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ARTICLE

Randomized Trial of Radiotherapy Plus Concurrent–Adjuvant Chemotherapy vs Radiotherapy Alone for Regionally Advanced Nasopharyngeal Carcinoma

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Background Current practice of adding concurrent–adjuvant chemotherapy to radiotherapy (CRT) for treating advanced nasopharyngeal carcinoma is based on the Intergroup-0099 Study published in 1998. However, the outcome for the radiotherapy-alone (RT) group in that trial was substantially poorer than those in other trials, and there were no data on late toxicities. Verification of the long-term therapeutic index of this regimen is needed.

Methods Patients with nonkeratinizing nasopharyngeal carcinoma staged T1-4N2-3M0 were randomly assigned to RT (176 patients) or to CRT (172 patients) using cisplatin (100 mg/m^2) every 3 weeks for three cycles in concurrence with radiotherapy, followed by cisplatin (80 mg/m^2) plus fluorouracil (1000 mg per m^2 per day for 4 days) every 4 weeks for three cycles. Primary endpoints included overall failure-free rate (FFR) (the time to first failure at any site) and progression-free survival. Secondary endpoints included overall survival, locoregional FFR, distant FFR, and acute and late toxicity rates. All statistical tests were two-sided.

Results The two treatment groups were well balanced in all patient characteristics, tumor factors, and radiotherapy parameters. Adding chemotherapy statistically significantly improved the 5-year FFR (CRT vs RT: 67% vs 55%; $P = .014$) and 5-year progression-free survival (CRT vs RT: 62% vs 53%; $P = .035$). Cumulative incidence of acute toxicity increased with chemotherapy by 30% (CRT vs RT: 83% vs 53%; $P < .001$), but the 5-year late toxicity rate did not increase statistically significantly (CRT vs RT: 30% vs 24%; $P = .30$). Deaths because of disease progression were reduced statistically significantly by 14% (CRT vs RT: 38% vs 24%; $P = .008$), but 5-year overall survival was similar (CRT vs RT: 68% vs 64%; $P = .22$; hazard ratio of CRT = 0.81, 95% confidence interval = 0.58 to 1.13) because deaths due to toxicity or incidental causes increased by 7% (CRT vs RT: 1.7% vs 0, and 8.1% vs 3.4%, respectively; $P = .015$).

Conclusions Adding concurrent–adjuvant chemotherapy statistically significantly reduced failure and cancer-specific deaths when compared with radiotherapy alone. Although there was no statistically significant increase in major late toxicity, increase in noncancer deaths narrowed the resultant gain in overall survival.

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Radiotherapy is the primary treatment modality for nasopharyngeal carcinoma (NPC), but the results for patients with advanced locoregional disease are unsatisfactory (1,2). The first randomized clinical trial that achieved statistically significant survival benefit by adding cisplatin-based concurrent–adjuvant chemotherapy to conventional-fractionation radiotherapy was the Intergroup-0099 Study (3), which was conducted from 1989 to 1995. Impressive increases in both 3-year progression-free survival (PFS) and overall survival (OS) were achieved for patients with stages equivalent to IIB–IVB by the criteria of the 5th edition of the *American Joint Committee on Cancer Staging System* (4) and the *International Union Against Cancer* (5). This regimen has since become the standard for patients with advanced NPC. However, there were serious concerns because the outcomes for the RT group were substantially poorer than those in other studies in the same period (6,7). Furthermore, there were no data on late toxicities.

To evaluate the long-term efficacy and safety of the Intergroup-0099 regimen (3) and to search for the most cost-effective treatment strategy for different risk groups, the Hong Kong Nasopharyngeal Cancer Study Group launched two parallel randomized trials in 1999, for which patients with tumor stages III–IVB were segregated into two groups. Information on eligibility criteria, treatment methods, and early results has been presented in

the respective preliminary reports (8,9). This final report of the NPC-9901 Trial, which focused on patients with advanced nodal disease, is, to our knowledge, the first study with detailed data on late toxicities and causes of death for evaluating the therapeutic index (benefit for tumor control vs the damage incurred by treatment).

Subjects and Methods

Eligible patients were those with histologically confirmed nonkeratinizing (differentiated or undifferentiated) carcinoma of the nasopharynx classified by the World Health Organization system (10) and T1-4N2-3M0 disease (T = NPC tumor stage; N = nodal stage; M = evidence of distant metastases) classified by the staging criteria of the 5th edition of the *American Joint Committee on Cancer Staging System* (4) and the *International Union Against Cancer* (5). Other inclusion criteria included performance status of 2 or lower by the Eastern Cooperative Oncology Group System (http://www.metrohealth.org/body.cfm?id=1055&oTopID=1055) and adequate hematologic (total leukocyte count ≥4000/μL; platelet count ≥100 000/μL) and renal function (creatinine clearance ≥60 mL/min). The exclusion criteria included age of 70 years or older, keratinizing squamous cell carcinoma or adenocarcinoma, pregnancy or lactation, history of previous treatment, or prior malignancy (except for adequately treated carcinoma in situ of the cervix, or basal or squamous cell carcinoma of the skin).

The protocol was approved by the institutional ethics committees of the individual participating centers (Pamela Youde Nethersole Eastern Hospital, Tuen Mun Hospital, Queen Mary Hospital, and Queen Elizabeth Hospital, Hong Kong; and Princess Margaret Hospital, Canada). The trial was monitored by an independent Data Monitoring Committee composed of radiation oncologists, medical oncologists, and statistical consultants. All patients provided written informed consent. The Clinical Trial Registry ID number is HARECCTR0500023.

All patients were assessed by complete physical examination, fiberoptic nasopharyngoscopy, computed tomography or magnetic resonance imaging of the nasopharyngeal region, chest radiograph, complete blood count, renal and liver function tests, and lactate hydrogenase. Additional investigations were performed for those with suspicious findings (such as hepatomegaly) or abnormal biochemical profile.

Eligible patients were stratified by participating center and NPC tumor (T1-2 vs T3-4) and nodal (N2 vs N3) staging categories (11). They were randomly assigned using a blocked randomization scheme in a 1:1 ratio to receive RT either alone (the RT group) or in combination with concurrent–adjuvant chemotherapy (the CRT group). Randomization was generated by the consulting statistician in sealed envelopes labeled by stratum, which were unsealed only after patient registration.

Patients in both treatment groups were irradiated with megavoltage photons using the same RT technique and dose consistent with the treatment policy practiced by each center. Techniques ranged from conventional two- to three-dimensional conformal or intensity-modulated techniques throughout the whole course of treatment. Conventional fractionation of 2 Gy per fraction, with five daily fractions per week, was used in all patients. A total dose of 66 Gy or greater was given to gross tumor targets and 50 Gy or greater to potential sites of local infiltration and bilateral cervical lymphatics. Additional boosts (not exceeding 20 Gy) could be given to the parapharyngeal space, the nasopharynx and/or nodal sites (when indicated); the boost field was confined to the involved site with exclusion of critical structures.

Patients assigned to the CRT group were given additional chemotherapy using the Intergroup-0099 regimen (3). Cisplatin (100 mg/m^2) was given intravenously every 3 weeks for three cycles starting with commencement of radiotherapy, followed subsequently by a combination of cisplatin (80 mg/m^2) plus fluorouracil (1000 mg per m^2 per day by 96-hour infusion) every 4 weeks for three cycles. Dose modifications were permitted according to the protocol-specified criteria.

The first assessment of tumor response was performed 6–16 weeks after completion of radiotherapy. All patients were assessed by complete physical examination and fiberoptic nasopharyngoscopy. Further investigations were performed with computed tomography or magnetic resonance imaging and other tests when indicated. For statistical purposes, persistent primary or nodal disease at 16 weeks after completion of RT was defined as locoregional failure. Patients were re-assessed at least every 3 months during the first 3 years and then every 6 months thereafter until death. The earliest dates of detecting tumor relapse at different sites were recorded. Treatment of residual disease and tumor relapse (if detected) was given in line with the policy of the individual center.

CONTEXTS AND CAVEATS

Prior knowledge

Current treatment of advanced nasopharyngeal carcinoma includes adding concurrent–adjuvant chemotherapy to radiotherapy (CRT), but there are no data on possible late toxic effects of chemotherapy.

Study design

In a randomized phase III trial, patients with nonkeratinizing nasopharyngeal carcinoma were randomly assigned to radiotherapy alone (RT) or to CRT.

Contribution

Adding chemotherapy statistically significantly reduced deaths attributable to disease progression, but 5-year overall survival was similar in both groups because of an increase in deaths attributable to other causes, including acute toxicity, infection, second malignancy, and suicide in the CRT group.

Implications

The late toxic effects of CRT and RT are similar, but the greater acute toxicity and other effects of CRT may reduce the advantage gained by lower disease progression in nasopharyngeal carcinoma patients given adjuvant concurrent chemotherapy.

Limitations

Patients with keratinizing squamous cell carcinoma and those with advanced local disease (stage T3-4N0-1) were not included in the trial. Thus, the current findings may not be applicable to these patients.

From the Editors

Radiotherapy-related toxicities were graded according to both the Acute and the Late Radiation Morbidity Scoring Criteria of the Radiation Therapy Oncology Group (12): late toxicities included those that occurred or persisted beyond 90 days from commencement of RT, whereas acute toxicities were the early transient toxicities. The earliest date of detecting late toxicity (except xerostomia and dental caries) grade 3 or greater was recorded. Chemotherapy-related toxicities (except nausea or alopecia) were graded by the World Health Organization criteria (13).

Study Design and Statistical Analysis

In this randomized phase III trial, all events were measured from the date of random assignment, which started on March 16, 1999, and was closed on January 30, 2004. The primary endpoints included overall failure-free rate (FFR), which was defined as the time to first failure at any site, and PFS, which was defined as the time to first failure or death from any cause; FFR was chosen to provide more direct inference on the efficacy of the experimental regimen without adding extra variation because of unrelated deaths. Secondary endpoints for treatment efficacy included OS (time to death from any cause), locoregional FFR (time to persistence or recurrence in the nasopharyngeal and/or cervical region), and distant FFR (time to hematogenous metastasis). Secondary endpoints for safety included incidence rates of acute toxicities and time to late toxicities of grade 3 or greater. For patients who had reirradiation for treatment of locoregional relapses, events were censored at commencement of reirradiation for assessing toxicities incurred solely by the primary treatment.

Our hypothesis was that addition of chemotherapy could increase the 5-year FFR by 15%. Assuming that the 5-year FFR by RT was 40%, we estimated that target accrual of 340 patients would provide a statistical power of 80% to detect a difference at a two-sided 5% statistical significance level (11). All analyses were performed on an intention-to-treat basis; statistical tests comparing treatment groups were two-sided, and P values less than .05 were considered to indicate statistical significance. Time-to-event endpoints were calculated by the Kaplan–Meier method (14), and the differences were compared by the log-rank test (15). The χ^2 test was used for comparing incidence rates and categorical variables, and the Student t test was used for comparing the means of continuous variables. The hazard ratios (HRs) were calculated by the Cox regression model (16), with the assumptions of proportional hazards confirmed based on Schoenfeld residuals (17); cumulative hazard plots estimated for the RT and CRT groups were parallel, verifying that the assumption of proportional hazards was appropriate. Further subgroup analyses (not specified in the protocol) were exploratory.

Results

From March 1999 to January 2004, 348 eligible patients were randomly assigned (Figure 1), and 96% were re-assessed regularly;

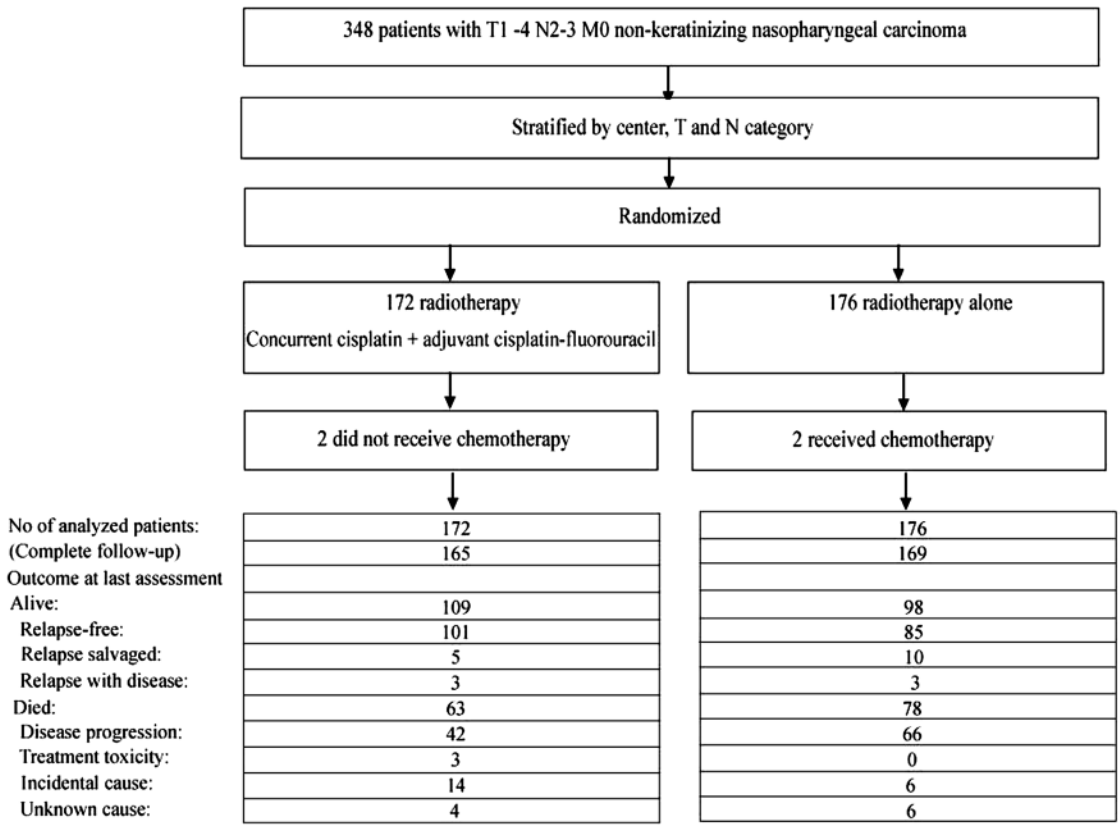


Figure 1. CONSORT flow diagram showing design, enrollment, and outcomes of this study (NPC-9901 Trial). Patients with T = 1 to 4; N = 2 to 3; M = 0 nasopharyngeal carcinoma were randomly assigned to radiotherapy either alone or with addition of concurrent–adjuvant chemotherapy (T = NPC tumor stage; N = nodal stage; M = evidence of distant metastases).

Table 1. Patient characteristics*

Characteristics	Chemoradiotherapy (N = 172)	Radiotherapy (N = 176)	P†
Age, mean ± SD, y	46 ± 10	47 ± 10	.42
Sex, No. (%)			
Men	124 (72)	139 (79)	.14
Women	48 (28)	37 (21)	
Performance status, No. (%)‡			
0	148 (86)	151 (86)	.37
1	24 (14)	23 (13)	
2	0	2 (1)	
T-category, No. (%)			
T1-2	100 (58)	103 (59)	.94
T3-4	72 (42)	73 (41)	
N-category, No. (%)			
N2	117 (68)	119 (68)	.94
N3	55 (32)	57 (32)	
Stage group, No. (%)			
III	98 (57)	108 (61)	.41
IVA-B	74 (43)	68 (39)	
Lactate dehydrogenase value, mean ± SD, IU/L	282 ± 152	271 ± 128	.45

* IU = international units; N-category = nodal stage; T-category = NPC tumor stage.

† All *P* values calculated by two-sided χ^2 test.

‡ Performance status: 0 = fully active, 1 = ambulatory but restricted by physically strenuous activity, 2 = ambulatory >50% of waking hours but unable to work.

those alive at the time of this analysis had a minimum follow-up of 5 years. The median duration of observation for the whole series was 5.9 years (range = 0.2–9.9 years).

The two treatment groups were well balanced in all patient characteristics, tumor factors (Table 1), and radiotherapy parameters (Table 2). The median total dose was 68 Gy, and the overall treatment time was 46 days. For patients who were given an additional boost to the nasopharynx or the parapharyngeal space, the median dose was 10 Gy. Only 1.2% of patients in the CRT group and 0.6% in the RT group did not complete the scheduled total dose; only 0.6% in each group had prolongation of overall treatment time beyond 7 days.

Four patients had major protocol violations (Figure 1): 1.2% in the CRT group did not receive chemotherapy (because of incidental cause and patient's choice) and 1.1% in the RT groups received chemotherapy (because of disease progression and patient's choice).

In the CRT group, the means and SDs of cycles given were 2.5 ± 0.6 during the concurrent phase and 2.6 ± 1.2 during the adjuvant phase. Altogether 66% of patients completed all six cycles of

Table 2. Primary treatment given

Primary treatment	Chemoradiotherapy (N = 172)	Radiotherapy (N = 176)	P*
Radiotherapy technique, No. (%)			
2-dimensional throughout	69 (40)	73 (41)	.89
2-dimensional + conformal	13 (8)	15 (9)	
Conformal throughout	90 (52)	88 (50)	
Total dose, mean ± SD, Gy	67.8 ± 7.4	68.5 ± 2.7	.28
Overall treatment time, mean ± SD, d	46 ± 6	46 ± 3	.59
Additional boost, No. (%)			
Nasopharynx/parapharynx	59 (34)	72 (41)	.20
Chemotherapy			
Concurrent, No. (%)	2 (1)	—	
1 cycle	8 (5)	—	
2 cycles	58 (34)	†	
3 cycles	104 (60)	†	
Adjuvant, No. (%)			
None	23 (13)	—	
1 cycle	10 (6)	—	
2 cycles	8 (5)	—	
3 cycles	108 (63)	†	
4 cycles‡	23 (13)	†	

* All *P* values calculated by two-sided χ^2 test.

† One patient in the radiotherapy group (in each of the cells shown) had been given chemotherapy (as explained in the text).

‡ A total of 24 patients had two concurrent plus four adjuvant cycles because the third concurrent cycle was actually given after completion of radiotherapy (as explained in the text).

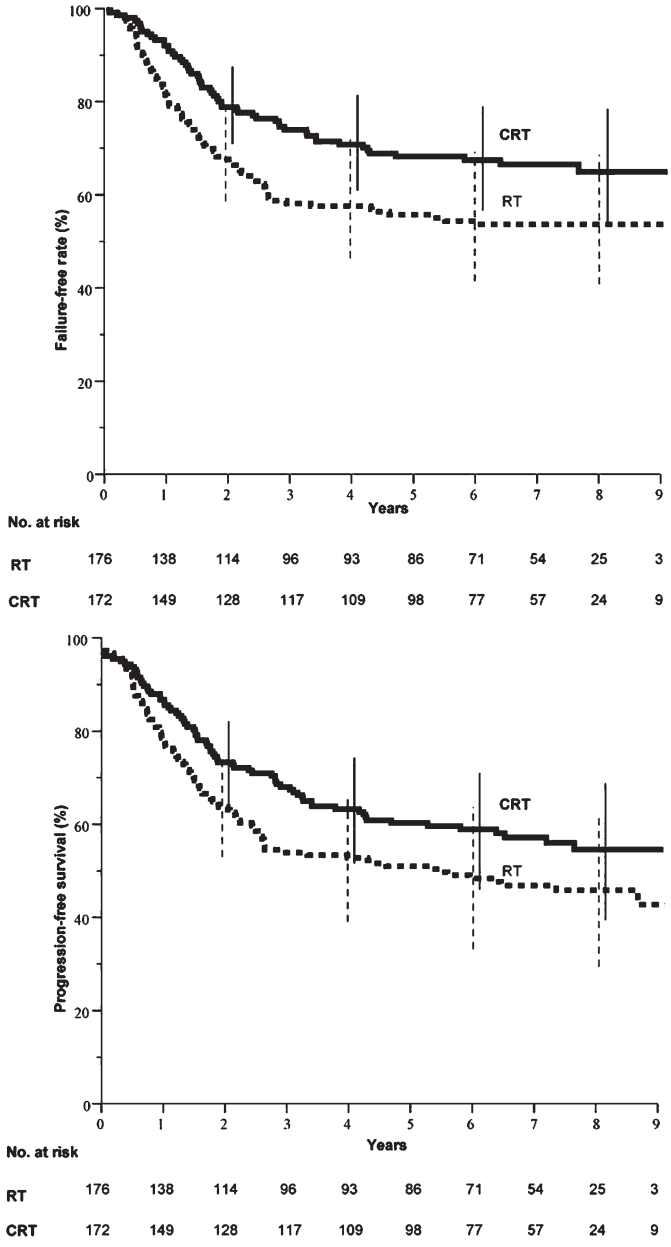


Figure 2. Kaplan–Meier estimates of patients who were randomly assigned to radiotherapy (RT) vs chemoradiotherapy (CRT). (**Top**) The failure-free rates were statistically significantly different (hazard ratio of CRT = 0.66, 95% confidence interval = 0.47 to 0.92; $P = .014$, two-sided log-rank test). (**Bottom**) The progression-free survival rates were statistically different (hazard ratio of CRT = 0.72, 95% confidence interval = 0.53 to 0.98; $P = .035$, two-sided log-rank test). The **vertical solid and broken lines** showed the 95% confidence interval of the estimates at different time points for the CRT group and the RT group, respectively.

chemotherapy, and 78% had five or more cycles. The mean total doses of cisplatin and fluorouracil received were 444 mg/m^2 and 9099 mg/m^2 (83% and 76% of the total scheduled doses), respectively.

Efficacy

A total of 139 patients failed at one or more sites, and 141 died (Figure 1). The FFR was statistically significantly higher in the CRT group compared with the RT group (67% vs 55%, respectively, at 5 years; $P = .014$; HR of CRT = 0.66; 95% confidence interval [CI] = 0.47 to 0.92) (Figure 2 and Table 3). This result was largely attributed to statistically significant improvement in 5-year locoregional FFR (CRT vs RT: 88% vs 78%; $P = .005$; HR of CRT = 0.45, 95% CI = 0.25 to 0.79). However, the 5-year distant FFR was not statistically significantly different (CRT vs RT: 74% vs 68%; $P = .32$; HR of CRT = 0.82, 95% CI = 0.56 to 1.21) (Figure 2 and Table 3).

Thirty-five patients in the CRT group and 56 patients in the RT group received further treatment for salvage of relapse. Besides aggressive locoregional treatment (including reirradiation, neck dissection, or nasopharyngectomy), chemotherapy was used in 16% of patients in the CRT group and in 26% of patients in the RT group (this difference in frequency of using salvage chemotherapy was statistically significant: $P = .025$ by χ^2 test). The successful salvage rates (alive without disease at last assessment) in the two groups were 3% and 6%, respectively.

Comparison of the causes of death (by χ^2 tests of absolute percent) showed that the CRT group had not only a statistically significant reduction in deaths because of disease progression (CRT vs RT: 24% vs 38%; $P = .008$) but also a statistically significant increase in deaths due to treatment-related toxicities (CRT vs RT: 1.7% vs 0) and incidental causes (CRT vs RT: 8.1% vs 3.4%); P for both noncancer causes = .015 (Figure 1). Among the incidental deaths in the CRT group, 2.9% were attributable to infection, 2.9% to second malignancy, 1.2% to suicide, 0.6% to cerebral vascular accident, and 0.6% to chronic lung disease. The corresponding causes in the RT group included 0.6% attributable to infection, 0.6% to second malignancy, 1.1% to cerebral vascular accident, 0.6% to dermatomyositis, and 0.6% to chronic lung disease. The times of occurrence of these incidental deaths ranged from 0.2 to 7.1 (median 3.5) years from random assignment. The second malignancies in the CRT group included cancers of lung, hard palate, stomach, and liver; no specific pattern or relationship suggestive of direct causation by treatment was observed.

The 5-year PFS was statistically significantly higher in the CRT group (CRT vs RT: 62% vs 53%; $P = .035$; HR of CRT for failure or death = 0.72, 95% CI = 0.53 to 0.98) (Figure 2). The OS rates were almost identical in both groups during the first 3 years and then showed improvement in the CRT group (CRT vs RT: 68% vs 64% at 5 years and 61% vs 54% at 8 years, $P = .22$; HR of CRT for death = 0.81, 95% CI = 0.58 to 1.13) (Figure 3).

Subgroup analyses (Table 3) showed that the beneficial effects of adding chemotherapy were statistically significant mainly in patients with stage III disease, and even OS showed an encouraging trend (HR of CRT = 0.64, 95% CI = 0.38 to 1.07; $P = .09$). For patients with stage IVA–B disease, the only statistical achievement was locoregional control. Statistically significant reduction of hazards was mainly achieved by patients with T1-2 tumors, among whom 67% had T2b primary and 35% had N3 nodal disease; the proportion of T2b tumors was actually higher in the CRT group than in the RT group (76% vs 58%), whereas the proportion of N3 disease was almost identical. None of the endpoints reached statistical significance in patients with T3-4 primary tumors. The impact on distant control was non-statistically significant in all subgroups.

Table 3. Effect of adding chemotherapy on tumor control*

Endpoint	All patients (N = 348), HR (95% CI)	Subgroup analyses			
		T-category		Stage group	
		T1-2 (N = 203), HR (95% CI)	T3-4 (N = 145), HR (95% CI)	III (N = 206), HR (95% CI)	IVA-B (N = 142), HR (95% CI)
Failure (all sites)	0.66 (0.47 to 0.92) P = .015	0.61 (0.37 to 0.99) P = .043	0.71 (0.45 to 1.14) P = .16	0.56 (0.33 to 0.95) P = .031	0.67 (0.43 to 1.05) P = .078
Progression†	0.72 (0.53 to 0.98) P = .036	0.65 (0.42 to 1.01) P = .058	0.79 (0.51 to 1.23) P = .30	0.61 (0.38 to 0.97) P = .036	0.75 (0.49 to 1.13) P = .17
Death (all causes)	0.81 (0.58 to 1.13) P = .22	0.76 (0.47 to 1.22) P = .25	0.88 (0.55 to 1.39) P = .58	0.64 (0.38 to 1.07) P = .09	0.88 (0.57 to 1.37) P = .58
Locoregional failure	0.45 (0.25 to 0.79) P = .006	0.22 (0.07 to 0.66) P = .007	0.66 (0.32 to 1.33) P = .24	0.43 (0.19 to 0.97) P = .043	0.44 (0.19 to 0.99) P = .047
Distant failure	0.82 (0.56 to 1.21) P = .32	0.85 (0.50 to 1.44) P = .54	0.79 (0.45 to 1.41) P = .44	0.79 (0.42 to 1.48) P = .46	0.75 (0.46 to 1.23) P = .26

* CI = confidence interval; HR = hazard ratio; P values were calculated by two-sided univariate test in the Cox regression model.

† Defining event for progression = either failure or death.

Figure 3. Kaplan–Meier estimates of patients who were randomly assigned to radiotherapy (RT) vs chemoradiotherapy (CRT). The overall survival rates were not statistically different (hazard ratio of CRT = 0.81, 95% confidence interval = 0.58 to 1.13; P = .22, two-sided log-rank test).

Safety

A total of 236 patients developed one or more acute toxicities and 101 patients developed late toxicity of grade 3 or greater (Table 4). The CRT group had statistically significantly higher incidence of acute toxicities (CRT vs RT: 83% vs 53%; P < .001); more were grade 4 in severity (CRT vs RT: 12% vs 1%) and 2 CRT patients (1.2%) died of sepsis. The CRT group had statistically significantly higher incidence of radiotherapy-related mucositis (CRT vs RT: 62% vs 48%; P = .02), and the incidence of chemotherapy-related toxicities was 59% in the CRT group. Besides the well-known toxicities of leukopenia and/or neutropenia (32%), anemia (20%) and vomiting (19%), 2% of CRT patients had reactivation of hepatitis and 1% had pulmonary tuberculosis.

The CRT group showed a higher late toxicity rate during the first 3 years, but this gradually leveled out to 30% vs 24% at 5 years (P = .30, HR of CRT = 1.23, 95% CI = 0.83 to 1.82) (Figure 4). The CRT group had slightly more grade 4 toxicities (CRT vs RT: 6% vs 3%), and one patient (0.6%) died of aspiration pneumonia related to damage of the last four cranial nerves, but these differences were not statistically significant (Table 4). The only statistically significant difference in damage between the two groups was peripheral neuropathy (CRT vs RT: 2.3% vs 0; P = .042) and cranial neuropathy (CRT vs RT: 1% vs 5%; P = .025).

Discussion

Addition of chemotherapy to radiotherapy is an important strategy for improving tumor control of advanced NPC because this treatment has potential for both enhancing the local effect of radiotherapy and eradicating micrometastases. A meta-analysis by Baujat et al. (18) of 1753 patients from eight randomized trials confirmed the value of adding chemotherapy and showed that concurrent chemotherapy is the most potent sequence for combining

Table 4. Maximum acute and late toxicities*

	CRT (N = 172)			RT (N = 176)		
	Toxicity grade					
Toxicity type	**3**	**4**	**5**	**3**	**4**	***P***
Acute toxicities, No. (%)						
Mucositis (radiation related)	104 (60)	2 (1)	—	85 (48)	—	.020
Skin reaction (radiation related)	31 (18)	3 (2)	—	27 (15)	2 (1)	.70
Leukopenia/neutropenia	51 (30)	3 (2)	1 (0.6)	1 (1)	—	<.001
Anemia	30 (17)	4 (2)	—	1 (1)	—	<.001
Thrombocytopenia	1 (1)	1 (1)	—	—	—	.36
Vomiting	26 (15)	6 (3)	—	1 (1)	—	<.001
Stomatitis	13 (8)	2 (1)	—	1 (1)	—	.001
Hearing loss	9 (5)	1 (1)	—	—	—	.005
Renal impairment	1 (1)	1 (1)	—	—	—	.36
Hyponatremia	1 (1)	2 (1)	—	—	—	.21
Hepatitis	2 (1)	1 (1)	—	—	—	.21
Chest infection	1 (1)	—	1 (0.6)	—	—	.36
Odynophagia	1 (1)	—	—	—	—	.31
Any acute toxicity	120 (70)	21 (12)	2 (1.2)	91 (52)	2 (1)	<.001
Late toxicities, No. (%)						
Brainstem damage	—	—	—	1 (1)	—	.32
Cranial neuropathy	1 (1)	—	1 (0.6)	9 (5)	—	.025
Peripheral neuropathy	4 (2)	—	—	—	—	.042
Brachial plexopathy				1 (1)	—	.32
Endocrine dysfunction	13 (8)	—	—	10 (6)	—	.48
Ear (deafness/otitis)	31 (18)	6 (3)		25 (14)	2 (1)	.19
Bone necrosis	—	1 (1)	—	—	1 (1)	.99
Mucosal damage	1 (1)	3 (2)	—	—	1 (1)	.35
Dysphagia	2 (1)	—	—	—	—	.15
Neck tissue damage	6 (3)	2 (1)	—	8 (5)	—	.32
Radiation-induced malignancy	—	—	—	—	1 (1)	.32
Vascular occlusion	—	1 (1)	—	—	—	.31
Any late toxicity	43 (25)	10 (6)	1 (0.6)	42 (24)	5 (3)	.37

* CRT = chemoradiotherapy; RT = radiotherapy alone. *P* values were calculated across toxicity grades by χ^2 test.

the two modalities. The current practice of adding cisplatin-based concurrent–adjuvant chemotherapy to conventional-fractionation radiotherapy is based on the Intergroup-0099 Study (3). However, with the serious concerns about the inferior results of the RT group and lack of data on late toxicities, confirmation of the actual magnitude of long-term benefit and safety is needed.

This trial, which focused on patients with N2-3 disease, provided a good opportunity for studying the efficacy of the Intergroup-0099 regimen (3), particularly for the key problem of control of distant metastases (because of especially high predilection in patients with extensive lymphatic spread). The two groups were well balanced in all patient characteristics and radiotherapy parameters (Tables 1 and 2), the sample size was large compared with other trials on NPC, and all surviving patients had a minimum follow-up of 5 years. The major limitations of this trial are that patients with keratinizing squamous cell carcinoma and those with T3-4N0-1 disease were not included; the current findings may not be extrapolated to patients with these characteristics without further testing.

Since the launch of this trial, there have been two other randomized trials (19,20) to evaluate similar chemotherapy regimens (Table 5). Along with the Intergroup-0099 Study (21) and this trial, they consistently showed that addition of concurrent–adjuvant chemotherapy could statistically significantly improve tumor control in terms of FFR and/or PFS. Progress reports by Al-Sarraf et al. (21) and Wee (22) confirmed the benefits reported in their initial publications (3,19). The absolute increase in 5-year PFS ranged from 29% in the Intergroup-0099 Study (21) to 13% by Wee (22) and 9% in this trial (Figure 2). Cross-series comparison is difficult because of differences in patient mix, particularly because the Intergroup-0099 Study (3) included patients with keratinizing carcinoma and stage IIB disease by the staging criteria (4,5) used in other studies. The 5-year PFS in the CRT group was similar among the three trials, ranging from 62% in this trial to 58% in the Intergroup-0099 Study (3), but the corresponding result for the RT groups of the three trials varied widely from 53% to 29%.

In concurrence with the Intergroup-0099 Study (3,21) and Chen et al. (20), this trial showed statistically significant improvement in locoregional control in the CRT group (absolute gain of 10% at 5 years, $P = .005$). The locoregional control rate in the CRT group was 88%, even though only 52% of patients were treated by conformal technique (which attained better tumor dose coverage than two-dimensional technique). However, our data showed that distant control only increased by 6% ($P = .32$) in the CRT group, even though the doses of chemotherapy were comparable to other trials. Reports by Hara et al. (23) and Lee et al. (24) from American centers similarly showed disappointingly high incidences of distant failure (30% and greater), despite achievement of excellent locoregional control by new technologies and extensive use of the Intergroup-0099 regimen (for more than 75% of patients included in the studies).

The incidence of acute toxicity increased by 30% in all four trials; similar to the Intergroup-0099 Study (3), this trial (Table 4) showed an acute toxicity rate of 83% in the CRT group as compared with 53% in the RT-alone group. The majority of patients with acute toxicity recovered, but similar to the trial by Wee et al (19) and Chen et al (20), 1% of the CRT group died because of chemotherapy-related toxicity.

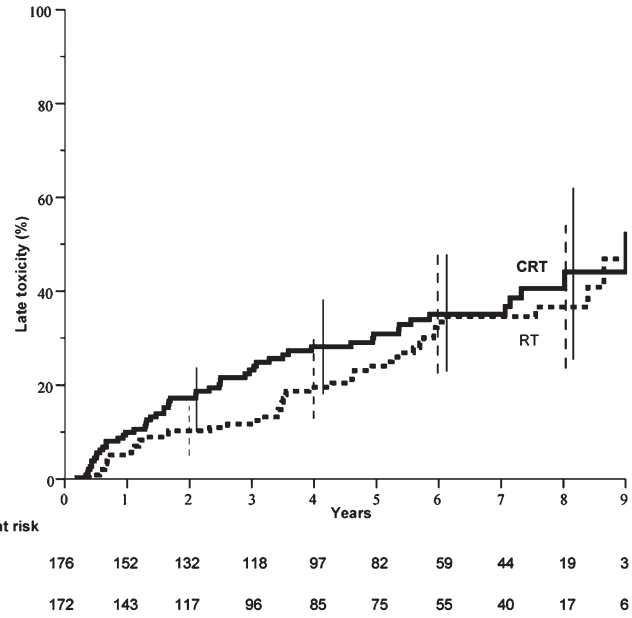
To our knowledge, this is the first trial to evaluate the effect on late toxicity. The increase in late toxicity observed during the first 3 years gradually leveled out; the increase at 5 years was 6% (CRT vs RT: 30% vs 24%) (Figure 4). The CRT group had slightly higher incidence of grade 4 toxicities (CRT vs RT: 6% vs 3%) (Table 4) and 1% direct treatment-related mortality, but these differences were non-statistically significant. The exact mechanism for this phenomenon is unknown; one hypothesis is that addition of chemotherapy aggravates the severity of damage by radiation and hence shortens the latency for manifestation of damage, but radiation parameters remain the key determinants of damage. However, it should be noted that the data were based largely on clinical observations; regular audiometry and/or imaging were not specified in the protocol; thus, underestimation cannot be excluded.

This trial revealed a worrisome increase in noncancer deaths in the CRT group. In addition to a 1.7% increase in direct treatment-related mortality, this group had a 4.7% increase in deaths because of "incidental" causes (including infection, second malignancy, and suicide). Whether these could be attributed to subtle damage by chemotherapy cannot be excluded.

Hence, despite a statistically significant 14% reduction in deaths because of cancer progression (CRT vs RT: 24% vs 38%; $P = .008$), the gain in the OS was non-statistically significant. The survival rates of the two groups were almost identical during the first 4 years; the gain was 4% at 5 years (CRT vs RT: 68% vs 64%) and then further diverged to 7% at 8 years (Figure 3; $P = .22$). Because the numbers of patients at risk toward the later years were small, longer follow-up is needed to confirm this trend. If confirmed, this magnitude of survival gain is still clinically valuable and comparable to the results commonly achieved for other solid cancers.

In comparison with other trials with 5-year results, the absolute increase in 5-year OS ranged from 40% in the Intergroup-0099 Study (21) to 18% by Wee (22) and 4% in this trial (Table 5). The 5-year OS in the CRT group was almost the same among the same three trials, ranging from 68% in this trial to 67% in the other two, but the corresponding result in the RT group varied widely from 64% to 37% among the three trials. The favorable result achieved by our RT group has been reproduced at least for nonkeratinizing carcinoma; in a retrospective study by the Hong Kong Nasopharyngeal Cancer Study Group on 905 patients with stages III–IVB disease treated by RT alone from 1996 to 2000 achieved a similar 5-year OS of 66% (25).

Subgroup analyses were added in an attempt to identify the focus for future improvement. However, it must be pointed out that these were not specified in the protocol and should be considered as purely exploratory. Our data (Table 3) suggest that it was patients with stage III disease who achieved the greatest benefit from adding chemotherapy; even OS showed an encouraging trend (HR for CRT = 0.64, 95% CI = 0.38 to 1.07; $P = .09$). Addition of the Intergroup-0099 regimen (3) at conventional fractionation



No. at risk										
RT	176	152	132	118	97	82	59	44	19	3
CRT	172	143	117	96	85	75	55	40	17	6

Figure 4. Kaplan–Meier estimates of patients who were randomly assigned to radiotherapy (RT) vs chemoradiotherapy (CRT). The late toxicity rates were not statistically different (hazard ratio of CRT = 1.23, 95% confidence interval = 0.83 to 1.82; $P = .30$, two-sided log-rank test).

mainly benefited patients with T1-2 tumors (67% of whom had T2b primary tumors); the efficacy was disappointing for those with T3-4 tumors. The latter observation concurs with the findings in the NPC-9902 Trial, which focused on patients with advanced local disease (9); further enhancement by incorporation of accelerated fractionation might be needed. Furthermore, more potent systemic therapy is needed for distant control in all subgroups.

One major question regarding the design of the Intergroup-0099 regimen (3) is the contribution of the adjuvant phase because available randomized trials (26,27) and a meta-analysis (18) showed that adjuvant chemotherapy per se had no statistically significant impact for all endpoints. To our knowledge, no randomized trial to date has compared the efficacy of concurrent–adjuvant chemotherapy vs concurrent chemotherapy alone. The only available data are from a retrospective comparison by Cheng et al. (28), who showed that inclusion of the adjuvant phase was beneficial for patients with intermediate risk (T2b-3N0-2M0); in that study, the 5-year OS by concurrent–adjuvant chemotherapy was 84%, compared with 63% for RT or concurrent CRT alone ($P = .005$).

A review of randomized trials using concurrent chemotherapy alone (27,29–31) showed less consistent conclusions. Lin et al. (29), using concurrent cisplatin plus fluorouracil, and Zhang et al. (30), using oxaliplatin, reported statistically significant benefit in both event-free survival and OS. However, reanalysis of the trial by Lin et al. (29) with retrospective restaging of the accrued patients into different risk groups showed that the benefit was statistically significant only for low-risk patients (32); and the trial by Zhang et al. (30) only had preliminary 2-year results. Kwong et al. (27), using uracil-tegafur with or without adjuvant cisplatin-based combination, and Chan et al. (31), using weekly cisplatin, only showed borderline improvement in OS ($P = .06$ and $P = .07$, respectively) and no statistically significant improvement in FFR ($P = .14$ and $P = .16$, respectively).

Table 5. Randomized trials comparing cisplatin-based concurrent–adjuvant chemotherapy plus radiotherapy vs radiotherapy alone for nasopharyngeal carcinoma*

Trial characteristics	Al-Sarraf (3,21)	Wee (19,22)	Chen (20)	This study†
Patient characteristics				
Number evaluated	147	221	316	348
Treatment period	1989–1995	1997–2003	2002–2005	1999–2004
Tumor stage‡	II–IVB	III–IVB	III–IVB	III–IVB
Nonkeratinizing type, %	78 vs 72	All	All	All
Radiotherapy				
Total dose, Gy	70	70	70	68 (mean)
Complete whole course, %	NR vs 91	95 vs 95	99 vs 98	99 vs 99
Chemotherapy, %				
Complete concurrent cycles	63	71	68	60
Complete adjuvant cycles	55	46	61	76
Results				
Assessment point, y	5	5	2	5
Efficacy				
Locoregional control, %	§	NR	98 vs 92 (P = .007)	88 vs 78 (P = .005)
Distant control, %	§	83 vs 63§	87 vs 79 (P = .024)	74 vs 68 (P = .32)
Failure-free rate, %	NR	NR	85 vs 73 (P = .001)	67 vs 55 (P = .014)
Progression-free survival, %	58 vs 29 (P < .01)	59 vs 46 (P = .032)	NR	62 vs 53 (P = .035)
Overall survival, %	67 vs 37 (P < .01)	67 vs 49 (P = .008)	90 vs 80 (P = .003)	68 vs 64 (P = .22)
Safety				
Acute toxicity	76 vs 50§	§	63 vs 32 (P < .001)	83 vs 53 (P < .001)
Late toxicity	NR	NR	NR	30 vs 24 (P = .30)

* NR = not reported

† All P values of this study calculated by two-sided log-rank test.

‡ Stages defined by the criteria of the 5th edition of the *American Joint Committee on Cancer Staging System* (4) and the *International Union Against Cancer* (5).

§ Statistically significant.

One strategy for improvement is to change the sequence from concurrent–adjuvant to addition of induction chemotherapy before concurrent chemoradiotherapy because meta-analysis showed that induction chemotherapy per se could statistically significantly reduce both locoregional and distant failures (18). Phase II studies on induction-concurrent chemoradiotherapy reported encouraging early results (33–41). A randomized Phase II trial by Hui et al. (33) showed that patients with stage III–IVB disease treated by induction-concurrent chemoradiotherapy achieved statistically significantly higher OS than those treated by concurrent weekly cisplatin alone (94% vs 68%, respectively, at 2 years; P = .012).

Studies by Lee et al. (34,35) on induction chemotherapy with cisplatin–fluorouracil followed by cisplatin in concurrence with accelerated RT showed that 98% of patients could complete three cycles of induction chemotherapy without substantial jeopardy of tolerance in the concurrent phase. Furthermore, this treatment regimen statistically significantly reduced the primary tumor volume by 61% (mean), leading to better radiation dose coverage by subsequent intensity-modulated RT (35). The Hong Kong Nasopharyngeal Cancer Study Group is currently conducting a randomized trial (NPC-0501 Trial) to evaluate the therapeutic benefits of changing the chemotherapy sequence from concurrent–adjuvant to induction–concurrent and/or changing the radiotherapy schedule from conventional to accelerated fractionation. In addition, this trial is attempting to study the possibility of replacing fluorouracil with the oral pro-drug capecitabine (ClinicalTrials.gov identifier: NCT00379262).

In conclusion, our results support the current practice of adding concurrent cisplatin plus adjuvant cisplatin–fluorouracil to radiotherapy for treating patients with advanced NPC because the highest priority is reduction of tumor relapse and cancer-specific deaths. However, patients should be duly informed that combined treatment induced statistically significantly more acute toxicities, and although the current data did not show a statistically significant increase in major late toxicities, there was a worrisome increase in noncancer deaths that could narrow the actual magnitude of survival gain. Therefore, vigilant follow-up is recommended. For improved treatment, both the search for more potent therapy, particularly for distant control, and more accurate prognostication are needed to avoid overtreatment.

References

1. Lee AW, Poon YF, Foo W, et al. Retrospective analysis of 5037 patients with nasopharyngeal carcinoma treated during 1976–1985: overall survival and patterns of failure. *Int J Radiat Oncol Biol Phys.* 1992;23(2):261–270.
2. Geara FB, Sanguinetti G, Tucker SL, et al. Carcinoma of the nasopharynx treated by radiotherapy alone: determinants of distant metastasis and survival. *Radiother Oncol.* 1997;43(1):53–61.

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. Fleming ID, Cooper JS, Henson DE, et al. *American Joint Committee on Cancer: AJCC Cancer Staging Manual.* 5th ed. Philadelphia, PA: Lippincott-Raven; 1997.
5. Sobin LH, Wittekind Ch. *International Union Against Cancer (UICC): TNM Classification of Malignant Tumors.* 5th ed. New York, NY: Wiley-Liss; 1997.
6. Chow E, Payne D, O'Sullivan B, et al. Radiotherapy alone in patients with advanced nasopharyngeal cancer: comparison with an Intergroup study—is combined modality treatment really necessary? *Radiother Oncol.* 2002;63(3):269–274.
7. Wolden SL, Zelefsky MJ, Kraus DH, et al. Accelerated concomitant boost radiotherapy and chemotherapy for advanced nasopharyngeal carcinoma. *J Clin Oncol.* 2001;19(4):1105–1110.
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. Lee AW, Tung SY, Chan AT, et al. Preliminary results of a randomized study (NPC-9902 Trial) on therapeutic gain by concurrent chemotherapy and/or accelerated fractionation for locally-advanced nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2006;66(1):142–151.
10. Shanmugarantnam K, Sobin LH. *Histological Typing of Tumors of the Upper Respiratory Tract and Ear.* 2nd ed. New York, NY: Springer-Verlag; 1991.
11. Freedman J, Furberg C, DeMets D. *Fundamentals of Clinical Trials.* New York, NY: Springer-Verlag; 1998.
12. 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.
13. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer.* 1981;47(1):207–214.
14. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53:457–481.
15. Peto R, Pike MC, Groupitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. *Br J Cancer.* 1977;35(1):1–39.
16. Cox DR. Regression models and life tables. *J Roy Statist Soc. Series B.* 1972;34(2):187–220.
17. Schoenfeld DA. Partial residuals for the proportional hazards regression model. *Biometrika.* 1982;39(2):499–503.
18. 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.
19. 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.
20. Chen Y, Liu MZ, Liang SB, et al. Preliminary results of a prospective randomized trial comparing concurrent chemoradiotherapy plus adjuvant chemotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma in endemic regions of China. *Int J Radiat Oncol Biol Phys.* 2008;71(5):1356–1364.
21. Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemo-radiotherapy (CT-RT) vs radiotherapy (RT) in patients (PTS) with advanced nasopharyngeal cancer (NPC). Intergroup (0099) (SWOG 8892, RTOG 8817, ECOG 2388) Phase III Study: progress report [abstract 1483]. *J Clin Oncol.* 1998;17:385a.
22. Wee J. Nasopharyngeal Cancer Workgroup—the past, the present and the future. *Ann Acad Med Singapore.* 2008;37(7):606–614.
23. Hara W, Loo BW, Goffinet DR, et al. Excellent local control with stereotactic radiotherapy boost after external beam radiotherapy in patients with nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2008;71(2):393–400.
24. Lee N, Xia P, Quivey JM, et al. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. *Int J Radiat Oncol Biol Phys.* 2002;53(1):12–22.
25. Lee AW, Sze WM, Au JS, et al. Treatment results for nasopharyngeal carcinoma in the modern era: the Hong Kong experience. *Int J Radiat Oncol Biol Phys.* 2004;61(4):1107–1116.
26. Chi KH, Chang YC, Guo WY, et al. A phase III study of adjuvant chemotherapy in advanced nasopharyngeal carcinoma patients. *Int J Radiat Oncol Biol Phys.* 2002;52(5):1238–1244.
27. 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.
28. Cheng SH, Tsai YC, 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.
29. Lin JC, Jan JS, Hsu CY, Liang WM, Jiang RS, Wang WY. 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.
30. Zhang L, Zhao C, Peng PJ, et al. Phase III study comparing standard radiotherapy with or without weekly oxaliplatin in treatment of locoregionally advanced nasopharyngeal carcinoma: preliminary results. *J Clin Oncol.* 2005;23(33):8461–8468.
31. Chan AT, Leung SF, Ngan RK, et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. *J Natl Cancer Inst.* 2005;97(7):536–539.
32. 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.
33. Hui EP, Ma BB, Leung SF, et al. Randomized phase II trial of cisplatin-radiotherapy with and without neoadjuvant docetaxel and cisplatin in advanced nasopharyngeal carcinoma. *J Clin Oncol.* 2009;27(2):242–249.
34. Lee AW, Yau TK, Wong HM, et al. Treatment of stage IV(A-B) nasopharyngeal carcinoma by induction-concurrent chemoradiotherapy and accelerated fractionation. *Int J Radiat Oncol Biol Phys.* 2005;63(5):1331–1338.
35. Lee AW, Lau KY, Hung WM, et al. Potential improvement of tumor control probability by induction chemotherapy for advanced nasopharyngeal carcinoma. *Radiother Oncol.* 2008;87(2):204–210.
36. Rischin D, Corry J, Smith J, Stewart J, Hughes P, Peters L. Excellent disease control and survival in patients with advanced nasopharyngeal cancer treated with chemoradiation. *J Clin Oncol.* 2002;20(7):1845–1852.
37. Oh JL, Vokes EE, Kies MS, et al. Induction chemotherapy followed by concomitant chemoradiotherapy in the treatment of locoregionally advanced nasopharyngeal cancer. *Ann Oncol.* 2003;14(4):564–569.
38. Chan AT, Ma BY, Lo YM, et al. Phase II study of neoadjuvant carboplatin and paclitaxel followed by radiotherapy and concurrent cisplatin in patients with locoregionally advanced nasopharyngeal carcinoma: therapeutic monitoring with plasma Epstein-Barr Virus DNA. *J Clin Oncol.* 2004;22(15):3053–3060.
39. Al-Amro A, Al-Rajhi N, Khafaga Y, et al. Neoadjuvant chemotherapy followed by concurrent chemo-radiation therapy in locally advanced nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2005;62(2):508–513.
40. Johnson FM, Garden AS, Palmer JL, et al. A phase I/II study of neoadjuvant chemotherapy followed by radiation with boost chemotherapy for advanced T-stage nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2005;63(3):717–724.
41. Yau TK, Lee AW, Wong HM, et al. Induction chemotherapy with cisplatin and gemcitabine followed by accelerated radiotherapy and concurrent

cisplatin in patients with stage IV(A-B) nasopharyngeal carcinoma. *Head Neck*. 2006;28(10):880–887.

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