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

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

Methods: A total of 3460 patients with locoregionally advanced NPC who were treated with IC plus cisplatin-based concurrent chemoradiotherapy or RT alone were included in this retrospective study. Three CCD groups (0 mg/m² ≤ CCD < 100 mg/m², 100 mg/m² ≤ CCD < 200 mg/m², CCD ≥ 200 mg/m²) were balanced through the inverse probability of treatment weighting based on propensity scores estimated by a general boosted model. The primary endpoint was overall survival (OS); the secondary endpoints were distant metastasis-free survival (DMFS) and locoregional recurrence-free survival (LRFS).

Results: CCD ≥ 200 mg/m² and < 200 mg/m² exhibited similar treatment effects for OS and DMFS, and were both superior to CCD < 100 mg/m² for OS and DMFS in patients with stage IVa NPC. The three CCD groups achieved similar treatment effects for patients with stage II–III NPC. After IC, CCD during RT appeared to exert little treatment effect on LRFS.

Conclusion: The CCD during RT exerts treatment effects and improves OS by reducing the risk of distant metastasis for patients with stage IVa NPC, and CCD < 200 mg/m² (mainly 160 mg/m² in this group) is recommended. However, RT alone may be sufficient after IC in patients with stage II–III NPC.

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

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Introduction
Cisplatin-based concurrent chemoradiotherapy (CCRT) has been established as the backbone of treatment for locoregionally advanced nasopharyngeal carcinoma (NPC).1–3 The cumulative cisplatin dose (CCD) during radiotherapy (RT) is an important prognostic factor in NPC.4–9 Previously, we demonstrated that a CCD of 240 mg/m² is optimal for patients with locoregionally advanced NPC who received CCRT alone.9 However, CCRT alone may not provide sufficient treatment intensity in patients with high-risk NPC.9

Recently, several studies have demonstrated that induction chemotherapy (IC) in addition to CCRT could improve distant control and survival in patients with locoregionally advanced NPC.10–12 Previously, we found that IC decreased patient tolerance of the CCD during RT.13 After IC, does the CCD during RT remain a prognostic factor for patients with locoregionally advanced...
NPC? Lv et al. attempted to answer this question and found no significant relationships between CCD during RT and the prognosis of patients who received IC plus CCRT. However, they only included 583 patients, and the use of propensity score matching further shrank the sample size, which might have weakened the statistical power. Besides, the simple dichotomization of the CCD during RT was too crude for the results to be interpreted. Liu et al. divided the post-IC CCD into three groups, however, the multivariate Cox regression model they used to control confounding factors may have led to unreliable estimations of the prognostic effects of the CCD, considering the relatively small sample size of one CCD group (84 patients) and the numerous covariates included in the regression model.

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

Materials and methods

Patients

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

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

Endpoints and follow up

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

Statistical analysis

We divided the CCD during RT into three groups: 0 mg/m² ≤ CCD < 100 mg/m², 100 mg/m² ≤ CCD < 200 mg/m², CCD ≥ 200 mg/m². To account for
higher CCD. Figure 1(a)–(c) shows the pairwise balance assessments among the three CCD groups. IPTW adjustment resulted in excellent balance of baseline characteristics.

**Treatment effects of CCD during RT**

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

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

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

**Subgroup analyses**

We conducted subgroup analyses based on risk stratification: the low-risk group had 1874
Table 1. Distributions of baseline characteristics among CCD groups before and after weighting in the whole cohort.

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

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

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

| Characteristic | Unweighted (%) | ASD | IPTW (%) | ASD |
|----------------|----------------|-----|----------|-----|
|                | CCD <100       |     | CCD <200 |     | CCD ≥200 |     |
| N2             | 26.4           | 0.041 | 28.2     | 0.007 |
| N3             | 16.0           | 0.158 | 19.6     | 0.033 |
| EBV DNA (copies/ml) |         |     |          |     |
| ≤2000          | 42.8           | 0.188 | 35.8     | 0.036 |
| >2000          | 57.2           | 0.188 | 64.2     | 0.036 |
| LDH (IU/L)     |                |     |          |     |
| ≤180           | 53.8           | 0.066 | 53.0     | 0.022 |
| >180           | 46.2           | 0.066 | 47.0     | 0.022 |
| IC regime      |                |     |          |     |
| TPF            | 25.0           | 0.569 | 43.5     | 0.048 |
| PF             | 20.3           | 0.086 | 21.5     | 0.012 |
| TP             | 44.1           | 0.579 | 29.5     | 0.035 |
| GP             | 10.7           | 0.265 | 5.4      | 0.029 |
| IC cycles      |                |     |          |     |
| 1              | 7.0            | 0.248 | 4.3      | 0.018 |
| 2              | 58.7           | 0.161 | 54.2     | 0.003 |
| 3              | 20.1           | 0.547 | 33.9     | 0.049 |
| ≥4             | 14.2           | 0.421 | 7.7      | 0.072 |
| Total number or ESS (weighted)* | 1037 | 1717 | 706 | 642.31 | 1458.01 | 560.05 |

*Weighted treatment effect estimates have greater sampling variance than the unweighted estimates from a sample of equal size. The ESS of the weighted group is a conservative means of capturing the impact of this increase in variance on precision and power.

Table 1. (Continued)
effects for the high-risk group. Regardless of IPTW adjustment, CCD ≥200 mg/m² and <200 mg/m² both exhibited a priority over CCD <100 mg/m² for OS for the high-risk patients, while no significant difference for OS was detected between CCD ≥200 mg/m² and <200 mg/m². The treatment effects of the CCD during RT on DMFS were similar to that for OS, except the difference for DMFS between CCD <200 mg/m² and <100 mg/m² was nearly, but not statistically, significant (p = 0.080) after weighting. There was no difference among the CCDs for LRFS before and after weighting.

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

**Discussion**

We explored the treatment effects of the CCD during RT for patients with locoregionally advanced NPC who had received IC. We collected real-world data, where the CCD was determined by numerous observable and unobservable factors. Simple comparison between the CCD groups without adjustment would lead to bias during estimation of the treatment effects. Therefore, to estimate the treatment effects of CCD accurately, we used propensity score weighting to balance the baseline characteristics among the CCD groups. Potential confounding factors related to patient, disease, and IC were considered during the propensity score estimation. Compared with regression-based covariate adjustment methods, propensity score weighting has several statistical advantages and yielded a reliable estimation of the treatment effects of the CCD during RT.17,18
For the whole cohort, we found that patients who received CCD $< 100 \text{mg/m}^2$ (mostly 0 mg/m$^2$, namely, RT alone after IC) (Supplemental Figure S2) had a higher risk of death compared with those who received CCD $\geq 200 \text{mg/m}^2$. This means that sufficient-intensity concurrent chemotherapy remains necessary for patients with locoregionally advanced NPC who have received IC, which is in accordance with the conclusions drawn by two previous meta-analyses.\textsuperscript{2,3} For high-risk patients (stage IVa), CCD $< 200 \text{mg/m}^2$ and $\geq 200 \text{mg/m}^2$ exhibited no differences for OS, and they both showed significantly improved OS compared with CCD $< 100 \text{mg/m}^2$. Based on the above results, we recommend CCD $< 200 \text{mg/m}^2$ (mostly CCD $= 160 \text{mg/m}^2$) (Supplemental Figure S2) for patients with stage IVa NPC who have received IC. On the contrary, the CCD during RT did not appear to be a prognostic factor for low-risk patients (stage II–III). The different treatment effects of the CCD in the risk subgroups may account for the statistically nonsignificant difference for OS between CCD $< 100 \text{mg/m}^2$ and $\geq 200 \text{mg/m}^2$.
m² and <200 mg/m² in the whole cohort. Considering the above, concurrent chemotherapy may be omitted after IC for patients with stage II–III NPC.

As shown in Figure 5, the whole cohort and high-risk subgroup had similar patterns of error bars representing the HR and 95% CI for OS and DMFS. This indicates that the treatment effects of the CCD during RT on OS may mainly be derived from its effects on reducing the risk of distant metastasis, which is in accordance with the study of Liu et al. IC can improve DMFS relying on early systemic interventions on subclinical micrometastasis and combinations of cytotoxic drugs. Moreover, the concurrent usage of cisplatin during RT can further reduce the risk of distant metastasis and improve OS for high-risk patients.
patients, which could be due to the additive effects of systemically used cisplatin on the micrometastasis. Another possible explanation for the CCD treatment effects in improving DMFS may be that the combination of concurrent cisplatin and RT results in more immunogenic cell death and hence more potent anti-tumor immune responses than RT alone, which would elicit absocopal effects to eliminate the micrometastasis.\textsuperscript{19–21} In the whole and sub-group cohorts, the patterns of error bars representing the HR and 95% CI for LRFS were the opposite of those for OS; a lower CCD was related to better LRFS. This unexpected phenomenon may have been due to an unobservable confounding factor, i.e. tumor response to IC. Patients with poor response to IC were more likely to receive a higher CCD during RT in clinical practice.
However, these patients remain at high risk of locoregional recurrence. According to our analyses, the CCD during RT appeared to exert little effect on LRFS for patients who had received IC, which is distinct from the situations for patients who received CCRT or RT alone.

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

In conclusion, the CCD during RT exerts treatment effects and improves OS by reducing the risk of distant metastasis for patients with stage IVa NPC following IC, and a CCD of 160 mg/m² is recommended. However, for patients with stage II–III NPC, RT alone may be sufficient after the IC. Considering the limitations of the current study, prospective clinical trials are warranted to validate our results in the future.

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Conflict of interest statement
The authors declare that there is no conflict of interest.

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