Impact of tumor volume enlargement after induction chemotherapy on subsequent radiotherapy in locally advanced nasopharyngeal carcinoma: A propensity-score matching analysis

Shan Li | Liangfang Shen

Abstract
A small proportion of nasopharyngeal carcinoma (NPC) patients show resistance to induction chemotherapy (IC). This study sought to investigate the impact of tumor volume enlargement after IC on the dosimetric parameters of subsequent radiotherapy. The records of a total of 240 locally advanced NPC patients who received IC followed by concurrent chemoradiotherapy were retrospectively reviewed. Patients with a tumor volume enlargement of ≥10% and patients with a tumor volume reduction of ≥10% after induction chemotherapy were classified as the enlargement group and the control group, respectively. The dosimetric parameters of the planning target volumes (PTVs) and the organs at risk (OARs) were compared between the matched groups after propensity score matching (PSM). For the gross tumor volume of nasopharynx (GTVnx), 21 patients and 127 patients were classified as the enlargement group and the control group, respectively. After matching, 20 sub-pairs of 40 patients were generated in the post-PSM cohort. The GTVnx enlargement group exhibited no significant disadvantages in all of the dosimetric parameters, except in the planning organ-at-risk volume (PRV) of contralateral lens (Dmax, 722 cGy vs. 634 cGy, \( p = 0.041 \)). For the gross tumor volume of lymph nodes (GTVnd), 44 patients and 144 patients were classified as the enlargement group and the control group, respectively. After matching, 39 sub-pairs of 78 patients were generated in the post-PSM cohort. The GTVnd enlargement group exhibited no significant disadvantages in all of the dosimetric parameters. Univariate and multivariate analyses showed that the enlargement of GTVnx and the enlargement of GTVnd were not independently associated with any of the dosimetric parameters. A tumor volume enlargement of ≥10% in GTVnx or GTVnd after induction chemotherapy has no significant impact on the dosimetric parameters of subsequent radiotherapy in locally advanced NPC.

KEYWORDS
dosimetry, induction chemotherapy, nasopharyngeal carcinoma, propensity score matching, tumor volume
1 | INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a common type of head and neck cancer, and radiotherapy is its principle treatment method due to the complicated anatomical location of the cancer and its high sensitivity to radiation.\(^1\)\(^2\) Recently, induction chemotherapy (IC) followed by concurrent chemoradiotherapy has become a standard treatment strategy for locally advanced NPC according to the National Comprehensive Cancer Network (NCCN) guidelines (version 1.2020). Several well-designed randomized controlled studies have shown that IC can improve the survival outcomes of NPC patients.\(^3\)\(^–\)\(^5\) However, it is noteworthy that although most NPC patients show resistance to IC, which has a negative influence on patient survival.\(^6\)\(^,\)\(^7\)

In addition to the impact on patient survival, another potential consequence of tumor progression after IC is the influence on subsequent radiotherapy. The location of NPC is surrounded by many important structures, such as the brainstem, spinal cord, and optic nerves.\(^8\)\(^,\)\(^9\) An increase in tumor volume after IC may have a significant influence on the dosimetric parameters of the subsequent radiotherapy plan. However, no publications have addressed this problem thus far. Therefore, we conducted this retrospective study to compare the radiotherapy plans of patients with tumor volume enlargement and patients with tumor volume reduction after IC using the propensity score matching (PSM) method.

2 | MATERIAL AND METHODS

2.1 | Patient selection

A total of 240 NPC patients were selected according to the following criteria: (a) locally advanced NPC (T1-2N1-3M0 or T3-4N0-3M0, according to the AJCC 8th staging system) with pathology confirmation; (b) treated with IC followed by concurrent chemoradiotherapy at our hospital from 2016 to 2019; (c) contrast-enhanced simulation CT and simulation MRI were performed before and after IC; and (d) the radiotherapy plan was available for review. Written informed consent was obtained from each subject.

2.2 | Induction chemotherapy

All of the patients received IC with docetaxel plus cisplatin (docetaxel 75 mg/m\(^2\) day 1, cisplatin 75 mg/m\(^2\) day 2) for two or three cycles. The chemotherapy cycle was repeated every 21 days. Adequate bone marrow function, liver function, and renal function were required before the start of each chemotherapy cycle. All of the patients underwent contrast-enhanced simulation CT and simulation MRI at a 3-mm slice thickness with immobilization devices before IC. The gross tumor volume of nasopharynx (pre-IC GTVnx) and the gross tumor volume of lymph nodes (pre-IC GTVnd) were contoured with CT and MRI fusion images by a medical team consisting of radiation oncologists and radiologists.

2.3 | Concurrent chemoradiotherapy

Radiotherapy was delivered 3 weeks after the last cycle of IC, concurrent with cisplatin 80–100 mg/m\(^2\) every three weeks or 30–40 mg/m\(^2\) every week.\(^10\) Contrast-enhanced simulation CT and simulation MRI at a 3-mm slice thickness with immobilization devices were performed again for the preparation of radiotherapy. The gross tumor volume of nasopharynx (post-IC GTVnx) and the gross tumor volume of lymph nodes (post-IC GTVnd) were contoured again by the same medical team.

The target volumes in the radiotherapy plan included the final GTVnx, the final GTVnd, the clinical target volume 1 (CTV1), and the clinical target volume 2 (CTV2) according to the recommendation of the international guideline for the delineation of the clinical target volumes for NPC.\(^11\) The final GTVnx was defined as the summation of the pre-IC GTVnx and the post-IC GTVnx, which included all of the areas involved by the primary tumor before and after IC. The final GTVnd was defined as the post-IC GTVnd only. CTV1 and CTV2 were defined as the high-risk volume and the low-risk volume, respectively.

An expansion of 3–5 mm around the final GTVnx, the final GTVnd, CTV1, and CTV2 was adopted to generate the corresponding planning target volumes (PGTVnx, PGTVnd, PTV1, and PTV2). The prescription doses delivered to PGTVnx, PGTVnd, PTV1, and PTV2 were 70.4 Gy (2.2 Gy per fraction), 70.4 Gy (2.2 Gy per fraction), 60.8 Gy (1.9 Gy per fraction), and 54 Gy (1.8 Gy per fraction), respectively. The organs at risk (OARs) included the spinal cord, brain stem, optic chiasm, optic nerves, lenses, temporal lobes, parotid glands, and pituitary. Additionally, an expansion of the brain stem, spinal cord, and lens by 1, 5, and 5 mm, respectively, was adopted to generate the corresponding planning organ-at-risk volumes (PRVs).

The radiotherapy planning techniques consisted of conventional intensity-modulated radiation therapy (IMRT) and tomotherapy. The conventional IMRT plans, which included the volumetric-modulated arc therapy and the step-and-shoot IMRT, were generated with the Eclipse treatment planning system (Eclipse version 11.3, Varian Medical Systems). The tomotherapy plans were generated with the TomoTherapy Planning Workstation (TomoHD version 2.0.7, Accuracy Inc.).
2.4 | Dosimetric comparisons

Patients with a tumor volume enlargement of $\geq 10\%$ and patients with a tumor volume reduction of $\geq 10\%$ after IC were classified as the enlargement group and the control group, respectively. PSM was adopted to control the balance between the enlargement group and its control group. Matching covariates in the score scale included T stage, N stage, plan type, pretreatment volume of GTVnx, and pretreatment volume of GTVnd. For the PTVs, the minimum coverage dose of 95\% of the target (D95) was selected as the dosimetric parameter for comparisons in the post-PSM cohort. For the OARs, the maximum dose (Dmax) was adopted to evaluate the dosimetric differences of the brainstem, brainstem PRV, spinal cord, spinal cord PRV, optic chiasm, optic nerve, lens PRV, and pituitary between the matched groups in the post-PSM cohort. In addition, the relative volume receiving over 30 Gy (V30 Gy) and the relative volume receiving over 60 Gy (V60 Gy) were selected to evaluate the dosimetry of the parotid glands and temporal lobes, respectively.

2.5 | Statistical analyses

All of the statistical analyses were performed with SPSS (version 25, IBM SPSS Statistics). The comparisons of baseline characteristics between the enlargement group and the control group were made with the independent $t$ test and chi-square test. Dosimetric comparisons between
the matched groups in the post-PSM cohort were conducted with the independent t test. Univariate and multivariate analyses of dosimetric parameters were performed with the linear regression model. The variants, which showed an $\alpha < 0.1$ in the univariate analysis, were enrolled in the multivariate analysis.

3 | RESULTS

3.1 | Impact of GTVnx enlargement after IC on the dosimetric parameters of subsequent radiotherapy

For GTVnx, 21 patients and 127 patients were classified as the enlargement group and the control group, respectively. After matching, 20 sub-pairs of 40 patients were generated in the post-PSM cohort. A mean volume enlargement of 20.2% was observed in the enlargement group, and a mean volume reduction of 27.1% was observed in the matched control group. Figure 1 shows a typical case of GTVnx enlargement and its matched case in the control group. Table 1 shows the comparisons of baseline characteristics between the GTVnx enlargement group and the control group in the pre- and post-PSM cohorts. As shown in Table 2, the enlargement group exhibited no significant disadvantages in all of the dosimetric parameters compared with the matched control group, except in the contralateral lens PRV ($D_{\text{max}}$, 722 cGy vs. 634 cGy, $p = 0.041$).

3.2 | Impact of GTVnd enlargement after IC on the dosimetric parameters of subsequent radiotherapy

For GTVnd, 44 patients and 144 patients were classified as the enlargement group and the control group, respectively. After matching, 39 sub-pairs of 78 patients were generated in the post-PSM cohort. A mean volume enlargement of 50.6% was observed in the enlargement group, and a mean volume reduction of 40.1% was observed in the matched control group. Figure 2 shows a typical case of GTVnd enlargement and its matched case in the control group. Table 3 shows the comparisons of baseline characteristics between the GTVnd enlargement group and the control group in the pre- and post-PSM cohorts. As shown in Table 4, the enlargement group exhibited no significant disadvantages in all of the dosimetric parameters, compared with the matched control group.

3.3 | Univariate and multivariate analyses of dosimetric parameters

To further confirm the association between the tumor volume enlargement and subsequent radiotherapy, univariate and

| TABLE 1 | Comparisons of baseline characteristics between the GTVnx enlargement group and its control group in the pre- and post-PSM cohorts |
|---------|-----------------------|-----------------------|
| T stage | Control group (N = 127) | Enlargement group (N = 21) | p | Control group (N = 20) | Enlargement group (N = 20) | p |
| T1      | 6 | 4 | 0.014 | 3 | 3 | 0.674 |
| T2      | 15 | 5 | | 5 | 5 | |
| T3      | 66 | 5 | | 8 | 5 | |
| T4      | 40 | 7 | | 4 | 7 | |
| N stage | Control group (N = 127) | Enlargement group (N = 21) | p | Control group (N = 20) | Enlargement group (N = 20) | p |
| N0      | 2 | 0 | 0.138 | 0 | 0 | 0.796 |
| N1      | 32 | 5 | | 3 | 5 | |
| N2      | 55 | 14 | | 14 | 13 | |
| N3      | 38 | 2 | | 3 | 2 | |
| Plan type | | | | | | |
| Tomotherapy | 99 | 21 | 0.037 | 19 | 20 | 1.00 |
| Conventional IMRT | 28 | 0 | | 1 | 0 | |
| Pretreatment GTVnx volume (cm$^3$) | $43.85 \pm 24.87$ | $36.58 \pm 26.92$ | 0.221 | $38.64 \pm 30.55$ | $37.84 \pm 26.97$ | 0.931 |
| Pretreatment GTVnd volume (cm$^3$) | $25.92 \pm 25.89$ | $18.93 \pm 17.17$ | 0.235 | $21.80 \pm 20.49$ | $19.29 \pm 17.54$ | 0.680 |

Abbreviation: PSM, propensity score matching.
Multivariate analyses were conducted to identify factors independently associated with the dosimetric parameters among all of the enrolled patients. As shown in Table 5, the tumor volume change of GTVnx (enlargement group vs. control group) and tumor volume change of GTVnd (enlargement group vs. control group) were not independently associated with any of the dosimetric parameters of PTVs and OARs.

| Parameters                        | Group           | Mean   | SD    | p    |
|-----------------------------------|-----------------|--------|-------|------|
| PGTVnx_D95 (cGy)                  | Control group   | 7037   | 45    | 0.755|
|                                   | Enlargement group | 7033   | 34    |       |
| PGTVnd_D95 (cGy)                  | Control group   | 7090   | 71    | 0.807|
|                                   | Enlargement group | 7095   | 74    |       |
| PTV1_D95 (cGy)                    | Control group   | 6223   | 64    | 0.452|
|                                   | Enlargement group | 6237   | 58    |       |
| PTV2_D95 (cGy)                    | Control group   | 5619   | 180   | 0.467|
|                                   | Enlargement group | 5652   | 86    |       |
| Spinal cord_Dmax (cGy)            | Control group   | 3254   | 265   | 0.617|
|                                   | Enlargement group | 3297   | 269   |       |
| Spinal cord PRV_Dmax (cGy)        | Control group   | 4021   | 464   | 0.685|
|                                   | Enlargement group | 4075   | 357   |       |
| Brainstem_Dmax (cGy)              | Control group   | 5071   | 285   | 0.079|
|                                   | Enlargement group | 5203   | 161   |       |
| Brainstem PRV_Dmax (cGy)          | Control group   | 5639   | 342   | 0.176|
|                                   | Enlargement group | 5765   | 222   |       |
| Optic chiasm_Dmax (cGy)           | Control group   | 4875   | 1398  | 0.132|
|                                   | Enlargement group | 5465   | 990   |       |
| Optic nerve_I_Dmax (cGy)          | Control group   | 5405   | 1073  | 0.376|
|                                   | Enlargement group | 5674   | 811   |       |
| Optic nerve_C_Dmax (cGy)          | Control group   | 5136   | 1082  | 0.546|
|                                   | Enlargement group | 5305   | 608   |       |
| Lens PRV_I_Dmax (cGy)             | Control group   | 697    | 185   | 0.270|
|                                   | Enlargement group | 762    | 183   |       |
| Lens PRV_C_Dmax (cGy)             | Control group   | 634    | 131   | 0.041|
|                                   | Enlargement group | 722    | 132   |       |
| Pituitary_Dmax (cGy)              | Control group   | 6118   | 876   | 0.650|
|                                   | Enlargement group | 6242   | 824   |       |
| Temporal lobe_I_V60 Gy (%)        | Control group   | 5.26   | 4.88  | 0.479|
|                                   | Enlargement group | 6.43   | 5.49  |       |
| Temporal lobe_C_V60 Gy (%)        | Control group   | 2.25   | 1.96  | 0.921|
|                                   | Enlargement group | 2.19   | 1.63  |       |
| Parotid gland_I_V30 Gy (%)        | Control group   | 52.37  | 14.27 | 0.648|
|                                   | Enlargement group | 54.52  | 15.22 |       |
| Parotid gland_C_V30 Gy (%)        | Control group   | 47.94  | 13.14 | 0.310|
|                                   | Enlargement group | 52.55  | 15.13 |       |

Abbreviations: C, contralateral; D95, the minimum dose delivered to 95% of the target; Dmax, maximum dose; I, ipsilateral; PSM, propensity score matching; V30 Gy, the relative volume of the structure receiving over 30 Gy; V60 Gy, the relative volume of the structure receiving over 60 Gy.

Table 2 Comparisons of dosimetric parameters between the GTVnx enlargement group and its matched control group in the post-PSM cohort.

## Discussion

Due to the complicated anatomical location, the tumor size of NPC has a significant influence on the dosimetric parameters of radiotherapy. Tumor volume enlargement after IC has been observed in a small proportion of NPC patients despite the high chemotherapy sensitivity of the cancer, but...
its influence on the subsequent radiotherapy plan has not yet been investigated. To the best of our knowledge, the current study is the first to address this problem. We compared the dosimetric parameters between patients with tumor volume enlargement and patients with tumor volume reduction after IC, and PSM was adopted to control the balance of other factors, including T stage, N stage, pretreatment GTVnx volume, pretreatment GTVnd volume, and plan type (tomotherapy vs. conventional IMRT).15–20

Our results showed that GTVnx enlargement after IC had no significant impact on most of the dosimetric parameters. This finding is unexpected because it is expected that the primary tumor of NPC is closely related to the dosimetry of PTVs and OARs. A possible explanation for this phenomenon is attributed to the method of delineating the final GTVnx after IC, which was the summation of pre-IC and post-IC GTVnx according to the recommendation of the international guidelines.11 Despite the difference in tumor volume change between the enlargement group and its matched control group, the difference in the final GTVnx was not statistically significant (47.5 cm³ vs. 40.1 cm³, p = 0.484). Additionally, the only disadvantage of the enlargement group was the protection of the contralateral lens PRV (Dmax, 722 cGy vs. 634 cGy, p = 0.041), which would not have significant influence on clinical outcomes because adherence to the dose limit of lens PRV (Dmax <900 cGy) was performed for both groups. Therefore, a GTVnx enlargement of ≥10% after IC has no significant influence on subsequent radiotherapy

FIGURE 2  A typical case of GTVnd enlargement (left) and its matched control case(right) in the post-PSM cohort. The red lines represent the contours of GTVnd before induction chemotherapy. The purple lines represent the contours of GTVnd after induction chemotherapy. (GTVnd = the gross tumor volume of lymph nodes)
when the final GTVnx is defined as the summation of pre-IC and post-IC GTVnx.

It is worth mentioning that several studies have investigated the feasibility of using the post-IC GTVnx as the final GTVnx. A randomized controlled study by Yang et al. showed that using the post-IC GTVnx as the final GTVnx did not reduce the local control and survival rate in locally advanced NPC, but the doses to OARs decreased, and the quality of life improved.21 Another study by Xue et al. also indicated that contouring GTVnx based on the post-IC images achieved satisfactory survival outcome and avoided overdosing of critical neurological structures.22 Similar results have been reported by several other studies.23,24 If the post-IC GTVnx is adopted as the final GTVnx in future practice, the potential influence of tumor volume enlargement on subsequent radiotherapy should not be ignored, as the volume of the final GTVnx between the enlargement group and the reduction group would be significantly different.

Our results also showed that GTVnd enlargement after IC had no significant impact on the dosimetric parameters of subsequent radiotherapy. It is noteworthy that the final GTVnd was defined as the post-IC GTVnd only, and there was a significant difference in the final GTVnd between the enlargement group and its matched control group (18.2 cm³ vs. 8.1 cm³, \( p = 0.017 \)). This insignificant influence of GTVnd enlargement can be attributed to the anatomical location of lymph nodes, which are not adjacent to the majority of the OARs, in most cases. Despite a GTVnd volume enlargement, the dose coverage of PTVs and the protection of OARs can be easily satisfied for most patients with modern radiotherapy techniques, such as the conventional IMRT and tomotherapy. This is supported by the results of the multivariate analysis of dosimetric parameters (Table 5), which indicated that N stage and pretreatment GTVnd volume were not independently associated with the dosimetry of almost all of the OARs. Similar results have also been reported by the study of Yao et al., which analyzed the radiation doses to OARs in 148 NPC patients and showed that N stage was not independently associated with the dosimetry of most OARs.25 Therefore, a GTVnd enlargement of \( \geq 10\% \) after IC has no significant impact on subsequent radiotherapy.

It should be noted that univariate and multivariate analyses of dosimetric parameters were also performed in the current study. As shown in Table 5, the volume changes of GTVnx and GTVnd after induction chemotherapy (enlargement group vs. control group) were not independently associated with any of the dosimetric parameters of PTVs and OARs, which is consistent with the results discussed above. In addition, the multivariate analysis indicated that T stage, pretreatment GTVnx volume, and plan type were independently associated with the parameters of most OARs, which is in accordance with the results of previous studies.15,16,18–20

Although PSM was adopted in our study to control the balance between the enlargement group and the control group, it should be noted that there were still some uncontrolled

| TABLE 3 | Comparisons of baseline characteristics between the GTVnd enlargement group and its control group in the pre- and post-PSM cohorts |
|---|---|
| **Pre-PSM** | **Post-PSM** |
| | **Control group (N = 144)** | **Enlargement group (N = 44)** | **Control group (N = 39)** | **Enlargement group (N = 39)** |
| | \( p \) | | \( p \) |
| **T stage** | 0.205 | 0.657 |
| T1 | 10 | 2 | 3 | 2 |
| T2 | 22 | 6 | 3 | 6 |
| T3 | 74 | 17 | 19 | 15 |
| T4 | 38 | 19 | 14 | 16 |
| **N stage** | 0.000 | 0.970 |
| N0 | 0 | 0 | 0 | 0 |
| N1 | 23 | 19 | 15 | 14 |
| N2 | 68 | 20 | 19 | 20 |
| N3 | 53 | 5 | 5 | 5 |
| **Plan type** | 0.064 | 1.000 |
| Tomotherapy | 31 | 4 | 34 | 35 |
| Conventional IMRT | 113 | 40 | 5 | 4 |
| **Pretreatment GTVnx volume (cm³)** | 39.79 ± 23.63 | 47.82 ± 28.83 | 0.063 | 46.09 ± 28.49 | 46.35 ± 27.75 | 0.967 |
| **Pretreatment GTVnd volume (cm³)** | 30.37 ± 26.09 | 12.52 ± 18.30 | 0.000 | 13.99 ± 12.79 | 13.74 ± 19.12 | 0.946 |

Abbreviation: PSM, propensity score matching.
biases. First, one case in the GTVnx enlargement group and five cases in GTVnd enlargement group were discarded due to the lack of matched case in the control group. Second, some important factors may be not included in the process of matching, such as the distance between the tumor and the OARs, as there was no practical method which can provide such information. Third, cases with larger tumors may be excluded during the matching process, because the pre-IC tumor volumes in the enlargement group were smaller than the control group before matching as shown in Table 1. It is worth mentioning that the larger pre-IC tumor volumes in the control group indicates that larger tumors may be more sensitive to chemotherapy. Similar finding has been reported in the study of Wang et al., which showed that a

| Parameters              | Group           | Mean   | SD    | p    |
|-------------------------|-----------------|--------|-------|------|
| PTV1_D95 (cGy)          | Control group   | 6245   | 89    | 0.967|
|                         | Enlargement group| 6244   | 98    |
| PTV2_D95 (cGy)          | Control group   | 5591   | 155   | 0.058|
|                         | Enlargement group| 5648   | 105   |
| Spinal cord_Dmax (cGy)  | Control group   | 3335   | 363   | 0.792|
|                         | Enlargement group| 3315   | 294   |
| Spinal cord PRV_Dmax (cGy) | Control group | 4129   | 507   | 0.784|
|                         | Enlargement group| 4156   | 314   |
| Brainstem_Dmax (cGy)    | Control group   | 5166   | 236   | 0.171|
|                         | Enlargement group| 5232   | 186   |
| Brainstem PRV_Dmax (cGy)| Control group   | 5752   | 316   | 0.152|
|                         | Enlargement group| 5843   | 233   |
| Optic chiasm_Dmax (cGy)| Control group   | 5505   | 1270  | 0.995|
|                         | Enlargement group| 5503   | 1338  |
| Optic nerve I_Dmax (cGy)| Control group   | 5761   | 1129  | 0.948|
|                         | Enlargement group| 5778   | 1244  |
| Optic nerve C_Dmax (cGy)| Control group   | 5453   | 1130  | 0.744|
|                         | Enlargement group| 5371   | 1061  |
| Lens PRV I_Dmax (cGy)   | Control group   | 940    | 871   | 0.481|
|                         | Enlargement group| 835    | 317   |
| Lens PRV C_Dmax (cGy)   | Control group   | 782    | 267   | 0.381|
|                         | Enlargement group| 739    | 141   |
| Pituitary_Dmax (cGy)    | Control group   | 6402   | 772   | 0.975|
|                         | Enlargement group| 6409   | 912   |
| Temporal lobe I_ V60 Gy (%) | Control group | 7.18   | 5.74  | 0.662|
|                         | Enlargement group| 7.91   | 8.70  |
| Temporal lobe C_ V60 Gy (%) | Control group | 2.62   | 2.62  | 0.617|
|                         | Enlargement group| 2.95   | 3.06  |
| Parotid gland I_ V30 Gy (%) | Control group | 57.22  | 15.64 | 0.613|
|                         | Enlargement group| 55.48  | 14.30 |
| Parotid gland C_ V30 Gy (%) | Control group | 54.44  | 14.23 | 0.432|
|                         | Enlargement group| 52.09  | 11.96 |

Abbreviation: C, contralateral; D95, the minimum dose delivered to 95% of the target; Dmax, maximum dose; I, ipsilateral; PSM, propensity score matching; V30 Gy, the relative volume of the structure receiving over 30 Gy; V60 Gy, the relative volume of the structure receiving over 60 Gy.
### TABLE 5 Univariate and multivariate analyses of dosimetric parameters

| T stage | N stage | Pretreatment GTVnx volume | Pretreatment GTVnd volume | Plan type | GTVnx volume change | GTVnd volume change |
|---------|---------|---------------------------|---------------------------|-----------|---------------------|---------------------|
| B       | p       | B                         | p                         | B         | p                   | B                   |
| PGTVnx_D95 | −28.9   | 0.000                     | 28.2  | 0.001          | −1.0  | 0.000          | 0.6  | 0.023          | 19.0  | 0.245          | 10.2  | 0.682          | −33.4  | 0.027          |
| PGTVnd_D95 | 2.0     | 0.003                     | −21.9 | 0.001          | 0.6   | 0.001          | −0.7 | 0.000          | 33.4  | 0.007          | 2.4   | 0.890          | 16.2  | 0.188          |
| PTV1_D95   | 12.3    | 0.057                     | 11.1  | 0.122          | 0.5   | 0.015          | 0.5  | 0.018          | −26.1 | 0.065          | −22.1 | 0.245          | −11.3  | 0.424          |
| PTV2_D95   | 8.0     | 0.389                     | 36.5  | 0.000          | 0.5   | 0.119          | 1.2  | 0.000          | 79.1  | 0.000          | 10.7  | 0.682          | 8.5   | 0.666          |
| Spinal cord_Dmax | 13.7   | 0.562                     | 42.2  | 0.010          | 1.8   | 0.015          | 1.5  | 0.062          | −266.7 | 0.000          | −56.2 | 0.462          | −40.1  | 0.449          |
| Spinal cord PRV_Dmax | 95.6 | 0.002                     | 26.8  | 0.431          | 5.4  | 0.000          | 1.6  | 0.138          | −117.5 | 0.080          | −64.7 | 0.512          | 21.7   | 0.756          |
| Brainstem_Dmax | 62.6 | 0.000                     | −1.7  | 0.912          | 2.2   | 0.000          | 0.1  | 0.857          | −34.9  | 0.254          | −3.3  | 0.939          | 21.7   | 0.503          |
| Brainstem PRV_Dmax | 115.3 | 0.000                     | −35.2 | 0.070          | 3.7   | 0.000          | −0.6 | 0.318          | 5.7   | 0.882          | −13.2 | 0.813          | 80.4   | 0.052          |
| Optic chiasm_Dmax | 933.8 | 0.000                     | −437.7 | 0.000          | 24.8  | 0.000          | −8.9 | 0.003          | 831.5  | 0.000          | 67.1  | 0.798          | 380.5  | 0.057          |
| Optic nerve I_Dmax | 706.2 | 0.000                     | −345.8 | 0.000          | 20.8  | 0.000          | −7.3 | 0.006          | 832.6  | 0.000          | −2.9  | 0.990          | 337.1  | 0.057          |
| Optic nerve C_Dmax | 536.4 | 0.000                     | −216.4 | 0.007          | 16.3  | 0.000          | −4.9 | 0.050          | 959.6  | 0.000          | 26.7  | 0.909          | 222.4  | 0.183          |
| Lens PRV I_Dmax | 219.6 | 0.000                     | −54.7  | 0.310          | 10.3  | 0.000          | −3.3 | 0.047          | −23.8  | 0.824          | −128.2 | 0.420          | 20.9   | 0.804          |
| Lens PRV C_Dmax | 92.7   | 0.000                     | −45.1  | 0.007          | 3.3   | 0.000          | −1.2 | 0.019          | −117.8 | 0.000          | −31.3 | 0.472          | −19.0  | 0.596          |
| Pituitary_Dmax | 609.1 | 0.000                     | −270.2 | 0.000          | 17.3  | 0.000          | −5.8 | 0.005          | 292.9  | 0.030          | −68.9 | 0.708          | 302.0  | 0.030          |
| Temporal lobe I_V60 Gy | 4.5    | 0.000                     | −1.7  | 0.006          | 0.1   | 0.000          | 0.0  | 0.010          | 2.2   | 0.067          | 0.1   | 0.949          | 2.9    | 0.007          |
| Temporal lobe C_V60 Gy | 1.4    | 0.000                     | −0.2  | 0.655          | 0.1   | 0.000          | 0.0  | 0.184          | 1.1   | 0.111          | −0.5  | 0.615          | 1.1    | 0.044          |
| Parotid gland I_V30 Gy | 1.1    | 0.355                     | 0.6   | 0.657          | 0.1   | 0.024          | 0.1  | 0.024          | −13.2  | 0.000          | −2.0  | 0.610          | −3.3   | 0.220          |
| Parotid gland C_V30 Gy | −1.0  | 0.373                     | 0.0   | 0.987          | 0.0   | 0.760          | 0.0  | 0.443          | −15.8  | 0.000          | −0.7  | 0.856          | −2.6   | 0.276          |

(Continues)
### TABLE 5 (Continued)

| T stage | N stage | Pretreatment GTV<sub>nx</sub> volume | Pretreatment GTV<sub>nd</sub> volume | Plan type | GTV<sub>nx</sub> volume change | GTV<sub>nd</sub> volume change |
|---------|---------|-------------------------------------|-------------------------------------|-----------|--------------------------------|--------------------------------|
| B | p | B | p | B | p | B | p |
| B p B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
| B p B p B p B p B p B p B p |
larger tumor volume was independently associated with a higher likelihood of response to induction chemotherapy in head and neck cancer patients. A possible explanation for this phenomenon is that larger tumors are more likely to be involved with abundant blood supply, resulting in higher concentration of chemotherapy drugs in the tumor tissues and better treatment responses.

The results of this study were potentially affected by several factors. First, 10% was adopted as the cut-off value to determine tumor volume enlargement in our study. A higher cutoff value would significantly reduce the number of cases available for the propensity matching (especially for GTVnx) as shown in the supplement Table 1, which depicts the distribution of the relative volume change of GTVnx and GTVnd after IC. Second, the current study did not analyze the potential influence of the chemotheraphy regimen, as docetaxel plus cisplatin was the only IC regimen administered at our center. Third, the survival outcomes were not analyzed in our study because the follow-up time (median follow-up time: 21 months) was too short to analyze the survival outcome of non-metastatic NPC, which has a 5-year OS of 70-90%. Last, the sample size of our research was small (only 20 pairs of matched patients for GTVnx and 39 pairs of matched patients for GTVnd), which should be taken into consideration while interpreting the results.

To summarize, a tumor volume enlargement of ≥10% in GTVnx or GTVnd after IC has no significant impact on the dosimetric parameters of subsequent radiotherapy in locally advanced NPC.

ETHICS APPROVAL
This study was approved by the Ethics Committee of the Xiangya Hospital of Central South University prior to commencement.

ACKNOWLEDGMENTS
This work was supported by National Natural Science Foundation of China (Grant No. 81974466). We thank LetPub (www.letpub.com) for its linguistic assistance during the preparation of this manuscript.

CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTION
Liangfang Shen conceived and designed the analysis. Shan Li collected the data and performed the analysis. Liangfang Shen and Shan Li wrote the paper.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are openly available in Mendeley Data at http://dx.doi.org/10.17632/gcg4j9y7cw.1

ORCID
Liangfang Shen https://orcid.org/0000-0001-9474-6329

REFERENCES
1. Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. Cancer Epidemiol Biomarkers Prevention. 2006;15(10):1765–1777.
2. Lee HM, Okuda KS, Gonzalez FE, et al. Current perspectives on nasopharyngeal carcinoma. Adv Exp Med Biol. 2019;1164:11–34.
3. 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. Eur J Cancer. 2017;75:14–23.
4. Hong RL, Hsiao CF, Ting LL, et al. Final results of a randomized phase III trial of induction chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in patients with stage IVA and IVB nasopharyngeal carcinoma-Taiwan Cooperative Oncology Group (TCOG) 1303 Study. Annals Oncol. 2018;29(9):1972–1979.
5. 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. J Clin Oncol. 2009;27(2):242–249.
6. Lu JJ, Niu X, Ou X, et al. Response to induction chemotherapy for locally advanced nasopharyngeal cancer to predict prognostic impact of chemosensitivity. J Clin Oncol. 2016;34(15_suppl):6033.
7. Peng H, Chen L, Zhang Y, et al. The tumour response to induction chemotherapy has prognostic value for long-term survival outcomes after intensity-modulated radiation therapy in nasopharyngeal carcinoma. Sci Rep. 2016;21(6):24835.
8. Wang Y, Zhao J, Zhao Y, et al. Impact of paranasal sinus invasion on advanced nasopharyngeal carcinoma treated with intensity-modulated radiation therapy: the validity of advanced T stage of AJCC/UICC eighth edition staging system. Cancer Med. 2018;7(7):2826–2836.
9. He Y, Zhou Q, Shen L, et al. A retrospective study of the prognostic value of MRI-derived residual tumors at the end of intensity-modulated radiotherapy in 358 patients with locally-advanced nasopharyngeal carcinoma. Radiat Oncol. 2015;10:89.
10. Meng DF, Sun R, Peng LX, et al. A comparison of weekly versus 3-weekly cisplatin during concurrent chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma using intensity modulated radiation therapy: a matched study. J Cancer. 2018;9(1):92–99.
11. Lee AW, Ng WT, Pan JJ, et al. International guideline for the delineation of the clinical target volumes (CTV) for nasopharyngeal carcinoma. Radiother Oncol. 2018;126(1):25–36.
12. Mneijja W, Daoud H, Fourati N, et al. Dosimetric impact on changes in target volumes during intensity-modulated radiotherapy for nasopharyngeal carcinoma. Rep Practical Oncol Radiother. 2020;25(1):41–45.
13. Zhou GQ, Yu XL, Chen M, et al. Radiation-induced temporal lobe injury for nasopharyngeal carcinoma: a comparison of intensity-modulated radiotherapy and conventional two-dimensional radiotherapy. PLoS One. 2013;8(7):e67488.
14. He Y, Wang Y, Shen L, et al. Prognostic value of the distance between the primary tumor and brainstem in the patients with...
locally advanced nasopharyngeal carcinoma. BMC Cancer. 2016;17(16):114.
15. Zeng L, Tian YM, Sun XM, et al. Late toxicities after intensity-modulated radiotherapy for nasopharyngeal carcinoma: patient and treatment-related risk factors. Br J Cancer. 2014;110(1):49–54.
16. Xu L, Yao JJ, Zhou GQ, et al. The impact of clinical stage on radiation doses to organs at risk following intensity-modulated radiotherapy in nasopharyngeal carcinoma: a prospective analysis. J Cancer. 2016;7(14):2157–2164.
17. Li M, Huang XG, Yang ZN, et al. Effects of omitting elective neck irradiation to nodal Level IB in nasopharyngeal carcinoma patients with negative Level IB lymph nodes treated by intensity-modulated radiotherapy: a Phase 2 study. Br J Radiol. 2016;89(1065):20150621.
18. Lee FK, Yip CW, Cheung FC, et al. Dosimetric difference amongst 3 techniques: TomoTherapy, sliding-window intensity-modulated radiotherapy (IMRT), and RapidArc radiotherapy in the treatment of late-stage nasopharyngeal carcinoma (NPC). Med Dosimetry. 2014;39(1):44–49.
19. Li S, Zhou Q, Shen LF, et al. Dosimetric comparisons of volumetric modulated arc therapy and tomotherapy for early T-stage nasopharyngeal carcinoma. Biomed Res Int. 2018;2018:2653497.
20. Chen W, Yang X, Jiang N, et al. Intensity-modulated radiotherapy, volume-modulated arc therapy and helical tomotherapy for locally advanced nasopharyngeal carcinoma: a dosimetric comparison. Transl Cancer Res. 2017;6(5):929–939.
21. Yang H, Chen X, Lin S, et al. Treatment outcomes after reduction of the target volume of intensity-modulated radiotherapy following induction chemotherapy in patients with locoregionally advanced nasopharyngeal carcinoma: a prospective, multi-center, randomized clinical trial. Radiother Oncol. 2018;126(1):37–42.
22. Xue F, Hu C, He X. Induction chemotherapy followed by intensity-modulated radiotherapy with reduced gross tumor volume delineation for stage T3–4 nasopharyngeal carcinoma. OncoTargets Ther. 2017;10:3329–3336.
23. Zhao C, Hua Y, Xiao W, et al. Delineation of the target volumes in locoregionally advanced nasopharyngeal carcinoma patients treated with neoadjuvant chemotherapy followed by concurrent chemoradiation therapy. Int J Radiation Oncol Biol Phys. 2016;96(2):E342–E343.
24. Wang L, Wu Z, Xie D, et al. Reduction of target volume and the corresponding dose for the tumor regression field after induction chemotherapy in locoregionally advanced nasopharyngeal carcinoma. Cancer Res Treatment. 2019;51(2):685–695.
25. Yao JJ, Chen FP, Zhou GQ, et al. A prospective study on radiation doses to organs at risk (OARs) during intensity-modulated radiotherapy for nasopharyngeal carcinoma patients. Oncotarget. 2016;7(16):21742–21752.
26. Wang HM, Wang CH, Chen JS, et al. Cisplatin and 5-fluorouracil as neoadjuvant chemotherapy: predicting response in head and neck squamous cell cancer. J Formosan Med Assoc. 1995;94(3):87–94.
27. Xia S, Dong Y, Kang H, et al. Ultrasonography is valuable in evaluation of papillary thyroid microcarcinoma based on 5 mm tumor size. J Cancer Res Therap. 2018;14(Supplement):S319–S323.
28. Nguyen-Kim TD, Frauenfelder T, Strobel K, et al. Assessment of bronchial and pulmonary blood supply in non-small cell lung cancer subtypes using computed tomography perfusion. Invest Radiol. 2015;50(3):179–186.
29. Kim ES. Chemotherapy resistance in lung cancer. Adv Exp Med Biol. 2016;893:189–209.
30. Ji X, Yang Q, Qin H, et al. Tumor blood supply may predict neoadjuvant chemotherapy response and survival in patients with gastric cancer. J Int Med Res. 2019;47(6):2524–2532.
31. 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. Lancet Oncol. 2016;17(11):1509–1520.

How to cite this article: Li S and Shen L. Impact of tumor volume enlargement after induction chemotherapy on subsequent radiotherapy in locally advanced nasopharyngeal carcinoma: A propensity-score matching analysis. Cancer Med. 2020;9:8832–8843. https://doi.org/10.1002/cam4.3494