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Optimizing the cumulative cisplatin dose during radiotherapy in nasopharyngeal carcinoma: Dose-effect analysis for a large cohort

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ABSTRACT

Objectives: Definitive concurrent chemoradiotherapy (CCRT) is the standard treatment for locoregionally advanced nasopharyngeal carcinoma (NPC). The cumulative cisplatin dose (CCD) during radiotherapy is an important prognostic factor; however, the optimal CCD is undetermined.

Materials and methods: In this retrospective analysis, patients with locoregionally advanced NPC treated with single-agent cisplatin-based CCRT or RT alone from 2009 through 2015 were identified. CCD was entered into a multivariate Cox regression model as a continuous variable using natural cubic splines to allow for a nonlinear relationship between CCD and outcomes. The primary endpoint was overall survival, and the secondary endpoints were locoregional relapse-free survival and distant metastasis-free survival.

Results: A total of 2 924 patients were included in our study, with a median CCD of 160 mg/m^2 (range, 0–300 mg/m^2). As the CCD increased, the risk of death remained steady until 180 mg/m^2, then decreased sharply until 250 mg/m^2, and then increased until 300 mg/m^2. The optimal CCD of 230–270 mg/m^2 was associated with the lowest risk of death and disease relapse. However, the CCD had less prognostic value for disease control, especially for distant control among high-risk patients (N2–3 or T4).

Conclusions: A CCD dose of 230–270 mg/m^2 (240 mg/m^2 is recommended) is optimal for patients with locoregionally advanced NPC, especially for those at low risk (T1–3 and N0–1). For high-risk patients (N2–3 or T4), additional chemotherapy should be administered before or after CCRT.

Introduction

Nasopharyngeal carcinoma (NPC) is an endemic disease prevalent in South China [1]. Definitive chemoradiotherapy has been established as the standard treatment for locoregionally advanced NPC because of its anatomical location, radiosensitivity, and chemosensitivity [2]. Two recent meta-analyses of individual patient data have concluded that concurrent chemoradiotherapy (CCRT) is the backbone of treatment for NPC [3,4].

According to the guidelines of the National Comprehensive Cancer Network, single-agent cisplatin has been recommended during radiotherapy (RT) [2]. In clinical trials where the treatment protocol was 100 mg/m^2 cisplatin every 3 weeks during RT for 3 cycles, a substantial proportion of patients failed to receive the third cycle due to its adverse effects; yet, they achieved a similar prognosis as the patients who received the full dose, suggesting that a cumulative cisplatin dose (CCD) of approximately 200 mg/m^2 might be sufficient to yield beneficial antitumor effects [5,6]. A clinical trial conducted by Loong et al. [7], in which 40 mg/m^2 cisplatin was administrated weekly for 6–7 cycles, a post-hoc analysis revealed that > 5 cycles of weekly cisplatin may be a positive prognostic factor. Although the CCD during RT (independent of its schedule) has been confirmed as an important prognostic factor in NPC, the optimal dose remains controversial.

Studies [6–10] that explored the prognostic effects of different CCDs have based their findings on arbitrary cutoff points, which transformed the CCD into a dichotomous variable. This manipulation caused loss of

Abbreviations: NPC, Nasopharyngeal carcinoma; CCRT, concurrent chemoradiotherapy; RT, radiotherapy; CCD, cumulative cisplatin dose; IC, induction chemotherapy; AC, adjuvant chemotherapy; RDD, research data deposit; MRI, magnetic resonance imaging; SPECT, single photon emission computed tomography; PET/CT, positron emission tomography and computed tomography; AJCC/UICC, American Joint Committee on Cancer/International Union against Cancer; IMRT, intensity-modulated radiotherapy; PTV, planning target volume; GTV, gross tumor volume; CTV1, high-risk clinical target volume; CTV2, low-risk clinical target volume; CCI, Charlson Comorbidity Index; LDH, lactate dehydrogenase; EBV, Epstein-Barr virus; OS, overall survival; LRFS, locoregional relapse-free survival; DMFS, distant metastasis-free survival; HR, hazard ratio

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information about CCDs, which could have been avoided if dose had been treated as a continuous variable. Therefore, the optimal CCD could not be deduced from these studies. Sometimes such manipulation is inevitable in the analysis of data from clinical trials given that the dose participants receive is often fixed with little variation. In clinical practice, cisplatin dose modulations often occur because of toxicity, the patient's status, the patient's will, and/or the physician's experience. Considering that the CCD is rather variable, real-world data could fulfill our goal of analyzing the CCD as a continuous variable. In the present study, we conducted a dose-effect analysis to explore the relationship between the CCD and the prognosis of patients with NPC based on real-world data with the goal of finding an optimal CCD for them.

Material and methods

Patients

We retrospectively reviewed an inpatient database that included 10 126 patients with newly diagnosed, biopsy-confirmed, non-metastatic NPC, who were treated at Sun Yat-sen University Cancer Center from April 2009 through December 2015. The inclusion criteria were patients with locoregionally advanced (stages II–IVa) disease and patients receiving single-agent cisplatin-based CCRT or RT alone. The exclusion criteria were patients receiving induction chemotherapy (IC) or adjuvant chemotherapy (AC) or patients without essential clinicopathological data. A total of 2 924 patients were included in our study. The clinical research ethics committee of Sun Yat-sen University Cancer Center approved this study. As this was a retrospective analysis of routine data, we were granted a waiver for written informed consent. We have uploaded the essential raw data onto the Research Data Deposit (RDD) public platform (http://www.researchdata.org.cn), with the RDD approval number as RDDA2018000822.

Staging workup

All patients underwent a comprehensive pre-treatment evaluation, including complete history, physical examination, haematology and biochemistry profiles, magnetic resonance imaging (MRI) of the neck and nasopharynx, chest radiography, abdominal ultrasonography, and whole-body bone scanning using single photon emission computed tomography (SPECT). Positron emission tomography and computed tomography (PET/CT) was performed when necessary. All patients were restaged according to the 8th edition of the American Joint Committee on Cancer/International Union against Cancer (AJCC/UICC) staging system based on imaging results and medical records.

Treatment

All the patients were treated with intensity-modulated radiotherapy (IMRT) consisting of 5 daily fractions delivered weekly. The prescribed doses were 66–72 Gy to the planning target volume (PTV) derived from the gross tumor volume (GTV) of the nasopharyngeal lesion, 64–70 Gy to the PTV from the GTV of the nodal lesion, 60–63 Gy to the PTV from the high-risk clinical target volume (CTV1), and 54–56 Gy to the PTV of the low-risk clinical target volume (CTV2) in 28–33 fractions. The planned concurrent chemotherapy was single-agent cisplatin, with a dosage of 80–100 mg/m^2 every 3 weeks for 2–3 cycles or 30–40 mg/m^2 weekly for 5–7 cycles. Of the whole cohort, 543 received cisplatin weekly, 1 757 received cisplatin every 3 weeks, and 624 did not receive concurrent chemotherapy and their CCD was defined as 0 mg/m^2 for the dose-effect analysis.

Variables and endpoints

In addition to the CCD, other potential prognostic factors were extracted and analysed as covariates, including age, sex, smoking, Charlson Comorbidity Index (CCI), WHO pathology type, T stage, N stage, pre-treatment serum lactate dehydrogenase (LDH), and pre-treatment plasma Epstein-Barr virus (EBV) DNA. Plasma EBV DNA quantification was performed using real-time quantitative polymerase chain reaction assay by amplifying the *Bam*HI-W region of the EBV genome [11]. The CCI was calculated using information from the patients' medical records [12].

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 of this study were locoregional relapse-free survival (LRFS), which was defined as the time from initiation of therapy to locoregional relapse, and distant metastasis-free survival (DMFS), defined as the time to distant metastasis. After a median follow-up duration of 45.4 months, 304 patients died, 210 patients experienced locoregional relapse, and 293 patients experienced distant metastasis. The 3-year OS, LRFS, and DMFS rates were 93.3%, 93.5%, and 90.9% respectively; the 4-year rates were 89.9%, 92.1%, and 89.7%, respectively.

Statistical analysis

The clinicopathological features of the different CCD subgroups were compared using Kendall's tau-b test. The actuarial survival rates were estimated using the Kaplan-Meier method. Hazard ratios (HR) of the categorized factors were calculated using univariate Cox proportional hazards regression. In order to investigate the prognostic effects of the CCD, which was treated as a continuous variable, we used natural cubic splines to reflect the nature of the CCD's effects in the multivariate additive Cox model adjusting for the covariates, and we constructed smoothing HR curves with confidence limits, with the help of the R-based smoothHR package [13]. To determine the number and location of the knots between which the smooth line was drawn, the dfmacox (degrees of freedom in multivariate additive Cox models) function in the smoothHR package was used to provide the optimal number of degrees of freedom in the multivariate Cox model by minimizing the corrected version of Akaike's Information Criterion [13]. We transformed CCD into a categorical variable based on the results of the dose-effect analysis, and proposed an optimal CCD. The multivariate Cox model was used to estimate the adjusted HR of the categorized CCD. Planned stratified analyses were performed on data from patients with different risks. SPSS version 22.0 (IBM Corporation, Armonk, NY, USA) and the smoothHR package in R, version 3.4.3 (http://www.r-project.org/) were used for all statistical analyses. Two-tailed P-values < 0.05 were considered statistically significant.

Results

Patients' characteristics

The median CCD for the whole cohort was 160 mg/m^2, and the range was 0–300 mg/m^2. The distribution of CCDs is shown in Supplementary Fig. S1. The characteristics of patients in different CCD subgroups are summarized in Table 1. Younger patients and male patients were more likely to receive a higher CCD; patients with a more advanced disease also tended to receive a higher CCD (see Table 1). Univariate analyses of the prognostic effects of the clinicopathological factors are summarized in Supplementary Table S1.

Dose-dependent prognostic effects of CCD

To quantify the dose-dependent effects of CCD, we entered CCD as a continuous variable into the multivariate Cox regression using natural cubic splines in smoothHR to allow for nonlinear relationships between CCD and endpoints. The model showed, as the CCD increased, the risk of death (measured as lnHR, the natural logarithm of the HR for OS) remained steady until the CCD reached 180 mg/m^2, after which it

Table 1
Clinicopathological characteristics of the patients (N = 2924).

Characteristics	0 ≤ CCD ≤ 180	180 < CCD ≤ 230	230 < CCD ≤ 270	270 < CCD ≤ 300	*P*-value†
Age (year)					< 0.001
≤ 60	1394 (81.5%)	564 (94.3%)	296 (96.1%)	301 (97.7%)	
> 60	316 (18.5%)	34 (5.7%)	12 (3.9%)	7 (2.3%)	
Sex					0.019
Male	1209 (70.7%)	417 (69.7%)	231 (75.0%)	242 (78.6%)	
Female	501 (29.3%)	181 (30.3%)	77 (25.0%)	66 (21.4%)	
Smoking					0.175
Yes	561 (32.8%)	195 (32.6%)	107 (34.7%)	117 (38.0%)	
No	1149 (67.2%)	403 (67.4%)	201 (65.3%)	191 (62.0%)	
CCI					0.575
0	1181 (69.1%)	406 (67.9%)	203 (65.9%)	215 (69.8%)	
> 0	529 (30.9%)	192 (32.1%)	105 (34.1%)	93 (30.2%)	
Pathology type					0.110
I/II	41 (2.4%)	3 (0.5%)	5 (1.6%)	7 (2.3%)	
III	1669 (97.6%)	595 (99.5%)	303 (98.4%)	301 (97.7%)	
T category*					< 0.001
T1	296 (17.3%)	82 (13.7%)	51 (16.6%)	38 (12.3%)	
T2	458 (26.8%)	119 (19.9%)	59 (19.2%)	50 (16.2%)	
T3	797 (46.6%)	334 (55.9%)	156 (50.6%)	161 (52.3%)	
T4	159 (9.3%)	63 (10.5%)	42 (13.6%)	59 (19.2%)	
N category*					< 0.001
N0	336 (19.6%)	79 (13.2%)	35 (11.4%)	25 (8.1%)	
N1	1039 (60.8%)	349 (58.4%)	192 (62.3%)	190 (61.7%)	
N2	245 (14.3%)	113 (18.9%)	57 (18.5%)	63 (20.5%)	
N3	90 (5.3%)	57 (9.5%)	24 (7.8%)	30 (9.7%)	
Overall Stage*					< 0.001
II	632 (37.0%)	139 (23.2%)	86 (27.9%)	57 (18.5%)	
III	843 (49.3%)	349 (58.4%)	160 (51.9%)	167 (54.2%)	
IVa	235 (13.7%)	110 (18.4%)	62 (20.1%)	84 (27.3%)	
LDH (IU/L)					0.010
≤ 175	891 (52.1%)	341 (57.0%)	185 (60.1%)	169 (54.9%)	
> 175	819 (47.9%)	257 (43.0%)	123 (39.9%)	139 (45.1%)	
EBV DNA (copies/ml)					< 0.001
0	697 (40.8%)	192 (32.1%)	105 (34.1%)	77 (25.0%)	
≤ 2000	402 (23.5%)	167 (27.9%)	72 (23.4%)	65 (21.1%)	
> 2000	611 (35.7%)	239 (40.0%)	131 (42.5%)	166 (53.9%)	

Data presented as number (%).
Abbreviations: CCD, cumulative cisplatin dose; CCI, Charlson Comorbidity Index; LDH, lactate dehydrogenase; EBV, Epstein-Barr virus.
† Calculated by Kendall's tau-b test.
* According to the 8th AJCC staging system.

decreased sharply until the CCD reached 250 mg/m^2, and then increased until the CCD reached 300 mg/m^2 (Fig. 1A). The lnHR curve revealed similar trend for LRFS (Fig. 1B). However, the risk of distant metastasis showed a negative linear relationship with the CCD, with a more gradual slope (Fig. 1C). The outcomes for OS are summarized in Supplementary Table S2.

The optimal CCD

Based on the lnHR curve for OS, we categorized the CCD into four groups: 0 ≤ CCD ≤ 180, 180 < CCD ≤ 230, 230 < CCD ≤ 270, 270 < CCD ≤ 300 mg/m^2. We assumed that the CCD in the range of 230–270 mg/m^2 would have optimal effects in terms of prognosis. Multivariate Cox analyses revealed that 230–270 mg/m^2 yielded optimal benefits compared to the other doses for OS and LRFS, and the effects were statistically significant. However, the advantage of 230–270 mg/m^2 compared to 180–230 and 270–300 mg/m^2 in terms of DMFS, was not statistically significant (Fig. 2).

The value of the optimal CCD was investigated in patients with different risks, including high-risk subgroup (patients with T4 or N2–3 disease) and low-risk subgroup (the remaining patients with T1–3 and N0–1 disease). The high-risk subgroup with 911 patients had 3-year OS, LRFS, and DMFS rates of 86.7%, 89.4%, and 83.3%, respectively, and 4-year rates of 80.8%, 86.9%, and 80.4%, respectively. Multivariate Cox analyses indicated that 230–270 mg/m^2 failed to have a significant advantage over the other doses in terms of OS, LRFS, and DMFS, except for its advantage over the 0–180 mg/m^2 dose for OS, among the high-risk patients (Fig. 2). Among the 2 013 low-risk patients, the 3-year OS, LRFS, and DMFS rates were 96.3%, 95.3%, and 94.3%, respectively, and the 4-year rates were 93.9%, 94.3%, and 93.7%, respectively. Overall, 230–270 mg/m^2 showed an advantage over the lower doses in terms of OS, LRFS, and DMFS rates among the low-risk patients (Fig. 2).

Discussion

This is the first study to quantify the dose-dependent effects of the CCD (as a continuous variable) on the prognosis of patients with locoregionally advanced NPC. As is shown in Fig. 1, CCD was an important prognostic factor for OS and LRFS, which had a nonlinear relationship. The similarity of the curves for OS and LRFS indicates that the OS benefit derived from the CCD may be mainly attributed to locoregional control, which is consistent with the results of a study by Lee et al. [6], in which most of the patients in the sample received 2-dimensional RT. Although IMRT can improve locoregional control significantly, compared to 2-dimensional RT, our study suggests that concurrent chemotherapy still plays an important role in improving LRFS in the era of IMRT [14]. The interaction of radiation and cisplatin promoted improved locoregional control by means of cytotoxic enhancement [15], but there seemed to be a CCD threshold for obtaining the OS and LRFS benefits given that a low CCD was not sufficient to reduce the risk of death and locoregional relapse in our study. Our finding that the risk of death and locoregional relapse increased as the CCD increased from 250 to 300 mg/m^2 was unexpected. A possible explanation for the finding is the confounding effects of factors

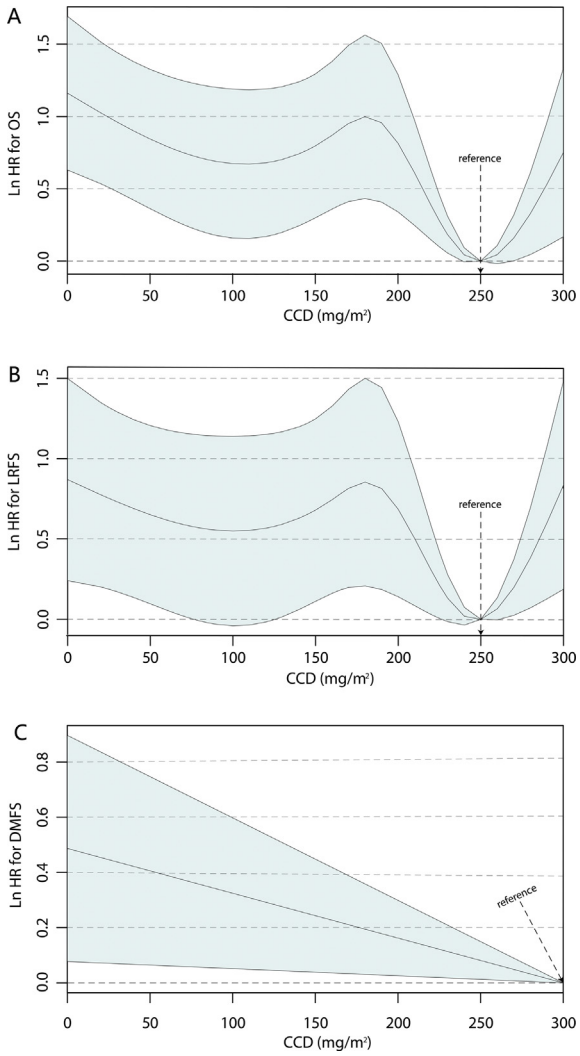

Fig. 1. Dose-dependent effects of CCD on OS (A), LRFS (B), and DMFS (C). Estimated natural logarithms of the HRs with 95% confidence intervals for the associations of CCD with OS, LRFS, and DMFS in 2 924 patients based on the dfmacox (degrees of freedom in multivariate additive Cox models) function in smoothHR—optimal extended Cox-type additive hazard regression model adjusted for age, sex, smoking, CCI, pathology type, T category, N category, LDH, and EBV DNA. The CCD, indicated by the arrow was the dose with the lowest risk of events and used as the reference value for calculating the HRs. CCD, cumulative cisplatin dose; OS, overall survival; LRFS, locoregional relapse-free survival; DMFS, distant metastasis-free survival; HR, hazard ratio; CCI, Charlson Comorbidity Index; LDH, lactate dehydrogenase; EBV, Epstein-Barr virus.

associated with the CCD, such as tumor stage, even after the multivariate analysis was conducted.

Our model incorporated the continuous variable CCD with a linear function into the multivariate Cox regression analysis of DMFS. It is known that distant relapse is mainly caused by occult micro-metastases, which exist at diagnosis; therefore, eradicating micro-metastases is the key to controlling distant relapse. In the CCRT setting, only systemic cisplatin could act on potential micro-metastases and our study indicated that the effect of cisplatin was dose-dependent. However, it seems that single-agent cisplatin might not be sufficiently potent in distant control considering the gradual slope of the lnHR curve (Fig. 1C).

The objective of this study was to determine the optimal CCD. For convenience, we defined an appropriate range in the analyses rather than a specific point as the optimal CCD. According to the lnHR curve for OS, we categorized the CCD and assumed the range 230–270 mg/m^2 corresponding to the trough of the curve to be the optimal CCD. Subsequent multivariate analyses confirmed 230–270 mg/m^2 as the optimal CCD range for the whole cohort. As most of the patients (257/308) in the optimal CCD subgroup received 240 mg/m^2, a dose of 240 mg/m^2 would be a preferable choice in clinical settings, where 40 mg/m^2 cisplatin weekly for 6 cycles or 80 mg/m^2 cisplatin every 3 weeks for 3 cycles could be delivered.

In the planned stratification analyses, the patients with different risks exhibited different responses to the CCD, which had prognostic value in low-risk patients but not in high-risk patients. This phenomenon is consistent with the results of previous reports [6,7]. The prognosis was rather good for patients at low risk, with 3-year and 4-year OS rates of 96.3% and 93.9%, respectively. Among the low-risk patients, the optimal CCD of 230–270 mg/m^2, compared to the lower CCD, was associated with a lower risk of death and disease relapse. After patients were stratified by disease stage, the effect of the higher CCD on OS did not differ significantly from the 230–270 mg/m^2 CCD. This change can be explained by the lower number of patients in the subgroup analysis and a decrease in statistical power. Another explanation is that stratification offset the effects of the confounding factors associated with the CCD to some extent.

However, the prognosis of high-risk patients was not good, despite the use of CCRT. The disappointing effect of the high tumor burden on disease control was such that distant metastasis was the main pattern of failure and cause of death. In the subgroup analysis, the optimal CCD had nonsignificant advantages over the other doses in terms of disease control. With respect to OS, the optimal CCD had a significant advantage over the 0–180 mg/m^2 CCD, which might have resulted from the additive effects of the nonsignificant improvements in LRFS and DMFS. The reasons for the CCD's prognostic failure among the high-risk patients are unknown. A possible explanation is the inherent poor prognosis of high-risk patients with a high tumor burden, irrespective of the CCD, which indicates that the CCRT alone might not be sufficient for treatment. The higher CCD failed to improve DMFS, which could be due to the primary resistance of the occult micro-metastasis to single-agent cisplatin. A combination of two or more cytotoxic drugs may be a solution, but not concurrent use with RT because of intolerable adverse effects. Given this problem, the use of IC or AC has gained acceptance in the treatment of high-risk NPC patients. Lee et al. [6] reported that the use of 5-fluorouracil in adjuvant chemotherapy was a prognostic factor for distant control, and a recent pooled analysis of individual patient data [16] found treatment with additional IC to be superior over CCRT alone for patients with locoregionally advanced NPC, with the survival benefit mainly associated with improved distant control. On the other hand, the optimal CCD tended to improve LRFS compared to the lower CCD; although not significant, this indicates that CCRT alone may be sufficient for high-risk patients for locoregional control. Previous pooled analyses [16,17] reported that additional IC or AC tended to improve LRFS compared to CCRT alone for locoregionally advanced NPC, but the value of IC or AC in locoregional control needs further investigation.

The current study has some limitations. First, it was a retrospective investigation conducted at a single center, and the survival outcomes might have been confounded by various undefined factors. Second, we only investigated the prognostic value of the CCD in settings using CCRT alone. In a preliminary study, Lv et al. [18] reported that decrease in the CCD during RT may be acceptable for NPC patients following IC. However, the optimal CCD concurrent with RT remains undetermined in the IC/AC plus CCRT setting.

Conclusions

We found that a CCD of 230–270 mg/m^2 (240 mg/m^2 recommended) is the optimal dose for patients with locoregionally advanced NPC, especially for those at low risk (T1–3 and N0–1). For high-

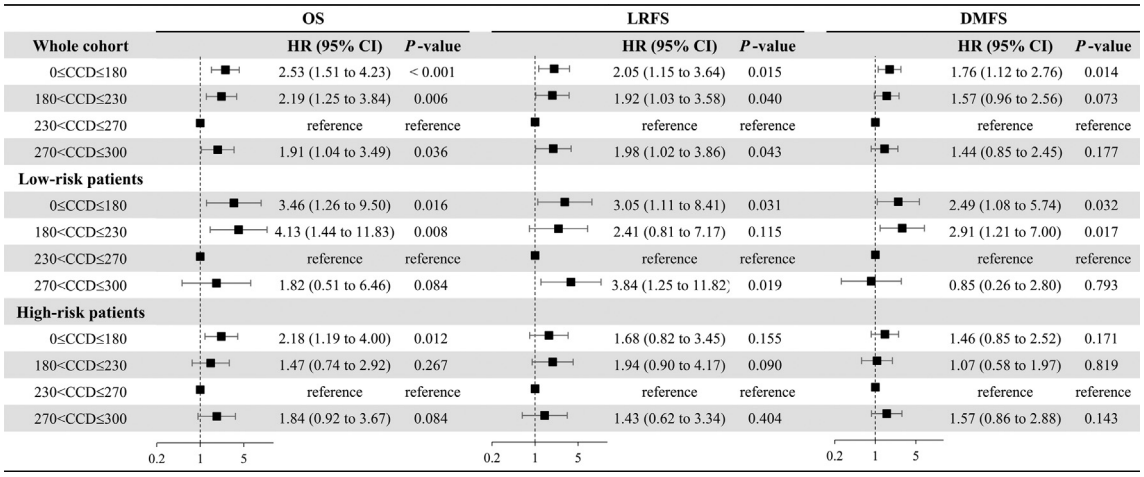

Fig. 2. The prognostic value of the categorized CCDs in the multivariate Cox analyses for the cohort and its subgroups. Variables in the multivariate analyses included CCD (230–270 mg/m^2 as the reference), age (> 60 vs. ≤ 60 year), sex (female vs. male), smoking (yes vs. no), CCI (> 0 vs. 0), pathology type (III vs. I/II), T category (T1 as the reference), N category (N0 as the reference), LDH (> 175 vs. ≤ 175 IU/L), and EBV DNA (0 copy/ml as the reference). Low-risk patients were those with T1–3 and N0–1 disease, except stage I disease. High-risk patients were those with T4 or N2–3 disease. OS, overall survival; LRFS, locoregional relapse-free survival; DMFS, distant metastasis-free survival; HR, hazard ratio; CI, confidence interval; CCD, cumulative cisplatin dose; CCI, Charlson Comorbidity Index; LDH, lactate dehydrogenase; EBV, Epstein-Barr virus.

risk patients (N2–3 or T4), additional chemotherapy should be administered before or after CCRT. Results of our study will give a valuable reference to determine the optimal CCD during RT for locoregionally advanced NPC.

Role of the funding sources

None declared.

Conflict of interest statement

None declared.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2018.12.028.

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