


Optimal cumulative cisplatin dose in nasopharyngeal carcinoma patients receiving additional induction chemotherapy

Jia-Wei Lv¹ | Zhen-Yu Qi¹ | Guan-Qun Zhou¹ | Xiao-Jun He¹ | Yu-Pei Chen¹ | Yan-Ping Mao^{1,2} | Lei Chen^{1,3} | Ling-Long Tang¹ | Wen-Fei Li¹ | Ai-Hua Lin⁴ | Jun Ma¹ | Ying Sun¹ 

¹Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China

²Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, USA

³Department of Experimental Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

⁴Department of Medical Statistics and Epidemiology, School of Public Health, Sun Yat-sen University, Guangzhou, China

Correspondence

Ying Sun, Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China.

Email: sunying@sysucc.org.cn

Funding information

National Natural Science Foundation of China (No. 81402532); Overseas Expertise Introduction Project for Discipline Innovation (111 Project, B14035); Innovation Team Development Plan of the Ministry of Education (No. IR_17R110); Science and Technology Project of Guangzhou City, China (No. 2014J4100182).

To clarify the optimal cumulative cisplatin dose (CCD) in locoregionally-advanced nasopharyngeal carcinoma (NPC) patients receiving induction chemotherapy (IC) plus concurrent chemoradiotherapy (CCRT). Using the NPC-specific database from the established big-data intelligence platform at Sun Yat-Sen University Cancer Center, 583 non-disseminated, locoregionally-advanced NPC patients receiving IC plus CCRT were enrolled. Propensity score matching (PSM) analysis was conducted to control for confounding factors. The median CCD was 160 mg/m² after IC (range, 40-300 mg/m²); only 74 patients (12.7%) achieved CCD >200 mg/m². Patients receiving >200 mg/m² CCD did not show significantly improved 5-year overall survival (OS) (HR = 1.19; 95% confidence intervals [CI] 0.69-2.06, *P* = .53) and progression-free survival (PFS) (HR = 1.03; 95% CI: 0.63-1.68, *P* = .92) compared with patients receiving <200 mg/m² CCD. Further investigations of the potential of median CCD (160 mg/m²) to yield survival benefits revealed that there were no significant differences in survival endpoints between patients receiving CCD >160 mg/m² and CCD < 160 mg/m² in both the original and PSM cohorts. In addition, subgroup analysis indicated a favorable PFS, but not OS, with higher cisplatin administration in patients with pretreatment Epstein-Barr virus deoxyribonucleic acid (EBV DNA) <1000 copies/mL (HR = 0.26, 95% CI: 0.07-0.93, *P* = .03) and receiving <3 IC cycles (HR = 0.59, 95% CI 0.33-1.07, *P* = .08). Our analysis of real world data provided references for the optimal CCD in locoregionally-advanced NPC receiving additional IC. The causal relationship between 200 mg/m² CCD and improved survival was not defined; 160 mg/m² CCD might be enough. However, for patients with EBV DNA <1000 copy/mL and receiving <3 IC cycles, a higher dose might be necessary.

KEYWORDS

cumulative cisplatin dose, induction chemotherapy, intensity-modulated radiation therapy, nasopharyngeal carcinoma, real world data

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2017 The Authors. *Cancer Science* published by John Wiley & Sons Australia, Ltd on behalf of Japanese Cancer Association.

1 | INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a unique head and neck cancer with skewed epidemiology, pathology and response to treatment.¹ The highest incidence worldwide is reported among the Cantonese population of Guangdong Province, where rates ranged from 22.2 to 27.2 per 100 000 males and 9.8 to 11.1 per 100 000 females.²

Radiotherapy (RT) is the primary treatment modality for non-disseminated NPC due to its radiosensitivity and anatomical location. NPC is also known to be chemosensitive. The integration of cisplatin-based chemotherapy during RT greatly enhances the effects of RT, facilitates local control and improves therapeutic outcomes.^{3,4} Recently, adding induction chemotherapy (IC) before concurrent chemoradiotherapy (CCRT) has been found to greatly improve survival outcomes, and has been increasingly adopted worldwide based on the clinical data from several important large-scale multi-centre phase II-III randomized controlled trials (RCT), which strongly support the application of IC plus CCRT for locoregionally-advanced NPC.⁵⁻⁹

The cumulative cisplatin dose (CCD) administered during RT is an important factor in conferring survival benefits. In the majority of RCTs, 100 mg/m² cisplatin was administered every 3 weeks during RT. The importance of a third planned cisplatin cycle was first questioned by Ang et al.¹⁰ who reviewed the compliance levels of CCRT in RCT, and found that a substantial fraction of patients failed to receive the third cycle, and a cumulative dose of 200 mg/m² was sufficient to yield beneficial antitumor effects. Peng et al. also demonstrated that CCD >240 mg/m² was not prognostic in patients with locoregionally-advanced NPC, and that 200 mg/m² cisplatin may be adequate.¹¹ Furthermore, Loong and colleagues found that 200 mg/m² CCD had prognostic value in patients with stage II and III NPC, but not in patients with the highest risk.¹²

Accordingly, 200 mg/m² has been widely used as the optimal cutoff value in clinical practice, regardless of the specific treatment strategies. However, patients enrolled in the studies on which this value is based all received CCRT and a subpopulation did not receive intensity-modulated radiotherapy (IMRT). Moreover, several factors require consideration regarding patients receiving IC plus CCRT in the era of IMRT. First, IC greatly reduced tumor volume burden. Clinical complete response (cCR) and partial response (cPR) were observed in 11.3% and 79.6% of patients, respectively.¹³ Second, patients may be less able to tolerate the subsequent highly intensive CCRT after 2-4 cycles of IC. Data from published RCT showed that 36% of patients could not adhere to the second planned cisplatin, and that 76.7% of patients could not achieve the third.⁵ Third, IMRT is superior in the management of local control compared to conventional RT.^{14,15} Given these facts and the current lack of data, the suitability of 200 mg/m² CCD as the optimal cutoff value for locoregionally-advanced NPC patients receiving IC plus CCRT in the era of IMRT remains to be elucidated.

Real world data (RWD) are increasingly used to guide clinical practice and assist in the assessment of the "value" of the intervention, as they are characterized by variety, veracity and are

unfiltered compared with RCT data, which can be confounded by the selection of the patient population, rigorous administration and physician preferences.^{16,17} Therefore, RWD represent an important resource in research, and are promising in answering this question. Using an NPC population from an endemic area, we aimed to clarify the optimal CCD in locoregionally-advanced NPC patients receiving IC plus CCRT.

2 | MATERIALS AND METHODS

2.1 | Patient population and data extraction

The NPC-specific database from the well-established big-data intelligence platform at Sun Yat-Sen University Cancer Centre (SYSUCC) was adopted to identify 2940 patients with histologically-proven, non-disseminated NPC, diagnosed between January 2005 and December 2012. A detailed description of this database is presented in the Appendix S1. Using the search terms "diagnosis," "histology type," "stage classification," "radiotherapy" and "chemotherapy," we identified patients fulfilling the following inclusion criteria: (i) patient diagnosed as histologically-proven non-keratinising NPC; (ii) disease classified as stages III-IVb; (iii) patient received IC plus CCRT; (iv) received 2-4 cycles of IC; (v) received cisplatin-based concurrent chemotherapy (weekly or 3-weekly); and (vi) radiation delivery technique was IMRT. Finally, 583 eligible patients were enrolled in our analysis. The detailed selection process and study design are presented in Figure 1. This study was approved by the Clinical Research Ethics Committee of SYSUCC. The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit (RDD) public platform (<http://www.researchdata.org.cn>), with the approval RDD number as RDDA2017000364.

2.2 | Chemotherapy

The concurrent chemotherapy consisted of 40 mg/m² cisplatin administered every week for a maximum of 7 cycles, 80 mg/m² cisplatin administered every 3 weeks for a maximum of 3 cycles, or 100 mg/m² cisplatin administered every 3 weeks for a maximum of 3 cycles, beginning on the first day of RT or 3 weeks after the last cycle of IC.

The IC regimens included docetaxel/cisplatin/fluorouracil (TPF), docetaxel/cisplatin (TP), cisplatin/fluorouracil (PF), gemcitabine/cisplatin (GP) and others. Details of the dose and algorithm for dose adjustment in IC and CCRT are presented in the Appendix S1.

2.3 | Radiotherapy

All patients were treated with radical IMRT comprising 5 daily fractions delivered each week for 6-7 weeks. The prescribed doses were 66-72 Gy at 2.12-2.43 Gy/fraction to the planning target volume (PTV) of the primary gross tumor volume (GTVnx), 64-70 Gy/28-33 fractions to the PTV of the GTV of the involved lymph nodes (GTVnd), 60-63 Gy/28-33 fractions to the PTV of the high-risk

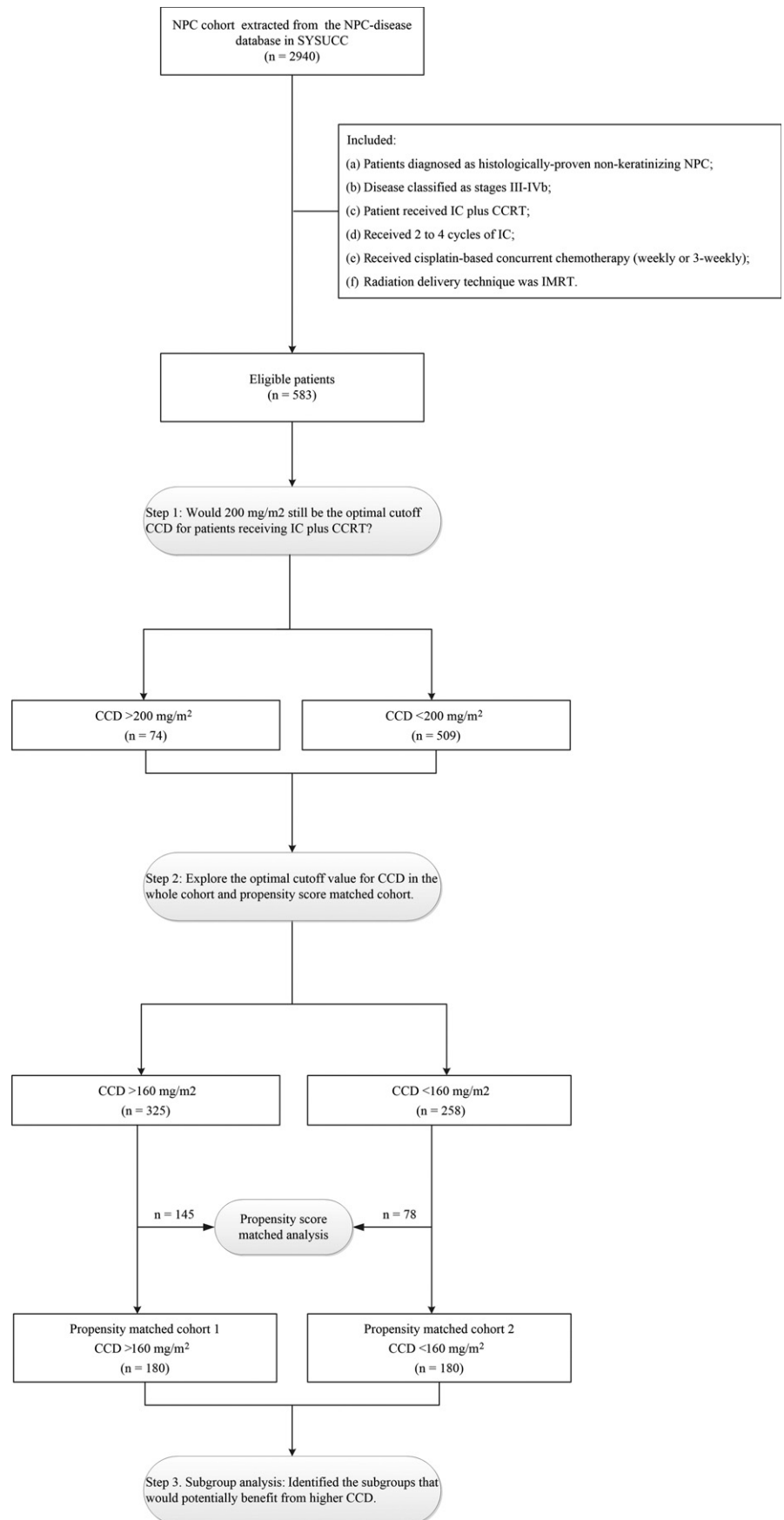


FIGURE 1 Flowchart showing the study design and patient selection process

clinical target volume (CTV1) and 54-56 Gy/28-33 fractions to the PTV of the low-risk clinical target volume (CTV2).

2.4 | Clinical staging, follow up and study endpoint

All patients were restaged according to the 8th edition of the UICC/AJCC staging system.¹⁸ Patients were followed up from the initiation of the treatment to the day of last examination or death. Details of the pretreatment examinations and follow-up strategies are shown in the Supplementary materials (Appendix S1).

The primary endpoint was overall survival (OS), which was calculated from the date of treatment initiation to death from any cause. The secondary endpoint was progression-free survival (PFS), defined as the time from treatment initiation to tumor progression or death; distant metastasis-free survival (DMFS) was defined as the time to tumor metastasis; and locoregional relapse-free survival (LRFS) was the time to the first locoregional relapse.

2.5 | Study design and statistical analysis

At the time this study was conducted, no data regarding the optimal CCD administered during RT for NPC patients receiving IC plus CCRT were available; however, published data suggested that a CCD of 200 mg/m², irrespective of the schedule, was necessary to confer benefit among patients treated with CCRT alone.^{11,12} Therefore, CCD of 200 mg/m² was used as the cutoff value in the first step of this study. We found that CCD of 200 mg/m² was not able to confer survival benefit in locoregionally-advanced NPC patients receiving IC plus CCRT. Next, we identified the median CCD after IC as 160 mg/m² in this cohort. Thus, we hypothesized that 160 mg/m² CCD might be sufficient to yield beneficial antitumor effects. Furthermore, we noted differences between 2 groups in terms of factors including age, tumor stage (T stage), node stage (N stage), disease stage, pretreatment Epstein-Barr virus deoxyribonucleic acid load (EBV DNA), IC regimens and IC cycles. To control for possible confounding factors and to minimize bias with respect to initial treatment selection, 2 well-balanced cohorts were generated through propensity score matching (PSM) analysis in the third step of the study,¹⁹ during which patients without complete data regarding EBV DNA were excluded (n = 111). Finally, subgroup analyses were conducted in the PSM cohort to identify the subgroups that might benefit most from the administration of higher doses of cisplatin after IC (Figure 1).

Propensity scores were calculated based on logistic regression for the following 8 variables: age, sex, year of diagnosis, T stage, N stage, pretreatment EBV DNA, IC cycles and IC regimens. Patients were matched without replacement at a 1:1 ratio using estimated propensity scores. The patient and tumor characteristics between groups were compared using the χ^2 -test (Fisher's exact test or Pearson's χ^2 -test where appropriate) for categorical variables and the Kruskal-Wallis test for continuous variables. Kaplan-Meier survival analysis was used to estimate the actuarial survival rates and log-rank tests were used for comparisons. The unadjusted Cox

proportional hazards model was used to calculate the hazard ratio (HR) in the subgroup analysis. The adjusted HR was calculated using the Cox regression mode, for the 8 factors (age, sex, year of diagnosis, T stage, N stage, pretreatment EBV DNA, IC cycles and IC regimens). The proportional hazards assumption was graphically verified on the basis of Schoenfeld residuals.²⁰ All analyses were performed using SPSS version 22.0 (SPSS, Chicago, IL, USA) and STATA version 12.0 (Stata Corporation, USA). Two-sided $P < .05$ was considered to indicate statistical significance.

3 | RESULTS

3.1 | Patient characteristics and treatment compliance

The baseline characteristics of 583 eligible patients were presented in Table 1. The median age at diagnosis was 44 years (range, 18-76 years); 48.5% of subjects were at stage III (n = 283) and 51.5% were at stage IV (n = 300). In total, 55.9% of patients (n = 326) received 2 cycles of IC, and 44.1% (n = 257) received 3-4 cycles. TPF was the most commonly used IC regimen (41.7%; n = 243). For 70.3% of the patients (n = 410), cisplatin was administered every 3 weeks during RT and 29.7% of the patients (n = 173) received weekly administration of cisplatin.

The median CCD for the whole cohort was 160 mg/m² (range, 40-300 mg/m²). In total, 325 patients (55.7%) received CCD >160 mg/m², and 258 (44.3%) received CCD <160 mg/m², while 509 patients (87.3%) received CCD <200 mg/m² and only 74 patients (12.7%) received CCD >200 mg/m².

During the median follow-up of 62.0 months (range, 3.3-85.6 months), 102 patients (17.5%) died, 102 patients (17.5%) developed distant metastases and 56 patients (9.6%) developed locoregional recurrence (34 patients had local recurrence, and 31 patients had regional recurrence). The 5-year OS, PFS, DMFS and LRFS values were 82.8%, 75.4%, 82.1% and 90.2%, respectively.

3.2 | Identification of the optimal cumulative cisplatin dose during radiotherapy in locoregionally-advanced nasopharyngeal carcinoma patients receiving induction chemotherapy plus concurrent chemoradiotherapy

Previously published data suggested that 200 mg/m² CCD was necessary to confer survival benefit among patients receiving CCRT alone. Therefore, we first investigated the potential of 200 mg/m² CCD in achieving survival benefit in locoregionally-advanced NPC patients treated with IC plus CCRT. Kaplan-Meier survival analysis indicated that there was no significant improvement in the prognosis of patients receiving CCD > 200 mg/m² in terms of 5-year OS (HR = 1.19; 95% confidence intervals [CI], 0.69-2.06, $P = .53$), PFS (HR = 1.03; 95% CI: 0.63-1.68, $P = .92$), DMFS (HR = 1.22; 95% CI: 0.70-2.10, $P = .49$) and LRFS (HR = 0.84; 95% CI: 0.36-1.96, $P = .68$; Figure 2).

TABLE 1 Basic characteristics of patients with nasopharyngeal carcinoma receiving induction chemotherapy plus concurrent chemoradiotherapy

Characteristics	All patients (n = 583)	CCD >160 mg/m ² (n = 325)	CCD <160 mg/m ² (n = 258)	P-value ^a
Sex				
Male	443 (76.0)	246 (75.7)	197 (76.4)	.85
Female	140 (24.0)	79 (24.3)	61 (23.6)	
Age (years)				
<45	306 (52.5)	183 (56.3)	123 (47.7)	.02
46-65	260 (44.6)	137 (42.2)	123 (47.7)	
>66	17 (2.9)	5 (1.5)	12 (4.7)	
Year of diagnosis				
2005-2010	224 (38.4)	114 (35.1)	110 (42.6)	.06
2011-2013	359 (61.6)	211 (64.9)	148 (57.4)	
T category ^b				
T1	25 (4.3)	16 (4.9)	9 (3.5)	.01
T2	46 (7.9)	22 (6.8)	24 (9.3)	
T3	317 (54.4)	161 (49.5)	156 (60.5)	
T4	195 (33.4)	126 (38.8)	69 (26.7)	
N category ^b				
N0	42 (7.2)	20 (6.2)	22 (8.5)	.22
N1	289 (49.6)	170 (52.3)	119 (46.1)	
N2	116 (19.9)	57 (17.5)	59 (22.9)	
N3	136 (23.3)	78 (24.0)	58 (22.5)	
Stage category ^b				
III	283 (48.5)	139 (42.8)	144 (58.5)	<.01
IV	300 (51.5)	186 (57.2)	114 (44.2)	
Pretreatment EBV DNA				
<1000 copies/mL	112 (19.2)	57 (17.5)	55 (21.3)	.21
≥1000 copies/mL	360 (61.7)	211 (64.9)	149 (57.8)	
Unkown	111 (19.0)	57 (17.5)	54 (20.9)	
IC cycles				
2 cycles	326 (55.9)	164 (50.5)	162 (62.8)	
3 cycles	218 (37.4)	153 (47.1)	65 (25.2)	
4 cycles	39 (6.7)	8 (2.5)	31 (12.0)	
IC regimens				
TPF	243 (41.7)	165 (50.8)	78 (30.2)	<.01
TP	185 (31.7)	84 (25.8)	101 (39.1)	
PF	142 (24.4)	71 (21.8)	71 (27.5)	
Others ^c	13 (2.2)	5 (1.5)	8 (3.1)	
CCRT regimens				
Weekly DDP	173 (29.7)	47 (14.5)	126 (48.8)	<.01
3-weekly DDP	410 (70.3)	278 (85.5)	132 (51.2)	

CCD, cumulative cisplatin dose; CCRT, concurrent chemotherapy; DDP, cisplatin; EBV DNA, Epstein-Barr virus deoxyribonucleic acid; IC, induction chemotherapy; N, node; T, tumor.

^aTwo-sided *P*-values were calculated using the χ^2 -test or Fisher's exact test if indicated.

^bAccording to the 8th edition of the American Joint Committee on Cancer.

^cOthers included gemcitabine plus cisplatin (GP) or patients with regimen alterations during the IC.

Having identified the median cisplatin dose after IC as 160 mg/m² in the whole cohort, we then hypothesized that 160 mg/m² CCD might be sufficient to yield beneficial effects. Kaplan-Meier survival analysis demonstrated that there were no statistically significant differences between patients receiving CCD > 160 mg/m² and patients receiving CCD <160 mg/m² in terms of 5-year OS (HR = 1.02; 95% CI: 0.69-1.50, *P* = .94), PFS (HR = 0.97; 95% CI: 0.70-1.35, *P* = .85), DMFS (HR = 1.04; 95% CI: 0.70-1.54, *P* = .85) and LRF5 (HR = 1.00; 95% CI: 0.59-1.69, *P* = .99; Figure 3).

3.3 | Clinical implications of 160 mg/m² cumulative cisplatin dose in the propensity score matched cohort

We then verified the role of 160 mg/m² CCD in the propensity score matched cohort to minimize bias in the initial treatment selection. After PSM, all covariates were well-balanced between the groups (Table 2). In a univariate analysis, no significant survival differences were observed between groups in terms of 5-year OS (HR = 0.81; 95% CI: 0.48-1.35, *P* = .41), PFS (HR = 0.89; 95% CI: 0.57-1.38, *P* = .59), DMFS (HR = 0.91; 95% CI: 0.56-1.49, *P* = .71) and LRF5 (HR = 0.73; 95% CI: 0.36-1.48, *P* = .38; Figure 4).

Multivariate analysis was performed to adjust for potential prognostic confounders, including IC cycles, IC regimens, age, sex, year of diagnosis, T category, N category and pretreatment EBV DNA. In accordance with the previous results, 160 mg/m² CCD was not identified as an independent prognostic factor for locoregionally-advanced NPC patients receiving IC plus CCRT in terms of 5-year OS (HR = 0.75; 95% CI: 0.44-1.27, *P* = .28), PFS (HR = 0.86; 95% CI: 0.55-1.33, *P* = .49), DMFS (HR = 0.90; 95% CI: 0.54-1.47, *P* = .66) and LRF5 (HR = 0.69; 95% CI: 0.34-1.42, *P* = .31). Table 3 shows all other variables associated with survival endpoints.

3.4 | Subgroup analysis

Subgroup analyses were further conducted for OS and PFS, to identify the subgroups that might benefit from the administration of higher cisplatin dose after IC. We found that there were no interactions between clinicopathologic variables and 160 mg/m² CCD with respect to OS (Figure 5A). However, interactions of 160 mg/m² CCD with pretreatment EBV DNA and IC cycles were observed with respect to PFS (*P*_{interaction} = 0.04; Figure 5B). In the subgroup of patients with pretreatment EBV DNA <1000 copies/mL, administration of CCD > 160 mg/m² tended to yield favorable prognosis (HR = 0.26; 95% CI: 0.07-0.93, *P* = .03), while the survival benefit was not observed in patients with pretreatment EBV DNA > 1000 copies/mL (HR = 1.12; 95% CI: 0.69-1.82, *P* = .64). In addition, there was potentially greater benefit for the subgroup of patients who received

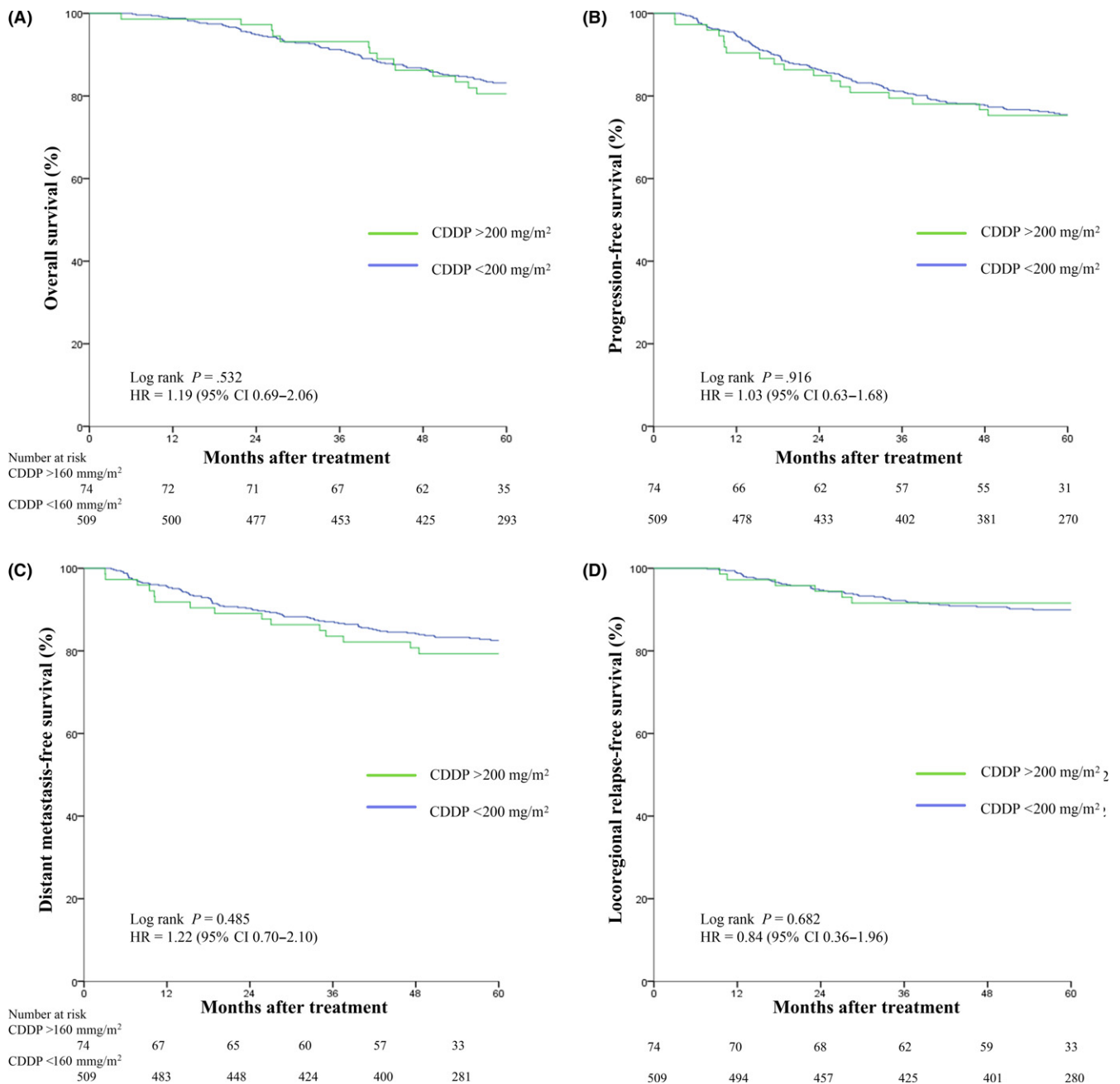


FIGURE 2 Kaplan-Meier survival analyses of: A, overall survival, B, progression-free survival, C, distant metastasis-free survival and D, locoregional relapse-free survival, in locoregionally-advanced NPC patients receiving IC plus CCRT, stratified by CCD >200 mg/m² and CCD <200 mg/m². CCD, cumulative cisplatin dose; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; NPC, nasopharyngeal carcinoma

2 cycles of IC with the higher dose of cisplatin administration (CCD > 160 mg/m²) after IC (HR = 0.59; 95% CI: 0.33–1.07, $P = .08$); however, this benefit was not observed in patients receiving more than 2 cycles of IC (HR = 1.50; 95% CI: 0.76–2.96, $P = .24$).

4 | DISCUSSION

It is generally recognized that 200 mg/m² CCD administered during RT is the optimal cutoff dose to yield survival benefit in NPC

patients receiving CCRT.^{11,12,21} However, with the success of several important large-scale multi-centre phase II–III RCT, an increasing number of patients are receiving IC plus CCRT; and a substantial proportion of patients are unable to tolerate 200 mg/m² CCD following IC, due to the increased therapeutic intensity. This has led to debate over the suitability of 200 mg/m² as the optimal cutoff CCD in these circumstances. To the best of our knowledge, this was the first real world investigation of the optimal cutoff CCD for locoregionally-advanced NPC patients receiving IC plus CCRT in the era of IMRT.

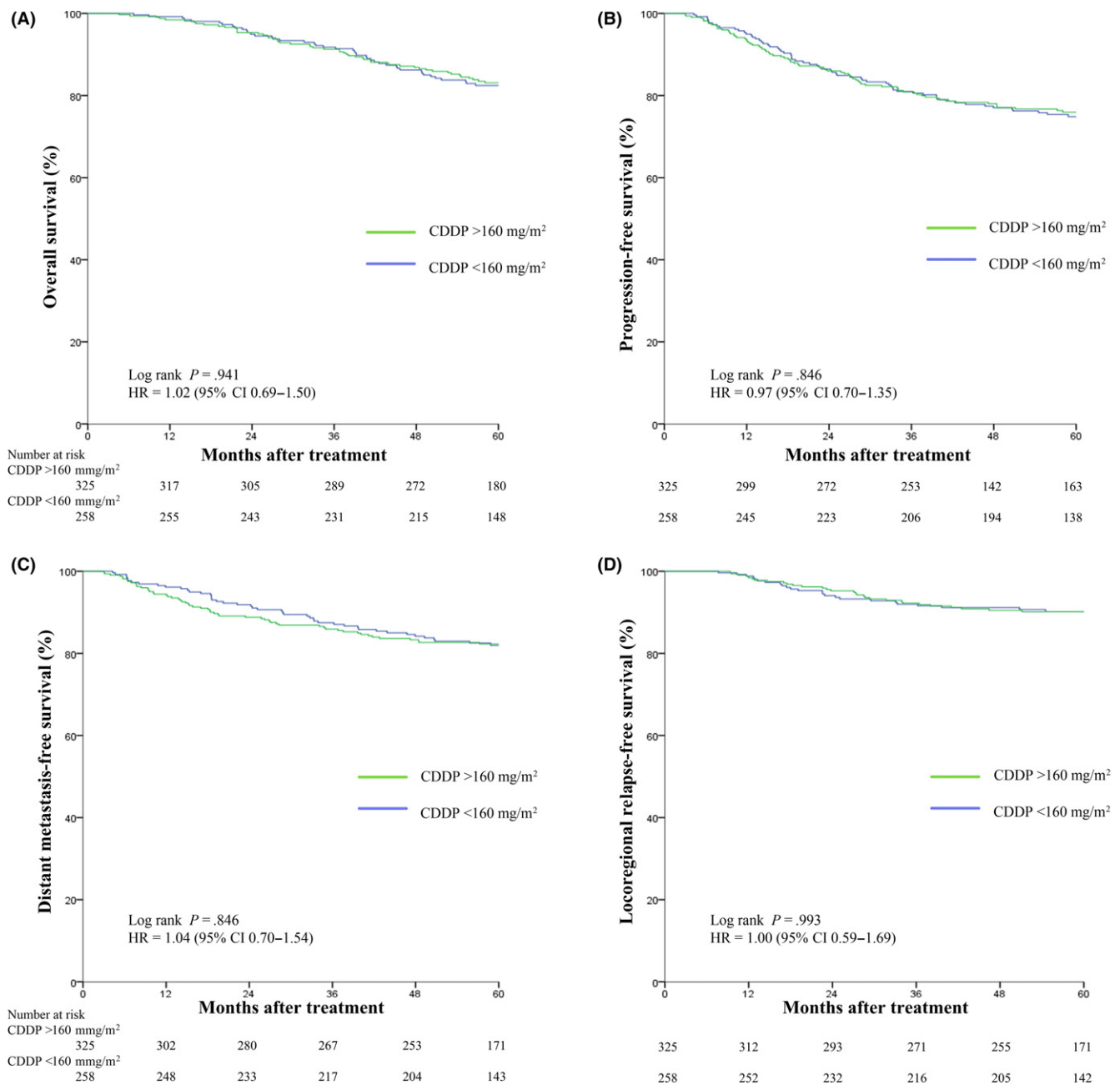


FIGURE 3 Kaplan-Meier survival analyses of: A, overall survival, B, progression-free survival, C, distant metastasis-free survival and D, locoregional relapse-free survival, in locoregionally-advanced NPC patients receiving IC plus CCRT, stratified by CCD >160 mg/m² and CCD <160 mg/m². CD, cumulative cisplatin dose; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; NPC, nasopharyngeal carcinoma

Our data indicate that there was no significant survival improvement in patients receiving >200 mg/m² CCD compared with those receiving <200 mg/m² CCD. In the whole cohort, the median CCD was 160 mg/m² after IC. Further investigations of the potential of a CCD of 160 mg/m² to yield survival benefits revealed that there were no significant differences between patients receiving CCD >160 mg/m² and those receiving CCD <160 mg/m² in relation to all survival endpoints both in the original and PSM cohorts. In addition, subgroup analysis demonstrated potentially favorable PFS, but not OS, in patients with pretreatment EBV

DNA <1000 copies/mL, and <3 cycles of IC with higher cisplatin administration.

In the present study, 200 mg/m² CCD did not yield significant improvements in survival outcomes in patients with locoregionally-advanced NPC receiving IC plus CCRT, while 160 mg/m² CCD might be enough to yield beneficial antitumor effects. This is in accordance with previously published reports.^{11,12,21} In the combined analyses of 2 prospective trials, NPC-9901 and NPC-9902,²¹ a total dose of cisplatin during the concurrent phase (>200 mg/m²) had a significant impact on LRFS and OS in the

TABLE 2 Comparison of basic characteristics in the entire cohort and propensity-score matched cohort

Characteristics	Entire cohort			Propensity-score matched cohort		
	CCD >160 mg/m ² (n = 325), %	CCD <160 mg/m ² (n = 258), %	P-value ^a	CCD >160 mg/m ² (n = 180), %	CCD <160 mg/m ² (n = 180), %	P-value ^a
Sex						
Male	246 (75.7)	197 (76.4)	.85	133 (73.9)	134 (74.4)	.90
Female	79 (24.3)	61 (23.6)		47 (26.1)	46 (25.6)	
Age (years)						
<45	183 (56.3)	123 (47.7)	.04	78 (43.3)	86 (47.8)	.40
≥45	142 (43.7)	135 (52.3)		102 (56.7)	94 (52.2)	
Year of diagnosis						
2005-2010	114 (35.1)	110 (42.6)	.06	58 (32.2)	54 (30.0)	.65
2011-2013	211 (64.9)	148 (57.4)		122 (67.8)	126 (70.0)	
T category ^b						
T1-2	38 (11.7)	33 (12.8)	.69	26 (14.4)	20 (11.1)	.34
T3-4	287 (88.3)	225 (87.2)		154 (85.6)	160 (88.9)	
N category ^b						
N0-1	190 (58.5)	141 (54.7)	.36	96 (53.3)	93 (51.7)	.75
N2-3	135 (41.5)	117 (45.3)		84 (46.7)	87 (48.3)	
Stage category ^b						
III	139 (42.8)	144 (58.5)	<.01	80 (44.4)	91 (50.6)	.25
IV	186 (57.2)	114 (44.2)		100 (55.6)	89 (49.4)	
Pretreatment EBV DNA						
<1000 copies/mL	57 (17.5)	55 (21.3)	.21	40 (22.2)	40 (22.2)	1.00
≥1000 copies/mL	211 (64.9)	149 (57.8)		140 (77.8)	140 (77.8)	
Unkown	57 (17.5)	54 (20.9)		—	—	
IC cycles						
2 cycles	164 (50.5)	162 (62.8)	<.01	104 (57.8)	97 (53.9)	.46
> 2 cycles	161 (49.5)	96 (37.2)		76 (42.2)	83 (46.1)	
IC regimen						
TPF	165 (50.8)	78 (30.2)	<.01	62 (34.4)	69 (38.3)	.44
TP+PF+others ^c	160 (49.2)	180 (69.8)		118 (65.6)	111 (61.7)	

CCD, cumulative cisplatin dose; CCRT, concurrent chemotherapy; DDP, cisplatin; EBV DNA, Epstein-Barr virus deoxyribonucleic acid; IC, induction chemotherapy; N, node; NPC, nasopharyngeal carcinoma; T, tumor.

^aTwo-sided *P*-values were calculated using the χ^2 -test or Fisher's exact test if indicated.

^bAccording to the 8th edition of the American Joint Committee on Cancer.

^cOthers included gemcitabine plus cisplatin (GP), or patients with regimen alterations during the IC. The following variables were used for propensity-score matching: age (≥45 vs <45 years), sex (female vs male), year of diagnosis (2011-2013 vs 2005-2010); tumor category (T 3-4 vs T 1-2); node category (N2-3 vs N0-1); pretreatment EBV DNA (≥1000 copies/mL vs <1000 copies/mL); IC cycles (>2 cycles vs 2 cycles); IC regimen (TPF vs all others).

stage III subgroup, but not in the stage IV subgroup. Loong and colleagues¹² also found that CCD > 200 mg/m² had prognostic value in patients with stage II and III NPC, but not in patients with stage IV disease. It can be speculated that this divergence in the results is because the patients enrolled in the previous studies received CCRT, and a substantial number of the patients did not receive IMRT. In contrast, all the patients included in the present study received IC plus CCRT, and the radiotherapy modality was consistently IMRT. The rationale for the decreased CCD was based on the reduced tumor volume after IC,^{7,13} impaired medication adherence after intensive IC,⁵ increased survival outcomes by

adding IC before CCRT^{6,7} and significant advances in RT delivery techniques (such as IMRT).^{22,23} The cCR plus pCR rates have been reported to reach 90% after IC;¹³ therefore, the subsequent administration of less intensive chemotherapy during RT is feasible.

Although a positive relationship between higher CCD and improved survival outcomes was not observed in the whole cohort, further subgroup analyses indicated that patients with pretreatment EBV DNA of <1000 copies/mL and receiving <3 cycles of IC benefit from a higher dose of cisplatin after IC. The relationship between pretreatment EBV DNA and CCD is an area of

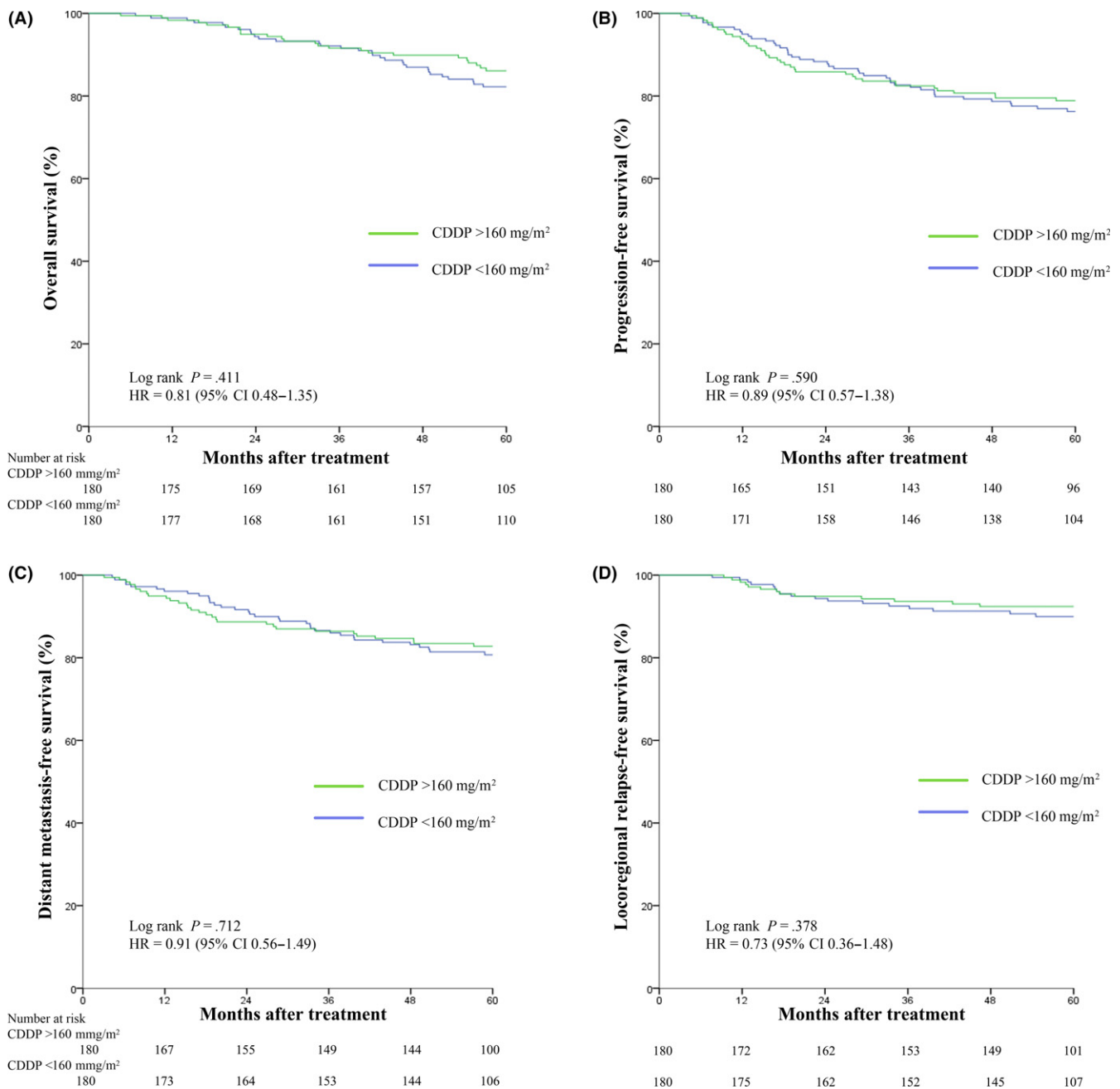


FIGURE 4 Kaplan-Meier survival analyses of: A, overall survival, B, progression-free survival, C, distant metastasis-free survival, and D, locoregional relapse-free survival, in the propensity score matched cohort, stratified by CDDP >160 mg/m² and CDDP <160 mg/m². CDDP, cumulative cisplatin dose; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; NPC, nasopharyngeal carcinoma

particular interest. It has been well documented that pretreatment EBV DNA is a robust factor in the diagnosis, risk stratification and relapse prediction of NPC.^{24–26} Patients with higher pretreatment EBV DNA loads were positively correlated with higher tumor burden, and associated with impaired prognosis. In this study, the subgroup with lower pretreatment EBV DNA was shown to benefit from higher cisplatin administration. It can be speculated that this effect is associated with the inherently poor prognosis of locoregionally-advanced NPC patients with high tumor burden (EBV DNA >1000 copies/mL), irrespective of the

concurrent cisplatin dose. This finding is in accordance with the reports of Lee et al²¹ and Loong et al¹² that CDDP had prognostic value in patients with lower risk (stage III), but not in patients with the highest risk (stage IV).

In addition to the influence of pretreatment EBV DNA, IC cycles also modified the prognostic effect of CDDP. Previous studies showed that there was no difference in survival between patients receiving 2 cycles of IC and patients receiving >2 cycles of IC, when the CCRT regimens and cycles were well-balanced between groups.²⁷ Our results shed light on the previous findings

TABLE 3 Cox proportional hazards analyses of prognostic factors for the propensity-score matched cohort

Endpoint	Variable	HR	95% CI	P-value ^a	
OS	CCD (>160 mg/m ² vs <160 mg/m ²)	0.75	0.44-1.27	.28	
	Year of diagnosis (2011-2013 vs 2005-2010)	0.49	0.28-0.87	.02	
	N (N3-4 vs N1-2)	2.31	1.30-4.08	<.01	
	IC regimens				
	PF	Reference			
	TPF	0.41	0.20-0.81	.01	
	TP	0.49	0.26-0.94	.03	
	Others	0.52	0.07-4.01	.53	
	PFS	CCD (>160 mg/m ² vs <160 mg/m ²)	0.86	0.55-1.33	.49
		N (N3-4 vs N1-2)	1.99	1.23-3.36	<.01
IC regimens					
PF		Reference			
TPF		0.57	0.31-1.04	.06	
TP		0.48	0.28-0.85	.01	
Others		0.99	0.29-3.36	.98	
DMFS		CCD (>160 mg/m ² vs <160 mg/m ²)	0.90	0.54-1.47	.66
		Year of diagnosis (2011-2013 vs 2005-2010)	0.62	0.36-1.08	.09
		N (N3-4 vs N1-2)	3.20	1.80-5.68	<.01
	IC regimens				
	PF	Reference			
	TPF	0.56	0.28-1.10	.09	
	TP	0.56	0.30-1.05	.06	
	Others	1.43	0.41-5.02	.58	
	LRFS	CCD (>160 mg/m ² vs <160 mg/m ²)	0.69	0.34-1.42	.31
		T category	4.67	0.60-36.13	.09
IC regimens					
PF		Reference			
TPF		0.48	0.19-1.24	.13	
TP		0.44	0.18-1.06	.06	
Others		0.00	—	.98	

CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; radiotherapy; LRFS, locoregional relapse-free survival; NS, not significant; OS, overall survival; PFS, progression-free survival.

^aThe following parameters were included in the Cox proportional hazards model multivariate analysis: cumulative cisplatin dose (CCD > 160 mg/m² vs CCD < 160 mg/m²); IC cycles (>2 cycles vs 2 cycles); IC regimens (TPF vs TP vs PF vs others); age (>66 vs 45-65 vs <45 years); sex (female vs male); year of diagnosis (2011-2013 vs 2005-2010); tumor category (T3-4 vs T1-2); node category (N2-3 vs N0-1) and pretreatment Epstein-Barr virus DNA (≥1000 copies/mL vs <1000 copies/mL).

that for patients received less than 3 cycles of IC, higher CCD (> 160 mg/m²) during CCRT might be necessary to yield the same antitumor effects.

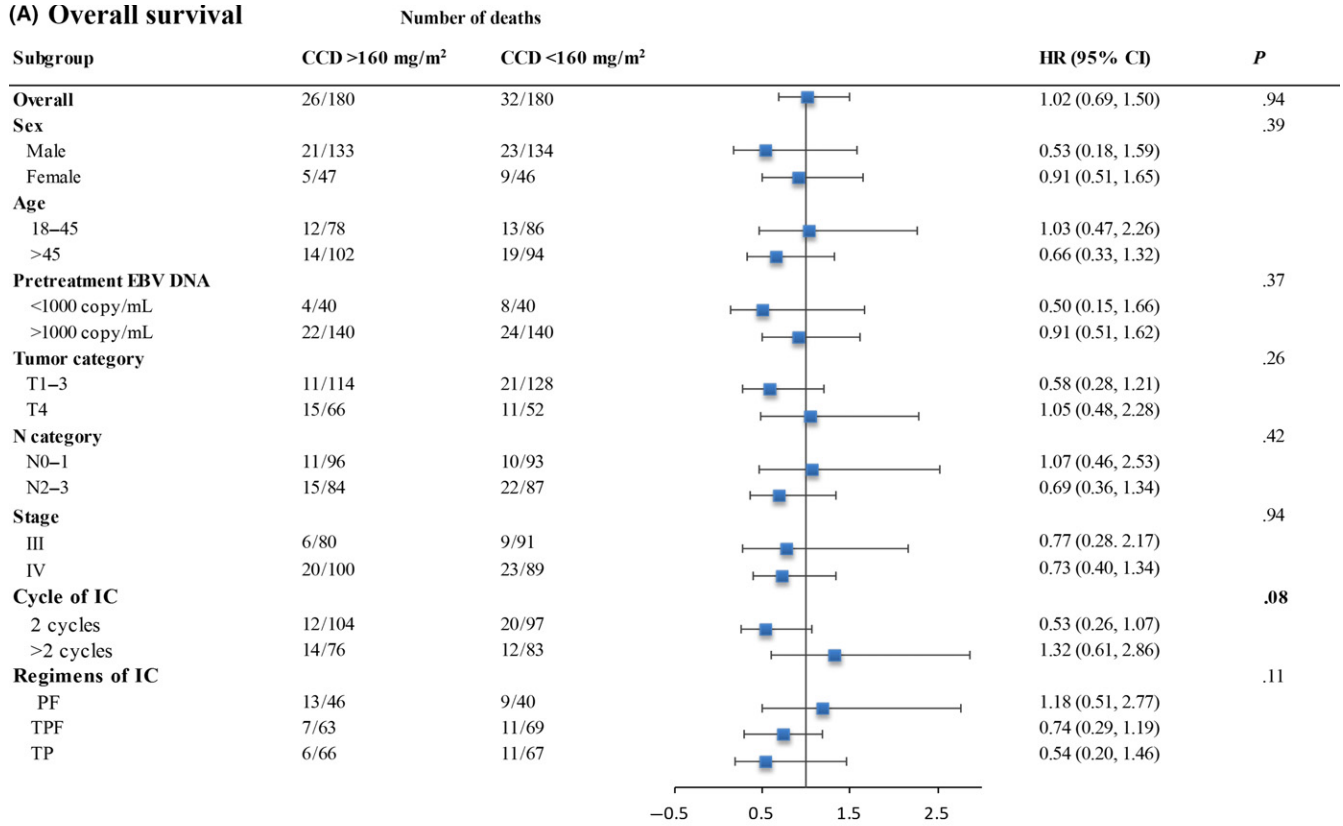
Although there was an association between CCD and PFS in subgroups of patients with pretreatment EBV DNA <1000 copies/mL and receiving <3 cycles of IC, the prognostic effect was not observed in terms of OS. This could be explained by the failure of the study to demonstrate a statistical difference; thus, longer follow-up time and/or larger sample sizes are needed to validate our findings in future prospective studies.

The aim of concurrent chemotherapy is to yield beneficial antitumor effects with acceptable toxicities. With a broad standard application of IC and the increased therapeutic intensity, a substantial proportion of patients are unable to tolerate 200 mg/m² CCD. Thus, it is crucial to define the optimal cutoff dose that can confer survival advantage, with the minimal and acceptable toxicities under these circumstances. Although the current study provides the basis of a hypothesis, further confirmatory prospective studies are required to guide changes in clinical practice. Nevertheless, our results provide a reference for the determination of optimal CCD in clinical practice, and reduce the requirement for rigorous application of the total dose of 200 mg/m² cisplatin in CCRT, when patient performance status is significantly decreased after IC. Furthermore, based on our findings, we recommend that 160 mg/m² CCD should be considered as a reference cisplatin dose in future clinical trials of IC plus CCRT in locoregionally-advanced NPC.

The strengths of the present study are that we enrolled a real world population, which included patients with both good and relatively poor performance status, and reflected the true conditions of concurrent chemotherapy after IC. Conceivably, patients in poor health are less likely to tolerate toxic treatments such as concurrent chemotherapy; and highly intensive treatment might lead to health deterioration and, consequently, to impaired survival. However, the strict inclusion criteria and rigorous administration of clinical trials could have biased the enrolment towards younger and healthier patients; in addition, participants are encouraged to follow up the predefined protocols. Second, compared with other retrospective studies, in which data were collected manually, data in the present study were stored and extracted from the established NPC-specific database affiliated to the big-data intelligence platform in our cancer center. This enabled the patient population, treatment schemes and follow-up schedules to be more consistent and reliable. Third, we carefully designed the methodology to control for confounding factors through PSM, which facilitated the provision of consistent and high-quality data.

Nevertheless, several limitations of the present study should be stated. First, as with all retrospective analyses of patients treated at a single centre, survival outcomes may have been confounded by various undefined factors. Large-scale, multi-institutional, prospective studies are warranted to further confirm our findings. Second, the efficacy of different IC regimens could have confounded the survival outcomes. However, to date, there is no evidence to indicate the superior IC regimen, and all regimens included in this study were

(A) Overall survival



(B) Progression-free survival

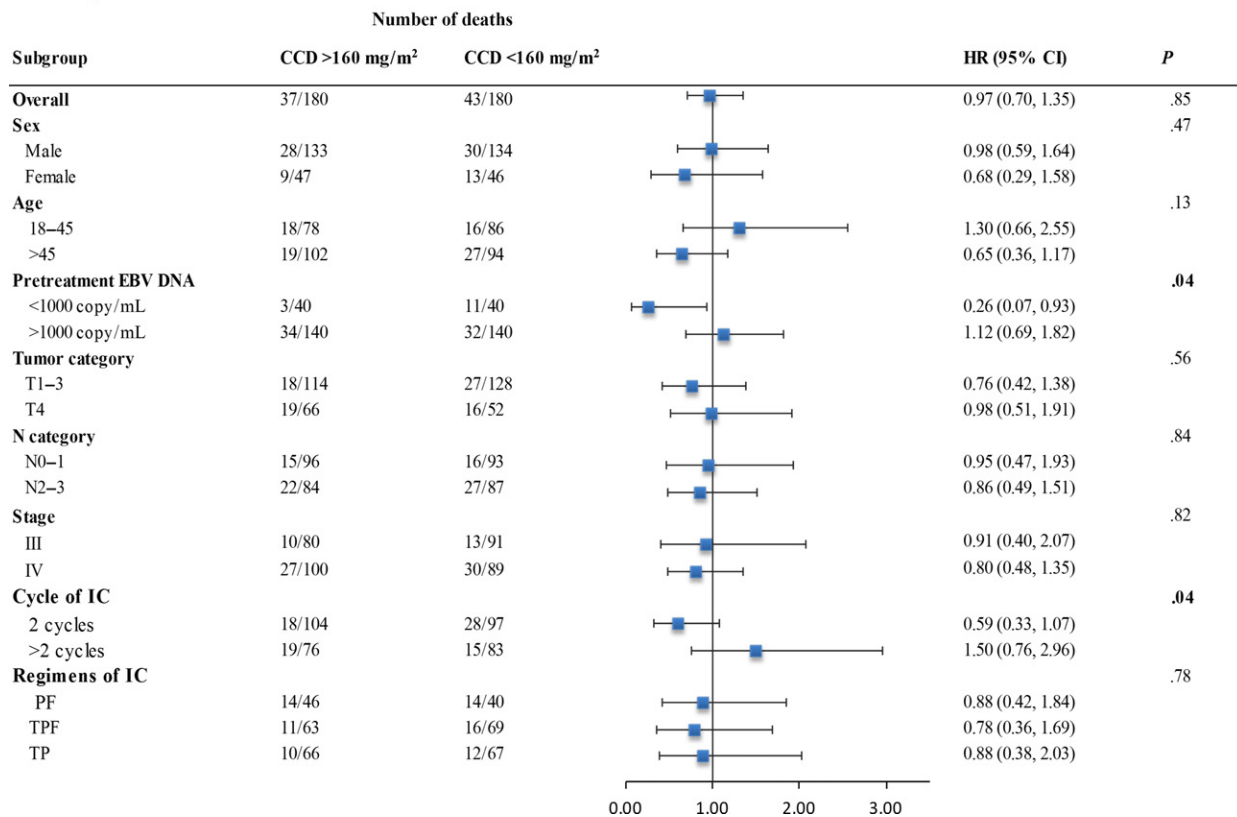


FIGURE 5 Prognostic effects of 160 mg/m² CCD on: A, overall survival, and B, progression-free survival, stratified by patient and treatment characteristics in subgroups. CCD, cumulative cisplatin dose

platinum-based; moreover, the propensity-matched analysis was applied to create well-balanced groups and to reduce the bias.

In conclusion, the causal relationship between 200 mg/m² CCD and improvement in survival outcomes was not defined in locoregionally-advanced NPC patients receiving IC plus CCRT, and our results indicated that 160 mg/m² CCD might be sufficient to yield beneficial antitumor effects in IC. However, higher doses of cisplatin delivered during RT are required to achieve beneficial effects in patients with pretreatment EBV DNA <1000 copies/mL and receiving <3 cycles of IC.

ACKNOWLEDGMENTS

We thank the staff members at Caradigm and Yiducloud (Beijing) technology for their assistance with establishment of the big-data intelligence platform for cancer research in our cancer centre. We are also grateful for their help with data mining, extraction and processing.

DISCLOSURE STATEMENT

The authors have no conflict of interest to declare.

ORCID

Ying Sun  <http://orcid.org/0000-0002-5888-2929>

REFERENCES

- Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65:87-108.
- Cao SM, Simons MJ, Qian CN. The prevalence and prevention of nasopharyngeal carcinoma in China. *Chin J Cancer*. 2011;30:114-119.
- Lee AW, Lau WH, Tung SY, et al. Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: NPC-9901 Trial by the Hong Kong Nasopharyngeal Cancer Study Group. *J Clin Oncol*. 2005;23:6966-6975.
- Lee AW, Tung SY, Chua DT, et al. Randomized trial of radiotherapy plus concurrent-adjuvant chemotherapy vs radiotherapy alone for regionally advanced nasopharyngeal carcinoma. *J Natl Cancer Inst*. 2010;102:1188-1198.
- Cao SM, Yang Q, Guo L, et al. Neoadjuvant chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase III multicentre randomised controlled trial. *Eur J Cancer*. 2017;75:14-23.
- Hui EP, Ma BB, Leung SF, et al. Randomized phase II trial of concurrent cisplatin-radiotherapy with or without neoadjuvant docetaxel and cisplatin in advanced nasopharyngeal carcinoma. *J Clin Oncol*. 2009;27:242-249.
- 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;17:1509-1520.
- 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;91:952-960.
- Lee AW, Ngan RK, Tung SY, et al. Preliminary results of trial NPC-0501 evaluating the therapeutic gain by changing from concurrent-adjuvant to induction-concurrent chemoradiotherapy, changing from fluorouracil to capecitabine, and changing from conventional to accelerated radiotherapy fractionation in patients with locoregionally advanced nasopharyngeal carcinoma. *Cancer*. 2015;121:1328-1338.
- Ang KK. Concurrent radiation chemotherapy for locally advanced head and neck carcinoma: are we addressing burning subjects? *J Clin Oncol*. 2004;22:4657-4659.
- Peng H, Chen L, Zhang Y, et al. Prognostic value of the cumulative cisplatin dose during concurrent chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma: a secondary analysis of a prospective phase III clinical trial. *Oncologist*. 2016;21:1369-1376.
- Loong HH, Ma BB, Leung SF, et al. Prognostic significance of the total dose of cisplatin administered during concurrent chemoradiotherapy in patients with locoregionally advanced nasopharyngeal carcinoma. *Radiother Oncol*. 2012;104:300-304.
- Peng H, Chen L, Li WF, et al. Tumor response to neoadjuvant chemotherapy predicts long-term survival outcomes in patients with locoregionally advanced nasopharyngeal carcinoma: a secondary analysis of a randomized phase 3 clinical trial. *Cancer*. 2017;123:1643-1652.
- Zhang B, Mo Z, Du W, Wang Y, Liu L, Wei Y. Intensity-modulated radiation therapy versus 2D-RT or 3D-CRT for the treatment of nasopharyngeal carcinoma: a systematic review and meta-analysis. *Oral Oncol*. 2015;51:1041-1046.
- Lai SZ, Li WF, Chen L, et al. How does intensity-modulated radiotherapy versus conventional two-dimensional radiotherapy influence the treatment results in nasopharyngeal carcinoma patients? *Int J Radiat Oncol Biol Phys*. 2011;80:661-668.
- Tran B, Keating CL, Ananda SS, et al. Preliminary analysis of the cost-effectiveness of the National Bowel Cancer Screening Program: demonstrating the potential value of comprehensive real world data. *Intern Med J*. 2012;42:794-800.
- Berger ML, Lipset C, Gutteridge A, Axelsen K, Subedi P, Madigan D. Optimizing the leveraging of real-world data to improve the development and use of medicines. *Value Health*. 2015;18:127-130.
- Amin MB, Edge S, Green F, et al. *AJCC Cancer Staging Manual*, 8th edn. New York: Springer; 2016.
- Austin PC. Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score. *Am J Epidemiol*. 2010;172:1092-1097.
- O'Quigley J, Moreau T. Testing the proportional hazards regression model against some general alternatives. *Rev Epidemiol Sante Publique*. 1984;32:199-205.
- Lee AW, Tung SY, Ngan RK, et al. Factors contributing to the efficacy of concurrent-adjuvant chemotherapy for locoregionally advanced nasopharyngeal carcinoma: combined analyses of NPC-9901 and NPC-9902 Trials. *Eur J Cancer*. 2011;47:656-666.
- Li JX, Huang SM, Jiang XH, et al. Local failure patterns for patients with nasopharyngeal carcinoma after intensity-modulated radiotherapy. *Rad Oncol*. 2014;9:87.
- Wolden SL, Chen WC, Pfister DG, Kraus DH, Berry SL, Zelefsky MJ. Intensity-modulated radiation therapy (IMRT) for nasopharynx

- cancer: update of the Memorial Sloan–Kettering experience. *Int J Radiat Oncol Biol Phys.* 2006;64:57-62.
24. Lin JC, Wang WY, Chen KY, et al. Quantification of plasma Epstein–Barr virus DNA in patients with advanced nasopharyngeal carcinoma. *N Engl J Med.* 2004;350:2461-2470.
 25. Chan KC. Plasma Epstein–Barr virus DNA as a biomarker for nasopharyngeal carcinoma. *Chin J Cancer.* 2014;33:598-603.
 26. Adham M, Greijer AE, Verkuijlen SA, et al. Epstein–Barr virus DNA load in nasopharyngeal brushings and whole blood in nasopharyngeal carcinoma patients before and after treatment. *Clin Cancer Res.* 2013;19:2175-2186.
 27. Peng H, Chen L, Li WF, et al. Optimize the cycle of neoadjuvant chemotherapy for locoregionally advanced nasopharyngeal carcinoma treated with intensity-modulated radiotherapy: a propensity score matching analysis. *Oral Oncol.* 2016;62:78-84.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Lv J-W, Qi Z-Y, Zhou G-Q, et al. Optimal cumulative cisplatin dose in nasopharyngeal carcinoma patients receiving additional induction chemotherapy. *Cancer Sci.* 2018;109:751–763.
<https://doi.org/10.1111/cas.13474>