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# Induction Chemotherapy Has No Prognostic Value in Patients with Locoregionally Advanced Nasopharyngeal Carcinoma and Chronic Hepatitis B Infection in the IMRT Era

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## Abstract

*BACKGROUND:* The effectiveness of induction chemotherapy (IC) followed by concurrent chemoradiotherapy (CCRT) over CCRT alone in patients with locoregionally advanced nasopharyngeal carcinoma (NPC) and chronic hepatitis B infection in the intensity-modulated radiotherapy (IMRT) era is unknown. *PATIENTS AND METHODS:* A total of 249 patients with stage T1-2 N2-3 or T3-4 N1-3 NPC and chronic hepatitis B infection treated with IMRT were retrospectively reviewed. Propensity score matching (PSM) was employed to balance covariates; 140 patients were propensity-matched (1:1 basis). Survival outcomes in the IC + CCRT and CCRT groups were compared using the Kaplan–Meier method, log-rank test and Cox proportional hazards model. *RESULTS*: No significant survival differences were observed between IC + CCRT and CCRT (5-year overall survival, 88.3% vs. 82.2%; $P = .484$; disease-free survival, 73.9% vs. 75.2%; $P = .643$; distant metastasis-free survival, 84.1% vs. 85.1%; $P = .781$; and locoregional failure-free survival, 87.9% vs. 85.1%; $P = .834$). After adjusting for known prognostic factors in multivariate analysis, IC was not an independent prognostic factor for any outcome (all $P > .05$); subgroup analysis based on T category (T1-2/T3-4), N category (N0-1/N2-3), and overall stage (III/IV) confirmed these results. The incidence of hepatic function damage in the IC + CCRT and CCRT groups was not significantly different. *CONCLUSION*: IC + CCRT leads to comparable survival outcomes and hepatic function damage compared to CCRT alone in patients with locoregionally advanced NPC with chronic hepatitis B infection in the IMRT era. Further investigations are warranted.

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## Introduction

Nasopharyngeal carcinoma (NPC) is a specific head and neck cancer with an extremely varied distribution; the incidence is extremely high in southern China (15 to 50 per 100,000) [1]. Over 70% of patients have locoregionally advanced disease at diagnosis [2]. The population of Southern China has one of the highest hepatitis B virus (HBV) surface antigen (HBsAg)-positive rates in the world (10% to 12%) [3,4]. Chronic HBV infection has been confirmed to be an independent adverse prognostic indicator of overall survival (OS), progression-free survival (PFS), and locoregional recurrence-free survival (LRRFS) in locoregionally advanced NPC [4].

The primary treatment modality for non-metastatic NPC is radiotherapy (RT), as the tumor is in an anatomically complex region

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and is radiosensitive [5,6]. NPC is also chemosensitive, and chemotherapy has been used in conjunction with RT to improve local control or reduce distant failure [7–10]. Indeed, concurrent chemoradiotherapy (CCRT) is now recommended as a standard treatment for locoregionally advanced NPC. Although additional induction chemotherapy (IC) has been suggested to further reduce the risk of locoregional recurrence, distant metastasis, and improve OS, clinical trials in the last few decades have reached conflicting conclusions regarding the value of IC followed by CCRT in locoregionally advanced NPC [11–15]. However, a meta-analysis by Ouyang et al. demonstrated IC could effectively improve overall survival and reduce distant metastasis [16]. To complicate matters, intensive chemotherapy regimens can contribute to reactivation of the HBV and lead to further liver function damage in patients with HBV infection [17,18], which may interrupt treatment and negatively affect prognosis.

Consequently, conservative treatment strategies need to be selected for NPC patients with chronic HBV. However, the prognostic value of IC in patients with locoregionally advanced NPC and chronic HBV in the IMRT era is unknown. Therefore, we conducted a retrospective study to compare survival outcomes and hepatic function damage in patients with chronic HBV treated with IC plus CCRT or CCRT based on IMRT in order to refine treatment strategy selection. To reduce possible biases to a minimum, a propensity score matching (PSM) method was employed to decrease potential bias in this retrospective analysis.

## Materials and Methods

### *Patient Selection and Clinical Staging*

We retrospectively assessed 2192 newly diagnosed patients with biopsy-proven stage I-IVB NPC treated with IMRT at our center between April 2009 and September 2013. The eligibility criteria were: (1) stage III-IVB NPC; (2) HBsAg seropositivity; (3) treated with IC ± CCRT; (4) Karnofsky performance score ≥70; (4) age ≥18 years old; 249 patients met these eligibility criteria. Conventional staging workup included a detailed patient history and physical examination, hematology and biochemistry profiles, magnetic resonance imaging (MRI) of the neck and nasopharynx, chest radiography or computed tomography (CT), abdominal ultrasonography or CT, single photon emission computed tomography (SPECT) bone scan, as well as positron emission tomography (PET)-CT if necessary.

All patients were restaged according to the 8th edition of the American Joint Commission on Cancer (AJCC)/International Union Against Cancer (UICC) staging system. All MRI imaging and clinical records were reviewed to minimize heterogeneity during restaging. Two radiologists employed at our hospital separately evaluated all scans and disagreements were resolved by consensus. As this was a retrospective analysis of routine clinical data, a waiver of the requirement for individual informed consent was granted by the ethics committee of our Cancer Center.

### *Treatment*

All patients received definitive IMRT as primary treatment. The target volumes were defined according to the International Commission on Radiation Units and Measurements reports 50 and 62 [19]. The cumulative radiation doses were 66 to 72 Gy in 28 to 33 fractions to the planning target volume (PTV) of the primary gross tumor volume (GTVnx), 64 to 70 Gy to the PTV of the GTV of the involved lymph nodes (GTVnd), 60 Gy or greater to the PTV of the high-risk clinical target volume (CTV1), and 50 Gy or greater to the PTV of the low-risk clinical target volume (CTV2). All patients were treated following a routine schedule with one fraction daily 5 days per week.

During the study period, institutional guidelines recommended CCRT ± define IC for stage III to IVA-B NPC. Concomitant chemotherapy was 30 to 40 $mg/m^2$ cisplatin administered weekly or 80 to 100 $mg/m^2$ cisplatin administered on weeks 1, 4, and 7 of radiotherapy, beginning the first day of IMRT. IC consisted of 80 $mg/m^2$ cisplatin plus 1000 $mg/m^2$ 5-fluorouracil (PF); 75 $mg/m^2$ cisplatin plus 75 $mg/m^2$ docetaxel (TP); or 60 $mg/m^2$ cisplatin plus 600 $mg/m^2$ 5-fluorouracil plus 60 $mg/m^2$ docetaxel (TPF); a total of two or three cycles were delivered every 3 weeks before radiotherapy. Prophylactic antiviral therapy was not routinely administered.

### *Liver Function Studies*

All patients underwent routine liver function tests, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBIL) before treatment, every 14 days during treatment, and at each follow-up visit. Hepatic dysfunction and adverse events were evaluated using National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 score, as follows: ALT/AST, Grade 1: upper limit of normal to ≤3 times upper limit of normal; Grade 2: 3 to ≤5 times upper limit of normal; Grade 3: 5 to ≤20 times upper limit of normal; Grade 4: >20 times upper limit of normal. TBIL: Grade 1: upper limit of normal to ≤1.5 times upper limit of normal; Grade 2: 1.5 to ≤3 times upper limit of normal; Grade 3: 3 to ≤10 times upper limit of normal; Grade 4: >10 times upper limit of normal. The highest grade of ALT/AST/TBIL was defined as the degree of liver function damage.

### *Follow-Up*

Every 3 to 6 months during the first 3 years and every 6 to 12 months thereafter (or until death), clinical symptoms, physical examination, and imaging protocols similar to the pretreatment assessment were conducted at every follow-up visit to detect possible relapse or distant metastasis. Local relapse was diagnosed by MRI of the nasopharynx, biopsy, or both. Regional relapse was defined by clinical examination and MRI of the neck and fine needle aspiration of the lymph nodes, if necessary. Distant metastases were diagnosed based on clinical symptoms, physical examinations and imaging methods including MRI, chest radiography, abdominal sonography and bone scan. Patients whose attendance at recent examinations tests was not recorded in their medical records were followed-up by telephone.

### *Statistical Analysis*

All statistical analyses were performed using Statistical Product and Service Solutions (SPSS) version 19.0 software (IBM, Armonk, NY, USA). A propensity score matching method was employed to match the patients from the IC + CCRT group to the CCRT group on a 1:1 basis. Propensity scores were computed for every patient by logistic regression based on the following covariates: age, gender, histological type, T category, N category and clinical stage. The chi-square test or Fisher's exact test were used to compare categorical and continuous variables between groups. OS, DMFS, DFS, and LRRFS curves were

plotted using the Kaplan–Meier method and compared using the log-rank test. Multivariate analysis was conducted via the Cox proportional hazard regression model to estimate hazard ratios (HR), 95% confidence intervals (CI) and test the independent significance of factors including age (≤ 45, >45 years), gender (male vs. female), histological type (type I vs. II, III); T category (T1-2 vs. T3-4), N category (N0-1 vs. N2-3), and IC (yes vs. no). Two-tailed $P < 0.05$ was considered significant.

## Results

### *Baseline Characteristics and Patterns of Failure*

Overall, 136 (54.6%) eligible patients received IC. Following propensity score matching, 70 patients belonging to the IC + CCRT group and 70 patients belonging to the CCRT group remained in the propensity-matched cohort. The patients in both groups were well-balanced with respect to age, gender, histological type, T category, N category and clinical stage (all $P > .05$; Table 1). Median follow-up was 61 months (range, 15.6 to 83.7 months); median age at diagnosis was 43 (range, 20 to 72)-years-old, the male ($n$ = 109)-to-female ($n$ = 31) ratio was 3.5:1. Histologically, 97.1% (136/140) patients had World Health Organization (WHO) type III disease and 2.8% (4/140) had WHO type I or type II disease, and 68/140 (48.6%) patients received prophylactic antiviral therapy.

By last follow-up, 19/70 patients (27.1%) in the IC + CCRT group and 17/70 (24.3%) in the CCRT group had experienced tumor progression ($P$ = .344): four (7.4%) patients in the IC + CCRT group and six (9.0%) in the CCRT group developed local recurrence; seven (10.3%) patients in the IC + CCRT group and five (7.6%) in the CCRT group experienced regional recurrence ($P$ = .582); and 11 (15.7%) patients in the IC + CCRT group and nine (12.9%) in the CCRT group experienced distant metastasis ($P$ = .629). A total of 21 patients (15.0%) died, including 20 (14.3%) who died due to NPC and one (0.7%) who died of another cause.

**Table 1.** Baseline characteristics of the 140 pair-matched HBsAg-positive patients with locoregionally advanced nasopharyngeal carcinoma

| | IC + CCRT | CCRT | $P$[a] |
|---|---|---|---|
| Characteristic | | | |
| Age (years) | | | 0.604 |
| ≤45 | 44 | 41 | |
| 45 | 26 | 29 | |
| Gender | | | 0.541 |
| Male | 56 | 53 | |
| Female | 14 | 17 | |
| WHO pathology | | | 0.506 |
| Type I | 1 | 2 | |
| Type II | 0 | 1 | |
| Type III | 69 | 67 | |
| T category[b] | | | 0.287 |
| T1 | 4 | 4 | |
| T2 | 5 | 2 | |
| T3 | 54 | 50 | |
| T4 | 7 | 14 | |
| N category[b] | | | 0.407 |
| N0 | 9 | 8 | |
| N1 | 35 | 44 | |
| N2 | 12 | 10 | |
| N3 | 14 | 8 | |
| Overall stage[b] | | | 1 |
| III | 49 | 49 | |
| IV | 21 | 21 | |

Abbreviations: IC = Induction chemotherapy; CCRT = concurrent chemotherapy.
[a] $P$-values were calculated using the chi-square test or Fisher exact test.
[b] According to the 8th edition of the AJCC/UICC staging system.

### *Prognostic Value of IC*

The 5-year OS, DFS, DMFS, and LRRFS rates for the entire cohort were 85.2%, 74.6%, 84.6%, and 86.6%, respectively. Five-year OS (88.3% vs. 82.2%; $P$ = .484; Figure 1*A*), DFS (73.9% vs. 75.2%; $P$ = .643; Figure 1*B*), DMFS (84.1% vs. 85.1%; $P$ = .781; Figure 1*C*) and LRRFS (87.9% vs. 85.1%; $P$ = .834; Figure 1*D*) were not significantly different between the IC + CCRT and CCRT groups. Multivariate analysis to adjust for various prognostic factors validated IC was not associated with a significant improvement in OS (HR, 0.665; 95% CI, 0.279 to 1.587; $P$ = .358), DFS (HR, 0.864; 95% CI, 0.546 to 2.055; $P$ = .864), DMFS (HR, 1.007; 95% CI, 0.425 to 2.386; $P$ = .987) or LRRFS (HR, 0.932; 95% CI, 0.372 to 2.333; $P$ = .880; Table 2).

### *Subgroup Analysis*

Subgroup analyses of IC based on T category, N category, and clinical stage are presented in Table 3. No survival differences were observed between the IC + CCRT and CCRT groups in the subgroups of patients with stage III NPC, stage IV NPC, N0-1 disease, N2-3 disease, T1-2 disease, or T3-4 disease (Table 3).

### *Hepatic Adverse Events*

The results of liver function tests performed before and during treatment were available for all patients. No grade 4 hepatic adverse events were observed in any patient either before or during treatment. The incidence of hepatic adverse events was similar in the IC + CCRT and CCRT groups both before and during treatment. Before treatment, 21, two, and no patients suffered grade 1, 2, and 3 hepatic adverse events, respectively, in the CCRT group compared to 14, four, and two in the IC + CCRT group ($P$ = .245). Thirty-four, eight, and five patients in the IC + CCRT group suffered grade 1, 2, and 3 hepatic adverse events during treatment compared to 35, five, and two patients in the CCRT group, respectively ($P$ = 0478).

## Discussion

This is the first attempt to compare the survival outcomes and toxicities of IC plus CCRT with CCRT alone in patients with locoregionally advanced NPC with chronic HBV infection treated using IMRT. Using PSM to balance the potential influence of age, gender, histological type, T category, N category and clinical stage ensured the matched patients were well-balanced; therefore, our comparisons of survival outcomes and toxicities should be reliable. The most important finding of this study was that the addition of IC to CCRT did not lower the risk of death, locoregional relapse or distant metastasis in patients with locoregionally advanced NPC with chronic HBV infection.

Liu et al. [4] retrospectively assessed 1301 patients with stage I to IVb NPC treated with radiotherapy or chemoradiotherapy, of whom 142 had chronic HBV infection. Chronic HBV infection was demonstrated to be an unfavorable, independent prognostic factor in patients with locoregionally advanced NPC: HBsAg-positive patients had poorer OS, PFS, and LRRFS compared to HBsAg-negative patients. The National Comprehensive Cancer Network currently recommended CCRT as the standard treatment for locoregionally advanced NPC and its survival benefits are well-demonstrated [7,9,10,20-24]. Over the last decade, much attention has been paid to assessment of the prognostic value of adding IC to CCRT in locoregionally advanced NPC [11–16,25,26], as it may improve LRRFS, DMFS and OS. Though the results obtained are

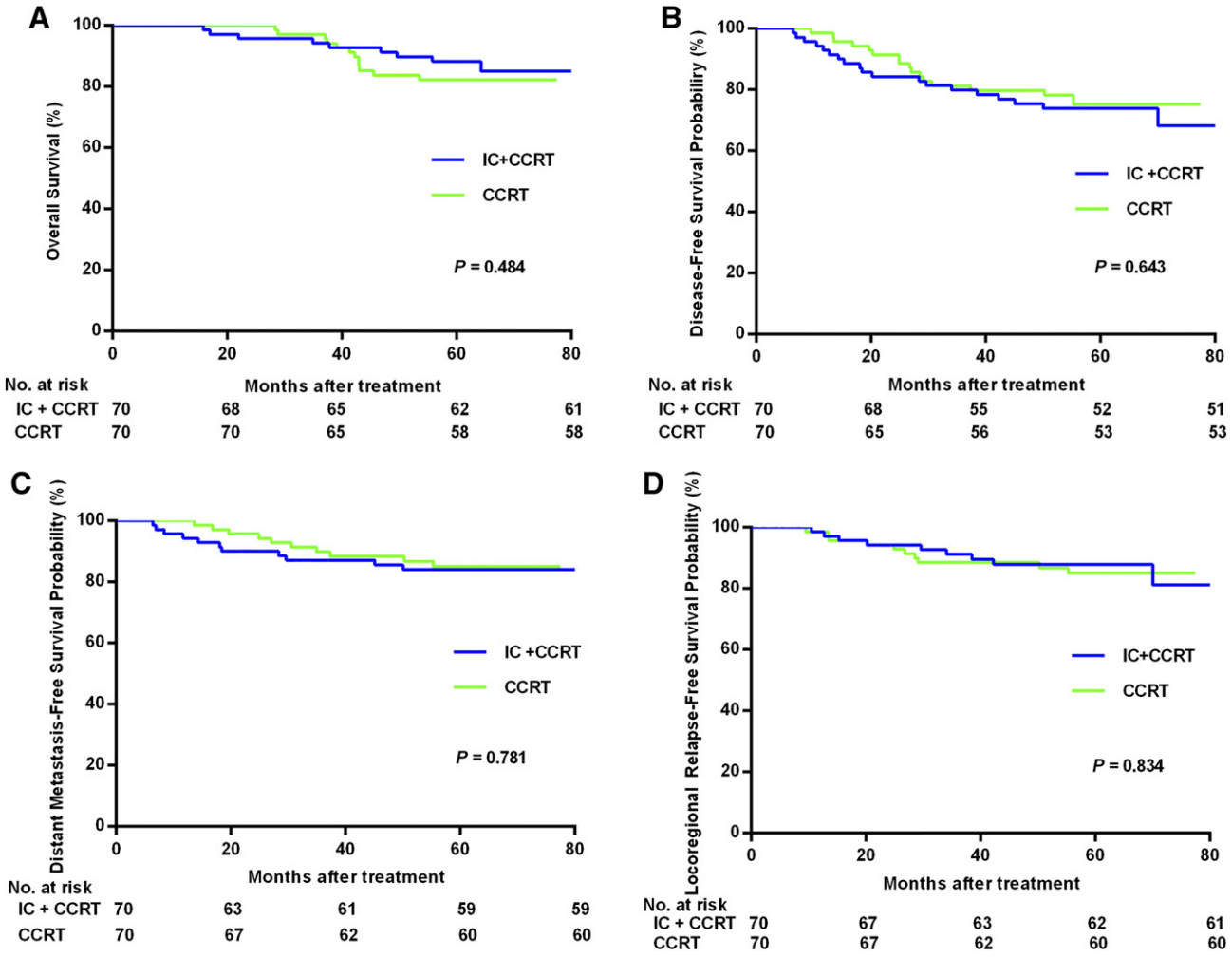


**Figure 1.** Kaplan–Meier overall (A), disease-free (B), distant metastasis-free (C), and locoregional relapse-free (D) survival curves for the 140 patients with nasopharyngeal stratified as the IC (induction chemotherapy) + CCRT (concurrent chemotherapy) group and CCRT group. All categories are based on the 8th edition of the Union for International Cancer Control/American Joint Committee on Cancer staging system.

controversial, a meta-analysis of these trials conducted by Ouyang et al. [16] indicated IC could effectively enhance OS and reduce distant metastasis in locoregionally advanced NPC. Due to the higher risk of death and recurrence among HBsAg-positive patients than HBsAg-negative patients, IC could possibly improve OS in HBsAg-negative patients with locoregionally advanced NPC. However, chemotherapy may contribute to HBV reactivation and liver function damage in HBV-infected patients with cancer [17,18]. Hence, we conducted this retrospective study to evaluate the prognostic value and toxicities of additional IC before CCRT in HBsAg-positive patients with locoregionally advanced NPC treated with IMRT.

**Table 2.** Multivariate analysis of prognostic factors for the 140 pair-matched HBsAg-positive patients with locoregionally advanced nasopharyngeal carcinoma

| Endpoints | Variable | HR (95% CI) | *P* |
|---|---|---|---|
| OS | | | |
| | IC | 0.665 (0.279–1.587) | 0.358 |
| | N category | 2.723 (1.097–6.762) | 0.031 |
| | Age | 3.010 (1.206–7.517) | 0.018 |
| DFS | IC | 0.864 (0.546–2.055) | 0.864 |
| | N category | 1.996 (1.028–3.874) | 0.041 |
| | Age | 2.295 (1.167–4.511) | 0.016 |
| DMFS | IC | 1.007 (0.425–2.386) | 0.987 |
| | N category | 2.727 (1.138–6.538) | 0.024 |
| LRRFS | IC | 0.932 (0.372–2.333) | 0.880 |
| | Age | 3.506 (1.331–9.236) | 0.011 |

Abbreviations: IC = Induction chemotherapy; OS = overall survival; DFS = disease free survival; DMFS = distant metastasis-free survival; LRRFS = locoregional relapse-free survival; CI = confidence interval; HR = hazard ratio; *The following parameters were included in the Cox proportional hazards model multivariate analysis with backward elimination: age (>45 vs. ≤45 years), gender (female vs. male), WHO pathology (Type I-II vs. Type III), T category (T1-2 vs. T3-4), N category (N1-2 vs. N2-3) chemotherapy (yes vs. no), and IC (yes vs. no).

Adjusting for the influence of age, gender, histological type, T category, N category, and clinical stage, the survival rates of HBsAg-positive patients with locoregionally advanced NPC were similar in the IC + CCRT and CCRT groups. Moreover, subgroup analysis based on T category, N category, and overall stage confirmed IC does not enhance OS. Several factors could explain these negative results. It is possible that IC does not actually improve OS in HBsAg-positive patients or alternatively, the relatively small sample size (70 matched patients per group) may result in low statistical power to detect survival differences.

The incidence and grade of hepatic adverse events was not significantly different between the IC + CCRT and CCRT groups before and during treatment, indicating IC does not aggravate HBV reactivation and related hepatic function damage. Two factors may

**Table 3.** Subgroup analysis of survival outcomes of patients with HBsAg-positive locoregionally advanced nasopharyngeal carcinoma in the IC + CCRT and CCRT groups

| | T1-2 | | *P* | T3-4 | | *P* | N0-1 | | *P* | N2-3 | | *P* | Stage III | | *P* | Stage IV | | *P* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | IC + CCRT | CCRT | | IC + CCRT | CCRT | | IC + CCRT | CCRT | | IC + CCRT | CCRT | | IC + CCRT | CCRT | | IC + CCRT | CCRT | |
| OS | 88.9% | 83.3% | 0.806 | 88.1% | 82.1% | 0.517 | 93.0% | 87.8% | 0.650 | 79.9% | 67.4% | 0.362 | 89.6% | 89.3% | 0.779 | 85.2% | 65.5% | 0.189 |
| DFS | 77.8% | 66.7% | 0.767 | 73.3% | 76.2% | 0.553 | 79.1% | 81.9% | 0.516 | 65.6% | 57.4% | 0.676 | 75.3% | 87.5% | 0.081 | 71.4% | 46.8% | 0.249 |
| DMFS | 77.8% | 83.3% | 0.735 | 85.0% | 85.3% | 0.901 | 90.7% | 89.6% | 0.923 | 72.9% | 73.0% | 0.980 | 85.6% | 91.6% | 0.352 | 81.0% | 69.8% | 0.598 |
| LRRFS | 100% | 80.0% | 0.206 | 86.2% | 85.6% | 0.898 | 88.0% | 89.9% | 0.549 | 88.6% | 71.8% | 0.202 | 87.2% | 91.5% | 0.331 | 90.2% | 69.3% | 0.134 |

Abbreviations: NPC = nasopharyngeal carcinoma; IC = induction chemotherapy. CCRT = concurrent chemotherapy; OS = 5-year overall survival; DFS = 5-year disease free survival; DMFS = 5-year distant metastasis-free survival; LRRFS = 5-year locoregional relapse-free survival.

explain this result. Firstly, compared with concurrent chemotherapy, additional IC may not be intense enough to further increase the severity of hepatic function damage. Secondly, as chemotherapy may contribute to HBV reactivation and hepatic complications in patients with cancer and chronic HBV infection, anti-HBV therapy was administered to almost half of patients during treatment in the current study. A previous study demonstrated anti-HBV therapy, such as prophylactic lamivudine, can significantly reduce the incidence of HBV reactivation and hepatic function damage in patients with NPC undergoing chemotherapy [27].

In summary, this study suggests IC plus CCRT is not more effective than CCRT alone in patients with locoregionally advanced NPC and chronic HBV infection treated using IMRT. With regards to limitations, it should be noted that this was a retrospective analysis of medical records from a single institution, and the sample size was relatively small. Thus, the findings of this study require validation in prospective trials with large cohorts.

## Conclusion

Additional IC results in comparable survival and toxicities should not be administered to patients with locoregionally advanced NPC and chronic HBV infection treated with CCRT based on IMRT. Further large-scale prospective studies are warranted.

## Conflict of Interest Statement

The authors declare no conflict of interest.

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