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Concurrent and Adjuvant Chemotherapy for Nasopharyngeal Carcinoma: A Factorial Study

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose
To study the efficacy of concurrent chemoradiotherapy (CRT) and adjuvant chemotherapy (AC) for nasopharyngeal carcinoma (NPC).

Patients and Methods
Patients with Ho's stage T3 or N2/N3 NPC or neck node ≥ 4 cm were eligible. Patients were randomly assigned to have radiotherapy (RT) or CRT with uracil and tegafur and to have AC or no AC after RT/CRT. AC comprised alternating cisplatin, fluorouracil, vincristine, bleomycin, and methotrexate for six cycles. There were four treatment groups: A, RT; B, CRT; C, RT and AC; D, CRT and AC. For CRT versus RT, groups B and D were compared with groups A and C. For AC versus no AC, groups C and D were compared with groups A and B.

Results
Three-year failure-free survival (FFS) and overall survival (OS) for CRT versus RT were 69.3% versus 57.8% and 86.5% versus 76.8%, respectively ($P = .14$ and .06; n = 110 *v* 109). Distant metastases rate (DMR) was significantly reduced with CRT (14.8% *v* 29.4%; $P = .026$). Locoregional failure rates (LRFR) were similar (20% *v* 27.6%; $P = .39$). Three-year FFS and OS for AC versus no AC were 62.5% versus 65% and 80.4% versus 83.1%, respectively ($P = .83$ and .69; n = 111 *v* 108). DMR and LRFR were not reduced with AC ($P = .34$ and .15, respectively). Cox model showed CRT to be a favorable prognostic factor for OS (hazard ratio, 0.42; $P = .009$).

Conclusion
An improvement in OS with CRT was observed but did not achieve statistical significance. The improvement seemed to be associated with a significant reduction in DMR. AC did not improve outcome.

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INTRODUCTION

Nasopharyngeal carcinoma (NPC) is endemic in Southern China and Southeast Asia. It is a radiosensitive tumor, and radiotherapy (RT) remains the backbone of treatment for all stages of nonmetastatic diseases. Treatment results with RT alone for early-stage disease are good. More than 70% to 80% overall survival (OS) rates can be expected for stages I and II disease. However, for advanced disease, there is a greater than 50% risk of recurrence after RT alone, and approximately half of all recurrences are distant failures.[1-4] NPC is also chemotherapy-sensitive. There had been many attempts at combining chemotherapy and RT for locoregionally advanced NPC. A meta-analysis performed on six randomized trials investigating the efficacy of combined chemotherapy and RT versus RT alone in NPC showed that the addition of chemotherapy to RT significantly improved disease-free/progression-free survival rates by 34% to 40%. OS was improved by 20%, which was marginally significant.[5] Most of the studies used neoadjuvant chemotherapy. There were too few studies on concurrent chemoradiotherapy (CRT) or adjuvant chemotherapy (AC) in NPC to allow identification of the optimal schedule in combining chemotherapy with RT for this disease.

The American Intergroup 0099 study, using both concurrent cisplatin and RT followed by post-RT AC with cisplatin and fluorouracil (FU), showed the greatest improvement in progression-free survival and was the first study that demonstrated improvement in OS with chemotherapy.[6] However, the relative importance and contribution of CRT and AC towards the improvement in disease control and survival remain unknown. There is also uncertainty in the applicability of the Intergroup results for NPC from endemic regions. NPCs in North America consist of a greater proportion of tumors with WHO type I and II histology, which are more akin to other head and neck squamous cell carcinomas. On the other hand, more than 90% of NPCs in endemic regions belong to WHO type III histology, which is more radiosensitive. Also, RT regimes used in endemic regions for the treatment of NPC tend to be more aggressive,[7] so that the margin of benefit potentially gained with additional chemotherapy may be reduced. Thus, whether CRT can improve the survival for endemic NPC and the optimal strategy for integrating the two treatment modalities remain unresolved issues.

We started a randomized, factorially designed study in 1995 to evaluate the efficacy and relative contributions of CRT and AC in treatment of NPC. Results from this study may shed light on the importance of dose scheduling in combining chemotherapy and RT for NPC.

PATIENTS AND METHODS

Patients with histologically proven, previously untreated NPC with Ho's[8] stage T3 or N2/N3 disease or with any lymph nodes $\geq$ 4 cm and no distant metastases at diagnosis were eligible for study. Pretreatment evaluation included complete history and physical examination, nasopharyngoscopy, chest x-ray, CBC count, liver and renal biochemistry, 24 hours urine for creatinine clearance, computed tomography (CT) and magnetic resonance imaging scan of the nasopharynx (NP) and neck. CT thorax, ultrasound/CT liver, and bone scan were performed if initial investigation showed abnormal findings suggestive of metastases. Inclusion criteria included WBC counts of at least 4,000/μL, platelet counts of at least 100,000/μL, creatinine clearance of at least 60 mL/min, normal liver function, and chest x-ray. Baseline lung function test was not required. The study was approved by the institutional ethics committee. Written informed consent was obtained from patients.

Patients recruited into the trial were first randomly assigned to receive RT or CRT with a FU prodrug, UFT (uracil and tegafur in 4:1 molar ratio), and then further randomly assigned to receive AC or no AC after completion of RT or CRT. Adjuvant chemotherapy consisted of cisplatin and FU alternating with vincristine, bleomycin, and methotrexate for a total of six cycles. Thus there were four groups in the trial: A, RT; B, CRT; C, RT and AC; and D, CRT, and AC.

Radiotherapy

A 4-MV or 6-MV linear accelerator was used for treatment. Radiotherapy started with two lateral opposing facial-cervical fields to cover NP and neck lymph nodes to 40 Gy. After 40 Gy, to avoid further irradiation to the spinal cord, a three-field technique consisting of one anterior facial and two lateral opposing facial fields was used to cover the primary. An anterior facial electron field may be added for nasal and ethmoidal extension of tumor. The neck was treated with an anterior cervical field. Between May 1995 and June 1997, patients were treated with split-course RT in 2.5-Gy fractions at four fractions per week to 40 Gy and then continued with 2.5-Gy fractions at five fractions per week with a three-field technique to a total of 62.5 Gy to primary and neck. A 1-week rest period was allowed after 40 Gy before the start of three-field RT. After June 1997, continuous-course RT with 2-Gy daily fractions was used. The doses to primary and neck were 68 Gy and 66 Gy, respectively. For disease with parapharyngeal extension or residual palpable neck node, an additional 10-Gy boost dose was given.

Chemotherapy

For CRT, patients received oral UFT, 200 mg three times per day, 7 days a week, concurrent with RT. The choice of UFT in this study was based on phase I and II studies showing that oral UFT can simulate continuous FU infusion, and there was selective concentration of FU in tumor five to 10 times greater than in blood.[9] The maximum-tolerated dose of UFT for long-term administration was 600 mg/d. FU is active in NPC and has a good radiosensitizing effect.[10-12] The constant presence of 5-FU in tumor cells resulting from continuous administration of oral UFT is considered useful for radiosensitization with daily fractions of RT.

With split-course RT before 1997, UFT was given from week 1 to week 3 of RT and was stopped in week 4 and during the rest period. UFT was restarted with the resumption of three-field RT and continued until the end of RT. With continuous course after 1997, UFT was given throughout the period of RT. Thus the scheduled total time of use of UFT ranged from 5 to 8 weeks.

Adjuvant chemotherapy was started 3 weeks after completion of RT. It consisted of alternating cisplatin and FU (PF; cisplatin 100 mg/m^2 by intravenous [IV] infusion over 4 hours, day 1; 5-FU 1,000 mg/m^2/d continuous IV infusion for 72 hours, days 1 through 3) and vincristine, bleomycin, and methotrexate (VBM; vincristine 2 mg, bleomycin 30 mg, methotrexate 150 mg/m^2, all by IV bolus injection on day 1; oral folinic acid, 30 mg every 6 hours for six doses, was started 24 hours after methotrexate), given every 3 weeks, for a total of six cycles. PF is the most effective combination for NPC. Vincristine, bleomycin, and methotrexate are active agents for head and neck cancers and for NPC.[13-16] Alternating combination chemotherapy with PF and VBM was used in this study to reduce the development of drug resistance and reduce the toxicity of individual chemotherapeutic agents, as well as to maximize the additive effects of different effective cytotoxic drugs.

Dose Modification

Patients were seen weekly during RT for monitoring of radiation reaction, body weight, drug compliance, and blood counts. Radiation toxicity was graded according to the Radiation Therapy Oncology Group toxicity scale. If the WBC count decreased to less than 3,000/μL or the platelet count decreased to less than 100,000/μL, UFT was withheld and blood counts were checked weekly. RT was continued and UFT was restarted when blood counts recovered. If grade 3 mucositis developed and a patient had weight loss greater than 15% of the baseline body weight or deterioration in performance status, UFT was stopped but RT was continued. Dose reduction for UFT was not allowed.

For patients receiving AC, adequate blood counts with neutrophil $\geq$ 1,500/μL and platelet $\geq$ 100,000/μL were required before the start of each cycle. If creatinine clearance decreased to less than 60 mL/min, cisplatin was substituted by giving carboplatin 350 mg/m^2 on day 1. Vincristine was reduced from 2 mg to 1 mg if the patient developed constipation or paresthesia after VBM. A 25% reduction in dose of chemotherapy was allowed if chemotherapy was delayed for more than 1 week as a result of inadequate blood counts. Further dose reduction was not allowed. If chemotherapy was delayed for more than 2 weeks, further AC was stopped. Toxicity was graded according to the WHO toxicity scale.

Follow-Up and Assessment

At 6 weeks and 8 weeks after completion of RT, nasopharyngoscopy and multiple biopsies were performed to assess the disease status in the NP. CT scan of the NP and neck was performed at 3 months after completion of RT. Residual neck nodes were evaluated by ultrasound-guided aspiration biopsy. Complete remission was defined as no histologic evidence of disease in the NP or neck node at 12 weeks after completion of RT. Appropriate treatments, including brachytherapy and surgery, were given for salvage of persistent locoregional disease. For patients receiving AC, chemotherapy was completed before additional salvage treatment. After completion of treatment, patients were followed up every month during the first year, every 2 months in the second year, and then every 3 to 6 months afterwards. Follow-up nasopharyngoscopy and CT scan were performed every 6 months for the first 2 years and thereafter when clinically indicated.

Statistical Considerations

This is a factorially designed study to test for the efficacy of CRT and AC independently. End points of interest are failure-free survival (FFS) and OS. Groups A and C were to be compared with groups B and D for efficacy of CRT (ie, patients receiving RT *v* patients receiving CRT). Groups A and B were to be compared with groups C and D for efficacy of AC (ie, patients without AC *v* patients with AC). The study was started in May 1995. The goal was to recruit 350 patients over 5 years to detect a 15% improvement in OS with a power of 80% at 5% level of significance with either CRT or AC. After publication of the Intergroup study, other multicenter randomized trials were organized in Hong Kong and other Southeast Asian countries to validate the results in endemic NPC. Competing recruitment of patients into other trials and the preference of some physicians and patients for combined-modality treatment over randomization in trial settings had led to unexpected slow recruitment for the present study. The study was closed before target accrual in October 2001 on advice from the data monitoring committee and ethics committee because of slow recruitment.

The χ^2 test was used for comparison of categoric data. Survival analysis was performed based on intention to treat. Analysis of toxicity was performed based on actual treatment received. Survival time was counted from the date of randomization to the date last seen or death. Time to failure was taken as zero for patients with persistent disease in NP or neck after primary treatment. Three-year survival was estimated by the Kaplan and Meier method, and the 95% CIs were indicated in brackets. Comparison of survivals between groups was performed with the log-rank test. A single multiple-variable Cox regression model was performed for multiple variables analysis using SAS (version 8.2; SAS Institute, Cary, NC).[17] Prognostic factors tested included age (continuous variable), sex (male *v* female), RT fractionation (split course *v* continuous course), Ho's stage (stage III *v* stage II and stage IV *v* stage II), CRT (CRT *v* RT), and AC (AC *v* no AC). All *P* values were two-sided, and *P* values less than .05 were considered statistically significant.

Possible treatment interaction effect between CRT and AC was explored. An interaction term, z, defined as the product of the two variables CRT and AC, was tested together with CRT and AC as covariates in the Cox model for FFS and OS using the proportional hazards regression procedure in SAS. The statistical significance of the interaction term was determined by the goodness of fit and its *P* value from the Cox regression analysis.

Secondary Analysis

Findings from primary analysis showed that Ho's stage was not a significant prognostic factor for either FFS or OS in the Cox model. This unusual finding may be due to the very skewed patient distribution according to Ho's staging in the present study. There were only eight patients with Ho's stage II and 18 patients with Ho's stage IV disease. The small number of patients in these two stage groups will render their prognostic results unstable and thus the prognostic findings according to Ho's stages unreliable. Since the new American Joint Committee on Cancer (AJCC) 1997 staging[18] was adopted, there have been a number of reports confirming its improvement over other staging classifications, including the Ho's staging, in better segregation of patients with different prognosis into respective stage groups.[19,20] In the present study, prognosis was better stratified with AJCC stages than with Ho's stages. A secondary analysis using AJCC 1997 stages in lieu of Ho's stages in Cox regression was performed to better account for the possible confounding effect of stage and to confirm results of the primary analysis. Possible interaction between CRT and AJCC stages was also explored. An interaction term for CRT and AJCC stage, z_1, was tested as a covariate in the Cox model, together with CRT and AJCC stages.

RESULTS

A total of 222 patients were recruited. Three patients were excluded from analysis because they refused participation in the study after randomization but before the start of any treatment: two refused CRT and one refused RT. Two hundred nineteen patients (64 female and 155 male patients) were included in this analysis. At the time of analysis, 44 patients had died, and median follow-up of the 175 patients who were alive was 37 months. Ninety-eight percent of patients had complete follow-up. Only 19 patients (8.7%) had less than 1 year of follow-up. Table 1 lists the number of patients in each group. Table 2 lists and compares patient characteristics according to the four treatment groups. The four groups were well balanced according to Ho's staging. However, case distribution was very skewed in this series, with 88.1% of patients having Ho's stage III disease. According to AJCC 97 staging, group A seemed to have a higher proportion of earlier stage disease (more AJCC stage II and less AJCC stage III/IV disease) than other groups. The difference was, however, not statistically significant.

Table 1. Number of Patients in Each Treatment Group

	No. of Patients		
	RT	CRT*	Total
No AC	Group A, 55	Group B, 53	108
AC	Group C, 54	Group D, 57	111
Total	109	110	219

Abbreviations: RT, radiotherapy; CRT, concurrent chemoradiotherapy; AC, adjuvant chemotherapy.
*Uracil and tegafur concurrent with RT.

All patients completed radical RT. The median dose to NP was 68 Gy, and median dose to neck was 66 Gy. The median time taken to complete RT including boost was 52 days, ranging from 39 to 64 days. One hundred ten patients had CRT. Median total dose of UFT used was 25,200 mg (range, 4,000 to 33,600 mg), corresponding to 6 weeks of treatment. Seventy percent of patients completed at least 5 weeks of UFT. Seven patients (13%) in group C and eight patients (14%) in group D did not proceed to AC. Thus 96 patients actually received AC. Of these 96 patients, 79 patients (82.3%) completed six courses of AC. Eighty-three patients (86.5%) completed at least four cycles of AC. Table 3 lists the details of actual chemotherapy delivered for each cycle.

Table 4 shows the pattern of disease failure. One hundred ninety-two patients (87.7%) achieved complete remission after primary treatment. Twenty-seven patients had persistent disease in NP or neck, and 24 (88.9%) were given salvage treatment, including brachytherapy, surgery, or additional external RT. Salvage treatment was given to 68.4% of patients with locoregional recurrence. At the time of analysis, a total of 77 patients had disease failure and 44 patients had died. All deaths, except for two in group B, were due to NPC.

Survival Analysis

Figure 1 shows FFS of all four groups. Three-year FFS for groups A, B, C, and D were 61.3% (95% CI, 47.8% to 74.8%), 68.8% (95% CI, 55.5% to 82.1%), 54.1% (95% CI, 39.4% to 68.8%), and 69.9% (95% CI, 57.4% to 82.4%), respectively. The apparently better FFS of group A compared with group C may be in part due to the higher proportion of patients with early AJCC stage II disease in this group, although the difference was statistically insignificant (Table 2). Three-year OS for groups A, B, C, and D were 82.7% (95% CI, 71.6% to 93.8%), 83.5% (95% CI, 71.3% to 95.8%), 71% (95% CI, 56.6% to 85.4%), and 89% (95% CI, 79.8% to 98.2%), respectively.

There were eight, 193, and 18 patients with Ho's stage II, III, and IV disease, respectively. Three-year FFS was 62.5% (95% CI, 28.9% to 96.1%) for stage II, 66% (95% CI, 58.8% to 73.2%) for stage III, and 39% (95% CI, 16.5% to 61.5%) for stage IV. Three-year OS was 100% for stage II, 85.6% (95% CI, 79.7% to 91.5%) for stage III, and 38.9% (95% CI, 16.4% to 61.4%) for stage IV disease. Change in the RT fractionation in 1997 did not significantly affect the outcome. FFS and OS of patients treated before and after June 1997 were not significantly different ($P = .27$ and .23, respectively).

Efficacy of CRT and AC

Primary analysis. One hundred ten patients receiving CRT were compared with 109 patients receiving RT. Three-year locoregional failure rate (LRFR) was 20% (95% CI, 12% to 28%) for patients receiving CRT and 27.6% (95% CI, 18.4% to 36.8%) for patients receiving RT (Fig 2; $P = .39$). Three-year distant metastases rate (DMR) was 14.8% (95% CI, 7.5% to 22%) for patients receiving CRT and 29.4% (95% CI, 19.6% to 39.2%) for patients receiving RT (Fig 3; $P = .026$). Three-year FFS rates for patients receiving CRT and RT were 69.3% (95% CI, 60.2% to 78.4%) and 57.8% (95% CI, 47.8% to 67.8%), respectively (Fig 4; $P = .14$), and 3-year OS rates were 86.5% (95% CI, 79% to 94%) and 76.8% (95% CI, 67.6% to 86%), respectively (Fig 5; $P = .06$). There was statistically significant improvement in DMR with CRT. Improvement in OS with CRT was observed but did not quite achieve statistical significance ($P = .06$). The difference in LRFR and FFS was not statistically significant.

One hundred eleven patients with AC were compared with 108 patients without AC. Three-year LRFR rates and DMR for patients with AC were 19.1% (95% CI, 11.2% to 27%) and 24.7% (95% CI, 15.7% to 33.7%), respectively, compared with 28.6% (95% CI, 19.4% to 37.8%) and 19.1% (95% CI, 10.7% to 27.5%), respectively, for patients without AC ($P = .15$ and .34, respectively). Three-year FFS and OS rates for patients with AC were 62.5% (95% CI, 52.9% to 72.1%) and 80.4% (95% CI, 71.8% to 89%), respectively, compared with 65% (95% CI, 55.5% to 74.5%) and 83.1% (95% CI, 74.9% to 91.3%), respectively, for patients without AC (Figs 6 and 7; $P = .83$ and .69, respectively). There was no significant difference in LRFR, DMR, FFS, or OS for patients treated with and without AC.

In the Cox model, none of the factors tested, including Ho's stage, age, sex, RT fractionation, CRT, and AC, were significant for FFS. For OS, age (hazard ratio, 1.05; 95% CI, 1.01 to 1.08; $P = .01$) and CRT (hazard ratio, 0.42; 95% CI, 0.22 to 0.81; $P = .009$) were significant prognostic factors. Ho's stage, sex, RT fractionation, and AC were not significant. The Cox model gave unstable results for Ho's stage, because the reference group for comparison, Ho's stage II, had only a small number of patients.

Test for interaction between treatments. The Cox model was performed using the interaction term z, CRT, and AC as covariates for FFS and OS. There was no significant treatment interaction effect between CRT and

Table 2. Patient Characteristics of the Four Treatment Groups

Characteristic	A (n = 55)		B (n = 53)		C (n = 54)		D (n = 57)		
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	χ^2 *P*
Age, years									
Median	45		48		45.5		45		
Range	22-65		26-62		25-64		22-65		
Sex									.77
Male	38	69.1	38	71.7	36	66.7	43	75.4	
Female	17	30.9	15	28.3	18	33.3	14	24.6	
Histology, WHO									.79
I	1	1.8	1	1.9	0	0	0	0	
II	4	7.3	7	13.2	6	11.1	7	12.3	
III	50	90.9	45	84.9	48	88.9	50	87.7	
Ho's[8]									
T stage									.82
T1	8	14.6	7	13.2	11	20.4	6	10.5	
T2	23	41.8	20	37.7	20	37	26	45.6	
T3	24	43.6	26	49.1	23	42.6	25	43.9	
N stage									.61
N0	11	20	10	18.9	8	14.8	10	17.5	
N1	3	5.4	10	18.9	11	20.4	7	12.3	
N2	37	67.3	28	52.8	30	55.5	34	59.7	
N3	4	7.3	5	9.4	5	9.3	6	10.5	
Overall stage									.98
II	3	5.4	1	1.9	2	3.7	2	3.5	
III	48	87.3	48	90.6	47	87	50	87.7	
IV	4	7.3	4	7.5	5	9.3	5	8.8	
AJCC 1997[18]									
T stage									.68
T1	8	14.5	7	13.2	11	20.4	6	10.5	
T2	23	41.8	20	37.7	20	37	26	45.6	
T3	20	36.4	16	30.2	18	33.3	19	33.4	
T4	4	7.3	10	18.9	5	9.3	6	10.5	
N stage									.53
N0	11	20	10	18.9	8	14.8	10	17.5	
N1	26	47.3	22	41.5	16	29.6	24	42.1	
N2	13	23.6	16	30.2	25	46.3	16	28.1	
N3	5	9.1	5	9.4	5	9.3	7	12.3	
Overall stage									.26
II	21	38.2	12	22.6	11	20.4	15	26.3	
III	26	47.3	26	49.1	33	61.1	29	50.9	
IV	8	14.5	15	28.3	10	18.5	13	22.8	
RT									.95
Split course	18	32.7	16	30.2	19	35.2	18	31.6	
Continuous course	37	67.3	37	69.8	35	64.8	39	68.4	

Abbreviations: AJCC, American Joint Committee on Cancer; RT, radiotherapy.

AC for FFS or OS (*P* values for z were .78 and .46, respectively) and supported the testing of CRT and AC as independent variables.

Secondary analysis. In primary analysis, CRT was found to significantly improve OS in multiple-variable analysis with the Cox model, whereas univariable analysis with the log-rank test only showed borderline significance of CRT. On the other hand, Ho's stage was not significant for either FFS or OS in Cox model, which is unusual because stage is usually the most powerful prognosticator. The very skewed distribution of patients according to Ho's staging may account for this unusual finding; 88.1% of patients in this study had Ho's stage III disease.

Patient distribution according to AJCC 97 staging was more even compared with Ho's staging (Table 2). Three-year FFS rates were 76.2% for AJCC stage II (95% CI, 64.7% to 87.7%), 63.3% for stage III (95% CI, 53.6% to 73%), and 49.1% for stage IV (95% CI, 34.5% to 63.7%), and the corresponding 3-year OS rates were 91.3% (95% CI, 83.1% to 99.5%), 86.1% (95% CI, 78.3% to 93.9%), and 64% (95%

Table 3. Actual Dose of Adjuvant Chemotherapy Delivered

	Cycle					
	1 (PF)	2 (VBM)	3 (PF)	4 (VBM)	5 (PF)	6 (VBM)
No. of patients who received chemotherapy	96	91	88	83	82	79
With full dose, %	100	100	85.2	92.8	79.3	91.1
With carboplatin replacing cisplatin, %	9.4	—	18.2	—	18.3	—
With vincristine reduced to 1 mg, %	—	0	—	20.5	—	24

NOTE. — indicates not applicable.
Abbreviations: PF, cisplatin and fluorouracil; VBM, vincristine, bleomycin, and methotrexate.

CI, 49.8% to 78.2%), respectively. The AJCC stages allowed better segregation of patients into prognostic groups than Ho's stages. To confirm the findings in primary analysis and to better account for the possible confounding effect of stage in multiple-variable analysis, a secondary analysis using AJCC stages in lieu of the Ho's stages in Cox model was performed. A single Cox regression model with multiple variables, including AJCC stages (stage IV *v* stage II and stage III *v* stage II), age, sex, RT fractionation, CRT, and AC, was performed.

Results of the Cox regression showed that the AJCC stage was significant for both FFS and OS. For FFS, hazard ratios of AJCC stage were 2.4 (stage IV *v* stage II, 95% CI, 1.2 to 4.9; $P = .012$) and 1.4 (stage III *v* stage II, 95% CI, 0.75 to 2.5; $P = .31$). For OS, hazard ratios of AJCC stage were 4.6 (stage IV *v* stage II, 95% CI, 1.7 to 13; $P = .004$) and 1.7 (stage III *v* stage II, 95% CI, 0.62 to 4.7; $P = .3$). Secondary analysis showed the superiority of AJCC stage over Ho's stage as a prognostic indicator. Other significant prognosticators remained the same as in the primary analysis. Concurrent chemoradiotherapy was statistically significant for OS (hazard ratio, 0.41; 95% CI, 0.21 to 0.78; $P = .007$) and of borderline statistical significance for FFS (hazard ratio, 0.65; 95% CI, 0.41 to 1.03; $P = .07$). Age was significant for OS (hazard ratio, 1.04; 95% CI, 1.004 to 1.08; $P = .028$). Sex, RT fractionation, and AC did not significantly affect FFS or OS.

Possible interaction between AJCC stages and CRT was explored. An interaction term, z_1, was tested as a covariate together with AJCC stages and CRT in a Cox model. There was no statistically significant interaction effect between AJCC stages and CRT for FFS or OS (P values of z_1 were .38 and .88, respectively).

Toxicity

There were no treatment-related deaths. Table 5 lists the acute radiation toxicity of patients. Overall, CRT was well tolerated. The most significant toxicity associated with CRT was increase in grade 3/4 mucositis and skin reaction (χ^2 test, $P = .001$ and .018, respectively). Seven patients (6.4%) receiving CRT and two patients (1.8%) receiving RT needed admission for management of radiation mucositis and/or skin reaction. Only one of these nine admitted patients was put on a tube feeding, and the others were hydrated with IV fluid. The mean percentage weight loss among patients who underwent CRT was higher than those who underwent RT (11.6% *v* 8.9%; *t* test, $P = .02$). The overall time taken to complete RT among patients undergoing CRT and RT were not significantly different (median, 51 and 53 days, respectively).

Ninety-six patients actually received AC. Table 6 lists acute toxicity of patients receiving AC. Hematologic and gastrointestinal toxicity were the most significant. Sixty-five percent of patients developed maximum grade 3/4 toxicity during the course of AC. Follow-up time of this group was

Table 4. Pattern of Disease Failure According to Treatment Group

	Group A (n = 55)		Group B (n = 53)		Group C (n = 54)		Group D (n = 57)		Total (n = 219)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Persistent locoregional disease	10	18.2	6	11.3	6	11.1	5	8.8	27	12.3
Recurrence										
Locoregional only	3	5.5	7	13.2	3	5.6	4	7	17	7.8
Distant metastases only	6	10.9	3	5.7	12	22.2	8	14	29	13.2
Locoregional and distant metastases	6	10.9	3	5.7	4	7.4	1	1.8	14	6.4
Death	11	20	9	17	16	29.6	8	14	44	20

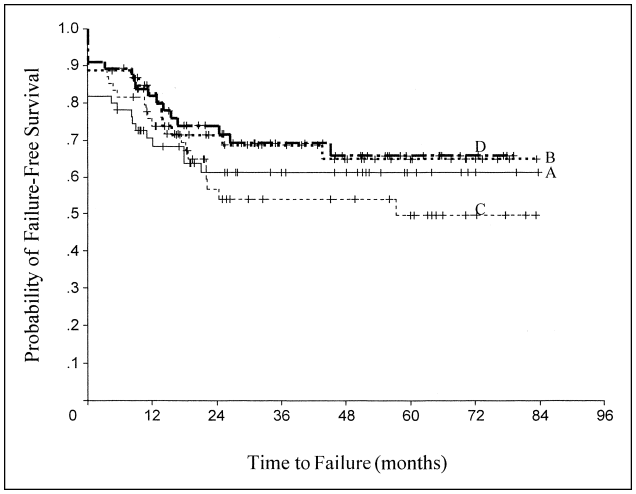

Fig 1. Failure-free survival of all groups. A, radiotherapy (RT); B, concurrent chemoradiotherapy (CRT); C, RT and adjuvant chemotherapy (AC); D, CRT and AC.

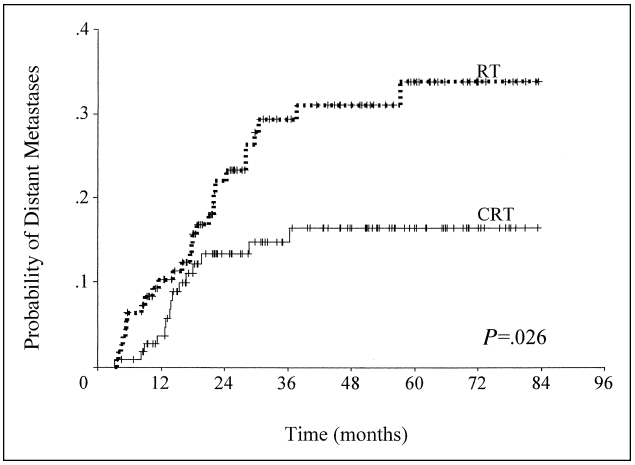

Fig 3. Distant metastases rate of patients receiving concurrent chemoradiotherapy (CRT) versus radiotherapy (RT).

relatively short, and it would take a longer time for the full spectrum of late toxicity to manifest. However, we have already observed some increased late toxicity probably associated with AC. Moderate to severe soft tissue fibrosis with neck stiffness and limitation in neck movement were more commonly observed among patients with AC than those without AC (26% *v* 7.3%; χ^2 test, $P < .001$). Three patients, two in group C and one in group D, developed serious neurologic complications after completion of AC. One patient developed radiation necrosis in the cerebellum 5 months after completion of RT. She had T4 disease with erosion of clivus. Treatment started with lateral opposing fields using 2.5-Gy fractions at four fractions per week to 30 Gy and then continued with conformal RT using 2-Gy daily fractions to a total dose of 66 Gy. The area of brain necrosis was inside the radiation field. This patient subsequently died of distant failure. Another two patients developed radiation myelitis at 8 and 12 months after completion of RT. Both were treated with conventional RT with 2-Gy daily fractions. Review of radiation check films showed the brainstem was adequately shielded after 40 Gy. None of these three patients had additional RT or surgery after primary RT. Both patients with myelitis are still surviving with neurologic impairment but without evidence of recurrence.

DISCUSSION

The present study showed that CRT significantly reduced DMR, and an improvement in OS with CRT was also found, although this did not reach statistical significance ($P = .06$). Adjusting for the effect of age and stage, Cox regression showed that CRT was a favorable prognostic factor for OS, and the result was confirmed in secondary analysis. On the

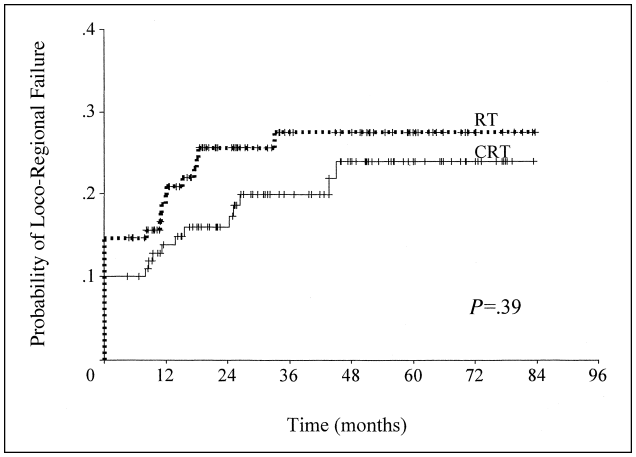

Fig 2. Locoregional failure rate of patients receiving concurrent chemoradiotherapy (CRT) versus radiotherapy (RT).

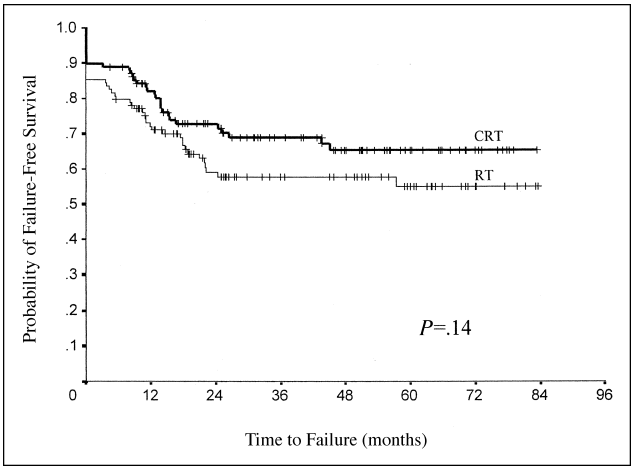

Fig 4. Failure-free survival of patients receiving concurrent chemoradiotherapy (CRT) versus radiotherapy (RT).

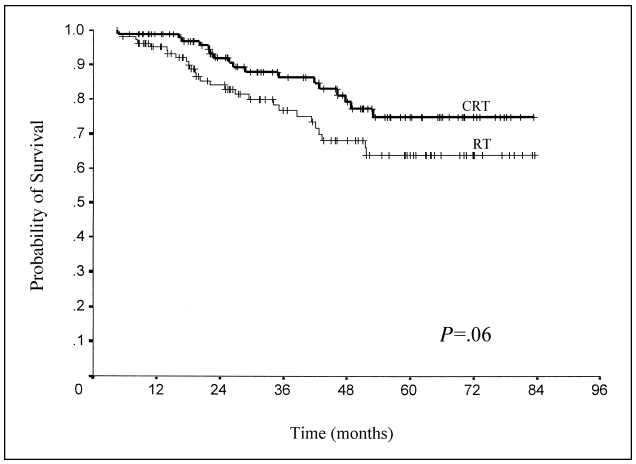

Fig 5. Overall survival of patients receiving concurrent chemoradiotherapy (CRT) versus radiotherapy (RT).

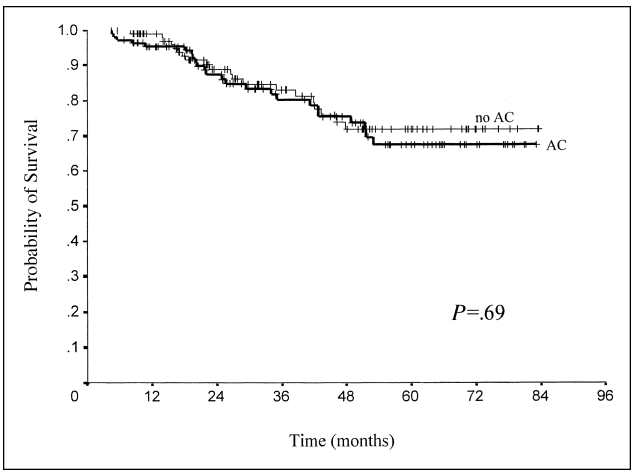

Fig 7. Overall survival of patients with and without adjuvant chemotherapy (AC).

other hand, AC showed no improvement of LRFR, DMR, FFS, or OS.

Chemotherapy is expected to improve survival through reducing disease failure. In the present study, CRT improved OS without significant improvement in FFS. There are two possible explanations for these findings. One possibility is that there were excessive deaths unrelated to disease among the RT groups. Another possible explanation is that disease failures in the RT groups were more lethal, and thus a statistically insignificant improvement in FFS may translate into early improvement in OS. As there was no treatment-related death in the present study and the two deaths unrelated to disease were both in the CRT group, there was no evidence to suggest the first possibility. The pattern of disease failure supports the second explanation. Concurrent CRT was found to significantly reduce DMR but not LRFR. For NPC, effective salvage treatments are available for locoregional failures. Patients can survive for years, and some may even be cured, after locoregional failure. In contrast, distant metastases are uniformly lethal and result in early death. FFS counts the first occurrence of disease failure, both locoregional and distant failures. Because there were approximately equal numbers of locoregional and distant failures in this series, the significant reduction of DMR with CRT did not translate into significant improvement in FFS but resulted in improvement in OS.

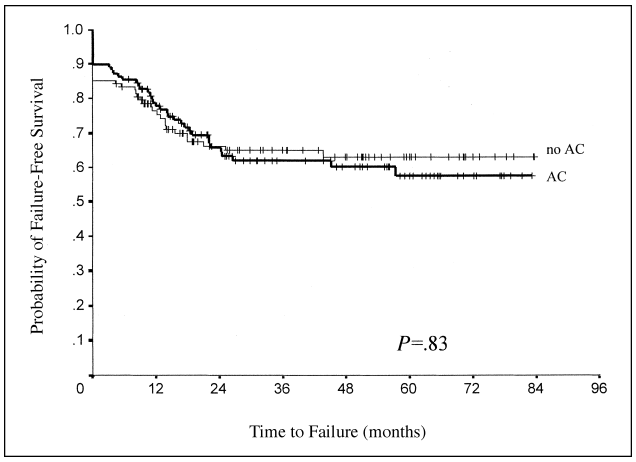

Fig 6. Failure-free survival of patients with and without adjuvant chemotherapy (AC).

In the design of this study, we hypothesized that CRT and AC would reduce disease failure and improve survival independently by radiosensitization with CRT and by eradicating occult micrometastases with AC. If CRT is effective through radiosensitization, disease control in irradiated areas will be improved, leading to reduced LRFR. In contrast, CRT was found to significantly reduce DMR without significant reduction in LRFR. This would suggest that UFT had systemic cytotoxic action besides radiosensitization. Seventy percent of patients receiving CRT in this series had 5 to 8 weeks of continuous UFT, corresponding to a total dose of 21,000 to 33,600 mg of FU. Earlier studies had reported the significant cytotoxic effect of UFT on its own without concurrent RT.[21-23] Most studies of CRT for head and neck cancers administered cisplatin concurrent with RT. Cisplatin is an active agent in head and neck cancers, including NPC, and is also a radiosensitizing agent. UFT was chosen in this study because oral administration of UFT can simulate continuous FU infusion and can be a convenient choice for radiosensitization. However, the activity of UFT in head and neck cancers has not been rigorously tested in clinical trials outside of Japan, and its usefulness in NPC has not been established. Results from the present study suggest that UFT is active in NPC, but its activity compared with other active agents such as cisplatin requires further investigation.

Table 7 lists the results of published randomized trials comparing CRT with RT for advanced NPC, including the

Table 5. Acute Toxicity for Patients Receiving Radiotherapy and Concurrent Chemoradiotherapy

	Maximum Toxicity Grade During RT/CRT								
	RT (n = 109)				CRT (n = 110)				
	0-2		3-4		0-2		3-4		
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	χ^2 P
Hematologic toxicity									
Anemia	109	100	0	0	110	100	0	0	
Leukopenia	109	100	0	0	106	96.4	4	3.6	.045
Thrombocytopenia	109	100	0	0	110	100	0	0	
Gastrointestinal toxicity									
Nausea/vomiting	108	99.1	1	0.9	104	94.5	6	5.5	.056
Diarrhea	109	100	0	0	110	100	0	0	
Skin	98	89.9	11	10.1	86	78.2	24	21.8	.018
Oral mucositis	82	75.2	27	24.8	59	53.6	51	46.4	.001

Abbreviations: RT, radiotherapy; CRT, concurrent chemoradiotherapy.

present study. Both the Intergroup study and the study reported by Lin et al[24]showed significant improvement in progression-free survival and OS with CRT over RT alone. In the study reported by Chan et al,[25] although there was no statistically significant difference in progression-free survival for the whole group, a highly significant improvement in progression-free survival and time to first distant failure was observed among patients with Ho's T3 disease treated with CRT. The present study also found that CRT significantly reduced DMR and was a highly significant favorable prognostic factor for OS in the Cox model. With the increasing evidence from recently published randomized studies in endemic populations showing survival benefit with the use of combined-modality treatment in advanced NPC, there is a need for change of practice for advanced endemic NPC patients in line with the standard North American practice. Combined-modality treatment should be considered the standard of care for all patients with AJCC stages III/IV NPC.

The expectation that AC can reduce DMR was not fulfilled. There were two previously published randomized trials studying the efficacy of AC in NPC. Both showed no improvement in outcomes. The Italian National Research Council Trial[26] randomly assigned 229 patients to receive AC after RT or RT alone. Adjuvant chemotherapy consisted of six cycles of vincristine, cyclophosphamide, and doxorubicin. No survival benefit with AC was observed. It is an old trial, and the regimen used for AC is now considered suboptimal, because cisplatin-based combination was not used. A modern phase III trial with 157 patients from the Taiwan Cooperative Oncology Group[27] comparing AC with 9 weekly cycles of cisplatin, FU, and leucovorin with RT alone also failed to show improvement in outcome with AC. In the present study, AC using six cycles of PF alternat-

Table 6. Toxicity Resulting From Adjuvant Chemotherapy (n = 96) According to WHO Grade

	0-1		2		3		4	
Toxicity	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Hematologic								
Anemia	90	93.7	4	4.2	2	2.1		
Leukopenia	15	15.7	25	26	55	57.3	1	1
Thrombocytopenia	91	94.8	2	2.1	2	2.1	1	1
Liver function derangement	93	96.9	2	2.1	1	1		
Renal impairment	90	93.8	6	6.2				
Stomatitis	94	97.9	2	2.1				
Vomiting	49	51.1	39	40.6	8	8.3		
Diarrhea	95	99	1	1				
Constipation	89	92.7	5	5.2	2	2.1		
Infection	93	96.9	3	3.1				
Peripheral neuropathy	95	99	1	1				
Maximum toxicity	8	8.3	26	27.1	60	62.5	2	2.1

Table 7. Summary of Randomized Studies Comparing Concurrent Chemoradiotherapy With Radiotherapy

Study	Chemotherapy	No. of Patients	Local/Regional Failure Rate (%)	Distant Failure Rate (%)	Progression-Free Survival (%)	Overall Survival (%)
Intergroup[6]	P, 100 mg/m^2	CRT, 78	14.1*	12.8*	69 (3 years)†	78 (3 years)†
	D1, 22, 43 (AC: PF × 3)	RT, 69	40.6*	34.8*	24	47
Lin et al[24]	P, 80 mg/m^2	CRT, 141	10.7	21.3	71.6 (5 years)†	72.3 (5 years)†
	F, 1,600 mg/m^2	RT, 143	27.4	30.1	53	54.2
	D1-4, D29-32					
Chan et al[25]	P, 40 mg/m^2	CRT, 174	6.9*	21.3*	76 (2 years)	NA
	Weekly, week 1-8	RT, 176	7.9*	25.6*	69	NA
Present	F, UFT 600 mg daily, week	CRT, 110	20	14.8	69.3 (3 years)	86.5 (3 years)
	1-8 (± AC)	RT, 109	27.6	29.4	57.8	76.8

Abbreviations: P, cisplatin; D, day; F, fluorouracil; AC, adjuvant chemotherapy; UFT, uracil and tegafur; CRT, concurrent chemoradiotherapy; RT, radiotherapy; NA, not available.
*Crude rate.
†Statistically significant difference.

ing with VBM did not improve FFS or OS. VBM is an old regimen and is a less effective combination than PF for head and neck cancers. It is possible that AC with the present regimen is ineffective because dose-intensity of the most effective combination, PF, was reduced by cycles of VBM sandwiched in between PF. However, results from the present study showed that CRT is more effective than AC for NPC.

Acute toxicity with CRT and AC in the present study was manageable. There were no treatment-related deaths in this study. Late toxicity with AC may be related to the agents that were used. Increased incidence of radiation-induced soft tissue fibrosis is likely related to bleomycin in AC.[28] Of concern is that all three patients with serious neurologic complications had received AC. The TCOG study[27] also reported one death owing to radiation myelitis in the AC arm. There was also a report of radiation myelitis with CRT using cisplatin, FU, and extended-field radiation in carcinoma of uterine cervix.[29] It is possible that aggressive chemotherapy can potentially enhance radiation damage in neural tissue when combined with aggressive RT. With no proven efficacy and potential serious complications associated with AC after radical RT, the use of AC outside of the trial setting for NPC is not advised.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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