Treatment effects of cumulative cisplatin dose during radiotherapy following induction chemotherapy in nasopharyngeal carcinoma: propensity score analyses

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Abstract

Background: The treatment effects of cumulative cisplatin dose (CCD) during radiotherapy (RT) following induction chemotherapy (IC) have not been determined for patients with locoregionally advanced nasopharyngeal carcinoma (NPC).

Methods: A total of 3460 patients with locoregionally advanced NPC who were treated with IC plus cisplatin-based concurrent chemoradiotherapy or RT alone were included in this retrospective study. Three CCD groups (0 mg/m^2 ⩽ CCD <100 mg/m^2, 100 mg/m^2 ⩽ CCD <200 mg/m^2, CCD ⩾200 mg/m^2) were balanced through the inverse probability of treatment weighting based on propensity scores estimated by a general boosted model. The primary endpoint was overall survival (OS); the secondary endpoints were distant metastasis-free survival (DMFS) and locoregional recurrence-free survival (LRFS).

Results: CCD ⩾200 mg/m^2 and <200 mg/m^2 exhibited similar treatment effects for OS and DMFS, and were both superior to CCD <100 mg/m^2 for OS and DMFS in patients with stage IVa NPC. The three CCD groups achieved similar treatment effects for patients with stage II–III NPC. After IC, CCD during RT appeared to exert little treatment effect on LRFS.

Conclusion: The CCD during RT exerts treatment effects and improves OS by reducing the risk of distant metastasis for patients with stage IVa NPC following IC, and CCD <200 mg/m^2 (mainly 160 mg/m^2 in this group) is recommended. However, RT alone may be sufficient after IC in patients with stage II–III NPC.

Keywords: cumulative cisplatin dose, induction chemotherapy, inverse probability of treatment weighting, nasopharyngeal carcinoma, propensity score

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Introduction

Cisplatin-based concurrent chemoradiotherapy (CCRT) has been established as the backbone of treatment for locoregionally advanced nasopharyngeal carcinoma (NPC).[1–3] The cumulative cisplatin dose (CCD) during radiotherapy (RT) is an important prognostic factor in NPC.[4–9] Previously, we demonstrated that a CCD of 240 mg/m^2 is optimal for patients with locoregionally advanced NPC who received CCRT alone.[9] However, CCRT alone may not provide sufficient treatment intensity in patients with high-risk NPC.[9]

Recently, several studies have demonstrated that induction chemotherapy (IC) in addition to CCRT could improve distant control and survival in patients with locoregionally advanced NPC.[10–12] Previously, we found that IC decreased patient tolerance of the CCD during RT.[13] After IC, does the CCD during RT remain a prognostic factor for patients with locoregionally advanced

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NPC? Lv *et al.* attempted to answer this question and found no significant relationships between CCD during RT and the prognosis of patients who received IC plus CCRT.[8] However, they only included 583 patients, and the use of propensity score matching further shrank the sample size, which might have weakened the statistical power.[8] Besides, the simple dichotomization of the CCD during RT was too crude for the results to be interpreted.[8] Liu *et al.* divided the post-IC CCD into three groups, however, the multivariate Cox regression model they used to control confounding factors may have led to unreliable estimations of the prognostic effects of the CCD, considering the relatively small sample size of one CCD group (84 patients) and the numerous covariates included in the regression model.[14]

Here, we investigated, *via* retrospective analyses of a large cohort, the treatment effects of the CCD during RT in patients with locoregionally advanced NPC who had received IC. By dividing the whole cohort into three CCD groups, we attempted to recommend the optimal CCD during RT after IC.

Materials and methods

Patients

We retrospectively reviewed an inpatient database that included 10,126 patients with newly diagnosed, biopsy-confirmed, nonmetastatic NPC who had been treated at the Sun Yat-sen University Cancer Center from April 2009 through to December 2015. Patients were included if they had stage II–IVa NPC and received typical IC regimens followed by single-agent cisplatin-based CCRT or RT alone. Patients were excluded if they lacked essential clinicopathological data. The typical IC regimens included: docetaxel plus cisplatin plus 5-fluorouracil (TPF); cisplatin plus 5-fluorouracil (PF); docetaxel plus cisplatin (TP); gemcitabine plus cisplatin (GP). A total of 3460 patients were included in this study (Supplemental Figure S1).

The clinical research ethics committee of the Sun Yat-sen University Cancer Center approved this study (YB2018-05). Written informed consents for the use of clinical data were obtained when the patients were admitted. We have uploaded the essential raw data on to the Research Data Deposit (RDD) public platform (http://www.researchdata.org.cn) with RDD approval number RDDA2019000822.

Treatment

The pretreatment evaluation procedures have been described previously.[13] Here patients were restaged in accordance with the eighth edition cancer staging system of the American Joint Committee on Cancer. All patients were treated with intensity-modulated RT consisting of five daily fractions delivered weekly. The prescribed doses have been described previously.[13] IC was administered every 3 weeks. TPF consisted of 60 mg/m^2 docetaxel on day 1, 60 mg/m^2 cisplatin on day 1, and 600–750 mg/m^2 5-fluorouracil from day 1 to day 5. PF consisted of 80 mg/m^2 cisplatin on day 1 and 750–1000 mg/m^2 5-fluorouracil from day 1 to day 5. TP consisted of 75 mg/m^2 docetaxel on day 1 and 75 mg/m^2 cisplatin on day 1. GP consisted of 1000 mg/m^2 gemcitabine on day 1 and day 8, and 80 mg/m^2 cisplatin on day 1. The concurrent chemotherapy was single-agent cisplatin, with a dosage of 80–100 mg/m^2 every 3 weeks or 30–40 mg/m^2 weekly. Of the whole cohort, 543 patients received cisplatin weekly, 2112 patients received cisplatin every 3 weeks, and 805 patients received RT alone, and their CCD was defined as 0 mg/m^2.

Endpoints and follow up

The primary endpoint was overall survival (OS), which was defined as the time from initiation of therapy to death from any cause. The secondary endpoints were distant metastasis-free survival (DMFS), which was defined as the time from initiation of therapy to distant metastasis, and locoregional recurrence-free survival (LRFS), defined as the time to locoregional recurrence. Patients were examined at least every 3 months during the first 2 years and every 6 months for 3 years thereafter. After a median follow up of 44.7 months, 451 patients had died, 459 patients had developed distant metastasis, and 305 patients had developed locoregional recurrence. The 4-year OS, DMFS, and LRFS rates were 87.3%, 86.6%, and 90.7%, respectively.

Statistical analysis

We divided the CCD during RT into three groups: 0 mg/m^2 $\leqslant$ CCD $<$ 100 mg/m^2, 100 mg/m^2 $\leqslant$ CCD $<$ 200 mg/m^2, CCD $\geqslant$ 200 mg/m^2. To account for

selection bias and potential cofounding factors among the groups, we performed weighted propensity score analysis to balance the baseline characteristics. The multiple treatment propensity scores were estimated using the general boosted model, a machine learning technique.[15] The cohort was adjusted using inverse probability of treatment weighting (IPTW) based on the propensity scores. The baseline characteristics were: demographic factors including age, sex, smoking; patient performance status-related factors including the Charlson comorbidity index,[16] pretreatment concentrations of hemoglobin and serum albumin; tumor-related factors including World Health Organization pathology type, T stage, N stage, pretreatment levels of serum lactate dehydrogenase and plasma Epstein–Barr virus DNA; IC-related factors including IC regimens and cycles. The balance of baseline characteristics was assessed between groups pairwise using the absolute standardized difference (ASD); ASD <0.2 was considered small, indicating an acceptable balance.[15] The propensity score weighting and balance assessment was completed through the twang package in R, version 3.6.0 (http://www.r-project.org/). The survival rates of the crude and weighted cohorts were calculated using the Kaplan–Meier method. The survival curves were compared using the log-rank test. The weighted hazard ratio (HR) was estimated using the Cox proportional hazards model. The above treatment effects estimation was completed using STATA (version 14.1; StataCorp, College Station, TX, USA). Predetermined subgroup analyses were conducted based on overall disease stage. Two-tailed p values < 0.05 were considered statistically significant.

Results

Patient characteristics

The distribution of the CCD during RT is shown in Supplemental Figure S2. The median CCD was 160 mg/m^2 (range, 0–300 mg/m^2). Table 1 summarizes the patient characteristics before and after IPTW adjustment. Before propensity adjustment, patients with younger age or T4 disease were more likely to receive a higher CCD during RT; patients who received TPF were more likely to receive a higher CCD, while patients who received TP were more likely to receive a lower CCD; patients who received only one cycle or four or more cycles of IC were more likely to receive a lower CCD, while patients who received three cycles of IC were more likely to receive a higher CCD. Figure 1(a)–(c) shows the pairwise balance assessments among the three CCD groups. IPTW adjustment resulted in excellent balance of baseline characteristics.

Treatment effects of CCD during RT

Before IPTW adjustment, the 4-year OS rates of the CCD <100 mg/m^2, <200 mg/m^2, and $\geqslant 200$ mg/m^2 groups were 85.9%, 87.5%, and 88.9%, respectively. Compared with CCD <100 mg/m^2, CCD $\geqslant 200$ mg/m^2 improved OS significantly ($p = 0.041$). There was a trend for CCD $\geqslant 200$ mg/m^2 to improve OS compared with CCD <200 mg/m^2 ($p = 0.074$). There was no difference between CCD <100 mg/m^2 and <200 mg/m^2 for OS ($p = 0.711$) (Figure 2(a)). After IPTW adjustment, the 4-year OS rates of the CCD <100 mg/m^2, <200 mg/m^2, and $\geqslant 200$ mg/m^2 groups were 85.0%, 88.0%, and 88.9%, respectively. Compared with CCD <100 mg/m^2, CCD $\geqslant 200$ mg/m^2 improved OS significantly ($p = 0.040$). However, there appeared to be no trend for a difference between CCD $\geqslant 200$ mg/m^2 and <200 mg/m^2 for OS ($p = 0.253$) (Figure 2(b)).

Before IPTW adjustment, the 4-year DMFS rates of the CCD <100 mg/m^2, <200 mg/m^2, and $\geqslant 200$ mg/m^2 groups were 85.6%, 86.1%, and 89.5%, respectively. After IPTW adjustment, the 4-year DMFS rates were 85.6%, 86.8%, and 89.5%, respectively. Compared with CCD <100 mg/m^2, CCD $\geqslant 200$ mg/m^2 improved DMFS significantly independently of weighting ($p = 0.044$ and 0.017, respectively). Notably, IPTW appeared to increase the uncertainty for concluding on the priority of CCD $\geqslant 200$ mg/m^2 over CCD <200 mg/m^2 for DMFS (Figure 2(c), (d)).

Before IPTW adjustment, the 4-year LRFS rates of the CCD <100 mg/m^2, <200 mg/m^2, and $\geqslant 200$ mg/m^2 groups were 91.5%, 90.7%, and 89.7%, respectively. There was no difference among the groups for LRFS (Figure 2(e)). After IPTW adjustment, the 4-year LRFS rates were 92.5%, 91.1%, and 88.0%, respectively. It is worth noting that CCD $\geqslant 200$ mg/m^2 appeared to increase the risk of locoregional recurrence compared with CCD <100 mg/m^2 and <200 mg/m^2 ($p = 0.019$ and 0.070, respectively) (Figure 2(f)).

Subgroup analyses

We conducted subgroup analyses based on risk stratification: the low-risk group had 1874

Table 1. Distributions of baseline characteristics among CCD groups before and after weighting in the whole cohort.

Characteristic	Unweighted (%)			ASD[$]	IPTW (%)			ASD[$]
	CCD < 100	CCD < 200	CCD ⩾ 200		CCD < 100	CCD < 200	CCD ⩾ 200	
Age (years)								
⩽60	86.5	93.5	96.5	**0.340**	92.0	92.6	93.8	0.064
>60	13.5	6.5	3.5	**0.340**	8.0	7.4	6.2	0.064
Sex								
Male	70.8	74.1	77.3	0.148	73.4	73.4	74.6	0.028
Female	29.2	25.9	22.7	0.148	26.6	26.6	25.4	0.028
Smoking								
Yes	32.7	38.3	37.3	0.118	35.7	36.3	37.3	0.035
No	67.3	61.7	62.7	0.118	64.3	63.7	62.7	0.035
CCI								
0	73.0	73.8	73.8	0.018	73.1	74.1	73.4	0.023
>0	27.0	26.2	26.2	0.018	26.9	25.9	26.6	0.023
Hb (g/L)								
⩽144	55.4	51.1	49.6	0.116	53.4	51.8	51.1	0.046
>144	44.6	48.9	50.4	0.116	46.6	48.2	48.9	0.046
ALB (g/L)								
⩽44	47.5	48.5	46.9	0.032	49.2	48.0	49.6	0.032
>44	52.5	51.5	53.1	0.032	50.8	52.0	50.4	0.032
WHO pathology								
I/II	3.1	2.9	1.6	0.099	2.4	2.5	1.8	0.051
III	96.9	97.1	98.4	0.099	97.6	97.5	98.2	0.051
T category								
T1	9.6	7.2	8.6	0.086	7.9	7.5	8.4	0.031
T2	17.0	11.8	11.6	0.151	12.8	12.9	12.5	0.013
T3	50.1	47.5	45.8	0.088	49.0	48.1	47.4	0.032
T4	23.2	33.5	34.0	**0.241**	30.4	31.5	31.7	0.030
N category								
N0	7.7	5.9	5.0	0.111	5.8	6.0	5.4	0.026
N1	49.9	43.9	49.2	0.119	46.4	46.6	47.0	0.012

(Continued)

Table 1. (Continued)

Characteristic	Unweighted (%)			ASD$	IPTW (%)			ASD$
	CCD <100	CCD <200	CCD ⩾200		CCD <100	CCD <200	CCD ⩾200	
N2	26.4	28.2	27.5	0.041	28.2	27.9	28.2	0.007
N3	16.0	22.0	18.4	0.158	19.6	19.5	19.5	0.003
EBV DNA (copies/ml)								
⩽2000	42.8	33.6	37.1	0.188	35.8	36.4	37.5	0.036
>2000	57.2	66.4	62.9	0.188	64.2	63.6	62.5	0.036
LDH (IU/L)								
⩽180	53.8	50.5	52.0	0.066	53.0	51.9	52.0	0.022
>180	46.2	49.5	48.0	0.066	47.0	48.1	48.0	0.022
IC regime								
TPF	25.0	52.1	49.0	**0.569**	43.5	44.8	45.8	0.048
PF	20.3	22.1	23.8	0.086	21.5	22.0	21.8	0.012
TP	44.1	23.3	16.9	**0.579**	29.5	28.2	27.9	0.035
GP	10.7	2.6	10.3	**0.265**	5.4	5	4.5	0.029
IC cycles								
1	7.0	3.8	1.7	**0.248**	4.3	3.9	4.0	0.018
2	58.7	50.7	51.1	0.161	54.2	54.3	54.4	0.003
3	20.1	39.6	45.2	**0.547**	33.9	35.6	36.1	0.049
⩾4	14.2	5.8	2.0	**0.421**	7.7	6.2	5.6	0.072
Total number or ESS (weighted)*	1037	1717	706		642.31	1458.01	560.05	

*Weighted treatment effect estimates have greater sampling variance than the unweighted estimates from a sample of equal size. The ESS of the weighted group is a conservative means of capturing the impact of this increase in variance on precision and power.
$The largest ASD of the three pairwise ASD among CCD groups is shown, and ASD ⩾0.2 is in bold.
ALB, albumin; ASD, absolute standardized difference; CCD, cumulative cisplatin dose (mg/m^2); CCI, Charlson comorbidity index; EBV, Epstein–Barr virus; ESS, effective sample size; GP, gemcitabine plus cisplatin; Hb, hemoglobin; IC, induction chemotherapy; IPTW, inverse probability of treatment weighting; LDH, lactate dehydrogenase; PF, cisplatin plus 5-fluorouracil; TP, docetaxel plus cisplatin; TPF, docetaxel plus cisplatin plus 5-fluorouracil; WHO, World Health Organization.

patients with stage II–III disease; the high-risk group had 1586 patients with stage IVa disease. Propensity scores weighting was conducted in the two subgroups separately. The characteristics of the low-risk and high-risk patients before and after IPTW adjustment are summarized in Supplemental Table S1 and Table S2, respectively. Figure 1(d)–(i) shows the balance assessments of the subgroups graphically, from which we were able to determine satisfactory balances after IPTW adjustment.

Figure 3 shows the estimation of the treatment effects for the low-risk group, from which we detected no prognostic difference among the CCDs during RT for OS, DMFS, and LRFS before and after weighting. Figure 4 provides an overview of the estimation of the treatment

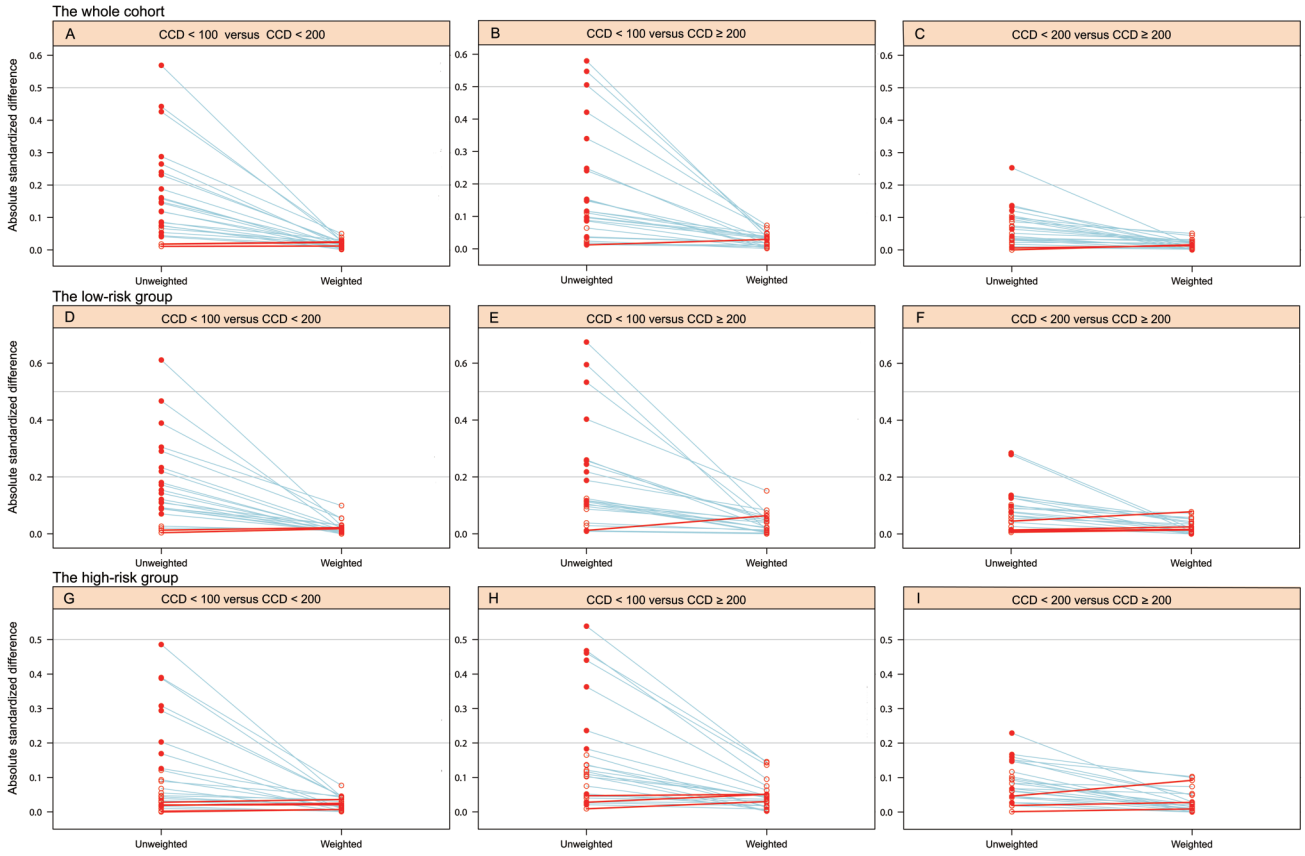

Figure 1. Pairwise plots assessing the balance of baseline characteristics among CCD groups for the whole ([a]–[c]), low-risk ([d]–[f]), and high-risk ([g]–[i]) cohorts.
CCD, cumulative cisplatin dose (mg/m^2).

effects for the high-risk group. Regardless of IPTW adjustment, CCD $\geqslant$200 mg/m^2 and $<$200 mg/m^2 both exhibited a priority over CCD $<$100 mg/m^2 for OS for the high-risk patients, while no significant difference for OS was detected between CCD $\geqslant$200 mg/m^2 and $<$200 mg/m^2. The treatment effects of the CCD during RT on DMFS were similar to that for OS, except the difference for DMFS between CCD $<$200 mg/m^2 and $<$100 mg/m^2 was nearly, but not statistically, significant ($p = 0.080$) after weighting. There was no difference among the CCDs for LRFS before and after weighting.

Figure 5 shows the results of the Cox proportional hazard model for estimating the HR and 95% confidence interval (CI) for the weighted whole cohort and subgroups, which were in accordance with the results of log-rank tests.

Discussion

We explored the treatment effects of the CCD during RT for patients with locoregionally advanced NPC who had received IC. We collected real-world data, where the CCD was determined by numerous observable and unobservable factors. Simple comparison between the CCD groups without adjustment would lead to bias during estimation of the treatment effects. Therefore, to estimate the treatment effects of CCD accurately, we used propensity score weighting to balance the baseline characteristics among the CCD groups. Potential confounding factors related to patient, disease, and IC were considered during the propensity score estimation. Compared with regression-based covariate adjustment methods, propensity score weighting has several statistical advantages and yielded a reliable estimation of the treatment effects of the CCD during RT.[17,18]

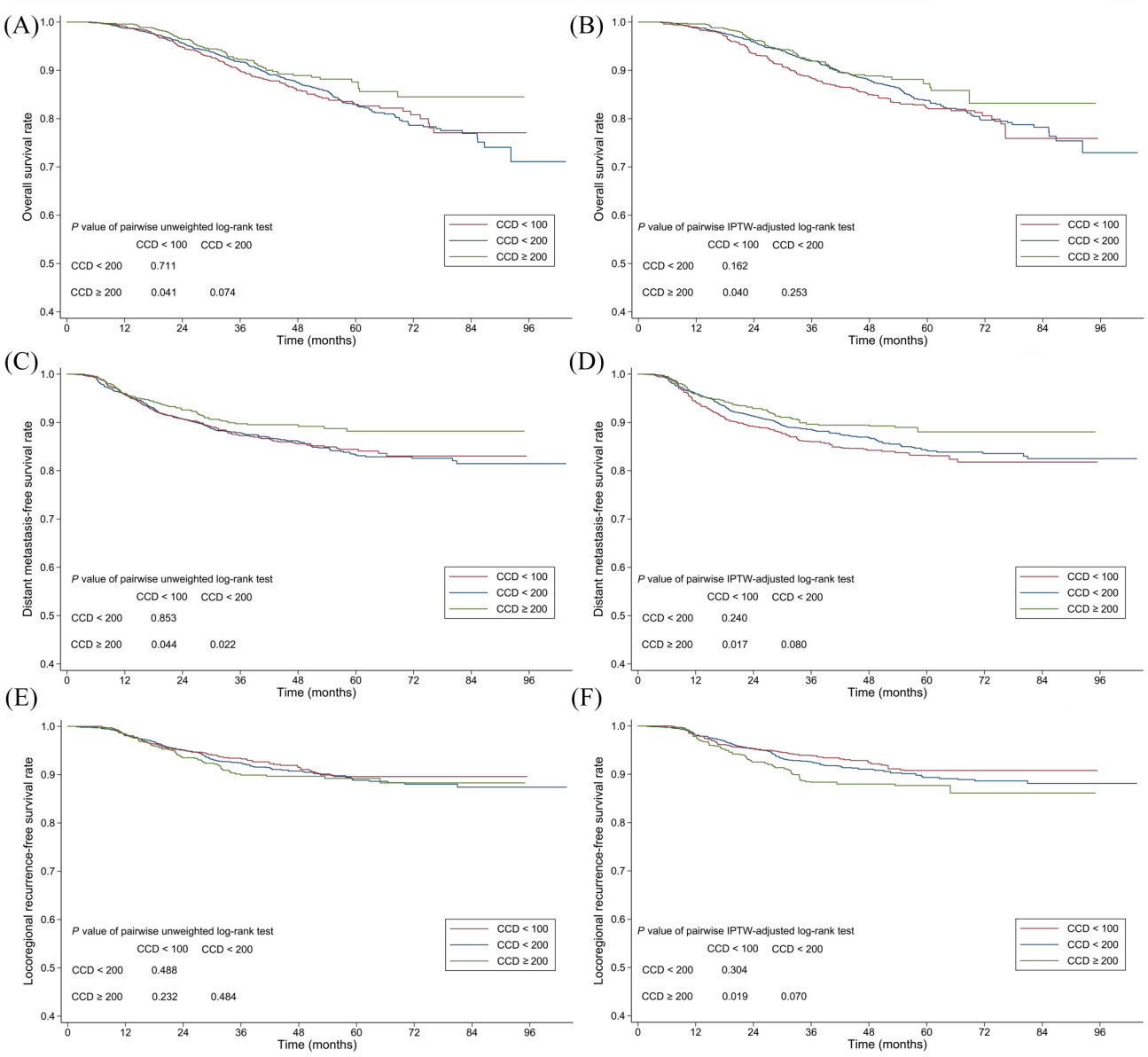

Figure 2. Kaplan–Meier curves for overall survival ((a), (b)), distant metastasis-free survival ((c), (d)), and locoregional recurrence-free survival ((e), (f)) before and after weighting in the whole cohort.
CCD, cumulative cisplatin dose (mg/m^2); IPTW, inverse probability of treatment weighting.

For the whole cohort, we found that patients who received CCD <100 mg/m^2 (mostly 0 mg/m^2, namely, RT alone after IC) (Supplemental Figure S2) had a higher risk of death compared with those who received CCD $\geqslant 200$ mg/m^2. This means that sufficient-intensity concurrent chemotherapy remains necessary for patients with locoregionally advanced NPC who have received IC, which is in accordance with the conclusions drawn by two previous meta-analyses.[2,3] For high-risk patients (stage IVa), CCD <200 mg/m^2 and $\geqslant 200$ mg/m^2 exhibited no differences for OS, and they both showed significantly improved OS compared with CCD <100 mg/m^2. Based on the above results, we recommend CCD <200 mg/m^2 (mostly CCD $= 160$ mg/m^2) (Supplemental Figure S2) for patients with stage IVa NPC who have received IC. On the contrary, the CCD during RT did not appear to be a prognostic factor for low-risk patients (stage II–III). The different treatment effects of the CCD in the risk subgroups may account for the statistically nonsignificant difference for OS between CCD <100 mg/

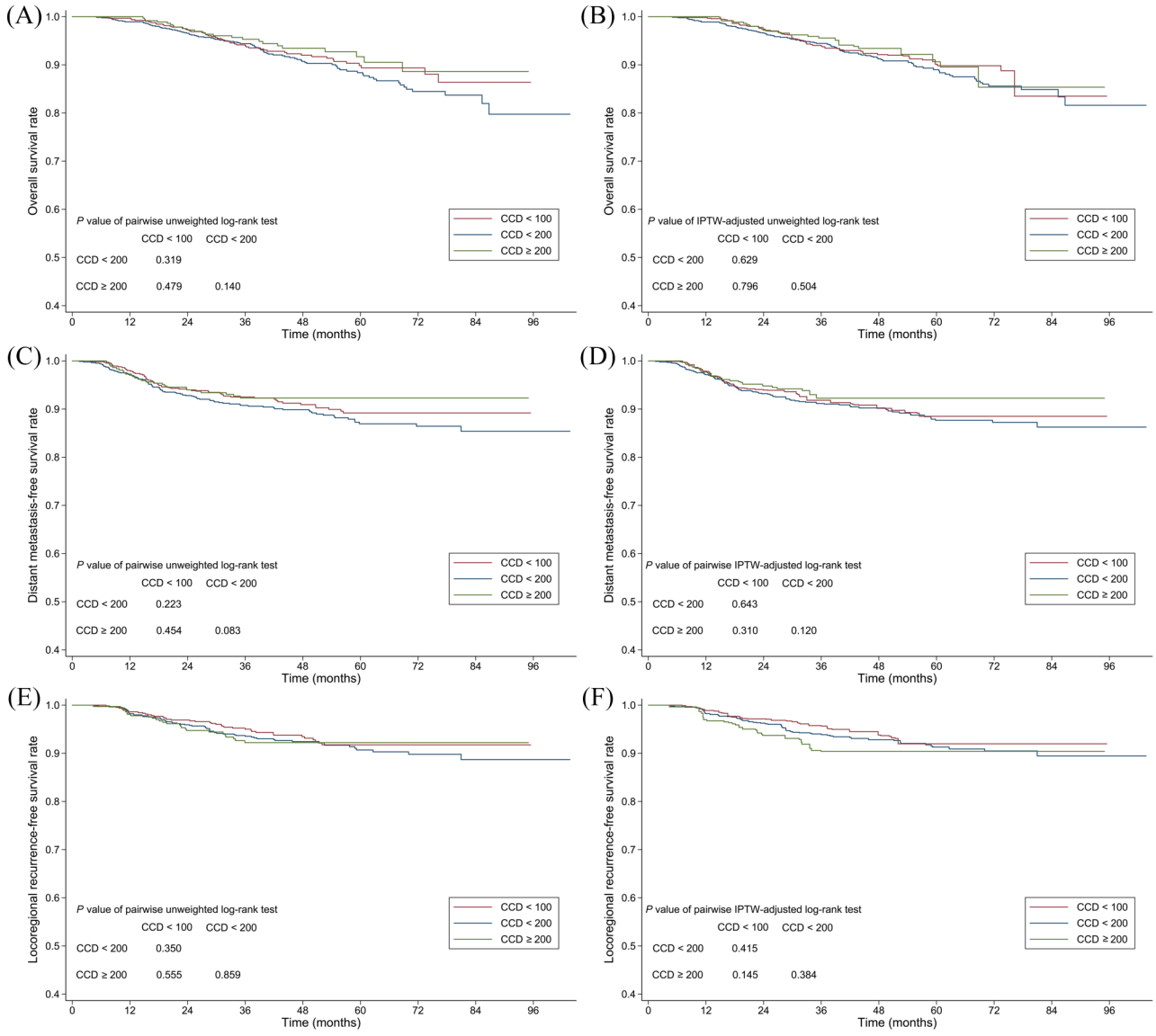

Figure 3. Kaplan–Meier curves for overall survival ((a), (b)), distant metastasis-free survival ((c), (d)), and locoregional recurrence-free survival ((e), (f)) before and after weighting in the low-risk cohort.
CCD, cumulative cisplatin dose (mg/m^2); IPTW, inverse probability of treatment weighting.

m^2 and <200 mg/m^2 in the whole cohort. Considering the above, concurrent chemotherapy may be omitted after IC for patients with stage II–III NPC.

As shown in Figure 5, the whole cohort and high-risk subgroup had similar patterns of error bars representing the HR and 95% CI for OS and DMFS. This indicates that the treatment effects of the CCD during RT on OS may mainly be derived from its effects on reducing the risk of distant metastasis, which is in accordance with the study of Liu *et al.*[14] IC can improve DMFS relying on early systemic interventions on subclinical micrometastasis and combinations of cytotoxic drugs.[10,11] Moreover, the concurrent usage of cisplatin during RT can further reduce the risk of distant metastasis and improve OS for high-risk

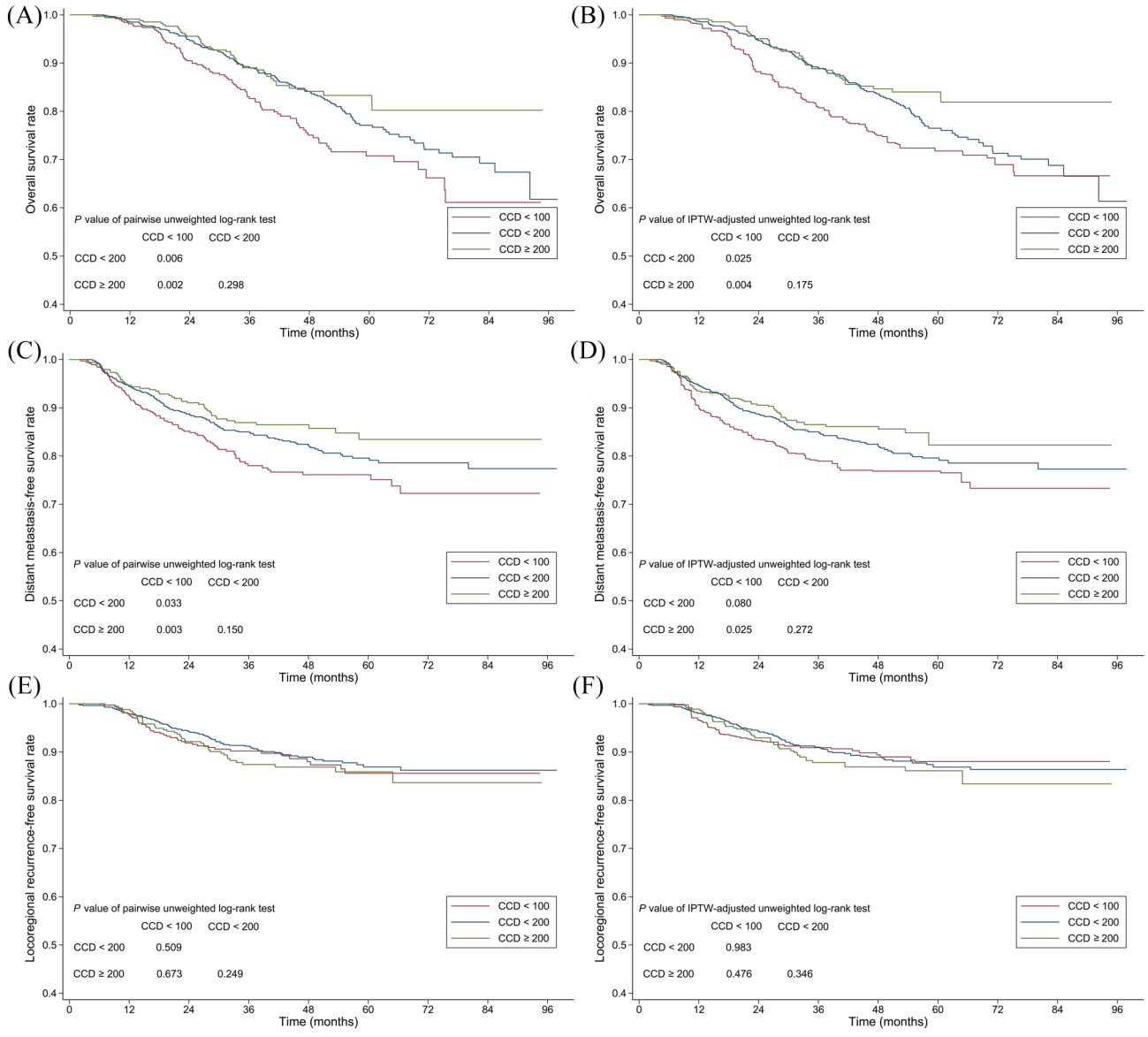

Figure 4. Kaplan–Meier curves for overall survival ((a), (b)), distant metastasis-free survival ((c), (d)), and locoregional recurrence-free survival ((e), (f)) before and after weighting in the high-risk cohort.
CCD, cumulative cisplatin dose (mg/m^2); IPTW, inverse probability of treatment weighting.

patients, which could be due to the additive effects of systemically used cisplatin on the micrometastasis. Another possible explanation for the CCD treatment effects in improving DMFS may be that the combination of concurrent cisplatin and RT results in more immunogenic cell death and hence more potent anti-tumor immune responses than RT alone, which would elicit abscopal effects to eliminate the micrometastasis.[19–21] In the whole and subgroup cohorts, the patterns of error bars representing the HR and 95% CI for LRFS were the opposite of those for OS; a lower CCD was related to better LRFS. This unexpected phenomenon may have been due to an unobservable confounding factor, i.e. tumor response to IC. Patients with poor response to IC were more likely to receive a higher CCD during RT in clinical practice.

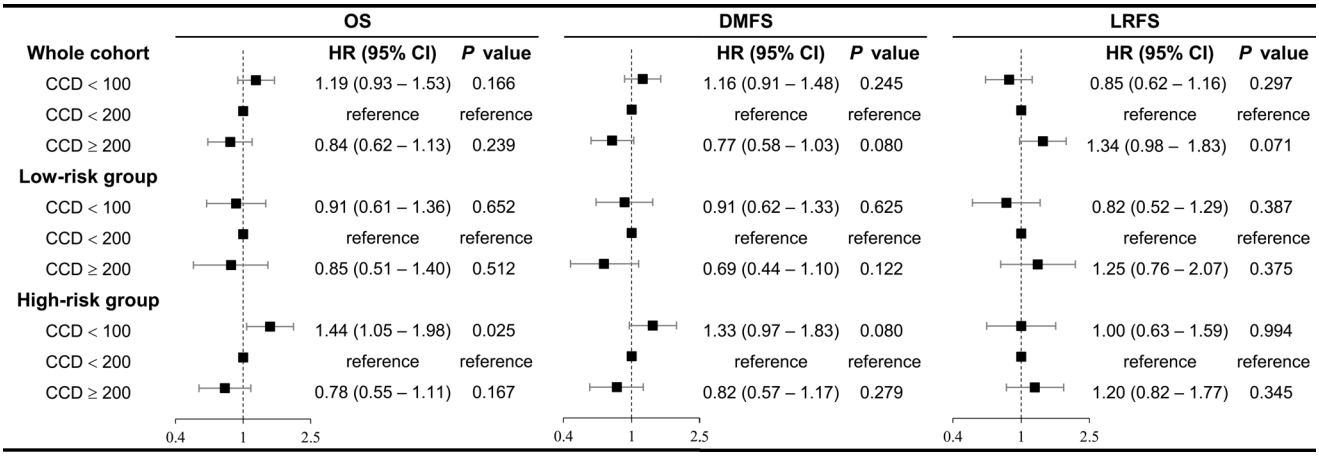

Figure 5. Forest plots showing results of univariate Cox regression for the weighted whole and subgroup cohorts.
CCD, cumulative cisplatin dose (mg/m^2); CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; LRFS, locoregional recurrence-free survival; OS, overall survival.

However, these patients remain at high risk of locoregional recurrence.[14,22] According to our analyses, the CCD during RT appeared to exert little effect on LRFS for patients who had received IC, which is distinct from the situations for patients who received CCRT or RT alone.[9]

Our study has several limitations. First, it is a retrospective study, and some unobservable factors may have confounded survival outcomes even though we used propensity score weighting. Second, the patients in this study were from a single center, and no external validation was performed because of data unavailability, which may have caused selection bias. However, despite these limitations, we believe that our study is credible and can be clinically helpful, considering the large sample size, and that all data were collected from the real world, which reflects the real situation.

In conclusion, the CCD during RT exerts treatment effects and improves OS by reducing the risk of distant metastasis for patients with stage IVa NPC following IC, and a CCD of 160 mg/m^2 is recommended. However, for patients with stage II–III NPC, RT alone may be sufficient after the IC. Considering the limitations of the current study, prospective clinical trials are warranted to validate our results in the future.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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