Medial retropharyngeal nodal region sparing radiotherapy versus standard radiotherapy in patients with nasopharyngeal carcinoma: open label, non-inferiority, multicentre, randomised, phase 3 trial

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ABSTRACT

OBJECTIVES

To address whether sparing the medial retropharyngeal lymph node (MRLN) region from elective irradiation volume provides non-inferior local relapse-free survival versus standard radiotherapy in patients with nasopharyngeal carcinoma.

DESIGN

Open-label, non-inferiority, multicentre, randomised, phase 3 trial.

SETTING

Three Chinese hospitals between 20 November 2017 and 3 December 2018.

PARTICIPANTS

Adults (18-65 years) with newly diagnosed, non-keratinising, non-distant metastatic nasopharyngeal carcinoma without MRLN involvement.

INTERVENTIONS

Randomisation was done centrally by the Clinical Trials Centre at Sun Yat-sen University Cancer Center. Eligible patients were randomly assigned (1:1; block size of four) to receive MRLN sparing radiotherapy or standard radiotherapy (both medial and lateral retropharyngeal lymph node groups), and stratified by institution and treatment modality as follows: radiotherapy alone; concurrent chemoradiotherapy; induction chemotherapy plus radiotherapy or concurrent chemoradiotherapy.

MAIN OUTCOME MEASURES

Non-inferiority was met if the lower limit of the one sided 97.5% confidence interval of the absolute difference in three year local relapse-free survival (MRLN sparing radiotherapy minus standard radiotherapy) was greater than −8%.

RESULTS

568 patients were recruited: 285 in the MRLN sparing radiotherapy group; 283 in the standard radiotherapy group. Median follow-up was 42 months (interquartile range 39-45), intention-to-treat analysis showed that the three year local relapse-free survival of the MRLN sparing radiotherapy group was non-inferior to that of the standard radiotherapy group (95.3% *v* 95.5%, stratified hazard ratio 1.04 (95% confidence interval 0.51 to 2.12), P=0.95) with a difference of −0.2% ((one sided 97.5% confidence interval −3.6 to ∞), $P_{non\text{-}inferiority}$<0.001). In the safety set (n=564), the sparing group had a lower incidence of grade ≥1 acute dysphagia (25.5% *v* 35.1%, P=0.01) and late dysphagia (24.0% *v* 34.3%, P=0.008). Patient reported outcomes at three years after MRLN sparing radiotherapy were better in multiple domains after adjusting for the baseline values: global health status (mean difference −5.6 (95% confidence interval −9.1 to −2.0), P=0.002), role functioning (−5.5 (−7.4 to −3.6), P<0.001), social functioning (−6.2 (−8.9 to −3.6), P<0.001), fatigue (7.9 (4.0 to 11.8), P<0.001), and swallowing (11.0 (8.4 to 13.6), P<0.001). The difference in swallowing scores reached clinical significance (>10 points difference).

CONCLUSION

Compared with standard radiotherapy, MRLN sparing radiotherapy showed non-inferiority in terms of risk of local relapse with fewer radiation related toxicity and improved patient reported outcomes in patients with non-metastatic nasopharyngeal carcinoma.

TRIAL REGISTRATION

ClinicalTrials.gov NCT03346109

WHAT IS ALREADY KNOWN ON THIS TOPIC

Complete coverage of the retropharyngeal lymph node region, including both medial (MRLN) and lateral groups, is the standard of care for patients with nasopharyngeal carcinoma

Less than 0.6% of retropharyngeal lymph node involvement occurred in the medial group; and a retrospective study showed that MRLN sparing radiotherapy led to no local failure and similar oncological outcomes to standard radiotherapy

Sparing the MRLN region from irradiation facilitated efforts to spare pharyngeal constrictors, which has the potential to lead to fewer toxic effects and improve quality of life

WHAT THIS STUDY ADDS

Incidence of late dysphagia was reduced and improvement in swallowing function was clinically significant in the MRLN sparing radiotherapy group compared with the standard radiotherapy group

High level evidence supporting MRLN sparing radiotherapy should be considered for future guidelines of nasopharyngeal carcinoma, which will benefit most people with non-metastatic non-keratinising nasopharyngeal carcinoma

Introduction

The retropharyngeal lymph nodes (RLN) are paired groups of lymph nodes located in the suprahyoid portion of the retropharyngeal space, and comprise medial (MRLN) and lateral (LRLN) groups. Because

retropharyngeal lymph node represent first echelon draining nodes for nasopharyngeal carcinoma and have a high proportions (70-80%) of involvement at initial diagnosis,[1] complete coverage of both MRLN and LRLN in radiotherapy volumes has been the standard in nasopharyngeal carcinoma for several decades.[2 3] The MRLN lies between the pharyngeal constrictors and the prevertebral fascia near the midline; therefore, prophylactic irradiation to the MRLN would inevitably expose pharyngeal constrictors to a relatively high dose of radiation.[4] Reports suggest that even in patients with nasopharyngeal carcinoma treated with intensity modulated radiation therapy, high proportions of late dysphagia (35.4%),[5] silent aspiration (66.9%)[6] among patients with dysphagia, and aspiration pneumonia related to swallowing (12.0%)[7] occur, resulting in poor quality of life.

Advanced imaging techniques has led to a better understanding of the route of retropharyngeal lymph node involvement. Based on magnetic resonance imaging (MRI), observations from our group and from others have showed that retropharyngeal lymph node involvement mainly occurs in the lateral group, with less than 0.6% occurring in the medial group.[1 4 8] More importantly, a recent retrospective study from our group showed that exclusion of the MRLN region from elective radiotherapy target volumes still resulted in no recurrence in this region.[9] Our results suggest that the risk of occult MRLN involvement is very low with contemporary imaging.

To address whether MRLN sparing radiotherapy provides uncompromised local control in patients with nasopharyngeal carcinoma, we conducted this trial comparing outcomes of MRLN sparing radiotherapy versus standard radiotherapy (radiotherapy volumes encompassed both MRLN and LRLN regions) in patients without clinical or radiological evidence of MRLN involvement. We hypothesised that MRLN sparing radiotherapy was non-inferior to standard radiotherapy in terms of local relapse-free survival, with a non-inferiority margin of 8%.[10-13] We also hypothesised that this method would result in adequate sparing of pharyngeal constrictors, preserving swallowing function and improving quality of life in patients with nasopharyngeal carcinoma.

Methods

Study design and patients

This open label, randomised, multicentre, non-inferiority, phase 3 clinical trial was conducted at three major hospitals in China (Sun Yat-sen University Cancer Center, First People's Hospital of Foshan, and Wuzhou Red Cross Hospital) between 20 November 2017 and 3 December 2018 (appendix page 9). Patients were eligible if they were treatment naive, had non-keratinising nasopharyngeal carcinoma (T1-4N0-3M0), aged 18-65 years, and had a Karnofksy performance score >70. We excluded patients if they had radiologically suspicious or confirmed MRLN involvement; were planned for palliative care; had a previous malignancy; or had received treatment (chemotherapy, radiotherapy, or surgery) to the head and neck region. The institutional ethics committee in each centre approved the study protocol (appendix 1), and written informed consent was provided by all patients.

Randomisation and masking

We randomly assigned the patients (1:1) to receive either MRLN sparing radiotherapy or standard radiotherapy (radiotherapy volumes encompassed both MRLN and LRLN regions). Randomisation was stratified by institution and treatment modality (radiotherapy alone *v* concurrent chemoradiotherapy *v* induction chemotherapy plus radiotherapy or concurrent chemoradiotherapy). Separate computer generated random lists were used for each treatment modality group per institution, with a block size of four. Treatment allocation was centrally generated at Sun Yat-sen University Cancer Center and provided to the institution via telephone when the participant was enrolled. Only the statistician, who was not involved in clinical care, was aware of the block structure. Treatment allocations were not masked to the enrolled patients and the physician; however, they were masked to the central responsible radiologists and the statistician.

Procedures

Pre-treatment assessment was carried out according to practical guidance described previously.[13] All enrolled patients received intensity modulated radiation therapy. The principles of target delineation followed the consensus guidelines[14 15] and are detailed in appendix 2 (pages 4-6). The gross tumour volume contained the primary tumour and the involved lymph nodes. Clinical target volumes were divided into high risk and low risk according to the incidence rates of tumour extension. We defined that the low risk clinical target volume included the retropharyngeal space extending from the base of the skull to the caudal border of the hyoid bone or caudal border of C3 as the lower limit, and we electively delineated according to the patient's treatment allocation. For the standard radiotherapy group, both the LRLN and MRLN regions were included in the low risk clinical target volume from the base of the base of skull to the caudal border of the hyoid bone or caudal border of C3; the whole superior pharyngeal constrictor and parts of the middle pharyngeal constrictor were inevitably included in the target volume. For the MRLN sparing radiotherapy group, only the LRLN region was included in the low risk clinical target volume, contoured in the spaces medial to the carotid arteries, and the MRLN region was not intended to be defined as a target.[16] However, the MRLN region was still not spared above a specific level (usually 10 mm inferior to the level of C1/2 junction, and if oropharyngeal or hypopharyngeal extension occurred, this level will move down and the spared MRLN region would be reduced) because of the crossover between the MRLN region and clinical target volume, even if our target volume did not

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intentionally include it. Whereas, the MRLN region below this level was excluded in the low risk clinical target volume, facilitating sparing of swallowing structures (appendix 2 pages 27–31). For patients who received induction chemotherapy, the gross tumour volume was delineated based on the pre-induction chemotherapy disease extension and included all structures involved by tumour at presentation. In cases where significant anatomical alteration occurred due to tumour regression that resulted in inclusion of adjacent uninvolved structures, the gross tumour volume was modified to take into account the patient's post-induction chemotherapy anatomy while reflecting the initial pattern of the disease.[17] In cases where an air cavity was present because of tumour regression, correction for natural anatomical boundaries was required accordingly (appendix 2 pages 32–33). Swallowing structures, including the superior pharyngeal constrictor, middle pharyngeal constrictor, inferior pharyngeal constrictor, and the glottic and supraglottic larynx, were contoured based on a scheme following Gray's Anatomy,[18] as detailed in appendix 2 (page 5). A uniform expansion of 0.3 cm from the gross tumour volume or clinical target volumes was built as the planning target volumes. The prescribed doses were 70 Gy (2.12 Gy/fraction) to the planning target volume of the gross tumour at the primary site and the involved RLNs , 66-70 Gy (2.00-2.12 Gy/fraction) to the planning target volume of the involved cervical lymph nodes, 60-62 Gy (1.81-1.87 Gy/fraction) to the planning target volume of the high risk clinical target volume, and 54-56 Gy (1.64-1.70 Gy/fraction) to the planning target volume of the low risk clinical target volume. These doses were delivered by use of the simultaneous integrated boost technique, with all planning target volumes irradiated simultaneously for 33 daily fractions, five fractions per week. The radiotherapy treatment plans and contours were centrally reviewed in accordance with the criteria detailed in appendix 2 (page 7). For patients with stage II-IVA disease, a combination of intravenous cisplatin-based chemotherapy was recommended.[19] The study protocol (appendix 1) details the preferred regimens and permitted chemoradiotherapy adjustments.

Clinicians monitored acute toxicity before and during radiotherapy, and assessed tumour relapse, survival, and late toxicity after a prescribed scheme and schedule post-therapy (appendix 2 page 7). The clinician in charge assessed the locoregional relapse or distant metastases. Fine needle aspiration or biopsy of suspected lesions was recommended to confirm locoregional or distant disease recurrence unless medically contraindicated or the lesion location was too high risk for biopsy. For inaccessible lesions, clinical diagnosis of recurrence was acceptable if the characteristic findings were present and concordant between at least two imaging modalities (with or without clinical symptoms). For equivocal imaging findings, recurrence status was confirmed by the blinded central imaging review committee including three radiologists (L-ZL, LT, and H-JL) with more than 10 years of experience in head and neck cancers at a subsequent follow-up. Mortality information was also obtained from the registry data. Salvage treatments were provided for patients with tumour residues, progression, or relapse, after the relevant guidelines in each centre whenever possible.

Outcomes

The primary outcome was local relapse-free survival (local relapse-free survival, defined as time from randomisation to documented local relapse including relapse in the primary site and in the retropharyngeal lymph node region, or death from any cause). Secondary outcomes consisted of overall survival (from randomisation to death from any cause), distant metastasis-free survival (from randomisation to documented distant metastasis or death from any cause), regional relapse-free survival (time from randomisation to documented regional relapse or death from any cause), acute and late toxic effects, and quality of life. Patients whose first event was a distant or regional recurrence were censored for the local relapse-free survival analysis, and vice versa.

We evaluated occurrence of acute toxicity using the National Cancer Institute Common Toxicity Criteria version 4.0 scale and assessed late toxicity using the Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) late radiation morbidity scoring schemes.[20] 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 quality of life at baseline and during survival follow-up.

Statistical analysis

This trial was designed to test the non-inferiority of three year local relapse-free survival in the MRLN sparing radiotherapy group versus the standard radiotherapy group. According to a previous report,[21] we assumed the three year local relapse-free survival rate to be 94% in both groups, and the non-inferiority margin was set as 8% (corresponding to a hazard ratio of 2.44). About 40 local relapse events would be required to achieve 80% power at a one-sided type I error of 0.025 with two years of accrual time and three years of follow-up time. After considering a 5% dropout rate in both groups, a total of 550 patients (275 per group) were required, which was based on the sample size determination method for the log-rank test of non-inferiority[22] (appendix 2 page 44). The 8% non-inferiority margin was predefined with reference to data from institutional experience and the published literature, and was considered acceptable and appropriate in view of low incidence of local failure in nasopharyngeal carcinoma.[10-13] Thus, the MRLN sparing radiotherapy group was deemed non-inferior if the lower boundary of the one-sided 97.5% confidence interval of the difference in three year local relapse-free survival (MRLN sparing radiotherapy minus standard radiotherapy) was greater than −8%.

Efficacy analyses were conducted primarily for the intention-to-treat population (ie, all randomly assigned patients) and repeated, for sensitivity reasons, for the per protocol population (ie, all patients who received at least one fraction of their allocated radiotherapy schedule). Time-to-event outcomes were calculated using the Kaplan-Meier method and the differences between two groups were compared by use of log-rank tests. The three year point survival rate difference between two groups was estimated using a z test. Patients were censored if no event was observed at the last follow-up. Missing time-to-event data due to loss of follow-up were treated as censored data based on the last observation carried forward. We also calculated hazard ratios (95% confidence intervals) using a Cox proportional hazards model, with the assumptions of proportional hazards confirmed based on Schoenfeld residuals.[23] Patients had been stratified and well balanced according to centre and treatment modality; therefore, the statistics of hazard ratio in the intention-to-treat population were presented as stratified hazard ratios (stratified by centre and treatment modality). However, the stratified randomisation was changed and broken when we performed analyses in the per protocol population that had excluded some of patients; therefore, corresponding hazard ratios were presented as unstratified hazard ratios.

Treatment-by-covariate interaction based on the intention-to-treat population was further assessed using the Cox proportional hazards model to investigate whether the treatment effect varied among patient subgroups.[24] Multivariable analyses (with covariates comprising sex, age, T category, N category, induction chemotherapy, trial centre, and assigned treatment) were done with use of the Cox proportional hazards model.

Acute and late toxicities were summarised as frequency and severity in the safety set (including patients who received at least one fraction of their allocated radiotherapy schedule and had recorded data regarding safety evaluation); differences were compared using Pearson's χ^2 test or Fisher's exact test when appropriate.

Patients who were disease-free at three years of follow-up in the per protocol population were analysed for quality of life. Responses to questionnaires were transformed into standardised scores for comparison, as described in appendix 2 (page 8). Difference between two groups were adjusted for the baseline values with generalised estimating equations, and a 10 point difference in scores was considered clinically meaningful.[25]

Post-hoc exploratory analyses comprised comparison of three year local relapse-free survival between patients with or without pre-treatment plasma Epstein-Barr virus DNA, and between those with or without a pre-treatment positron emission tomographycomputed tomography (PET-CT) scan. We also tested the primary hypothesis in post hoc subgroups including chemotherapy (no *v* yes) and pre-treatment plasma Epstein-Barr virus DNA (a cut-off of 2000 copies per mL was chosen according to our previous study[26]).

The primary outcome local relapse-free survival was analysed at a one sided significance level of 0.025. Statistical tests for other outcomes were two sided, and P<0.05 was deemed significant. Statistical analyses were performed using SPSS software (version 25.0) and R (version 3.6.1). This study is registered with ClinicalTrials.gov, number NCT03346109.

Patient and public involvement

Participants were aware of the purpose and content of this trial during recruitment, although they were not involved in the initial design of the trial. During implementation, patients reported their quality of life at pre-set timepoints by answering the QLQ-H&N35 and QLQ-C30 questionnaires, which was related to one of the secondary outcomes. Considering the confidentiality of clinical data, patients did not participate in the subsequent statistical analysis or manuscript writing. However, the results were communicated to patients who expressed an interest during clinic visits.

Results

Between 20 November 2017, and 3 December 2018, we recruited 568 patients of the 599 screened in this trial, and randomly assigned 285 to the MRLN sparing radiotherapy group and 283 to the standard radiotherapy group (fig 1). We present the baseline characteristics of the two groups in table 1, and the pre-treatment imaging methods used for disease staging in appendix 2 (page 9). After randomisation in the MRLN sparing radiotherapy group, one participant withdrew consent before treatment and two patients discontinued treatment after induction chemotherapy when radiotherapy had not been carried out. One patient withdrew consent before treatment in the standard radiotherapy group for unknown reasons; thus, they were included in the intention-to-treat population but were removed from the per protocol analysis. Among the remaining patients, one patient in the MRLN sparing radiotherapy group discontinued radiotherapy because of unwillingness and the others completed their assigned radiotherapy. Additional chemotherapy was given to 527 (92.8%) of the 568 patients with II-IVA disease (266 (93.3%) of 285 in the MRLN sparing radiotherapy group *v* 261 (92.2%) of 283 in the standard radiotherapy group). Of these patients, 341 (60.0%) of 568 were given induction chemotherapy (170 (59.6%) of 285 in the MRLN sparing radiotherapy group *v* 171 (60.4%) of 283 in the standard radiotherapy group), and 518 (91.2%) of 568 patients received concurrent chemotherapy (261 (91.6%) of 285 in the MRLN sparing radiotherapy group *v* 257 (90.8%) of 283 in the standard radiotherapy group). Full details of the radiotherapy and chemotherapy given to the two groups are provided in appendix 2 (pages 10-12).

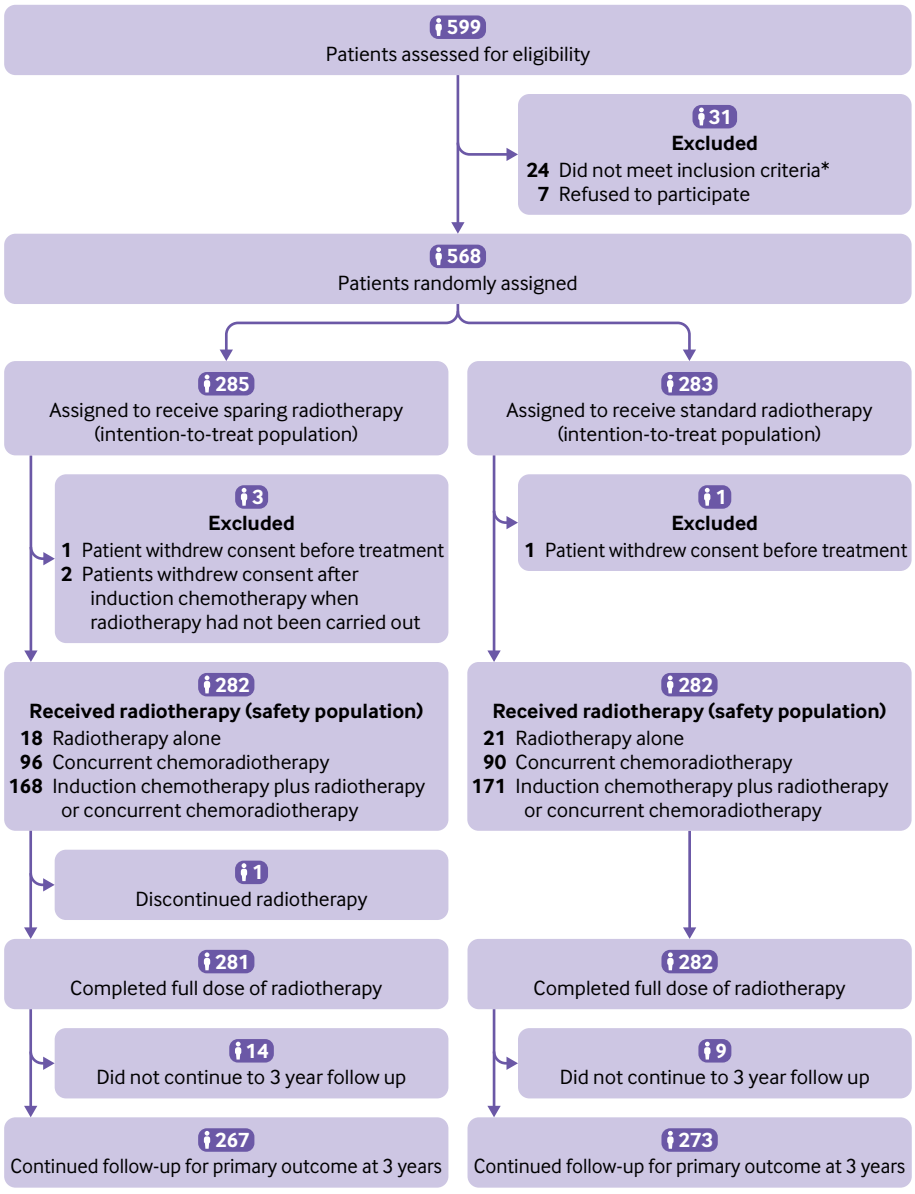

Fig 1 | Trial profile. The intention-to-treat population comprised all randomly assigned patients. The safety population comprised all patients who received at least one fraction of their allocated radiotherapy schedule. *14 patients older than 65 years, four younger than 18 years, one with involved medial retropharyngeal lymph nodes, four with severe coexisting illness, and one with previous malignancy

Primary outcome

At the time of analysis (26 April 2022), three year visit forms were available for 540 (95.1%) of the 568 patients (267 (93.7%) of 285 in the MRLN sparing radiotherapy group *v* 273 (96.5%) of 283 in the standard radiotherapy group). The difference in the three year visit forms was statistically not significant (χ^2 test, P=0.13), and can be explained by random error. After a median follow-up of 42 months (interquartile range 39-45), local recurrence was recorded for 26 (4.6%) of 568 patients (14 (4.9%) in the MRLN sparing radiotherapy group *v* 12 (4.2%) in the standard radiotherapy group). Among them, 22 (3.9%) of 568 patients developed in-field recurrences (12 (4.2%) in the MRLN sparing radiotherapy group *v* 10 (3.5%) in the standard radiotherapy group), two (0.4%) patients developed out-of-field recurrences (one (0.4%) in the MRLN sparing radiotherapy group *v* one (0.4%) in the standard radiotherapy group). Two (0.4%) patients had residual local disease at 16 weeks after treatment (one (0.4%) in the MRLN sparing radiotherapy group *v* one (0.4%) in the standard radiotherapy group). Six (1.1%) patients had retropharyngeal lymph node recurrence, and none of them developed relapse in the MRLN region (appendix 2 page 15). Histopathological evidence was obtained for 20 (3.5%) of 568 patients (12 (4.2%) in the MRLN sparing radiotherapy group *v* 8 (2.8%) in the standard radiotherapy group), and the remaining local recurrences were identified by both head and neck MRI and PET-CT. MRI evaluation frequency and subsequent salvage treatments for the two groups are shown in appendix 2 (pages 12-14).

Table 1 | Baseline characteristics. Data are number (percentage) unless otherwise stated

	MRLN sparing RT (n=285)	Standard RT (n=283)
Sex		
Male	215 (75.4)	209 (73.9)
Female	70 (24.6)	74 (26.1)
Median age (range), years	46 (19-64)	49 (23-65)
Karnofsky performance score		
70-80	9 (3.2)	8 (2.8)
90-100	276 (96.8)	275 (97.2)
Histology		
WHO II	0	3 (1.1)
WHO III	285 (100)	280 (98.9)
Tumour category*		
T1	26 (9.1)	26 (9.2)
T2	47 (16.5)	51 (18.0)
T3	129 (45.3)	133 (47.0)
T4	83 (29.1)	73 (25.8)
Nodal category*		
N0	23 (8.1)	25 (8.8)
N1	109 (38.2)	106 (37.5)
N2	106 (37.2)	96 (33.9)
N3	47 (16.5)	56 (19.8)
Stage*		
I	7 (2.5)	8 (2.8)
II	38 (13.3)	25 (8.8)
III	123 (43.2)	126 (44.5)
IVA	117 (41.1)	124 (43.8)
Treatment modality†		
RT	18 (6.3)	21 (7.4)
Concurrent chemoradiotherapy	96 (33.7)	90 (31.8)
IC+concurrent chemoradiotherapy	165 (57.9)	167 (59.0)
IC+RT	5 (1.8)	4 (1.4)
Pre-treatment Epstein-Barr virus DNA test‡	250 (87.7)	251 (88.7)
DNA<2000 copies per mL	147 (51.6)	154 (54.4)
DNA ≥2000 copies per mL	103 (36.1)	97 (34.3)
DNA (copies per mL), median (IQR)	1190 (271-7853)	1030 (388-6030)

CCRT=concurrent chemoradiotherapy; EBV=Epstein-Barr virus; IC=induction chemotherapy; IQR=interquartile range; MRLN=medial retropharyngeal lymph node; RT=radiotherapy.
*According to the eighth edition tumour, node, metastases (TNM) staging system.
†Two patients withdrew consent after randomisation, and were lost to follow-up.
‡The plasma Epstein-Barr virus DNA test was optional in this trial and was not done for all enrolled patients.

Based on the intention-to-treat population, the three year local relapse-free survival was 95.3% (95% confidence interval 92.8 to 97.8) in the MRLN sparing radiotherapy group compared with 95.5% (93.0 to 98.0) in the standard radiotherapy group (estimated absolute difference −0.2% (one sided 97.5% confidence interval −3.6 to ∞); $P_{non\text{-}inferiority}$<0.001; stratified hazard ratio 1.04 (95% confidence interval 0.51 to 2.12); log-rank P=0.95; fig 2 top panel; appendix 2 page 16). Schoenfeld test P value for local relapse-free survival was 0.51 (appendix 2 page 34). Non-inferiority was confirmed if the lower boundary of the one sided 97.5% confidence interval for the difference in three year local relapse-free survival was greater than the predefined non-inferiority margin of −8% (appendix 2 page 35). Results from analyses based on the per protocol population were consistent: the three year local relapse-free survival was 95.3% (95% confidence interval 92.8 to 97.8) for the MRLN sparing radiotherapy group and 95.5% (93.0 to 98.0) for the standard radiotherapy group (estimated absolute difference −0.2% (one sided 97.5% confidence interval −3.7 to ∞); $P_{non\text{-}inferiority}$<0.001; unstratified hazard ratio 1.02 (95% confidence interval 0.50 to 2.10); log rank P=0.95; appendix 2 page 16).

Secondary outcomes

The incidences of regional recurrence, distant metastasis, and death were similar in the two groups. Details of the regional recurrence, distant metastasis, death, and the corresponding subsequent therapies are summarised in appendix 2 (pages 13-14).

Three year outcomes by intention-to-treat in the MRLN sparing radiotherapy group and standard radiotherapy group were as follows: overall survival was 95.2% (95% confidence interval 92.7 to 97.7) *v* 96.4% (94.2 to 98.6) (estimated absolute difference −1.2% (−4.5 to 2.1); stratified hazard ratio 1.79 (95% confidence interval 0.82 to 3.91); log rank P=0.16; fig 2B); distant metastasis-free survival was 89.7% (95% confidence interval 86.0 to 93.4) *v* 92.3% (89.2 to 95.4) (estimated absolute difference −2.6% (−7.3 to 2.1); stratified hazard ratio 1.41 (0.83 to 2.39); log rank P=0.25; fig 2C); and regional relapse-free survival was 96.9% (95% confidence interval 94.7 to 99.1) *v* 94.0% (91.1 to 96.9) (estimated absolute difference 2.9% (−0.5 to 6.3); stratified hazard ratio 0.67 (0.31 to 1.43); log rank P=0.28; fig 2D). Schoenfeld residuals analysis confirmed that the proportionality assumption was not violated (P=0.34 for overall survival, 0.74 for distant metastasis-free survival, and 0.82 for regional relapse-free survival; appendix 2 page 34).

Similar three year results were reported from the per protocol analysis: overall survival was 95.2% (92.7 to 97.7) *v* 96.4% (94.2 to 98.6) (estimated absolute difference −1.2% (−4.5 to 2.1); unstratified hazard ratio 1.74 (0.80 to 3.81); log rank P=0.16); distant metastasis-free survival was 89.6% (85.9 to 93.3) *v* 92.3% (89.2 to 95.4) (estimated absolute difference −2.7% (−7.4 to 2.0); unstratified hazard ratio 1.37 (0.80 to 2.32); log rank P=0.25); and regional relapse-free survival was 96.9% (94.7 to 99.1) *v* 94.0% (91.1 to 96.9) (estimated absolute difference 2.9% (−0.5 to 6.3); unstratified hazard ratio 0.66 (0.31 to 1.41); log rank P=0.28). The sensitivity analyses regarding efficacy endpoints by use of competing risk models also showed the robustness of our findings (appendix 2 page 19).

Subgroup analyses

Prespecified subgroup analyses of three year local relapse-free survival indicated no significant interactions with the allocated treatment (appendix 2 page 36). Subgroups stratified by tumour category, nodal category, and use of induction chemotherapy also showed no significant difference in three year local relapse-free survival by treatment groups (appendix 2 pages 37-39). Multivariable analysis, adjusted for other covariates, confirmed that MRLN sparing radiotherapy was non-inferior to standard radiotherapy in terms of local relapse-free survival, overall survival, distant metastasis-free survival, and regional relapse-free survival (appendix 2 pages 17-18). Plasma Epstein-Barr virus DNA testing and PET-CT scans might affect clinical staging and risk stratification. In this trial, no differences were found in the three year local relapse-free survival between patients with or without pre-

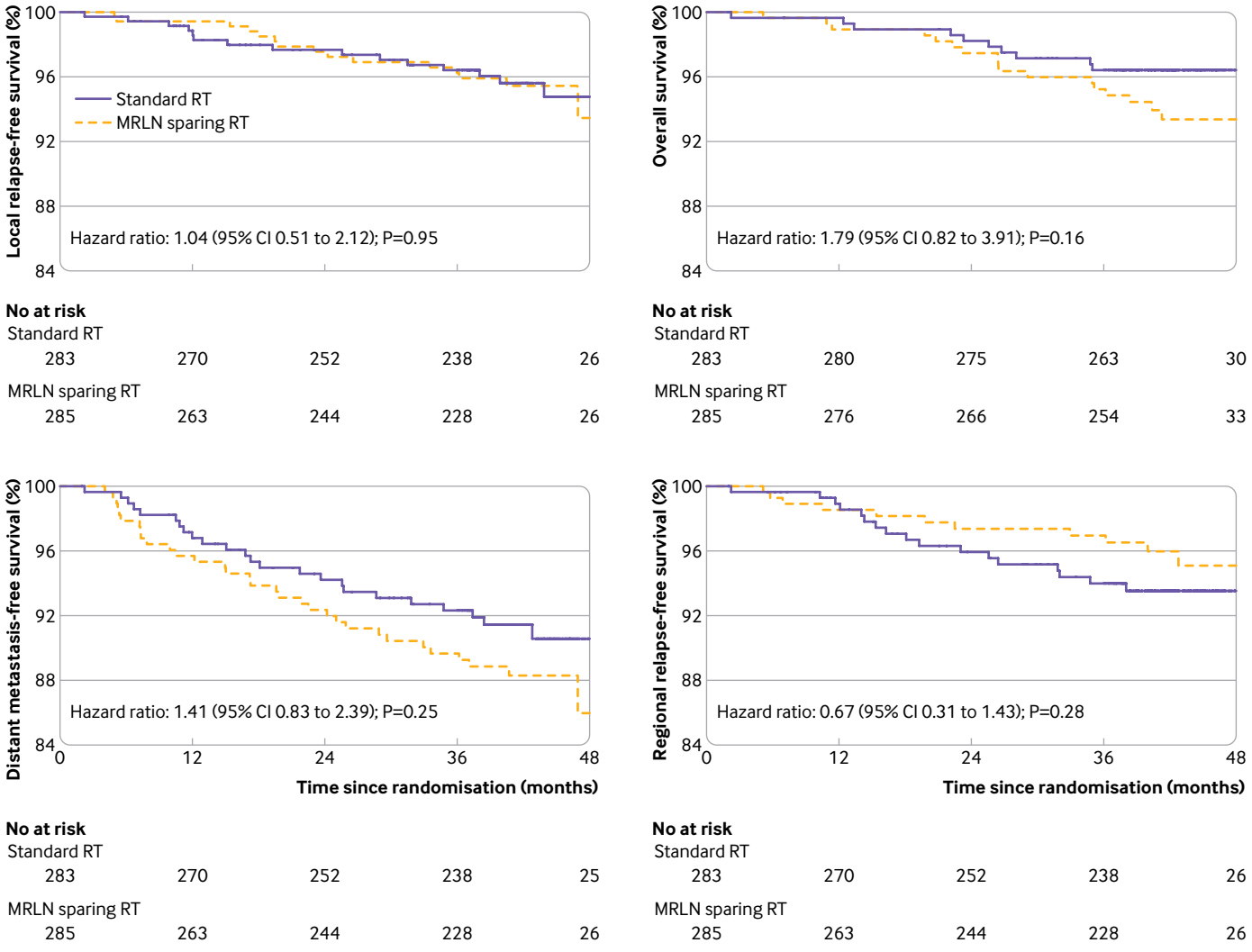

Fig 2 | Kaplan-Meier curves displaying the local relapse-free survival (top left), overall survival (top right), distant metastasis-free survival (bottom left), and regional relapse-free survival (bottom right) in the intention-to-treat population. A stratified Cox proportional hazards model was used to calculate the hazard ratios (HRs) and their associated 95% confidence intervals (CIs). RT=radiotherapy; MRLN=medial retropharyngeal lymph node

treatment plasma Epstein-Barr virus DNA testing, and between those with or without pre-treatment PET-CT scan according to the post-hoc exploratory analysis (appendix 2 page 40). Furthermore, when patients with pre-treatment plasma Epstein-Barr virus DNA testing were stratified by use of a cut-off of 2000 copies/mL, the three year local relapse-free survival was similar between the treatment groups (appendix 2 page 41). Additionally, the two treatment groups showed similar three year local relapse-free survival rates irrespective of the use of chemotherapy according to post-hoc exploratory analysis (appendix 2 page 42).

Adverse events and dosimetry

Analyses of acute and late toxicity were based on the safety population: 282 patients in the MRLN sparing radiotherapy group and 282 patients in the standard radiotherapy group. We recorded a lower incidence of acute radiotherapy related toxicities in the MRLN sparing radiotherapy group *v* standard radiotherapy group, including grade 1 or higher mucositis (67.7% *v* 79.8%, P=0.001), dysphagia (25.5% *v* 35.1%, P=0.01), weight loss (46.8% *v* 57.8%, P=0.009), and grade 3 or higher mucositis (10.6% *v* 16.7%, P=0.04). Regarding late toxicity, the MRLN sparing radiotherapy group had a lower frequency of grade 1 or worse late dysphagia (24.0% *v* 34.3%, P=0.008, table 2). We found that based on the approximative irradiation doses and volumes delivered to the low risk clinical target volume, the MRLN sparing radiotherapy group had a significant reduction in irradiation doses and volumes delivered to the superior pharyngeal constrictor, middle pharyngeal constrictor, and glottic and supraglottic larynx (appendix 2 pages 20-22).

Quality of life

Of the 564 sent out, at baseline, 451 (80.0%) patients returned EORTC QLQ-C30 questionnaires (MRLN sparing radiotherapy *v* standard radiotherapy: 221/282 (78.4%) *v* 230/282 (81.6%)), and 445 (78.9%) returned QLQ-H&N35 questionnaires (217 (77.0%) *v* 228 (80.9%)). At three years, 418 (74.1%)

Table 2 | Acute and late toxicities related to radiation. Data are number (percentage), unless otherwise specified

	MRLN sparing RT (n=282)				Standard RT (n=282)				P value for events grade ≥1	P value for events grade ≥3
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4		
Any acute toxicities										
Dermatitis	106 (37.6)	41 (14.5)	3 (1.1)	0	127 (45.0)	30 (10.6)	3 (1.1)	1 (0.4)	0.35*	>0.99*
Mucositis	55 (19.5)	106 (37.6)	28 (9.9)	2 (0.7)	34 (12.1)	144 (51.1)	43 (15.2)	4 (1.4)	0.001*	0.04*
Dry mouth	88 (31.2)	98 (34.8)	2 (0.7)	0	88 (31.2)	106 (37.6)	4 (1.4)	0	0.36*	0.68*
Dysphagia	34 (12.1)	34 (12.1)	4 (1.4)	0	51 (18.1)	39 (13.8)	9 (3.2)	0	0.01*	0.16*
Weight loss	100 (35.5)	31 (11.0)	1 (0.4)	0	63 (22.3)	95 (33.7)	5 (1.8)	0	0.009*	0.22*
Trismus	0	0	0	0	0	1 (0.4)	0	0	>0.99†	—
Subcutaneous soft tissue	0	0	0	0	0	0	0	0	—	—
Any late toxicities‡										
Skin	63 (22.6)	8 (2.9)	0	0	56 (20.0)	22 (7.9)	0	0	0.52*	—
Neck tissue damage	48 (17.2)	22 (7.9)	0	0	52 (18.6)	20 (7.1)	4 (1.4)	0	0.58*	0.13*
Dysphagia	51 (18.3)	15 (5.4)	1 (0.4)	0	71 (25.4)	24 (8.6)	1 (0.4)	0	0.008*	>0.99*
Hoarseness	2 (0.7)	0	0	0	4 (1.4)	0	0	0	0.68*	—
Dry mouth	116 (41.6)	66 (23.7)	8 (2.9)	0	112 (40.0)	72 (25.7)	16 (5.7)	0	0.39*	0.10*
Trismus	11 (3.9)	3 (1.1)	0	0	13 (4.6)	6 (2.1)	0	0	0.38*	—
Auditory/hearing	108 (38.7)	21 (7.5)	4 (1.4)	0	107 (38.2)	40 (14.3)	8 (2.9)	0	0.07*	0.25*
Temporal lobe injury	18 (6.5)	1 (0.4)	0	0	24 (8.6)	0	0	0	0.43*	—

Safety analyses were done in the safety population, comprising all patients who commenced the randomly assigned treatment. MRLN=medial retropharyngeal lymph node; RT=radiotherapy.
*P values were calculated by χ^2 tests.
†P values were calculated by Fisher's exact tests.
‡Three patients in the MRLN sparing RT group and two patients in the standard RT group were lost to follow-up or died within three months after RT and thus the late toxicity analysis included 279 patients in the MRLN sparing RT group and 280 patients in the standard RT group.

returned EORTC QLQ-C30 questionnaires (201 (71.3%) *v* 217 (77.0%)), and 422 (74.8%) returned QLQ-H&N35 questionnaires (204 (72.3%) *v* 218 (77.3%)). Reasons for the missing questionnaires were reported as time and language constraints. At baseline, the two groups showed similar scores on the items assessed in the questionnaires, except for the role functioning item of the QLQ-C30, for which the MRLN sparing radiotherapy group showed a higher baseline score than the standard radiotherapy group (appendix 2 page 23). After three years of follow-up, questionnaires were completed at both baseline and year three by 340 (60.3%) patients for the EORTC QLQ-C30 questionnaires (162 (57.4%) in the MRLN sparing radiotherapy group *v* 178 (63.1%) in the standard radiotherapy group) and 367 (65.1%) patients for the QLQ-H&N35 questionnaires (174 (61.7%) in the MRLN sparing group *v* 193 (68.4%) in the standard radiotherapy group). The demographic and clinical characteristics of these patients were balanced between the treatment groups (appendix 2 pages 24-25). Quality-of-life analyses adjusted for the baseline values showed that compared with participants in the standard radiotherapy group, patients in the MRLN sparing radiotherapy group reported significantly better outcomes regarding global health status, role functioning, social functioning, and fatigue on the QLQ-C30 scale, and swallowing on the QLQ-H&N35 scale at three years post-radiotherapy, with improvement in the swallowing domain reaching clinical significance (mean difference 11.0 (95% confidence interval 8.4 to 13.6); table 3).

Discussion

Principal findings

To our knowledge, this randomised trial is the first to evaluate the noninferiority of sparing the MRLN region from elective radiotherapy volumes in comparison with standard radiotherapy encompassing both MRLN and LRLN regions in patients with non-metastatic nasopharyngeal carcinoma (T1-4, N0-3, M0). Our results showed that MRLN sparing radiotherapy is non-inferior to standard radiotherapy, with a small difference (−0.2%) in the primary endpoint of three year local relapse-free survival. Furthermore, the benefit of MRLN sparing radiotherapy was evident with fewer acute and late radiationinduced toxicities (especially in late dysphagia reduction) and improved scores in some health-related quality of life items (especially in swallowing domains, which reached clinical meaningful improvement).

Comparison with other studies

To date, no other report has shown how sparing the MRLN region from elective radiotherapy volumes affects patient outcome in nasopharyngeal carcinoma, except for our retrospective study[9] that formed the basis for this trial. The only similar published literature is a phase 2, single arm clinical trial of people with oropharyngeal cancer by Feng and colleagues,[27] in which the researchers also excluded the MRLN region from the radiotherapy targets, aiming to spare the important swallowing structures. The authors also reported high locoregional control rates and no recurrence adjacent the spared region.[27] Our prospective results were consistent with those results for the oncological outcomes after sparing the MRLN region from irradiation. Before this trial was conducted, several clues suggested the feasibility of including only the LRLN region in the targets and excluding the medial retropharyngeal lymph node in patients with nasopharyngeal carcinoma. Firstly, retropharyngeal lymph node involvement was mainly found at the lateral group, with few in the medial group, based on

Table 3 | Quality-of-life score at three years by treatment group. Data are mean (standard deviation), unless otherwise specified

	MRLN sparing RT	Standard RT	LS mean difference (95% CI)	P value
EORTC QLQ-C30*				
General QoL (the higher the better):				
Global health status	85.1 (13.1)	79.5 (19.8)	−5.6 (−9.1 to −2.0)	0.002
Physical functioning	98.8 (3.9)	97.4 (9.6)	−1.4 (−3.0 to 0.1)	0.07
Role functioning	99.6 (2.6)	94.0 (12.8)	−5.5 (−7.4 to −3.6)	<0.001
Emotional functioning	95.6 (9.3)	95.6 (8.6)	−0.04 (−1.9 to 1.8)	0.96
Cognitive functioning	95.4 (10.0)	95.3 (10.6)	0.02 (−2.2 to 2.2)	0.98
Social functioning	96.6 (7.2)	90.4 (16.4)	−6.2 (−8.9 to −3.6)	<0.001
Symptom burden (the lower the better):				
Fatigue	8.7 (14.2)	16.6 (22.2)	7.9 (4.0 to 11.8)	<0.001
Nausea and vomiting	1.3 (4.9)	2.7 (10.0)	1.4 (−0.3 to 3.0)	0.11
Pain	4.3 (10.9)	6.6 (12.9)	2.4 (−0.2 to 4.9)	0.07
Dyspnoea	3.5 (10.9)	3.6 (11.5)	0.08 (−2.3 to 2.4)	0.95
Insomnia	9.5 (17.2)	12.7 (20.7)	3.3 (−0.7 to 7.3)	0.11
Appetite loss	4.9 (14.5)	7.3 (15.5)	2.4 (−0.8 to 5.6)	0.14
Constipation	3.9 (11.4)	1.9 (7.7)	−2.2 (−4.3 to −0.05)	0.045
Diarrhoea	0.8 (5.2)	1.5 (6.9)	0.7 (−0.6 to 2.0)	0.31
Financial difficulties	12.3 (19.3)	13.5 (19.5)	1.2 (−2.9 to 5.4)	0.56
EORTC QLQ-H&N35†				
Symptom burden (the lower the better):				
Pain	2.5 (6.3)	3.4 (8.6)	0.9 (−0.6 to 2.4)	0.26
Swallowing	10.2 (12.4)	21.2 (13.1)	11.0 (8.4 to 13.6)	<0.001
Sense problems	4.1 (10.5)	4.6 (10.1)	0.4 (−1.7 to 2.5)	0.69
Speech problems	2.0 (6.2)	3.4 (7.8)	1.4 (−0.1 to 2.8)	0.06
Trouble eating in social environments	1.1 (6.1)	1.6 (6.1)	0.4 (−0.9 to 1.6)	0.54
Issues with social contact	0.9 (4.6)	1.3 (4.1)	0.4 (−0.5 to 1.3)	0.36
Lower libido	5.4 (12.0)	6.0 (12.9)	0.7 (−1.9 to 3.2)	0.60
Teeth	1.1 (7.1)	1.6 (7.0)	0.5 (−1.0 to 1.9)	0.54
Difficulty opening mouth	4.6 (13.1)	5.5 (14.2)	0.9 (−1.8 to 3.7)	0.51
Dry mouth	28.5 (15.9)	29.9 (15.2)	1.3 (−1.9 to 4.5)	0.41
Sticky saliva	28.0 (16.3)	29.9 (15.2)	2.0 (−1.3 to 5.2)	0.23
Coughing	5.7 (12.6)	6.7 (13.4)	1.0 (−1.7 to 3.6)	0.47
Felt ill	2.7 (9.8)	3.5 (11.3)	0.8 (−1.3 to 2.9)	0.46
Pain killers	8.6 (28.1)	8.3 (27.6)	−0.4 (−6.1 to 5.3)	0.90
Nutrition supplement	8.6 (28.1)	11.9 (32.5)	3.3 (−2.9 to 9.5)	0.30
Feeding tube	0.6 (7.6)	1.0 (10.2)	0.5 (−1.4 to 2.3)	0.62
Weight loss	8.6 (28.1)	14.0 (34.8)	5.3 (−1.1 to 11.7)	0.10
Weight gain	7.5 (26.4)	7.8 (26.8)	0.3 (−5.0 to 5.7)	0.90

The mean differences were adjusted for the baseline values. A higher score represented greater symptom severity (on symptom domains), or better health status (on the global health status) or function (on functioning domains). CI=confidence interval; EORTC=European Organization for Research and Treatment of Cancer; MRLN=medial retropharyngeal lymph node; RT=radiotherapy; LS=least squares; QLQ-C30=Quality-of-Life Core 30 items; QLQ-H&N35=Quality-of-Life Head and Neck 35 items; QoL=quality of life.
*N=162 for MRLN sparing RT and N=178 for standard RT.
†N=174 for MRLN sparing RT and N=193 for standard RT.

previous data from our group and others concerning the patterns of nodal spread for nasopharyngeal carcinoma,[1 4 8] which provided the rationale for excluding the MRLN region from the targets. Secondly, the contemporary imaging modality (eg, MRI and PET-CT) has improved accuracy in recognition of MRLN involvement at diagnosis. Thirdly, advances in radiotherapy techniques, such as intensity modulated radiation therapy with daily image guidance, permits the medial group to be distinguished dimensionally from the lateral group. Additionally these techniques allow for the delivery of different anticipated dose intensities to each group separately, which would not have been possible in the two dimensional radiotherapy era. Therefore, a method to spare the MRLN region instead of the complete coverage of the retropharyngeal lymph node region is achievable.

The exclusion of the MRLN region from the radiotherapy targets aided efforts to spare parts of the swallowing structures outside of the planning target volumes, resulting in significant dose reduction in the middle pharyngeal constrictor, inferior pharyngeal constrictor, and glottic and supraglottic larynx. We also found significant dose or volume reduction delivered to pharyngeal constrictors, which has translated into a clinical benefit in swallowing function as evident by a nearly 10% reduction in the incidence of clinician rated late dysphagia (24.0% *v* 34.3%). This reduction is clinically important for patients with nasopharyngeal carcinoma because late dysphagia is an irreversible morbidity that might lead to swallowing disfunction, malnutrition, and aspiration pneumonia, thus decreasing patients' quality of life. The incidence of late dysphagia in our control group was similar to that of the 35.4% reported previously after standard coverage irradiation in people with nasopharyngeal carcinoma,[5] providing a reliable reference for comparison. Additionally, a significant decrease in

acute dysphagia, mucositis, and weight loss were also observed in the MRLN sparing radiotherapy group. The acute inflammation of the mucosa attached to the surface of pharyngal constrictors is an important cause contributing to subjective disphysia.[28] Early after radiotherapy, acute mucositis is often accompanied with swallowing disfunction, which causes continuous pain, resulting in difficulty with oral eating, malnutrition, and weight loss for patients with head and neck cancer.[29] Late period after radiotherapy, inflammatory processes are major factors causing late anatomical changes and dysfunction of the submucosal pharyngeal constrictors.[30]

Notably, in our trial, compared with patients in the standard radiotherapy group, patients in the MRLN sparing radiotherapy group had significantly better outcomes regarding global health status, social functioning, role functioning, and fatigue on the QLQ-C30 scale, and swallowing on the QLQ-H&N35 scale, at three years after radiotherapy, with improvement in the swallowing domain reaching clinical significance. Our findings confirmed previous observations that reducing radiotherapy dose to a smaller volume of dysphagia or aspiration related structures contributes to improved patient reported swallowing function.[16 18 31] As far as we know, no study on quality of life has been published that compares MRLN sparing radiotherapy and standard radiotherapy in patients with nasopharyngeal carcinoma or other head and neck cancers, highlighting the importance of this article. The non-inferior design of tumour control met by MRLN sparing radiotherapy compared with standard radiotherapy should prompt more homogeneity research to confirm that sparing the MRLN region from elective irradiation volumes is the preferred treatment for patients with nasopharyngeal carcinoma.

Strengths and limitations of this study

Our trial shows the general applicability of sparing the MRLN region from elective radiotherapy volumes for patients with non-distant metastatic nasopharyngeal carcinoma, irrespective of its disease stage, treatment modality (radiotherapy alone *v* concurrent chemoradiotherapy *v* induction chemotherapy plus concurrent chemoradiotherapy), and pre-treatment examination (plasma Epstein-Barr virus value, with or without PET-CT). The reason for this generalisability is the wide ranging eligibility criteria: almost all patients who were screened and had stage I-IVA disease were included, except for the exclusion of only one patient with MRLN involvement, which was in accordance with the incidence of MRLN metastasis mentioned previously.[1 4 8] Furthermore, we analysed several subgroups, all of which had similar conclusions. Thus, we expect that most patients with non-metastatic, non-keratinising nasopharyngeal carcinoma could benefit from this treatment.

We are aware of the possibility of delayed disease failures and its impact on our results. However, our previous data for patients with nasopharyngeal carcinoma treated with intensity modulated radiation therapy showed that 83% of distant failure and 74% of death manifested before 42 months (the median follow-up of this trial) after primary treatment (taking the total number of corresponding events in five years as the denominator).[21] Thus, we believe that most events have already occurred at the end of our trial and that the number of events will not increase much, even with an extended follow-up, thereby supporting the robustness of our findings. Another factor is the extra events of distant metastases and deaths in the MRLN sparing radiotherapy group compared with the standard radiotherapy group. The non-significant difference of the absolute incidences in distant metastasis and death between the two groups, and the similar distant metastasis-free survival and overall survival of the two groups, provided evidence that such extra events in the intervention group were random errors.

The main limitation of our study is that the trial was conducted in nasopharyngeal carcinoma endemic regions where almost all nasopharyngeal carcinomas are caused by the Epstein-Barr virus. Therefore, the applicability our findings to non-endemic nasopharyngeal carcinoma cohorts (ie, nasopharyngeal carcinomas related to Epstein-Barr virus, HPV, and non-viral causes) is unclear. We believe that our results would be still applicable for nasopharyngeal carcinoma related to the Epstein-Barr virus in the non-endemic cohort because of their similar biology and patterns of failure; however, we are less certain for non-viral related nasopharyngeal carcinoma or HPV positive nasopharyngeal carcinoma because of a paucity of available data regarding lymphatic drainage patterns in these two groups. Also, PET-CT was not routinely used for staging in our trial because of the limitation of medical insurance. However, use of MRI in all patients could effectively prevent the need for PET-CT at baseline because of the superiority of MRI to PET-CT for showing retropharyngeal lymph nodes at their involvement.[32]

Conclusion

Our findings provided robust data to suggest that sparing the MRLN region from elective radiotherapy volumes is a safe way for local control and effectively preserves swallowing function, which could benefit almost all patients with non-keratinising, non-metastatic nasopharyngeal carcinoma. Our data provide high level evidence supporting routine MRLN sparing for non-metastatic nasopharyngeal carcinoma as a valid option to be considered by future nasopharyngeal carcinoma guidelines.

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Contributors: Y-PM, S-XW, T-SG, NZ, X-YL, and F-YX contributed equally to this study. Senior authors (Y-PM, L-LT, LC, YS, and JM) jointly directed this work. Y-PM, JM, YS, T-SG, and NZ were responsible for the study conception and design, supervision of the project, quality assessment, review, and approval of the manuscript. Y-PM, S-XW, L-LT, LC, and X-YL contributed to the design of clinical trial, writing of the protocol, the recruitment and treatment of patients, data and trial management, data analysis and interpretation, and writing and final approval of the report. Y-PM, S-QL, G-JQ, YZ, G-QZ, RG, W-JL, Y-JL, S-QL, LL, W-FL, XL, CX, Y-PC, J-WL, and F-YX were involved in the design of the clinical trial, the recruitment and treatment of patients, data and trial management, and review of the report. S-HH contributed to writing or review of the completed report. J-BL was responsible for the statistical analysis and interpretation, and the toxicity and data review. L-ZL was in charge of imaging diagnosis. Y-PM, JM, and L-LT were involved in the trial management and toxicity review. Y-PM, LC, JM, and YS have verified the underlying data. All authors read and approved the final draft of the report. The corresponding author (JM) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: This study was approved by the institutional review board or ethics committee at each site (5010-2017-04-02) and was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All participants provided written informed consent.

Data sharing: The key raw data underlying this study were uploaded to the Research Data Deposit public platform (RDDA2023145985). Reasonable requests for data sharing should be made to the corresponding author and will be handled in line with the data access and sharing policy of Human Genetic Resource Administration of China and other participating sites outside of China.

The corresponding author (JM) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities: Participating sites were informed of the results. The results can be communicated to study participants who express an interest during clinic visits. Dissemination to the public will be achieved through media outreach.

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Web appendix: Protocol and statistical analysis plan
Web appendix: Supplementary material