DOI: 10.1093/jnci/djr432
Advance Access publication on November 4, 2011.

ARTICLE

Concurrent Chemoradiotherapy vs Radiotherapy Alone in Stage II Nasopharyngeal Carcinoma: Phase III Randomized Trial

Qiu-Yan Chen, Yue-Feng Wen, Ling Guo, Huai Liu, Pei-Yu Huang, Hao-Yuan Mo, Ning-Wei Li, Yan-Qun Xiang, Dong-Hua Luo, Fang Qiu, Rui Sun, Man-Quan Deng, Ming-Yuan Chen, Yi-Jun Hua, Xiang Guo, Ka-Jia Cao, Ming-Huang Hong, Chao-Nan Qian, Hai-Qiang Mai

Manuscript received April 25, 2011; revised September 15, 2011; accepted September 27, 2011.

Correspondence to: Hai-Qiang Mai, MD, PhD, Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, 651 Dongfeng Rd East, Guangzhou 510060, People's Republic of China (e-mail: maihq@mail.sysu.edu.cn).

Background Concurrent chemoradiotherapy (CCRT) has been shown to improve outcomes for stage III–IV nasopharyngeal carcinoma (NPC) patients compared with radiotherapy (RT) alone, but the effectiveness of the combined therapy for stage II NPC patients is unknown.

Methods Patients with Chinese 1992 stage II NPC were randomly assigned to receive either RT alone (n = 114) or CCRT (n = 116). The CCRT patients were given concurrent cisplatin (30 mg/m^2 on day 1) weekly during RT. The primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival (PFS), distant metastasis-free survival, and locoregional relapse-free survival. All patients were analyzed by the intent-to-treat principle. The Cox proportional hazards model was used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) and in multivariable analyses to test the independent statistical significance of treatment intervention. Toxic effects and the response to treatment were analyzed using the χ^2 test. All statistical tests were two-sided.

Results With a median follow-up of 60 months, adding chemotherapy statistically significantly improved the 5-year OS rate (94.5% vs 85.8%; HR of death = 0.30, 95% CI = 0.12 to 0.76; P = .007), PFS (87.9% vs 77.8%; HR of progression = 0.45, 95% CI = 0.23 to 0.88; P = .017), and distant metastasis-free survival (94.8% vs 83.9%; HR of distant relapse = 0.27, 95% CI = 0.10 to 0.74; P = .007); however, there was no statistically significant difference in the 5-year locoregional relapse-free survival rate (93.0% vs 91.1%; HR of locoregional relapse = 0.61, 95% CI = 0.25 to 1.51; P = .29). Multivariable analysis showed that the number of chemotherapy cycles was the only independent factor that was associated with OS, PFS, and distant control in stage II NPC. The CCRT arm experienced statistically significantly more acute toxic effects (P = .001), although the rate of late toxic effects did not increase statistically significantly.

Conclusion Concurrent chemotherapy and radiotherapy is associated with a considerable survival benefit for patients with stage II NPC.

J Natl Cancer Inst 2011;103:1761–1770

Nasopharyngeal carcinoma (NPC) is endemic in Southern China and Southeast Asia (1,2). Radiotherapy (RT) is the primary treatment modality. Several prospective randomized trials (3–8) and meta-analyses (9–11) have demonstrated that concurrent chemoradiotherapy (CCRT) with or without adjuvant chemotherapy is superior to RT alone in the treatment of locoregionally advanced NPC. The prognosis of patients with stage I–II NPC is generally favorable, and this group of patients has largely been excluded from clinical trials of the combined modality treatment.

Although the National Comprehensive Cancer Network has recommended CCRT for stage II NPC, the evidence for its efficacy is weak. The role of adjunctive chemotherapy for stage II patients has not been defined as a primary endpoint by a phase III study, and some studies advocate the use of CCRT (12,13) or neoadjuvant chemotherapy (14). Cheng et al. (12) have shown that disease-free survival of patients with stage II disease with CCRT is equal to that of patients with stage I disease with RT alone. Their study suggests that CCRT reverses the unfavorable prognosis of patients with stage II NPC, reducing their risk of failure to that in patients with stage I disease. Chemotherapy for stage II NPC is not recommended in the guidelines proposed by the Chinese Anti-Cancer Association because current evidence has not demonstrated the advantage of CCRT compared with RT alone. It has been reported (14,15) that chemotherapy is more effective for low-risk patients than for high-risk NPC patients. The primary objective of this study was to determine the overall survival (OS) benefits for

CONTEXTS AND CAVEATS

Prior knowledge

Treatment of stage III–IV nasopharyngeal carcinoma (NPC) patients with concurrent chemoradiotherapy (CCRT) has been shown to improve outcomes, but there are no data on treatment outcomes of the combined therapy for stage II NPC patients.

Study design

In a randomized phase III trial, patients with stage II NPC were randomly assigned to radiotherapy alone (RT) or to CCRT.

Contribution

Adding chemotherapy to RT statistically significantly improved the 5-year overall survival, progression-free survival, and distant metastasis-free survival. Acute toxic effects were higher for patients treated with CCRT. However, late toxic effects were similar for the two groups.

Implication

Combined chemotherapy and radiotherapy treatment also confers survival benefits to stage II NPC patients.

Limitations

Computed tomography of the chest was not performed as part of pretreatment evaluation or follow-up. Thus, some early lung metastases may not have been detected. All patients underwent conventional two-dimensional RT. However, intensity-modulated RT may be more effective for locoregional control, thus reducing the added benefit of chemotherapy.

From the Editors

patients with Chinese 1992 stage II NPC with the addition of concurrent, weekly cisplatin-based (30 mg/m^2) CRT. The secondary objectives of this study were to compare the tumor response, progression-free survival (PFS), distant metastasis-free survival (DMFS), locoregional relapse-free survival (LRRFS), and acute and late toxic effects of patients between the two treatment arms.

Methods

Eligibility Criteria

Patients were evaluated using the Chinese 1992 staging system (16) (widely adopted in mainland China; Supplementary Table 1, available online) and were eligible for this study if they fulfilled all of the following criteria: biopsy-proven World Health Organization (WHO) types II–III NPC (17), Stage II disease (T1-2N1M0 or T2N0M0 with parapharyngeal space involvement), between ages 18 and 70 years, adequate hematologic function (white blood cell counts $\geq$ 4000/μL and platelet counts $\geq$ 100 000/μL), adequate renal function (creatinine clearance $\geq$ 50 mL/min), adequate hepatic function (serum bilirubin level < 1.5 mg/dL), and satisfactory performance status (a score of 0 or 1 using the Eastern Cooperative Oncology Group System). The exclusion criteria included previous treatment of NPC, the presence of a distant metastasis, or prior malignancy (except carcinoma in situ of the cervix or basal/squamous cell carcinoma of the skin). All of the patients were recruited from Sun Yat-sen University Cancer Center. This study was approved by the Clinical Research Ethics Committee of the Sun Yat-sen University Cancer Center, and patients were required to provide written informed consent before entering the study.

Study Design

Based on previous data, the 5-year OS rate of patients with Chinese 1992 stage II NPC using RT alone was assumed to be 80%, whereas it was 92% for stage I NPC patients (18). The goal of our study was to achieve equal outcomes for stages I and II NPC after CCRT. To detect an increase in the 5-year OS rate from 80% to 92% using CCRT at a significance level of 5% and a statistical power of 90% (19), a minimum of 202 patients would be needed. The associated patient registration and randomization procedures were conducted by telephone at the Good Clinical Practices Center of the Sun Yat-sen University Cancer Center. New Drug Statistical Treatment software version 8.0 (Anhui Provincial Center for Drug Clinical Evaluation, Wuhu, China) (20) was used to generate a random number table, and all of the included patients were stratified by nodal status classification (N0 vs N1) and randomly divided into the CCRT or RT-alone arms using blocks of 4 and 6 based on a 1:1 treatment allocation.

Pretreatment Evaluation

All patients were evaluated by a complete physical examination, a fiber-optic nasopharyngoscopy, magnetic resonance imaging (MRI) of the head and neck, chest radiography, abdominal sonography, electrocardiography, a bone scan, a complete blood count with differential count, a biochemical profile, and Epstein–Barr virus serology. All patients were referred for dental examination before RT.

Radiotherapy

All patients underwent conventional RT using a two-dimensional technique. The technique and dose schedule of RT for the two groups were identical. Patients were treated with a uniform RT protocol that was consistent with the treatment policy for NPC at the Sun Yat-sen University Cancer Center (21). Brachytherapy was not part of the radiation protocol. Megavoltage photons (6 MV) were used to treat the primary tumor and neck lymph nodes. RT was given five times a week at 2 Gy/d. The planning computed tomography (CT) scan was not performed. The patients were immobilized in a thermoplastic cast, and a faciocervical radiograph was taken using a simulator. Irradiation fields were chosen according to the extent of the tumor as evaluated by MRI. The target volume, which consisted of the entire tumor with a 2-cm margin in all directions, received at least 90% of the mid-depth central axis dose. All patients were treated in the supine position, usually through two block–shielding lateral-opposing faciocervical portals, to irradiate the nasopharynx and upper neck in one volume for the first 40 Gy, followed by the shrinking field technique (two lateral-opposed facial fields or smaller faciocervical fields when the tumor involved the oropharynx or retropharyngeal lymph node) to limit irradiation of the spinal cord. The spinal cord was excluded from the photon fields after 40 Gy of radiation were administered. The posterior boundaries of the portals were shifted to the posterior margin of the cervical vertebral body, and the posterior cervical triangular regions were irradiated by an 8- to 12-MeV electric beam. The lower neck was treated through a single anterior field with

midline shielding. The accumulated radiation dose to the primary tumor was 68–70 Gy. The metastatic lymph node–positive and lymph node–negative neck tissues received RT to a total dose of 60–62 Gy and 50 Gy, respectively.

Chemotherapy

Patients who were randomly assigned to the CCRT arm were scheduled to receive 30 mg/m^2 cisplatin in 1 L of normal saline over 2 hours on a weekly basis during external RT, starting on the first day of RT. All patients received an antiemetic prophylaxis consisting of 5-hydroxytryptamine-3 receptor antagonist plus 20 mg of dexamethasone. In addition, prochlorperazine and lorazepam antiemetics were added as needed. Complete blood counts and blood chemistry were checked before each chemotherapy cycle. Dose modification for cisplatin during CCRT was not allowed, and cisplatin was delayed until the absolute neutrophil count was at least 1500/μL and the platelet count was at least 100 000/μL. Cisplatin was stopped if creatinine clearance fell to less than 50 mL/min. RT delays were strongly discouraged.

Management of Mucositis

Radiation-induced mucositis is a common toxic effect for NPC patients. Weight loss during RT is primarily attributable to dysphagia because of mucositis pain. Strategies to limit the extent of mucositis and to manage its symptoms included basic oral care and supportive medications.

Patient Assessment and Follow-up

Complete blood cell counts and biochemical profiles were assessed once a week during the treatment period. The National Cancer Institute Common Toxicity Criteria version 3.0 scale (ctep.cancer.gov/forms/CTCAEv3.pdf) was used to assess chemotherapy and acute radiation toxic effects. Late radiation toxic effects were assessed using the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer late radiation morbidity scoring schema (22). Tumor response was evaluated by physical examination, nasopharyngoscopy, and MRI of the head and neck at 3 months after the completion of RT. Tumor response was classified according to the WHO response criteria (23). A complete response was defined as the complete disappearance of all objective evidence of disease, which was confirmed by physical examination, direct nasopharyngoscopy, and MRI. After the completion of treatment, patients were evaluated at least once every 3 months during the first 3 years and then every 6 months thereafter until death. Nasopharyngoscopy, MRI of the head and neck, chest radiography, and abdominal sonography were routinely performed annually or at the time of the clinical suggestion of tumor relapse.

When possible, salvage treatments were given to patients after documented relapse or when the disease was persistent. The salvage treatments included reirradiation, chemotherapy, and surgery.

Statistical Analysis

The OS rate was the primary endpoint of this study. Secondary endpoints included PFS, DMFS, LRRFS, and the incidence of toxic effects. An intention-to-treat principle was applied to all of the patients in the analysis. The OS was defined as the duration from the date of each patient's random assignment to the date of death from any cause or the censoring of the patient at the date of the last follow-up. The PFS was defined as the duration from the date of each patient's random assignment to the date of disease progression or the censoring of the patient at the date of the last follow-up. The LRRFS and DMFS were also evaluated and calculated from the date of each patient's random assignment until the day of the first locoregional or distant relapse or until the date of the last follow-up visit.

Toxic effects and the response to treatment were analyzed using the χ^2 test. Kaplan–Meier survival curves were used to analyze the time-to-event endpoints (24), and the log-rank test was used to compare the differences between the two arms (25). The hazard ratios (HRs) with 95% confidence interval (CI) were calculated by the Cox proportional hazards model (26), with the assumptions of proportional hazards confirmed based on Schoenfeld residuals (27); cumulative hazard plots estimated for the RT and CCRT groups were parallel, verifying that the assumption of proportional hazards was appropriate. Multivariable analyses were performed using the Cox proportional hazards model (26) to test the independent statistical significance of treatment intervention. Potentially important prognostic factors that were considered in the modeling process were patient age (≤45 vs >45 years), sex, parapharyngeal space involvement (yes or no), Chinese 1992 tumor stage (T1 vs T2), Chinese 1992 node stage (N0 vs N1), and number of chemotherapy cycles (continuous). Analyses were performed using the statistical software package SPSS 16.0 (SPSS, Chicago, IL). All statistical tests were two-sided, and a P less than .05 was considered to be statistically significant.

Results

Patient Characteristics

We assessed 236 patients for eligibility from October 2003 to September 2007. Six patients were excluded, including two patients who did not meet the inclusion criteria and four patients who refused to participate. The remaining 230 patients were randomly assigned to one of the two study arms. In total, 114 patients were randomly assigned to the RT arm, and 116 patients were randomly assigned to the CCRT arm (Figure 1). Four patients in the CCRT arm did not receive any chemotherapy, but they were included in the analysis according to the intention-to-treat principle. The two treatment arms were well balanced with respect to baseline characteristics (Table 1). Patients were restaged according to the American Joint Committee on Cancer (AJCC) staging system (28). Because invasion into the nasal cavity is assigned to T2 with the Chinese 1992 staging system (Supplementary Table 1, available online) but to T1 with the AJCC staging system, 25 of the included patients were reclassified as T1. In addition, in the AJCC system, the involvement of the retropharyngeal lymph node is classified as N1 and the involvement of the bilateral neck lymph nodes is classified as N2. Thus, seven patients were reclassified as N1 and 31 were reclassified as N2 and stage III.

Response

The complete response rate, which was evaluated 3 months after the completion of RT, was 96.5% (110/114) for the RT arm and

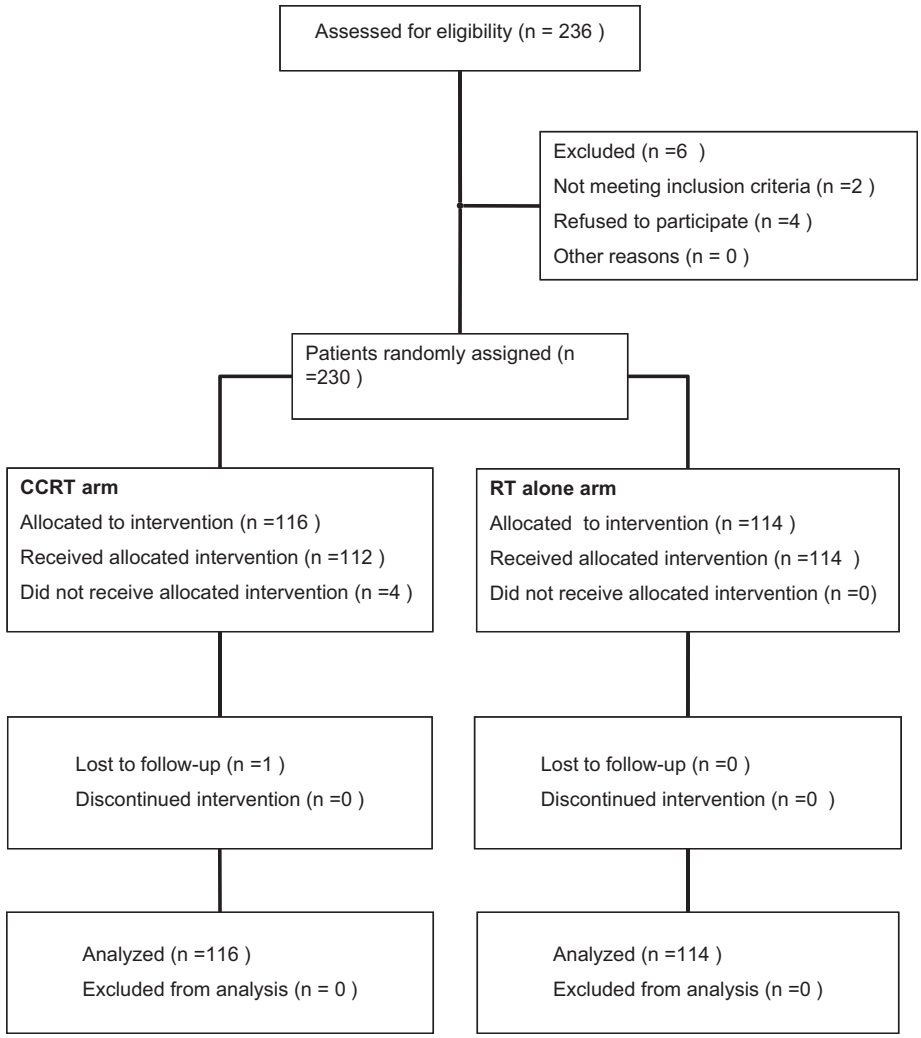

Figure 1. CONSORT flow diagram. Patients with stage II nasopharyngeal carcinoma (Chinese 1992 staging system) were randomly assigned to the RT alone arm or the CCRT arm. CCRT = concurrent chemoradiotherapy; RT = radiotherapy.

99.1% (115/116) for the CCRT arm. There were no statistically significant differences between the two arms ($P = .35$). In the RT arm, two patients had residual neck lymph nodes and two had residual nasopharyngeal tumors. One patient in the CCRT arm had residual neck lymph nodes. There was only one patient with residual neck lymph nodes in the RT arm when evaluated 6 months after the completion of RT. He successfully received neck lymph node resection.

Toxic Effects and Compliance

All patients in both treatment arms completed the prescribed dose of RT. Ninety-one patients (78.4%) received at least six cisplatin cycles, 30 patients (25.9%) received a seventh dose, and six patients (5.2%) received an eighth dose because of the timing and duration of their RT course. The reasons for withdrawal of cisplatin included the patient's refusal, severe mucositis, prolonged severe neutropenia, and cisplatin-induced renal toxicity. The main grade 3–4 acute toxic effects during CCRT were hematologic and gastrointestinal reactions (Table 2). No grade 5 toxicity (death) occurred during treatment. The overall incidence of grade 3–4 acute toxic effects in the CCRT arm was statistically significantly higher than in the RT arm (63.8% vs 40.4%, $P = .001$). With respect to hematologic toxicity, the incidence of grade 3 leukopenia/neutropenia was statistically significantly higher in patients given CCRT as compared with RT alone (12.9% vs 0%, $P < .001$). With respect to gastrointestinal reactions, the incidence of grade 3 nausea or vomiting was statistically significantly higher with CCRT than with RT alone (8.6% vs 0%, $P = .001$). The incidence of grade 3–4 mucositis was statistically significantly higher in the CCRT arm than in the RT arm (45.6% vs 32.5%, $P = .04$). In the CCRT arm, two patients had grade 4 mucositis.

There were no statistically significant differences between the two study arms in the cumulative incidence of grade 3 or higher late radiation morbidity during follow-up (Table 2).

Patterns of Treatment Failure

After a median follow-up of 60 months (range = 5–87 months), 22.8% (26 of 114) and 11.2% (13 of 116) of patients in the RT and CCRT groups, respectively, developed tumor progression (Table 3). Three patients had both locoregional failures and distant failures in the RT alone arm, as opposed to none in the CCRT arm (Table 3). Among those patients who developed distant organ metastases, nine developed bone metastases, eight developed liver metastases, five developed lung metastases, and five developed distant lymph node metastases. Some patients had metastases in more than one organ. Thirty patients received salvage treatment for relapse.

Table 1. Patient characteristics*

Characteristic	RT alone No. of patients (%)	CCRT No. of patients (%)
Total	114	116
Age, y		
Median	43	42
Range	28–70	26–65
Sex		
Men	84 (73.7)	82 (70.7)
Women	30 (26.3)	34 (29.3)
Pathology		
WHO type 2	4 (3.5)	5 (4.3)
WHO type 3	110 (96.5)	111 (95.7)
Chinese 1992 T stage		
T1	7 (6.1)	8 (6.9)
T2	107 (93.9)	108 (93.1)
Chinese 1992 N stage		
N0	18 (15.8)	19 (16.4)
N1	96 (84.2)	97 (83.6)
Chinese 1992 stage group		
T1N1	7 (6.1)	8 (6.9)
T2N0	18 (15.8)	19 (16.4)
T2N1	89 (78.1)	89 (76.7)
AJCC T stage†		
T1	21 (18.4)	19 (16.4)
T2	93 (81.6)	97 (83.6)
AJCC N stage†		
N0	13 (11.4)	17 (14.7)
N1	89 (78.1)	80 (68.9)
N2	12 (10.5)	19 (16.4)
AJCC stage group†		
II	102 (89.5)	97 (83.6)
III	12 (10.5)	19 (16.4)
Parapharyngeal involvement		
Yes	91 (79.8)	98 (84.5)
No	23 (20.2)	18 (15.5)
Maximum lymph node size, mm		
≤20	94 (82.5)	96 (82.8)
>20 and <40	20 (17.5)	20 (17.2)
Hemoglobin level, g/L		
>130	101 (88.6)	105 (90.5)
≤130	13 (11.4)	11 (9.5)

* AJCC = American Joint Committee on Cancer; CCRT = concurrent chemoradiotherapy; RT = radiotherapy; WHO = World Health Organization.

† Defined by the criteria of the seventh edition of the AJCC staging system (28).

Among them, 12 patients received chemotherapy, nine received chemotherapy plus reirradiation, five received traditional Chinese medicine, one received neck dissection, one received stereotactic RT, one received brachytherapy, and one received nasopharyngectomy.

Survival

Twenty-five deaths (19 in the RT arm and six in the CCRT arm) were reported, of which 21 (16 in the RT alone arm and six in the CCRT arm) were disease related (Table 4). The 5-year OS, PFS, and DMFS were statistically significantly higher in the CCRT arm than in the RT arm (OS: 94.5% vs 85.8%, HR of death = 0.30, 95% CI = 0.12 to 0.76; P = .007; Figure 2, A; PFS: 87.9% vs 77.8%, HR of progression = 0.45, 95% CI = 0.23 to 0.88; P = .017; Figure 2, B; DMFS: 94.8% vs 83.9%, HR of distant relapse = 0.27, 95% CI = 0.10 to 0.74; P = .007; Figure 3, A). There was no statistically significant difference in LRRFS rates between the CCRT and RT groups (LRRFS: 93.0% vs 91.1%, HR of locoregional relapse = 0.61, 95% CI = 0.25 to 1.51; P = .29; Figure 3, B). The addition of cisplatin-based chemotherapy to RT resulted in 8.7%, 10.1%, and 10.9% increases in the 5-year OS, PFS, and DMFS rates, respectively, in the CCRT arm.

A multivariable analysis showed that the number of chemotherapy cycles was the only independent factor that was associated with OS (HR of death = 0.79, 95% CI = 0.67 to 0.93; P = .007), PFS (HR of progression = 0.89, 95% CI = 0.80 to 0.99; P = .04), and distant control (HR of metastasis = 0.82, 95% CI = 0.69 to 0.96; P = .01) in stage II NPC (Table 5).

Discussion

This randomized trial demonstrated substantial survival benefits of CCRT for patients with stage II NPC as compared with treatment with RT alone, which supports the important role of concurrent chemotherapy for stage II NPC patients. Thus, the recommendation of CCRT by the National Comprehensive Cancer Network for stage II NPC patients seems reasonable.

To the best of our knowledge, this study is the first randomized trial to compare CCRT with RT alone in early-stage NPC. The possible impact of combined modality treatment for patients with AJCC 1997 stage I–II NPC has been investigated by Cheng et al. (12), who reported the treatment outcomes of 44 patients with AJCC 1997 stage I–II disease. Specifically, patients with stage II disease who were treated using CCRT exhibited a disease-free survival rate equal to those with stage I disease given RT alone (12). Chua et al. (14) reported the results of a pooled analysis of two randomized controlled trials that compared the treatment results of neoadjuvant chemotherapy and RT with RT alone for different disease stages. The results demonstrated that neoadjuvant chemotherapy improved survival and reduced the risk of distant metastases in only those patients with T1-2N0-1M0. In contrast to the studies by Chua et al. (14), Song et al. (29) compared the outcomes for 31 patients with early-stage NPC given RT alone with those for 29 patients following neoadjuvant chemotherapy followed by RT. Neoadjuvant chemotherapy showed no additional benefit compared with treatment with RT alone. Notably, the above studies were all retrospective analyses (12,14,29), and the numbers of patients therein were small.

The OS rate for early-stage patients is approximately 80%–90% with RT alone (30–33). The outcomes for this group after RT alone have been moderately satisfactory; however, a study demonstrated that after RT, patients who had stage II disease had worse outcomes than patients who had stage I disease (34). It is recognized that the risk of distant failure experienced by some patients with stage IIB NPC approaches that of stage III disease following RT (33,35). In one report by Leung et al. (33), who evaluated the treatment results of 1070 NPC patients mostly treated with RT alone between 1990 and 1998, isolated distant metastases occurred in 5.7% and 14.9% of patients with stage IIA and stage IIB disease, respectively. In addition, several studies have reported that patients with T1-2N1 disease had a relatively poor

Table 2. Maximum acute and late toxic effects*

Toxic effect	Toxic effects, No. (%)				
	RT alone (n =114)		CCRT (n =116)		
	Toxicity grade				
	3	4	3	4	P†
Acute toxic effects					
Leukopenia/neutropenia	0	0	15 (12.9)	0	<.001
Thrombocytopenia	0	0	1 (0.8)	0	.32
Liver dysfunction	1 (0.9)	0	0	0	.31
Renal impairment	0	0	1 (0.9)	0	.32
Nausea/vomiting	0	0	10 (8.6)	0	.001
Mucositis	37 (32.5)	0	51 (43.9)	2 (1.7)	.04
Skin reaction	10 (8.8)	0	13 (11.2)	0	.53
Weight loss	3 (2.6)	0	1 (0.9)	0	.60
Total (any)	46 (40.4)	0	72 (62.1)	2 (1.7)	.001
Late toxic effects					
Ear (deafness/otitis)	8 (7.0)	0	11 (9.5)	1 (0.9)	.47
Skin fibrosis	2 (1.8)		3 (2.6)		.66
Trismus	1 (0.9)		2 (1.7)		.57
Total (any)	11 (9.6)	0	15 (12.9)	1 (0.9)	.32

* CCRT = concurrent chemoradiotherapy; RT = radiotherapy.

† *P* values, calculated with the χ^2 test, are for the difference in the incidence of grade 3 and 4 adverse events between the two treatment arms. All statistical tests were two-sided.

outcome and that more aggressive therapy, such as combined modality treatment, may be indicated for such patients (34,36,37). Zong et al. (36) demonstrated that the 5-year accumulated distant metastasis rate of T1-T2N1 (Chinese 1992 staging system) NPC patients was much greater than that of T1-T2N0 NPC patients, resulting in a much lower OS rate in the former group. Xiao et al. (37) revealed that the 5-year OS rate of patients with T2N1 disease (Chinese 1992 staging system) was only 73.1%, which differs statistically significantly from those of the other groups of early-stage NPC patients. Xiao et al. (37) also found that the accumulated distant metastasis rate was 21.2% for the T2N1 group, which differed from those of the other groups. They concluded that distant metastasis after curative RT was the main reason for treatment failure in the T2N1 group. This study demonstrates similar results, with distant metastasis (14.9%) accounting for most of the treatment failures in the RT arm.

Our observation that concurrent chemotherapy improves survival in patients with stage II NPC is encouraging. Kwong et al. (6) reported that CCRT with daily low doses of oral uracil and tegafur statistically significantly decreased the incidence of distant metastasis and increased survival in advanced-stage NPC. How can the distinct effect of concurrent chemotherapy on stage II NPC patients be explained? We speculate that early-stage disease may have a smaller distant tumor bulk that is more easily eradicated by concurrent chemotherapy. In this study, the CCRT arm had a lower distant failure rate than the RT arm. It is possible that concurrent chemotherapy, at least with the chemotherapy regimens and dose intensity used in the present analysis, is more effective in eradicating distant micrometastases in early-stage NPC. Two studies (14,15) support this opinion. Lin et al. (15) divided NPC patients into high-risk and low-risk subgroups according to their grading system. High-risk patients met at least one of the following criteria: 1) nodal size greater than 6 cm, 2) supraclavicular node metastases, 3) 1992 AJCC stage T4N2, or 4) multiple neck node metastases with one node greater than 4 cm. They found that the OS (CCRT vs RT: 83.2% vs 59.7%, $P = .004$) and PFS (CCRT vs RT: 87.3% vs 61.5%, $P < .001$) were statistically significantly better in patients receiving CCRT than those receiving RT alone in the low-risk group; however, no survival benefit was gained for high-risk patients. Chua et al. (14) studied the effect of induction chemotherapy on NPC patients. The results showed that statistically significant differences in the OS and DMFS rates were only observed in the T1-T2N0-N1 group and favored the combined

Table 3. Incidence and site of first progression*

Site	Incidence, No. (%)	
	RT alone (n = 114)	CCRT (n = 116)
Locoregional only	9 (7.9)	8 (6.9)
Distant only	14 (12.3)	5 (4.3)
Locoregional and distant	3 (2.6)	0

* CCRT = concurrent chemoradiotherapy; RT = radiotherapy.

Table 4. Primary outcome of treatment*

Survival status	Primary outcome, No. (%)		
	RT alone (n = 114)	CCRT (n = 116)	All (n = 230)
Alive	95 (83.3)	109 (94.0)	204 (88.7)
Lost to follow-up	0	1 (0.9)	1 (0.4)
Death	19 (16.7)	6 (5.2)	25 (10.9)
Disease progression	16 (14.0)	5 (4.3)	21 (9.1)
Treatment related	0	0	0
Other cause	3 (2.6)	1 (0.9)	4 (1.7)

* CCRT = concurrent chemoradiotherapy; RT = radiotherapy.

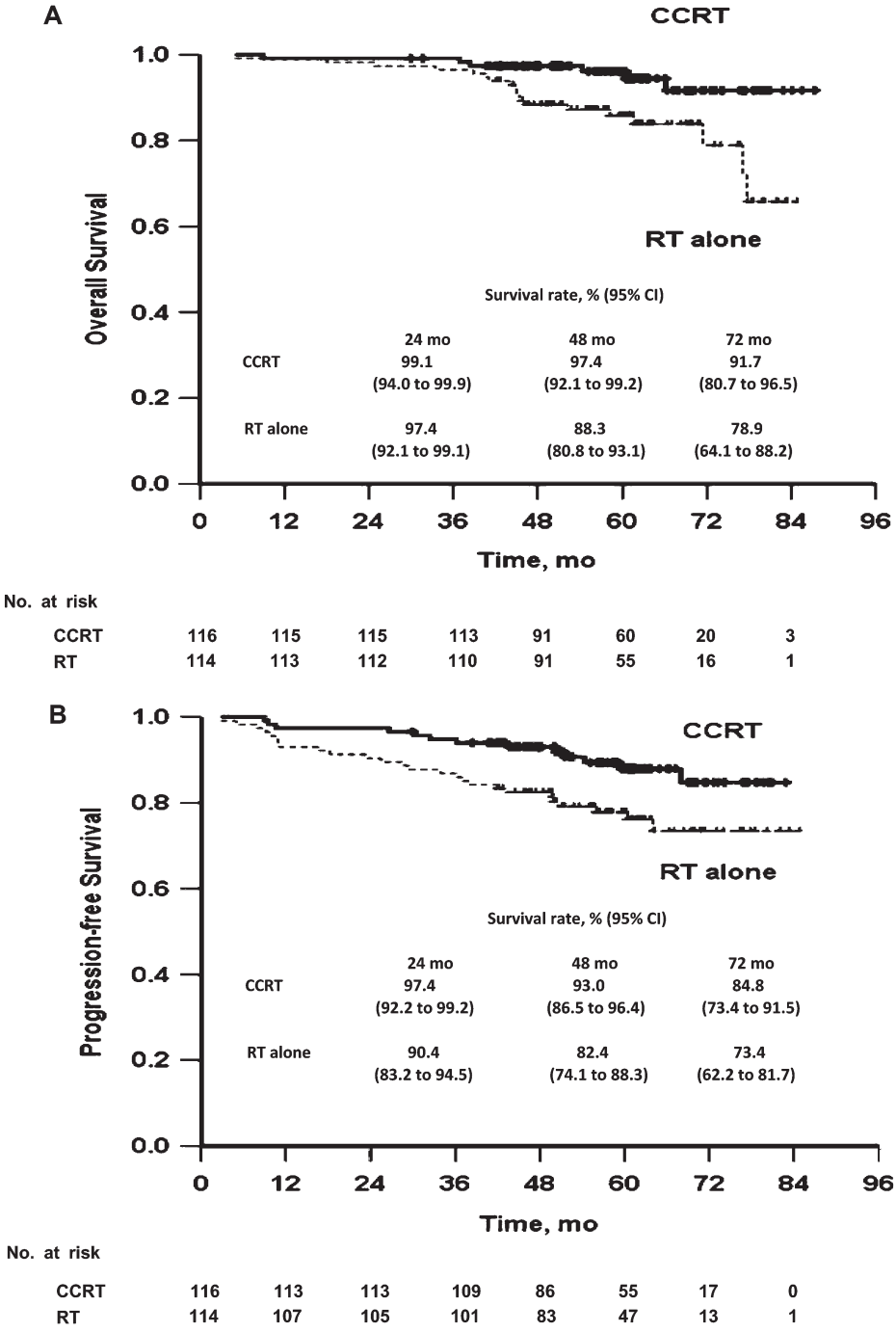

Figure 2. Kaplan–Meier estimates of patients who were randomly assigned to RT vs CCRT. **A**) Overall survival (HR of death = 0.30, 95% CI = 0.12 to 0.76; $P = .007$, two-sided log-rank test). **B**) Progression-free survival (HR of progression = 0.45, 95% CI = 0.23 to 0.88; $P = .017$, two-sided log-rank test). CCRT = concurrent chemoradiotherapy; CI = confidence interval; HR = hazard ratio; RT = radiotherapy.

chemotherapy and RT arm. The 5-year OS was 79% in the combined arm and 67% in the RT-alone arm ($P = .048$). The corresponding 5-year DMFS rates were 86% and 74% ($P = .005$); however, the improved outcomes did not appear in the advanced NPC group in their study (14). In this study, all patients with Chinese 1992 stage II NPC were low-risk patients according to the grading system previously mentioned by Lin et al. (15). Stage II NPC had a smaller distant tumor bulk, and chemotherapy was more effective in eradicating distant tumors. We found that the addition of cisplatin-based chemotherapy to RT showed a 10.9% increase in the 5-year DMFS rates, which suggests that concurrent cisplatin chemotherapy has systemic cytotoxic action in addition to radiosensitization. The large reduction of the distant metastasis rate with concurrent cisplatin chemotherapy might translate into substantial improvements in OS. However, concurrent cisplatin chemotherapy might also compensate for the dosimetric inadequacy of the two-dimensional RT technique, leading to better outcomes.

Cisplatin-based chemotherapy has been shown to result in higher response rates in previously untreated, recurrent, or metastatic NPC compared with non-cisplatin regimens (38,39). The optimal combination schedule of cisplatin and RT has not yet been established; daily low-dose, weekly intermediate-dose, and 3-week high-dose regimens have been used. Toxic effects are considerable

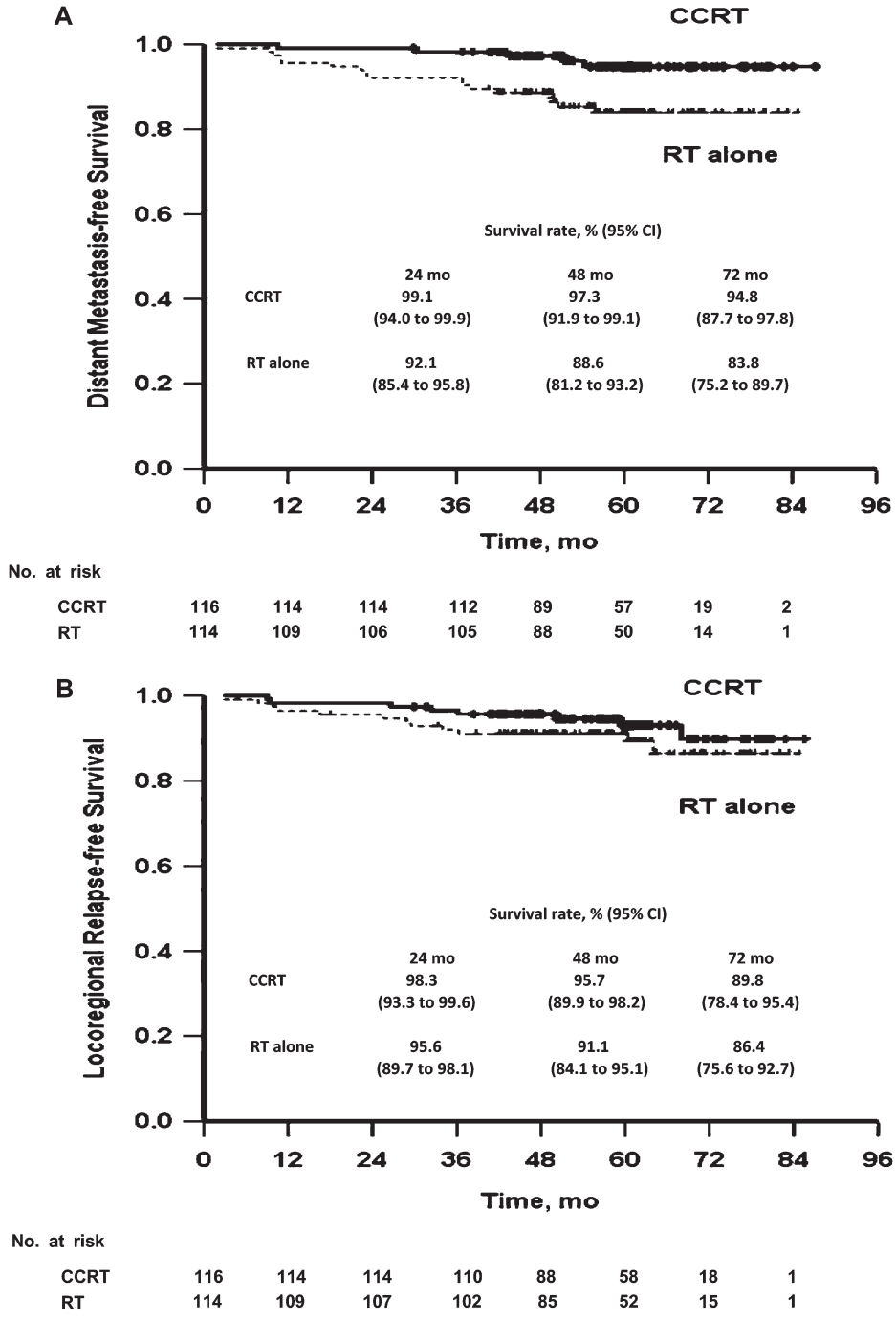

Figure 3. Kaplan–Meier estimates of patients who were randomly assigned to RT vs CCRT. **A**) Distant metastasis-free survival (HR of distant relapse = 0.27, 95% CI = 0.10 to 0.74; $P = .007$, two-sided log-rank test). **B**) Locoregional relapse-free survival (HR of locoregional relapse = 0.61, 95% CI = 0.25 to 1.51; $P = .29$, two-sided log-rank test). CCRT = concurrent chemoradiotherapy; CI = confidence interval; RT = radiotherapy; HR = hazard ratio.

with the standard chemotherapy regimen of cisplatin at 100 mg/m^2 every 3 weeks during RT. The intergroup study by Al-Sarraf et al. (3) revealed that only 63% of patients who were scheduled to receive three courses of concurrent 100 mg/m^2 cisplatin actually did so. Chan et al. (4) reported that CCRT using a weekly intermediate dose of cisplatin (40 mg/m^2) improved the survival rate as compared with RT alone in locoregionally advanced NPC; however, patient compliance was unsatisfactory because only 44% of patients actually completed six cycles of chemotherapy during RT. Weekly cisplatin at a dose of 30 mg/m^2 decreases toxic effects without compromising tumor control in patients who receive CCRT for locally advanced squamous cell carcinoma of the head and neck (40). Kim et al. (41) reported that a weekly intermediate dose of cisplatin (30 mg/m^2) is practical and feasible for the CCRT treatment of NPC, resulting in decreased interruptions in radiation treatment and minimal acute toxic effects without compromising local control. This study had good compliance for the CCRT regimen; 78.4% completed at least six cycles of chemotherapy. We believe that the excellent distant control that was established in this series is attributable to the good compliance with the CCRT regime. A multivariable analysis also showed that the number of chemotherapy cycles was the only independent factor that was associated with OS and distant control in stage II NPC. We attribute good compliance with CCRT in this study to

Table 5. Multivariable analysis of prognostic factors in Chinese 1992 stage II nasopharyngeal carcinoma*

Endpoint	HR (95% CI)	P†
Death (all causes)		
Sex	0.62 (0.23 to 1.67)	.34
Age	1.71 (0.76 to 3.81)	.18
Parapharyngeal space involvement	3.46 (0.73 to 16.25)	.11
T stage	0.81 (0.09 to 6.89)	.85
N stage	0.86 (0.31 to 2.35)	.77
No. of chemotherapy cycles	0.79 (0.67 to 0.93)	.007
Progression		
Sex	0.91 (0.44 to 1.89)	.80
Age	1.31 (0.69 to 2.48)	.39
Parapharyngeal space involvement	1.33 (0.51 to 3.47)	.55
T stage	1.24 (0.26 to 5.84)	.78
N stage	1.46 (0.56 to 3.79)	.42
No. of chemotherapy cycles	0.89 (0.80 to 0.99)	.04
Distant failure		
Sex	0.66 (0.24 to 1.82)	.43
Age	1.09 (0.47 to 2.55)	.83
Parapharyngeal space involvement	6.82 (0.78 to 59.14)	.08
T stage	0.66 (0.07 to 5.79)	.71
N stage	1.44 (0.42 to 4.93)	.55
No. of chemotherapy cycles	0.82 (0.69 to 0.96)	.01
Locoregional control		
Sex	1.25 (0.47 to 3.33)	.64
Age	1.41 (0.58 to 3.47)	.44
Parapharyngeal space involvement	0.57 (0.19 to 1.75)	.33
T stage	1.90 (0.22 to 16.22)	.55
N stage	1.09 (0.31 to 3.83)	.88
No. of chemotherapy cycles	0.94 (0.81 to 1.10)	.49

* Categorical variables were patient age (≤45 vs >45 years), parapharyngeal space involvement (yes or no), Chinese 1992 tumor stage (T1 vs T2), and Chinese 1992 node stage (N0 vs N1). Number of chemotherapy cycles was continuous. CI = confidence interval; HR = hazard ratio.

† *P* values were calculated using the two-sided Wald test in the Cox proportional hazard model.

admission for intravenous nutrition when the patients developed 5% weight loss. Although CCRT patients experienced more severe hematologic, gastrointestinal, and mucositis acute toxic effects than the patients undergoing RT alone, they were all tolerant of this regimen. In summary, we think that the optimal choice for early-stage NPC is cisplatin, at a weekly dose of 30 mg/m^2, for both an optimal chemotherapy effect to eradicate small distant tumors and to ensure NPC patient compliance.

There were a few limitations to this study. First, a chest CT was not part of the pretreatment evaluation and follow-up schedule. Conventional medical evaluation with chest radiography, abdominal ultrasonography, and skeletal scintigraphy is routinely performed to detect distant metastases in NPC (42). One of the hypotheses of this study was that the outcome in terms of survival would improve by reducing the occurrence of distant metastases. From this point of view, chest CT should be included as part of the evaluation and follow-up of NPC patients because the sensitivity of chest x-ray is comparatively low for the detection of lung metastases. Second, because of a lack of medical resources in China, all patients in this study underwent conventional RT using a two-dimensional technique. Because intensity-modulated RT (IMRT) for the treatment of NPC tends to be more effective in locoregional control (43,44), the margin of benefit gained with additional chemotherapy in stage II NPC may be reduced when IMRT is used.

In conclusion, this randomized study demonstrated several distinct and substantial survival benefits of CCRT for patients with stage II NPC. An increasing number of NPC patients have been treated with IMRT in China since 2009 because of improving medical resources. Further investigation of this prospective setting is warranted to explore the role of CCRT in the treatment of stage II NPC when IMRT is used.

References

1. Cao SM, Simons MJ, Qian CN. The prevalence and prevention of nasopharyngeal carcinoma in China. *Chin J Cancer*. 2011;30(2):114–119.
2. Wee JT, Ha TC, Loong SL, Qian CN. Is nasopharyngeal cancer really a "Cantonese cancer"? *Chin J Cancer*. 2010;29(5):517–526.
3. Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol*. 1998;16(4):1310–1317.
4. Chan AT, Teo PM, Ngan RK, et al. Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. *J Clin Oncol*. 2002;20(8):2038–2044.
5. Lin JC, Jan JS, Hsu CY, Liang WM, Jiang RS, Wang WY. Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival. *J Clin Oncol*. 2003;21(4):631–637.
6. Kwong DL, Sham JS, Au GK, et al. Concurrent and adjuvant chemotherapy for nasopharyngeal carcinoma: a factorial study. *J Clin Oncol*. 2004;22(13):2643–2653.
7. Wee J, Tan EH, Tai BC, et al. Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. *J Clin Oncol*. 2005;23(27):6730–6738.
8. Lee AW, Lau WH, Tung SY, et al. Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: NPC-9901 Trial by the Hong Kong Nasopharyngeal Cancer Study Group. *J Clin Oncol*. 2005;23(28):6966–6975.
9. Huncharek M, Kupelnick B. Combined chemoradiation versus radiation therapy alone in locally advanced nasopharyngeal carcinoma: results of a meta-analysis of 1,528 patients from six randomized trials. *Am J Clin Oncol*. 2002;25(3):219–223.
10. Langendijk JA, Leemans CR, Buter J, Berkhof J, Slotman BJ. The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma: a meta-analysis of the published literature. *J Clin Oncol*. 2004;22(22):4604–4612.
11. Baujat B, Audry H, Bourhis J, et al. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. *Int J Radiat Oncol Biol Phys*. 2006;64(1):47–56.
12. Cheng SH, Tsai SY, Yen KL, et al. Concomitant radiotherapy and chemotherapy for early-stage nasopharyngeal carcinoma. *J Clin Oncol*. 2000;18(10):2040–2045.
13. Cheng SH, Tsai SY, Yen KL, et al. Prognostic significance of parapharyngeal space venous plexus and marrow involvement: potential landmarks of dissemination for stage I-III nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2005;61(2):456–465.
14. Chua DT, Ma J, Sham JS, et al. Improvement of survival after addition of induction chemotherapy to radiotherapy in patients with early-stage nasopharyngeal carcinoma: subgroup analysis of two phase III trials. *Int J Radiat Oncol Biol Phys*. 2006;65(5):1300–1306.
15. Lin JC, Liang WM, Jan JS, Jiang RS, Lin AC. Another way to estimate outcome of advanced nasopharyngeal carcinoma—is concurrent chemoradiotherapy adequate? *Int J Radiat Oncol Biol Phys*. 2004;60(1):156–164.

16. Min H, Hong M, Ma J, et al. A new staging system for nasopharyngeal carcinoma in China. *Int J Radiat Oncol Biol Phys.* 1994;30(5):1037–1042.
17. Shanmugarantnam K, Sobin LH. *Histological Typing of Tumors of the Upper Respiratory Tract and Ear.* 2nd ed. New York, NY: Springer-Verlag; 1991.
18. Hong MH, Min HQ, Guo X, et al. To prove the rationality of '92 staging with results of nasopharyngeal carcinoma treated by stratified multitherapies. *Chin J Cancer.* 2000;19(5):460–462.
19. Machin D, Campbell MJ, Fayers PM. *Sample Size Tables for Clinical Studies.* Oxford, UK: Blackwell; 1997.
20. Cheng NN, Sun RY. Introduction of software of the new drug statistical treatment (NDST). *Chin J Clin Pharmacol Ther.* 1997;2(2):137–149.
21. Lu TX, Luo W, Zhao C, et al. A probe of design methods of block shielding faciocervical portals at isocenter for radiotherapy of nasopharyngeal carcinoma. *Chin J Cancer.* 2000;19(10):930–933.
22. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys.* 1995; 31(5):1341–1346.
23. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer.* 1981;47(1):207–214.
24. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53:457–481.
25. Peto R, Pike MC, Armitage P. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. *Br J Cancer.* 1977; 35(1):1–39.
26. Cox DR. Regression models and life tables. *J R Stat Soc B.* 1972;34(2): 187–220.
27. Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika.* 1982;69(1):239–241.
28. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. *American Joint Committee on Cancer: AJCC Cancer Staging Manual.* 7th ed. New York, NY: Springer; 2009.
29. Song CH, Wu HG, Heo DS, Kim KH, Sung MW, Park CI. Treatment outcomes for radiotherapy alone are comparable with neoadjuvant chemotherapy followed by radiotherapy in early-stage nasopharyngeal carcinoma. *Laryngoscope.* 2008;118(4):663–670.
30. Lu TX, Zhao C, Wu SX, et al. Retrospective analysis of 934 nasopharyngeal carcinoma patients treated with conventional external beam radiotherapy alone. *Chin J Oncol.* 2005;27(10):620–622.
31. Cao XP, Lu TX, Ye WJ, Cui NJ. Prospective study on long-term efficacy of external plus intracavitary radiotherapy on stage I-II nasopharyngeal carcinoma. *Chin J Oncol.* 2007;26(2):204–207.
32. Yeh SA, Tang Y, Lui CC, Huang YJ, Huang EY. Treatment outcomes and late complications of 849 patients with nasopharyngeal carcinoma treated with radiotherapy alone. *Int J Radiat Oncol Biol Phys.* 2005;62(3): 672–679.
33. Leung TW, Tung SY, Sze WK, et al. Treatment results of 1070 patients with nasopharyngeal carcinoma: an analysis of survival and failure patterns. *Head Neck.* 2005;27(7):555–565.
34. Chua DT, Sham JS, Kwong DL, Au GK. Treatment outcome after radiotherapy alone for patients with stage I-II nasopharyngeal carcinoma. *Cancer.* 2003;98(1):74–80.
35. Leung SF, Chan AT, Zee B, et al. Pretherapy quantitative measurement of circulating Epstein-Barr virus DNA is predictive of posttherapy distant failure in patients with early-stage nasopharyngeal carcinoma of undifferentiated type. *Cancer.* 2003;98(2):288–291.
36. Zong J, Ma J, Tang L, et al. A study of the combined treatment strategy for patients with nasopharyngeal carcinoma based on the analysis of the treatment results from 749 cases. *Bulletin Chin Cancer.* 2005;14(8):538–542.
37. Xiao WW, Han F, Lu TX, Chen CY, Huang Y, Zhao C. Treatment outcomes after radiotherapy alone for patients with early-stage nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2009;74(4):1070–1076.
38. Dugan M, Choy D, Ngai A, et al. Multicenter phase II trial of mitoxantrone in patients with advanced nasopharyngeal carcinoma in Southeast Asia: an Asian-Oceanian Clinical Oncology Association Group study. *J Clin Oncol.* 1993;11(1):70–76.
39. Choo R, Tannock I. Chemotherapy for recurrent or metastatic carcinoma of the nasopharynx. A review of the Princess Margaret Hospital experience. *Cancer.* 1991;68(10):2120–2124.
40. Newlin HE, Amdur RJ, Riggs CE, Morris CG, Kirwan JM, Mendenhall WM. Concomitant weekly cisplatin and altered fractionation radiotherapy in locally advanced head and neck cancer. *Cancer.* 2010;116(19):4533–4540.
41. Kim TH, Ko YH, Lee MA, et al. Treatment outcome of cisplatin-based concurrent chemoradiotherapy in the patients with locally advanced nasopharyngeal cancer. *Cancer Res Treat.* 2008;40(2):62–70.
42. Kumar MB, Lu JJ, Loh KS, et al. Tailoring distant metastatic imaging for patients with clinically localized undifferentiated nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2004;58(3):688–693.
43. Lee N, Harris J, Garden AS, et al. Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. *J Clin Oncol.* 2009;27(22): 3684–3690.
44. Lai SZ, Li WF, Chen L, et al. How does intensity-modulated radiotherapy versus conventional two-dimensional radiotherapy influence the treatment results in nasopharyngeal carcinoma patients? *Int J Radiat Oncol Biol Phys.* 2011;80(3):661–668.

Funding

This work was supported by the National Natural Science Foundation of China (81072226 to H.-Q.M.), Project 863 (2006AA02A404 to H.-Q.M.), the Sci-Tech Project Foundation of Guangdong Province (2007B060401064 to H.-Q.M.), the Guangdong Provincial Medical Research Foundation (B2006063 to H.-Q.M.), the Sci-Tech Project Foundation of Guangzhou City (2007Z1-E4022 to H.-Q.M.), the Sun Yat-sen University Clinical Research 5010 Program, and the Fundamental Research Funds for the Central Universities.

Notes

We thank the Good Clinical Practices Center and all of the colleagues and patients who were involved in this trial. We also thank professor Qing Liu for statistical assistance. The funding agencies had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the article; or the decision to submit the article for publication. Q.-Y. Chen, Y.-F. Wen, L. Guo, and H. Liu contributed equally to this article. The authors have no potential conflicts of interest to declare.

Affiliations of authors: State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Center, Guangzhou, People's Republic of China and Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, Guangzhou, People's Republic of China (Q-YC, Y-FW, LG, HL, P-YH, H-YM, N-WL, Y-QX, D-HL, FQ, RS, M-QD, M-YC, Y-JH, XG, K-JC, C-NQ, H-QM); Good Clinical Practices Center, Sun Yat-sen University Cancer Center, Guangzhou, People's Republic of China (M-HH).