Evaluation of the Effect of Cumulative Cisplatin Dose in Locoregionally Advanced Nasopharyngeal Carcinoma Patients Receiving Intensity-Modulated Radiotherapy

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Abstract

Background: In nasopharyngeal carcinoma (NPC), the cut-off value of cumulative cisplatin dose (CCD) associated with survival benefits remains controversial. This study aimed to determine a CCD cut-off value for favorable survival outcomes and to identify specific patient groups benefitting from higher CCDs.

Methods: We retrospectively reviewed the records of 161 patients (male-to-female ratio of 2.6:1.0) with NPC receiving concurrent chemoradiotherapy ± adjuvant chemotherapy (AC) from February 2006 through September 2015 at our referral center. The CCD was calculated for each patient, and 3-year locoregional-free survival (LRFS), distant-metastasis free survival (DMFS), disease-specific survival (DSS), and overall survival (OS) were analyzed using a multivariable Cox regression model.

Results: Stage N3 patients and stage IV patients had lower DMFS, DSS, and OS. A CCD ≥ 200 mg/m 2 or AC was not associated with survival benefits. After adjusting for other factors, N3 status remained robustly correlated with DMFS ($p < 0.001$) and DSS ($p = 0.001$). In subgroup analyses, stage N3 patients treated with CCD ≥ 200 mg/m 2 exhibited evident trends toward higher OS ($p = 0.119$), DSS ($p = 0.119$), DMFS ($p = 0.201$), and LRFS ($p = 0.125$) than patients treated with CCD < 200 mg/m 2 .

Conclusions: A CCD ≥ 200 mg/m 2 might result in better survival outcomes in stage N3 patients. Larger CCDs may be exclusively used in cases of regionally advanced disease to avoid rigorous toxicity.

Background

Nasopharyngeal carcinoma (NPC) is an endemic cancer in China, Indonesia, Vietnam, India, and Malaysia.[1] In some areas in China, the annual incidence of NPC is 26.95 cases per 100,000 people; the annual mortality was 14.28 cases per 100,000 people in 2013.[2] Owing to the anatomical positioning of the disease and the radiosensitive and chemosensitive nature of NPC, radiotherapy (RT) with or without chemotherapy (CT) has become a mainstream treatment. It yields 5-year disease-specific survival (DSS) rates as high as 94% and 84% for patients with stage I–II and stage III–IV disease, respectively.[3] The advancement of CT has significantly enhanced survival advantage, locoregional control, and distant control.[4, 5] However, late toxicity and the rate of hearing impairments notably increased after the advent of CT.[3, 6, 7] Therefore, we have investigated whether specific groups of patients may benefit from higher cumulative cisplatin doses (CCDs) to achieve better survival outcomes and avoid adverse morbidity.

Higher CCDs have played a role in improving survival in patients with head and neck squamous cell carcinoma undergoing primary concurrent chemoradiotherapy (CCRT).[8] Beneficial survival outcomes have been obtained using CCD cut-offs above 200 mg/m^2 in concurrent CT.[9, 10] In NPC, despite the fact that superior survival rates have been reported for CCDs ≥ 200 mg/m^2,[5, 11–14] cut-off points remain controversial. Ou et al.[15] reported significantly higher distant metastasis-free survival (DMFS) and overall survival (OS) rates with CCD ≥ 300 mg/m^2 in concurrent CT, especially for patients with N2–3

lesions. On the other hand, Peng et al.[16] reported significantly higher disease-free survival with CCD ≥ 240 mg/m^2 in concurrent CT.

We aimed to determine a CCD cut-off value linked to favorable survival outcomes and, most importantly, determine the target group of patients benefitting from higher CCDs during CCRT.

Methods

Ethical considerations

This study was approved by the Institutional Review Board of Kaohsiung Veterans General Hospital, Taiwan (IRB: VGHKS17-CT5-17). The requirement for informed consent was waived because all identifying information was removed from the dataset prior to analysis.

Study design

We retrospectively reviewed the electronic medical records of patients with NPC undergoing primary CCRT and/or adjuvant chemotherapy (AC) at a tertiary medical center in Taiwan from February 2006 through September 2015. We excluded patients who had received prior RT or CT, who had aborted the RT, who did not have complete dosage records of CT, and who had received concurrent or adjuvant injectable regimens other than cisplatin. We enrolled 161 patients in the study.

Data collection

Either the clinical stage or pathological tumor stage was recorded according to the seventh edition of the staging system from the American Joint Committee on Cancer. The CCD was only calculated the patients receiving concurrent cisplatin dosage.

Radiotherapy, chemotherapy, and follow-up

At our institute, patients with stage I–II NPC were treated by RT alone or CCRT. Patients with stage III–IVB lesions were treated with CCRT with or without induction/adjuvant CT. The total cumulative dose of radiation applied to the gross nasopharyngeal tumor ranged from 66–78 Gray (Gy). The clinical negative nodal regions were prophylactically covered by 50–56 Gy; 60–66 Gy were used for positive nodal areas. The regimens for AC included cisplatin (80 mg/m^2, on Day 1) and fluorouracil (1,000 mg/m^2, 96-hour continuous infusion from Days 2–5) administered every 3–4 weeks for 2–3 cycles. The regimen for concurrent CT was 80–100 mg/m^2 of cisplatin on Days 1, 22, and 43 or 30–40 mg/m^2 of cisplatin every week for 6–8 cycles during the period of RT. Patients were instructed to receive regular follow-ups at our clinic every 3 months during the first 3 years following treatment. The follow-up frequency gradually decreased to every 6 months in the following 2 years and to once yearly after the sixth year.

Clinical end points

Clinical endpoints included 3-year OS, DSS, and any recurrence or distant metastasis. The OS was defined as the time elapsed between the diagnosis and the date of death from any cause; it was defined as three years if patient was still alive at the end of the study period. The DSS, locoregional-free survival (LRFS), and DMFS were otherwise calculated from the start of RT. Patients who were lost to follow-up within 3 years were censored at their last date of follow-up.

Statistical analysis

All of the statistical analyses were performed using SPSS ver. 22 (SPSS, Inc., Chicago, IL, USA). Pearson's chi-squared test or Fisher's exact test were used to explore the differences between categorical variables; the *t*-test was used for continuous variables. The OS, DSS, DMFS, and LRFS were generated according to the Kaplan and Meier methods. Differences between survival curves were compared using the log-rank test. The prognostic influence of factors during therapy was assessed using the Cox proportional hazards multivariate model after adjusting for other variables. Furthermore, subgroup analyses with log-rank test was used to evaluate the survival benefit for the stage N3 patients receiving CCD $\geq$ 200 mg/m^2.

Results

Ultimately, 161 patients with NPC (mean age: 49.4 ± 10.4 years; 116 males [72%], and 45 females [28%]) were included in the analysis. The demographic characteristics of the cohort are summarized in Table 1. Among these patients, 60.2% were in stages T3–4 (n = 97) and 83.2% were in stages N2–3 (n = 134). The mean CCD was 170.0 ± 67.8 mg/m^2. Eighty-six patients (53.4%) cases received a CCD less than 200 mg/m^2; 75 patients (46.6%) received a CCD of at least 200 mg/m^2. In the group receiving a CCD $\geq$ 200 mg/m^2, there was a predominance of males (p = 0.036) and a higher percentage of N3 (p = 0.032) and stage IV (p = 0.022) individuals. In total cohort, the 3-year LRFS, DMFS, DSS, and OS were 91.3%, 90.2%, 87.3%, and 83.6%, respectively. The significant factors associated with a lower 3-year DMFS according to the univariate analysis included a female gender (p = 0.036) and stage T1–2 disease (p = 0.035). Furthermore, stage N3 or stage IV disease was significantly associated with a reduced DMFS (p < 0.001 and p = 0.004, respectively), DSS (p < 0.001 and p = 0.002, respectively), and OS (p = 0.006 and p = 0.018, respectively) (Table 2).

Table 1

Patient characteristics

		Cumulative cisplatin dose in CCRT		
Variable	**All**	Cisplatin dose < 200 mg/m^2	Cisplatin dose ≧ 200 mg/m^2	*p*
Age		49.21 ± 10.98	49.64 ± 9.76	0.794
Sex (%)				0.036
male	116(72.0)	56(65.1)	60(80.0)	
female	45(28.0)	30(34.9)	15(20.0)	
Smoke (%)				0.107
No	109(67.7)	63(73.3)	46(61.3)	
Yes	52(32.3)	23(26.7)	29(38.7)	
CCIS (%)				0.992
0	131(81.4)	70(81.4)	61(81.3)	
≧1	30(18.6)	16(18.6)	14(18.7)	
Histology type				0.232
NUC	143(88.8)	74(86.0)	69(92.0)	
NDC	18(11.2)	12(14.0)	6(8.0)	
T stage (%)				0.527
T1	43(26.7)	24(27.9)	19(25.3)	
T2	21(13.0)	10(11.6)	11(14.7)	
T3	67(41.6)	39(45.3)	28(37.3)	
T4	30(18.6)	13(15.1)	17(22.7)	
N stage (%)				0.032*
N0	8(5.0)	5(5.8)	3(4.0)	
N1	19(11.8)	11(12.8)	8(10.7)	

CCIS, Charlson Comorbidity Index Score; NUC, nonkeratinizing undifferentiated carcinoma; NDC, nonkeratinizing differentiated carcinoma; CT, chemotherapy; CCRT, concurrent chemoradiotherapy

Values are numbers (percentage)

*Fisher's exact test

		Cumulative cisplatin dose in CCRT		
N2	113(70.2)	65(75.6)	48(64.0)	
N3	21(13.0)	5(5.8)	16(21.3)	
AJCC Stage (%)				0.022
Stage 3	113 (70.2)	67(77.9)	46(61.3)	
Stage 4	48(29.8)	19(22.1)	29(38.7)	
Adjuvant CT				0.009
No	107(66.5)	65(75.6)	42(56.0)	
Yes	54(33.5)	21(24.4)	33(44.0)	
RT duration		7.10 ± 0.77	7.07 ± 0.84	0.765
Hemoglobin		13.95 ± 1.83	14.09 ± 1.31	0.570
CCIS, Charlson Comorbidity Index Score; NUC, nonkeratinizing undifferentiated carcinoma; NDC, nonkeratinizing differentiated carcinoma; CT, chemotherapy; CCRT, concurrent chemoradiotherapy				
Values are numbers (percentage)				
*Fisher's exact test				

Table 2
Univariate analyses of risk factors for 3-year LRFS, DMFS, DSS, and OS rates

Variable	LRFS (%)	*p*	DMFS (%)	*p*	DSS (%)	*p*	OS (%)	*p*
Age (y)		0.482		0.428		0.098		0.151
< 50	92.8		92.2		92.2		87.7	
≥ 50	90.0		88.1		82.1		79.2	
Sex		0.754		0.036		0.213		0.917
Male	91.0		93.5		89.6		83.4	
Female	92.3		82.2		81.6		84.1	
Smoke		0.490		0.662		0.913		0.940
No	92.3		89.4		87.3		83.4	
Yes	89.3		91.7		87.4		83.9	
CCIS		0.185		0.229		0.358		0.389
0	92.9		88.8		86.2		82.2	
≧ 1	84.9		96.2		92.1		89.7	
T stage		0.652		0.035		0.249		0.659
T1/T2	92.8		83.9		83.8		81.9	
T3/T4	90.4		94.5		89.7		84.7	
N stage		0.498		< 0.001		< 0.001		0.006
N0/N1/N2	91.8		94.0		90.8		86.5	
N3	88.1		63.2		63.2		63.2	
AJCC Stage		0.065		0.004		0.002		0.018
Stage 3	93.9		94.4		92.3		88.1	
Stage 4	84.5		79.6		74.9		72.0	
Cumulative Cisplatin dose ($mg/m^{2)}$		0.795		0.639		0.590		0.557
< 200	91.7		89.1		88.8		85.6	
≧ 200	91.0		91.3		85.7		81.4	

Variable	LRFS (%)	*p*	DMFS (%)	*p*	DSS (%)	*p*	OS (%)	*p*
Adjuvant CT		0.476		0.560		0.461		0.506
No	90.2		89.2		85.9		82.5	
Yes	93.4		92.1		89.9		85.9	

Abbreviations: LRFS = locoregional-free survival; DMFS = distant metastasis-free survival; DSS = disease-specific survival; OS = overall survival. Other abbreviations as in Table 1.

After adjusting for other factors, the results remained robust for DMFS and DSS for stage N3 disease ($p < 0.001$, hazard ratio [HR] = 12.395, 95% confident interval [CI] = 3.862–39.777; HR = 4.78, 95% CI = 1.881–12.151). Female gender ($p = 0.045$, HR = 2.899, 95% CI = 1.026–8.193) and stage T1–2 disease (HR = 0.290, 95% CI = 0.095–0.885) were significantly have a lower DMFS (Table 3). Because of the significant impact of N3 status on survival, patients with a stage N3 disease ($n = 21$) were recruited for the subgroup analysis for CCD (Table 4). For a CCD ≥ 200 mg/m^2, we noted higher OS, DSS, DMFS, and LRFS ($p = 0.125$, $p = 0.201$, $p = 0.119$, and $p = 0.119$, respectively) (Fig. 1). Due to the small sample size, we could only find the survival benefit trends on the stage N3 patients treating with CCD ≥ 200 mg/m^2. Compared to stage N3 patients, stage N2 patients had similar OS, DSS, DMFS and LRFS among different CCD (supplementary table 1).

Table 3

Multivariate analysis for 3-year DMFS, DSS and OS for all patients

		DMFS		DSS		OS	
Variable	Comparison	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)
Sex	Female vs. Male	0.043	2.898 (1.034–8.121)				
T stage	T3/T4 T3/T4 vs. T1/T2	0.080	0.385 (0.132–1.122)				
N stage	N3 vs. N0/N1/N2	< 0.001	11.555 (3.693–36.156)	0.001	4.78 (1.881–12.151)	0.009	3.195 (1.333–7.659)
Concurrent Cisplatin Dose ($mg/m^{2)}$	≧ 200 vs. <200						
Adjuvant CT	Yes vs. No	0.079	0.308 (0.083–1.145)				
Abbreviations: HR = hazard ratio; CI = confidence interval. Other abbreviations as in Tables 1 and 2.							

Table 4

Subgroup analyses of cumulative cisplatin dose on N3 patients (n = 21) for 3-year LRFS, DMFS, DSS, and OS rates

Variable	**LRFS (%)**	***P***	**DMFS (%)**	***P***	**DSS (%)**	***P***	**OS (%)**	***P***
Concurrent Cisplatin dose		0.125		0.201		0.119		0.119
< 200 mg/m^2	40.0		40.0		40.0		40.0	
≧ 200 mg/m^2	71.4		71.4		71.4		71.4	
Abbreviations: LRFS = locoregional-free survival ; DMFS = distant metastasis-free survival; DSS = disease-specific survival; OS = overall survival. Other abbreviations as in Table 1.								

Discussion

Synopsis of key findings

We identified that a CCD ≥ 200 mg/m^2 might result in better survival outcomes in stage N3 patients. In the entire group of NPC patients, a CCD ≥ 200 mg/m^2 or AC did not confer survival benefits. A higher CCD may be exclusively applied for patients with N3 disease to avoid unfavorable toxicity.

Strengths of the study

The strength of our study was its pure cohort recruitment of only patients with NPC treated with intensity-modulated RT (IMRT). This study is the first investigation of IMRT to identify the specific staged of disease (N3) might benefit from a CCD ≥ 200 mg/m^2.

Comparisons with other studies

Previous studies of CCD cut-off values associated with better survival outcomes have reported inconsistent results.[5, 11–16] Some studies have noted superior survival with a CCD > 200 mg/m^2, but these investigations used heterogeneous modalities of RT, including two-dimensional RT (2D-RT), three-dimensional RT (3D-RT), and IMRT.[5, 11, 12, 14] Lee et al.[5] applied NPC-9901 and NPC-9902 trials and found that the locoregional failure-free rate plateaued (88%) after a CCD of 200 mg/m^2. Wei et al.[11] noted that patients with stage III disease rather than stage IV receiving a CCD > 200 mg/m^2 benefitted from longer 5-year progression-free survival and DMFS. Loong et al.[14] showed that a CCD > 200 mg/m^2 significantly improved OS in patients with stage II–III disease.

However, IMRT has been shown to yield better OS and LRFS than 2D-RT or 3D-CRT.[17, 18]. In our study that used IMRT, concurrent CT with a CCD ≥ 200 mg/m^2 failed to yield better LRFS, DMFS, DSS, or OS outcomes. These findings are consistent with those of another study that used IMRT.[13] Considering the impact on survival of RT modalities in the era of IMRT, the benefit the target group derived from a higher CCD should be investigated further. However, there may be no obvious cut-off CCD value that predicts favorable survival outcomes for treating an entire cohort group of patients with NPC.

In the subgroup analyses, a CCD ≥ 200 mg/m^2 resulted in better OS, DSS, DMFS, and LRFS outcomes in patients with stage N3 NPC. Consistent with previous studies that used IMRT, Ou et al.[15] found that a CCD ≥ 300 mg/m^2 resulted in superior DMFS and OS in NPC patients with advanced nodal status (N2–3). Nonetheless, highly diverse treatment arms—including IMRT with or without induction, concurrent CT, or AC—were all included in that study; only 6.5% patients received CCRT with or without AC. On the other hand, our study specifically focused on patients receiving CCRT with or without AC. Although our finding was not statistically significant due to our small sample size (n = 21), our results motivate future investigations enrolling larger cohorts to confirm the survival effect of a larger CCD on patients with regionally advanced NPC.

Weaknesses of the study

There were some limitations to this study. First and foremost, this retrospective study was conducted at a single institution and included a relatively small number of patients. This made further subgroup analysis by separating patients into intervention and reference cohorts difficult. Furthermore, records of acute side

effects and late toxicities were incomplete, which prevented us from more thoroughly investigating the association between CCD and adverse effects. We did not routinely measure plasma Ebstein-barr virus DNA level, either. Ebstein-barr virus is known to contribute to the development of nasopharyngeal carcinoma. Last but not least, our study enrolled patients treated with CCRT with or without AC. Therefore, the survival effect of AC may be concerned. Nevertheless, the majority of studies that have reported the efficacy of CCRT with AC compared with CCRT alone failed to demonstrate superior survival outcomes. [19–22]

Conclusions

N3 status was a clear and independent factor associated with lower DSS and DMFS. A CCD ≥ 200 mg/m^2 might result in better survival outcomes in stage N3 patients on the basis of OS, DSS, DMFS, and LMFS. In a cohort of patients with NPC receiving CCRT utilizing IMRT with or without AC, there was no statistically significant association between a higher CCD during concurrent CT and survival outcomes. A higher CCD may be exclusively applied in cases of regionally advanced disease to avoid rigorous toxicity.

Abbreviations

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NPC, nasopharyngeal carcinoma

RT, radiotherapy

CT, chemotherapy

CCD, cumulative cisplatin dose

CCRT, concurrent chemoradiotherapy

DMFS, distant-metastasis free survival

OS, overall survival

AC, adjuvant chemotherapy

LRFS, locoregional-free survival

DSS, disease-specific survival

Gy, Gray

IMRT, intensity-modulated radiotherapy

2D-RT, two-dimensional radiotherapy

3D-RT, three-dimensional radiotherapy

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Kaohsiung Veterans General Hospital, Taiwan (IRB: VGHKS17-CT5-17). The requirement for informed consent was waived because all identifying information was removed from the dataset prior to analysis.

Consent for publication

Not applicable.

Availability of data and material

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' contributions

Dr. LSC and CTS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read and approved the manuscript

Concept and design: LSC, CTS

Acquisition, analysis, or interpretation of data: LSC, LYH, LYS, KBH, CKP, CTS

Drafting the manuscript: LSC, CTS

Critical revision of the manuscript for important intellectual content: LSC, LYH, LYS, KBH, CKP, CTS

Final approval: LSC, LYH, LYS, KBH, CKP, CTS

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Figures

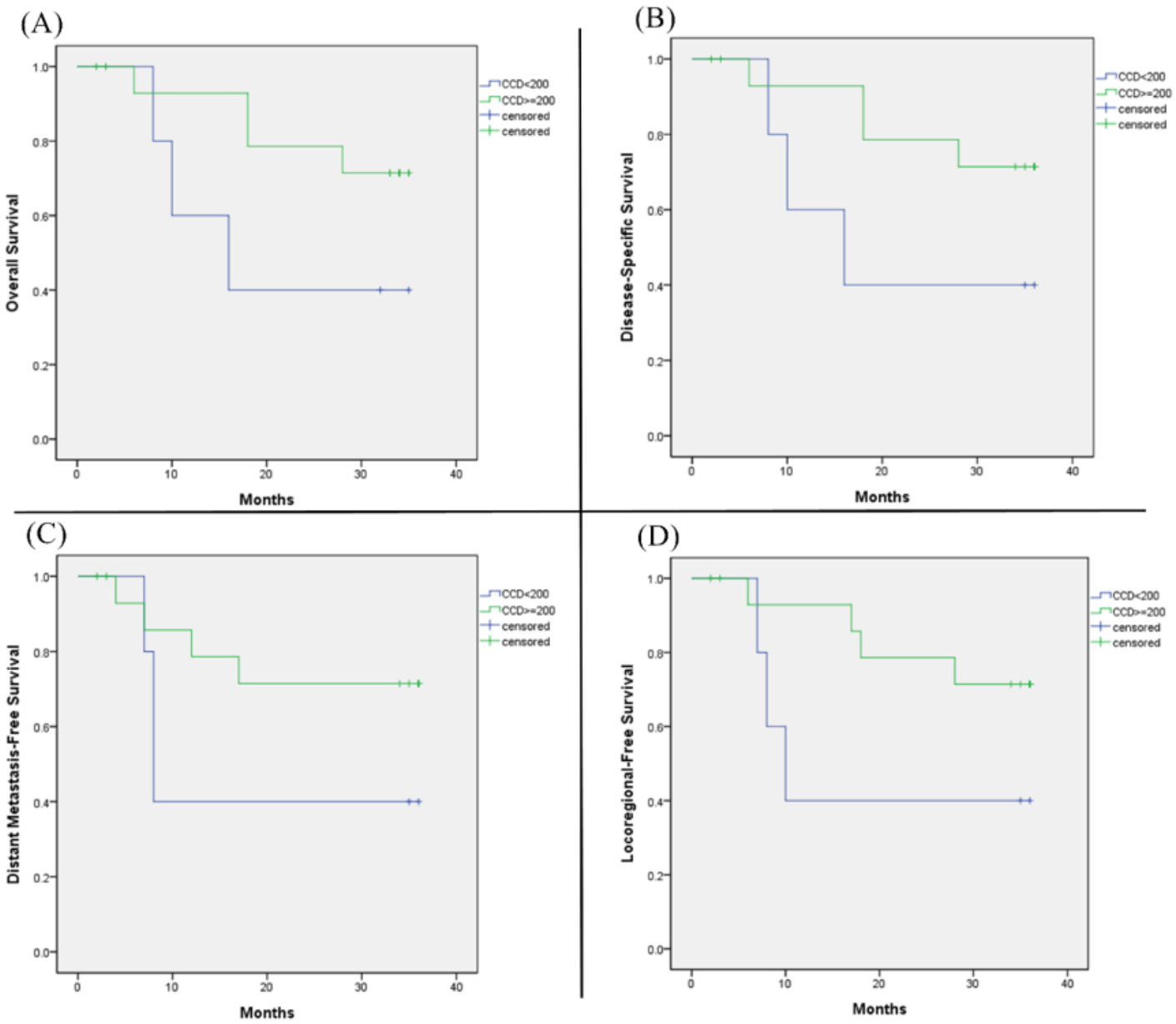

Figure 1

OS, DSS, DMFS and LRFS for N3 stage patients with high CCD (≥ 200 mg/m2) and low CCD (< 200 mg/m2). Patients receiving high CCD have trends toward better (A) 3-year OS (p = 0.125), (B) 3-year DSS (p = 0.201), (C) 3-year DMFS (p = 0.119), and (D) 3-year LRFS (p = 0.119)

Supplementary Files

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- Supplementarytable120200402.docx