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Original Article

Optimal cumulative cisplatin dose in nasopharyngeal carcinoma patients based on induction chemotherapy response

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ABSTRACT

Background and purpose: Nasopharyngeal carcinoma (NPC) patients can be separated into two risk subgroups according to tumor responses to induction chemotherapy (IC). We aimed to elucidate the optimal cumulative cisplatin dose (CCD) of concurrent chemoradiotherapy (CCRT) for different NPC patient subgroups.

Participants and methods: A total of 990 patients with incident NPC diagnosed between 2008 and 2017 treated with IC plus CCRT were included in our observational study. The clinicopathological features of patients with different tumor responses were compared using the Chi-square test or Fisher's exact test. Prognosis was assessed using a multivariate Cox proportional hazards model. In addition, acute and late toxicities were compared between different CCD groups.

Results: After IC, 761/990 (76.9%) patients had a complete tumor response (CR)/partial response (PR) and 229 (23.1%) had stable disease (SD)/disease progression (PD). An unsatisfactory tumor response (SD/PD) after IC correlated with poor clinical outcome (3-year PFS 61.4% vs. 83.2%, $P < 0.001$ and 3-year LRFS 80.9% vs. 94.5%, $P < 0.001$). Patients who achieved CR/PR after IC received a CCD >200 mg/m^2 and showed higher 3-year PFS and DMFS rates than those receiving a CCD <100 mg/m^2 (PFS: 85.4% vs. 77.9%, $P = 0.045$; DMFS: 89.4% vs. 77.9%, $P = 0.015$). Multivariate analysis also showed that CCD was an independent prognostic factor for PFS and DMFS in CR/PR subgroup. Moreover, the medium dose group showed similar efficacy as high dose group but was associated with fewer grade 1–4 acute toxicities. However, application of different CCD didn't result in significantly different survival outcomes in SD/PD subgroup.

Conclusions: Tumor response to IC was an independent prognostic factor for patients with NPC. For the patients who achieved CR/PR after IC, patients receiving high CCD showed significantly improved 3-year PFS and DMFS compared with patients receiving low CCD. Balancing toxicity and efficacy, 200 mg/m^2 seemed to be the optimal dose in the CR/PR groups. However, enhancement of CCD did not provide survival benefit for patients who achieved SD/PD after IC, and treatment options for these patients require further consideration.

Abbreviations: NPC, nasopharyngeal carcinoma; RT, radiotherapy; IC, induction chemotherapy; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; SD, stable disease; PD, disease progression; CR, complete response; PR, partial response; CCD, cumulative cisplatin dose; IMRT, intensity-modulated radiotherapy; KPS, Karnofsky's performance score; MRI, magnetic resonance imaging; CT, computed tomography; PET/CT, positron emission tomography computed tomography; TPF, taxanes, cisplatin and 5-fluorouracil; PF, cisplatin and 5-fluorouracil; TP, taxanes and cisplatin; 2DRT, two-dimensional radiotherapy; EBV, Epstein–Barr virus; OS, overall survival; PFS, progression-free survival; LRFS, locoregional relapse-free survival; DMFS, distant metastasis-free survival; DFS, disease free survival; HR, hazard ratio; CI, confidence interval.

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Nasopharyngeal carcinoma (NPC) is an endemic malignancy in South China [1]. Based on its epidemiology and biological characteristics, NPC is different from other head and neck cancers [2]. Cisplatin-based concurrent chemoradiotherapy (CCRT) has been established as the standard treatment regimen for local advanced NPC patients [3,4]. Recently, the application of induction chemotherapy (IC) before CCRT has received considerable attention. According to previous studies, IC plays an important role in decreasing risk of distant metastasis and improving clinical outcomes [5–7]. Despite the increased survival rate associated with the development of modern treatment modalities and techniques, 20–30% of patients experience distant metastasis or locoregional relapse [8]. Therefore, it is necessary to identify patients at different risk levels and provide evidence for individualized therapy.

Our previous studies demonstrated that tumor response to IC was closely correlated with clinical outcome [9,10]. Patients who experienced stable disease (SD)/disease progression (PD) after IC had a lower progression free survival (PFS) rate and loco-regional relapse free (LRFS) rate compared with patients who experienced complete response (CR)/partial response (PR). Thus, we divided patients into two risk subgroups according to their tumor response to IC in the current study.

In terms of concurrent chemotherapy dosage, cisplatin-based regimens can be delivered by either 30–40 mg/m^2 per week or one administration of 100 mg/m^2 every three weeks (100 mg/m^2). This is standard practice for concurrent chemotherapy [11–13]. Our group also compared the long-term survival outcomes of patients receiving a different cumulative cisplatin dose (CCD) concurrently with intensity-modulated radiotherapy (IMRT) [14]. However, there have been no studies, which have explored the relationship of CCD and clinical outcome in patients receiving IC.

In this study, we analyzed the prognostic value of CCD in patients applying IC. Furthermore, subgroup analysis was conducted to compare the therapeutic value of CCD in different patient risk groups. Our findings will help clinicians better predict NPC prognosis and guide treatment strategies in these patients.

Methods

Patients

From 2008 to 2017, 990 local advanced NPC patients in Sun Yat-sen University Cancer Center, China, were involved in our study. The eligibility criteria for this study were as follow: (1) pathologically confirmed NPC at stage II–IV; (2) Karnofsky's performance score (KPS) >70; (3) first line IC and cisplatin-based concurrent chemotherapy regimen; (4) available imaging evaluation data after IC; (5) no secondary pregnancy, lactation, and other malignant disease and (6) adequate organ function. All patients received a series of routine examinations before treatment, including complete physical examination, nasopharyngoscopy, head and neck magnetic resonance imaging (MRI) with contrast, chest radiograph/computed tomography (CT) with contrast, abdominal sonography/CT with contrast, electrocardiography, and bone scans, complete blood count with differential count, biochemical profile, plasma Epstein–Barr virus (EBV) DNA load measured by quantitative PCR before treatment, and EBV serology at baseline. The positron emission tomography computed tomography (PET-CT) was alternatively applied to evaluate distant metastasis lesions. This retrospective study was approved by the Clinical Research Ethics Committee of the Sun Yat-sen University Cancer Center, and all participants provided written informed consent before treatment.

Treatment and evaluation

All patients received one of the following IC regimens: PF (consisting of cisplatin [1 day of 80–100 mg/m^2] and 5-fluorouracil [800–1000 mg/m^2, by 120 h continuous intravenous infusion]), TP (consisting of docetaxel [1 day of 75 mg/m^2] or paclitaxel [1 day of 150–180 mg/m^2] or paclitaxel liposome [1 day of 150–180 mg/m^2] and cisplatin [20–25 mg/m^2 on days 1–3]) and TPF (consisting of docetaxel [1 day of 60 mg/m^2] or paclitaxel [1 day of 135 mg/m^2] or paclitaxel liposome [1 day of 135 mg/m^2], cisplatin [1 day of 60 mg/m^2] and 5-fluorouracil [500–800 mg/m^2, by 120 hours continuous intravenous infusion]). All regimens were administered at intervals of 3 weeks for 2–4 cycles.

All patients underwent another MRI at day 8(6–10) from the last cycle IC (day 1–5). The tumor response in different patients was evaluated by two independent clinicians on the basis of evaluation criteria for efficacy of solid tumors (RECIST) [15], which classified patients into CR, PR, SD, and PD according to the response of primary and nodal disease. Patients that experienced CR or PR were considered as favorable responders.

The RT method was IMRT. Gross tumor volume included the primary tumor and the positive retropharyngeal lymph node. A total dose of 68–70 Gy was given with the daily fraction dose ranging from 2.00 Gy to 2.34 Gy. Radiotherapy was started at day 22 (20–24) from the last cycle IC (day 1–5). Other details of the IMRT plan followed the principle of previous studies [16–18]. Concurrent cisplatin-based chemotherapy (80–100 mg/m^2 every three weeks or 30–40 mg/m^2 weekly) was administered during radiotherapy [4,19].

Outcome and follow-up

PFS served as the first endpoint in our study, defined as the period from the first day of IC to the date of disease progression or death from any cause. Overall survival (OS) (defined as the period from the first day of IC to the date of death from any cause), LRFS (defined as the time from the first day of IC to the date of local/regional relapse) and distant metastasis-free survival (DMFS) (defined as the time from the first day of IC to the date of distant metastasis) were the secondary endpoints. Physical examination, nasopharyngoscopy, chest radiography, abdominal sonography, MRI of the head and neck and plasma EBV DNA testing were performed every 3–6 months in the first three years, and then every 6 months thereafter until death. PET-CT and other diagnoses were considered if necessary. Acute hematological toxicities during concurrent chemotherapy were graded according to the Common Terminology Criteria for Adverse Events (version 3.0) and compared between different groups. Moreover, the late toxicities were graded according to the Radiation Therapy Oncology Group radiation morbidity scoring criteria and the Common Terminology Criteria for Adverse Events (Version 3.0).

Statistical analysis

All statistical analysis in our study was executed using SPSS package for Windows, version 22.0 (Chicago, IL). Correlation between the different tumor responses to IC and clinical characteristics was calculated using the χ^2 test or Fisher's exact test. Survival curves were estimated using the Kaplan–Meier method with the log-rank test. Multivariate analyses were calculated using the Cox proportional hazards regression model. All the following potential prognostic factors were considered in the model: age, gender, T stage, N stage, clinical stage, EBV-DNA before treatment, EBV-DNA after IC, IC regimen, IC response, cisplatin regimen, total

radiation dose, fractionation dose and CCD. All analyses were two-sided. The level of significance was set at $P < 0.05$.

Results

Patient characteristics

From 2008 to 2017, 990 patients were involved in this study. For the entire cohort, the median age was 43 (range 8–74) years, with 240 (24.2%) females and 750 (75.8%) males. For all patients, the response to IC was as follows: 19 (1.9%) patients experienced CR, 742 (74.9%) patients were evaluated as PR, 224 (22.6%) patients achieved SD, and 5 (0.5%) patient experienced PD. The differences in demographics and clinical characteristics between the CR/PR and SD/PD groups are shown in Table 1. The χ^2 test showed significantly more patients with SD/PD were males (83.8% vs. 73.3%, $P = 0.001$) and had T4 category (48.0% vs. 36.8%, $P = 0.023$), N3 category (30.1% vs. 22.5%, $P = 0.025$), advanced clinical cancer stage

Table 1
Patient demographics and clinical characteristics.

Characteristics	No. (%)	CR + PR (n = 761) No. (%)	SD + PD (n = 229) No. (%)	*P value*
Age, years				0.607[a]
Median (range)	43(8–74)	43(8–72)	43(10–74)	
<45	530(53.5)	404(53.1)	126(55.0)	
≥45	460(46.5)	357(46.9)	103(45.0)	
Sex				0.001[a]
Female	240(24.2)	203(26.7)	37(16.2)	
Male	750(75.8)	558(73.3)	192(83.8)	
Pathological type				0.529[b]
WHO type I	3(0.3)	3(0.4)	0(0.0)	
WHO type II	5(0.5)	3(0.4)	2(0.9)	
WHO type III	982(99.1)	755(99.2)	227(99.1)	
T stage*				0.023[a]
T1	18(1.8)	14(1.8)	4(1.7)	
T2	108(10.9)	88(11.6)	20(8.7)	
T3	474(47.9)	379(49.8)	95(41.5)	
T4	390(39.4)	280(36.8)	110(48.0)	
N stage*				0.025[a]
N0	24(2.4)	19(2.5)	5(2.2)	
N1	255(25.8)	211(27.7)	44(19.2)	
N2	471(47.6)	360(47.3)	111(48.5)	
N3	240(24.2)	171(22.5)	69(30.1)	
Clinical stage*				0.004[a]
II	21(2.1)	19(2.5)	2(0.9)	
III	409(41.3)	334(43.9)	75(32.8)	
IVa	320(32.3)	237(31.1)	83(36.2)	
IVb	240(24.2)	171(22.5)	69(30.1)	
EBV DNA before treatment				0.414[a]
<1500	473(47.8)	369 (48.5)	104(45.4)	
≥1500	517(52.2)	392 (51.5)	125(54.6)	
EBV DNA after IC				<0.001[a]
0	282(66.2)	241(73.5)	41(41.8)	
>0	144(33.8)	87(26.5)	57(58.2)	
IC regimen				0.006[a]
TPF	715(72.2)	568(74.6)	147(64.2)	
PF	132(13.3)	90(11.8)	42(18.3)	
TP	143(14.4)	103(13.5)	40(17.5)	
Cisplatin regimen				0.567[a]
Triweekly	900(90.9)	694(91.2)	206(90.0)	
Weekly	90(9.1)	67(8.8)	23(10.0)	
CCD (mg/m^2)				0.263[a]
Median(range)	160(30–300)	160(30–300)	160(30–300)	
≤100	84(8.5)	59(7.8)	25(10.9)	
101–200	686(69.3)	535(70.3)	151(65.9)	
>200	220(22.2)	167(21.9)	53(23.1)	
Total radiation dose (Gy)				0.001[a]
Median(range)	70(68–70)	70(68–70)	70(68–70)	
<70	138(13.9)	122(16.0)	16(7.0)	
70	852(86.1)	639(84.0)	213(93.0)	
Radiation fractionation dose (Gy)				0.003[a]
Median(range)	2.19(2.0–2.34)	2.19(2.0–2.34)	2.19(2.0–2.34)	
<2.19	622(62.8)	459(60.3)	163(71.2)	
≥2.19	368(37.2)	302(39.7)	66(28.8)	

Abbreviations: IC = induction chemotherapy; TPF = taxanes plus cisplatin with fluorouracil; PF = cisplatin with fluorouracil; TP = taxanes with cisplatin; EBV, Epstein–Barr virus; CCD = cumulative cisplatin dose.

[a] P values were calculated by the Chi-square test.

[b] P value calculated with Fisher's exact test.

* According to the 7th edition of the UICC/AJCC staging system.

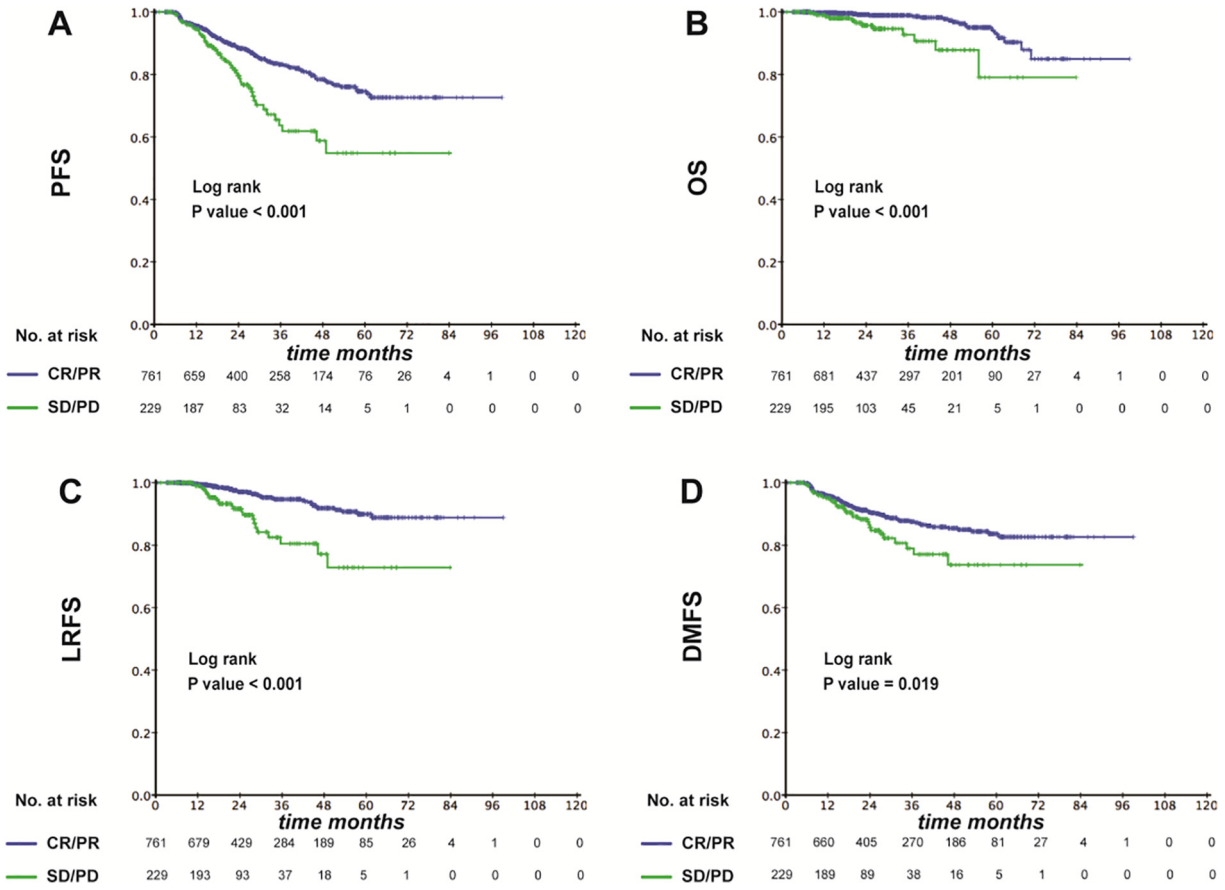

Fig. 1. Kaplan–Meier's PFS (A), OS (B), LRFS (C) and DMFS (D) curves for 990 patients with NPC stratified by CR/PR and SD/PD groups based on tumor response after induction chemotherapy. Abbreviations: NPC, nasopharyngeal carcinoma; PFS = progression-free survival; OS = overall survival; LRFS = local–regional relapse-free survival; DMFS = distant metastasis-free survival. CR = complete response; PR = partial response; SD = stable disease, PD = disease progression.

(IVa–IVb) (66.3% vs. 53.6%, $P = 0.004$), detectable EBV DNA after IC (58.2% vs. 26.5%, $P = 0.001$), high radiotherapy dose (93.0% vs. 84.0%, $P = 0.001$) and low dose per fraction (71.2% vs. 60.3%, $P = 0.003$) compared with patients who achieved CR/PR. Obviously, a greater percentage of patients in the CR/PR group received TPF regimens as the IC regimen ($P = 0.003$). No significant associations were observed between any other clinicopathological feature and the overall tumor response.

Survival outcomes

Median follow-up time for the CR/PR and SD/PD groups was 28.2 months (range, 5–99 months) and 22.7 months (range, 3.5–83.8 months), respectively. As shown in Fig. 1, unsatisfactory tumor response (SD/PD) predicted poorer clinical outcome compared with a satisfactory tumor response (CR/PR) at all endpoints. In essence this could be demonstrated as follows: 3-year PFS: 61.4% (95% CI: 51.0–71.8) vs. 83.2% (95% CI: 79.9–86.5), $P < 0.001$; 3-year OS: 92.7% (95% CI: 87.4–98.0) vs. 98.2% (95% CI: 96.8–99.6), $P = 0.001$; 3-year LRFS: 80.9% (95% CI: 72.3–89.5) vs. 94.5% (95% CI: 92.3–96.7), $P < 0.001$; 3-year DMFS: 75.7% (95% CI: 66.9–84.5) vs. 87.6% (95% CI: 84.9–90.3), $P = 0.019$) (Fig. 1). In terms of CCD, median CCD for all 990 patients was 160 mg/m^2 (range, 30–300 mg/m^2). 900 (90.9%) patients treated with cisplatin 3 weekly and 90 (9.1%) patients treated with cisplatin weekly. Due to the poor compliance of patients, 84 (8.5%) patients received a CCD $\leq$100 mg/m^2. In total, 686 (69.3%) patients received a CCD of 101–200 mg/m^2, and 220 (22.2%) patients received a CCD of >200 mg/m^2. Patients in the low dose group exhibited low 3-year PFS rates than patients in the high dose group (72.3% vs. 82.3%, $P = 0.023$) and exhibited lower 3-year DMFS rates than patients in the medium dose group (72.3% vs. 85.6%, $P = 0.013$) and high dose group (72.3% vs. 87.6%, $P = 0.005$). However, there were no significant differences between >200 mg/m^2 and 101–200 mg/m^2 for all endpoints (Fig. 2). From the multivariable analysis of the entire cohorts, the following variables were considered in the Cox proportional hazards model: age, gender, T stage, N stage, clinical stage, EBV–DNA before treatment, EBV–DNA after IC, IC regimen, IC response, cisplatin regimen, total radiation dose, fractionation dose and CCD. As shown in Table 2, SD/PD after IC was associated with a higher risk of tumor progression (hazard ratio [HR]: 1.505; 95% confidence interval [CI]: 1.051–2.156; $P = 0.026$), deaths (HR, 4.147, 95% CI 1.798–9.564, $P = 0.001$) and locoregional relapse (HR: 2.671; 95% CI: 1.519–4.695, $P = 0.001$). Besides, CCD was an independent prognostic factor for DMFS ([>200 mg/m^2 vs. $\leq$100 mg/m^2]: HR: 0.438, 95%, CI: 0.221–0.866, $P = 0.018$).

Subgroups analysis for whole patients based on IC response

As patients with different tumor responses after IC exhibited different rates of treatment failure, we divided all patients into CR/PR and SD/PD subgroups and comparatively evaluated the prognostic impact of CCD. For patients that achieved CR/PR after IC, patients receiving a CCD >200 mg/m^2 showed higher 3-year PFS and DMFS rates than patients receiving a CCD <100 mg/m^2 (PFS: 85.4% vs. 68.2%, $P = 0.045$; DMFS: 89.4% vs. 68.2%, $P = 0.015$) and patients receiving a medium CCD (101–200 mg/m^2) showed

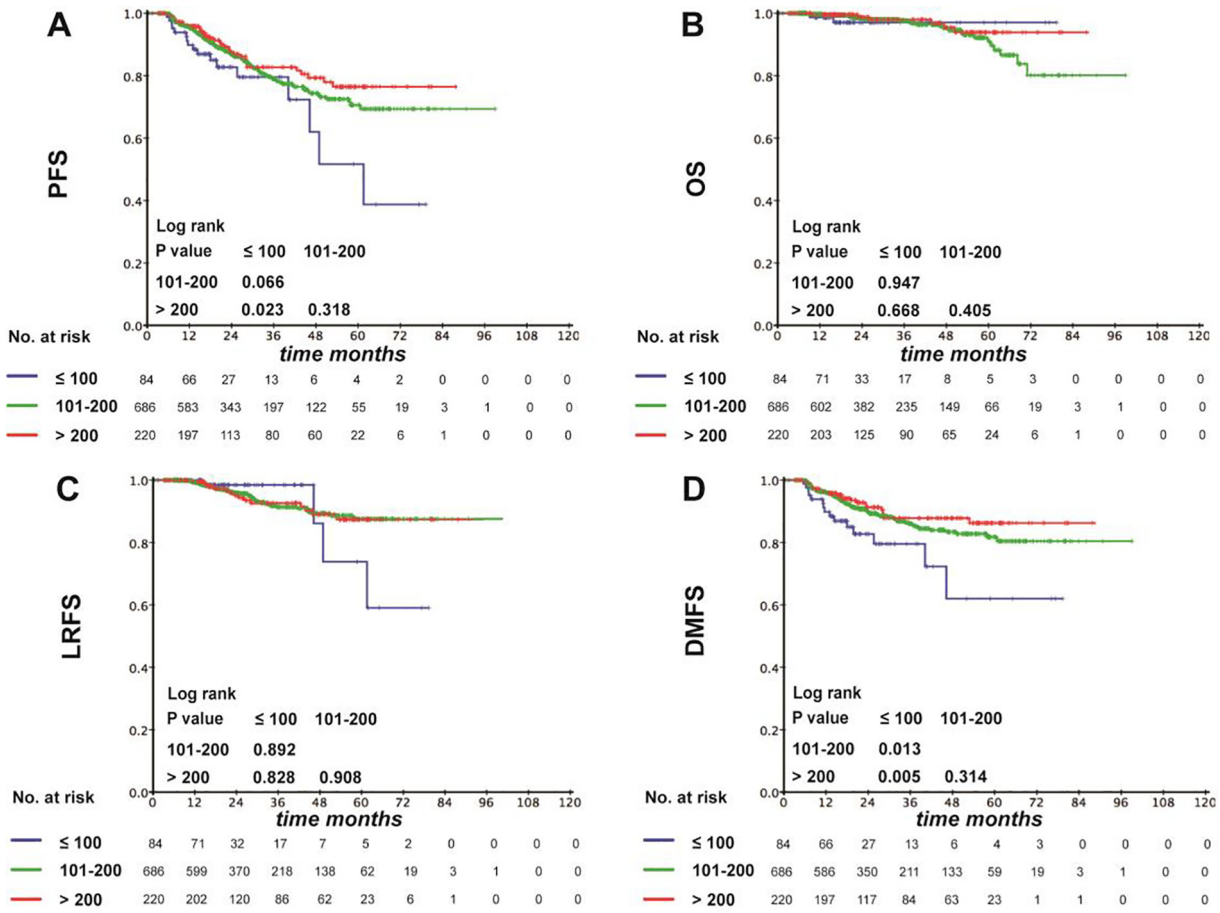

Fig. 2. Kaplan–Meier's PFS (A), OS (B), LRFS (C) and DMFS (D) curves for 990 NPC patients stratified by CCD ≤100 mg/m^2, CCD >100 mg/m^2 and ≤200 mg/m^2, and CCD >200 mg/m^2. Abbreviations: NPC, nasopharyngeal carcinoma; PFS = progression-free survival; OS = overall survival; LRFS = local–regional relapse-free survival; DMFS = distant metastasis-free survival; CCD = cumulative cisplatin dose.

higher 3-year DMFS rates than patients receiving a CCD <100 mg/m^2 (DMFS: 89.4% vs. 68.2%, $P = 0.030$) as shown in Fig. 3. Similarly, the medium dose group showed similar efficacy as high dose group for all endpoints in the CR/PR group. In addition, application of different CCD did not result in significantly different survival outcomes in the SD/PD subgroup (Fig. 4). In the multivariable analysis, CCD was an independent prognostic factor for PFS (>200 mg/m^2 vs. ≤100 mg/m^2: HR: 0.410, 95%CI: 0.195–0.861, $P = 0.019$) and DMFS ([101–200 mg/m^2 vs. ≤100 mg/m^2]: HR: 0.478, 95%CI: 0.238–0.961, $P = 0.038$; [>200 mg/m^2 vs. ≤100 mg/m^2]: HR: 0.329, 95%CI: 0.143–0.753, $P = 0.009$) in the CR/PR subgroup, while it was not significantly associated with any survival outcome in the SD/PD group (Table 3).

Subgroups analysis for stage IVa–b patients based on IC response

The non-responding patients had a higher rate of stage IVa–b disease. Subgroup analysis was conducted in stage IVa–b NPC patients based on IC response to further investigate the prognostic value of the CCD. For stage IVa–b NPC patients that achieved CR/PR after IC, patients receiving a CCD 101–200 mg/m^2 showed higher 3-year PFS and DMFS rates than patients receiving a CCD <100 mg/m^2 as shown in Supplement Fig. 1 (PFS: 80.6% vs. 74.5%, $P = 0.025$; DMFS: 86.1% vs. 74.5%, $P = 0.020$). However, application of different CCD did not result in significantly different survival outcomes in the SD/PD subgroup (data not shown). In the multivariable analysis, CCD was an independent prognostic factor for PFS ([101–200 mg/m^2 vs. ≤100 mg/m^2]: HR: 0.354, 95%CI: 0.154–0.811, $P = 0.014$; [>200 mg/m^2 vs. ≤100 mg/m^2]: HR: 0.334, 95% CI: 0.133–0.839, $P = 0.020$) and DMFS ([101–200 mg/m^2 vs. ≤100 mg/m^2]: HR: 0.357, 95%CI: 0.144–0.886, $P = 0.026$; [>200 mg/m^2 vs. ≤100 mg/m^2]: HR: 0.350, 95%CI: 0.126–0.973, $P = 0.044$) in the CR/PR subgroup, and similarly it was not significantly associated with any survival outcome in the SD/PD group (Supplement Table 1).

Acute toxicity

We evaluated acute toxicity at the time when toxic and side effect was most obvious during CCRT between the three CCD groups. The number of patients with grade 1, 2, 3, 4 toxicities in detail is shown in the Table 4. High CCD was significantly associated with an increased incidence of grade 1–4 leucocytopenia (78.6% vs. 86.2% vs. 91.4%, $P = 0.010$), neutropenia (61.9% vs. 65.6% vs. 74.5%, $P = 0.027$), increased alanine transaminase (ALT) (26.2% vs. 24.8% vs. 39.0%, $P = 0.008$) and increased blood urea nitrogen (BUN) (19.0% vs. 32.8% vs. 39.5%, $P = 0.017$). Intergroup differences in other acute toxicities such as anemia, as well as increases in levels of creatinine (CRE), and aspartate transaminase (AST) were not significant (P >0.05 for all) (Table 4).

Late radiation-related toxicity

Xerostomia was the most common chief complaint in patients' routine follow-up visits among all late radiation-related toxicities. By the time of last follow-up, 71.7% (525 of 732) patients suffered

Table 2
Multivariable analysis of prognostic factors for 990 NPC patients receiving induction chemotherapy.

	Hazard ratio* (95% CI)	*P* value
Progression-free survival		
Age (y) (≥45 vs. <45)	0.945(0.690–1.293)	0.724
Gender (M vs. F)	1.600(1.050–2.437)	0.029
T category (3–4 vs. 1–2)	1.209(0.742–1.968)	0. 446
N category (2–3 vs. 0–1)	1.178(0.813–1.707)	0.387
Overall stage (IVa–b vs. II–III)	1.368(0.976–1.919)	0.069
EBV DNA before treatment(≥1500 vs. <1500)	1.474(1.055–2.061)	0.023
EBV DNA after IC (>0 vs. 0)	1.279(0.868–1.885)	0.213
IC regimen (triplet vs doublet)	0.604(0.428–0.852)	0.004
IC response (SD + PD vs. CR + PR)	1.505 (1.051–2.156)	0.026
Cisplatin regimen (Triweekly vs. Weekly)	0.977(0.583–1.635)	0.928
Total radiation dose (70 vs. <70)	0.925(0.553–1.547)	0.767
Fractionation dose (≥2.19 vs. <2.19)	0.800(0.546–1.172)	0.252
CCD (101–200 vs. ≤100)	0.778(0.461–1.311)	0.346
CCD (>200 vs. ≤100)	0.601(0.330–1.097)	0.098
Overall survival		
Age (y) (≥45 vs. <45)	1.989(0.955–4.143)	0.066
Gender (M vs. F)	0.897(0.375–2.149)	0.808
T category (3–4 vs. 1–2)	0.970(0.351–2.682)	0.953
N category (2–3 vs. 0–1)	0.997(0.433–2.294)	0.994
Overall stage (IVa–b vs. II–III)	1.720(0.786–3.762)	0.175
EBV DNA before treatment (≥1500 vs. <1500)	2.595(1.039–6.480)	0.041
EBV DNA after IC(>0 vs. 0)	2.758(0.828–9.183)	0.098
IC regimen (triplet vs doublet)	0.694(0.317–1.520)	0.361
IC response (SD + PD vs. CR + PR)	4.147(1.798–9.564)	0.001
Cisplatin regimen (Triweekly vs. Weekly)	0.588(0.170–2.039)	0.403
Total radiation dose (70 vs. <70)	0.718(0.268–1.925)	0.511
Fractionation dose (≥2.19vs. <2.19)	1.080(0.463–2.519)	0.858
CCD (101–200 vs. ≤100)	1.770(0.401–7.807)	0.451
CCD (>200 vs. ≤100)	1.433(0.278–7.395)	0.668
Locoregional relapse-free survival		
Age (y) (≥45 vs. <45)	0.983(0.581–1.661)	0.948
Gender (M vs. F)	1.801(0.839–3.864)	0.131
T category (3–4 vs. 1–2)	1.566(0.656–3.739)	0.312
N category (2–3 vs. 0–1)	1.163 (0.636–2.124)	0.624
Overall stage (IVa–b vs. II–III)	1.027(0.594–1.776)	0.925
EBV DNA before treatment (≥1500 vs. <1500)	1.847(1.025–3.327)	0.041
EBV DNA after IC(>0 vs. 0)	1.349(0.691–2.636)	0.380
IC regimen (triplet vs doublet)	0.815(0.458–1.450)	0.486
IC response (SD + PD vs. CR + PR)	2.671(1.519–4.695)	0.001
Cisplatin regimen (Triweekly vs. Weekly)	1.079 (0.465–2.504)	0.859
Total radiation dose (70 vs. <70)	1.446(0.596–3.508)	0.415
Fractionation dose (≥2.19 vs. <2.19)	1.018(0.562–1.846)	0.953
CCD (101–200 vs. ≤100)	1.387(0.486–3.962)	0.541
CCD (>200 vs. ≤100)	1.385(0.446–4.300)	0.574
Distant metastasis-free survival		
Age (y) (≥45 vs. <45)	0.924(0.634–1.345)	0.679
Gender (M vs. F)	1.392(0.860–2.253)	0.178
T category (3–4 vs. 1–2)	1.171(0.653–2.102)	0.596
N category (2–3 vs. 0–1)	1.327(0.840–2.095)	0.226
Overall stage (IVa–b vs. II–III)	1.437(0.954–2.163)	0.083
EBV DNA before treatment (≥1500 vs. <1500)	1.252(0.847–1.851)	0.260
EBV DNA after IC(>0 vs. 0)	1.280(0.804–2.036)	0.298
IC regimen (triplet vs doublet)	0.517(0.345–0.775)	0.001
IC response (SD + PD vs. CR + PR)	1.201 (0.776–1.859)	0.411
Cisplatin regimen (Triweekly vs. Weekly)	0.776(0.409–1.472)	0.437
Total radiation dose (70 vs. <70)	0.730(0.396–1.343)	0.312
Fractionation dose (≥2.19 vs. <2.19)	0.732(0.438–1.169)	0.191
CCD (101–200 vs. ≤100)	0.592(0.335–1.046)	0.071
CCD (>200 vs. ≤100)	0.438(0.221–0.866)	0.018

Abbreviations: CI = confidence interval; EBV = Epstein–Barr virus; IC = induction chemotherapy; CCD = cumulative cisplatin dose.
A Cox proportional hazards regression model was used to detect variables individually without adjustment. All variables were transformed into categorical variables. HRs were calculated for age (years) (≥45 vs. <45), sex (male vs. female), T stage (T3–4 vs. T1–2), N stage (N2–3 vs. N0–1), overall stage (IVa–b vs. II–III), plasma EBV DNA before the first treatment (≥1500 copies/ml vs. <1500 copies/ml), plasma EBV DNA after IC (>0 copies/ml vs. 0 copies/ml), IC regimen (triplet vs doublet), Cisplatin regimen (Triweekly vs. Weekly), Total radiation dose (70 Gy vs. <70 Gy), Fractionation dose (≥2.19 Gy vs. <2.19 Gy), CCD (101–200 vs. ≤100, > 200 vs. ≤100).

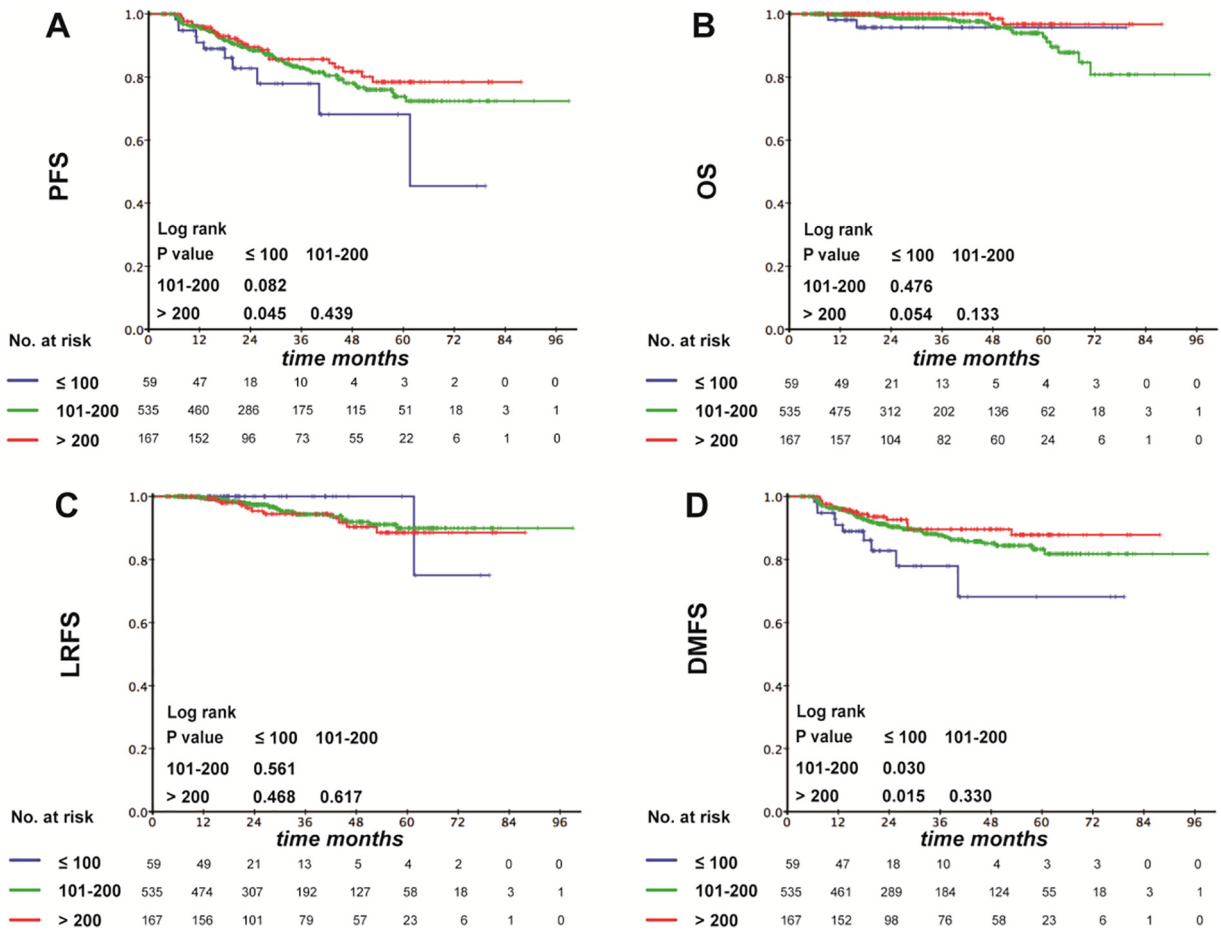

Fig. 3. Kaplan–Meier's PFS (A), OS (B), LRFS (C) and DMFS (D) curves for the subgroup of 761 NPC patients achieved CR/PR after induction chemotherapy stratified by CCD ≤100 mg/m^2, CCD >100 mg/m^2 and ≤200 mg/m^2, and CCD >200 mg/m^2. Abbreviations: NPC, nasopharyngeal carcinoma; PFS = progression-free survival; OS = overall survival; LRFS = local–regional relapse-free survival; DMFS = distant metastasis-free survival; CCD = cumulative cisplatin dose.

from xerostomia. In addition, a total of 357 patients (48.8%) developed skin fibrosis and a total of 265 patients (36.2%) were bothered by hearing impairment. Eighteen patients developed grade 1–2 endocrine dysfunction and there was no grade 3 to grade 4 endocrine dysfunction. With regard to trismus, temporal lobe injury, eye damage and neurological damage, the incidence rates were parallel in different CCD group. There were 4 patients developed second malignancy. More CCD did not increase or magnify relevant late adverse events (Table 5).

Discussion

The outcomes of this current study revealed that a satisfactory tumor response to IC was associated with significantly improved PFS, OS, LRFS, and DMFS in NPC patients. In the subgroup of patients who achieved CR/PR after IC, patients receiving ≤100 mg/m^2 CCD showed significantly decreased 3-year PFS compared with patients receiving >200 mg/m^2 CCD and DMFS compared with patients receiving medium/high CCD. However, there were no significant differences between >200 mg/m^2 and 101–200 mg/m^2 for all endpoints. In addition, application of different CCD did not result in significantly different survival outcomes in the subgroup of patients who were SD/PD after IC.

The cisplatin based concurrent chemotherapy administered during RT is important in conferring survival benefits [3,4]. Many previous studies have reported the prognostic value of CCD, and it is found that a CCD of 200 mg/m^2 can significantly improve the prognosis in NPC [20–23]. Wei et al. demonstrated that cumulative cisplatin >200 mg/m^2 improved the 5-year PFS rates and significantly improved distant failure-free survival compared with cumulative cisplatin of ≤200 mg/m^2 in 214 NPC patients [21]. Lee et al. found that the dose of cisplatin during the concurrent phase had a significant impact on the locoregional-failure free and OS rates; the difference between 0–1 (0–100 mg/m^2) and 2 cycles (200 mg/m^2) was significant [22]. The study by Peng [23] showed that a CCD of ≥240 mg/m^2 was not an independent prognostic factor in patients with locoregionally advanced NPC at high risk of distant metastasis, and 200 mg/m^2 cisplatin may be adequate to achieve a survival benefit from a secondary analysis of a prospective phase III clinical trial. In addition, our previous study [14] also suggested that patients who received 0–100 mg/m^2 of cisplatin had lower OS and DMFS rates than the patients who received >100 mg/m^2 and no significant difference was observed between the patients in the medium (101–200 mg/m^2) and high (>200 mg/m^2) dose groups. Our results are consistent with the previous ones for the whole cohort. However, patients enrolled in the aforementioned studies on which this value is based, all received CCRT and few studies have clarified the optimal CCD in locoregionally advanced NPC patients receiving IC plus CCRT. Lv and colleagues found that 160 mg/m^2 CCD might be sufficient in precipitating beneficial antitumor effects in IC [24]. However, the sample of their study was relatively small. Moreover, the prognostic difference was only

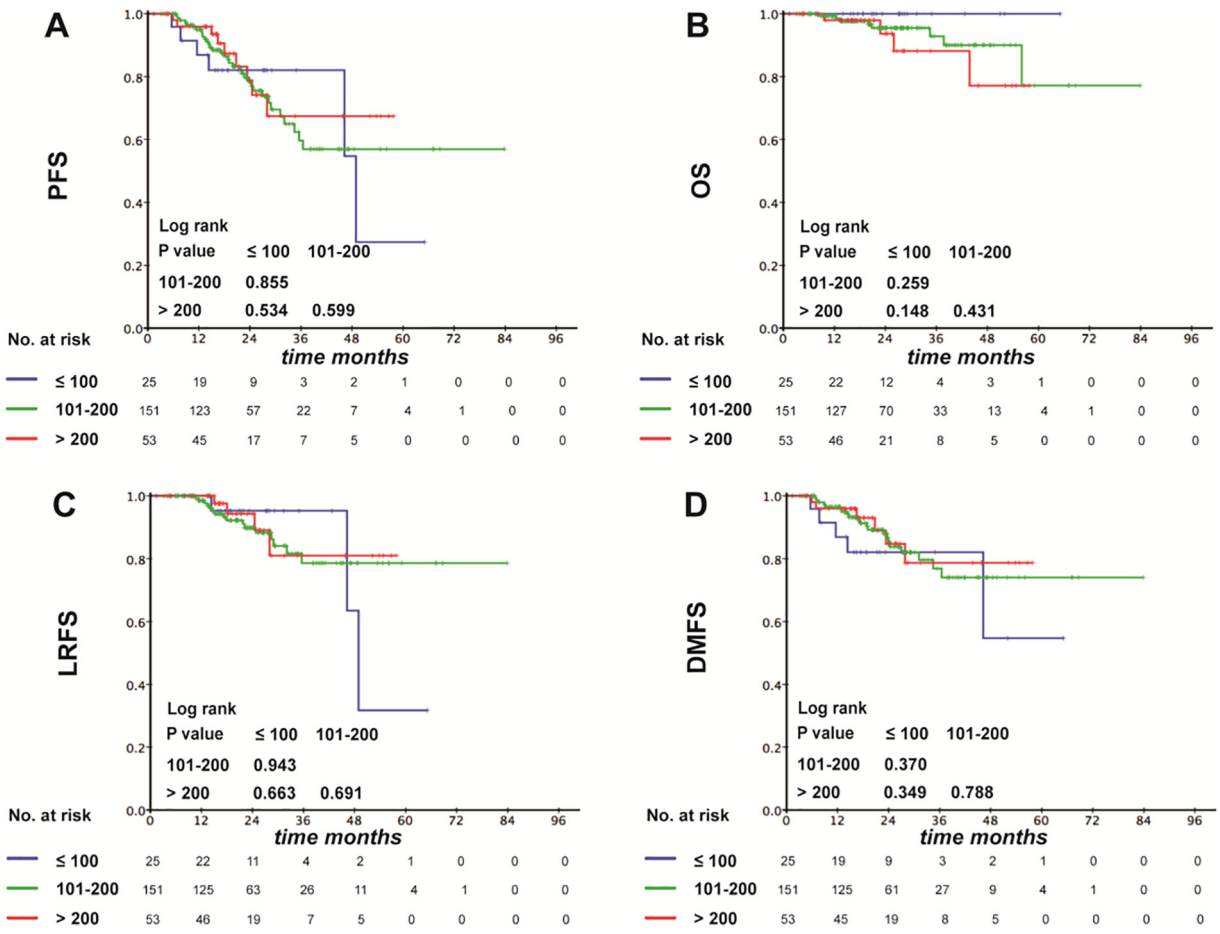

Fig. 4. Kaplan–Meier's PFS (A), OS (B), LRFS (C) and DMFS (D) curves for the subgroup of 229 NPC patients achieved SD/PD after induction chemotherapy stratified by CCD 100 mg/m^2, CCD >100 mg/m^2 and ≤200 mg/m^2, and CCD >200 mg/m^2. Abbreviations: NPC, nasopharyngeal carcinoma; PFS = progression-free survival; OS = overall survival; LRFS = local–regional relapse-free survival; DMFS = distant metastasis-free survival; CCD = cumulative cisplatin dose.

discussed for the whole cohort and was not investigated by subgroup according to the response to IC.

Patients who achieved CR/PR after IC seemed to be more sensitive to chemotherapy than patients who experienced SD/PD. Our study showed that favorable responders in the low dose group exhibited lower 3-year PFS rates than patients in the high dose group and lower 3-year DMFS rates than patients in the medium/high dose group. It indicated that an increased CCD could provide survival benefit for those patients who were sensitive to chemotherapy. For those favorable responders, an increasing CCD seemed to achieve a better prognosis. Moreover, we found that medium dose group showed similar efficacy as high dose group but was associated with fewer grade 1–4 acute toxicities. Balancing toxicity and efficacy, 200 mg/m^2 seemed to be the optimal dose in the CR/PR groups in our study, which was consistent with previous studies.

Previous study has also shown that once-weekly cisplatin combined with radiation for the treatment of locally advanced NPC has comparable efficacy and safety compared to a triweekly regimen. Our study showed the same result with previous study that the efficacy of triweekly and once-weekly regimen was consistent. Therefore, in the clinic, at least five cycles of 40 mg/m^2 may be considered when delivering the weekly cisplatin regimen, whereas two cycles of 100 mg/m^2 may be adequate for the 3-weekly regimen. Future studies are needed to evaluate whether patients who achieved CR/PR after IC receive medium dose cisplatin chemotherapy gain the same long-term survival benefit as those who receive high-dose cisplatin chemotherapy.

However, in the SD/PD subgroup, our data showed that application of different CCD regimens did not result in significantly different survival outcomes. As for patients who experienced SD/PD after IC, these patients were often insensitive to chemotherapy and thus were the subgroup that experienced the most locoregional failures. Finding a more suitable treatment is necessary for these patients. A study conducted by Chen and colleagues showed that weekly cisplatin concurrent with IMRT improved the treatment parameters for locally advanced NPC with resistance to IC based on cisplatin [25]. Weekly administration of cisplatin is based on the hypothesis that cisplatin can act as a radiosensitizor when it is used at a smaller dose, and administered more frequently. On the other hand, a number of molecular mechanisms have been linked to chemoresistance and poor prognosis, and such molecular pathways may have potential as therapeutic targets to improve the prognosis of patients who are insensitive to chemotherapy [26–29]. In addition, more intensive treatment regimens such as a higher dose of RT, and the combined use of a second anti-tumor drug, such as paclitaxel, to enhance the radiosensitizing effect of CCRT could be used. The administration of an EGFR inhibitor during CCRT could also be an available treatment option for these patients. The application of ineffective IC has not only resulted in unnecessary side effects for the patients who achieve SD/PD after IC but also lengthens the waiting times for radical RT, which is associated with a poorer prognosis [30]. Therefore, the best way to solve the aforementioned problems is identifying the most suitable patients who will benefit from IC before treatment

Table 3
Multivariable analysis of prognostic factors for 761 NPC patients achieved CR/PR after induction chemotherapy.

	Hazard ratio* (95% CI)	*P* value
Progression-free survival		
Age (y) (≥45 vs. <45)	0.835(0.574–1.214	0.344
Gender (M vs. F)	1.903(1.158–3.128)	0.011
T category (3–4 vs. 1–2)	1.232(0.697–2.177)	0. 472
N category (2–3 vs. 0–1)	1.283(0.825–1.996)	0.269
Overall stage (IVa–b vs. II–III)	1.537(1.031–2.290)	0.035
EBV DNA before treatment (≥1500 vs. <1500)	1.405(0.945–2.090)	0.093
EBV DNA after IC(>0 vs. 0)	1.328(0.853–2.068)	0.210
IC regimen (triplet vs doublet)	0.513(0.348–0.809)	0.003
Cisplatin regimen (Triweekly vs. Weekly)	0.847(0.437–1.642)	0.623
Total radiation dose (70 vs. <70)	0.754(0.418–1.359)	0.347
Fractionation dose (≥2.19 vs. <2.19)	0.659(0.409–1.062)	0.087
CCD (101–200 vs. ≤100)	0.551(0.287–1.059)	0.074
CCD (>200 vs. ≤100)	0.410(0.195–0.861)	0.019
Overall survival		
Age (y) (≥45 vs. <45)	1.270(0.499–3.233)	0.616
Gender (M vs. F)	1.476(0.474–4.596)	0.502
T category (3–4 vs. 1–2)	1.082(0.382–3.574)	0.897
N category (2–3 vs. 0–1)	1.335(0.413–4.310)	0.629
Overall stage (IVa–b vs. II–III)	1.179 (0.456–3.049)	0.734
EBV DNA before treatment (≥1500 vs. <1500)	4.986(1.108–22.435)	0.036
EBV DNA after IC(>0 vs. 0)	2.913(0.645–13.155)	0.165
IC regimen (triplet vs doublet)	0.396(0.143–1.095)	0.074
Cisplatin regimen (Triweekly vs. Weekly)	0.190(0.022–1.626)	0.130
Total radiation dose (70 vs. <70)	0.380(0.106–1.363)	0.138
Fractionation dose (≥2.19 vs. <2.19)	0.318(0.094–1.067)	0.064
CCD (101–200 vs. ≤100)	0.477(0.098–2.326)	0.360
CCD (>200 vs. ≤100)	0.139(0.017–1.123)	0.064
Locoregional relapse-free survival		
Age (y) (≥45 vs. <45)	0.812(0.418–1.577)	0.539
Gender (M vs. F)	4.056(1.233–13.348)	0.021
T category (3–4 vs. 1–2)	1.226(0.457–3.289)	0.686
N category (2–3 vs. 0–1)	1.434 (0.636–3.233)	0.384
Overall stage (IVa–b vs. II–III)	1.387(0.695–2.765)	0.353
EBV DNA before treatment (≥1500 vs. <1500)	2.302(1.030–5.146)	0.042
EBV DNA after IC (>0 vs. 0)	1.373(0.612–3.081)	0.442
IC regimen (triplet vs doublet)	0.895(0.393–2.036)	0.791
Cisplatin regimen (Triweekly vs. Weekly)	0.793(0.220–2.855)	0.723
Total radiation dose (70 vs. <70)	1.308(0.462–3.698)	0.613
Fractionation dose (≥2.19 vs. <2.19)	0.947(0.423–2.124)	0.895
CCD (101–200 vs. ≤100)	2.107(0.278–15.978)	0.471
CCD (>200 vs. ≤100)	2.183(0.269–17.708)	0.465
Distant metastasis-free survival		
Age (y) (≥45 vs. <45)	0.781(0.500–1.220)	0.277
Gender (M vs. F)	1.410(0.822–2.418)	0.212
T category (3–4 vs. 1–2)	1.291(0.645–2.585)	0.471
N category (2–3 vs. 0–1)	1.281(0.758–2.163)	0.355
Overall stage (IVa–b vs. II–III)	1.649(1.022–2.660)	0.040
EBV DNA before treatment (≥1500 vs. <1500)	1.165(0.738–1.840)	0.512
EBV DNA after IC(>0 vs. 0)	1.367(0.805–2.319)	0.247
IC regimen (triplet vs doublet)	0.405(0.251–0.654)	<0.001
Cisplatin regimen (Triweekly vs. Weekly)	0.758(0.353–1.628)	0.478
Total radiation dose (70 vs. <70)	0.619(0.312–1.228)	0.170
Fractionation dose (≥2.19 vs. <2.19)	0.676(0.386–1.186)	0.172
CCD (101–200 vs. ≤100)	0.478(0.238–0.961)	0.038
CCD (>200 vs. ≤100)	0.329(0.143–0.753)	0.009

Abbreviations: CI = confidence interval; EBV = Epstein–Barr virus; IC = induction chemotherapy; CCD = cumulative cisplatin dose.
A Cox proportional hazards regression model was used to detect variables individually without adjustment. All variables were transformed into categorical variables. HRs were calculated for age (years) (≥45 vs. <45), sex (male vs. female), T stage (T3–4 vs. T1–2), N stage (N2–3 vs. N0–1), overall stage (IVa–b vs. II–III), plasma EBV DNA before the first treatment (≥1500 copies/ml vs. <1500 copies/ml), plasma EBV DNA after IC (>0 copies/ml vs. 0 copies/ml), IC regimen (triplet vs doublet), Cisplatin regimen (Triweekly vs. Weekly), Total radiation dose (70 Gy vs. <70 Gy), Fractionation dose (≥2.19 Gy vs. <2.19 Gy), CCD (101–200 vs. ≤100, >200 vs. ≤100).

[31–36], which will play an important role in the person-specific therapeutic strategy for NPC patients.

Nevertheless, several limitations of the present study should be stated. First, as a retrospective study, there was an inevitable selection bias caused. Second, the data were obtained exclusively from 1 center; therefore, these results must be validated by other datasets. Third, the follow-up duration was short. A longer follow-up period is necessary to both evaluate the long-term outcomes of these patients and validate our results.

Conclusions

A tumor response to IC was an independent prognostic factor for patients with NPC. For the patients who achieved CR/PR after IC, patients receiving high CCD showed significantly improved 3-year PFS and DMFS compared with patients receiving low CCD. Moreover, the medium dose group showed similar efficacy as high dose group but was associated with fewer grade 1–4 acute toxicities. Balancing toxicity and efficacy, 200 mg/m^2 seemed

Table 4
Grade 1–4 acute toxicities due to CCRT between the three different CCD groups.

Adverse event (toxicity grade)	CCD ≤100 (*n* = 84)				CCD (101–200) (*n* = 686)				CCD >200 (*n* = 220)				*p* value for events grade ≥1
	1(%)	2(%)	3(%)	4(%)	1(%)	2(%)	3(%)	4(%)	1(%)	2(%)	3(%)	4(%)	
Leucocytopenia	13 (15.5)	35 (41.7)	17 (20.2)	1 (1.2)	160 (23.3)	305 (44.5)	116 (16.9)	10 (1.5)	33 (15.0)	112 (50.9)	53 (24.1)	3 (1.4)	0.010
Neutropenia	19 (22.6)	20 (23.8)	8(9.5)	5 (6.0)	195 (28.4)	169 (24.6)	71(10.3)	15 (2.2)	63 (28.6)	74(33.6)	23 (10.5)	4 (1.8)	0.027
Anemia	31 (36.9)	26 (31.0)	4(4.8)	1 (1.2)	301 (43.9)	213 (31.0)	29(4.2)	8(1.2)	98 (44.5)	65(29.5)	17(7.7)	3 (1.4)	0.183
Thrombocytopenia	14 (16.7)	8(9.5)	4(4.8)	1 (1.2)	87(12.7)	57(8.3)	17(2.5)	10 (1.5)	41 (18.6)	16(7.3)	8(3.6)	1 (0.5)	0.165
AST increase	5(6.0)	4(4.8)	1(1.2)	0 (0.0)	49(7.1)	3(0.4)	0(0.0)	0(0.0)	20(9.1)	0(0.0)	0(0.0)	1 (0.5)	0.314
ALT increase	16 (19.0)	2(2.4)	4(4.8)	0 (0.0)	149 (21.7)	18(2.6)	3(0.4)	0(0.0)	75 (34.1)	2(0.9)	0(0.0)	1 (0.5)	0.008
BUN increase	14 (16.7)	2(2.4)	0(0.0)	0 (0.0)	193 (28.1)	28(4.1)	1(0.1)	3(0.4)	59 (26.8)	19(8.6)	0(0.0)	1 (0.5)	0.017
Creatinine increase	8(9.5)	2(2.4)	0(0.0)	0 (0.0)	89(13.0)	8(1.2)	1(0.1)	0(0.0)	36 (16.4)	5(2.3)	1(0.5)	1 (0.5)	0.113

Abbreviations: CCRT = concurrent chemoradiotherapy; CCD = cumulative cisplatin dose; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen.
[a]*P* values were calculated by Chi-square test.
[b]*P* value calculated with Fisher's exact test.

Table 5
Major late adverse events.

Adverse event (toxicity grade)	CCD ≤100 (n = 58)				CCD (101–200) (n = 502)				CCD >200 (n = 172)				p value for events grade ≥1
	1(%)	2(%)	3(%)	4(%)	1(%)	2(%)	3(%)	4(%)	1(%)	2(%)	3(%)	4(%)	
Hearing impairment/otitis	12 (20.7)	5(8.6)	1 (1.7)	0 (0.0)	115 (22.9)	50(10.0)	10 (2.0)	0 (0.0)	46 (26.7)	19 (11.0)	5 (2.9)	2 (1.2)	0.180[a]
Dry mouth	13 (22.4)	27 (46.6)	3 (5.2)	0 (0.0)	95(18.9)	251 (50.0)	15 (3.0)	0 (0.0)	46 (26.7)	72 (41.9)	3 (1.7)	0 (0.0)	0.836[a]
Skin fibrosis	16 (27.6)	7(12.1)	1 (1.7)	1 (1.7)	115 (22.9)	70(13.9)	10 (2.0)	5 (1.0)	43 (25.0)	27 (15.7)	8 (4.7)	3 (1.7)	0.243[a]
Trismus	7(12.1)	2(3.4)	2 (3.4)	0 (0.0)	75(14.9)	15(3.0)	15 (3.0)	0 (0.0)	26 (15.1)	5(2.9)	3 (1.7)	0 (0.0)	0.095[a]
Temporal lobe injury	7(12.1)	5(8.6)	0 (0.0)	0 (0.0)	65(12.9)	40(8.0)	5(1.0)	0 (0.0)	22 (12.8)	12(7.0)	2 (1.2)	0 (0.0)	0.945[a]
Endocrine dysfunction	2(3.4)	1(1.7)	0 (0.0)	0 (0.0)	9(1.8)	2(0.6)	0(0.0)	0 (0.0)	3(1.7)	1(0.6)	0 (0.0)	0 (0.0)	0.317[b]
Eye damage	0(0.0)	1(1.0)	0 (0.0)	0 (0.0)	5(1.0)	0(0.0)	0(0.0)	0 (0.0)	1(0.6)	0(0.0)	1 (0.6)	0 (0.0)	0.705[b]
Cranial neuropathy	4(6.9)	5(8.5)	1 (1.7)	0 (0.0)	60(12.0)	31(6.2)	12 (2.4)	1 (0.2)	18 (10.5)	13(7.5)	7 (4.1)	1 (0.6)	0.668[a]
V	1(1.7)	1(1.7)	0 (0.0)	0 (0.0)	15(3.0)	12(2.4)	3(0.6)	0 (0.0)	3(1.7)	5(2.9)	2 (1.2)	0 (0.0)	0.761[a]
VI	3(5.2)	2(3.4)	0 (0.0)	0 (0.0)	26(5.2)	13(2.6)	1(0.2)	0 (0.0)	7(4.1)	3(1.7)	3 (1.7)	1 (0.6)	1.000[a]
IX	0(0.0)	0(0.0)	1 (1.7)	0 (0.0)	3(0.6)	1(0.2)	0(0.0)	0 (0.0)	0(0.0)	2(1.2)	0 (0.0)	0 (0.0)	0.533[b]
XII	0(0.0)	2(3.4)	0 (0.0)	0 (0.0)	16(3.2)	5(1.0)	8(1.6)	1 (0.2)	8(4.7)	3(1.7)	2 (1.2)	0 (0.0)	0.497[a]
Second malignancy*	0(0.0)				3(0.6)				1(0.6)				1.000[b]

Abbreviations: CCD = cumulative cisplatin dose.
Second malignancy refers to radiation-induced malignancy: soft tissue sarcoma over the irradiated area (n = 4).
[a] P values were calculated by Chi-square test. [b]P value calculated with Fisher's exact test.

to be the optimal dose in the CR/PR groups. However, enhancement of CCD was not associated with survival benefit in patients who achieved SD/PD after IC, and treatment options for these patients require further consideration.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HQM, LG, and LQT carried out the study concepts; SLL, XSS, and XYL participated in study design; SLL, XSS, XYL, YJL, JJY, CL, YFW, SSG, LTL, HJX, QNT, and ZCY participated in data acquisition; SLL, XSS and XYL participated in quality control of data and algorithms; SLL and XSS participated in data analysis and interpretation; SLL, XSS and XYL participated in statistical analysis; SLL, QYC and HXL participated in manuscript preparation; SLL, QYC and HXL participated in manuscript editing; HQM, LG and LQT participated in Manuscript review. All authors have read and approved the manuscript.

Ethics approval and consent to participate

This retrospective study was approved by the Clinical Research Committee of Sun Yat-sen University Cancer Center. Patients were required to provide written informed consent before enrolling in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.04.020.

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