Overall Survival After Concurrent Cisplatin–Radiotherapy Compared With Radiotherapy Alone in Locoregionally Advanced Nasopharyngeal Carcinoma

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This phase III randomized study compared concurrent cisplatin–radiotherapy (CRT) versus radiotherapy (RT) alone in patients with locoregionally advanced nasopharyngeal carcinoma. A total of 350 patients were randomly assigned to receive external RT alone or concurrently with cisplatin at a dosage of 40 mg/m² weekly. The primary endpoint was overall survival, and the median follow-up was 5.5 years. The 5-year overall survival was 58.6% (95% confidence interval [CI] = 50.9% to 66.2%) for the RT arm and 70.3% (95% CI = 63.4% to 77.3%) for the CRT arm. In Cox regression analysis adjusted for T stage, age, and overall stage, the difference in overall survival was statistically significantly in favor of concurrent CRT (*P* = .049, hazard ratio [HR] = 0.71 [95% CI = 0.5 to 1.0]). Subgroup analysis demonstrated that there was no difference between overall survival in the arms for T1/T2 stage (*P* = .74, HR = 0.93 [95% CI = 0.59 to 1.4]), whereas there was a difference between the arms for T3/T4 stage (*P* = .013, HR = 0.51 [95% CI = 0.3 to 0.88]), favoring the CRT arm. The regimen of weekly concurrent CRT is a promising standard treatment strategy for locoregionally advanced nasopharyngeal carcinoma patients. [J Natl Cancer Inst 2005;97:536–9]

The mainstay treatment for nasopharyngeal carcinoma (NPC) has been radiotherapy *(1)*. Despite encouraging response rates to chemotherapy, randomized studies of neoadjuvant and/or adjuvant chemotherapy have not shown an improvement in overall survival (OS) *(2–7)*. The United States Intergroup conducted a study demonstrating superior OS using concurrent cisplatin 100 mg/m² D1 every 3 weeks for three cycles during radiotherapy followed by adjuvant cisplatin 80 mg/m² D1, 5-fluorouracil 1 g/m² D1–4 every 4 weeks for three cycles *(8)*. However, the poor results of the radiotherapy-alone arm, the relatively high percentage of squamous cell carcinoma, and the poor compliance to adjuvant chemotherapy emphasized the need for confirmatory studies, particularly in endemic populations. Lin et al. *(9)* randomly assigned 284 patients to concurrent chemotherapy–radiotherapy using infusional cisplatin and 5-fluorouracil, demonstrating a positive effect on OS. However, the general applicability of infusional therapy is limited.

This is an updated final report on OS of the previously published progression-free survival (PFS) analysis of a phase III randomized study addressing whether adding cisplatin concurrently to radiotherapy improves survival compared with radiotherapy alone in locally advanced NPC *(10)*. Patients with Ho's N2- or N3-stage or N1-stage with node size of at least 4 cm *(11)* were eligible for this trial, and patients were also classified according to the 1997 International Union Against Cancer (UICC) staging system *(12)* (Table 1). The protocol was approved by the institutional review boards of Prince of Wales Hospital (PWH) and Queen Elizabeth Hospital (QEH), and all patients gave written informed consent. Patients were stratified by center and randomly assigned to concurrent cisplatin–radiotherapy or radiotherapy alone. The external radiotherapy technique (ERT) of the two institutions has been published previously *(10)*. The nasopharynx was treated to 66 Gy in 33 fractions per 6.5 weeks; parapharyngeal boost was given to patients with parapharyngeal involvement to 20 Gy in 10 fractions in 2 weeks (PWH) and 10 Gy in five fractions in 1 week (QEH). Patients with any palpable residual nodes after ERT were treated with 7.5 Gy in two fractions in 4 days. Patients with biopsy-proven persistent local disease were given intracavitary brachytherapy using iridium-192 sources to 24 Gy in three fractions in 15 days (PWH) and 21 Gy in three fractions in 15 days (QEH). The parapharyngeal boost and brachytherapy doses reflect the standard local practice of PWH and QEH, with no published data of impact on treatment outcome. Patients randomly assigned to the chemotherapy–radiotherapy arm received cisplatin 40 mg/m² in 1 L of normal saline over 2 hours weekly during ERT *(10)*. Patients were seen every 8 weeks in the first year, every 12 weeks in the second and third years, and every 16–24 weeks thereafter. At each follow-up visit, patients would undergo history and physical examination, routine mirror or endoscopic examination of the nasopharynx, and tests for distant failure if clinical suspicion existed.

OS is defined as the time from randomization to the time of death or last follow-up, analyzed by the Kaplan–Meier method. The log-rank test was used to assess the difference in survival between treatment groups. Cox regression modeling was used to assess and control for statistically significant prognostic factors and included adjustments for center, age, sex, histology, and stage. The proportional hazards assumption was verified by both log-minus-log survival plots and time-dependent variable method based on the Cox model. For the primary analysis, adjustments for statistically significant prognostic factors were performed. All other exploratory analyses on the treatment effect within subgroups were unadjusted. A test of treatment-by-covariate interaction for the final Cox model was carried out. Time to local recurrence or distant metastasis was defined from time of random assignment to the time of

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Table 1. Characteristics of randomly assigned, eligible patients, by study arm*

Characteristic	Radiotherapy (n = 176)	Cisplatin–radiotherapy (n = 174)
Age, y		
Median (range)	45.5 (25–68)	44 (20–69)
Mean (SD)	46.9 (9.9)	44.8 (9.6)
Sex, No. (%)		
Male	136 (77)	140 (80)
Female	40 (23)	34 (20)
Histology (WHO classification), No. (%)		
I	1 (1)	2 (1)
II	7 (4)	12 (7)
III	168 (95)	160 (92)
UICC overall stage, No. (%)		
II	56 (32)	45 (26)
III	47 (27)	56 (32)
IV	73 (41)	73 (42)
UICC T stage, No. (%)		
T1	20 (11)	28 (16)
T2	102 (58)	95 (55)
T3	24 (14)	33 (19)
T4	30 (17)	18 (10)
UICC N stage, No. (%)		
N1	70 (40)	59 (34)
N2	51 (29)	51 (29)
N3	55 (31)	64 (37)

*SD = standard deviation; WHO = World Health Organization; UICC = International Union Against Cancer; T = tumor; N = lymph node.

local recurrence or distant metastasis or censored at last follow-up. All statistical tests were two-tailed, and $P<.05$ was considered statistically significant.

Eight patients who were randomly assigned to the chemotherapy–radiotherapy arm who received no chemotherapy were included in the analysis according to the intention-to-treat principle (Fig. 1). All patients were evaluated for treatment toxicity, disease control, and PFS. Ten patients were lost to follow-up and were censored in the OS analysis. The treatment details and response, toxicity, and PFS analysis after 108 events had occurred have been published previously. Although systemic toxicity was more frequent in the CRT arm, 78% of patients completed at least four cycles of concurrent cisplatin during radiotherapy, and there were no treatment-related deaths *(10)*. At the time of this analysis, 156 tumors had progressed. The unadjusted analysis showed that there was no statistically significant difference between the two arms with respect to PFS (P = .16). The 5-year PFS was 52.1% for the radiotherapy arm and 60.2% for the CRT arm. The difference in PFS reached borderline statistical significance in the Cox regression analysis adjusted for T stage and overall stage (HR = 0.74 [95% confidence interval {CI} = 0.54 to 1.0], P = .06, Supplementary Fig. 1, which can be viewed at http://jncicancerspectrum.oupjournals.org/jnci/content/vol97/issue7). Subgroup analysis demonstrated that there was no statistically significant difference in PFS between the arms for T1/T2 stage (HR = 0.99 [95% CI= 0.66 to 1.5], P = .97), whereas there was a statistically significant difference between the arms for T3/T4 stage (HR = 0.53 [95% CI = 0.33 to 0.88], P = .012, Supplementary Fig. 2, which can be viewed at http://jncicancerspectrum.oupjournals.org/jnci/content/vol97/issue7) favoring the CRT arm. At the time of this analysis, 133 deaths had been reported. The unadjusted analysis shows a borderline statistically significant difference in OS in favor of the concurrent arm (P = .065). The 5-year OS was 58.6% (95% CI = 50.9% to 66.2%) for RT and 70.3% (95% CI = 63.4% to 77.3%) for CRT. In the Cox regression analysis, the difference in OS was statistically significantly in favor of CRT after adjusting for T stage, age, and overall stage (HR = 0.71 [95% CI = 0.5 to 1.0]; P = .049, Fig. 2). Subgroup analysis demonstrated that there was no difference between OS in the arms for T1/T2 stage (HR = 0.93 [95% CI = 0.59 to 1.4]; P = .74), whereas there was a difference between the arms for T3/T4 stage (HR = 0.51 [95% CI = 0.3 to 0.88]; P = .013, Fig. 3), favoring the CRT arm. No statistically significant difference in locoregional recurrence between the arms was observed, although there was a clear trend favoring the CRT arm for the T3/T4 stage subgroup (HR = 0.45 [95% CI = 0.21 to 1.0]; P = .051, Supplementary Fig. 3, which can be viewed at http://jncicancerspectrum.oupjournals.org/jnci/content/vol97/issue7. No statistically significant difference in occurrence of distant metastases was observed between the arms (HR = 0.65 [95% CI = 0.37 to 1.2]; P = .15, Supplementary Fig. 4, which can be viewed at http://jncicancerspectrum.oupjournals.org/jnci/content/vol97/issue7).

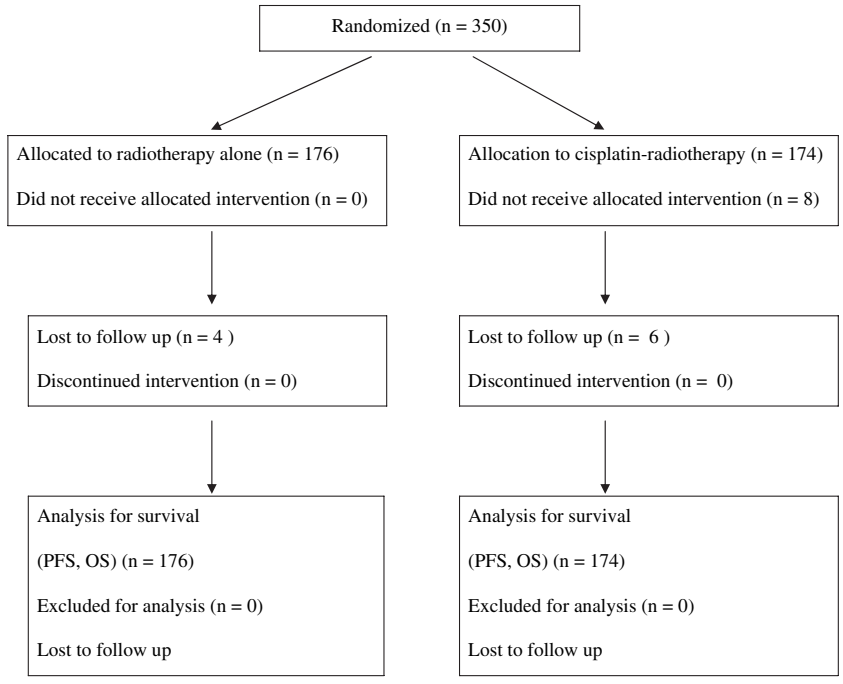

Fig. 1. Trial allocation. PFS = progression-free survival; OS = overall survival.

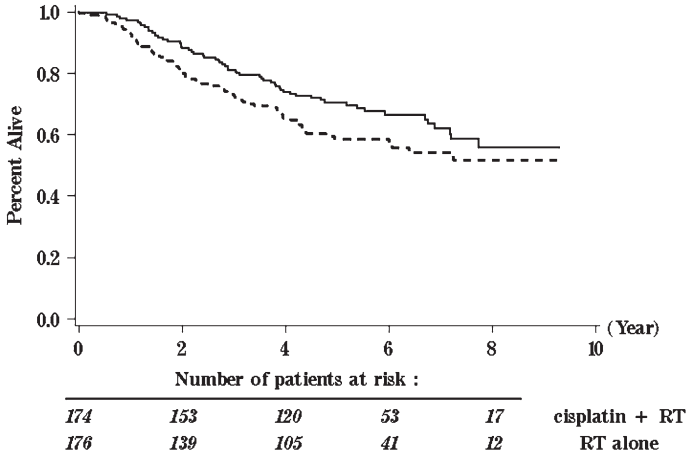

Fig. 2. Overall survival by treatment arm for all patients. Patients treated with cisplatin and radiotherapy (RT) (**solid lines**). Patients treated with RT alone (**broken lines**). Numbers in italics represent numbers of patients at risk. HR = 0.71 (95% CI = 0.5 to 1.0); $P = .049$ (two-sided), using Cox regression analysis after adjustment for tumor stage, age, and overall stage.

At a median follow-up of 5.5 years, the improvement in OS demonstrated in this study confirms that CRT should be used as standard treatment in locoregionally advanced endemic NPC. The relatively low toxicity and convenience of weekly outpatient cisplatin 40 mg/m^2 infusion make this regimen an attractive alternative to the high-dose cisplatin 100 mg/m^2 infusion every 3 weeks used in the United States Intergroup regimen. The modest dose of cisplatin given during radiotherapy may not be adequate to maximize the benefit of chemotherapy in locoregionally advanced NPC, and the rate of local and distant failure may be further reduced by adding neoadjuvant or adjuvant chemotherapy. Patient tolerance to adjuvant chemotherapy is limited by the cumulative toxic effects of concurrent chemotherapy. Recent phase II studies using intensive neoadjuvant chemotherapy followed by concurrent cisplatin–radiotherapy have shown encouraging toxicity profiles and disease control *(13–15)*.

References

(1) Teo P, Yu P, Lee WY, Leung SF, Kwan WH, Yu KH, et al. Significant prognosticators after primary radiotherapy in 903 nondisseminated nasopharyngeal carcinoma evaluated by computer tomography. Int J Radiat Oncol Biol Phys 1996;36:291–304.

(2) Chan AT, Teo PM, Leung TW, Leung SF, Lee WY, Yeo W, et al. A prospective randomized study of chemotherapy adjunctive to definitive radiotherapy in advanced nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 1995;33:569–77.

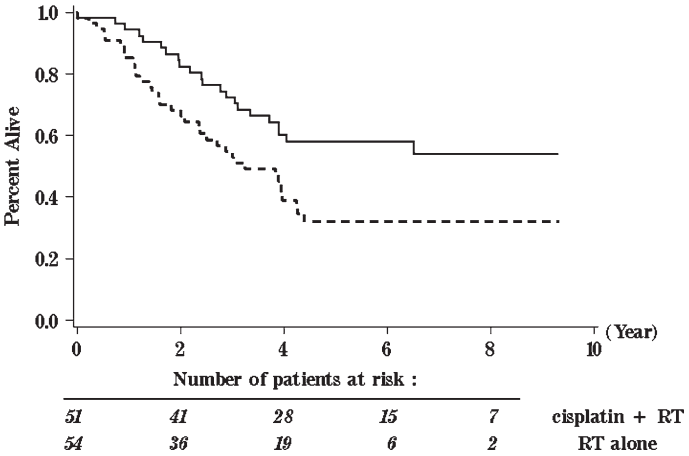

Fig. 3. Overall survival by treatment arm for patients with tumor stage 3 and 4. Patients treated with cisplatin and radiotherapy (RT) (**solid lines**). Patients treated with RT alone (**broken lines**). Numbers in italics represent numbers of patients at risk. HR = 0.51 (95% CI = 0.3 to 0.87); $P = .013$ (two-sided), using Cox regression analysis.

(3) Rossi A, Molinari R, Boracchi P, Del Vecchio M, Marubini E, Nava M, et al. Adjuvant chemotherapy with vincristine, cyclophosphamide, and doxorubicin after radiotherapy in local-regional nasopharyngeal cancer: results of a 4-year multicenter randomized study. J Clin Oncol 1988;6:1401–10.

(4) Chua DT, Sham JS, Choy D, Lorvidhaya V, Sumitsawan Y, Thongprasert S, et al. Preliminary report of the Asian-Oceanian Clinical Oncology Association randomized trial comparing cisplatin and epirubicin followed by radiotherapy versus radiotherapy alone in the treatment of patients with locoregionally advanced nasopharyngeal carcinoma. Asian-Oceanian Clinical Oncology Association Nasopharynx Cancer Study Group. Cancer 1998;83:2270–83.

(5) Preliminary results of a randomized trial comparing neoadjuvant chemotherapy (cisplatin, epirubicin, bleomycin) plus radiotherapy vs. radiotherapy alone in stage IV(> or = N2, M0) undifferentiated nasopharyngeal carcinoma: a positive effect on progression-free survival. International Nasopharynx Cancer Study Group. VUMCA I trial. Int J Radiat Oncol Biol Phys 1996;35:463–9.

(6) Chi KH, Chang YC, Guo WY, Leung MJ, Shiau CY, Chen SY, et al. A phase III study of adjuvant chemotherapy in advanced nasopharyngeal carcinoma patients. Int J Radiat Oncol Biol Phys 2002;52:1238–44.

(7) Ma J, Mai HQ, Hong MH, Min HQ, Mao ZD, Cui NJ, et al. Results of a prospective randomized trial comparing neoadjuvant chemotherapy plus radiotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma. J Clin Oncol 2001;19:1350–7.

(8) Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol 1998;16:1310–7.

(9) 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;21:631–7.

(10) Chan AT, Teo PM, Ngan RK, Leung TW, Lau WH, Zee B, 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;20:2038–44.

(11) Ho JH. An epidemiologic and clinical study of nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 1978;4:182–98.

(12) Fleming ID, Cooper JS, Henson DE, Hutter RV, Kennedy BJ, Murphy GP, et al. American Joint Committee on Cancer: AJCC Cancer Staging Manual. 5th ed. Philadelphia: Lippincott-Raven; 1997.

(13) Chan AT, Ma BB, Lo YM, Leung SF, Kwan WH, Hui EP, 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;22:3053–60.

(14) 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;20:1845–52.

(15) Oh JL, Vokes EE, Kies MS, Mittal BB, Witt ME, Weichselbaum RR, et al. Induction chemotherapy followed by concomitant chemoradiotherapy in the treatment of locoregionally advanced nasopharyngeal cancer. Ann Oncol 2003;14:564–9.

Notes

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