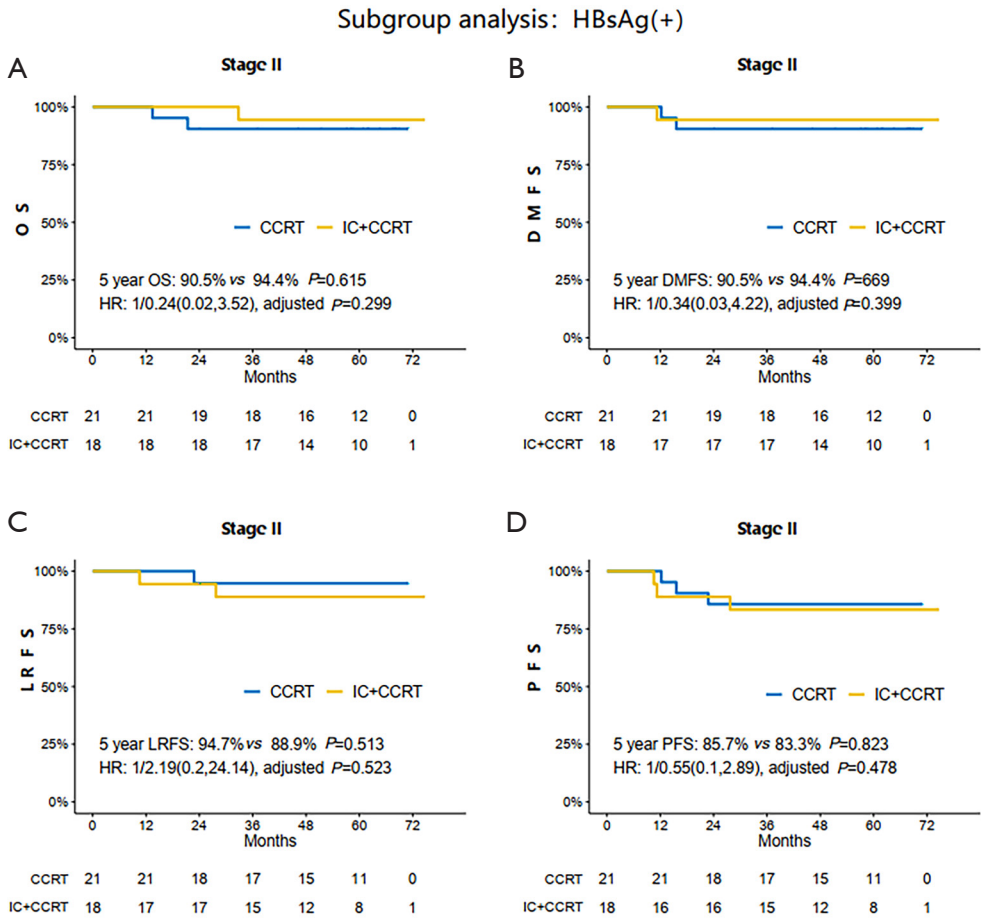

Figure S2 Survival analysis in stage II NPC patients with HBsAg(+). Stage II NPC patients with HBsAg(+) showed no significant differences in OS (A), DMFS (B), LRFS (C), and PFS (D) between those treated with IC + CCRT or CCRT. Kaplan–Meier survival analysis with the log-rank test was used to calculate 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 analysis. A table of detailed results will be provided if necessary. NPC, Nasopharyngeal carcinoma; HBsAg, hepatitis B surface antigen; +, positive; CCRT, concurrent chemotherapy; IC, induction chemotherapy; OS, overall survival; DMFS, distant metastasis-free survival; LRFS, local recurrence-free survival; PFS, progression-free survival; HR, hazard ratio.

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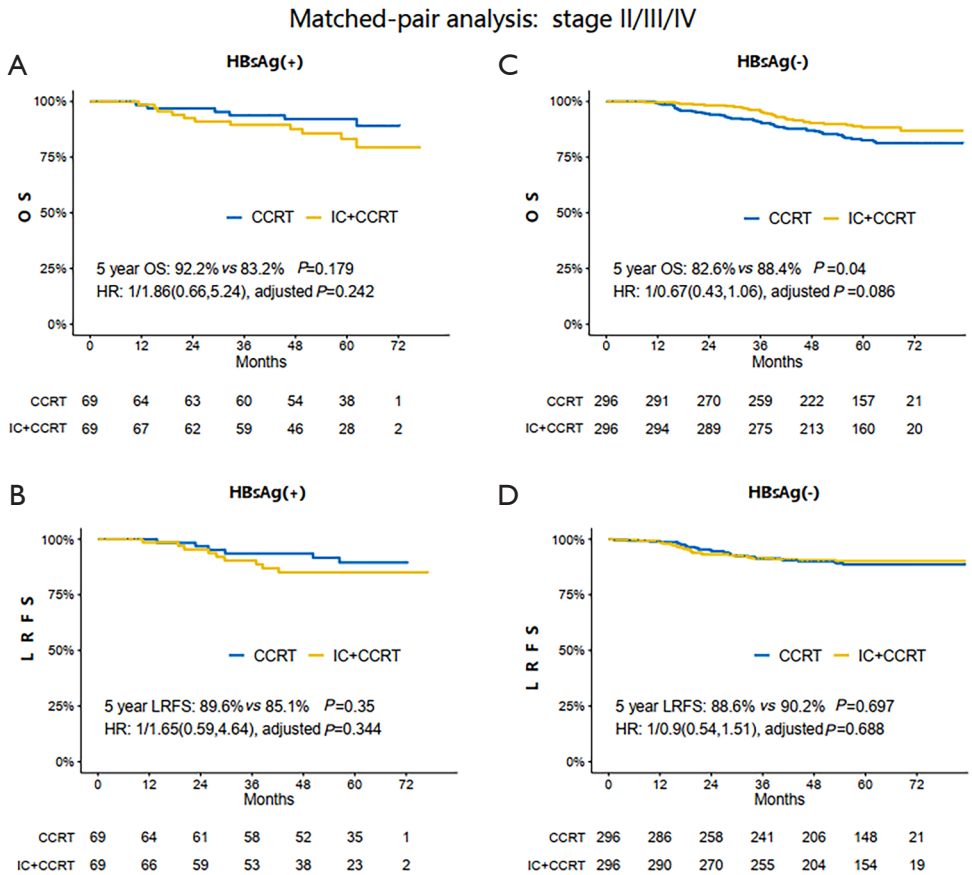

Figure S3 Matched-pair analysis for OS and LRFS between IC + CCRT and CCRT in stage II/III/IV NPC patients with different HBsAg status. For 69 pairs of NPC patients with HBsAg(+), no significant differences were observed in OS (A) and LRFS (B) between those treated with IC + CCRT or CCRT. For 296 pairs of NPC patients with HBsAg(–), patients treated with IC + CCRT had a significantly higher OS (C) than those treated with CCRT; however, this was no longer significant after adjusting for confounding factors. The LRFS survival curves of HBsAg(–) patients overlapped (D). 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 analysis. A table of detailed results will be provided if necessary. OS, overall survival; LRFS, local recurrence-free survival; IC, induction chemotherapy; NPC, nasopharyngeal carcinoma; HBsAg, hepatitis B surface antigen; +, positive; –, negative; CCRT, concurrent chemotherapy.

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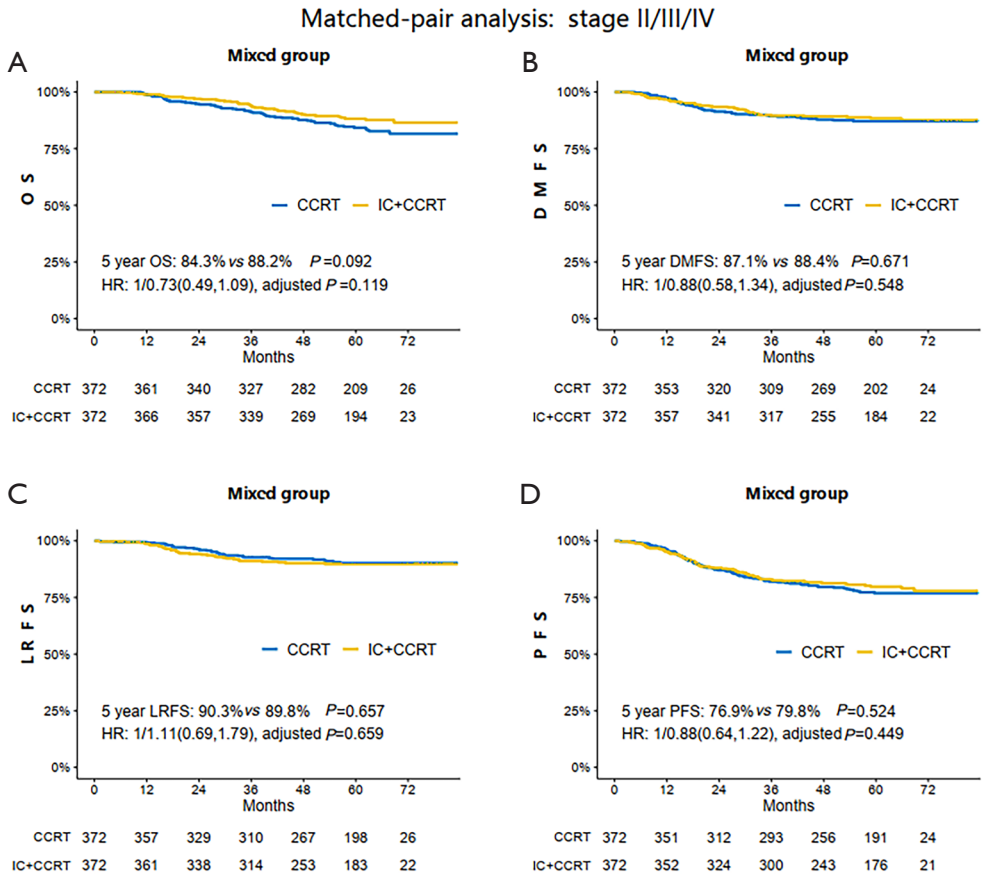

Figure S4 Survival in NPC with mixed HBsAg status using matched-pair analysis. For 372 pairs of NPC patients in stage II/III/IV, the OS (A) in patients treated with IC + CCRT was not significantly different than that in patients treated with CCRT. The survival curves between patients treated with IC + CCRT and CCRT overlapped for DMFS (B), LRFS (C), and PFS (D). 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 analysis. Mixed group refers to patients without considering the HBsAg status when pairing. A table of detailed results will be provided if necessary. NPC, nasopharyngeal carcinoma; HBsAg, hepatitis B surface antigen; CCRT, concurrent chemotherapy; IC, induction chemotherapy; OS, overall survival; DMFS, distant metastasis-free survival; LRFS, local recurrence-free survival; PFS, progression-free survival; HR, hazard ratio.

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Table S1 Clinical characteristics of nasopharyngeal carcinoma patients in the two hospitals

Variables	Total (N=1,076)	Hospital 1 (N=719)	Hospital 2 (N=357)	P value[†]
Age (years)				<0.001*
Median (IQR)	46.0 (38.0–55.0)	45 (37–53)	47 (40–58)	
Sex				0.408
Male	799 (74.3%)	528 (73.4%)	271 (75.9%)	
Female	277 (25.7%)	191 (26.6%)	86 (24.1%)	
Histologic type				<0.001*
WHO type 1/2	41 (3.8%)	41 (5.7%)	0 (0%)	
WHO type 3	1035 (96.2%)	678 (94.3%)	357 (100%)	
Plasma EBV DNA level (1000 copy/mL)				<0.001*
<1	482 (44.8%)	287 (39.9%)	195 (54.6%)	
<10	337 (31.3%)	184 (25.6%)	153 (42.9%)	
≥10	257 (23.9%)	248 (34.5%)	9 (2.5%)	
T classification[‡]				0.567
T1	205 (19.1%)	131 (18.2%)	74 (20.7%)	
T2	150 (13.9%)	97 (13.5%)	53 (14.8%)	
T3	429 (39.9%)	296 (41.2%)	133 (37.3%)	
T4	292 (27.1%)	195 (27.1%)	97 (27.2%)	
N classification[‡]				0.019*
N0	143 (13.3%)	109 (15.2%)	34 (9.5%)	
N1	655 (60.9%)	438 (60.9%)	217 (60.8%)	
N2	189 (17.6%)	113 (15.7%)	76 (21.3%)	
N3	89 (8.3%)	59 (8.2%)	30 (8.4%)	
Stage[‡]				0.844
II	264 (24.5%)	175 (24.3%)	89 (24.9%)	
III	447 (41.5%)	303 (42.1%)	144 (40.3%)	
IV	365 (33.9%)	241 (33.5%)	124 (34.7%)	
Chemotherapy				0.084
CCRT	480 (44.6%)	334 (46.5%)	146 (40.9%)	
IC + CCRT	596 (55.4%)	385 (53.5%)	211 (59.1%)	
HBsAg				0.056
(–)	897 (83.4%)	588 (81.8%)	309 (86.6%)	
(+)	179 (16.6%)	131 (18.2%)	48 (13.4%)	

Hospital 1, Sun Yat-sen University Cancer Center; Hospital 2, First People's Hospital of Foshan. No significant difference was found in terms of stage, treatment mode, and HBsAg(+/–) between the two hospitals. [†], 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. *, P value <0.05. IQR, interquartile range; WHO, World Health Organization; plasma EBV DNA level, plasma Epstein-Barr virus DNA level; CCRT, concurrent chemotherapy; IC, induction chemotherapy; HBsAg, hepatitis B surface antigen; +, positive; –, negative.

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Table S2 Univariate analysis for elucidating confounding variables associated with prognosis

Variables	OS		DMFS		LRFS		PFS	
	5-years	P value†	5-years	P value†	5-years	P value†	5-years	P value†
Age (years)	–	<0.001*	–	0.394	–	0.453	–	0.008*
Sex		0.061		0.736		0.972		0.391
Male	83.57		85.76		88.92		75.25	
Female	88.30		86.77		89.11		78.21	
Histologic type		0.405		0.250		0.578		0.313
WHO type 1/2	79.10		79.45		86.83		69.65	
WHO type 3	85.02		86.30		89.06		76.29	
Plasma EBV DNA level (10^3 copy/mL)		0.001*		<0.001*		0.131		<0.001*
<1	88.60		91.02		91.04		82.32	
<10	85.49		82.82		87.21		73.19	
≥10	78.73		81.15		87.20		68.88	
T classification‡		<0.001*		<0.001*		0.133		<0.001*
T1	93.08		92.38		92.81		84.94	
T2	84.67		87.43		90.72		78.61	
T3	88.03		87.54		88.54		77.93	
T4	74.16		78.36		85.75		65.45	
N classification‡		<0.001*		<0.001*		0.035*		<0.001*
N0	88.93		92.84		95.60		85.55	
N1	88.16		88.67		88.84		78.56	
N2	77.12		78.50		86.56		68.14	
N3	68.00		70.19		83.63		58.00	
Stage‡		<0.001*		<0.001*		0.015*		<0.001*
II	93.40		93.77		93.34		86.63	
III	88.51		88.06		89.07		78.90	
IV	73.67		77.55		85.35		64.61	
Chemotherapy		0.123		0.014*		0.068		0.026*
CCRT	86.91		88.99		90.91		79.13	
IC + CCRT	83.07		83.58		87.43		73.52	
HBsAg		0.873		0.500		0.927		0.876
–	84.80		86.34		89.00		75.90	
+	84.89		84.44		88.82		76.78	
ALT		0.088		0.425		0.741		0.300
<50 U/L	84.26		85.750		88.95		75.68	
≥50 U/L	91.99		89.380		89.22		80.43	
AST		0.309		0.394		0.467		0.262
<40 U/L	84.55		85.810		88.85		75.72	
≥40 U/L	90.91		90.800		91.52		82.81	

The above significant factors (P<0.05) in the univariate analysis were entered in the multivariate analysis to further test and determine the confounding variables; this table will be provided if necessary. †, P values were calculated using the log-rank test. ‡, According to the eighth edition of the AJCC/UICC staging system. *, P value <0.05. OS, overall survival; DMFS, distant metastasis-free survival; LRFS, locoregional recurrence-free survival; PFS, progression-free survival; WHO, World Health Organization; plasma EBV DNA level, plasma Epstein-Barr virus DNA level; CCRT, concurrent chemotherapy; IC, induction chemotherapy; HBsAg, hepatitis B surface antigen; +, positive; –, negative; ALT, alanine aminotransferase; AST, aspartate transaminase.

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Table S3 Stage-based subgroup survival analysis in NPC patients with HBsAg(+)

Subgroups	Variables	OS		DMFS		LRFS		PFS	
		HR (95% CI)[†]	P value[‡]	HR (95% CI)[†]	P value[‡]	HR (95% CI)[†]	P value[‡]	HR (95% CI)[†]	P value[‡]
Stage II/III/IV	Age (years)	1.05 (1.01–1.08)	0.007*	Na		Na		1.03 (1–1.05)	0.069
	Plasma EBV DNA level (1000 copy/mL)					Na			
	<1	1 (reference)		1 (reference)		1 (reference)			
	<10	1.12 (0.42–3.01)	0.817	0.49 (0.14–1.68)	0.259	1.27 (0.56–2.91)		0.564	
	≥10	1.05 (0.38–2.89)	0.926	2.81 (1.15–6.88)	0.023*	1.91 (0.86–4.25)		0.112	
	Stage[§]								
	II	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
	III	1.37 (0.37–5.11)	0.642	1.59 (0.44–5.75)	0.48	1.45 (0.39–5.36)	0.579	1.27 (0.49–3.26)	0.621
	IV	3.01 (0.82–11.1)	0.097	2 (0.54–7.41)	0.298	1.19 (0.28–5.05)	0.811	1.56 (0.59–4.13)	0.369
	Chemotherapy								
	CCRT	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
	IC + CCRT	1.37 (0.59–3.19)	0.464	2.47 (1.04–5.88)	0.041*	1.95 (0.7–5.43)	0.2	1.97 (0.98–3.99)	0.059
Stage III/IV	Age (years)	1.04 (1.01–1.08)	0.016*	Na		Na		1.03 (1–1.06)	0.04*
	Plasma EBV DNA level (1,000 copy/mL)					Na			
	<1	1 (reference)		1 (reference)		1 (reference)			
	<10	0.83 (0.28–2.41)	0.728	0.24 (0.05–1.19)	0.081	0.69 (0.27–1.77)		0.438	
	≥10	1.01 (0.36–2.82)	0.989	2.7 (1.08–6.75)	0.033*	1.63 (0.73–3.66)		0.233	
	Stage[§]								
	III	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
	IV	2.23 (0.91–5.49)	0.081	1.21 (0.52–2.79)	0.659	0.83 (0.27–2.59)	0.754	1.21 (0.59–2.46)	0.603
	Chemotherapy								
	CCRT	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
	IC + CCRT	1.75 (0.69–4.39)	0.236	3.42 (1.3–8.97)	0.013*	1.92 (0.62–5.96)	0.259	2.69 (1.23–5.88)	0.014*

Variables that were statistically significant in the univariate analysis (as shown in Table S2) were selected. Survival curves are shown in *Figure 1* and Figure S1. [†,‡], Hazard ratios (HRs) and P values were calculated using multivariate Cox regression analysis. [§], According to the eighth edition of the AJCC/UICC staging system. *, P value <0.05. NPC, Nasopharyngeal carcinoma; HBsAg, hepatitis B surface antigen; +, positive; CCRT, concurrent chemotherapy; IC, induction chemotherapy; plasma EBV DNA level, plasma Epstein-Barr virus DNA level; OS, overall survival; DMFS, distant metastasis-free survival; LRFS, local recurrence-free survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

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Table S4 Clinical characteristics of nasopharyngeal carcinoma patients in the matched-pair analysis

Variables	HBsAg(+)			HBsAg(–)			Mixed		
	CCRT (N=69)	IC + CCRT (N=69)	P value†	CCRT (N=296)	IC + CCRT (N=296)	P value†	CCRT (N=372)	IC + CCRT (N=372)	P value†
Age (years)			1.000			0.004*			0.006*
Median (IQR)	44 (37–53)	45 (37–49)		47 (40–58)	45 (39–52)		47 (39–56)	45 (38–52)	
Sex			0.532			0.399			0.675
Male	56 (81.2%)	52 (75.4%)		211 (71.3%)	221 (74.7%)		272 (73.1%)	278 (74.7%)	
Female	13 (18.8%)	17 (24.6%)		85 (28.7%)	75 (25.3%)		100 (26.9%)	94 (25.3%)	
Histologic type			1.000			0.680			1.000
WHO type 1/2	2 (2.9%)	2 (2.9%)		14 (4.7%)	11 (3.7%)		12 (3.2%)	12 (3.2%)	
WHO type 3	67 (97.1%)	67 (97.1%)		282 (95.3%)	285 (96.3%)		360 (96.8%)	360 (96.8%)	
Plasma EBV DNA level (1000 copy/mL)			0.000*			0.034*			0.003*
<1	44 (63.8%)	20 (29%)		155 (52.4%)	124 (41.9%)		194 (52.2%)	149 (40.1%)	
<10	11 (15.9%)	28 (40.6%)		80 (27%)	103 (34.8%)		99 (26.6%)	136 (36.6%)	
>10	14 (20.3%)	21 (30.4%)		61 (20.6%)	69 (23.3%)		79 (21.2%)	87 (23.4%)	
T classification‡			1.000			1.000			1.000
T1	14 (20.3%)	14 (20.3%)		58 (19.6%)	58 (19.6%)		73 (19.6%)	73 (19.6%)	
T2	7 (10.1%)	7 (10.1%)		40 (13.5%)	40 (13.5%)		53 (14.2%)	53 (14.2%)	
T3	38 (55.1%)	38 (55.1%)		129 (43.6%)	129 (43.6%)		167 (44.9%)	167 (44.9%)	
T4	10 (14.5%)	10 (14.5%)		69 (23.3%)	69 (23.3%)		79 (21.2%)	79 (21.2%)	
N classification‡			1.000			1.000			1.000
N0	12 (17.4%)	12 (17.4%)		28 (9.5%)	28 (9.5%)		40 (10.8%)	40 (10.8%)	
N1	42 (60.9%)	42 (60.9%)		215 (72.6%)	215 (72.6%)		257 (69.1%)	257 (69.1%)	
N2	11 (15.9%)	11 (15.9%)		48 (16.2%)	48 (16.2%)		64 (17.2%)	64 (17.2%)	
N3	4 (5.8%)	4 (5.8%)		5 (1.7%)	5 (1.7%)		11 (3%)	11 (3%)	
Stage‡			1.000			1.000			1.000
II	18 (26.1%)	18 (26.1%)		87 (29.4%)	87 (29.4%)		105 (28.2%)	105 (28.2%)	
III	37 (53.6%)	37 (53.6%)		135 (45.6%)	135 (45.6%)		177 (47.6%)	177 (47.6%)	
IV	14 (20.3%)	14 (20.3%)		74 (25%)	74 (25%)		90 (24.2%)	90 (24.2%)	
Volume (cm^3)			0.967			0.919			0.652
Median (IQR)	27.6 (18.1–47.5)	28.2 (16.8–49.7)		30 (17.7–50.6)	29 (17–48.8)		30 (17.8–49.9)	28.6 (16.8–47.5)	

T and N classifications were used for 1:1 random pairing matching, which can be used to eliminate some known confounding factors such as stage and may further eliminate some unknown confounding factors. The mixed pairs were set as reference pairs, which do not consider the status of HBsAg when pairing. †, 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. *, P value <0.05. HBsAg, hepatitis B surface antigen; +, positive; –, negative; CCRT, concurrent chemotherapy; IC, induction chemotherapy; IQR, interquartile range; WHO, World Health Organization; plasma EBV DNA level, plasma Epstein-Barr virus DNA level.

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Table S5 HBV-related clinical characteristics of nasopharyngeal carcinoma patients during chemotherapy

Variables	Hospital 1 (N=719)	HBsAg(–) (N=897)	HBsAg(+) (N=179)	P value[a]
ALT				0.002
<50 U/L	584 (81.2%)	490 (83.3%)	94 (71.8%)	
≥50 U/L	135 (18.8%)	98 (16.7%)	37 (28.2%)	
AST				0.004
<40 U/L	640 (89%)	533 (90.6%)	107 (81.7%)	
≥40 U/L	79 (11%)	55 (9.4%)	24 (18.3%)	
ALT/AST				0.013
≤1	579 (80.5%)	484 (82.3%)	95 (72.5%)	
>1	140 (19.5%)	104 (17.7%)	36 (27.5%)	
Antiviral treatment				<0.001
None treatment/record	690 (96%)	588 (100%)	102 (77.9%)	
Yes	29 (4%)	0 (0%)	29 (22.1%)	
HBV DNA level				<0.001
None record/undetected	690 (96%)	588 (100%)	102 (77.9%)	
<1000 copies/mL	6 (0.8%)	0 (0%)	6 (4.6%)	
≥1000 copies/mL	23 (3.2%)	0 (0%)	23 (17.6%)	

[a], P values were calculated using Fisher's exact test or the Chi-square test for categorical variables. ALT, alanine aminotransferase; AST, aspartate transaminase.

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