# 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

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## Summary

**Background** The aim of this trial was to address whether elective ipsilateral upper-neck irradiation (UNI) sparing the uninvolved lower neck provides similar regional relapse-free survival compared with standard whole-neck irradiation (WNI) in patients with nasopharyngeal carcinoma.

**Methods** This open-label, non-inferiority, randomised, controlled, phase 3 trial was done at three Chinese medical centres. Patients aged 18–65 years with untreated, non-keratinising, non-distant metastatic (M0) nasopharyngeal carcinoma; with N0–N1 disease (according to International Union Against Cancer–American Joint Committee on Cancer TNM classification, seventh edition); and a Karnofsky performance status score of 70 or higher were randomly assigned (1:1) to receive elective UNI or WNI of the uninvolved neck. Total radiation doses of 70 Gy (for the primary tumour volume and the enlarged retropharyngeal nodes), 66–70 Gy (for the involved cervical lymph nodes), 60–62 Gy (for the high-risk target volume), and 54–56 Gy (for the low-risk target volume) were administered in 30–33 fractions, five fractions per week. Patients with stage II–IVA disease were recommended to receive combined intravenous cisplatin-based chemotherapy (either induction chemotherapy followed by concurrent chemoradiotherapy or concurrent chemoradiotherapy alone). Randomisation was done centrally by the Clinical Trials Centre of Sun Yat-sen University Cancer Centre by means of a computer-generated random number code with a block size of four. Patients were stratified according to treatment centre and nodal status. Investigators and patients were not masked to treatment allocation. The primary endpoint was regional relapse-free survival in the intention-to-treat population. Non-inferiority was indicated if the upper limit of the 95% CI of the difference in 3-year regional relapse-free survival between the UNI and WNI groups was within 8%. Adverse events were analysed in the safety population (defined as all patients who commenced the randomly assigned treatment). This study is registered with ClinicalTrials.gov, NCT02642107, and is closed.

**Findings** Between Jan 22, 2016, and May 23, 2018, 446 patients from 469 screened were randomly assigned to receive UNI (n=224) or WNI (n=222). Median follow-up was 53 months (IQR 46–59). 3-year regional relapse-free survival was similar in the UNI and WNI groups (97·7% [95% CI 95·7–99·7] in the UNI group *vs* 96·3% [93·8–98·8] in the WNI group; difference –1·4% [95% CI –4·6 to 1·8]; $p_{non\text{-}inferiority}<0·0001$). Although acute radiation-related toxic effects were similar between the groups, the incidence of late toxicity was lower in the UNI group than in the WNI group, including any-grade hypothyroidism (66 [30%] of 222 patients *vs* 87 [39%] of 221), skin toxicity (32 [14%] *vs* 55 [25%]), dysphagia (38 [17%] *vs* 71 [32%]), and neck tissue damage (50 [23%] *vs* 88 [40%]). No patients died during treatment. After treatment, one patient in the WNI group died from a non-cancer-related cause (dermatomyositis).

**Interpretation** Elective UNI of the uninvolved neck provides similar regional control and results in less radiation toxicity compared with standard WNI in patients with N0–N1 nasopharyngeal carcinoma.

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For the Chinese translation of the abstract see Online for appendix 1

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## Introduction

Nasopharyngeal carcinoma is a unique head and neck cancer with a specific geographical distribution. Approximately 70% of the estimated 130 000 worldwide cases in 2018 occurred in southeast Asia (including south China) and in north Africa.[1,2] Because the nasopharyngeal lymphatic network is well developed, lymph node metastases in nasopharyngeal carcinoma are very common. More than 70% of patients with nasopharyngeal carcinoma present with cervical lymph node involvement at diagnosis.[3] Previous studies have found that nodal metastasis in nasopharyngeal carcinoma often follows

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## Research in context

### Evidence before this study

We searched PubMed for relevant published studies and the WHO International Clinical Trial Registry Platform for ongoing or completed trials, from database inception to April 20, 2021. Search terms were "nasopharyngeal carcinoma" or "nasopharyngeal cancer" or "nasopharyngeal neoplasm", "radiotherapy", "elective neck irradiation", and "clinical trials". The search was limited to randomised clinical trials, with no language restrictions. To date, only one randomised clinical trial, published in 2013, comparing upper-neck irradiation versus standard whole-neck irradiation in patients with lymph node-negative nasopharyngeal carcinoma, showed a similar proportion of regional control and survival between the two treatment groups. However, that trial was done in a single institution, with around two-thirds of patients receiving conventional two-dimensional radiotherapy, rather than contemporary intensity-modulated radiotherapy, and did not include quality-of-life data. Moreover, that trial was confined to lymph node-negative disease, which is an uncommon presentation in patients with nasopharyngeal carcinoma. Whether lower-neck sparing of the uninvolved neck can be safely expanded to include patients with ipsilateral cervical nodal disease, a more common presentation in clinical practice, remains unaddressed in a clinical trial setting. Therefore, we designed a non-inferiority, large-scale, multicentre, randomised phase 3 trial to assess whether elective upper-neck irradiation of the uninvolved neck (including patients with both N0 and N1 disease) was non-inferior to standard whole-neck irradiation in patients with nasopharyngeal carcinoma.

### Added value of this study

To the best of our knowledge, this study is the first multicentre, phase 3, non-inferiority, randomised, controlled trial to assess the value of lower-neck sparing of the uninvolved neck in patients with N0–N1 nasopharyngeal carcinoma. We showed that elective upper-neck irradiation sparing the uninvolved lower neck results in similarly high regional relapse-free survival and overall survival with reduced late toxic effects and improved quality of life compared with standard whole-neck irradiation.

### Implications of all the available evidence

We believe that our data could guide practice change in the management of patients with nasopharyngeal carcinoma. Our trial provides high-level evidence supporting lower-neck sparing of the uninvolved neck as a valid option to be considered in future treatment guidelines for N0–N1 nasopharyngeal carcinoma, which will benefit the majority (>70%) of the patient population presenting with non-metastatic nasopharyngeal carcinoma.

an orderly pattern, involving the retropharyngeal lymph nodes first,[4] followed by upper-neck levels II, III, or upper level V [VA] nodes, and finally moving to the lower-neck (levels IV and lower level B [VB]) nodes.[5] Lower-neck lymph node involvement in patients is the consequence of the spread from lymph nodes in the upper neck (levels II and III). Lower-neck lymph node metastases without involvement of the upper-neck lymph nodes (ie, so-called skip nodal metastasis) are extremely rare.[5]

Radiotherapy is the primary treatment approach for non-metastatic nasopharyngeal carcinoma. To eradicate micrometastatic tumour foci, the traditional elective nodal target for radiotherapy often encompasses the bilateral whole neck. However, such an approach frequently results in substantial late toxic effects. Up to 40% of patients are reported to develop hypothyroidism within 2 years after radiotherapy,[6] with approximately 30% of patients being affected by late toxic effects in the subcutaneous tissue and approximately 40% being affected by late toxic effects in the oesophagus,[7] all of which can have a negative effect on the patient's quality of life (QOL).

Considering the pattern of lymph node metastisation, the necessity of including the lower neck in the irradiation of the uninvolved neck has been debated. Several retrospective studies and one randomised trial have shown similar survival outcomes with ipsilateral upper-neck irradiation (UNI; ie, omitting irradiation to the ipsilateral lower neck) of the uninvolved neck versus standard whole-neck irradiation (WNI) in N0 and even N1 disease.[5,8–10] However, robust trial data regarding the safety and benefit of UNI on QOL are scarce, and WNI is still recommended for the treatment of nasopharyngeal carcinoma. To guide practice change in this population, we conducted this multicentre, phase 3, non-inferiority, randomised trial to compare the efficacy and benefit of elective UNI versus WNI of the uninvolved neck.

See Online for appendix 2

## Methods

### Study design and participants

This open-label, multicentre, non-inferiority, randomised, controlled, phase 3 trial was done in three major cancer centres in China (Sun Yat-sen University Cancer Centre [Guangzhou], First People's Hospital of Foshan [Foshan], and Affiliated Hospital of Guilin Medical University [Guilin]).

The eligibility criteria included: newly diagnosed, untreated, non-distant metastatic (M0), and non-keratinising nasopharyngeal carcinoma with N0–N1 stage disease (according to the International Union Against Cancer American Joint Committee on Cancer TNM classification, seventh edition; criteria for lymph node positivity are provided in appendix 2, p 3); age 18–65 years; Karnofsky performance status score of 70 or higher; and adequate haematological function (leukocyte count of at least $4\times10^9$ per L, haemoglobin 90 g/L or

higher, and a platelet count of at least $100\times10^9$/L). The exclusion criteria included previous chemotherapy treatment, surgery (except diagnostic), or radiotherapy to the head and neck region; previous malignancy; lactation or pregnancy; or severe coexisting illness (see appendix 2 pp 45–46 for full list of exclusion criteria). Written informed consent was obtained from all participants. The study protocol was approved by the institutional ethics committee at each centre (appendix 2).

### Randomisation and masking

Randomisation was done by the Clinical Trials Centre of Sun Yat-sen University Cancer Centre (Guangzhou, China). Random assignment was generated by a computerised random list generator. The randomisation was stratified by treatment centre and by nodal status (patients with no cervical or retropharyngeal lymph node involvement [cN0 subgroup] *vs* those with retropharyngeal lymph node involvement only [retropharyngeal lymph node-only subgroup; these two groups are the bilateral subsets] *vs* those with unilateral cervical lymph node involvement, regardless of the status of retropharyngeal lymph node [cN1 neck subgroup]). Eligible patients were randomly assigned to received elective UNI or WNI in a 1:1 ratio in blocks of four. The block structure was known only by the study coordinator and the statistician, who were not clinically involved in the study. After completion of all screening procedures at each centre, the investigators contacted the study coordinator to obtain the treatment assignment. Patients and investigators were aware of the treatment group assignment, whereas the central imaging group and statisticians were masked. The central imaging group were unaware of the treatment assignment for each patient, and the statisticians were unaware of the treatment assignment of the two groups.

### Procedures

Before treatment, patients underwent a complete medical history, physical examination, haematological and biochemical profiling, nasopharyngoscopy, histopathological diagnosis, contrast-enhanced MRI of the head and neck, chest CT or radiography, abdominal CT or sonography, a bone scan, quantitative PCR determination of plasma Epstein-Barr virus DNA load (optional, according to the availability of a laboratory at the participating centres), and Epstein-Barr virus serology. Whole-body [$^{18}$F]-fluorodeoxyglucose ([$^{18}$F]FDG) PET–CT examination was optional and done according to local practice.

Intensity-modulated radiotherapy was required for all patients. Target delineation was based on consensus guidelines.[11,12] Gross tumour volume included the primary tumour volume, the enlarged retropharyngeal lymph nodes, and the involved cervical lymph nodes. High-risk clinical target volume was defined as the primary tumour volume and the enlarged retropharyngeal lymph nodes plus a 5–10 mm margin (2–3 mm posteriorly if adjacent to the brainstem or spinal cord) to encompass the high-risk sites of microscopic extension and the whole nasopharynx. Low-risk clinical target volume was defined as the high-risk clinical target volume plus a 5–10-mm margin (2–3 mm posteriorly if adjacent to the brainstem or spinal cord) to encompass the low-risk sites of microscopic extension, including the foramen lacerum, sphenoid sinus, clivus, oval foramen, parapharyngeal space, pterygoid fossae, posterior parts of the nasal cavity, pterygopalatine fossae, retropharyngeal nodal regions, the cervical level where the involved lymph nodes were located, and the elective neck area from level II to level V (according to the patient's treatment group). The recommended doses for the planning target volumes were 70 Gy for the primary tumor volume and the enlarged retropharyngeal lymph nodes, 66–70 Gy for cervical lymph nodes, 60–62 Gy for high-risk clinical target volume, and 54–56 Gy for low-risk clinical target volume, in 30–33 fractions (once per day, five fractions every week). For patients who received induction chemotherapy, the pre-induction volumes received the full prescription dose whenever possible (without exceeding the maximal tolerance of critical organs at risk), regardless of post-induction chemotherapy shrinkage.[13] The detailed guidelines for radiotherapy are provided in appendix 2 (pp 4–5). To ensure trial quality, all intensity-modulated radiotherapy plans were reviewed by the research team at the Sun Yat-sen University Cancer Center. The review criteria are detailed in appendix 2 (p 6).

In patients allocated to WNI, both the upper-neck (levels II, III, and VA) and lower-neck (levels IV and VB) lymphatic drainage areas were encompassed by the low-dose clinical target volume in the uninvolved neck. Patients in the UNI group without cervical lymph node involvement (regardless of retropharyngeal lymph node status) received elective irradiation to the bilateral upper-neck lymphatic drainage areas only (ie, bilateral lower-neck sparing); those with unilateral cervical lymph node involvement received irradiation to the ipsilateral whole neck and elective irradiation to the contralateral upper neck only (ie, contralateral lower-neck sparing; appendix 2 p 26).

Radiotherapy alone was recommended for stage I nasopharyngeal carcinoma. Combined intravenous cisplatin-based chemotherapy (either induction chemotherapy followed by concurrent chemoradiotherapy or concurrent chemoradiotherapy alone) was recommended for stage II–IVA nasopharyngeal carcinoma. According to local practice, the recommended regimens for induction chemotherapy included docetaxel (75 mg/m² on day 1) plus cisplatin (75 mg/m² on day 1), every 3 weeks for 3 cycles; docetaxel (60 mg/m² on day 1) plus cisplatin (60 mg/m² on day 1) plus fluorouracil (600 mg/m² per day, continuous intravenous infusion days 1–5), every 3 weeks for 3 cycles; and gemcitabine (1000 mg/m² on day 1 and day 8) plus cisplatin (80 mg/m² d1), every 3 weeks for 3 cycles The recommended concurrent regimen was cisplatin (80–100 mg/m² on day 1, every 3 weeks).[12] Details of permitted chemoradiotherapy

adjustment are provided in the protocol (appendix 2). Patients were removed from the trial if they had tumour progression or severe comorbidities during treatment, or withdrew consent at any time during the study.

After completion of treatment, patients were followed up every 3 months during the first 3 years and every 6 months thereafter. Schema of follow-up procedures are detailed in appendix 2 (p 6). Nodal assessments included complete physical examination and head and neck contrast-enhanced MRI (or CT if MRI was contra-indicated). Whenever possible, suspected nodes were subjected to fine-needle aspiration or biopsy to confirm nodal relapses. Other assessments included naso-pharyngoscopy, chest CT or radiography, abdominal CT or sonography, and a bone scan. Fine-needle aspiration or biopsy were also used to confirm distant or local relapse. For inaccessible lesions with classic radiographic features for disease relapse on at least two imaging methods (with or without clinical symptoms), including MRI, CT, chest radiograph, abdominal sonography, bone scans, and [$^{18}$F]FDG PET–CT, a clinical diagnosis of recurrence was accepted. For equivocal imaging findings, progression status was confirmed by the central imaging group at a subsequent follow-up. Registry data was also used to obtain information on mortality. All endpoints were assessed and confirmed by the attending physician and further reviewed centrally. Following the standard procedures at each centre, salvage treatments (chemo-therapy, reirradiation, surgery, immunotherapy, and targeted therapy) were provided to patients with persistent disease or documented relapse whenever possible.

The National Cancer Institute Common Toxicity Criteria version 4.0 was used to assess acute radiation toxicity, and the Radiation Therapy Oncology Group and European Organisation for Research and Treatment of Cancer (EORTC) late radiation morbidity scoring schemes were used to assess late radiation toxic effects.[14] EORTC Quality-of-Life Core 30 items (QLQ-C30) and Quality-of-Life Head and Neck 35 items (QLQ-H&N35) version 1.0 questionnaires were used to assess QOL, by means of paper-based questionnaires before treatment and paper-based questionnaires or telephone interviews during survival follow-up.

### Outcomes

The primary endpoint was regional relapse-free survival, defined as the time from randomisation to documented nodal relapse or non-cancer-specific death. Secondary endpoints were overall survival, distant metastasis-free survival, local relapse-free survival, radiation-related toxicity profile, and QOL. Overall survival was defined as the time from randomisation to death from any cause. Distant metastasis-free survival was calculated from randomisation to documented distant metastasis or non-cancer-specific death. Local relapse-free survival was estimated from randomisation to documented local relapse or non-cancer-specific death. Definitions of the endpoints are provided in appendix 2 (p 7).

### Statistical analysis

The trial was designed to establish whether elective UNI in the uninvolved neck was non-inferior in 3-year regional relapse-free survival versus WNI in patients with nasopharyngeal carcinoma in the overall cohort. In both groups, regional relapse-free survival at 3 years was assumed to be 97% on the basis of previously reported survival data from a retrospective study examining the effect of treatment with intensity-modulated radiotherapy in non-metastatic nasopharyngeal carcinoma.[15] The non-inferiority margin was set at 8% on the basis of expert consensus, data from institutional experiences, and published literature.[16–18] Therefore, to show non-inferiority, the upper limit of the one-sided 95% CI of the difference in 3-year regional relapse-free survival between the WNI group and the UNI group could not be greater than 8%. To achieve a one-sided type I error of 2·5% and 80% power, at least 434 patients (217 per group) were required, allowing for a dropout or loss to follow-up rate of 5%.

Efficacy analyses were carried out in both the intention-to-treat population (which included all randomly assigned patients) and the per-protocol population; safety analyses were done in the safety population. The per protocol and safety populations comprised all patients who commenced randomly assigned treatment.

Kaplan-Meier estimates of actuarial survival in the two treatment groups and log-rank tests were used to compare efficacy endpoints between the two groups. Results were stratified by trial centre and nodal status. Time-to-event data were censored if there was no event being observed at the date of the last follow-up or loss to follow-up. Patients were not censored from future nodal relapse if they first developed local or distant recurrence, and vice versa. A stratified Cox proportional hazards model was used to calculate the hazard ratios (HRs) and their associated 95% CIs (with treatment as a single covariate), in which Schoenfeld residuals were used to confirm the assumptions of proportional hazards.[19]

To establish whether the treatment effect varied among prespecified patient subgroups (on the basis of baseline characteristics, including sex, age, tumour category, nodal status, and induction chemotherapy), a further interaction analysis for regional relapse-free survival based on the intention-to-treat population was done. The Cox proportional hazards model was used to test the treatment-by-covariate interaction.[20] The Cox proportional hazard model was also used for multivariable analyses to identify significant independent factors. The covariates comprised sex (female *vs* male), age (a continuous variable), tumour stage (T category: T1–2 *vs* T3 *vs* T4), nodal status (without lymph node involvement *vs* with retropharyngeal lymph node involvement only *vs* with unilateral cervical lymph node involvement), induction chemotherapy (no *vs* yes), and radiotherapy cohorts

(WNI *vs* UNI). The frequency of toxic effects was summarised by descriptive statistics.

Analyses of QOL were done in patients who were free of disease 3 years after radiotherapy. For a patient who was not assessed at this exact timepoint, a timeframe of 1 year either side of the 3-year visit was used. Patient responses to each of the EORTC QLQ-C30 and QLQ-H&N35 questionnaire items were scored through scales representing function, symptoms, or health status; all items pointing to a domain were averaged and then transformed to a scale of 0–100 according to the EORTC scoring manual.[21] Higher scores on the functioning scales and global health status suggested better function or health, whereas higher scores on the symptom scales indicated more severe symptoms. A clinically meaningful change in a QOL score was defined as a difference of at least a 10 points.[22] The Mann-Whitney U test was used to compare the difference in QOL scores between groups.

A post-hoc exploratory analysis was done to discern differences in 3-year regional relapse-free survival between patients who did or did not undergo pretreatment plasma Epstein-Barr virus DNA testing, and between those who did or did not have a pretreatment [$^{18}$F]FDG PET–CT scan. We also did a post-hoc exploratory analysis of 3-year regional relapse-free survival in patients who received any type of chemotherapy (whether induction, concurrent, or adjuvant) or received no chemotherapy and in those who had a pretreatment Epstein-Barr virus DNA value above or below a cutoff of 2000 copies per mL, which was chosen on the basis of our previous study.[23] Additionally, we did post-hoc analysis to compare the adverse events and the QOL score between the ipsilateral (cN1-neck) and bilateral (cN0 and retropharyngeal lymph node-only) subgroups in patients given UNI.

Analyses were done using SPSS (version 25.0) and R (version 3.5.1) software. The statistical test used to assess regional relapse-free survival (the primary endpoint) was one-sided, and a p value of less than 0·025 indicated significance. The other statistical tests were two-sided and a p value of less than 0·05 indicated significance. The key raw data underlying this study were uploaded to the Research Data Deposit public platform (RDDA2021002040). This study is registered with ClinicalTrials.gov, NCT02642107.

### Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

Between Jan 22, 2016, and May 23, 2018, 446 patients from 469 screened were randomly assigned (1:1) to receive elective UNI (n=224) or WNI (n=222; figure 1). Baseline characteristics are shown in table 1. The pre-treatment imaging methods used for disease staging were similar for the two groups (appendix 2 p 8). After randomisation, two (1%) of the 224 patients who had been assigned to the UNI group withdrew their consent and therefore received WNI, and one (<1%) of the 222 patients in the WNI group discontinued radiotherapy because of dermatomyositis; all other patients completed their assigned course of radiotherapy. 122 (27%) of 446 patients received induction chemotherapy (61 [27%] of 224 in the UNI group *vs* 61 [27%] of 222 in the WNI group), 367 (82%) patients received concurrent chemotherapy (179 [80%] in the UNI group *vs* 188 [85%] in the WNI group), and only one (<1%) patient in the UNI group received adjuvant chemotherapy. Detailed information on the chemotherapy and radiotherapy received by the two groups is shown in appendix 2 (pp 9–10).

The data cutoff date for the analyses was Sept 30, 2021, which corresponded to a follow-up of 41 months for the last patient enrolled in the study. Overall, 431 (97%) of 446 patients underwent regular physical examinations and follow-up at the participating centres until death or the latest scheduled assessment. The frequency of head and neck MRI follow-up was similar between the two groups (appendix 2 p 11). Median

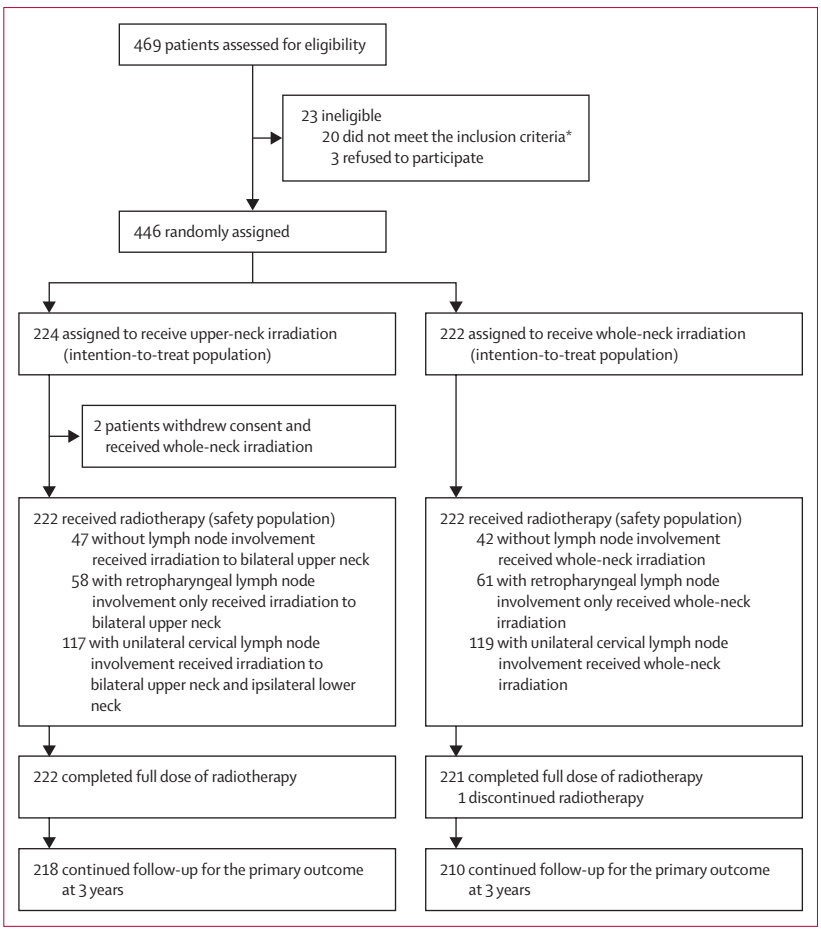


***Figure 1:*** **Trial profile**
*13 patients with previous chemotherapy, two with previous therapeutic surgery to the neck, two without adequate haematological function, two without adequate hepatic function, and one without adequate renal function.

For the **Research Data Deposit platform** see https://www.researchdata.org.cn

| | Upper-neck irradiation group (n=224) | Whole-neck irradiation group (n=222) |
|---|---|---|
| Sex | | |
| Male | 155 (69%) | 158 (71%) |
| Female | 69 (31%) | 64 (29%) |
| Median age, years | 47 (19–65) | 49 (20–65) |
| Karnofsky performance status score | | |
| 70–80 | 10 (4%) | 9 (4%) |
| 90–100 | 214 (96%) | 213 (96%) |
| Histology | | |
| WHO grade II | 3 (1%) | 4 (2%) |
| WHO grade III | 221 (99%) | 218 (98%) |
| Tumour category* | | |
| T1 | 22 (10%) | 12 (5%) |
| T2 | 35 (16%) | 29 (13%) |
| T3 | 125 (56%) | 126 (57%) |
| T4 | 42 (19%) | 55 (25%) |
| Nodal status* | | |
| N0 | 47 (21%) | 42 (19%) |
| N1 | 177 (79%) | 180 (81%) |
| With retropharyngeal lymph node involvement only | 59 (26%) | 61 (27%) |
| With cervical lymph node metastasis | 118 (53%) | 119 (54%) |
| Stage* | | |
| I | 13 (6%) | 6 (3%) |
| II | 43 (19%) | 34 (15%) |
| III | 126 (56%) | 127 (57%) |
| IV | 42 (19%) | 55 (25%) |
| Pretreatment Epstein-Barr virus DNA test† | 215 (96%) | 216 (97%) |
| DNA <2000 copies per mL | 153 (68%) | 169 (76%) |
| DNA ≥2000 copies per mL | 62 (28%) | 47 (21%) |
| DNA, copies per mL | 489 (85–2828) | 372 (0–1830) |

Data are n (%) or median (IQR). *According to the seventh edition of the American Joint Committee on Cancer staging system. †The plasma Epstein-Barr virus DNA test was optional in this trial and was not done for all enrolled patients.

***Table 1:*** **Baseline characteristics**

follow-up was 53 months (IQR 46–59). 3 years of follow-up data were available for 218 (97%) of 224 patients in the UNI group and 210 (95%) of 222 patients in the WNI group.

As of the last follow-up (Sept 30, 2021), 13 (3%) of 446 patients had regional nodal relapses (six [3%] in the UNI group *vs* seven [3%] in the WNI group): 12 in the retropharyngeal or upper-neck regions (six [3%] in the UNI group *vs* six [3%] in the WNI group), without relapse in the lower neck, and one (treated with WNI) in both the upper-neck and lower-neck regions. Three patients (all with regional nodal relapse in the retropharyngeal region; one [<1%] in the UNI group *vs* two [1%] in the WNI group) were clinically diagnosed by both MRI and [$^{18}$F]FDG PET–CT and the remaining ten (five [2%] in the UNI group *vs* five [2%] in the WNI group) confirmed by histopathology; none had residual nodal disease 16 weeks after treatment. All the post-treatment diagnostic neck biopsies were positive on histopathology except one (from a patient treated with UNI), which was negative. No patients without documented nodal relapse underwent neck dissection at the time of surgical salvage for local relapse.

Detailed data on the nodal relapse and subsequent therapies are shown in appendix 2 (pp 11, 13). For regional relapse-free survival, the median follow-up duration was 52 months (IQR 45–59) for all patients. Intention-to-treat analysis showed that 3-year regional relapse-free survival was similar between UNI (97·7% [95% CI 95·7–99·7]) and WNI (96·3% [93·8–98·8]), with a difference of –1·4% (95% CI –4·6 to 1·8; $p_{non\text{-}inferiority}$<0·0001); the stratified HR was 0·73 (95% CI 0·25–2·09; log-rank p=0·85; figure 2A). The results of the per-protocol analysis were similar to those of the intention-to-treat analysis: 3 year regional relapse-free survival was 97·7% (95% CI 95·7–99·7) with UNI versus 96·3% (93·8–98·8) with WNI, with a difference of –1·4% (95% CI –4·6 to 1·8; $p_{non\text{-}inferiority}$<0·0001), and an unstratified HR of 0·73 (95% CI 0·25–2·11; log-rank p=0·56).

As of the last follow-up, 14 patients had died (four [2%] of 224 in the UNI group *vs* ten [5%] of 222 in the WNI group): 13 of these patients died from the primary cancer (four [2%] of 224 in the UNI group *vs* nine [4%] of 222 in the WNI group) and one patient (in the WNI group) died from non-cancer related (and non-treatment related) dermatomyositis. No patients died during treatment. Local relapse was identified in 18 patients (nine [4%] in the UNI group *vs* nine [4%] in the WNI group), and distant metastasis was identified in 27 patients (13 [6%] in the UNI group *vs* 14 [6%] in the WNI group). Detailed information on deaths, local relapses, and distant metastases is in appendix 2 (p 12). 3-year overall survival, distant metastasis-free survival, and local relapse-free survival by intention-to-treat analysis were all similar between the UNI and WNI groups. 3-year overall survival was 99·1% (95% CI 97·9–100) in the UNI group versus 96·4% (93·9–98·9) in the WNI group (stratified HR 0·39 [95% CI 0·12–1·25]; p=0·10; figure 2B); 3-year distant metastasis-free survival was 94·6% (91·7–97·5) with UNI versus 93·5% (90·2–96·8) with WNI (0·85 [0·40–1·78]; p=0·15; figure 2C), and 3-year local relapse-free survival was 97·3% (95·1–99·5) with UNI versus 95·4% (92·7–98·1) with WNI (0·88 [0·36–2·16]; p=0·67; figure 2D). The per-protocol analysis yielded similar results: 3-year overall survival was 99·1% (95% CI 97·9–100) in the UNI group versus 96·4% (93·9–98·9) in the WNI group (unstratified HR 0·39 [95% CI 0·12–1·25]; p=0·10); 3-year distant metastasis-free survival was 95·0% (92·1–97·9) with UNI versus 93·5% (90·2–96·8) with WNI (0·78 [0·37–1·68]; p=0·53),

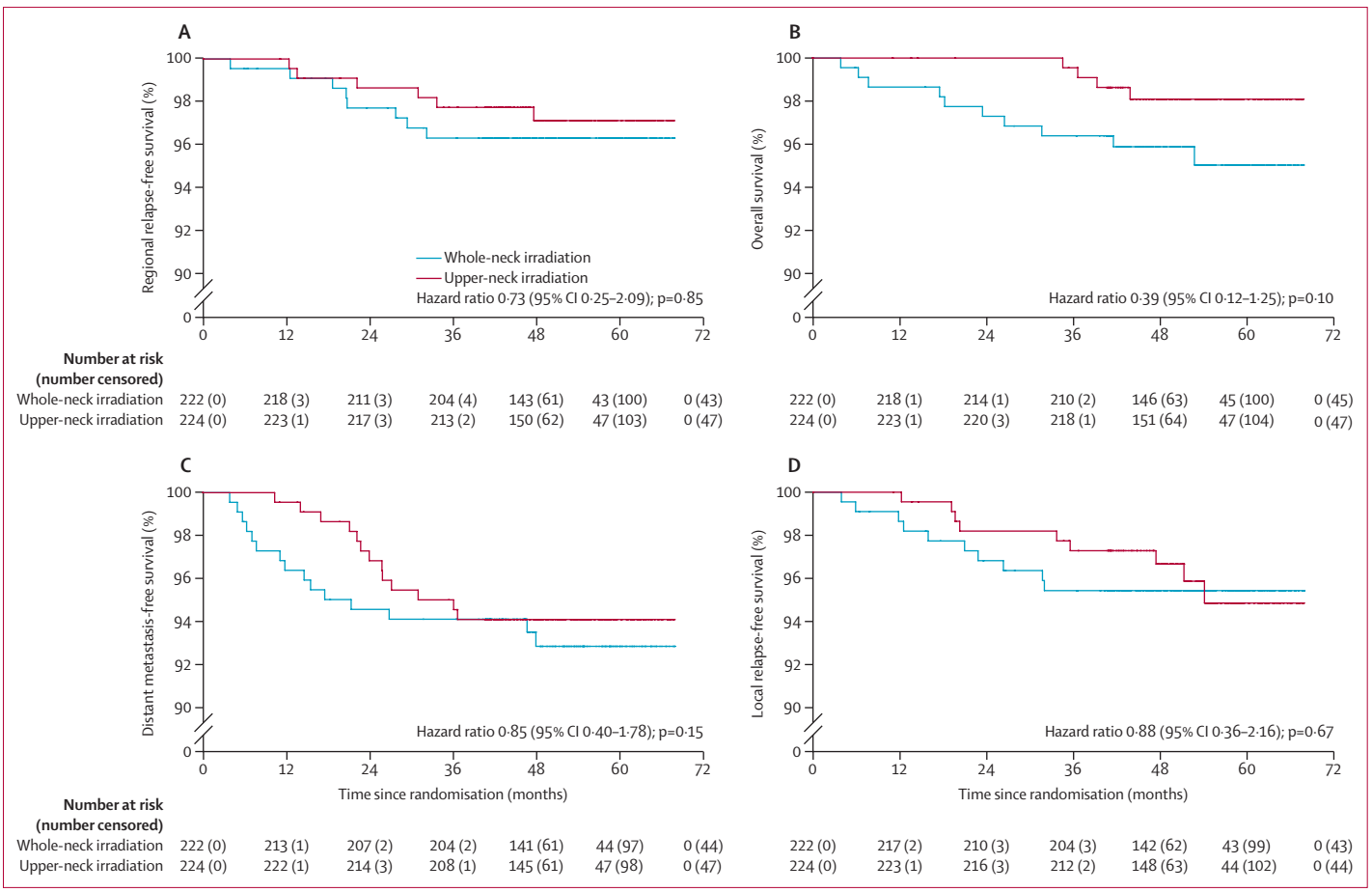


***Figure 2:*** **Kaplan-Meier curves of regional relapse-free survival (A), overall survival (B), distant metastasis-free survival (C), and local relapse–free survival (D) in the intention-to-treat population**

A stratified Cox proportional-hazards model was used to calculate the hazard ratios and their associated 95% CIs.

and 3-year local relapse-free survival was 97·7% (95·7–99·7) with UNI versus 95·4% (92·7–98·1) with WNI (0·79 [95% CI 0·31–1·99]; p=0·61).

In the analyses across all prespecified patient subgroups that were based on baseline characteristics, we observed no significant interactions between the treatment groups and the subgroups, and consistent intergroup 3-year regional relapse-free survival (figure 3), including different nodal status, tumour categories, and the use of induction chemotherapy or not (appendix 2 pp 27–29). The 3-year regional relapse-free survival in the UNI versus WNI groups for the cN0 subgroup, the retropharyngeal lymph node-only subgroup, and the cN1 neck subgroup groups are given in the appendix 2 (p 27).

Before random assignment, 215 (96%) of 224 patients receiving UNI and 216 (97%) of 222 patients receiving WNI were tested for pretreatment plasma Epstein-Barr virus DNA, and 66 (29%) versus 72 (32%) had a [$^{18}$F]FDG PET–CT scan. Post-hoc exploratory analysis showed no clear differences in the 3-year regional relapse-free survival between patients who did or did not undergo pretreatment plasma Epstein-Barr virus DNA testing, and between those who did or did not have a pretreatment PET–CT scan (appendix 2 p 30). In a further post-hoc exploratory analysis in which patients were stratified by the pretreatment plasma Epstein-Barr virus DNA value (≥2000 copies/mL *vs* <2000 copies/mL), 3-year regional relapse-free survivals in the UNI versus WNI groups were similar irrespective of the pretreatment plasma Epstein-Barr virus DNA value (appendix 2 p 31). Moreover, in an additional post-hoc exploratory analysis, 3-year regional relapse-free survival was similar between the groups when patients were stratified by use of chemotherapy (whether induction, concurrent, or adjuvant) or not (appendix 2 p 32). Similar non-inferiority was shown for UNI versus WNI for regional relapse-free survival, overall survival, distant metastasis-free survival, and local relapse-free survival in multivariable analysis adjusted for other confounders (appendix 2 pp 14–15).

The radiation dose to the low-risk clinical tumour volume did not differ between the two groups (UNI mean dose 64·6 Gy [SD 4·5] *vs* WNI 64·7 Gy [2·0]). However, the mean low-risk clinical tumour volume was smaller in the UNI group (401·7 cm$^3$ [SD 115·8]) than in

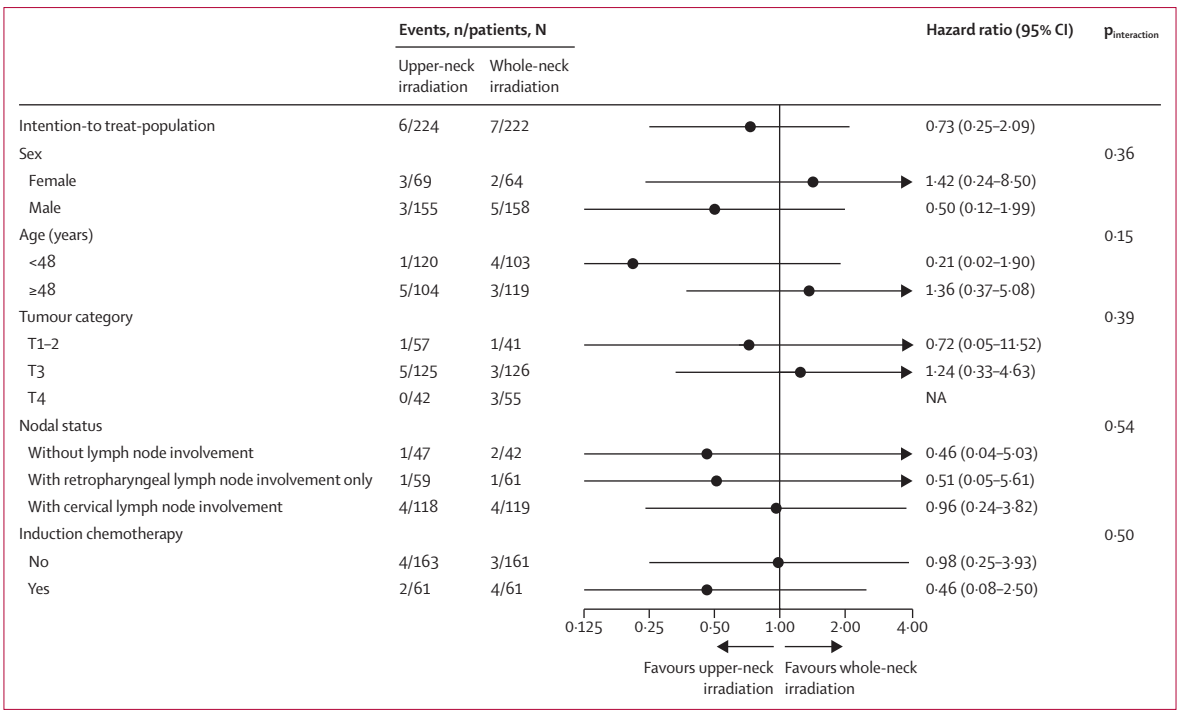


***Figure 3:*** **Regional relapse-free survival by subgroup**
An unstratified Cox proportional hazards model was used to calculate the hazard ratios and their associated 95% CIs. The unstratified Cox proportional hazards model was also used to do the interaction test, incorporating the trial group, a covariate of interest (eg, sex), the interaction term (eg, sex and treatment). A reduced risk of nodal relapse after upper-neck irradiation versus after whole-neck irradiation was implied by a hazard ratio less than 1. No nodal relapse occurred in patients with T4 disease in the upper-neck irradiation group, and thus the hazard ratio was not calculated. NA=not available.

the WNI group (477·6 cm³ [109·9]). Furthermore, the irradiation doses to the thyroid, oesophagus, and trachea were lower in patients receiving UNI than in those receiving WNI (appendix 2 pp 16–17, 33–35).

No substantial differences in acute radiation-related toxic effects were observed between the two groups (table 2). Compared with the WNI group, patients in the UNI group had a lower incidence of late toxic effects, including any-grade hypothyroidism (66 [30%] of 222 *vs* 87 [39%] of 221 ), skin toxicity (32 [14%] *vs* 55 [25%]), dysphagia (38 [17%] *vs* 71 [32%]), and neck tissue damage (50 [23%] *vs* 88 [40%]). In an exploratory post-hoc analysis, we compared the adverse events between the ipsilateral (cN1-neck) and bilateral (cN0 and retropharyngeal lymph node-only) subgroups in patients treated with UNI and showed that patients in the bilateral subset had a lower incidence of late toxic effects, including any-grade hypothyroidism and skin toxicity (appendix 2 pp 18–19).

At baseline, 334 (75%) of the 444 patients who started the assigned treatment completed the EORTC QLQ-C30 questionnaire (160 [72%] of 222 in the UNI group *vs* 174 [78%] of 222 in the WNI group), and 324 (73%) completed the QLQ-H&N35 questionnaire (156 [70%] of 222 in the UNI group *vs* 168 [76%] of 222 in the WNI group). No results for any of the items were different between the two groups, except for the QLQ-C30 item of physical functioning, for which the baseline score was higher in the UNI group than in the WNI group (appendix 2 pp 20–21). In year 3, among the 443 patients who were disease free (206 [93%] of 222 in the UNI group *vs* 201 [91%] of 222 in the WNI group) the EORTC QLQ-C30 questionnaire was completed by 360 (81%) patients (185 [83%] of 222 in the UNI group *vs* 175 [79%] of 222 in the WNI group) and the QLQ-H&N35 questionnaire was completed by 353 (80%) patients (185 [83%] of 222 in the UNI group *vs* 168 [76%] of 222 in the WNI group), whereas the remaining patients did not answer the questionnaires because of time or language constraints. The baseline characteristics among patients included for year 3 QOL analyses did not differ by treatment group (appendix 2 pp 22–23). The UNI group had significantly better QOL outcomes than the WNI group for global health status, emotional functioning, and fatigue on the QLQ-C30 scale, and for swallowing on the QLQ-H&N35 scale (table 3; appendix 2 p 36). The improvement in QoL score in the swallowing domain was clinically significant (with a difference in mean change from baseline of 10·1 points). In a post-hoc exploratory analysis comparing the QOL score between the ipsilateral (cN1 neck subgroup) and bilateral subgroups (cN0 and retropharyngeal lymph node-only subgroups) in patients who received UNI, the bilateral subset had significantly better swallowing outcomes than the ipsilateral subset (appendix 2 pp 24–25).

## Discussion

To our knowledge, this study is the first multicentre, non-inferiority, randomised, controlled trial showing similar efficacy and a significant functional benefit with elective UNI of the uninvolved neck compared with standard WNI in terms of regional relapse-free survival. The 3-year overall survival, distant metastasis-free survival, and local relapse-free survival rates were also similar between the two treatment groups. Importantly, our trial shows a clinical benefit of UNI versus WNI, with fewer late toxic effects and improvement in some measures of QOL but most were not clinically significant. Our results support the adoption of elective UNI of the uninvolved neck in patients with N0–N1 nasopharyngeal carcinoma. Because more than 70% of newly diagnosed patients with nasopharyngeal carcinoma present with unilateral cervical lymph node involvement or with no nodal involvement,[24] we expect that a substantial number of patients could benefit from this effective and less toxic treatment.

A wide range of non-inferiority margins has been used in clinical trials. A systematic review showed that the median non-inferiority margin used in oncology trials was 10·0% (IQR 7·5–13·8) for mortality-related outcomes.[17] For this trial, we set the non-inferiority margin at 8% for 3-year regional relapse-free survival, which we believe is clinically acceptable in light of the high salvage proportion of regional failure in nasopharyngeal carcinoma with anticipated toxicity reduction and QOL improvement.[25]

Similar oncological outcomes with UNI for uninvolved neck versus WNI in patients with nasopharyngeal carcinoma are not surprising. First, nasopharyngeal carcinoma nodal metastases follow a known pattern, starting from the retropharyngeal nodes and upper neck and proceeding to the ipsilateral lower neck. If there is no nodal involvement in the upper neck, the risk of the lower neck harbouring occult nodal metastasis is very low.[4] Elective UNI for the uninvolved neck could effectively prevent further metastasis to the lower neck. Second, WNI was proposed by Lee and colleagues[26] in 1992, on the basis of their finding that 40% of patients with N0 nasopharyngeal carcinoma subsequently developed nodal relapse when they did not receive neck irradiation. In that study, the nodal status was established by clinical palpation without aid from high-quality imaging.[24] Almost a third (29·7%) of patients without clinically palpable nodes have been shown to have CT-detectable nodal involvement.[27] Therefore, with contemporary imaging techniques (eg, CT, PET–CT, and MRI), the risk of occult nodal metastasis in the lower neck in the absence of upper-neck nodal disease is significantly reduced. Our trial is built on previous observations from our group and others that showed excellent outcomes with elective UNI in the uninvolved neck in patients with nasopharyngeal carcinoma with negative lymph nodes,[5,28] with retropharyngeal lymph node involvement only,[10] or with unilateral cervical lymph-node involvement.[8] In a single-institution, randomised trial in which different radiotherapy techniques were used (approximately 65% of patients received conventional two-dimensional radiotherapy and 35% received intensity-modulated radiotherapy), Li and colleagues[27] confirmed the feasibility of UNI for a relatively small population with N0 nasopharyngeal carcinoma; however, their trial did not include QOL data.

Besides non-inferiority in efficacy, our trial showed the benefit of UNI over WNI in the reduction of late toxic effects. We found a nearly 10% reduction in the proportion of hypothyroidism with UNI, which is clinically important because hypothyroidism is an irreversible condition that requires lifelong thyroid hormone replacement, and might lead to many complications that affect patients' function and their QOL. A reduction in late toxic effects on the skin, dysphagia, and neck tissue damage with UNI were also found in our trial, which is probably a consequence of a lower radiation dose to relevant organs and tissues. Notably, no differences in acute toxicities were detected between the two groups. A possible explanation is that the most common acute toxic effects, such as dry mouth and mucositis, were often dominated by treatment volumes in the nasopharynx and upper-neck region, where there was no dose or volume reduction, masking the potential benefit in toxicity reduction attributable to

| | Upper-neck irradiation group (n=222) | | | Whole-neck irradiation group (n=222) | | |
|---|---|---|---|---|---|---|
| | Grade 1–2 | Grade 3 | Grade 4 | Grade 1–2 | Grade 3 | Grade 4 |
| **Any acute toxicities** | | | | | | |
| Dermatitis | 114 (51%) | 1 (<1%) | 0 | 123 (55%) | 1 (<1%) | 0 |
| Mucositis | 125 (56%) | 20 (9%) | 0 | 131 (59%) | 22 (10%) | 1 (<1%) |
| Dry mouth | 159 (72%) | 0 | 0 | 161 (73%) | 0 | 0 |
| Dysphagia | 7 (3%) | 0 | 0 | 14 (6%) | 0 | 0 |
| Weight loss | 114 (51%) | 0 | 0 | 125 (56%) | 0 | 0 |
| Trismus | 0 | 0 | 0 | 1 (<1%) | 0 | 0 |
| Subcutaneous oedema | 1 (<1%) | 0 | 0 | 0 | 0 | 0 |
| **Any late toxicities*** | | | | | | |
| Skin† | 32 (14%) | 0 | 0 | 55 (25%) | 0 | 0 |
| Neck tissue damage | 50 (23%) | 0 | 0 | 86 (39%) | 2 (1%) | 0 |
| Hypothyroidism | 63 (28%) | 3 (1%) | 0 | 84 (38%) | 3 (1%) | 0 |
| Dysphagia | 38 (17%) | 0 | 0 | 69 (31%) | 2 (1%) | 0 |
| Hoarseness | 3 (1%) | 0 | 0 | 1 (<1%) | 0 | 0 |
| Dry mouth | 153 (69%) | 11 (5%) | 0 | 160 (72%) | 15 (7%) | 0 |
| Trismus | 2 (1%) | 0 | 0 | 5 (2%) | 0 | 0 |
| Auditory | 110 (50%) | 0 | 0 | 137 (62%) | 2 (1%) | 0 |
| Temporal lobe injury | 17 (8%) | 0 | 0 | 21 (10%) | 0 | 0 |

Data are n (%). Safety analyses were done in the safety population, comprising all patients who commenced the randomly assigned treatment. *One patient in the whole-neck irradiation group died within 3 months after radiotherapy and thus the late toxicity analysis included 221 patients in the whole-neck irradiation group. †Grade 1 skin toxicity included slight atrophy, pigmentation change, and some hair loss; grade 2, included patch atrophy, moderate telangiectasia, and total hair loss; grade 3 or 4 skin toxicity was not observed in this trial.

*Table 2:* **Acute and late radiation-related toxicities**

| | Upper-neck irradiation group | Whole-neck irradiation group | Difference (95% CI) | p value* |
|---|---|---|---|---|
| EORTC QLQ-C30† | n=136 | n=137 | .. | .. |
| General quality of life (the higher the better) | | | | |
| Global health status | 9·7 (23·4) | 4·3 (23·4) | 5·4 (−0·2 to 10·9) | 0·035 |
| Physical functioning | 2·8 (10·1) | 3·1 (7·9) | −0·3 (−2·4 to 1·9) | 0·37 |
| Role functioning | 4·8 (13·3) | 3·8 (15·1) | 1·0 (−2·4 to 4·4) | 0·68 |
| Emotional functioning | 9·0 (18·6) | 3·7 (21·0) | 5·3 (0·6 to 10·0) | 0·018 |
| Cognitive functioning | 2·2 (17·4) | 1·6 (16·2) | 0·6 (−3·4 to 4·6) | 0·88 |
| Social functioning | 21·9 (23·1) | 24·2 (24·0) | −2·3 (−7·9 to 3·3) | 0·52 |
| Symptom burden (the lower the better) | | | | |
| Fatigue | 0·2 (13·9) | 5·2 (17·4) | −5·0 (−8·8 to −1·3) | 0·0058 |
| Nausea and vomiting | −3·8 (10·5) | −3·3 (11·4) | −0·5 (−3·1 to 2·1) | 0·55 |
| Pain | −6·3 (16·3) | −6·8 (23·7) | 0·5 (−4·3 to 5·4) | 0·64 |
| Dyspnoea | −5·9 (15·1) | −2·4 (18·8) | −3·5 (−7·5 to 0·6) | 0·14 |
| Insomnia | −4·2 (28·2) | −0·7 (30·4) | −3·5 (−10·4 to 3·6) | 0·29 |
| Appetite loss | −2·7 (18·2) | −2·4 (26·4) | −0·3 (−5·7 to 5·1) | 0·48 |
| Constipation | −2·9 (16·0) | −2·2 (16·8) | −0·7 (−4·7 to 3·1) | 0·79 |
| Diarrhoea | −0·7 (15·4) | −2·2 (16·3) | 1·5 (−2·3 to 5·2) | 0·28 |
| Financial difficulties | −30·4 (33·1) | −32·6 (30·9) | 2·2 (−5·4 to 9·8) | 0·38 |
| EORTC QLQ-H&N35† | n=131 | n=126 | .. | .. |
| Symptom burden (the lower the better) | | | | |
| Pain | −3·2 (8·2) | −2·6 (10·1) | −0·6 (−2·9 to 1·7) | 0·20 |
| Swallowing | 6·4 (15·4) | 16·5 (16·9) | −10·1 (−14·0 to −6·1) | <0·0001 |
| Sensory impairment | 0·1 (12·8) | 0·8 (17·4) | −0·7 (−4·4 to 3·1) | 0·91 |
| Speech difficulties | −1·6 (9·3) | −0·6 (8·7) | −1·0 (−3·2 to 1·2) | 0·090 |
| Difficulties in social eating | −0·6 (5·1) | −0·3 (5·7) | −0·3 (−1·7 to 1·0) | 0·28 |
| Difficulties in social contact | 0·2 (2·2) | 0·2 (2·8) | 0·0 (−0·6 to 0·6) | 0·55 |
| Less libido | −4·3 (22·4) | −5·3 (23·8) | 1·0 (−4·7 to 6·6) | 0·98 |
| Dental problems | −2·8 (16·0) | −6·6 (22·7) | 3·8 (−1·0 to 8·7) | 0·37 |
| Mouth opening problems | 0·3 (10·5) | 1·9 (15·9) | −1·6 (−4·9 to 1·7) | 0·63 |
| Dry mouth | 26·5 (25·1) | 28·3 (28·3) | −1·8 (−8·4 to 4·7) | 0·66 |
| Sticky saliva | 24·2 (25·2) | 28·6 (29·4) | −4·4 (−11·1 to 2·3) | 0·24 |
| Coughing | 0·5 (17·5) | 0·3 (20·4) | 0·2 (−4·4 to 4·9) | 0·62 |
| Feeling ill | −18·6 (28·1) | −19·6 (27·4) | 1·0 (−5·8 to 7·8) | 0·63 |
| Requiring pain killers | −6·9 (37·6) | 1·6 (43·8) | −8·5 (−18·5 to 1·6) | 0·10 |
| Requiring nutrition supplements | 4·6 (34·8) | 2·4 (31·2) | 2·2 (−6·0 to 10·4) | 0·60 |
| Requiring a feeding tube | 0·0 (0·0) | 1·6 (12·5) | −1·6 (−3·7 to 0·6) | 0·15 |
| Weight loss | −16·0 (46·1) | −9·5 (46·4) | −6·5 (−17·9 to 4·9) | 0·27 |
| Weight gain | 4·6 (24·4) | 8·7 (33·5) | −4·1 (−11·4 to 3·1) | 0·24 |

Data are mean change in score from baseline (SD) unless stated otherwise. *p values were calculated using Mann-Whitney U tests. †A higher score represented greater symptom severity (on symptom domains), or better health status (on the global health status) or function (on functioning domains).

***Table 3:*** **Quality-of-life score change from baseline to follow-up at 3 years**

lower-neck sparing. Because patients were not stratified by T category nor age, some slight differences were observed between the two groups in the age of the patients (patients in the WNI group were a median 2 years older than those in the UNI group) and in T categories (slightly more T3–4 tumours in the WNI group than in the UNI group), which are factors that might affect QOL outcomes and patients' susceptibility to toxic effects.

Preserving QOL becomes increasingly important in contemporary cancer management, especially in the context of improved survival.[29,30] Reducing the radiotherapy volume has been shown to improve QOL scores in a small retrospective study involving 71 patients with nasopharyngeal carcinoma[9] and several non-nasopharyngeal carcinoma head and neck cancer trials.[29,30] Al-Mamgani and colleagues[31] found improvements in the EORTC QLQ-H&N35 items of swallowing, dry mouth, and mouth opening in patients with oropharyngeal cancer who received unilateral neck irradiation, compared with those who received bilateral neck irradiation. de Veij Mestdagh and colleagues[32] did single-photon emission CT–CT-guided elective neck irradiation for head and neck cancer and found that patients receiving elective neck irradiation had a lower cumulative incidence of grade 2 or worse dysphagia and xerostomia, a better EORTC QLQ-C30 summary score, and improved QLQ-H&N35 dry mouth and swallowing compared with patients receiving standard bilateral neck irradiation.[32] At the time of writing, no previous prospective QOL data are available in the published literature on UNI versus WNI in patients with nasopharyngeal carcinoma, which emphasises the importance of this current report. Notably, in our trial, significant benefits with lower-neck sparing in UNI were observed in multiple domains, especially in swallowing (with clinical significance) and fatigue with no clinical significance. Because UNI resulted in similar disease control to that achieved with WNI, these findings further support the use of UNI as the preferred treatment option for patients with nasopharyngeal carcinoma with at least one side of the neck without cervical nodal disease. Although the patients in this trial had stage N0–N1 disease as per the seventh edition of the TNM classification, the results should be readily applicable to patients with N0–N1 disease as per the more recent eighth edition. Whether or not such an approach would be suitable for patients with ipsilateral N3 disease remains to be evaluated.

Our study has several limitations. First, about 25% of patients did not provide baseline QOL data, potentially because they were overwhelmed with their diagnoses and therefore did not complete the QOL questionnaire. Second, although the results are compelling, they should be interpreted cautiously in the context of the high risk of regional failure, such as in ipsilateral N3 disease as per TNM classification (eighth edition), in which omission of contralateral lower-neck irradiation remains to be evaluated. Third, the enrolled patients were from an endemic area, and whether or not the results can be applied to non-endemic patient populations requires further investigation. Finally, this was an open-label trial, which could introduce bias. However, the masking of the radiologists might circumvent this limitation to some extent.

In conclusion, our trial provides high-level evidence supporting lower-neck sparing of the uninvolved neck as

a valid option to be considered in future treatment guidelines for patients with N0–N1 nasopharyngeal carcinoma, which will benefit most patients with non-metastatic nasopharyngeal carcinoma.

#### Contributors

L-LT, JM, G-QZ, and LC were responsible for study conception and design, supervision of the project, quality assessment, review, and approval of the manuscript. L-LT, C-LH, NZ, and WJ contributed to the design of the clinical trial, writing of the protocol, recruitment and treatment of patients, data and trial management, data analysis and interpretation, and writing and approval of the final report. Y-SW, G-QZ, Y-PM, S-QL, G-JQ, W-HH, and F-YX were involved in the design of the clinical trial, recruitment and treatment of patients, data and trial management, and review of the report. QL and J-BL were responsible for the statistical analysis and interpretation, and toxicity and data review. SHH contributed to patient accrual and writing or review of the completed report. L-LT, JM, and G-QZ were involved in trial management and toxicity review. L-LT, LC, JM, and YS verified the underlying data. All authors read and approved the final draft of the report. All authors had full access to all the data in the study and JM had the final responsibility to submit for publication. Sun Yat-sen University participated in auditing and trial management.

#### Declaration of interests

We declare no competing interests.

#### Data sharing

The data that support the findings of this study are available from the corresponding author on reasonable request to the corresponding author. De-identified participant data will be made available after approval from the corresponding author and Sun Yat-sen University Cancer Centre. After publication of study findings, the data will be available for others to request. The research team will provide an email address for communication once the data are approved to be shared with others. The proposal with a detailed description of study objectives and the statistical analysis plan will be needed for evaluation of the reasonability to request our data. The corresponding author and Sun Yat-sen University Cancer Centre have the right to decide whether to share the data or not on the basis of these materials. Additional materials might also be required during the process of evaluation.

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