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Effect of Radiotherapy Alone vs Radiotherapy With Concurrent Chemoradiotherapy on Survival Without Disease Relapse in Patients With Low-risk Nasopharyngeal Carcinoma
A Randomized Clinical Trial

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IMPORTANCE Concurrent chemoradiotherapy has been the standard treatment for stage II nasopharyngeal carcinoma (NPC) based on data using 2-dimensional conventional radiotherapy. There is limited evidence for the role of chemotherapy with use of intensity-modulated radiation therapy (IMRT).

OBJECTIVE To assess whether concurrent chemotherapy can be safely omitted for patients with low-risk stage II/T3N0 NPC treated with IMRT.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, open-label, randomized, phase 3, noninferiority clinical trial was conducted at 5 Chinese hospitals, including 341 adult patients with low-risk NPC, defined as stage II/T3N0M0 without adverse features (all nodes <3 cm, no level IV/Vb nodes; no extranodal extension; Epstein-Barr virus DNA <4000 copies/mL), with enrollment between November 2015 and August 2020. The final date of follow-up was March 15, 2022.

INTERVENTIONS Patients were randomly assigned to receive IMRT alone (n = 172) or concurrent chemoradiotherapy (IMRT with cisplatin, 100 mg/m^2 every 3 weeks for 3 cycles [n = 169]).

MAIN OUTCOMES AND MEASURES The primary end point was 3-year failure-free survival (time from randomization to any disease relapse or death), with a noninferiority margin of 10%. Secondary end points comprised overall survival, locoregional relapse-free survival, distant metastasis-free survival, adverse events, and health-related quality of life (QOL) measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30; range, 0-100 points; minimum clinically important difference ≥10 for physical function, symptom control, or health-related QOL; higher score indicates better functioning and global health status or worse symptoms).

RESULTS Among 341 randomized patients (mean [SD] age, 48 [10] years; 30% women), 334 (98.0%) completed the trial. Median follow-up was 46 months (IQR, 34-58). Three-year failure-free survival was 90.5% for the IMRT-alone group vs 91.9% for the concurrent chemoradiotherapy group (difference, −1.4%; 1-sided 95% CI, −7.4% to ∞; *P* value for noninferiority, <.001). No significant differences were observed between groups in overall survival, locoregional relapse, or distant metastasis. The IMRT-alone group experienced a significantly lower incidence of grade 3 to 4 adverse events (17% vs 46%; difference, −29% [95% CI, −39% to −20%]), including hematologic toxicities (leukopenia, neutropenia) and nonhematologic toxicities (nausea, vomiting, anorexia, weight loss, mucositis). The IMRT-alone group had significantly better QOL scores during radiotherapy including the domains of global health status, social functioning, fatigue, nausea and vomiting, pain, insomnia, appetite loss, and constipation.

CONCLUSIONS AND RELEVANCE Among patients with low-risk NPC, treatment with IMRT alone resulted in 3-year failure-free survival that was not inferior to concurrent chemoradiotherapy.

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Visual Abstract
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Concurrent chemoradiotherapy is recommended for patients with stage II nasopharyngeal carcinoma (NPC) based on a single randomized clinical trial using 2-dimensional conventional radiotherapy.[1] Intensity-modulated radiotherapy (IMRT), a precision radiotherapy technique enabling conformation of high doses to concave-shaped tumors while protecting normal tissues, is now the standard of care for NPC. However, high-level evidence regarding the role of chemotherapy in stage II NPC with the use of IMRT is lacking.

Cisplatin-based concurrent chemoradiotherapy increases severe acute hematological and nonhematological toxicities.[2-4] It also increases critical weight loss during radiotherapy, which is independently associated with poor survival in NPC.[5,6] Moreover, concurrent chemoradiotherapy also increases risk of treatment-related death, which could decrease the therapeutic gain.[7]

Evidence suggests that most patients with stage II NPC treated with IMRT alone without chemotherapy may have excellent outcomes with 3-year or 5-year locoregional failure-free survival and distant metastatic-free survival exceeding 90%.[8-10] A retrospective propensity-matched cohort study showed that for patients with stage II and T3N0M0 NPC, addition of concurrent chemotherapy to IMRT was not associated with significantly better survival but induced significantly more severe toxicities.[8] The only phase 2 randomized clinical trial using IMRT also showed no improvement in survival or disease control using concurrent chemoradiotherapy but found damage to bone marrow function in patients with stage II NPC.[10] This raises the question of whether chemotherapy can be properly omitted from a subgroup of this patient population when proper exclusion criteria are applied.

The purpose of this clinical trial was to determine if the omission of concurrent chemotherapy (ie, treatment with IMRT alone) was noninferior to treatment with concurrent chemoradiotherapy in patients with low-risk NPC. For this trial, low risk was defined as stage II or T3N0M0 disease without adverse features.

Key Points

Question Is treatment with intensity-modulated radiation therapy (IMRT) alone noninferior to concurrent chemoradiotherapy among patients with low-risk nasopharyngeal carcinoma, defined as stage II and T3N0M0 without adverse features?

Findings In this randomized clinical trial that included 341 participants with low-risk nasopharyngeal carcinoma who received IMRT alone vs concurrent chemoradiotherapy, the 3-year failure-free survival rate was 90.5% vs 91.9%, respectively. The difference met the noninferiority margin criterion of 10%.

Meaning Among patients with low-risk nasopharyngeal carcinoma, IMRT alone compared with concurrent chemoradiotherapy was not inferior for 3-year failure-free survival.

Methods

Study Design and Participants

Patients were enrolled from 5 institutions in China to participate in an open-label, parallel-group, randomized, phase 3 noninferiority clinical trial (eTable 1 in Supplement 1). The study protocol and statistical analysis plan are provided in Supplement 2. The trial was carried out according to the principles of Good Clinical Practice guideline and the Declaration of Helsinki, as defined by the International Conference on Harmonisation, including compliance with relevant regulations. The study protocol was approved by the institutional ethics review board at each participating center. Written informed consent was obtained from all patients.

The eligibility criteria included histologically confirmed stage II and T3N0 NPC (by the 7th edition TNM) without adverse features (all lymph node[s] <3 cm,[11] no level IV/VB lymph nodes,[12,13] no extranodal extension,[14,15] and Epstein-Barr virus DNA<4000 copies/mL[8]); age between 18 and 65 years; Karnofsky performance scale score of at least 70; leukocyte count greater than 4×10^9/L, neutrophil count greater than 2×10^9/L, hemoglobin greater than 120 g/L, and a platelet count greater than 100×10^9/L; and adequate hepatic and kidney function.

Randomization and Masking

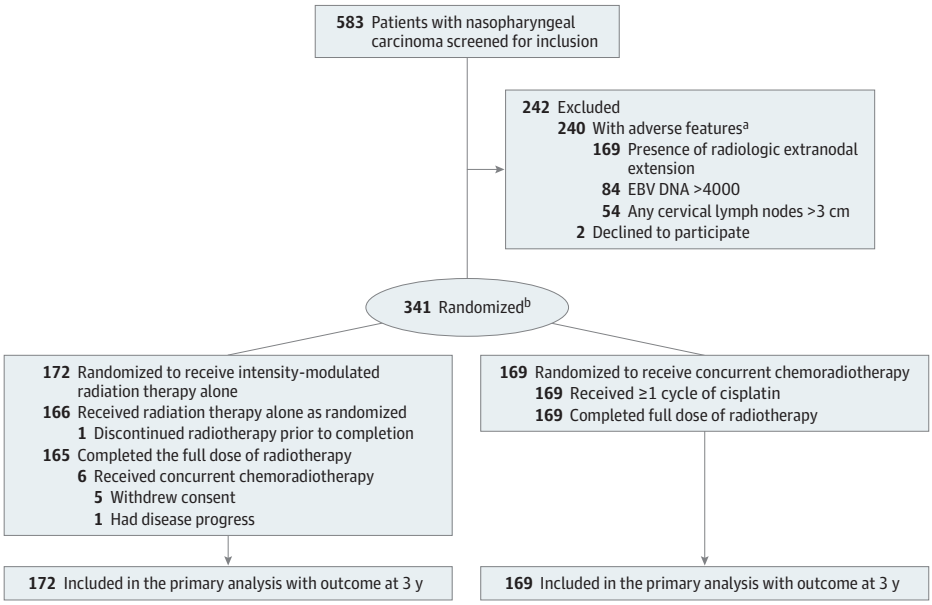
Randomization was carried out at the Clinical Trials Center of the Sun Yat-sen University Cancer Center. A computer program generated the assignment list. The randomization was stratified by trial center and T-N subset. Before treatment, patients were assigned randomly to receive either IMRT alone or concurrent chemoradiotherapy in a 1:1 ratio in blocks of 4. The block structure was known only to the statistician and the study coordinator. Once screening procedures were carried out completely at each center, the investigators received the treatment assignment from the study coordinator by telephone. Investigators and patients knew the treatment group assignment; however, the statisticians and the central imaging group, who were not involved in the trial clinically, were blinded to each patient's treatment assignment.

Procedures

Each patient underwent a complete assessment before treatment that comprised a physical examination; medical, biochemical, and hematological profiling; histopathological diagnosis; contrast-enhanced magnetic resonance imaging (MRI) of the head and neck; nasopharyngoscopy; radiography or computed tomography (CT) imaging of the chest; sonography or CT imaging of the abdomen; a bone scan; and baseline plasma Epstein-Barr virus DNA load determination. Optionally, whole-body fludoxyglucose F 18 (^{18}F-FDG) positron emission tomography (PET)-CT examination was carried out following local practices. Assessment of baseline characteristics was carried out within the 2 weeks prior to randomization.

In the concurrent chemoradiotherapy group, cisplatin was administered concurrently with radiotherapy at 100 mg/m^2 every 3 weeks for 3 cycles. All patients underwent IMRT. Target delineation was based on consensus guidelines.[16,17] The recommended prescribed dose was 68 to 70 Gy at 2.0 to 2.2 Gy per fraction administered (once per day, 5 fractions every week) (see eAppendix 2 in Supplement 1 for details of the radiotherapy guidelines; see Supplement 2 for supportive measures and the dose modifications of chemotherapy).

Figure 1. Screening, Randomization, and Patient Flow in a Trial of Intensity-Modulated Radiation Therapy (IMRT) Alone for Low-risk Nasopharyngeal Carcinoma



[a] Subcategorical numeric values exceed 240 because 56 patients had more than 1 adverse feature.

[b] Randomization was stratified by trial center and staging subset.

EBV indicates Epstein-Barr virus.

Follow-up was scheduled every 3 months for the first 3 years and every 6 months in subsequent years. Fine-needle aspiration or biopsy was used to confirm distant metastasis or locoregional failure whenever possible. For the clinical diagnosis of disease relapse, at least 2 imaging modalities (in the presence or absence of clinical symptoms) were used for inaccessible lesions with typical radiographic features, including ^{18}F-FDG PET-CT, bone scans, abdominal sonography, chest radiograph, MRI, and CT. In cases of equivocal imaging findings, the diagnosis was ascertained at subsequent follow-up. In cases of confirmed tumor progression, salvage therapies (eg, reirradiation, chemotherapy, or surgery) were administered whenever possible (eTable 2 in Supplement 1).

The National Cancer Institute Common Toxicity Criteria for Adverse Events (version 4.0 scale) was used to grade acute radiation and chemotherapy toxicities. The Radiation Therapy Oncology Group and European Organisation for Research and Treatment of Cancer (EORTC) were used to grade late radiation toxic effects.[18] The EORTC Quality of Life Core 30 items (QLQ-C30) questionnaire was used to assess overall quality of life (QOL).[19]

Outcomes

The primary end point was 3-year failure-free survival, defined as the time between randomization and disease relapse (either locoregional failure or distant metastasis) or any cause of death, whichever occurred first. The secondary end points comprised overall survival (the period between randomization and death), locoregional relapse-free survival (the period between randomization and documented locoregional failure or death), distant metastasis-free survival (the period between randomization and documented distant metastasis or death), safety, and health-related QOL.

Data for QOL were collected using printed questionnaires before the initiation of treatment and thereafter once per week during the remaining course of radiotherapy. Scales representing health status, symptoms, or function were used to score the patients' responses to items on the EORTC QLQ-C30 questionnaire. All items pointing to a domain were transferred to mean points, which were then transformed to a 0-100 scale following the instructions in the EORTC scoring manual. 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. For QOL analysis, a mean difference of 10 points or greater in QOL score was considered to be clinically important.[20] Late toxicities were assessed at every scheduled follow-up visit. Patients who first experienced locoregional failure were censored for distant metastasis and vice versa. At the last follow-up date, patients who remained alive with no locoregional failure or distant metastasis or who were lost to follow-up were censored.

Sample Size Calculation

The trial was designed to establish whether in the low-risk NPC cohort, IMRT alone was noninferior compared with concurrent chemoradiotherapy in terms of 3-year failure-free survival. Based on previous reports,[8] the 3-year failure-free survival was assumed to be 90%. According to expert consensus, data from institutional experiences, and published literature,[21-23] a 10% difference was set as the noninferiority margin. Noninferiority was concluded if the upper boundary of the 1-sided 95% CI for the difference in 3-year failure-free survival was not greater than 10%. Assuming a 5% 1-sided type I error rate and a 5% dropout rate, at least 338 patients (169 per group) were estimated to be necessary to provide the trial with 80% power.

Statistical Analysis

Patients in the full analysis set were analyzed according to their randomization group regardless of any subsequent deviation of the protocol. Missing time-to-event data due to patient loss of follow-up were treated as censored data. For the 2 treatment groups, the Kaplan-Meier method was used to estimate actuarial rate of survival with log-rank tests for comparisons. The hazard ratios (HRs) and their associated 95% CIs (adopting treatment as a single covariate) were calculated using a stratified Cox proportional hazards model (stratified by trial center, T categories and N categories); the assumption of proportional hazards was confirmed using Schoenfeld residuals.[24] The Cox proportional hazards model was also used to test the treatment-by-covariate interaction, which determined if the treatment effect varied among prespecified subgroups of patients: interaction with age, Karnofsky performance scales, sex, T categories, and N categories.[19] Multivariable analyses were also carried out using a Cox proportional hazards model. The covariates were nodal status (N1 vs N0), T-categories (T3 vs T1, T2 vs T1), age (a continuous variable), and sex (male vs female).

Safety analysis was performed on the safety population, defined as patients who received actual treatment consistent with the protocol (patients treated with IMRT alone in the IMRT-alone group, and patients who received at least 1 cycle of concurrent chemotherapy in concurrent chemoradiotherapy group). Each week during treatment, health-related QOL was assessed, which was analyzed using a mixed-effect model.

Analyses were performed using SPSS software (version 26.0; IBM Corp) and R (version 3.5.1). The statistical test used to assess the primary end point was 1-sided, and a *P* value of less than .05 indicated statistical significance. Other statistical tests were 2-sided, and a *P* value of less than .05 also indicated statistical significance. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory.

Results

Between November 11, 2015, and August 4, 2020, a total of 341 patients with NPC across 5 sites underwent randomization and were included in the primary analyses. The IMRT-alone group consisted of 172 patients, and the concurrent chemoradiotherapy group consisted of 169 patients (**Figure 1**). Between the 2 groups, the baseline characteristics were well-balanced (**Table 1**). All were nonkeratinizing tumors. Of the 341 patients enrolled in this trial, 163 had tumors assayed for Epstein-Barr virus-encoded RNA (EBER), and 159 (97.5%) were positive.

In the IMRT-alone group, 165 of 172 (95.9%) completed the protocol-defined therapy and were included in the safety population. Six of the 172 patients received concurrent chemoradiotherapy of whom 5 (2.9%) withdrew consent and 1 (<1%) had disease progression during treatment. One (<1%) of the 172 patients discontinued radiotherapy because of patient decision. All 169 patients (100%) in the concurrent chemoradiotherapy group received at least 1 concurrent cycle of chemotherapy and were included in the safety population.

Table 1. Baseline Characteristics

Variable	Group, No. (%)	
	IMRT alone (n = 172)	Concurrent chemoradiotherapy (n = 169)
Age, median (range), y	48 (22-65)	48 (23-65)
Sex		
Male	117 (68)	122 (72)
Female	55 (32)	47 (28)
Smoking history, past or current[a]	130 (76)	125 (74)
Positive family history of NPC	15 (9)	20 (12)
Karnofsky performance scales[b]		
70-80	1 (1)	1 (1)
90-100	171 (99)	168 (99)
Parapharyngeal involvement	122 (71)	115 (68)
Maximum lymph nodes size >20 mm	29 (17)	39 (23)
Hemoglobin level, median, (IQR), g/dL	146 (136-156)	144 (134-154)
EBV DNA, copies/mL >1000	17 (10)	18 (11)
Nonkeratinizing histology[c]	172 (100)	169 (100)
Positive EBV-encoded RNA status	74/76 (97)	85/87 (98)
Staging group[d]		
T2N0	28 (16)	21 (12)
T3N0	43 (25)	44 (26)
T1N1	36 (21)	33 (20)
T2N1	65 (38)	71 (42)

Abbreviations: EBV, Epstein-Barr virus; IMRT, intensity-modulated radiation therapy; NPC, nasopharyngeal carcinoma.

[a] Smoking did not include other methods, such as smoking of cigars or pipes, vaping, or chewing of tobacco.

[b] The index of Karnofsky performance scales is a primarily subjective score of physical ability used to assess the ability of a patient to carry on normal activities in life from normal health (100) to disabled (50) and death (0).

[c] The World Health Organization has historically classified NPC into 3 histologic types: keratinizing, nonkeratinizing, and basaloid squamous cell carcinoma. Nonkeratinizing histology type is generally considered viral-mediated nasopharyngeal carcinoma.

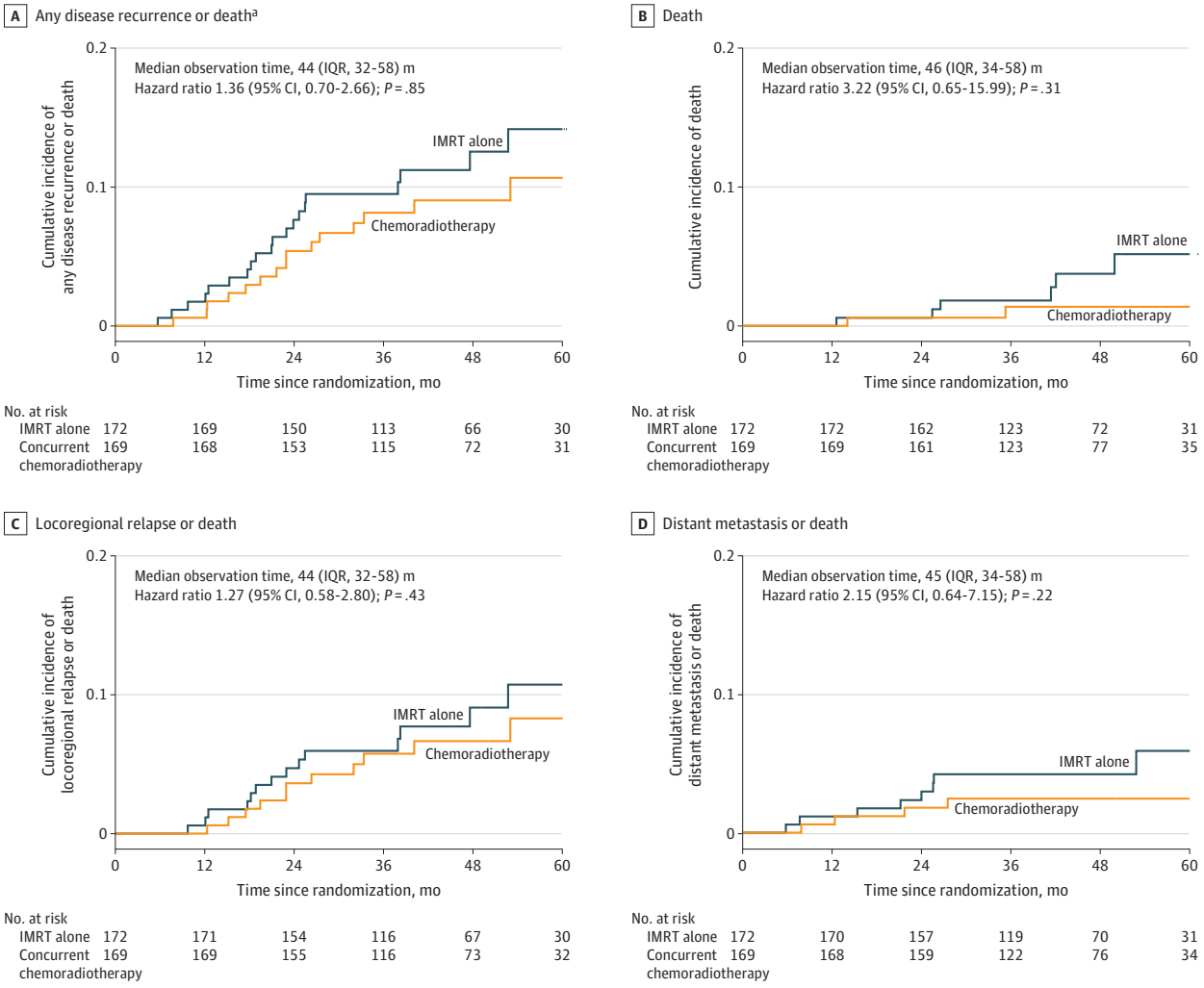
[d] Indicates descriptions according to the 7th edition TNM staging system: T1, nasopharynx, oropharynx or nasal cavity without parapharyngeal extension; T2, parapharyngeal extension; T3, bony structures of skull base and/or paranasal sinuses; N0, no regional lymph node metastasis; N1, unilateral cervical, unilateral, or bilateral retropharyngeal lymph nodes above the supraclavicular fossa and less than or equal to ≤6 cm.

In the concurrent chemoradiotherapy group, 102 of the 169 patients (60.4%) received 3 cycles of concurrent cisplatin chemotherapy, 62 (36.7%) received 2 cycles, and 5 (3.0%) received 1 cycle (eTable 4 in Supplement 1). The main reasons for not receiving all 3 cycles included adverse events and patient decision not to receive. Overall, 150 of 169 patients (88.8%) in the concurrent chemoradiotherapy group were administered at least 200 mg/m^2 of cisplatin. Between the 2 groups, the time taken to complete radiotherapy and the doses of radiotherapy delivered were not significantly different (eTable 4 in Supplement 1).

Primary Outcome

The median follow-up on the last follow-up date (March 15, 2022) was 46 months (IQR, 34-58 months). Locoregional failure

Figure 2. Kaplan-Meier Estimates in 341 Patients With Low-risk Nasopharyngeal Carcinoma Stratified by the Randomization Group



The hazard ratios (HRs) and their associated 95% CIs were determined using an adjusted Cox proportional-hazards model.

was identified in 24 patients (13 of 172 [7.6%] in the IMRT-alone group vs 11 of 169 [6.5%] in the concurrent chemoradiotherapy group; $P = .71$), and distant metastasis was identified in 12 patients (8 [4.7%] in the IMRT-alone group vs 4 [2.4%] in the concurrent chemoradiotherapy group; $P = .25$). Detailed information on death, locoregional failure, and distant metastasis is reported in eTable 3 in Supplement 1.

The primary outcome of estimated 3-year failure-free survival in the IMRT-alone vs concurrent chemoradiotherapy groups was 90.5% vs 91.9% (difference, −1.4% [1-sided 95% CI, −7.4% to ∞]), which met the noninferiority criterion ($P < .001$ for noninferiority). The adjusted HR was 1.36 (95% CI, 0.70-2.66; $P = .85$) (**Figure 2**A).

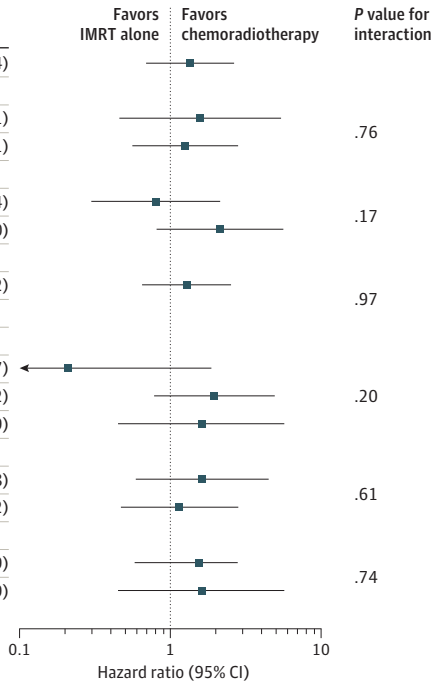
Secondary Outcomes

For the secondary end points, the 3-year overall survival, locoregional relapse-free survival, and distant metastasis-free survival were not significantly different between the IMRT-alone and concurrent chemoradiotherapy groups: 98.2% vs 98.6% for overall survival (difference, −0.4%; [95% CI, −3.1% to 2.3%]; $P = .31$; Figure 2B), 94.0% vs 94.3% for locoregional relapse-free survival (difference, −0.3% [95% CI, −5.3% to 4.7%]; $P = .43$; Figure 2C) and 95.8% vs 97.6% for distant metastasis-free survival (difference, −1.8% [95% CI, −5.6% to 2.0%]; $P = .22$; Figure 2D).

QOL data at all valid time points (at initiation of treatment and thereafter [once per week during the whole course of radiotherapy]) were collected from 108 (65.5%) patients in the IMRT-alone group and 109 (64.5%) patients in the concurrent chemoradiotherapy group. The baseline characteristics and pretreatment QOL did not differ significantly between groups (eTables 6 and 7 in Supplement 1). The IMRT-alone group had significantly better QOL during radiotherapy for symptom burden (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation) and presented better general QOL scores (global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning; all $P < .001$ for all categories)

Figure 3. Failure-Free Survival According to Subgroup

	Disease recurrence or death No./total No.		Absolute difference of failure-free survival (95% CI)	Hazard ratio[a] (95% CI)	*P* value for interaction
	IMRT alone	Chemoradiotherapy			
Overall	20/172	15/169	-0.01 (-0.07 to ∞)	1.35 (0.69 to 2.64)	
Sex					
Female	7/55	4/47	-0.05 (-0.15 to 0.06)	1.58 (0.46 to 5.41)	.76
Male	13/117	11/122	0 (-0.07 to 0.07)	1.26 (0.56 to 2.81)	
Age, y					
<48	7/80	9/80	0.01 (-0.08 to 0.10)	0.80 (0.30 to 2.14)	.17
≥48	13/92	6/89	-0.04 (-0.12 to 0.04)	2.13 (0.81 to 5.60)	
Karnofsky performance scale[b]					
90-100	19/171	15/168	-0.01 (-0.07 to 0.05)	1.28 (0.65 to 2.52)	.97
70-80	1/1	0/1	NA	NA	
T category[a]					
T1	1/36	4/33	0.07 (-0.05 to 0.18)	0.21 (0.02 to 1.87)	
T2	13/93	7/92	-0.02 (-0.10 to 0.06)	1.96 (0.78 to 4.92)	.20
T3	6/43	4/44	-0.07 (-0.20 to 0.06)	1.61 (0.45 to 5.69)	
N category[c]					
N0	10/71	6/65	-0.05 (-0.15 to 0.06)	1.63 (0.59 to 4.48)	.61
N1	10/101	9/104	0.01 (-0.06 to 0.08)	1.15 (0.47 to 2.82)	
Stage[d]					
II	14/129	11/125	0 (-0.06 to 0.07)	1.27 (0.58 to 2.79)	.74
III	6/43	4/44	-0.07 (-0.20 to 0.06)	1.61 (0.45 to 5.69)	



[a] Hazard ratios (HRs) and the associated 95% CIs were calculated using an unadjusted Cox proportional hazards model, which was also used to carry out the interaction test, incorporating the interaction term (eg, age × treatment), a covariate of interest (eg, sex), and the trial group. An HR of less than 1 indicated a decreased risk of failure-free survival after intensity-modulated radiation therapy alone compared with that after concurrent chemoradiotherapy.

[b] The index of Karnofsky performance scales is a primarily subjective score of physical ability used to assess the ability of a patient to carry on normal activities in life from normal health (100) to disabled (50) and death (0).

[c] According to the 7th edition TNM Staging System. ; T1: Nasopharynx, oropharynx or nasal cavity without parapharyngeal extension; T2: Parapharyngeal extension; T3: Bony structures of skull base and/or paranasal sinuses; N0: No regional lymph node metastasis; N1: Unilateral cervical, unilateral or bilateral retropharyngeal lymph nodes, above the supraclavicular fossa; ≤6 cm.

[d] Stage II includes T2N0 and the T1-2N1 subset; stage III includes T3N0 subset.

(eTable 8 in Supplement 1). There were significant differences favoring IMRT alone in the QOL score for global health status (mean difference, 12.2 [95% CI, 10.6 to 13.8]), social functioning (mean difference, 10.8 [95% CI, 8.7 to 12.8]), fatigue (mean difference, −11.8 [95% CI, −13.4 to −10.2]), nausea and vomiting (mean difference, −12.8 [95% CI, −14.5 to −11.1]), pain (mean difference, −10.2 [95% CI, −11.7 to −8.7]), insomnia (mean difference, −10.4 [95% CI, −12.5 to −8.2]), appetite loss (mean difference, −15.2 [95% CI, −17.4 to −13.1]), and constipation (mean difference, −17.8 [95% CI, −19.8 to −15.9]) (eFigure 5 in Supplement 1).

Prespecified Exploratory Analyses

A prespecified subgroup analysis was conducted based on baseline characteristics, and no significant interactions were observed between the treatment groups and the subgroups. Failure-free survival was consistent across all subgroups, including age, Karnofsky performance scales, sex, T and N cancer stages, and overall categories (**Figure 3**). Failure-free survival was not significantly different between the treatment groups for T and N cancer stages, overall categories, and centers (eFigures 1-4 in Supplement 1). Multivariable analyses in full set also showed concurrent chemotherapy was not an independently prognostic factor (eTable 5 in Supplement 1).

Adverse Events

During the entire treatment course, in the safety population there was a significantly lower incidence of reported grade 3 or 4 adverse events in the IMRT-alone group (28 [17%]) vs the concurrent chemoradiotherapy group (78 [46%]) with a difference of −29% (95% CI, −39% to −20%; $P < .001$). No treatment-related deaths occurred in either group. Compared with the concurrent chemoradiotherapy group, there was a significantly lower incidence of grade 3 or 4 hematological toxicities and nonhematological toxicities in the IMRT-alone group for leukopenia (2 [1%] vs 17 [10%]), neutropenia (3 [2%] vs 11 [7%]), nausea (1 [1%] vs 22 [13%]), vomiting (2 [1%] vs 25 [15%]), anorexia (8 [5%] vs 49 [29%]), weight loss (1 [1%]) vs 8 [5%]), and mucositis (16 [10%] vs 32 [19%]). The incidence of grade 1 or 2 toxicities was also significantly lower in the IMRT-alone group than in the concurrent chemoradiotherapy group (**Table 2**).

Regarding late toxicities, 73% (121/165) of the patients in the IMRT-alone group experienced late toxic effects compared

Table 2. Acute and Late Adverse Events Related to Radiotherapy and Chemotherapy

Event[a]	Group, No. (%)[b]			
	IMRT alone (n = 165)		Concurrent chemoradiotherapy (n = 169)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Acute toxicities				
Hematologic				
Leukocytes <4000/μL	37 (22)	2 (1)	103 (61)	17 (10)
Hemoglobin <lower limits of normal	27 (16)	0	127 (75)	3 (2)
Neutropenia <2000/μL	12 (7)	3 (2)	60 (36)	11 (7)
Thrombocytopenia <10^5/μL	2 (1)	1 (1)	41 (24)	1 (1)
Nonhematologic				
Mucositis	116 (70)	16 (10)	113 (67)	32 (19)
Dry mouth	33 (20)	0	50 (30)	0
Dermatitis	31 (19)	0	54 (32)	0
Weight loss	28 (17)	1 (1)	94 (56)	8 (5)
Anorexia	22 (13)	8 (5)	28 (17)	49 (29)
Vomiting	14 (8)	2 (1)	48 (28)	25 (15)
Nausea	14 (8)	1(1)	57 (34)	22 (13)
Dysphagia	5 (3)	1 (1)	22 (13)	3 (2)
Fever	0	0	0	1 (1)
Increase > upper limits of normal				
Creatinine	16 (10)	0	58 (34)	1 (1)
ALT	10 (6)	0	34 (20)	1 (1)
GGT	8 (5)	1 (1)	28 (17)	0
AST	3 (2)	0	14 (8)	0
ALP	1 (1)	0	7 (4)	0
Late toxicities				
Dry mouth	90 (55)	0	96 (57)	1 (1)
Auditory/hearing	66 (40)	1 (1)	80 (47)	1 (1)
Skin/neck tissue damage	35 (21)	1 (1)	50 (30)	0
Hypothyroidism	31 (19)	4 (2)	60 (36)	1 (1)
Peripheral neuropathy	6 (4)	0	17 (10)	0
Temporal lobe injury	6 (4)	0	6 (4)	0
Trismus	3 (2)	0	3 (2)	0
Bone necrosis	1 (1)	0	0	0

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, gammaglutamyl transferase; IMRT, intensity-modulated radiation therapy.

[a] The National Cancer Institute Common Toxicity Criteria version 4.0 scale was used to grade acute radiation and chemotherapy toxicities. The late radiation morbidity scoring schemes of The Radiation Therapy Oncology Group and European Organisation for Research and Treatment of Cancer (EORTC) was used to grade late radiation toxic effects. (as detailed in the study protocol, see Supplement 2). The adverse event grading system rates adverse events from mild (1) to death (5) with 3 or 4 representing severe or potentially life-threatening events.

[b] Indicates patients who received actual treatment consistent with protocol (patients treated only with IMRT in IMRT-alone group and patients who received at least 1 cycle of concurrent chemotherapy in concurrent chemoradiotherapy group). No treatment-related deaths occurred in either group.

with 80% (136/169) of those in the concurrent chemoradiotherapy group (Table 2). The IMRT-alone group had lower incidence for grade 1 or 2 peripheral neuropathy (4% vs 10%; $P = .02$) and hypothyroidism (19% vs 36%; $P = .001$) (Table 2). The overall incidences of grade 3 or 4 were not significantly different (4% vs 2%; $P = .48$).

Discussion

In this multicenter randomized phase 3 clinical trial of patients with low-risk stage II or T3N0 NPC, treatment with IMRT alone resulted in 3-year failure-free survival that was not inferior to concurrent chemoradiotherapy. To the best of our knowledge, this is the first trial to demonstrate these findings.

Current National Comprehensive Cancer Network guidelines (version 2; 2022) report use of IMRT alone as an option only for a small subset of stage II (T2N0) NPC, while the remaining stage II (T1-2N1) and T3N0 disease mandates chemotherapy together with IMRT. This study of patients with nodal size less than 3 cm, absence of radiologic extranodal extension, and Epstein-Barr virus DNA titer less than 4000 copies/mL identified a low-risk subset of patients within stage II and T3N0 NPC who are suitable for IMRT-alone approach. The findings of this trial are consistent with the propensity-matched analysis from Zhang et al,[8] which showed that for patients with stage II and T3N0M0 disease treated using IMRT, concurrent chemotherapy was not associated with significant survival benefit but was associated with significantly more severe acute toxicities.

The trial results were different from studies on stage II NPC conducted in the 2-dimensional conventional radiotherapy era that showed concurrent cisplatin chemotherapy provided radio sensitization to enhance locoregional control and overall survival.[4,25,26] It is possible that IMRT may have maximized locoregional control in many patients with low-risk NPC, which is generally radiosensitive, as supported by more than 90% locoregional relapse-free survival rates in almost all

contemporary series for stage II disease.[9] This suggests little therapeutic gain and worse QOL when adding concurrent cisplatin to IMRT if a patient is at low risk of disease relapse.

This trial demonstrated better functional outcome with omission of chemotherapy. In the era of IMRT use, only 1 phase 2 randomized clinical trial (NCT01187238) has been carried out, including 84 eligible patients with stage II NPC (by 6th edition TNM).[10] That study showed no improvement in survival or disease control using concurrent chemoradiotherapy but had a small sample and lacked QOL data. Liu et al[27] performed a meta-analysis that also showed that for patients with stage II NPC, adding concurrent chemotherapy to IMRT was not associated with a survival benefit but was associated with increased acute toxicities.

In contemporary cancer management, QOL preservation has become increasingly important,[28] particularly when considered together with improved survival. To our knowledge, there have been no prior studies reporting prospective QOL data for concurrent chemoradiotherapy vs IMRT alone in patients with NPC. However, patients affected by psychological and physical factors, such as depression and fatigue, might have been less able to complete the QOL assessment, which depended on the length, delivery, and response format of the questionnaire.[28]

Adherence with 3 cycles of concurrent chemotherapy in this trial (60.4%) was similar to other studies (52%-63%),[3,4] and 88.8% in the concurrent chemoradiotherapy group were administered at least 200 mg/m^2 of cisplatin. Previous research demonstrated that 200 mg/m^2 during concurrent chemoradiotherapy is adequate to achieve satisfactory survival outcomes for patients with locoregionally advanced NPC.[29] The most common reasons for concurrent chemotherapy discontinuation were due to of patient decision and treatment toxicities. Regarding late toxicities, patients in the IMRT-alone group had lower incidence for grade 1 or 2 peripheral neuropathy and hypothyroidism. Both groups had low rates of severe late complications and no treatment-related deaths were recorded.

Limitations

This trial had several limitations. First, it was carried out in an endemic area where almost all NPCs were caused by Epstein-Barr virus; therefore, whether the findings are applicable in nonendemic populations (eg, North America and Europe), where NPC might be related to factors other than Epstein-Barr virus infection remains to be determined. However, contemporary studies from nonendemic regions showed that the majority of NPC in those regions were still caused by Epstein-Barr virus or human papillomavirus, while nonviral NPC was very rare.[14] There is no evidence to suggest that Epstein-Barr virus–positive NPC in a nonendemic cohort would respond differently. Moreover, Epstein-Barr virus–related and human papillomavirus–related NPC appear to have similar radiosensitivity.[30-32]

Second, the Epstein-Barr virus DNA cutoff of greater than 4000 copies/mL was used as an exclusion criterion based on a previous publication from the same center as this trial. This cutoff may not be applicable to all other centers without international harmonization of Epstein-Barr virus DNA assays.[33]

Third, this trial used 7th edition TNM for inclusion and exclusion. The eligibility criteria for N classification would not change using the 8th edition TNM. However, there might be rare occasions (<5%)[34] in which the 7th edition T4 with adjacent soft tissue extension would be reclassified as T2 in the 8th edition. Caution is needed to apply the trial's findings to such cases.

Fourth, although the noninferiority criterion was met, the effectiveness in a clinical rather than trial setting may not be the same.

Conclusions

Among patients with low-risk nasopharyngeal carcinoma, treatment with intensity-modulated radiation therapy alone resulted in 3-year failure-free survival that was not inferior to concurrent chemoradiotherapy.

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