Chemoradiotherapy Versus Radiotherapy in Patients With Advanced Nasopharyngeal Cancer: Phase III Randomized Intergroup Study 0099

By Muhyi Al-Sarraf, Michael LeBlanc, P.G. Shanker Giri, Karen K. Fu, Jay Cooper, Te Vuong, Arlene A. Forastiere, George Adams, Wael A. Sakr, David E. Schuller, and John F. Ensley

Purpose: **The Southwest Oncology Group (SWOG) coordinated an Intergroup study with the participation of Radiation Therapy Oncology Group (RTOG), and Eastern Cooperative Oncology Group (ECOG). This randomized phase III trial compared chemoradiotherapy versus radiotherapy alone in patients with nasopharyngeal cancers.**

Materials and Methods: **Radiotherapy was administered in both arms: 1.8- to 2.0-Gy/d fractions Monday to Friday for 35 to 39 fractions for a total dose of 70 Gy. The investigational arm received chemotherapy with cisplatin 100 mg/m² on days 1, 22, and 43 during radiotherapy; postradiotherapy, chemotherapy with cisplatin 80 mg/m² on day 1 and fluorouracil 1,000 mg/m²/d on days 1 to 4 was administered every 4 weeks for three courses. Patients were stratified by tumor stage, nodal stage, performance status, and histology.**

Results: **Of 193 patients registered, 147 (69 radiotherapy and 78 chemoradiotherapy) were eligible for primary analysis for survival and toxicity. The median progression-free survival (PFS) time was 15 months for eligible patients on the radiotherapy arm and was not reached for the chemo-radiotherapy group. The 3-year PFS rate was 24% versus 69%, respectively ($P < .001$). The median survival time was 34 months for the radiotherapy group and not reached for the chemo-radiotherapy group, and the 3-year survival rate was 47% versus 78%, respectively ($P = .005$). One hundred eighty-five patients were included in a secondary analysis for survival. The 3-year survival rate for patients randomized to radiotherapy was 46%, and for the chemo-radiotherapy group was 76% ($P < .001$).**

Conclusion: **We conclude that chemoradiotherapy is superior to radiotherapy alone for patients with advanced nasopharyngeal cancers with respect to PFS and overall survival.**

J Clin Oncol 16:1310-1317. © 1998 by American Society of Clinical Oncology.

From the Department of Medicine, Providence Cancer Center, Southfield; Departments of Pathology and Medicine Wayne State University, The Barbara Ann Karmanos Cancer Institute, Detroit, MI; Southwest Oncology Group Statistical Center, Seattle, WA; Department of Radiotherapy, University of Kansas, Kansas City, KS; Department of Radiation Oncology, University of California San Francisco, San Francisco, CA; Division of Radiation Oncology, New York University Medical Center, New York, NY; Department of Radiotherapy, McGill University, Montreal, Canada; Department of Oncology, John Hopkins University, Baltimore, MD; Department of Otolaryngology, University of Minnesota, Minneapolis, MN; and Department of Otolaryngology, Arthur G. James Cancer Hospital and Research Institute, Ohio State University, Columbus, OH.

Submitted May 8, 1997; accepted December 9, 1997.

Supported in part by the following Public Health Service Cooperative Agreement grants awarded by the National Cancer Institute, Department of Health and Human Services, Bethesda, MD: CA38926, CA04920, CA42028, CA58723, CA46136, CA46282, CA58686, CA46113, CA20319, CA12213, CA32734, CA22433, CA35176, CA27057, CA35281, CA58861, CA58416, CA46441, CA12644, CA35128, and CA04919.

Presented in part at the 32nd Annual Meeting of the American Society of Clinical Oncology, Philadelphia, PA, May 18-21, 1996.

Address reprint requests to Southwest Oncology Group (SWOG-8892), Operations Office, 14980 Omicron Dr, San Antonio, TX 78245-3217.

0732-183X/98/1604-0001$3.00/0

IN THE UNITED STATES and western europe, nasopharyngeal carcinoma is a rare neoplasm of the head and neck region. It is more common among the Southern Chinese, Southeast Asian, Northern African, and Eskimo populations.[1-5] Nasopharyngeal cancer differs from other squamous cell carcinomas of the head and neck in many aspects.[6,7]

Because of the anatomic location of nasopharyngeal tumors, they are traditionally treated by radiotherapy,[2,5,8-13] rather than surgery. The 5-year survival rate reported for patients with stage III treated by radiotherapy is 46%,[2] and for stage IV, approximately 30%. Nasopharyngeal cancer is responsive to chemotherapy, especially to platinol-based combinations.[14-24] Cisplatin was reported to be effective in patients with squamous cell cancers of the head and neck, and an enhanced response was reported when combined with ionizing irradiation.[25-30] In patients with stage IV disease, the Radiation Therapy Oncology Group (RTOG) tested the combination of concurrent cisplatin and radiotherapy.[31-33] Promising results in response and survival in these phase II trials led to this National Head and Neck Cancer Intergroup randomized phase III trial of advanced nasopharyngeal carcinoma. The primary objectives of this study were to compare the progression-free survival (PFS)

and overall survival of patients with stage III and IV nasopharyngeal cancers who received radiotherapy alone versus radiotherapy and concurrent cisplatin followed by adjuvant chemotherapy with cisplatin and fluorouracil infusion.

MATERIALS AND METHODS

Patients with biopsy-proven stage III and IV cancers of the nasopharynx that was bidimensionally measurable and without evidence of systemic metastasis (M0) were eligible for this trial. There could be no history of previous radiotherapy or chemotherapy, and no history of previous cancer except for carcinoma-in-situ of the cervix or basal cell or squamous carcinoma of the skin.

There must be no plan for resection following radiotherapy except for neck dissection for persistent neck nodes after completion of radiotherapy. Patients were required to have the following laboratory values: WBC count $\geq$ 4,000/μL, platelet count $\geq$ 100,000/μL, creatinine concentration $\leq$ 1.6 mg/dL, and/or creatinine clearance $\geq$ 60 mL/min. Patients were also required to have a Southwest Oncology Group (SWOG) performance score of 0 to 2.

Pretreatment evaluation included a complete history and physical examination with an assessment of the patient's performance status. Diagrams of the primary and any nodal metastases were required. Laboratory studies included the following: hemoglobin and/or hematocrit, WBC with differential and platelet count, urinalysis, blood chemistry 12 or 18, and a 24 hour creatinine clearance. Extent of disease evaluation included a chest x-ray, liver scan or bone scan if liver enzymes were elevated, computed tomography (CT) scan or magnetic resonance imaging (MRI) scan of the nasopharynx and base of skull, bilateral audiogram, triple endoscopy, and fiberoptic nasopharyngoscopy with a satisfactory biopsy of the primary tumor site. All patients were required to have a dental examination and appropriate care before radiotherapy. On December 1, 1994, the study was amended to delete the panendoscopy requirement. All patients were required to provide written informed consent before registration. Patients were stratified by tumor and nodal stage, histology (World Health Organization [WHO] stage I to III), and performance status.

Radiotherapy

CT-based treatment planning was used. Only megavoltage equipment with a source skin distance $\geq$ 80 cm and megavoltage machines with beam energy equal to cobalt 60 or higher were used. For tumor localization, all patients were simulated, and the simulator films were submitted for rapid review. CT scans were used to assess the extend of the primary tumor, as well as the neck nodes. All isodose plans were submitted for review. Port films taken on the treatment machine were submitted for rapid review. The treatment volume included the primary tumor site and the neck nodes up to the clavicle. The nasopharynx and the upper neck were treated by means of an upper neck field. The field arrangement was individualized, but was expected to include two opposed lateral fields so that the neck nodes are treated. The superior margin of the primary field encompassed at least 2 cm beyond what was visible on CT scan, and included the entire base of skull and the sphenoid sinus. Posteriorly, the field included at least 2 cm beyond the mastoid process and the field was extended further posteriorly, at least a 1.5 cm margin beyond any palpable nodal disease. Anteriorly, the field included the posterior third of the maxillary sinus and nasal cavity. Appropriate shielding was performed to exclude as much of the retrobulbar structures without compromising the margins around the tumor. Inferiorly, the field extended to the thyroid notch. A separate anterior supraclavicular field with spinal cord shield was used for the low neck and supraclavicular fossa. The target volume, which was the entire tumor with a 2-cm margin in all directions, received at least 90% or greater of the mid-depth central axis dose. Variation within the target volume was not to exceed $\pm$ 10% of the target dose. The dose to the nasopharynx was specified. The dose to the neck nodes was separately specified and the dose prescribed to at least 3 cm below the skin surface at the appropriate level of anatomic spread. The spinal cord dose was not to exceed 45 Gy at the midline. The dose to the supraclavicular nodes was calculated to 3 cm depth. Fractionation was 1.80 to 2.0-Gy/d, Monday through Friday. The total dose to the primary tumor (plus a minimum of 2 cm surrounding margin) was 70 Gy. The suggested minimum total dose to the neck nodes was 50 Gy for N0 disease, 66 Gy for nodes $\leq$ 2 cm, and 70 Gy for nodes greater than 2 cm in size. Treatment breaks, if necessary, were allowed only for healing of severe normal tissue reactions (ie, confluent mucositis). If the patient's radiation treatment was interrupted for more than 21 days, the patient was to be removed from protocol treatment.

Chemotherapy

Patients on the investigational arm were randomized to receive cisplatin every 3 weeks on days 1, 22, and 43 during radiotherapy. Severe malnutrition or continuous weight loss during therapy was an indication for intravenous or nasogastric hyperalimentation. Forced hydration was used with 2,000 mL 5% dextrose in ½ normal saline plus 40 mEq potassium chloride infused over 24 hours before and 24 hours after administration of cisplatin and the second mannitol infusion. Mannitol 12.5 g by intravenous bolus was administered just before cisplatin, and mannitol 25 g in 1,000 mL D5 ½ normal saline plus 30 mEq potassium chloride to run over 4 hours was administered immediately after cisplatin. An antiemetic, such as 25 mg compazine suppository, was given 30 minutes before cisplatin, and 10 mg of compazine as an intramuscular injection was administered every 4 hours as needed after the cisplatin injection. An accurate measurement of fluid intake and output for 48 hours after cisplatin administration was required, with additional intravenous fluids administered to compensate for emesis or excess urinary output. Cisplatin was given at 100 mg/m^2 as a rapid intravenous infusion (not using an aluminum needle) over 15 to 20 minutes. Chemotherapy was repeated every 3 weeks or until recovery from all toxicities. Regardless of initial response to concurrent chemoradiotherapy, subsequent therapy with cisplatin 80 mg/m^2 intravenously on days 71, 99, and 127 and fluorouracil 1,000 mg/m^2/d by 96-hour infusion on days 71 to 74, 99 to 102, and 127 to 130 was given 4 weeks after radiotherapy or the last dose of cisplatin.

Dose Modification

Chemotherapy was not administered until the absolute neutrophil count was $\geq$ 2,000/μL and the platelet count was $\geq$ 100,000/μL. If the absolute neutrophil count nadir was $\geq$ 1,500 and/or platelet count nadir $\geq$ 75,000, no dose modification was made. If the absolute neutrophil count nadir was between 1,000 and 1,499 and/or the platelet nadir between 50,000 and 74,999, cisplatin was decreased to 80 mg/m^2. If the absolute neutrophil count was less than 1,000 and/or the platelet nadir less than 50,000, chemotherapy was withheld until the WBC count and platelet counts were greater than 2,000 and 100,000/μL, respectively, and then cisplatin was decreased to 60 mg/m^2. The dose of cisplatin was adjusted according to the value of creatinine after the last

course. If the creatinine concentration was ≤ 2 mg/dL or creatinine clearance ≥ 60 mL/min, no dose adjustment was required. If the creatinine concentration increased to 2.1 to 4.0 mg/dL or creatinine clearance was between 40 and 59 mL/min, cisplatin was reduced to 80 mg/m^2 for the next course. If the creatinine concentration was greater than 4 mg/dL or creatinine clearance was less than 40 mL/min, no further cisplatin was given. No cisplatin was administered until complete recovery from renal toxicity occurred.

Serum creatinine and electrolytes measurements were obtained before each course of chemotherapy, daily for 2 days starting the day after cisplatin administration and as needed. Complete blood cell counts and platelet counts were obtained weekly, before each course of chemotherapy and as needed. Performance status, weight, symptoms, and tumor measurements were to be recorded. Bilateral audiograms were obtained before therapy, at 3 months, and after the last course of chemotherapy. Appropriate x-rays, scans, and/or other laboratory tests were repeated as needed. Partial or radical neck dissections were performed for persistent lymph nodes at the completion of radiotherapy. Any other clinically indicated therapy, if performed, was reported on appropriate SWOG forms. Representative slides were mailed to the Central Pathology office for review.

Patient Assessments

The primary end points of the study were PFS and overall survival. PFS was defined as the time from registration to the date of first observation of progressive disease or death due to any cause. Overall survival was defined as the date from registration to death due to any cause. Standard SWOG criteria were used for response and toxicity. Disease was evaluated every 2 months during the first year and included a repeat CT scan or MRI to confirm response in 4 weeks. Patients were planned to be seen every 3 months for the second and third year and every 6 months thereafter. Responses were defined as follows: complete response—complete disappearance of measurable and palpable tumor confirmed by CT scan or MRI; partial response—tumor shrinkage ≥ 50% of the sum of the product of the perpendicular diameters of all measurable lesions with no progression of assessable disease and no new lesions; stable/no change—disease parameters do not qualify as complete or partial response or progression; and progressive disease—growth of tumor by greater than 50% or an increase of 10^2 cm (whichever is smaller) of the sum of the product of the perpendicular diameters of all measurable lesions over the smallest sum observed, or reappearance of any lesion that had disappeared, or clear worsening of any assessable disease, or appearance of any new lesion or site. Patients who developed local or distant recurrence following therapy could be treated by any means considered appropriate by the responsible physician. However, any such additional therapy was required to be reported and submission of follow-up data continued.

Statistical Considerations

The accrual goal of the study was 270 patients. Interim analyses were planned after 56% and 78% of the patients were accrued. To preserve an overall critical level of .05, one-sided tests at levels .003 and .004 were planned for the first and second interim analyses. In addition, reporting of the results shortly after closure of the study was to be considered if the results were significant at the .005 level. Otherwise, results were to be reported after approximately 1 more year of follow-up evaluation using a significance level of .046. Response and toxicity rates were compared using the χ^2 test statistic. Survival curves were estimated by the product-limit method.[34] Survival differences for treatment were analyzed using the log-rank test,[35] partial likelihood score tests, and Cox regression.[36] All P values reported for survival and PFS were two-sided and analyses were adjusted for the randomization stratification factors of tumor stage, node stage, performance status, and histology.

RESULTS

Between May 1989 and early closure of the study on December 1, 1995, 193 patients were registered onto the study: 103 from the RTOG, 60 from the SWOG, and 30 from the Eastern Cooperative Oncology Group (ECOG). Thirty-eight patients were ineligible for primary analysis for insufficient documentation due to incomplete scans or evaluations (n = 17), no confirmed central pathology review (n = 5), scans or assessments out of date (n = 11), or incomplete forms (n = 9) (some patients were ineligible for more than one reason). An additional eight patients were ineligible for primary or intent-to-treat analysis. Two patients had prior surgery, two did not have measurable disease, two had nonnasopharyngeal primary tumors, one did not have a malignancy, and one was not randomized. The resulting 147 (69 radiotherapy and 78 chemotherapy) patients were considered for survival and toxicity analysis. One hundred forty-six patients were assessable for induction treatment toxicity and one patient on the radiotherapy arm was not assessable for toxicity due to incomplete follow-up documentation. Fifty-three patients on the chemoradiotherapy arm were evaluated for toxicity for the subsequent chemotherapy after radiotherapy. A secondary analysis based on 185 patients is reported in Discussion.

There was good balance in the prognostic factors, including performance status, tumor and nodal stages, and histology, between the two groups (Table 1).

Major treatment deviations were recorded for three patients on the combined arm. One patient received no chemotherapy due to pneumonia and increased creatinine concentration, one patient switched to radiotherapy alone after the first course of cisplatin, and one patient was given radiotherapy in conjunction with cisplatin and fluorouracil.

At the time of the first planned interim analysis in October 1995, a null-hypothesis test of no difference in survival for radiotherapy versus chemoradiotherapy was rejected at the .001 level. The hazards ratio between the radiotherapy and the combined arm was 3.28, which corresponds to a median survival duration of 30 months in the radiotherapy arm versus median survival not reached in the chemoradiotherapy arm. The Data and Safety Monitoring Committee of the SWOG reviewed the interim analysis, which included survival, progression, toxicity, and other outcome information, and recommended that the study be closed and reported early.

Table 1. Patient Characteristics

Characteristic	RT (n = 69) No.	RT (n = 69) %	CT/RT (n = 78) No.	CT/RT (n = 78) %
Age, years				
Median	52		50	
Range	14-81		16-79	
Sex				
Male	53	77	52	67
Female	16	23	26	33
Race				
White	44	64	42	54
Black	11	16	8	10
Other	14	20	28	36
Stage				
III	6	9	7	9
IV	63	91	71	91
Tumor stage				
1	6	9	8	10
2	10	14	13	17
3	23	33	22	28
4	30	43	35	45
Nodal stage				
0	15	22	14	18
1	11	16	8	10
2				
a	7	10	5	6
b	12	17	12	15
c	15	22	24	31
3	9	13	15	19
Performance status				
0-1	62	90	72	92
2	7	10	6	8
Histology				
KSCC (WHO stage I)	19	28	17	22
NKSCC (WHO stage II)	22	32	29	37
UDC (WHO stage III)	28	41	32	41

Abbreviations: RT, radiation; CT, chemotherapy; KSCC, keratonizing squamous cell carcinoma; NKSCC, nonkeratonizing squamous cell carcinoma; UDC, undifferentiated carcinoma.

PFS and Overall Survival

The median PFS time for the radiotherapy group was 15 months and had not been reached for the combined group. The 3-year actuarial PFS rates were 24% and 69%, respectively ($P < .001$) (Fig 1). Forty-five patients on the radiotherapy arm and 20 on the chemoradiotherapy arm had progressed. The estimated hazards ratio was 4.34, with a 95% confidence interval of 2.47 to 7.69. The median overall survival durations for the radiotherapy and chemoradiotherapy groups were 34 months and not reached, respectively. The 3-year survival rate was 47% and 78%, respectively ($P = .005$) (Fig 2). The estimated hazards ratio was 2.50, with a 95% confidence interval of 1.29 to 4.84. At the time of analysis, 29 patients had died in the radiotherapy group, two of them with no evidence of disease. Sixteen patients had died in the chemoradiotherapy group, one of them died with no evidence of disease. The median follow-up duration for all randomized patients was 2.7 years and the percentage of patients that had been followed for less than 2 years was 33%.

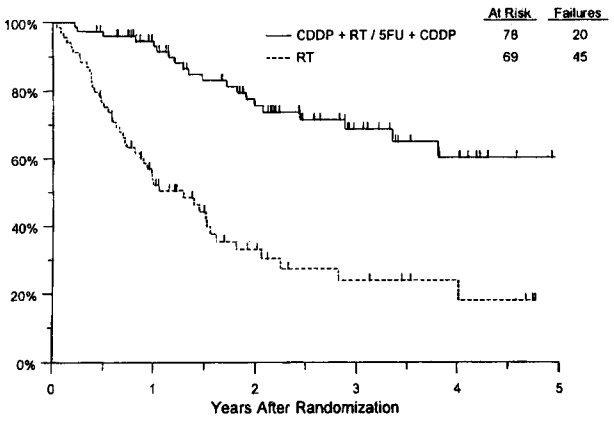

Fig 1. PFS for completely eligible patients on radiation (RT) only and combined chemotherapy (CT)/RT. CDDP, cisplatin; F5U, fluorouracil.

Toxicity

One hundred forty-six patients were evaluated for initial treatment toxicity (68 radiotherapy only *v* 78 cisplatin plus radiotherapy) (Table 2). No fatal toxicity related to planned treatment occurred in either group. A higher incidence of grade 3 or 4 leukopenia and vomiting was observed in patients on the chemoradiotherapy treatment arm ($P < .05$). The type and degree of toxicity from adjuvant chemotherapy are listed in Table 3. Grade 4 (life-threatening) toxicity occurred in six patients, and 22 patients had grade 3 (severe) side effects from chemotherapy. One ineligible patient on the chemoradiotherapy arm died of aspiration pneumonia.

A higher percentage of patients did not complete protocol

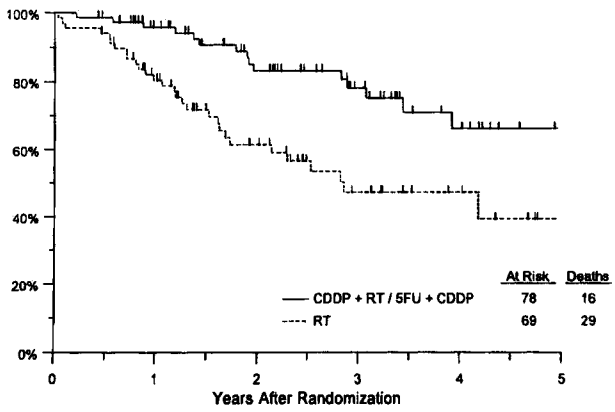

Fig 2. Overall survival for completely eligible patients on RT only and combined CT/RT (----).

Table 2. Severe and Life-Threatening Toxicity Due to Initial Treatment

Toxicity	Toxicity Grade					
	RT (n = 68)			CT + RT (n = 78)		
	0	3	4	0	3	4
Hematologic						
Anemia	60	—	—	59	—	—
Leukopenia	56	1	—	19	23	—
Granulocytopenia	67	—	—	68	3	2
Thrombocytopenia	63	1	—	65	1	—
Gastrointestinal						
Anorexia	58	—	—	71	—	—
Diarrhea	67	—	—	68	—	—
Nausea	41	5	—	15	14	—
Vomiting	44	1	1	24	10	1
Renal	68	—	—	75	—	—
Hearing impairment	51	3	—	52	9	—
Infection	59	1	—	70	2	—
Desquamation, RT field	45	3	—	62	2	—
Erythema, RT field	40	—	—	54	—	—
Dry mouth	46	—	—	56	—	—
Stomatitis	10	18	1	21	20	9
Taste alteration	55	—	—	72	—	—
Weight loss	36	1	—	49	5	—
Maximum grade any toxicity	1	28	6	0	43	16

chemoradiotherapy compared with radiotherapy (Table 4). For induction chemoradiotherapy, 13 went off permanently due to toxicity, six refused further chemotherapy, documented as unrelated to toxicity, and two were off for non–protocol-specified reasons. In the radiotherapy arm, two patients died, one progressed, and three went off for other non–protocol-specified reasons before completion of treatment. For adjuvant chemotherapy, five patients were off permanently due to toxicities, two refused treatment unrelated to toxicity, one died, and two went off for other reasons before completion of treatment. Four other patients who completed induction chemotherapy did not start adjuvant chemotherapy for the following reasons: two due to toxicities, one due to refusal, and one patient was too weak to start adjuvant chemotherapy. As shown in Table 5, 63% patients received three courses of induction chemotherapy concurrent with irradiation and 55% received all three courses of adjuvant chemotherapy.

Table 3. Severe and Life-Threatening Toxicity Due to Adjuvant Chemotherapy (N = 53)

Toxicity	Grade		
	0	3	4
Hematologic			
Anemia	41	3	—
Leukopenia	14	12	—
Granulocytopenia	47	1	1
Thrombocytopenia	43	—	—
Gastrointestinal			
Anorexia	48	—	—
Diarrhea	47	—	—
Nausea	17	5	—
Vomiting	25	1	—
Renal	49	—	—
Hearing impairment	35	5	1
Infection	48	1	—
Stomatitis	23	7	4
Maximum grade of any toxicity	2	22	6

Table 4. Treatment Summary

Variable	Total (N = 147)	RT (n = 69)	CT + RT (n = 78)
Treatment completed as planned	120	63	57
Reason off treatment			
Toxicity	13	—	13
Refusal (unrelated to toxicity)	6	—	6
Progression	1	1	—
Death	2	2	—
Other (not protocol-specified)	5	3	2
Major protocol deviations	2	0	2

Response to Treatments

The SWOG response criteria were strictly followed, including repeat scans. The complete response rate to radiotherapy was 36% versus 49% to chemoradiotherapy ($P = .14$).

Two patients on the radiotherapy arm and one patient on the chemoradiotherapy arm underwent radical neck dissection for persistent nodal disease after the end of planned therapy. These three patients were not considered to have had a complete response to the intended treatment.

The incidence and sites of progression or recurrent disease are listed in Table 6. The combined treatment of chemoradiotherapy had significantly less local, regional, and systemic failures than radiotherapy alone.

DISCUSSION

Nasopharyngeal carcinomas are highly responsive to standard radiotherapy. Since the majority of the patients present with advanced disease (stages III and IV), the overall 5-year survival rate reported in large series was 41%.[2] A higher 5-year actuarial local control rate has also been reported using accelerated hyperfractionated radiation as

Table 5. Compliance to Chemotherapy

No. of Courses	Concurrent		Adjuvant	
	No.	%	No.	%
3	49	63	43	55
2	18	23	4	5
1	9	12	5	6
0	2	3	26	33

Table 6. Incidence and Site of Progression or Recurrent Disease

Site	RT (n = 69) No.	RT (n = 69) %	CT & RT (n = 78) No.	CT & RT (n = 78) %
Local only	12		3	
Local and nodal	4		3	
Local and distant	6		1	
Local, nodal, and distant	1		1	
Nodal only	2		2	
Nodal and distant	3		1	
Distant only	14		7	
Total	42	61	18	23
Bone	15	22	3	4
Lung	9	13	5	6
Liver	5	7	3	4
Brain	1	1	1	1

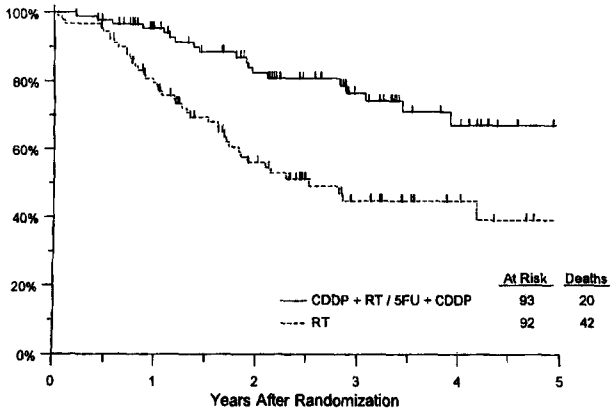

Fig 3. Overall survival for randomized patients on RT only and combined CT/RT.

compared with historical controls with nasopharyngeal cancers treated with standard fractionated radiation.[37]

Nasopharyngeal cancers were found to be highly responsive to chemotherapy.[14-24] This led to many phase II pilot studies of combination chemotherapy and radiotherapy.[14-21,31,32,38-40] Chemotherapy has been given sequentially before radiotherapy or concurrently with radiotherapy. There appeared to be improved complete response rates and survival for chemotherapy and radiotherapy when compared with historical controls that used radiotherapy alone, especially as compared with the use of cisplatin and fluorouracil infusion or concurrent cisplatin and radiation.[31-33,39]

In an attempt to decrease the incidence of distant metastasis, and increase the local and regional control rates, we elected to compare concurrent cisplatin and radiotherapy followed by three courses of adjuvant cisplatin and fluorouracil infusion every 4 weeks after the completion of initial chemoradiotherapy versus the same radiotherapy alone. As expected, the systemic toxicities were higher in patients who received the combined treatment. The incidence and degree of drug toxicity with adjuvant chemotherapy is listed in Table 3 and was as expected.

The complete response rate according to SWOG criteria was 49% versus 36% ($P = .14$) for combined treatment and radiotherapy alone, respectively. The complete response rate is not based on investigator-reported response as commonly done.

At the present analysis, 29 patients in the radiotherapy group died, and 16 were dead in the chemoradiotherapy group. On the radiotherapy arm, 24 of 69 had no evidence of disease, or no progression of disease, as compared with 58 of 78 in the combined group. The PFS ($P < .001$), and overall survival ($P = .005$) were significantly better in the combined chemoradiotherapy group. The survival rate for patients on radiotherapy only is higher than expected, and this may be due to the salvage rate of these patients after disease progression or recurrence. As a secondary analysis, we included patients who were missing preregistration documentation along with previously analyzed patients. In this larger data set, there were 185 patients with follow-up information: 93 on the combined arm and 92 on the radiotherapy arm. The 3-year overall survival estimate for the combination arm was 76%, and for the radiotherapy arm it was 46% (Fig 3 and Table 7) ($P < .001$). The 3-year PFS estimate for the chemoradiotherapy arm was 66%, and for the radiotherapy arm it was 26% (Fig 4 and Table 7) ($P < .001$). These results are almost identical to the primary analysis with 147 patients. Chemoradiotherapy was superior to radiotherapy in preventing locoregional node recurrence and distant metastases in this study. The European phase III randomized trial[18,41] showed significant improvement in overall response and disease free-survival, but not overall survival, for chemotherapy followed by radiotherapy compared with radiotherapy only. The lack of improvement in overall survival in that study may be related to the type of drugs used, to the limited amount of chemotherapy (only sequential), and/or to the high incidence (9%) of treatment-related deaths in the combined arm.

Our study is the first randomized trial to demonstrate an overall survival benefit with the use of concurrent chemoradiotherapy followed by adjuvant chemotherapy as compared

Table 7. Survival and PFS of Eligible and Randomized Patients

Variable	Eligible Patients (n = 147) RT	Eligible Patients (n = 147) RT/CT	Randomized Patients (n = 185) RT	Randomized Patients (n = 185) RT/CT
3-year survival (%)	47	78	46	76
Hazards ratio	2.50		2.92	
3-year PFS (%)	24	69	26	66
Hazards ratio	4.34		4.24	

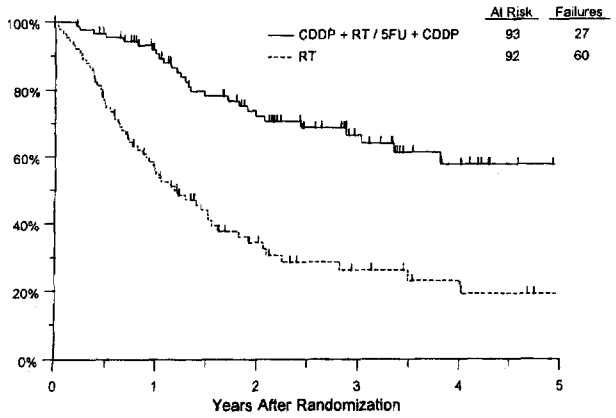

Fig 4. PFS for randomized patients on RT only and combined CT/RT.

with radiotherapy alone. The improvement in survival in this study confirms the initial observation of the phase II pilot studies with this combined approach. Other investigators[42,43] have used a sequential chemotherapy and higher dose of radiation for less advanced disease without an improvement in overall survival compared with radiotherapy alone. Unfortunately, the dose of chemotherapy given in that trial was reduced, only two courses of chemotherapy were given before radiotherapy, and the dose of fluorouracil was 60% of the usual dose.

The use of concurrent high-dose cisplatin and full-dose radiotherapy has produced improved results in patients with advanced nasopharyngeal cancers and other unresectable head and neck cancers[31-33,39,44] without a substantial increase in local toxicity. Our results clearly demonstrate that in patients with advanced nasopharyngeal cancers, the addition of high-dose cisplatin to radiotherapy simultaneously is of benefit. Due to the high incidence of late systemic recurrences in these patients, additional effective chemotherapy is needed to improve the results further of the combined modality treatment in advanced nasopharyngeal cancers.

ACKNOWLEDGMENT

We thank M. Yee and D. Lew for their work on this study.

REFERENCES

1. Ho JHC: An epidemiological and clinical study of nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 4:183-197, 1978

2. Qin D, Hu Y, Yan J, et al: Analysis of 1379 patients with nasopharyngeal carcinoma treated by radiation. Cancer 61:1117-1124, 1988

3. Flores AD, Dickson RI, Riding K, et al: Cancer of the nasopharynx in British Columbia. Am J Clin Oncol 9:281-291, 1986

4. Rahima M, Rakowsky E, Barzilay J, et al: Carcinoma of the nasopharynx. An analysis of 91 cases and a comparison of differing treatment approaches. Cancer 58:843-849, 1986

5. Wang DC, Cai WM, Hu VC: Long term survival of 1035 cases of nasopharyngeal carcinoma. Cancer 61:2338-2341, 1988

6. Hoppe RI, Williams J, Warnke R, et al: Carcinoma of the nasopharynx. The significance of histology. Int J Radiat Oncol Biol Phys 4:199-205, 1978

7. Shanmugaratuum K, Sobin L: Histologic typing of upper respiratory tract tumors, in International Histologic Typing of Tumors. Geneva, Switzerland, World Health Organization, 1978, pp 32-33

8. Hoppe RT, Goffinet DR, Bagshaw MA: Carcinoma of the nasopharynx. Eighteen years experience with megavoltage radiation therapy. Cancer 37:2605-2612, 1976

9. Mesic JB, Fletcher GH, Goepfert H: Megavoltage irradiation of epithelial tumors of the nasopharynx. Int J Radiat Oncol Biol Phys 7:447-453, 1981

10. Perez CA, Ackerman LV, Mill WB, et al: Cancer of the nasopharynx. Factors influencing prognosis. Cancer 24:1-17, 1969

11. Wang CC, Meyer JE: Radiotherapeutic management of carcinoma of the nasopharynx. Analysis of 170 patients. Cancer 28:566-570, 1971

12. Marks JE, Bedwinek JM, Lee F, et al: Dose response analysis for nasopharyngeal carcinoma. Cancer 50:1042-1050, 1982

13. Marcial VA, Hanley JA, Chang C, et al: Split-course radiation therapy of carcinoma of the nasopharynx: Results of a national collaborative clinical trial of the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys 6:409-414, 1980

14. Al-Kourainy K, Crissman J, Ensley J, et al: Excellent response to cisplatinum (CACP) based combination for recurrent and previously untreated locally advanced nasopharyngeal carcinoma. Proc Am Soc Clin Oncol 4:131, 1985 (abstr)

15. Al-Kourainy K, Crissman J, Ensley J, et al: Excellent response to cis-platinum based chemotherapy in patients with recurrent or previously untreated advanced nasopharyngeal carcinoma. Am J Clin Oncol 11:553-557, 1988

16. Atichartakan V, Kraiphibul P, Clongsusuek P, et al: Nasopharyngeal carcinoma: Result of treatment with cis-diamminedichloroplatinum II, 5 fluorouracil and radiation therapy. Int J Radiat Oncol Biol Phys 14:461-469, 1988

17. Bachouchi M, Cvitkovic E, Azli N, et al: High complete response in advanced nasopharyngeal carcinoma with bleomycin, epirubicin, and cisplatin before radiotherapy. J Natl Cancer Inst 82:616-620, 1990

18. Cvitkovic E, Grange GRL, Temple S: Neoadjuvant chemotherapy (NACT) with epirubicin (EPI) cisplatin (CDDP), bleomycin (BLEO) (BEC) in undifferentiated nasopharyngeal cancer (UCNT): Preliminary results of an international phase III trial. Proc Am Soc Clin Oncol 13:283, 1994 (abstr)

19. Dimery IW, Legha SS, Peters LJ, et al: Adjuvant chemotherapy for advanced nasopharyngeal carcinoma. Cancer 60:943-949, 1989

20. Dimery IW, Peters LJ, Goepfert H, et al: Effectiveness of combined induction chemotherapy and radiotherapy in advanced nasopharyngeal carcinoma. J Clin Oncol 11:1919-1928, 1993

21. Tannock I, Payne D, Cummings B, et al: Sequential chemotherapy and radiation for nasopharyngeal cancer: Absence of long-term benefit despite a high rate of tumor response to chemotherapy. J Clin Oncol 5:629-634, 1987

22. Preliminary results of a randomized trial comparing neoadjuvant chemotherapy (cisplatin, epirubicin, bleomycin) plus radiotherapy vs

radiotherapy alone in stage VI (≥N2,M0) undifferentiated nasopharyngeal carcinoma: A positive effect on progression-free survival. Int J Radiat Oncol Biol Phys 35:463-469, 1996

23. Choo R, Tannock I: Chemotherapy for recurrent or metastatic carcinoma of the nasopharynx: A review of the Princess Margaret Hospital experience. Cancer 68:2120-2124, 1991

24. Decker D, Drelichman A, Al-Sarraf M, et al: Chemotherapy for nasopharyngeal carcinoma. Cancer 52:602-605, 1983

25. Zak M, Drobnik J: Effect of cis-dichlorodiammineplatinum (II) on the post-irradiation lethality in mice after irradiation with x-rays. Strahlentherapie 142:112-115, 1971

26. Wodkinsky II, Swiniarski J, Kensler CJ, et al: Combination radiotherapy and chemotherapy for P388 lymphocytic leukemia in vivo. Cancer Treat Rep 4:73-78, 1974

27. Richmond RC, Zimbrick JD, Hykes DL: Radiation induced DNA damage and lethality in E coli as modified by the antitumor agent cisdichlorodiammineplatinum (II). Radiat Res 71:447-460, 1977

28. Douple EB, Richmond RC, Logan ME: Therapeutic potentiation in a mouse mammary tumor and an intracerebral rat brain tumor by combined treatment with cis-dichlorodiammineplatinum (II) and radiation. J Clin Hematol Oncol 7:585-603, 1977

29. Soloway MS, Morris CR, Sudderth B: Radiation therapy and cis-diamminedichloroplatinum (II) in transplantable and primary murine bladder cancer. Int J Radiat Oncol Biol Phys 5:1355-1360, 1979

30. Szumiel I, Nias AHW: The effect of combined treatment with a platinum complex and ionizing radiation on Chinese hamster ovary cells in vitro. Br J Cancer 33:450-458, 1976

31. Al-Sarraf M, Zundmanis M, Monciol V, et al: Concurrent cisplatin and radiotherapy in patients with locally advanced nasopharyngeal carcinoma. RTOG study. Proc Am Soc Clin Oncol 5:142, 1986 (abstr)

32. Al-Sarraf M, Pajak TF, Cooper JS, et al: Chemo-radiotherapy in patients with locally advanced nasopharyngeal carcinoma: A Radiation Therapy Oncology Group study. J Clin Oncol 8:1342-1351, 1990

33. Al-Sarraf M, Pajak T, Jacobs J, et al: Combined modality therapy (CMT) in patients with head and neck (HN-CA): Timing of chemotherapy (CT). Radiation Therapy Oncology Group (RTOG) study, in Salmon S (ed): Adjuvant Therapy of Cancer VI. Philadelphia, PA, Saunders, 1990, pp 60-70

34. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958

35. Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 50:163-170, 1966

36. Cox DR: Regression models and life tables. Stat Soc 34:187-202, 1972

37. Wang CC: Accelerated hyperfractionation radiation therapy for carcinoma of the nasopharynx. Cancer 63:2461-2467, 1989

38. Rossi A, Molinari R, Boracchi P: Adjuvant chemotherapy with vincristine, cyclophosphamide, and doxorubicin after radiotherapy in loco-regional nasopharyngeal cancer: Results of a 4-year multicenter randomized study. J Clin Oncol 6:1401-1410, 1988

39. Marcial VA, Pajak TF, Mohiuddin M, et al: Concomitant cis-platin chemotherapy and radiotherapy in advanced mucosal squamous cell carcinoma of the head and neck: Long-term results of the Radiation Therapy Oncology Group study 81-17. Cancer 66:1861-1868, 1990

40. Garden AS, Morrison WH, Ang KK, et al: Does induction chemotherapy have a role in the management of nasopharyngeal carcinoma? Int J Radiat Oncol Biol Phys 32:192, 1995 (abstr; suppl 1)

41. Eschwege F, El Gueddari B, Wierzbicki R, et al: Randomized multicentric international phase III trial of neoadjuvant chemotherapy (NACT) with bleomycin (B), epirubicin (E), cisplatin (C) followed by radiotherapy versus radiotherapy alone in undifferentiated carcinoma of nasopharyngeal type (UCNT): Preliminary results. Int J Radiat Oncol Biol Phys 32:192, 1995 (abstr)

42. Chan TC, Teo PML, Leung TWT, et al: Prospective randomized trial conducted to compare chemo-radiotherapy against radiotherapy alone in the treatment of locoregionally advance nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 33:569-577, 1995

43. Al-Sarraf M, McLaughlin WP: Nasopharyngeal carcinoma: Choice of treatment. Int J Radiat Oncol Biol Phys 33:761-763, 1995

44. Al-Sarraf M, Pajak TF, Marcial VA, et al: Concurrent radiotherapy and chemotherapy with cisplatin in in-operable squamous cell carcinoma of the head and neck. RTOG study. Cancer 59:259-265, 1987