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Title page

The Optimal Cumulative Cisplatin Dose in Nasopharyngeal Carcinoma Patients Receiving Additional Induction Chemotherapy

Running Title: Optimal CCD in NPC receiving IC plus CCRT

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Summary

To clarify the optimal cumulative cisplatin dose (CCD) in locoregionally-advanced nasopharyngel carcinoma (NPC) patients receiving induction chemotherapy (IC) plus concurrent chemoradiotherapy (CCRT). Using the NPC-specific database from the established big-data intelligence platform at Sun Yat-Sen University Cancer Center, 583 non-disseminated, locoregionally-advanced NPC patients receiving IC plus CCRT were enrolled. Propensity score matching (PSM) analysis was conducted to control for

confounding factors.The median CCD was 160 mg/m^2 after IC (range, 40–300mg/m^2); only 74 patients (12.7%) achieved CCD>200 mg/m^2. Patients receiving>200 mg/m^2 CCD did not show significantly improved 5-year overall survival (OS) (HR=1.19; 95% confidence intervals [CI] 0.69–2.06,*P*=0.53) and progression-free survival (PFS) (HR=1.03; 95% CI 0.63–1.68,*P*=0.92) compared with patients receiving<200 mg/m^2 CCD. Further investigations of the potential of median CCD (160 mg/m^2) to yield survival benefits revealed that there were no significant differences in survival endpoints between patients receiving CCD>160 mg/m^2 and CCD<160 mg/m^2 in both the original and PSM cohorts. Additionally, subgroup analysis indicated a favourable PFS, but not OS, with higher cisplatin administration in patients with pretreatment Epstein–Barr virus deoxyribonucleic acid (EBV DNA)<1000 copies/ml (HR=0.26, 95% CI 0.07–0.93,*P*=0.03) and receiving<3 IC cycles (HR=0.59, 95% CI 0.33–1.07,*P*=0.08). Our analysis of real world data provided references for the optimal CCD in locoregionally-advanced NPC receiving additional IC. The causal relationship between 200 mg/m^2 CCD and improved survival was not defined; 160 mg/m^2 CCD might be enough. However, for patients with EBV DNA<1000 copy/ml, and receiving<3 IC cycles, higher dose might be necessary**.**

Keywords: Nasopharyngeal carcinoma; Cumulative cisplatin dose; Induction chemotherapy; Intensity-modulated radiation therapy; Real world data

Introduction

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

Radiotherapy (RT) is the primary treatment modality for non-disseminated NPC due to its radiosensitivity and anatomical location. NPC is also known to be

chemosensitive. The integration of cisplatin-based chemotherapy during RT greatly enhances the effects of RT, facilitates local control, and improves therapeutic outcomes[3, 4]. Recently, adding induction chemotherapy (IC) before concurrent chemoradiotherapy (CCRT) has been found to greatly improve survival outcomes, and has been increasingly adopted worldwide based on the clinical data from several important large-scale multi-centre phase II–III randomised controlled trials (RCTs), which strongly support the application of IC plus CCRT for locoregionally-advanced NPC[5-9].

The cumulative cisplatin dose (CCD) administered during RT is an important factor in conferring survival benefits. In the majority of RCTs, 100 mg/m^2 cisplatin was administered every 3 weeks during RT. The importance of a third planned cisplatin cycle was first questioned by Ang et al.[10], who reviewed the compliance levels of CCRT in RCTs, and found that a substantial fraction of patients failed to receive the third cycle, and a cumulative dose of 200 mg/m^2 was sufficient to yield beneficial antitumor effects. Peng et al. also demonstrated that CCD >240 mg/m^2 was not prognostic in patients with locoregionally-advanced NPC, and that 200 mg/m^2 cisplatin may be adequate[11]. Furthermore, Loong and colleagues found that 200 mg/m^2 CCD had prognostic value in patients with stage II and III NPC, but not in patients with the highest risk[12].

Accordingly, 200 mg/m^2 has been widely used as the optimal cutoff value in clinical practice, regardless of the specific treatment strategies. However, patients enrolled in the studies on which this value is based all received CCRT and a subpopulation did not receive intensity-modulated radiotherapy (IMRT). Moreover, several factors require consideration regarding patients receiving IC plus CCRT in the era of IMRT. First, IC greatly reduced tumor volume burden. Clinical complete response (cCR) and partial response (cPR) were observed with 11.3%, 79.6% patients, respectively[13]. Second, patients may be less able to tolerate the subsequent highly intensive CCRT after 2 to 4 cycles of IC. Data from published RCTs showed that 36%

patients could not adhere to the second planned cisplatin, and that 76.7% patients could not achieve the third[5]. Third, IMRT is superior in the management of local control compared to conventional RT[14, 15]. Given these facts and the current lack of data, the suitability of 200 mg/m^2 CCD as the optimal cutoff value for locoregionally-advanced NPC patients receiving IC plus CCRT in the era of IMRT remains to be elucidated.

Real world data (RWD) are increasingly used to guide clinical practice and assist in the the assessment of the "value" of the intervention, as they are characterised by variety, veracity and are unfiltered compared with RCT data, which can be confounded by the selection of the patient population, rigorous administration, and physician preferences[16, 17]. Therefore, RWD represent an important resource in research, and are promising in answering this question. Using the NPC population in the real world practice from an endemic area, we aimed to clarify the optimal CCD in locoregionally-advanced NPC patients receiving IC plus CCRT.

Materials and Methods

Patient population and data extraction

The NPC-specific database from the well-established big-data intelligence platform at Sun Yat-Sen University Cancer Centre (SYSUCC) was adopted to identify 2940 patients with histologically-proven, non-disseminated NPC, diagnosed between January 2005 to December 2012. A detailed description of this database is presented in the Supplementary materials (Doc. S1). Using the search terms 'diagnosis', 'histology type', 'stage classification', 'radiotherapy', 'chemotherapy', we identified patients fulfilling the following inclusion criteria: a) patient diagnosed as histologically-proven non-keratinising NPC; b) disease classified as stages III–IVb; c) patient received IC plus CCRT; d) received 2 to 4 cycles of IC; e) received cisplatin-based concurrent chemotherapy (weekly or 3-weekly); f) radiation delivery technique was IMRT. Finally, 583 eligible patients were enrolled in our analysis. Detailed selection process and study design were presented in Figure 1. This study was approved by the Clinical

Research Ethics Committee of SYSUCC. The authenticitu of this article has been validated by uploading the key raw data onto the Research Data Deposit (RDD) public platform (http://www.researchdata.org.cn), with the approval RDD number as RDDA2017000364.

Chemotherapy

The concurrent chemotherapy consisted of 40 mg/m^2 cisplatin administered every week for a maximum of seven cycles, 80 mg/m^2 cisplatin administered every 3 weeks for a maximum of three cycles, or 100 mg/m^2 cisplatin administered every 3 weeks for a maximum of three cycles, beginning on the first day of RT or 3 weeks after the last cycle of IC.

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

Radiotherapy

All patients were treated with radical IMRT comprising five daily fractions delivered per week for 6–7 weeks. The prescribed doses were 66–72 Gy at 2.12–2.43 Gy/fraction to the planning target volume (PTV) of the primary gross tumour volume (GTVnx), 64–70 Gy/28–33 fractions to the PTV of the GTV of the involved lymph nodes (GTVnd), 60–63 Gy/28–33 fractions to the PTV of the high-risk clinical target volume (CTV1), and 54–56 Gy/28–33 fractions to the PTV of the low-risk clinical target volume (CTV2).

Clinical staging, follow-up, and study endpoint

All patients were restaged according to the 8th edition of the UICC/AJCC staging system[18]. Patients were followed-up from the initiation of the treatment to the day of

last examination or death. Details of the pretreatment examinations and follow-up strategies are shown in the Supplementary materials (Doc. S1).

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

Study design and statistical analysis

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

Propensity scores were calculated based on logistic regression regarding the following eight variables: age, sex, year of diagnosis, T stage, N stage, pretreatment EBV DNA, IC cycles and IC regimens. Patients were matched without replacement at a 1:1 ratio using estimated propensity scores. The patient and tumour characteristics between groups were compared using the χ^2 test (Fisher's exact test or Pearson's χ^2 test where appropriate) for categorical variables and the Kruskal–Wallis test for continuous variables. Kaplan–Meier survival analysis was used to estimate the actuarial survival rates, and log-rank tests were used for comparisons. The unadjusted Cox proportional hazards model was used to calculate the hazard ratio (HR) in subgroup analysis. The adjusted HR was calculated using the Cox regression mode, for the eight factors (age, sex, year of diagnosis, T stage, N stage, pretreatment EBV DNA, IC cycles and IC regimens). The proportional hazards assumption was graphically verified on the basis of Schoenfeld residuals[20]. All analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) and STATA version 12.0 (Stata Corporation, USA). Two-sided $P < 0.05$ was considered to indicate statistical significance.

Results

Patient characteristics and treatment compliance

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

The median CCD for the whole cohort was 160 mg/m^2 (range, 40–300 mg/m^2). In total, 325 patients (55.7%) received CCD >160 mg/m^2, and 258 (44.3%) received CCD <160 mg/m^2, while 509 patients (87.3%) received CCD <200 mg/m^2 and only 74

patients (12.7%) received CCD >200 mg/m^2.

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

Identification of the optimal CCD during RT in locoregionally-advanced NPC patients receiving IC plus CCRT

Previously publsihed data suggested that 200 mg/m^2 CCD was necessary to confer survival benefit among patients receiving CCRT alone. Therefore, we first investigated the potential of 200 mg/m^2 CCD in achieving survival benefit in locoregionally-advanced NPC patients treated with IC plus CCRT. Kaplan–Meier survival analysis indicated that there was no significant improvement in the prognosis of patients receiving CCD >200 mg/m^2 in terms of 5-year OS (HR=1.19; 95% confidence intervals [CI], 0.69–2.06, *P*=0.53), PFS (HR=1.03; 95% CI, 0.63–1.68, *P*=0.92), DMFS (HR=1.22; 95% CI, 0.70–2.10, *P*=0.49), and LRFS (HR=0.84; 95% CI, 0.36–1.96, *P*=0.68; Fig. 2).

Having identified the median cisplatin dose after IC as 160 mg/m^2 in the whole cohort, we then hypothesised that 160 mg/m^2 CCD might be sufficient to yield beneficial effects. Kaplan–Meier survival analysis demonstrated that there were no statistically significant differences between patients receiving CCD >160 mg/m^2 and patients receiving CCD <160 mg/m^2 in terms of 5-year OS (HR=1.02; 95% CI, 0.69–1.50, *P*=0.94), PFS (HR=0.97; 95% CI, 0.70–1.35, *P*=0.85), DMFS (HR=1.04; 95% CI, 0.70–1.54, *P*=0.85), and LRFS (HR=1.00; 95% CI, 0.59–1.69, *P*=0.99; Fig. 3).

Clinical implications of 160 mg/m^2 CCD in the propensity score matched cohort

We then verified the role of 160 mg/m^2 CCD in the propensity score matched cohort to minimise bias in the initial treatment selection. After PSM, all covariates were well-balanced between the groups (Table 2). In univariate analysis, no significant survival differences were observed between groups in terms of 5-year OS (HR=0.81; 95% CI, 0.48–1.35, *P*=0.41), PFS (HR=0.89; 95% CI, 0.57–1.38, *P*=0.59), DMFS (HR=0.91; 95% CI, 0.56–1.49, *P*=0.71), and LRFS (HR=0.73; 95% CI, 0.36–1.48, *P*=0.38; Fig. 4)

Multivariate analysis was performed to adjust for potential prognostic confounders, including IC cycles, IC regimens, age, sex, year of diagnosis, T category, N category, and pretreatment EBV DNA. In accordance with the previous results, 160 mg/m^2 CCD was not identified as an independent prognostic factor for locoregionally-advanced NPC patients receiving IC plus CCRT in terms of 5-year OS (HR=0.75; 95% CI, 0.44–1.27, *P*=0.28), PFS (HR=0.86; 95% CI, 0.55–1.33, *P*=0.49), DMFS (HR=0.90; 95% CI, 0.54–1.47, *P*=0.66), and LRFS (HR=0.69; 95% CI, 0.34–1.42, *P*=0.31). Table 3 shows all other variables associated with survival endpoints.

Subgroup analysis

Subgroup analyses were further conducted for OS and PFS, to identify the subgroups that might benefit from the administration of higher cisplatin dose after IC. We found that there were no interactions between clinicopathologic variables and 160 mg/m^2 CCD with respect to OS (Fig. 5A). However, interactions of 160 mg/m^2 CCD with pretreatment EBV DNA and IC cycles were obersevd regarding PFS ($P_{interaction}$=0.04; Fig. 5B). In the subgroup of patients with pretreatment EBV DNA <1 000 copies/ml, administration of CCD >160 mg/m^2 tended to yield favourable prognosis (HR=0.26; 95% CI, 0.07–0.93, *P*=0.03), while the survival benefit was not observed in patients with pretreatmentEBV DNA >1 000 copies/ml (HR=1.12; 95% CI, 0.69–1.82, *P*=0.64). Additionally, potentially greater benefit was conferred on the

subgroup of patients who received two cycles of IC by the higher dose of cisplatin administration (CCD >160 mg/m^2) after IC (HR=0.59; 95% CI, 0.33–1.07, *P*=0.08); however, this benefit was not observed in patients receiving more than two cycles of IC (HR=1.50; 95% CI, 0.76–2.96, *P*=0.24).

Discussion

It is generally recognised that 200 mg/m^2 CCD administered during RT is the optimal cutoff dose to yield survival benefit in NPC patients receiving CCRT[11, 12, 21]. However, with the success of several important large-scale multi-centre phase II–III RCTs, an increasing number of patients receive IC plus CCRT; and a substantial proportion of patients is unable to tolerate 200 mg/m^2 CCD following IC, due to the increased therapeutic intensity. This has led to a debate over the suitability of 200 mg/m^2 as the optimal cutoff CCD in these circumstances. To the best of our knowledge, this was the first real world investigation of the optimal cutoff CCD for locoregionally-advanced NPC patients receiving IC plus CCRT in the era of IMRT.

Our data indicate that there was no significant survival improvement in patients receiving >200 mg/m^2 CCD compared with those receiving <200 mg/m^2 CCD. In the whole cohort, the median CCD was 160 mg/m^2 after IC. Further investigations of the potential of a CCD of 160 mg/m^2 to yield survival benefits revealed that there were no significant differences between patients receiving CCD >160 mg/m^2 and those receiving CCD <160 mg/m^2 regarding all survival endpoints both in the original and PSM cohorts. Additionally, subgroup analysis demonstrated potentially favourable PFS, but not OS, in patients that with pretreatment EBV DNA <1000 copies/ml, and <3 cycles of IC with higher cisplatin administration.

In the present study, 200 mg/m^2 CCD did not yield significant improvements in survival outcomes in patients with locoregionally-advanced NPC receiving IC plus CCRT, while 160 mg/m^2 CCD might be enough to yield beneficial antitumor effects. This is in accordance with previously published reports[11, 12, 21]. In the combined

analyses of two prospective trials NPC-9901 and NPC-9902[21], a total dose of cisplatin during the concurrent phase (>200 mg/m^2) had a significant impact on LRFS and OS in the stage III subgroup, but not in the stage IV subgroup. Loong and colleagues[12] also found that CCD >200 mg/m^2 had prognostic value in patients with stage II and III NPC, but not in patients with stage IV disease. It can be speculated that this divergence in the results is because the patients enrolled in the previous studies received CCRT, and a substantial number of the patients did not receive IMRT. In contrast, all the patients included in the present study received IC plus CCRT, and the radiotherapy modality was consistently IMRT. The rationale for the decreased CCD was based on the reduced tumour volume after IC[7, 13], impaired medication adherence after intensive IC[5], increased survival outcomes by adding IC before CCRT[6, 7], and significant advances in RT delivery techniques (such as IMRT)[22, 23]. The cCR plus pCR rates have been reported to reach 90% after IC[13]; therefore, the subsequent administration of less intensive chemotherapy during RT is feasible.

Although the positive relationship between higher CCD and improved survival outcomes was not observed in the whole cohort, further subgroup analyses indicated that patients with pretreatment EBV DNA of <1000 copies/ml, and receiving <3 cycles of IC benefit from a higher dose of cisplatin after IC. The relationship between pretreatment EBV DNA and CCD is an area of particular interest. It has been well documented that pretreatment EBV DNA is a robust factor in the diagnosis, risk stratification, and relapse prediction of NPC[24-26]. Patients with higher pretreatment EBV DNA loads positively correlated with higher tumour burden, and associated with impaired prognosis. In this study, subgroup with lower pretreatment EBV DNA was shown to benefit from higher cisplatin administration. It can be speculated that this effect is associated with the inherently poor prognosis of locoregionally-advanced NPC patients with high tumor burden (EBV DNA>1000 copoes/ml), irrespective of the concurrent cisplatin dose. This finding is in accordance with the reports of Lee et al.[21] and Loong et al.[12] that CCD had prognostic value in patients with lower risk (stage III),

but not in patients with the highest risk (stage IV).

In addition to the influence of pretreatment EBV DNA, IC cycles also modified the prognostic effect of CCD. Previous studies showed that there was no difference in survival between patients receiving two cycles of IC and patients receiving >2 cycles of IC, when the CCRT regimens and cycles were well-balanced between groups[27]. Our finding shed light on the previous findings that for patients received less than 3 cycles of IC, higher CCD (> 160 mg/m^2) during CCRT might be necessary to yield the equal antitumor effects.

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

The aim of concurrent chemotherapy is to yield beneficial antitumor effects with acceptable toxicities. With a broad standard application of IC and the increased therapeutic intensity, a substantial proportion of patients are unable to tolerate 200 mg/m^2 CCD. Thus, it is crucial to define the optimal cutoff dose that can confer survival advantage, with the minimal and acceptable toxicities under these circumstances. Although the current study provides the basis of a hypothesis, further confirmatory prospective studies are required to guide changes in clinical practice. Nevertheless, our results provide a reference for the determination of optimal CCD in clinical practice, and reduce the requirement for rigorous application of the total dose of 200 mg/m^2 cisplatin in CCRT, when patient performance status is significantly decreased after IC. Furthermore, based on our findings, we recommend that 160 mg/m^2 CCD should be considered as a reference cisplatin dose in future clinical trials of IC plus CCRT in locoregionally-advanced NPC.

The strengths of this study are that we enrolled a real world population, which

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

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

In conclusion, the causal relationship between 200 mg/m^2 CCD and improvement in survival outcomes was not defined in locoregionally-advanced NPC patients receiving IC plus CCRT, and our results indicated that 160 mg/m^2 CCD might be sufficient to yield beneficial antitumor effects in the circumstance of IC. However, higher doses of cisplatin delivered during RT are required to achieve beneficial effects

in patients with pretreatment EBV DNA <1000 copies/ml, and receiving <3 cycles of IC.

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Disclosure Statement

We declare that we have no conflict of interest.

REFERENCES

[1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: a cancer journal for clinicians. 2015; 65: 87-108.

[2] Cao SM, Simons MJ, Qian CN. The prevalence and prevention of nasopharyngeal carcinoma in China. Chinese journal of cancer. 2011; 30: 114-9.

[3] Lee AW, Lau WH, Tung SY, et al. Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: NPC-9901 Trial by the Hong Kong Nasopharyngeal Cancer Study Group. Journal of clinical oncology : official journal of the American

Society of Clinical Oncology. 2005; 23: 6966-75.

[4] Lee AW, Tung SY, Chua DT, et al. Randomized trial of radiotherapy plus concurrent-adjuvant chemotherapy vs radiotherapy alone for regionally advanced nasopharyngeal carcinoma. Journal of the National Cancer Institute. 2010; 102: 1188-98.

[5] Cao SM, Yang Q, Guo L, et al. Neoadjuvant chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: A phase III multicentre randomised controlled trial. European journal of cancer. 2017; 75: 14-23.

[6] Hui EP, Ma BB, Leung SF, et al. Randomized phase II trial of concurrent cisplatin-radiotherapy with or without neoadjuvant docetaxel and cisplatin in advanced nasopharyngeal carcinoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009; 27: 242-9.

[7] Sun Y, Li WF, Chen NY, et al. Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial. The Lancet Oncology. 2016; 17: 1509-20.

[8] Tan T, Lim WT, Fong KW, et al. Concurrent chemo-radiation with or without induction gemcitabine, Carboplatin, and Paclitaxel: a randomized, phase 2/3 trial in locally advanced nasopharyngeal carcinoma. International journal of radiation oncology, biology, physics. 2015; 91: 952-60.

[9] Lee AW, Ngan RK, Tung SY, et al. Preliminary results of trial NPC-0501 evaluating the therapeutic gain by changing from concurrent-adjuvant to induction-concurrent chemoradiotherapy, changing from fluorouracil to capecitabine, and changing from conventional to accelerated radiotherapy fractionation in patients with locoregionally advanced nasopharyngeal carcinoma. Cancer. 2015; 121: 1328-38.

[10] Ang KK. Concurrent radiation chemotherapy for locally advanced head

and neck carcinoma: are we addressing burning subjects? Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2004; 22: 4657-9.

[11] Peng H, Chen L, Zhang Y, et al. Prognostic Value of the Cumulative Cisplatin Dose During Concurrent Chemoradiotherapy in Locoregionally Advanced Nasopharyngeal Carcinoma: A Secondary Analysis of a Prospective Phase III Clinical Trial. The oncologist. 2016.

[12] Loong HH, Ma BB, Leung SF, et al. Prognostic significance of the total dose of cisplatin administered during concurrent chemoradiotherapy in patients with locoregionally advanced nasopharyngeal carcinoma. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2012; 104: 300-4.

[13] Peng H, Chen L, Li WF, et al. Tumor response to neoadjuvant chemotherapy predicts long-term survival outcomes in patients with locoregionally advanced nasopharyngeal carcinoma: A secondary analysis of a randomized phase 3 clinical trial. Cancer. 2017; 123: 1643-52.

[14] Zhang B, Mo Z, Du W, Wang Y, Liu L, Wei Y. Intensity-modulated radiation therapy versus 2D-RT or 3D-CRT for the treatment of nasopharyngeal carcinoma: A systematic review and meta-analysis. Oral oncology. 2015; 51: 1041-6.

[15] Lai SZ, Li WF, Chen L, et al. How does intensity-modulated radiotherapy versus conventional two-dimensional radiotherapy influence the treatment results in nasopharyngeal carcinoma patients? International journal of radiation oncology, biology, physics. 2011; 80: 661-8.

[16] Tran B, Keating CL, Ananda SS, et al. Preliminary analysis of the cost-effectiveness of the National Bowel Cancer Screening Program: demonstrating the potential value of comprehensive real world data. Internal medicine journal. 2012; 42: 794-800.

[17] Berger ML, Lipset C, Gutteridge A, Axelsen K, Subedi P, Madigan D.

Optimizing the leveraging of real-world data to improve the development and use of medicines. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2015; 18: 127-30.

[18] Amin MB AJCoC. AJCC cancer staging manual (ed 8th). New York: Springer. 2016.

[19] Austin PC. Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score. American journal of epidemiology. 2010; 172: 1092-7.

[20] O'Quigley J, Moreau T. Testing the proportional hazards regression model against some general alternatives. Revue d'epidemiologie et de sante publique. 1984; 32: 199-205.

[21] Lee AW, Tung SY, Ngan RK, et al. Factors contributing to the efficacy of concurrent-adjuvant chemotherapy for locoregionally advanced nasopharyngeal carcinoma: combined analyses of NPC-9901 and NPC-9902 Trials. European journal of cancer. 2011; 47: 656-66.

[22] Li JX, Huang SM, Jiang XH, et al. Local failure patterns for patients with nasopharyngeal carcinoma after intensity-modulated radiotherapy. Radiation oncology. 2014; 9: 87.

[23] Wolden SL, Chen WC, Pfister DG, Kraus DH, Berry SL, Zelefsky MJ. Intensity-modulated radiation therapy (IMRT) for nasopharynx cancer: update of the Memorial Sloan-Kettering experience. International journal of radiation oncology, biology, physics. 2006; 64: 57-62.

[24] Lin JC, Wang WY, Chen KY, et al. Quantification of plasma Epstein-Barr virus DNA in patients with advanced nasopharyngeal carcinoma. The New England journal of medicine. 2004; 350: 2461-70.

[25] Chan KC. Plasma Epstein-Barr virus DNA as a biomarker for nasopharyngeal carcinoma. Chinese journal of cancer. 2014; 33: 598-603.

[26] Adham M, Greijer AE, Verkuijlen SA, et al. Epstein-Barr virus DNA load in nasopharyngeal brushings and whole blood in nasopharyngeal carcinoma patients before and after treatment. Clinical cancer research : an official journal of the American Association for Cancer Research. 2013; 19: 2175-86.

[27] Peng H, Chen L, Li WF, et al. Optimize the cycle of neoadjuvant chemotherapy for locoregionally advanced nasopharyngeal carcinoma treated with intensity-modulated radiotherapy: A propensity score matching analysis. Oral oncology. 2016; 62: 78-84.

Figure legends

Figure 1. Flowchart showing the study design and patients selection process.

Figure 2. Kaplan–Meier survival analyses of (A) overall survival, (B) progression-free survival, (C) distant metastasis-free survival, and (D) locoregional relapse-free survival, in locoregionally-advanced NPC patients receiving IC plus CCRT, stratified by CCD >200 mg/m^2 and CCD <200 mg/m^2.

CCD, cumulative cisplatin dose; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; NPC, nasopharyngeal carcinoma.

Figure 3. Kaplan–Meier survival analyses of (A) overall survival, (B) progression-free survival, (C) distant metastasis-free survival, and (D) locoregional relapse-free survival, in locoregionally-advanced NPC patients receiving IC plus CCRT, stratified by CCD >160 mg/m^2 and CCD <160 mg/m^2.

CCD, cumulative cisplatin dose; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; NPC, nasopharyngeal carcinoma.

Figure 4. Kaplan–Meier survival analyses of (A) overall survival, (B) progression-free

survival, (C) distant metastasis-free survival, and (D) locoregional relapse-free survival, in the propensity score matched cohort, stratified by CCD >160 mg/m^2 and CCD <160 mg/m^2.

CCD, cumulative cisplatin dose; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; NPC, nasopharyngeal carcinoma.

Figure 5. Prognostic effects of 160 mg/m^2 CCD on (A) overall survival, and (B) progression-free survival, stratified by patient and treatment characteristics in subgroups.

CCD, cumulative cisplatin dose.

List of Supporting Information：

Supplementary materials Doc.S1. Detailed information regarding materials and methods

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

Characteristics	All patients n = 583	CCD >160 mg/m^2 n = 325	CCD <160 mg/m^2 n = 258	P-value*
Sex				0.85
Male	443 (76.0)	246 (75.7)	197 (76.4)	
Female	140 (24.0)	79 (24.3)	61 (23.6)	
Age (years)				0.02
<45	306 (52.5)	183 (56.3)	123 (47.7)	
46–65	260 (44.6)	137 (42.2)	123 (47.7)	
>66	17 (2.9)	5 (1.5)	12 (4.7)	
Year of diagnosis				0.06
2005–2010	224 (38.4)	114 (35.1)	110 (42.6)	
2011–2013	359 (61.6)	211 (64.9)	148 (57.4)	
T category†				0.01

T1	25 (4.3)	16 (4.9)	9 (3.5)	
T2	46 (7.9)	22 (6.8)	24 (9.3)	
T3	317 (54.4)	161 (49.5)	156 (60.5)	
T4	195 (33.4)	126 (38.8)	69 (26.7)	
N category[†]				0.22
N0	42 (7.2)	20 (6.2)	22 (8.5)	
N1	289 (49.6)	170 (52.3)	119 (46.1)	
N2	116 (19.9)	57 (17.5)	59 (22.9)	
N3	136 (23.3)	78 (24.0)	58 (22.5)	
Stage category[†]				<0.01
III	283 (48.5)	139 (42.8)	144 (58.5)	
IV	300 (51.5)	186 (57.2)	114 (44.2)	
Pretreatment EBV DNA				0.21
<1 000 copies/ml	112 (19.2)	57 (17.5)	55 (21.3)	
≥1 000 copies/ml	360 (61.7)	211 (64.9)	149 (57.8)	
Unkown	111 (19.0)	57 (17.5)	54 (20.9)	

IC cycles				
2 cycles	326 (55.9)	164 (50.5)	162 (62.8)	
3 cycles	218 (37.4)	153 (47.1)	65 (25.2)	
4 cycles	39 (6.7)	8 (2.5)	31 (12.0)	
IC regimens				<0.01
TPF	243 (41.7)	165 (50.8)	78 (30.2)	
TP	185 (31.7)	84 (25.8)	101 (39.1)	
PF	142 (24.4)	71 (21.8)	71 (27.5)	
Others‡	13 (2.2)	5 (1.5)	8 (3.1)	
CCRT regimens				<0.01
Weekly DDP	173 (29.7)	47 (14.5)	126 (48.8)	
Three-weekly DDP	410 (70.3)	278 (85.5)	132 (51.2)	

Abbreviations: CCD = cumulative cisplatin dose; IC = induction chemotherapy; CCRT = concurrent chemotherapy; DDP = cisplatin; EBV DNA = Epstein–Barr virus deoxyribonucleic acid; T = tumor; N = node

* Two-sided P-values were calculated using the chi-square test or Fisher's exact test if indicated.

† According to the 8th edition of the American Joint Committee on Cancer.

‡ Others included gemcitabine plus cisplatin (GP), or patients with regimen alterations during the IC.

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

Characteristics	Entire cohort			Propensity-score matched cohort		
	CCD >160 mg/m^2 (n = 325), %	CCD <160 mg/m^2 (n = 258), %	P-value*	CCD >160 mg/m^2 (n = 180), %	CCD <160 mg/m^2 (n = 180), %	P-value*
Sex			0.85			0.90
Male	246 (75.7)	197 (76.4)		133 (73.9)	134 (74.4)	
Female	79 (24.3)	61 (23.6)		47 (26.1)	46 (25.6)	
Age (years)			0.04			0.40
<45	183 (56.3)	123 (47.7)		78 (43.3)	86 (47.8)	
≥45	142 (43.7)	135 (52.3)		102 (56.7)	94 (52.2)	
Year of diagnosis			0.06			0.65
2005–2010	114 (35.1)	110 (42.6)		58 (32.2)	54 (30.0)	
2011–2013	211 (64.9)	148 (57.4)		122 (67.8)	126 (70.0)	
T category†			0.69			0.34
T1-2	38 (11.7)	33 (12.8)		26 (14.4)	20 (11.1)	
T3-4	287 (88.3)	225 (87.2)		154 (85.6)	160 (88.9)	
N category†			0.36			0.75
N0–1	190 (58.5)	141 (54.7)		96 (53.3)	93 (51.7)	

N2–3	135 (41.5)	117 (45.3)		84 (46.7)	87 (48.3)	
Stage category[†]			< 0.01			0.25
III	139 (42.8)	144 (58.5)		80 (44.4)	91 (50.6)	
IV	186 (57.2)	114 (44.2)		100 (55.6)	89 (49.4)	
Pretreatment EBV DNA			0.21			1.00
<1 000 copies/ml	57 (17.5)	55 (21.3)		40 (22.2)	40 (22.2)	
≥1 000 copies/ml	211 (64.9)	149 (57.8)		140 (77.8)	140 (77.8)	
Unkown	57 (17.5)	54 (20.9)		--	--	
IC cycles			< 0.01			0.46
2 cycles	164 (50.5)	162 (62.8)		104 (57.8)	97 (53.9)	
> 2 cycles	161 (49.5)	96 (37.2)		76 (42.2)	83 (46.1)	
IC regimen			< 0.01			0.44
TPF	165 (50.8)	78 (30.2)		62 (34.4)	69 (38.3)	
TP+PF+others[‡]	160 (49.2)	180 (69.8)		118 (65.6)	111 (61.7)	

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

* Two-sided P-values were calculated using the chi-square test or Fisher's exact test if indicated.

† According to the 8th edition of the American Joint Committee on Cancer.

‡ Others included gemcitabine plus cisplatin (GP), or patients with regimen alterations during the IC.

NOTE: The following variables were used for propensity-score matching: age (≥45 vs. <45 years), sex (female vs. male), year of diagnosis (2011–2013 vs. 2005–2010); tumor category (T 3–4 vs. T 1–2); node category (N2–3 vs. N0–1); pretreatment EBV DNA (≥1 000 copies/ml vs. <1 000 copies/ml); IC cycles (>2 cycles vs. 2 cycles); IC regimen (TPF vs. all others).

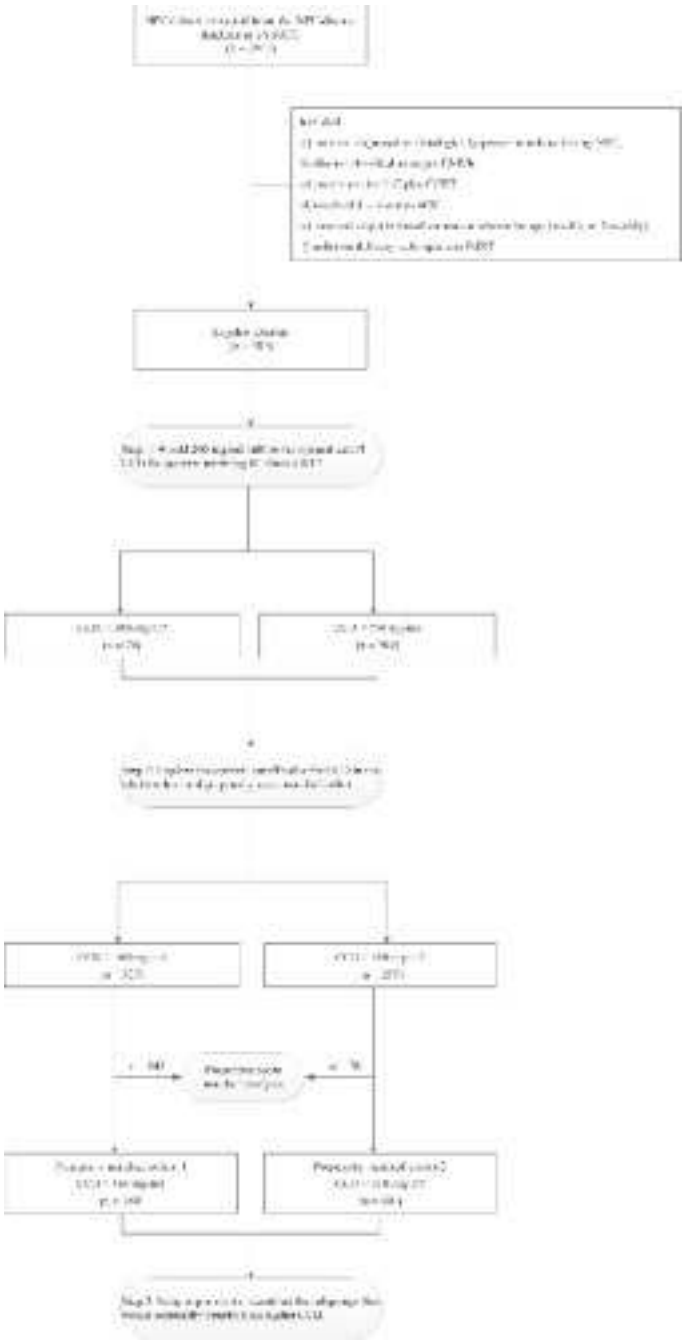
Table 3: Cox proportional hazards analyses of prognostic factors for the propensity-score matched cohort

Endpoint	Variable	HR	95% CI	P-value*
OS	CCD (>160 mg/m^2 vs. < 160 mg/m^2)	0.75	0.44 to 1.27	0.28
	Year of diagnosis (2011–2013 vs. 2005–2010)	0.49	0.28 to 0.87	0.02
	N (N3–4 vs. N1–2)	2.31	1.30 to 4.08	<0.01
	IC regimens			
	PF	Reference		
	TPF	0.41	0.20 to 0.81	0.01
	TP	0.49	0.26 to 0.94	0.03
	Others	0.52	0.07 to 4.01	0.53
PFS	CCD (>160 mg/m2 vs. < 160 mg/m2)	0.86	0.55 to 1.33	0.49
	N (N3-4 vs. N1-2)	1.99	1.23 to 3.36	<0.01
	IC regimens			
	PF	Reference		
	TPF	0.57	0.31 to 1.04	0.06
	TP	0.48	0.28 to 0.85	0.01
	Others	0.99	0.29 to 3.36	0.98

DMFS	CCD (>160 mg/m^2 vs. <160mg/m^2)	0.90	0.54 to 1.47	0.66
	Year of diagnosis (2011–2013 vs. 2005–2010)	0.62	0.36 to 1.08	0.09
	N (N3–4 vs. N1–2)	3.20	1.80 to 5.68	<0.01
	IC regimens			
	PF	Reference		
	TPF	0.56	0.28 to 1.10	0.09
	TP	0.56	0.30 to 1.05	0.06
	Others	1.43	0.41 to 5.02	0.58
LRFS	CCD (>160 mg/m^2 vs. < 160 mg/m^2)	0.69	0.34 to 1.42	0.31
	T category	4.67	0.60 to 36.13	0.09
	IC regimens			
	PF	Reference		
	TPF	0.48	0,19 to 1.24	0.13
	TP	0.44	0.18 to 1.06	0.06
	Others	0.00	--	0.98

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

*The following parameters were included in the Cox proportional hazards model multivariate analysis: cumulative cisplatin dose (CCD >160 mg/m^2 vs. CCD < 160 mg/m^2); IC cycles (>2 cycles vs. 2 cycles); IC regimens (TPF vs. TP vs. PF vs. others); age (>66 vs. 45–65 vs. <45 years); sex (female vs. male); year of diagnosis (2011–2013 vs. 2005–2010); tumor category (T3–4 vs. T1–2); node category (N2–3 vs. N0–1), and pretreatment Epstein–Barr virus DNA (≥1 000 copies/ml vs. <1 000 copies/ml).



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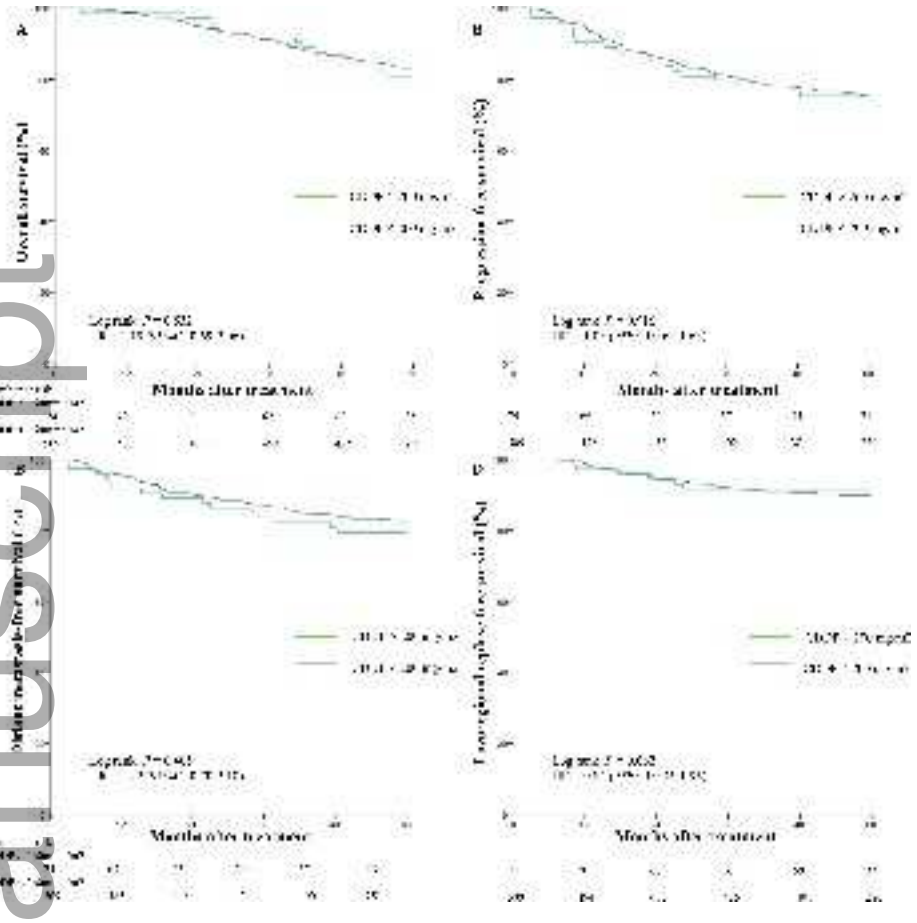

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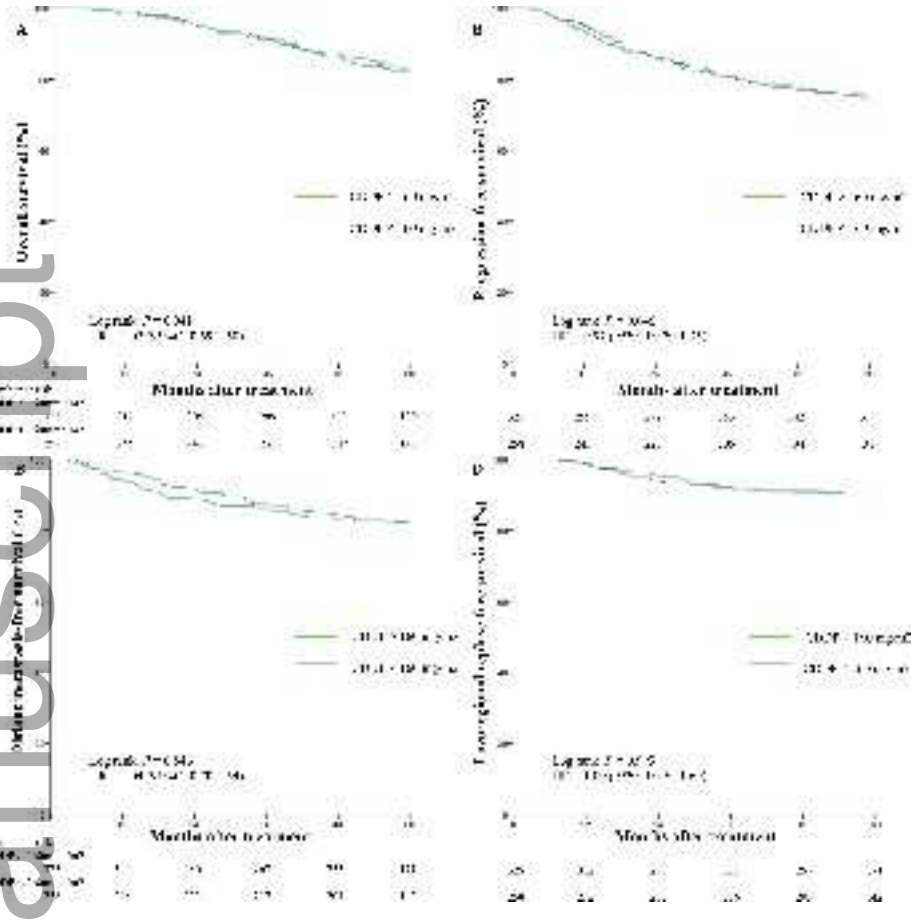

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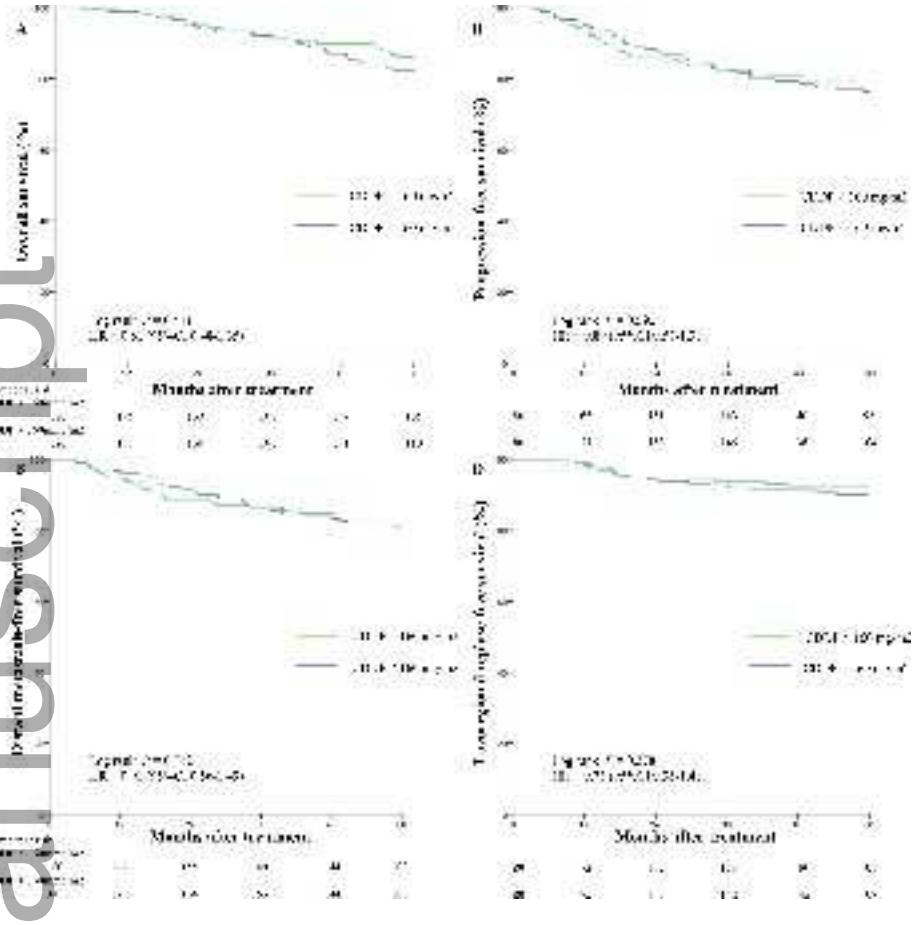

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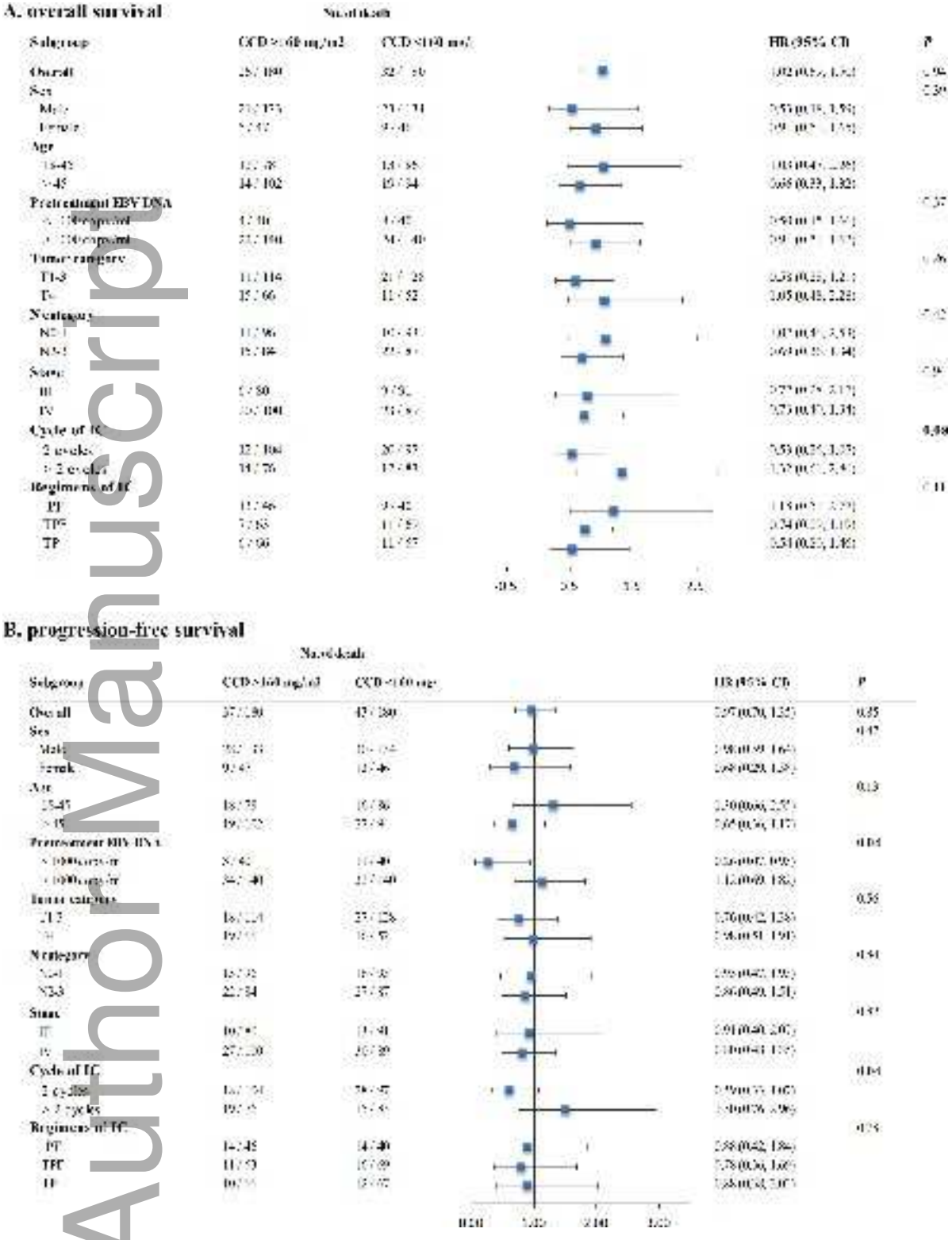

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