Received: 25 September 2024 | Revised: 26 November 2024 | Accepted: 27 December 2024

DOI: 10.3322/caac.21881

ARTICLE

# Reduced-volume radiotherapy versus conventional-volume radiotherapy after induction chemotherapy in nasopharyngeal carcinoma: An open-label, noninferiority, multicenter, randomized phase 3 trial

Ling-Long Tang MD[1] | Lin Chen MD[1] | Gui-Qiong Xu MD[2] | Ning Zhang MD[3] | Cheng-Long Huang MD[1] | Wen-Fei Li MD[1] | Yan-Ping Mao MD[1] | Guan-Qun Zhou MD[1] | Feng Lei MD[2] | Lu-Si Chen MD[3] | Shao Hui Huang MD[4] | Lei Chen MD[1] | Yu-Pei Chen MD[1] | Yuan Zhang MD[1] | Xu Liu MD[1] | Cheng Xu MD[1] | Yin Zhao PhD[1] | Ji-Bin Li MD[5] | Na Liu PhD[1] | Fang-Yun Xie MD[1] | Rui Guo MD[1] | Ying Sun MD[1] | Jun Ma MD[1]

[1]Department of Radiation Oncology, State Key Laboratory of Oncology in South China, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, Guangzhou, China

[2]Nasopharyngeal Head and Neck Carcinoma Radiotherapy Department, Zhongshan City People's Hospital, Zhongshan, China

[3]Department of Nasopharyngeal Oncology, First People's Hospital of Foshan, Foshan, China

[4]Department of Radiation Oncology, Princess Margaret Cancer Center, University of Toronto, Toronto, Ontario, Canada

[5]Clinical Trials Center, Sun Yat-sen University Cancer Center, Guangzhou, China

**Correspondence**

Jun Ma, Ying Sun, Ling-Long Tang, Rui Guo and Fang-Yun Xie, Department of Radiation Oncology, State Key Laboratory of Oncology in South China, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, No. 651 Road Dong Feng East, Guangzhou, Guangdong, China.
Email: majun2@mail.sysu.edu.cn; sunying@sysucc.org.cn; tangll@sysucc.org.cn; guorui@sysucc.org.cn and xiefy@sysucc.org.cn

**Funding information**

Noncommunicable Chronic Diseases-National Science and Technology Major Project, Grant/Award Number: 2024ZD0520701; National Natural Science Foundation of China, Grant/Award Numbers: U24A20725, 82430085, 82172870; Guangzhou Municipal Health Commission, Grant/Award Number:

## Abstract

**Background:** Nearly 90% locoregionally advanced nasopharyngeal carcinoma (LANPC) responds to induction chemotherapy (IC) with significant tumor volume shrinkage. Radiotherapy always follows IC, and reduced volume has been proposed. However, the efficacy and safety of reduced-volume radiotherapy is uncertain.

**Methods:** In this multi-center, noninferiority, randomized, controlled trial, patients with LANPC who completed IC were randomly assigned (1:1) to receive reduced-volume radiotherapy based on post-IC tumor volume (Post-IC group) or conventional volume radiotherapy based on pre-IC tumor volume (Pre-IC group). The primary endpoint was locoregional relapse-free survival, with a noninferiority margin of 8%. Secondary endpoints comprised adverse events, and quality of life (QoL).

**Results:** Between August 7, 2020, and May 27, 2022, 445 patients were randomly assigned to Post-IC ($n$ = 225) or Pre-IC ($n$ = 220) groups. The average volume receiving radical dose was 66.6 $cm^3$ in Post-IC group versus 80.9 $cm^3$. After a median follow-up of 40.4 months, the 3-year locoregional relapse-free survival was

Ling-Long Tang, Lin Chen, Gui-Qiong Xu, Ning Zhang, and Cheng-Long Huang contributed equally to this article.

2023P-GX04; Cancer Innovative Research Program of Sun Yat-sen University Cancer Center, Grant/Award Numbers: CIRP-SYSUCC-0005, CIRP-SYSUCC-0046; Sun Yat-sen University Clinical Research 5010 Program, Grant/Award Number: 2019014; Audiology Development Foundation of China, Grant/Award Number: ADFC-XM-2022003; Overseas Expertise Introduction Project for Discipline Innovation, Grant/Award Number: 111Project, B14035

91.5% in the Post-IC group versus 91.2%, with a difference of 0.3% (95% confidence interval −4.9% to 5.5%). The incidence of grade 3-4 radiation-related toxicity was lower in the Post-IC group including: acute mucositis (19.8% vs 34.1%), late otitis media (9.5% vs 20.9%) and late dry month (3.6% vs 9.5%). The Post-IC group had better QoL for global health status, physical functioning, emotional functioning, dry mouth and sticky saliva.

**Conclusions:** In this trial, reduced-volume radiotherapy was noninferior to conventional volume radiotherapy in locoregional relapse-free survival, and was associated with lower toxicities and improved QoL. (ClinicalTrials.gov identifier NCT04384627).

**KEYWORDS**
clinical trial, nasopharyngeal carcinoma, noninferiority, reduced-volume radiotherapy

## INTRODUCTION

Induction chemotherapy (IC) followed by concurrent chemoradiotherapy is the standard of care for locoregionally advanced nasopharyngeal carcinoma.[1–4] Nearly 90% patients respond, with an average tumor volume shrinkage from 20.1% to 54.7%.[5]

For decades, full radical dose coverage, calculated based on the pre-IC tumor volume, has been recommended, regardless of the response to IC and concurrent chemoradiotherapy.[6] This results in high-dose exposure to the surrounding functional structures, represented by the inner ear, parotid gland and temporal lobe, resulting in high proportions of hearing impairment (72%),[7] dry mouth (57%),[8] and temporal lobe injury (12%)[9] and reducing patients' quality of life (QoL) far beyond the end of treatment.[10]

Reduced-volume radiotherapy with a full dose only to the residual tumors after the completion of IC may achieve comparable outcomes with less associated toxicities.[11–15] Properly designed trials regarding the safety of reduced-volume radiotherapy and its benefit to QoL are needed. Therefore, we designed this multicenter, phase 3 trial to test the hypothesis that reduced-volume radiotherapy based on post-IC tumor volume (the post-IC group) would be noninferior to conventional-volume radiotherapy based on pre-IC tumor volume (the pre-IC group) in patients with locoregional, advanced nasopharyngeal carcinoma who receive IC.

## MATERIALS AND METHODS

### Trial design and participants

This multicenter, noninferiority, open-label, phase 3, randomized controlled trial was conducted in three Chinese medical centers (see Supporting Information S1: Supporting Methods, p 13). The key eligibility criteria comprised patients who had: newly diagnosed, histologically confirmed, nonkeratinizing nasopharyngeal carcinoma, stage III–IVA disease (according to the 8th edition American Joint Committee on Cancer/Union for International Cancer Control staging system); aged 18–70 years; a Karnofsky performance status score ≥70; and adequate hematologic function. Patients had to be treatment-naive, and all patients were required to have completed three cycles of IC with gemcitabine plus cisplatin before enrolment. The key exclusion criteria included: tumor progression after IC; previous receipt of chemotherapy, radiotherapy, or surgery (except diagnostic) to the nasopharynx or neck; a history of cancer; lactation or pregnancy; severe coexisting illness; or requiring palliative treatment. The trial protocol was approved by the institutional ethics committee at each participating center. All participants provided written informed consent. Patient consent could be withdrawn post-enrolment at any time for any reason. Comprehensive details of the trial are provided in the protocol (see Supporting Information S2: Supporting Materials).

### Randomization and masking

Eligible patients were randomly assigned to receive reduced-volume radiotherapy (in the post-IC group) or conventional-volume radiotherapy (in the pre-IC group), at a 1:1 ratio in blocks of four and stratified by trial center and disease stage (III or IVA). Centralized randomization was performed at the Clinical Trials Center of Sun Yat-sen University Cancer Center (Guangzhou, China). Random assignment was generated by using a computerized, randomized list generator. Treatment group assignment was not masked to the patients or physician, although it was masked to the Central Imaging Review Committee (CIRC) and the statisticians. The block structure was known only to the statistician and the study coordinator, who were not involved clinically in the trial. Rigorous quality-control measures were implemented to ensure the scientific integrity of the trial (see Supporting Information S1: Supporting Methods, p. 11–12).

### Procedures

Intensity-modulated radiotherapy was required for all patients. The definition of radiotherapy target volumes was done according to the

International Commission on Radiation Units and Measurements (ICRU) reports 50 and 62.[16,17] The gross tumor volume (GTV) contained the primary tumor (GTVnx) and the involved cervical lymph nodes (GTVnd) that would receive the full prescribed radical dose of irradiation and was delineated according to the allocation group. In the post-IC group, the GTVnx was delineated based on post-IC magnetic resonance imaging (MRI), which included only the residual soft tissue mass of the nasopharynx for patients without initial bony structural invasion. However, in patients with initial bony structural invasion, the involved bony structures were delineated based on pre-IC imaging to ensure that all initial disease within the bone was encompassed regardless of signal changes after induction, although the soft tissue component of the GTVnx was still delineated based on postinduction MRI. The GTVnd was delineated based on post-IC imaging. In patients without bone invasion, if no tumor signal was detected after induction, as confirmed by the CIRC, the GTVnx would not be delineated for the post-IC group. The GTVnd would not be delineated for any lymph node with complete resolution on the post-IC MRI for the post-IC group. Instead, the high-risk clinical target volume (CTV) covered the originally involved fat space.

In the pre-IC group, the GTV would be delineated based on pre-IC MRI and should include all structures that tumor involved before IC, even if they are no longer grossly involved. And pre-treatment $^{18}$F-fluorodeoxyglucose examination was also used for delineation when available. Detailed delineation methods, including skull base invasion, paranasal sinus invasion, parapharyngeal muscle invasion, etc., are shown in Figures S1–S9.

The high-risk CTV was defined as the GTVnx plus a margin of 5–10 mm (2–3 mm posteriorly if adjacent to the brainstem or spinal cord) and the GTVnd plus a margin of 3–5 mm. In addition, in the post-IC group, the volume should encompass all tumor volume before IC. The low-risk CTV was defined as the high-risk CTV plus a margin of 5–10 mm (2–3 mm posteriorly if adjacent to the brainstem or spinal cord). The planning target volume was defined as the GTV or CTV plus a margin of 3–5 mm. The prescribed doses were 70 grays (Gy) to the primary tumor, 66–70 Gy to the cervical lymph nodes, 60–62 Gy to the high-risk CTV, and 54–56 Gy to the low-risk CTV in 30–33 fractions (once daily, five fractions every week). To ensure the quality of the trial, the research team at the Sun Yat-sen University Cancer Center reviewed all radiotherapy plans. During radiotherapy, two or three cycles of concurrent cisplatin were administered intravenously at a dose of 100 mg/m$^2$ every 3 weeks. Details of the radiotherapy and chemotherapy are provided in Supporting Information S1: Supporting Methods (p. 3–8).

In this trial, essential baseline evaluations were required within 2 weeks before IC (see Supporting Information S1: Supporting Methods, p. 3). At day 7 after IC completion, and at week 16 after chemoradiotherapy, nasopharyngoscopy was used to assess the primary tumor. Acute toxicity was assessed using the National Cancer Institute's Common Toxicity Criteria, version 4.0, and radiation-related late toxicities were assessed according to the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer (EORTC) late-radiation morbidity scoring scheme.[18] The EORTC Quality-of-Life Core 30-item questionnaire (QLQ-C30), version 3.0, and the Quality-of-Life Head and Neck 35-item questionnaire (QLQ-H&N35), version 1.0, were used to evaluate QoL during follow-up.

Patients were followed at 3-month intervals for the first 3 years and then at 6 month intervals until death (see Supporting Information S1: Supporting Methods, p. 8–9). The initial radiologic examination and Epstein–Barr virus DNA test were performed 3 months after the completion of treatment. Subsequently, these tests were conducted at least once every 6 months for the next 3 years and annually thereafter. Physical examinations were scheduled every 3 months during the first 3 years and every 6 months thereafter. Whenever possible, histology was used to confirm distant or locoregional relapses. In patients for whom histologic confirmation was medically contraindicated or technically infeasible, the CIRC confirmed relapses while blinded to treatment assignment by using at least two imaging methods. For those patients who were lost to follow-up, mortality information was obtained from their death certificates.

## Outcomes

The primary end point was locoregional relapse-free survival, defined as the time from randomization to either documented local and/or regional relapse or death from any cause (except for metastasis), whichever occurred first. Secondary end points were overall survival, distant metastasis-free survival, failure-free survival, radiation-related toxicity profile, and QoL (see Supporting Information S1: Supporting Methods, p. 9–10). If a patient's first relapse event was a locoregional relapse, they were censored for distant metastasis analysis, and vice versa. If both distant and locoregional relapses occurred simultaneously, patients were designated as having events for both distant metastasis-free survival and locoregional relapse-free survival analyses. Patients were censored at the last follow-up visit if they remained alive without any treatment failure or if they were lost to follow-up.

## Statistical analysis

This trial was designed to determine whether reduced-volume radiotherapy would be noninferior in terms of 3-year locoregional relapse-free survival compared with conventional-volume radiotherapy. In both groups, locoregional relapse-free survival at 3 years was assumed to be 92% on the basis of previous data.[2] We set the noninferiority margin at 8% based on expert consensus, institutional experience, and published studies.[19–22] Consequently, to demonstrate noninferiority, the lower boundary of the 95% confidence

interval (CI) for the difference in 3-year locoregional relapse-free survival rate between the two groups must not exceed −8%. With 80% power and a 5% one-sided type I error, at least 435 patients were required to allow for a 5% loss to follow-up or dropout.

Efficacy analyses were performed in the intention-to-treat population and were repeated in the per-protocol population. The safety analyses were done in the safety population. All patients who started the randomly assigned treatment were included in the per-protocol and safety populations. An independent data monitoring committee was assembled in this trial and reviewed the efficacy and safety data to determine whether the trial design should be modified every 6 months. No protocol-mandated interim analysis was done in our trial for noninferiority.[23]

The Kaplan–Meier method was used to calculate time-to-event outcomes with log-rank tests for comparisons between groups. The results were stratified according to disease stage and trial center. Patients were censored at the last follow-up visit if they remained alive without any treatment failure or were lost to follow-up. A *z* test was used to estimate the difference in the 3-year survival rate between the two groups. The hazard ratios (HRs) and 95% CIs were calculated with a stratified Cox proportional hazards model (using treatment as a single covariate), in which the assumptions of proportional hazards were confirmed using Schoenfeld residuals.[24]

A Cox proportional hazards model further evaluated treatment-by-covariate interaction based on the intention-to-treat population to ascertain whether the treatment effect was different among the prespecified patient subgroups; interactions with age, sex, tumor categories, lymph node categories, and disease stages. A Cox proportional hazard model was also used for multivariable analyses to identify significant independent factors. We summarized acute and late toxicities according to frequency and severity.

Analyses of QoL were performed in patients who were without disease relapse or metastasis in the safety population. The Supporting Information S1: Supporting Methods (p. 10) detail the analytical methods used for patient-reported outcomes. Post-hoc analyses of locoregional relapse-free survival were conducted between patients with or without baseline plasma Epstein–Barr virus DNA testing and between those with or without baseline $^{18}$F-fluorodeoxyglucose PET/CT examination. In addition, a post-hoc analysis also was done to test the primary hypothesis in patients who had different baseline Epstein–Barr virus DNA levels (with a cutoff of 2000 copies/mL chosen based on our previous study[25]).

SPSS (version 27.0; IBM Corporation) or R (version 4.3.0; R Foundation for Statistical Computing) software were used for all analyses. A one-sided statistical test was used for a noninferiority test of locoregional relapse-free survival, with $p$ values $< .05$ indicating statistical significance. All other statistical tests were two-sided, with the same significant $p$ value. The key raw data underlying this study were uploaded to the Research Data Deposit public platform (RDDA2025934346). This study is registered with ClinicalTrials.gov, NCT04384627.

## RESULTS

### Participants and treatment

Between August 7, 2020, and May 27, 2022, we enrolled and randomly assigned 445 patients to the post-IC group ($n = 225$) or the pre-IC group ($n = 220$; Figure 1). Baseline characteristics were well balanced between the groups (Table 1). Most patients ($n = 354$; 80%) were treated with a volumetric-modulated arc therapy technique. All patients underwent daily guided imaging with either cone-beam computed tomography ($n = 319$; 72%) or kilovoltage orthogonal imaging ($n = 126$; 28%). The proportions of those who underwent volumetric-modulated arc therapy and an image-guided modality did not differ between the study groups (see Table S2).

Of the 445 patients who underwent randomization, 222 of 225 (98.7%) in the post-IC group and 220 of 220 (100%) in the pre-IC group started protocol-defined radiotherapy and were included in the safety population (Figure 1). Three of 225 patients (1.3%) who had been assigned to the post-IC group withdrew their consent and received conventional-volume radiotherapy. Two patients (0.9%) in the post-IC group discontinued radiotherapy before completion, one (0.4%) because of dermatomyositis and the other was because of suicidal tendency. In the post-IC group, four of 225 patients (1.8%) patients discontinued concurrent cisplatin, of whom two (0.9%) received nedaplatin-concurrent chemotherapy instead. In the pre-IC group, three of 220 patients (1.4%) discontinued concurrent cisplatin, of whom two (0.9%) received nedaplatin-concurrent chemotherapy instead. Details of the chemotherapy and radiotherapy received are provided in Table S3.

### Dosimetry

The mean ± standard deviation GTVs were smaller in the post-IC group compared with those in the pre-IC group (66.6 ± 34.8 vs. 80.9 ± 39.7 $cm^3$; $p < .001$). The mean ± standard deviation GTVnx (50.6 ± 29.9 vs. 60.8 ± 35.6 $cm^3$; $p = .002$) and GTVnd (15.9 ± 17.3 vs. 20.4 ± 20.4 $cm^3$; $p = .02$) values also were smaller in the post-IC group. No difference was observed in the radiation dose delivered to the GTV. Furthermore, the dose delivered to the surrounding functional structures was significantly reduced in the post-IC group, represented by the inner ear, middle ear, parotid, and temporal lobe. The detailed dose and volume statistics are provided shown in Table S11.

### Efficacy

After a median follow-up of 40.4 months (interquartile range, 36.4–44.8 months), locoregional relapse was recorded in 38 of 445 patients (8.5%; $n = 17$ [7.6%] in the post-IC group vs. $n = 21$ [9.5%] in the pre-IC group). Based on the intention-to-treat population, the 3-year locoregional relapse-free survival rate was 91.5% (95% CI, 87.9%–95.4%) in the post-IC group compared with 91.2% (95% CI,

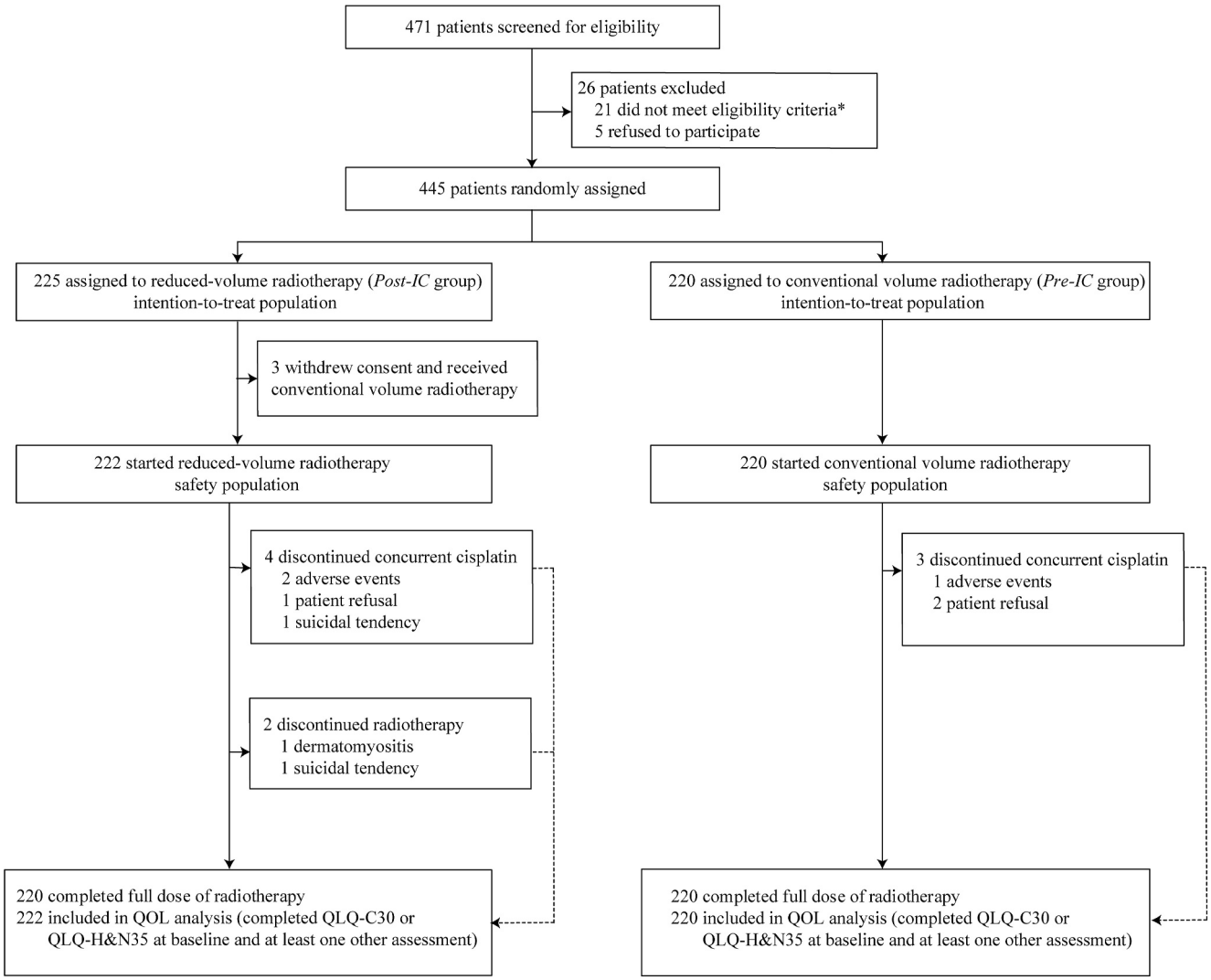


**FIGURE 1** Flowchart of screening, randomization, and treatment. The intention-to-treat population comprised all randomly assigned patients. The safety population comprised all patients who received at least one fraction of their allocated radiotherapy schedule. *Four patients had disease progression after induction chemotherapy, four underwent previous therapeutic surgery to the neck or nasopharynx, three were without adequate hematologic function, two were without adequate renal function, two were without adequate liver function, two with lactation, two with previous malignancy, one with symptomatic heart failure, and one with symptomatic asthma. IC indicates induction chemotherapy; QLQ-C30, the European Organization for Research and Treatment of Cancer Quality-of-Life Core 30-item questionnaire; QLQ-H&N35, the European Organization for Research and Treatment of Cancer Quality-of-Life Head and Neck 35-item questionnaire; QOL, quality of life.

87.5%–95.1%) in the pre-IC group, with a difference of 0.3% (95% CI, −4.9%, 5.5%); the stratified HR was 0.82 (95% CI, 0.44–1.50; Figure 2A). The Schoenfeld test *p* value for locoregional relapse-free survival was 0.99 (see Table S10). The per-protocol analysis produced similar results: the 3-year locoregional relapse-free survival rate was 91.4% (95% CI, 87.7%–95.3%) in the post-IC group compared with 91.2% (95% CI, 87.5%–95.1%) in the pre-IC group, with a difference of 0.2% (95% CI, −5.1%, 5.5%), and the unstratified HR was 0.82 (95% CI, 0.45–1.51).

At the last follow-up, 18 of 445 patients (4.0%) had died ($n = 10$ [4.4%] in the post-IC group vs. $n = 8$ [3.6%] in the pre-IC group). The 3-year overall survival rate was 96.8% (95% CI, 94.4%–99.2%) in the post-IC group versus 96.7% (95% CI, 94.3%–99.1%) in the pre-IC group, with a stratified HR of 1.22 (95% CI, 0.48–3.10; Figure 2B); the 3-year distant metastasis-free survival rate was 91.7% (95% CI, 88.0%–95.4%) in the post-IC group versus 93.3% (95% CI, 89.9%–96.8%) in the pre-IC group, with a stratified HR of 1.27 (95% CI, 0.63–2.55; Figure 2C); and the 3-year failure-free survival rate was 85.1% (95% CI, 80.4%–90.0%) in the post-IC group versus 85.9% (95% CI, 81.4%–90.8%) in the pre-IC group, with a stratified HR of 0.96 (95% CI, 0.60–1.55; Figure 2D). Schoenfeld residuals analysis confirmed that the proportionality assumption was not violated

**TABLE 1** Baseline characteristics.

| Characteristic | No. (%) | | $p^b$ |
|---|---|---|---|
| | Post-IC, $n = 225$ | Pre-IC, $n = 220$ | |
| Sex | | | 0.10 |
| Male | 164 (72.9) | 175 (79.5) | |
| Female | 61 (27.1) | 45 (20.5) | |
| Age, Median [IQR], years | 46 (37, 53) | 47 (39, 53) | 0.52[c] |
| Karnofsky performance score | | | 0.59 |
| 70–80 | 15 (6.7) | 12 (5.5) | |
| 90–100 | 210 (93.7) | 208 (94.5) | |
| Histology | | | 0.25 |
| WHO grade 2 | 16 (7.1) | 10 (4.5) | |
| WHO grade 3 | 209 (92.9) | 210 (95.5) | |
| Tumour category[a] | | | 0.70 |
| T1–2 | 27 (12.0) | 22 (10.0) | |
| T3 | 124 (55.1) | 129 (58.6) | |
| T4 | 74 (32.9) | 69 (31.4) | |
| Nodal category[a] | | | 0.11 |
| N0–1 | 91 (40.4) | 68 (30.9) | |
| N2 | 64 (28.4) | 74 (33.6) | |
| N3 | 70 (31.1) | 78 (35.5) | |
| Stage[a] | | | 0.99 |
| III | 94 (41.7) | 92 (41.8) | |
| IVA | 131 (58.2) | 128 (58.2) | |
| Pre-treatment EBV DNA test | 219 (97.3) | 215 (97.7) | 0.79 |

Abbreviations: EBV, Epstein-Barr virus; IC, induction chemotherapy; IQR, interquartile range; RT, radiotherapy; WHO, World Health Organization.
[a]According to the 8th edition of American Joint Committee on Cancer–Union for International Cancer Control stage classification system.
[b]*p*-values were calculated using unadjusted $\chi^2$ tests, unless specified noticed.
[c]Calculated using Mann–Whitney *U* test.

($p = .81$ for overall survival; $p = .86$ for distant metastasis-free survival, and $p = .95$ for failure-free survival; see Figure S10). Details of the locoregional relapse, death, distant metastasis and treatment failure are summarized in Table 2. The results of the per-protocol analysis were similar to those of the intention-to-treat analysis: the 3-year overall survival rate was 96.7% (95% CI, 94.3%–99.1%) in the post-IC group versus 96.7% (95% CI, 94.3%–99.1%) in the pre-IC group, with an unstratified HR of 1.26 (95% CI, 0.50–3.18); the 3-year distant metastasis-free survival rate was 92.0% (95% CI, 88.4%–95.7%) in the post-IC group versus 93.3% (95% CI, 89.9%–96.8%) in the pre-IC group, with an unstratified HR of 1.23 (95% CI, 0.60–2.49); and the 3-year failure-free survival rate was 85.3% (95% CI, 80.7%–90.3%) in the post-IC group versus 85.9% (95% CI, 81.4%–90.8%) in the pre-IC group, with an unstratified HR of 0.94 (95% CI, 0.58–1.52).

## Adverse events and quality of life

In the safety population, no substantial differences in acute chemotherapy-related toxic effects were observed in the two groups (Table 3). However, there was a significantly reduced incidence of acute radiation-related toxicities in post-IC group, including grade 3 or 4 mucositis ($n = 44$ [19.8%] vs. $n = 75$ [34.1%]; $p < .001$) and grade 3 dry mouth ($n = 9$ [4.1%] vs. $n = 19$ [8.6%]; $p = .048$). Patients in the post-IC group also had a lower incidence of late radiation toxicities, including grade 3 or 4 otitis media ($n = 21$ [9.5%] vs. $n = 46$ [20.9%]; $p < .001$), hearing impairment ($n = 9$ [4.1%] vs. $n = 20$ [9.1%]; $p = .03$), and grade 3 dry mouth ($n = 8$ [3.6%] vs. $n = 21$ [9.5%]; $p = .01$).

In the safety population, the two groups had comparable baseline QoL scores (see Tables S13 and S14). Among the 282 of 442 patients

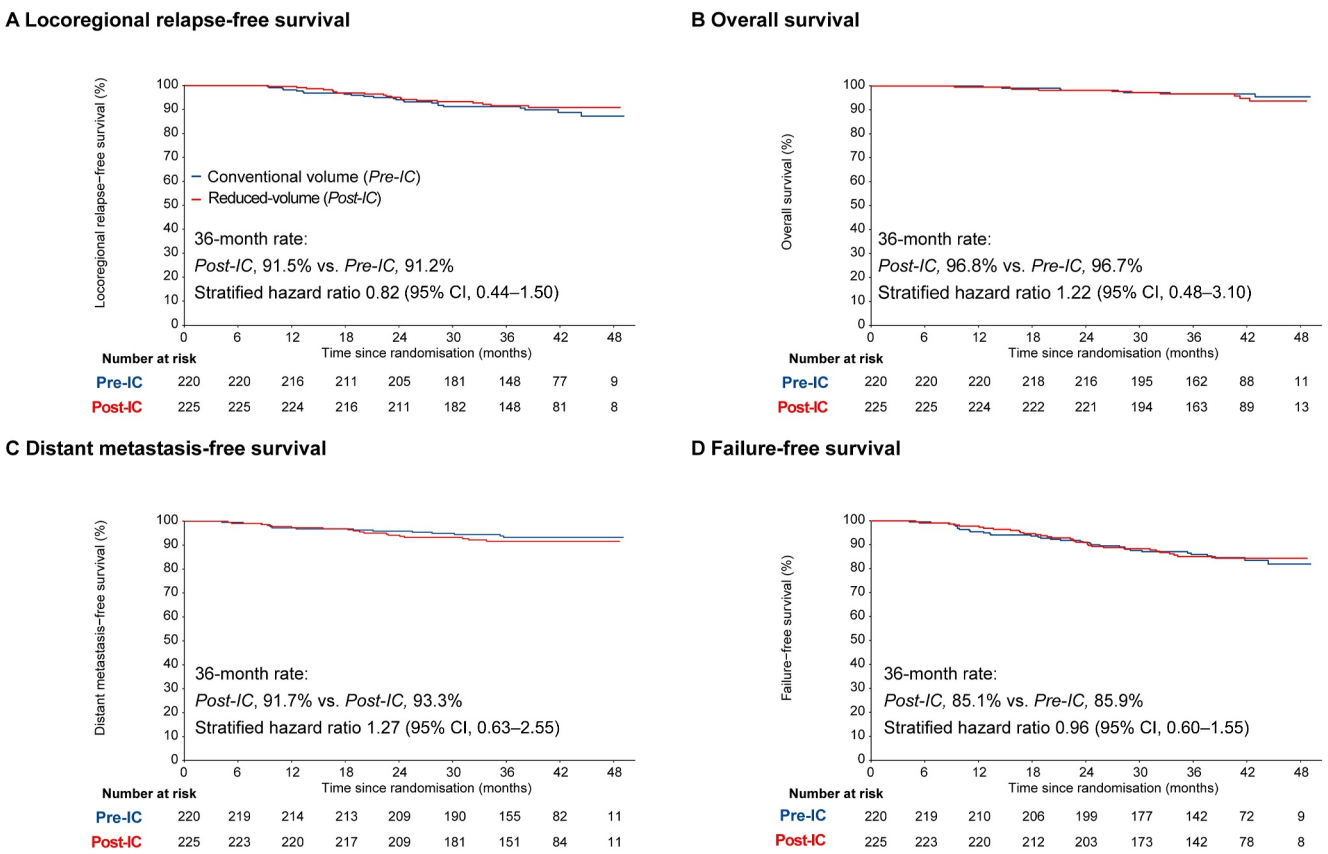


**FIGURE 2** Kaplan–Meier curves of (A) locoregional relapse-free survival, (B) overall survival, (C) distant metastasis-free survival, (D) and failure–free survival in the intention-to-treat population. A stratified Cox proportional-hazards model was used to calculate the hazard ratios and their associated 95% CIs. The stratified log-rank test was used to calculate *p* values. All stratified analyses used the same stratification factors that were used for randomization (center and stage). CI indicates confidence interval; IC, induction chemotherapy.

(63.8%) who were disease free and completed the 3-year follow-up, 274 (62.0%) completed the EORTC QLQ-C30 questionnaire, and 273 (61.8%) completed the QLQ-H&N35 questionnaire. Compared with baseline scores, the post-IC group had significantly better QoL outcomes for global health status (difference, 6.8 [95% CI, 1.9–1.6]; $p = .005$), physical functioning (difference, 3.5 [95% CI, 0.3–6.8]; $p = .005$), and emotional functioning (difference, 4.5 [95% CI, 0.1–8.9]; $p = .02$) on the QLQ-C30 scale and for dry mouth (difference, −8.4 [95% CI, −14.3, −2.4]; $p = .02$) and sticky saliva (difference, −7.1 [95% CI, −12.5, −1.6]; $p = .04$) on the QLQ-H&N35 scale at 3 years (Table 4).

## DISCUSSION

In this phase 3, multicenter, randomized controlled trial, we observed that reduced-volume radiotherapy based on post-IC tumor volume (the post-IC group) was noninferior to conventional-volume radiotherapy based on pre-IC tumor volume (the pre-IC group) in patients with nasopharyngeal carcinoma who received IC. We observed fewer radiation-related acute and late toxicities and improved QoL in the post-IC group.

Current consensus on radiotherapy target volume for nasopharyngeal carcinoma after IC was proposed in 2018 and indicates that the pre-IC tumor volume should receive the full radical dose regardless of volume shrinkage.[6] However, that consensus was proposed based on the experience in head and neck cancer, and robust data were lacking. Nasopharyngeal carcinoma has unique characteristics in biologic behavior, clinical manifestations, and response to chemoradiotherapy, leading investigators to reassess the current consensus on radiotherapy.[26]

The advantages of reduced-volume radiotherapy lie in the noninferiority of survival and the superiority of toxicities and QoL. The noninferiority of survival was achieved because of the inherent characteristics of the trial. Generally, the enlargement and peripheral invasion of the tumor lesion conform to the principle of the tumor's clonogenic density, increasing gradually from subclinical, to microscopic, to clinically detectable lesions, which require increased irradiation doses from 54–56 Gy, to 60–62 Gy, and to 66–70, Gy respectively.[27] With the significant efficacy of IC in tumor shrinkage,

**TABLE 2** Distribution of disease failure.

| | No. of events (%) | | |
|---|---|---|---|
| **Event** | **Post-IC group, *n* = 225** | **Pre-IC group, *n* = 220** | ***p*[a]** |
| Locoregional | 17 (7.6) | 21 (9.5) | 0.45 |
| Local | 10 (4.4) | 13 (5.9) | 0.49 |
| Regional | 9 (4.0) | 13 (5.9) | 0.36 |
| Distant | 16 (7.1) | 12 (5.5) | 0.47 |
| Lung | 10 (4.4) | 6 (2.7) | 0.33 |
| Bone | 3 (1.3) | 4 (1.8) | 0.72[b] |
| Liver | 7 (3.1) | 4 (1.8) | 0.38 |
| Other | 4 (1.8) | 1 (0.5) | 0.37[b] |
| Multiple | 6 (2.7) | 2 (0.9) | 0.29[b] |
| Death | 10 (4.4) | 8 (3.6) | 0.67 |
| Cancer-specific | 8 (3.6) | 6 (2.7) | 0.62 |
| Noncancer-specific | 2 (0.9) | 2 (0.9) | 1.00[b] |
| Accident | 2 (0.9) | 1 (0.5) | 1.00[b] |
| COVID-19 | 0 (0.0) | 1 (0.5) | — |
| Any events | 31 (13.8) | 32 (14.5) | 0.82 |
| Local alone | 8 (3.6) | 8 (3.6) | 0.96 |
| Regional alone | 5 (2.2) | 8 (3.6) | 0.38 |
| Distant alone | 14 (6.2) | 11 (5.0) | 0.58 |
| Local and regional | 2 (0.9) | 5 (2.3) | 0.28[b] |
| Local and distant | 0 (0.0) | 1 (0.5) | — |
| Regional and distant | 2 (0.9) | 1 (0.5) | 1.00[b] |

Abbreviations: COVID-19, coronavirus disease 2019; IC, induction chemotherapy.

[a]All *p* values were calculated using unadjusted $\chi^2$ tests, unless otherwise specified.

[b]Calculated using the Fisher exact test.

some clinically detectable lesions could be reduced to microscopic or subclinical disease and required a lower radiation dose. In our trial, we ensured that all clinically detectable lesions after IC received at least 66 Gy of irradiation (70 Gy for the GTVnx and 66–70 Gy for the GTVnd). Because there is great difficulty in accurately assessing the extent of tumor within bony structures after IC, and because tumor signals in bone do not usually recover in time after IC,[28] our trial incorporated bone structures that had tumor invasion into the GTV, and such tumors received at least 70 Gy of irradiation. For other structures that had reduced tumor volume after IC, our trial ensured a minimum of 60 Gy of irradiation to guarantee that subclinical or microscopic lesions received an adequate dose. Despite a lack of shrinkage in the superior and posterior directions within the bony structures, the significant reduction in the soft tissue component of the GTV in the other directions resulted in significant improvements in parotid gland-related and inner ear-related symptoms observed in the post-IC group in our trial.

With regard to the superiority of toxicities and QoL, reducing the range of the radical irradiation dose to the post-IC tumor volume inevitably led to a reduced radiation dose to surrounding structures. For toxicities, a significant reduction in late grade 3 or higher otitis media was observed in our trial. These reductions are clinically vital for patients who have nasopharyngeal carcinoma because the otitis media caused by radiation is usually an irreversible morbidity that may lead to social and emotional dysfunction or mental disorders, thus decreasing the QoL causing disability.[29–31] In addition, a significant decrease in acute mucositis was also observed. Mucositis is the most common acute toxic during radiotherapy, leading to weight loss and reduced QoL.[32,33] In our trial, reduced-volume radiotherapy reduced the incidence of grade 3 or higher mucositis by almost 15%,

**TABLE 3** Acute and late treatment-related toxicities.

| | No. (%) | | | | | |
|---|---|---|---|---|---|---|
| | Post-IC group, $n = 222$ | | Pre-IC group, $n = 220$ | | $p$[a] | |
| | Grade 1 or 2 | Grade 3 or 4 | Grade 1 or 2 | Grade 3 or 4 | Grade ≥1 | Grade ≥3 |
| Any acute toxicities | | | | | | |
| Leukopenia | 142 (64.0) | 21 (9.5) | 129 (58.6) | 19 (8.6) | 0.16 | 0.76 |
| Neutropenia | 97 (43.7) | 8 (3.6) | 103 (46.8) | 8 (3.6) | 0.51 | 0.99 |
| Anemia | 206 (92.8) | 10 (4.5) | 195 (88.6) | 13 (5.9) | 0.14 | 0.51 |
| Thrombocytopenia | 47 (21.2) | 7 (3.2) | 42 (19.1) | 9 (4.1) | 0.78 | 0.60 |
| Nausea | 179 (80.6) | 7 (3.2) | 181 (82.3) | 2 (0.9) | 0.87 | 0.18[b] |
| Vomiting | 129 (58.1) | 9 (4.1) | 141 (64.1) | 6 (2.7) | 0.31 | 0.44 |
| Elevated transaminase levels | 20 (9.0) | 0 (0.0) | 25 (11.4) | 1 (0.5) | 0.33 | 0.50[b] |
| Mucositis | 172 (77.5) | 44 (19.8) | 143 (65.0) | 75 (34.1) | 0.16 | < .001[c] |
| Dry mouth | 203 (91.4) | 9 (4.1) | 192 (87.3) | 19 (8.6) | 0.83 | 0.048[c] |
| Dysphagia | 206 (92.8) | 6 (2.7) | 202 (91.8) | 11 (5.0) | 0.47 | 0.21 |
| Weight loss | 151 (68.0) | 5 (2.3) | 170 (77.3) | 3 (1.4) | 0.04[b] | 0.50[b] |
| Trismus | 7 (3.2) | 0 (0.0) | 7 (3.2) | 0 (0.0) | 0.99 | — |
| Any late toxicities | | | | | | |
| Skin | 46 (20.7) | 0 (0.0) | 58 (26.4) | 0 (0.0) | 0.10 | — |
| Dysphagia | 134 (60.4) | 1 (0.5) | 136 (61.8) | 3 (1.4) | 0.61 | 0.37[b] |
| Hoarseness | 79 (35.6) | 0 (0.0) | 89 (40.5) | 0 (0.0) | 0.29 | — |
| Dry mouth | 195 (87.8) | 8 (3.6) | 187 (85.0) | 21 (9.5) | 0.20 | 0.01[c] |
| Trismus | 14 (6.3) | 0 (0.0) | 17 (7.7) | 0 (0.0) | 0.56 | — |
| Auditory/hearing | 138 (62.2) | 9 (4.1) | 147 (66.8) | 20 (9.1) | 0.03[c] | 0.03[c] |
| Otitis media | 135 (60.8) | 21 (9.5) | 124 (56.4) | 46 (20.9) | 0.09 | < .001[c] |
| Temporal lobe injury | 13 (5.9) | 0 (0.0) | 27 (12.3) | 0 (0.0) | 0.02[c] | — |
| Osteonecrosis | 7 (3.2) | 0 (0.0) | 7 (3.2) | 0 (0.0) | 0.99 | — |

*Note*: The safety analyses were done in the safety population, comprising all patients who commenced the randomly assigned treatment.

Abbreviation: IC, induction chemotherapy.

[a]All $p$ values were calculated using $\chi^2$ tests unless otherwise specified.

[b]These $p$ values were calculated using the Fisher exact test.

[c]This $p$ value indicates a statistically significant difference.

which, in turn, reduced weight loss in about 10% of patients and improved their QoL. The main findings of our study are consistent with those of the trial initially reported by Yang et al. and updated by Xiang et al., with a larger sample size and more comprehensive late toxicity assessment and addition of QoL evaluation. We also used a relatively reduced dose to the high-risk CTV, which encompassed the pre-IC GTV (60 Gy vs. 64 Gy to the post-IC GTV). The similarities and differences of the two trials are summarized in Table S15.

The main limitation of our study is that this trial was conducted in an endemic area of nasopharyngeal carcinoma, and almost all patients had tumors with WHO grade 3 histology and related Epstein–Barr virus infection. Therefore, for patients in nonendemic areas, applicability of the current finding remains unclear. However, similar treatment responses have been observed, especially in those with nasopharyngeal carcinoma related to Epstein–Barr virus.[34]

In conclusion, our trial provides robust data establishing that reduced-volume radiotherapy based on the post-IC tumor volume is a safe method for locoregional control with reduced toxicity and improved QoL, suggesting that, for nondistant metastatic and non-keratinizing nasopharyngeal carcinoma, reduced-volume

**TABLE 4** Changes in quality-of-life scores from baseline to 3 years after treatment.

| | Mean score ± SD | | | |
|---|---|---|---|---|
| | Post-IC group | Pre-IC group | Difference (95% CI) | p[a] |
| EORTC QLQ-C30: General quality of life [the higher the better][b] | | | | |
| Global health status | 8.0 ± 17.9 | 1.3 ± 22.5 | 6.8 (1.9–11.6) | 0.005[c] |
| Physical functioning | 4.8 ± 10.8 | 1.2 ± 16.1 | 3.5 (0.3–6.8) | 0.005[c] |
| Role functioning | 6.7 ± 18.2 | 7.7 ± 20.8 | −1.0 (−5.7, 3.6) | 0.96 |
| Emotional functioning | 6.5 ± 14.0 | 2.0 ± 22.1 | 4.5 (0.1–8.9) | 0.02[c] |
| Cognitive functioning | 1.0 ± 13.8 | 1.0 ± 18.1 | 0.0 (−3.8, 3.9) | 0.60 |
| Social functioning | 9.5 ± 19.2 | 10.6 ± 24.2 | −1.0 (−6.2, 4.1) | 0.67 |
| Symptom burden [the lower the better] | | | | |
| Fatigue | −12.3 ± 17.0 | −10.1 ± 24.1 | −2.2 (−7.2, 2.8) | 0.31 |
| Nausea and vomiting | −9.6 ± 16.7 | −10.8 ± 21.9 | 1.2 (−3.5, 5.8) | 0.78 |
| Pain | −1.6 ± 12.7 | −0.8 ± 14.9 | −0.8 (−4.1, 2.5) | 0.79 |
| Dyspnea | −6.4 ± 18.0 | −2.6 ± 22.4 | −3.8 (−8.6, 1.0) | 0.13 |
| Insomnia | −2.2 ± 23.1 | −5.5 ± 24.9 | 3.3 (−2.4, 9.0) | 0.57 |
| Appetite loss | −14.6 ± 21.8 | −18.9 ± 26.6 | 4.4 (−1.4, 10.2) | 0.23 |
| Constipation | −3.2 ± 19.5 | −6.2 ± 20.3 | 3.0 (−1.7, 7.8) | 0.34 |
| Diarrhea | −1.7 ± 11.0 | −0.5 ± 11.3 | −1.2 (−3.9, 1.4) | 0.44 |
| Financial difficulties | −11.1 ± 28.8 | −10.6 ± 31.6 | −0.6 (−7.7, 6.6) | 0.96 |
| EORTC QLQ-H&N35: Symptom burden [the lower the better][d] | | | | |
| Pain | 2.3 (7.8) | 2.1 (8.0) | −0.2 (−1.7 to 2.1) | 0.94 |
| Swallowing | 1.7 ± 6.0 | 1.8 ± 8.3 | 0.0 (−1.7, 1.7) | 0.83 |
| Sensory impairment, taste/smell | 4.3 ± 11.9 | 4.7 ± 12.2 | −0.4 (−3.3, 2.5) | 0.77 |
| Speech difficulties | 2.8 ± 9.2 | 2.8 ± 9.5 | 0.0 (−2.2, 2.2) | 0.70 |
| Difficulties in social eating | −2.3 ± 8.2 | −3.0 ± 11.8 | 0.7 (−1.7, 3.1) | 0.30 |
| Difficulties in social contact | −5.0 ± 11.3 | −4.8 ± 11.4 | −0.2 (−2.9, 2.5) | 0.96 |
| Less libido | −11.6 ± 25.3 | −8.1 ± 28.7 | −3.5 (−10.0, 2.9) | 0.31 |
| Dental problems | 9.4 ± 28.7 | 10.6 ± 21.3 | −1.2 (−7.3, 4.8) | 0.28 |
| Mouth opening problems | 1.0 ± 10.7 | 1.9 ± 11.9 | −0.9 (−3.6, 1.8) | 0.49 |
| Dry mouth | 15.6 ± 24.4 | 23.9 ± 25.8 | −8.4 (−14.3, −2.4) | 0.02[c] |
| Sticky saliva | 8.9 ± 20.4 | 15.9 ± 25.2 | −7.1 (−12.5, −1.6) | 0.04[c] |
| Coughing | 3.5 ± 13.7 | 5.6 ± 15.4 | −2.1 (−5.6, 1.4) | 0.25 |
| Feeling ill | −16.0 ± 25.4 | −16.9 ± 26.8 | 0.9 (−5.4, 7.1) | 0.75 |
| Requiring pain killers | −5.2 ± 33.1 | −13.0 ± 44.9 | 7.9 (−1.5, 4.5) | 0.09 |
| Requiring nutrition supplements | −23.7 ± 53.5 | −15.9 ± 57.0 | −7.8 (−20.9, 5.4) | 0.28 |
| Requiring a feeding tube | 0.7 ± 8.6 | 0.7 ± 8.5 | 0.0 (−2.0, 2.1) | 0.99 |
| Weight loss | −54.8 ± 54.3 | −62.3 ± 52.9 | 7.5 (−5.3, 20.3) | 0.22 |
| Weight gain | 23.7 ± 49.2 | 30.4 ± 52.1 | −6.7 (−18.8, 5.3) | 0.26 |

*Note*: A higher score indicates greater symptom severity (on symptom domains) or better health status (on global health status) or function (on functioning domains).

Abbreviations: CI, confidence interval; IC, induction chemotherapy; QLQ-C30, the European Organization for Research and Treatment of Cancer Quality-of-Life Core 30-item questionnaire; QLQ-H&N35, the European Organization for Research and Treatment of Cancer Quality-of-Life Head and Neck 35-item questionnaire; SD, standard deviation.

[a]All *p* values were calculated using the Mann–Whitney *U* test.

[b]*N* = 135 for the post-IC group, and *N* = 139 for the pre-IC group.

[c]This *p* value indicates a statistically significant difference.

[d]*N* = 135 for the post-IC group, and *N* = 138 for the pre-IC group.

radiotherapy after IC as a valid option to be considered in future treatment guidelines.

## AUTHOR CONTRIBUTIONS

**Ling-Long Tang**: Study conception and design; acquired, analyzed, or interpreted the data; verified the underlying data; statistical analysis and interpretation; toxicity and data review; writing–original draft; supervision, quality assessment; and obtained funding. **Lin Chen**: Acquired, analyzed, or interpreted the data; writing–original draft; quality assessment; writing–review and editing; and supervision. **Gui-Qiong Xu**: Acquired, analyzed, or interpreted the data; writing–original draft; supervision, and quality assessment. **Ning Zhang**: Acquired, analyzed, or interpreted the data and writing–original draft. **Cheng-Long Huang**: Acquired, analyzed, or interpreted the data and writing–original draft. **Wen-Fei Li**: Clinical trial design and recruitment; treatment of patients; data and trial management; acquired, analyzed, or interpreted the data; and writing–review and editing. **Yan-Ping Mao**: Clinical trial design and recruitment; treatment of patients; data and trial management; acquired, analyzed, or interpreted the data; and writing–review and editing. **Guan-Qun Zhou**: Clinical trial design and recruitment; treatment of patients; data and trial management; acquired, analyzed, or interpreted the data; and writing–review and editing. **Feng Lei**: Clinical trial design and recruitment; treatment of patients; data and trial management; acquired, analyzed, or interpreted the data; and writing–review and editing. **Lu-Si Chen**: Clinical trial design and recruitment; treatment of patients; data and trial management; acquired, analyzed, or interpreted the data; and writing–review and editing. **Shao Hui Huang**: Acquired, analyzed, or interpreted the data and writing–review and editing. **Lei Chen**: Acquired, analyzed, or interpreted the data. **Yu-Pei Chen**: Acquired, analyzed, or interpreted the data. **Yuan Zhang**: Acquired, analyzed, or interpreted the data; statistical analysis and interpretation; and toxicity and data review. **Xu Liu**: Acquired, analyzed, or interpreted the data; statistical analysis and interpretation; and toxicity and data review. **Cheng Xu**: Acquired, analyzed, or interpreted the data. **Yin Zhao**: Acquired, analyzed, or interpreted the data. **Ji-Bin Li**: Acquired, analyzed, or interpreted the data; statistical analysis and interpretation; and toxicity and data review. **Na Liu**: Acquired, analyzed, or interpreted the data. **Fang-Yun Xie**: Study conception and design; acquired, analyzed, or interpreted the data; supervision; and quality assessment. **Rui Guo**: Study conception and design; acquired, analyzed, or interpreted the data; verified the underlying data; supervision; and quality assessment. **Ying Sun**: Study conception and design; acquired, analyzed, or interpreted the data; verified the underlying data; supervision; and quality assessment. **Jun Ma**: Study conception and design; acquired, analyzed, or interpreted the data; supervision; verified the underlying data; statistical analysis and interpretation; toxicity and data review; quality assessment; funding acquisition; and had final responsibility for submitting the article for publication. All authors had full access to all data in the study and critically revised the article for important intellectual content. Sun Yat-sen University participated in auditing and trial management.

## ACKNOWLEDGMENTS

We thank the patients who participated in this study, their families, and the medical, nursing, and research staff at the study centers. We also thank Feng-Ping Tang, Ying Wang, and Juan Liu (Department of Radiation Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China) for assistance with data management and logistic support. We thank the National Clinical Study Center and Sun Yat-sen University Cancer Center for trial monitoring and data management. We are grateful to Ye-Xiong Li (Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China), Xiao-Zhong Chen (Zhejiang Cancer Hospital, Hangzhou, China) and Ying Guo (Sun Yat-sen University Cancer Center, Guangzhou, China) for their contribution as members of the Independent Data Monitoring Committee. We are also grateful to Drs Hao-Jiang Li, Li Tian, and Li-Zhi Liu from Sun Yat-sen University Cancer Center, Guangzhou, China for their contributions as members of the Central Imaging Review Committee.

This is an investigator-initiated study supported by grants from the Noncommunicable Chronic Diseases-National Science and Technology Major Project (Grant 2024ZD0520701), the National Natural Science Foundation of China (Grant U24A20725; 82430085; 82172870), the Guangzhou Municipal Health Commission (Grant 2023P-GX04), the Cancer Innovative Research Program of Sun Yat-sen University Cancer Center (Grant CIRP-SYSUCC-0005; CIRP-SYSUCC-0046), the Sun Yat-sen University Clinical Research 5010 Program (Grant 2019014), the Audiology Development Foundation of China (Grant ADFC-XM-2022003), and the Overseas Expertise Introduction Project for Discipline Innovation (111 Project, Grant B14035).

## CONFLICT OF INTEREST STATEMENT

The authors declared no conflicts of interest.

## DATA AVAILABILITY STATEMENT

Data can be requested from the corresponding authors beginning 1 year after publication of the study. De-identified participant data can be available upon approval by the corresponding authors and Sun Yat-sen University Cancer Center. A detailed research protocol will be required to evaluate the reasonability of a request for data. The corresponding authors and Sun Yat-sen University Cancer Center reserve the right to decide whether or not to share the data based on the materials provided by researchers.

## ORCID

*Ling-Long Tang* https://orcid.org/0000-0002-8561-1454
*Lin Chen* https://orcid.org/0009-0000-0297-806X
*Cheng-Long Huang* https://orcid.org/0009-0007-9019-0280
*Wen-Fei Li* https://orcid.org/0000-0001-7605-3609
*Yu-Pei Chen* https://orcid.org/0000-0002-0010-3494
*Yuan Zhang* https://orcid.org/0000-0002-7141-1208
*Xu Liu* https://orcid.org/0000-0003-4827-5524
*Cheng Xu* https://orcid.org/0000-0002-4503-6029

*Yin Zhao* https://orcid.org/0000-0001-7007-2999
*Na Liu* https://orcid.org/0000-0001-8654-3636
*Fang-Yun Xie* https://orcid.org/0000-0003-4800-6025
*Rui Guo* https://orcid.org/0000-0003-1683-0837
*Ying Sun* https://orcid.org/0000-0002-5888-2929
*Jun Ma* https://orcid.org/0000-0002-1137-9349

## REFERENCES

1. 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. doi:10.1016/s1470-2045(16)30410-7
2. Zhang Y, Chen L, Hu GQ, et al. Gemcitabine and cisplatin induction chemotherapy in nasopharyngeal carcinoma. *N Engl J Med*. 2019;381(12):1124-1135. doi:10.1056/nejmoa1905287
3. Li WF, Chen NY, Zhang N, et al. Concurrent chemoradiotherapy with/without induction chemotherapy in locoregionally advanced nasopharyngeal carcinoma: long-term results of phase 3 randomized controlled trial. *Int J Cancer*. 2019;145(1):295-305. doi:10.1002/ijc.32099
4. Caudell JJ, Gillison ML, Maghami E, et al. NCCN Guidelines® Insights: Head and Neck Cancers, Version 1.2022. *J Natl Compr Canc Netw*. 2022;20(3):224-234. doi:10.6004/jnccn.2022.0016
5. Li Y, Bi J, Pi G, et al. Optimizing induction chemotherapy regimens for radiotherapy in patients with locoregionally advanced nasopharyngeal carcinoma. *Cancer Med*. 2023;12(8):9449-9457. doi:10.1002/cam4.5707
6. 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. doi:10.1016/j.radonc.2017.10.032
7. McDowell LJ, Rock K, Xu W, et al. Long-term late toxicity, quality of life, and emotional distress in patients with nasopharyngeal carcinoma treated with intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys*. 2018;102(2):340-352. doi:10.1016/j.ijrobp.2018.05.060
8. Zhao DW, Teng F, Meng LL, et al. Development and validation of a nomogram for prediction of recovery from moderate-severe xerostomia post-radiotherapy in nasopharyngeal carcinoma patients. *Radiother Oncol*. 2023;184:109683. doi:10.1016/j.radonc.2023.109683
9. Wen DW, Lin L, Mao YP, et al. Normal tissue complication probability (NTCP) models for predicting temporal lobe injury after intensity-modulated radiotherapy in nasopharyngeal carcinoma: a large registry-based retrospective study from China. *Radiother Oncol*. 2021;157:99-105. doi:10.1016/j.radonc.2021.01.008
10. Jiang W, Lv JW, Tang LL, Sun Y, Chen YP, Ma J. Enhancing efficacy and reducing toxicity: therapeutic optimization in locoregionally advanced nasopharyngeal carcinoma. *Cell Rep Med*. 2024;5(6):101594. doi:10.1016/j.xcrm.2024.101594
11. 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. doi:10.1016/j.radonc.2017.07.020
12. 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 Treat*. 2019;51(2):685-695. doi:10.4143/crt.2018.250
13. Zhao C, Miao JJ, Hua YJ, et al. Locoregional control and mild late toxicity after reducing target volumes and radiation doses in patients with locoregionally advanced nasopharyngeal carcinoma treated with induction chemotherapy (IC) followed by concurrent chemoradiotherapy: 10-year results of a phase 2 study. *Int J Radiat Oncol Biol Phys*. 2019;104(4):836-844. doi:10.1016/j.ijrobp.2019.03.043
14. Hahn E, Ng WT. Small changes, big impact: excitement and caution in dose and volume reduction for nasopharyngeal carcinoma radiation therapy after induction chemotherapy. *Int J Radiat Oncol Biol Phys*. 2023;117(4):925-927. doi:10.1016/j.ijrobp.2023.06.276
15. Xiang L, Rong JF, Xin C, et al. Reducing target volumes of intensity modulated radiation therapy after induction chemotherapy in locoregionally advanced nasopharyngeal carcinoma: long-term results of a prospective, multicenter, randomized trial. *Int J Radiat Oncol Biol Phys*. 2023;117(4):914-924.
16. International Commission on Radiation Units and Measurements (ICRU). Report 50, Prescribing, Recording, and Reporting Photon Beam Therapy. ICRU; 1993.
17. International Commission on Radiation Units and Measurements (ICRU). Report 62, Prescribing, Recording and Reporting Photon Beam Therapy (Supplement to ICRU 50). ICRU; 1999.
18. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys*. 1995;31(5):1341-1346. doi:10.1016/0360-3016(95)00060-c
19. Pong S, Urner M, Fowler RA, et al. Testing for non-inferior mortality: a systematic review of non-inferiority margin sizes and trial characteristics. *BMJ Open*. 2021;11(4):e044480. doi:10.1136/bmjopen-2020-044480
20. Tang LQ, Chen DP, Guo L, et al. Concurrent chemoradiotherapy with nedaplatin versus cisplatin in stage II–IVB nasopharyngeal carcinoma: an open-label, non-inferiority, randomised phase 3 trial. *Lancet Oncol*. 2018;19(4):461-473. doi:10.1016/s1470-2045(18)30104-9
21. Tang LL, Huang CL, Zhang N, et al. Elective upper-neck versus whole-neck irradiation of the uninvolved neck in patients with nasopharyngeal carcinoma: an open-label, non-inferiority, multicentre, randomised phase 3 trial. *Lancet Oncol*. 2022;23(4):479-490. doi:10.1016/s1470-2045(22)00058-4
22. Mao YP, Wang SX, Gao TS, et al. Medial retropharyngeal nodal region sparing radiotherapy versus standard radiotherapy in patients with nasopharyngeal carcinoma: open label, non-inferiority, multicentre, randomised, phase 3 trial. *BMJ*. 2023;380:e072133. doi:10.1136/bmj-2022-072133
23. Korn EL, Freidlin B. Interim monitoring for non-inferiority trials: minimizing patient exposure to inferior therapies. *Ann Oncol*. 2018;29(3):573-577. doi:10.1093/annonc/mdx788
24. Schoenfeld DA. Sample-size formula for the proportional-hazards regression model. *Biometrics*. 1983;39(2):499-503. doi:10.2307/2531021
25. Guo R, Tang LL, Mao YP, et al. Proposed modifications and incorporation of plasma Epstein–Barr virus DNA improve the TNM staging system for Epstein–Barr virus-related nasopharyngeal carcinoma. *Cancer*. 2019;125(1):79-89. doi:10.1002/cncr.31741
26. Cantù G. Nasopharyngeal carcinoma. A "different" head and neck tumour. Part A: from histology to staging. *Acta Otorhinolaryngol Ital*. 2023;43(2):85-98. doi:10.14639/0392-100x-n2222
27. Fletcher GH. Lucy Wortham James Lecture. Subclinical disease. *Cancer*. 1984;53(6):1274-1284. doi:10.1002/1097-0142(19840315)53:6<1274::aid-cncr2820530610>3.0.co;2-u

28. Lecouvet FE, Larbi A, Pasoglou V, et al. MRI for response assessment in metastatic bone disease. *Eur Radiol*. 2013;23(7):1986-1997. doi:10.1007/s00330-013-2792-3
29. Chen L, Li J, Li K, et al. Evaluation and analysis of risk factors of hearing impairment for nasopharyngeal carcinoma treated using intensity-modulated radiotherapy. *Radiother Oncol*. 2024;190:109985. doi:10.1016/j.radonc.2023.109985
30. Sommat K, Hussain A, Ong WS, et al. Clinical and dosimetric predictors of physician and patient reported xerostomia following intensity modulated radiotherapy for nasopharyngeal cancer—a prospective cohort analysis. *Radiother Oncol*. 2019;138:149-157. doi:10.1016/j.radonc.2019.05.023
31. Jereczek-Fossa BA, Zarowski A, Milani F, Orecchia R. Radiotherapy-induced ear toxicity. *Cancer Treat Rev*. 2003;29(5):417-430. doi:10.1016/s0305-7372(03)00066-5
32. Pulito C, Cristaudo A, Porta C, et al. Oral mucositis: the hidden side of cancer therapy. *J Exp Clin Cancer Res*. 2020;39(1):210. doi:10.1186/s13046-020-01715-7
33. Wang SZ, Wang WF, Zhang HY, Guo M, Hoffman MR, Jiang JJ. Analysis of anatomical factors controlling the morbidity of radiation-induced otitis media with effusion. *Radiother Oncol*. 2007;85(3):463-468. doi:10.1016/j.radonc.2007.10.007
34. Howlett J, Hamilton S, Ye A, et al. Treatment and outcomes of nasopharyngeal carcinoma in a unique non-endemic population. *Oral Oncol*. 2021;114:105182. doi:10.1016/j.oraloncology.2021.105182

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Tang L-L, Chen L, Xu G-Q, et al. Reduced-volume radiotherapy versus conventional-volume radiotherapy after induction chemotherapy in nasopharyngeal carcinoma: an open-label, noninferiority, multicenter, randomized phase 3 trial. *CA Cancer J Clin*. 2025;75(3):203-215. doi:10.3322/caac.21881