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ORIGINAL REPORT

Randomized Trial of Radiotherapy Versus Concurrent Chemoradiotherapy Followed by Adjuvant Chemotherapy in Patients With American Joint Committee on Cancer/International Union Against Cancer Stage III and IV Nasopharyngeal Cancer of the Endemic Variety

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ABSTRACT

Purpose
The Intergroup 00-99 Trial for nasopharyngeal cancer (NPC) showed a benefit of adding chemotherapy to radiotherapy. However, there were controversies regarding the applicability of the results to patients in endemic regions. This study aims to confirm the findings of the 00-99 Trial and its applicability to patients with endemic NPC.

Patients and Methods
Between September 1997 and May 2003, 221 patients were randomly assigned to receive radiotherapy (RT) alone (n = 110) or chemoradiotherapy (CRT; n = 111). Patients in both arms received 70 Gy in 7 weeks using standard RT portals and techniques. Patients on CRT received concurrent cisplatin (25 mg/m^2 on days 1 to 4) on weeks 1, 4, and 7 of RT and adjuvant cisplatin (20 mg/m^2 on days 1 to 4) and fluorouracil (1,000 mg/m^2 on days 1 to 4) every 4 weeks (weeks 11, 15, and 19) for three cycles after completion of RT. All patients were analyzed by intent-to-treat analysis. The median follow-up time was 3.2 years.

Results
Distant metastasis occurred in 38 patients on RT alone and 18 patients on CRT. The difference in 2-year cumulative incidence was 17% (95% CI, 14% to 20%; $P = .0029$). The hazard ratio (HR) for disease-free survival was 0.57 (95% CI, 0.38 to 0.87; $P = .0093$). The 2- and 3-year overall survival (OS) rates were 78% and 85% and 65% and 80% for RT alone and CRT, respectively. The HR for OS was 0.51 (95% CI, 0.31 to 0.81; $P = .0061$).

Conclusion
This report confirms the findings of the Intergroup 00-99 Trial and demonstrates its applicability to endemic NPC. This study also confirms that chemotherapy improves the distant metastasis control rate in NPC.

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INTRODUCTION

Nasopharyngeal carcinoma (NPC) is endemic in Singapore and makes up approximately 60% of all head and neck cancers.[1] It is generally accepted as a disease of the Chinese, particularly individuals from Southern China, where the rates vary from 30 to 50 per 100,000 people. In most other populations, the disease is rare, with intermediate incidence seen among Singapore Malays and Inuits in Greenland.

NPC has traditionally been treated with radiotherapy (RT), and overall cure rates of between 50% and 60% have been obtained in countries in East Asia.[2,3] Attempts to improve overall survival (OS) by the addition of chemotherapy either before[4-7] or after[8,9] the course of RT have previously been unsuccessful.

The US Intergroup Trial 00-99[10] was the first randomized study to show significant survival benefit by adding cisplatin (CDDP) concurrent with RT followed by adjuvant CDDP and fluorouracil (FU). A 25% improvement in the 2-year OS rate compared with RT alone was demonstrated in the initial report.

Although the results were impressive, there was reluctance among oncologists from the endemic regions in East Asia to adopt this new regimen because there were controversies regarding the applicability of the results to the endemic form of NPC.[11] A quarter of the patients in the Intergroup trial had the keratinizing type (WHO type I) of NPC, whereas more than 90% of patients in endemic areas have the nonkeratinizing type (mainly WHO type III). It had previously been shown that the two histologic subtypes of NPC have different prognoses.[12,13] In addition, the outcome of the RT alone arm in the Intergroup trial was much poorer than what is generally achieved in areas treating the stage-equivalent endemic form of NPC. In fact, the survival outcome of patients in the chemoradiotherapy (CRT) arm in the Intergroup trial seems similar to the outcome of their counterparts in endemic areas who received RT alone. Finally, on a related issue, the RT technique used in the Intergroup study was different and deemed to be less aggressive than the techniques used in East Asia, where parapharyngeal and intracavitary boost radiation were used as adjuncts in selected subsets of patients, thereby reaching a higher overall dose to the disease sites. This could partly explain the inferior results in the RT arm in the Intergroup trial that could have been compensated for by the addition of chemotherapy in the study arm.

However, we could not ignore the results of the Intergroup trial because a significant proportion of our patients with stage III or IV endemic NPC relapsed locoregionally and/or systemically with RT alone. Hence, we embarked on a phase II trial[14] using the Intergroup CRT protocol with slight modifications to assess the ability of our population to tolerate the combined regimen. CDDP was fractionated into four daily doses in our treatment protocol during the concurrent and adjuvant phases to reduce the emesis rate and, thus, improve tolerability. From this trial, we found that we were able to deliver the same dose-intensity of CDDP and FU without compromising on the RT delivered and with acceptable toxicities. We subsequently mounted a randomized trial to confirm the findings of the Intergroup trial and its applicability to our population of endemic NPC patients.

PATIENTS AND METHODS

Eligibility Criteria

All patients who had American Joint Committee on Cancer/International Union Against Cancer (1997) T3-4NxM0 or TxN2-3M0 previously untreated NPC with WHO type II or III histology; an Eastern Cooperative Oncology Group performance status of 0 or 1; and adequate bone marrow, renal, and hepatic functions and who were deemed fit to undergo CRT were eligible for entry onto the trial. The diagnosis of NPC was histologically confirmed on biopsy. The exclusion criteria include previous treatment for NPC, presence of distant metastasis, and other concomitant malignant disease. Written informed consent was obtained before random assignment. The protocol was approved by the ethics committees of the participating institutions, and the trial was conducted in accordance with the Declaration of Helsinki.

Study Design

On the basis of a two-sided test size of 5% and a power of 90%,[15] it was anticipated that a minimum of 200 patients would need to be recruited to detect the difference in absolute survival at 2 years of 25% that was observed by Al-Sarraf et al.[10] This assumes that the survival rate was 55% for RT alone and 80% for CRT.

Random assignment into the trial was conducted through the Central Randomization Office of the Clinical Trials and Epidemiology Research Unit, Singapore, by means of a telephone call. Patients were randomly assigned using blocks of four and six (stratified by nodal stage) based on a 1:1 treatment allocation.

Treatment

All patients received standard-course RT to a dose of 70 Gy in 35 fractions (2 Gy per fraction), using a modified Ho's technique.[16,17] All patients were treated using 6-MV linear accelerators. The primary tumor was treated with two lateral opposed facial fields to 20 Gy followed by a three-field technique (anterior facial and lateral opposed facial fields) to a total dose of 70 Gy. The neck was treated to a dose of 60 Gy, and lymph nodes were boosted with electrons for another 10 Gy. All fields were treated once daily, 5 times a week. Patients who had high cervical lymph nodes or inferior extension of the tumor toward the oropharynx were treated with a shrinking field technique using long opposing faciocervical fields for the first 40 Gy and followed by the three-field plan for the rest of the treatment.

For patients who were allocated to CRT, three cycles of concurrent CDDP were administered on weeks 1, 4, and 7 of RT. Subsequently, a further three cycles of adjuvant chemotherapy comprising a combination of CDDP and FU were administered between weeks 11 and 19. The dose schedules for chemotherapy are listed in Table 1.

Treatment modifications were carried out according to the following scheme. CDDP was omitted for a cycle during the concurrent RT phase if the minimum hematologic criteria were not met (absolute neutrophil count $> 1{,}000/\mu L$ and platelet count $> 100{,}000/\mu L$). During the adjuvant phase, deferment of the chemotherapy by up to a maximum of 2 weeks was allowed if the same hematologic criteria were not met, beyond which the patient would be taken out of the trial. Substitution of CDDP with carboplatin (dose, area under the curve of 5) was allowed in the event of grade 2 or more peripheral neuropathy or intolerable emesis with CDDP. Chemotherapy was also discontinued completely in the event of patient refusal, physician's decision for fear of RT compromise, and unacceptable toxicities such as severe sepsis or renal

Table 1. Dose Schedules for Concurrent Chemoradiotherapy and adjuvant chemotherapy

Therapy	Dose	Route	Week	Day
Concurrent chemoradiotherapy				
CDDP	1.) 25 mg/m^2/d for 4 days	IV over 6-8 hrs	1	1-4
			4	22-25
			7	43-46
	2.) Alternatively, 30/30/40 mg/m^2/d for 3 days if patient starts RT on a Wednesday and only for the first cycle		1	1-3
			4	22-25
			7	43-46
RT	2 Gy/d 5 fractions/wk			35 daily fractions
Adjuvant chemotherapy				
CDDP	20 mg/m^2/d for 4 days	IV over 6-8 hrs	11	71-74
			15	99-102
			19	127-130
FU	1,000 mg/m^2/d for 4 days	IV over 6-8 hrs	11	71-74
			15	99-102
			19	127-130

Abbreviations: CDDP, cisplatin; RT, radiotherapy; IV, intravenous; FU, fluorouracil.

impairment. Every effort was taken not to delay or break the course of RT.

Assessment

The primary end point was OS. The other end points of interest were the distant metastasis and disease-free survival (DFS) rates. For the assessment of these outcomes, the trial patients were observed every 4 months for the first year, every 6 months for the subsequent 2 years, and annually thereafter.

Patients were staged according to the American Joint Committee on Cancer/International Union Against Cancer (1997) system. All patients had a computed tomography scan or magnetic resonance imaging of the head and neck region to confirm the stage of disease at random assignment. Scans were repeated at 4 months after RT and annually thereafter and at recurrence. In addition, chest x-ray, liver ultrasound, and bone scan were performed to confirm the absence of distant metastasis at random assignment.

The toxicity during treatment was classified based on the Radiation Therapy Oncology Group Acute Radiation Morbidity Scoring Criteria. Treatment toxicity was evaluated at the completion of each cycle for CRT and at the completion of treatment for RT alone.

Statistical Methods

The competing risks approach was used to compute the cumulative incidence of distant metastasis as a first cause of failure.[18,19] This method takes into account other competing causes of first failure, such as local and neck relapses, in its calculation. A comparison between cumulative incidence curves was made using Gray's test.[20] The time to distant metastasis was calculated from the date of random assignment to the date when distant metastasis first occurred. This included patients in whom distant metastasis was reported to have occurred together with persistent disease or other relapses. Patients in whom distant metastasis as a first event has not occurred were censored at the date last known to be alive.

In the analysis of DFS, a patient was considered to have had an event if he relapsed after the completion of all primary treatment. Patients who had persistent disease after treatment or relapsed at any site after remission and patients who died of intercurrent causes were not considered disease free. The starting point for DFS was the date of random assignment, and the terminating point was the date when a relapse first occurred or, in the case of persistent disease and other causes of deaths, the dates of first follow-up and death, respectively. Patients in whom there was no evidence of disease after treatment were censored at the date of last follow-up.

Similarly, the OS time was computed from the date of random assignment to the date when the patient was last known to be alive. The DFS and OS curves were constructed using the Kaplan-Meier method,[21] and comparisons between the two treatment procedures were made using the log-rank test.[22]

Data Quality and Integrity

The trial data were collected on printed forms and entered into CLINTRIAL (Domain Pharma Corporation, Lexington, MA). The statistical analyses were generated using SAS version 8.0 (SAS Institute Inc, Cary, NC) and performed according to the intent-to-treat method.

An independent Data Monitoring Committee (DMC) was established to examine all facets of the trial. The DMC formally met to review the results in October 1999, August 2000, and February 2003. In the last review, the DMC recommended that the data be released only after all patients had been observed for at least 6 months and 50 deaths from any cause had occurred.

Role of the Funding Source

The National Medical Research Council of Singapore sponsored the study. The sponsor had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or decision to submit the report for publication.

RESULTS

A total of 221 patients were randomly assigned between September 27, 1997, and May 28, 2003, with 110 patients allocated to RT alone and 111 patients allocated to CRT (Fig

1). Four patients were ineligible because of the presence of distant metastases (two patients), a second malignancy (one patient), and stage II disease (one patient). In addition, one patient in each arm was lost to follow-up. Nevertheless, all randomly assigned patients were included in the intent-to-treat analysis for the duration that they were observed. The median follow-up time was 3.2 years (range, 0.1 to 5.9 years).

Table 2 demonstrates that patients in the two treatment arms were well balanced with respect to most characteristics. Their median age was 47 years (range, 14 to 76 years), with all but one patient (14 years old) being ≥ 18 years old. Eighty-one percent of the patients were male. The racial composition was 92% Chinese, 7% Malay, and 1% other races. Overall, tumor status T1 accounted for 13% of patients, with the rest of the patients distributed evenly between T2, T3, and T4. However, T2 was somewhat more frequent in RT alone patients, and T4 was more frequent in CRT patients. For most patients, the nodal status was either N2 (49%) or N3 (28%). The distribution of disease stages was as follows: stage II, 1%; stage III, 45%; and stage IV, 54%.

Treatment Compliance

Of patients assigned to RT alone, 105 received the recommended RT dose of 70 Gy. One patient received only 24 Gy because he died before treatment completion (unrelated to treatment), whereas another patient received only 50 Gy because he defaulted treatment. A further three patients defaulted treatment soon after random assignment and, hence, did not receive any RT. In addition, chemotherapy was administered to one patient who started on RT (70 Gy) 9 months after random assignment.

Eighty-three of 111 patients on the CRT arm did not fully comply with the protocol treatment (Fig 1). Forty-six patients had treatment deviation for the concurrent CRT component, including five patients who declined all cycles of chemotherapy, one patient who developed a stroke after completing the first cycle of chemotherapy, and two patients who died before treatment completion (one as a result of neutropenic sepsis and one as a result of suicide). In addition, 24 patients had reduced concurrent cycles because of toxicity (n = 11), refusal of further treatment (n = 12), or miscalculation of treatment timing (n = 1). There were also seven patients who experienced delay in cycle(s), six patients who had their dose of chemotherapy reduced, and one patient who was administered paclitaxel instead of CDDP for all cycles. Thus, in all, 79 patients (71%) received all three cycles of concurrent chemotherapy. Protocol deviation for the RT component of concurrent CRT arm included six patients who received a total RT

Table 2. Patient Characteristics by Treatment

Characteristic	Radiotherapy Alone Patients (n = 110) No.	%	Chemoradiotherapy Patients (n = 111) No.	%	All Patients (N = 221) No.	%
Age, years						
Median	46		49		47	
Range	28-72		14-76		14-76	
Sex						
Male	88	80	92	83	180	81
Female	22	20	19	17	41	19
Race						
Chinese	104	95	99	89	203	92
Malay	5	4	11	10	16	7
Other	1	1	1	1	2	1
Tumor size						
T1	10	9	18	16	28	13
T2	40	36	23	21	63	29
T3	33	30	32	29	65	29
T4	27	25	38	34	65	29
Nodal status						
N0	12	11	11	10	23	10
N1	12	11	16	14	28	13
N2	53	48	55	50	108	49
N3	33	30	29	26	62	28
TNM staging						
Stage II	—	—	1	1	1	1
Stage III	53	48	48	43	101	45
Stage IV	57	52	62	56	119	54

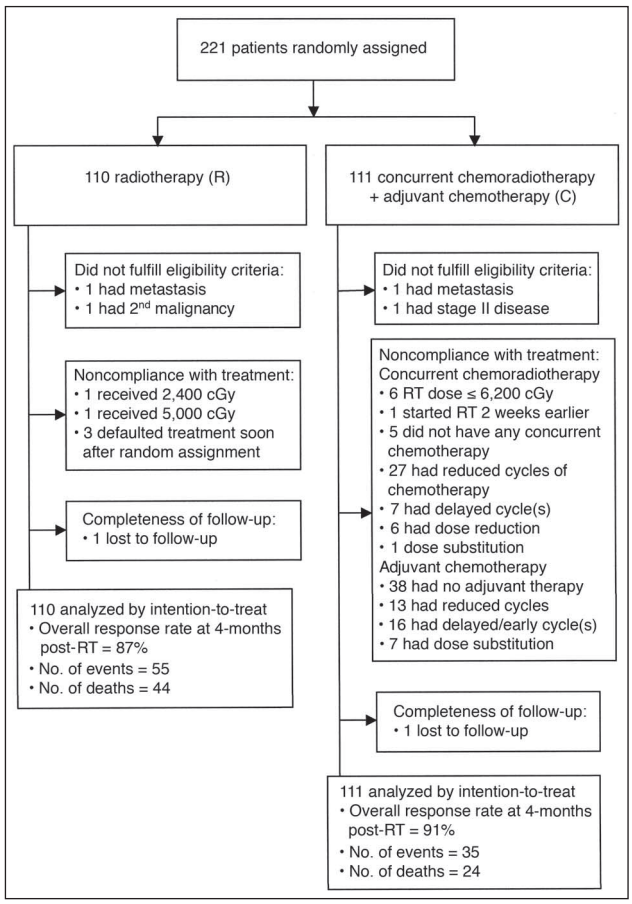

Fig 1. Trial profile.

dose of no more than 62 Gy and one patient who was started on RT 2 weeks before the scheduled chemotherapy.

Seventy-four patients had protocol deviations during the adjuvant chemotherapy phase of the trial. In addition to the patient who developed a stroke and the two patients who died before treatment completion, 35 patients did not receive any of the adjuvant cycles because of toxicity (n = 12) or refusal of treatment (n = 23). In the 13 patients who had a reduced number of adjuvant cycles, six reductions were a result of toxicity, six were a result of refusal of further treatment, and one was a result of hospitalization after a fall. Fifteen patients had delayed cycle(s), whereas one patient was scheduled for treatment a week in advance because of miscalculation of treatment timing. In addition, CDDP was substituted with carboplatin for at least one cycle for six patients and with paclitaxel for all cycles for one patient.

Treatment Toxicity

Altogether, 107 patients (48%) experienced grade 3, 4, or 5 toxicity. There was one treatment-related death in the CRT arm as a result of neutropenic sepsis. There were notably higher incidences of toxicity with CRT. In particular, for nonhematologic toxicity, the incidences of oropharyngeal mucositis (48% in CRT *v* 32% in RT alone, $P = .0149$), anorexia (22% in CRT *v* 4% in RT alone, $P < .0001$), and emesis (5% in CRT *v* 0% in RT alone, $P = .0291$) were significantly higher in the CRT arm during the initial phase of treatment. In the case of hematologic toxicity, the incidence of severe neutropenia was significantly higher on CRT than RT alone (14% *v* 0%, respectively; $P = .0001$), and it was appreciable in both the initial and adjuvant (33%) phases of chemotherapy. Details of other types of toxicity are listed in Table 3.

Clinical Response

The tumor response was evaluated by endoscopy and imaging at 4 months after RT. Ten patients were not assessable in the RT alone arm, including one patient who died before completion of treatment, one patient who completed treatment but died before he was due for evaluation of response, one patient who did not attend the evaluation of response, three treatment defaults, one patient lost to follow-up, an ineligible patient who was diagnosed with distant metastases, and two patients who reported with early distant relapses. Three patients were not assessable in the CRT arm, including two patients who died before completion of treatment and one patient who received four cycles and then did not attend the clinic again. In the RT alone arm, 89 patients (81%) and seven patients (6%) had a complete response and a partial response, respectively, at the primary site (Table 4), giving an overall response rate at the primary site of 87%. In the CRT arm, 96 patients (86%) and five patients (5%) had a complete response and a partial response, respectively, giving a corresponding overall response rate of 91% at the primary site. Similarly, the overall response rate at the neck region was 87% for RT alone patients and 95% for CRT patients. When both the primary site and neck were considered together, the composite overall response rates were 86% for RT alone and 90% for CRT.

Distant Metastasis

Table 5 lists the distributions of the site of first relapse. Distant relapse was the most common, occurring in 38 patients on RT alone and 18 patients on CRT. The 2-year cumulative incidence of relapse was 30% for RT alone and

Table 3. Patients Experiencing Their Worst Toxicity (grade 3, 4, or 5) by Treatment Group

	Initial Phase										Adjuvant Phase				
	Radiotherapy Alone Patients (n = 107)					Chemoradiotherapy Patients (n = 106)					Chemoradiotherapy Patients (n = 73)				
Toxicity	Grade 3 (No.)	Grade 4 (No.)	Grade 5 (No.)	Grades 3, 4, and 5 No.	Grades 3, 4, and 5 %	Grade 3 (No.)	Grade 4 (No.)	Grade 5 (No.)	Grades 3, 4, and 5 No.	Grades 3, 4, and 5 %	Grade 3 (No.)	Grade 4 (No.)	Grade 5 (No.)	Grades 3, 4, and 5 No.	Grades 3, 4, and 5 %
Nonhematologic															
Mucositis/pharyngitis	34	0	0	34	31.8	51	0	0	51	48.1	4	0	0	4	5.5
Anorexia	4	0	0	4	3.7	23	0	0	23	21.7	3	0	0	3	4.1
Emesis	0	0	0	0	0.0	5	0	0	5	4.7	1	0	0	1	1.4
Skin	5	0	0	5	4.7	5	0	0	5	4.7	0	0	0	0	0.0
Others*	0	0	0	0	0.0	2	2	0	4	3.8	0	2	0	2	2.7
Hematologic															
Neutrophils	0	0	0	0	0.0	10	4	1	15	14.2	13	11	0	24	32.9
Platelets	0	0	0	0	0.0	1	1	0	2	1.9	0	0	0	0	0.0
Others†	0	0	0	0	0.0	0	0	0	0	0.0	3	0	0	3	4.1

NOTE. The Radiation Therapy Oncology Group Acute Radiation Morbidity Scoring Criteria does not have a classification for renal, infection, metabolic, and GI toxicities. Thus, these were classified based on the National Cancer Institute Common Toxicity Criteria.

*Initial phase: grade 3 toxicities include renal toxicity and admission; grade 4 toxicities include infection and metabolic toxicity. Adjuvant phase: includes GI toxicity and infection.

†Includes one hemoglobin and two WBC toxicities.

Table 4. Tumor Response by Treatment Group

Response	Primary				Neck				Composite*			
	Radiotherapy Alone Patients (n = 110)		Chemoradiotherapy Patients (n = 111)		Radiotherapy Alone Patients (n = 110)		Chemoradiotherapy Patients (n = 111)		Radiotherapy Alone Patients (n = 110)		Chemoradiotherapy Patients (n = 111)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Complete	89	81	96	86	85	77	101	91	78	71	92	83
Partial	7	6	5	5	11	10	5	4	17	15	8	7
Static	3	3	1	1	3	3	1	1	3	3	1	1
Equivocal	1	1	2	2	0	0	0	0	1	1	2	2
Progression	0	0	4	3	1	1	1	1	1	1	5	4
Not assessable	10	9	3	3	10	9	3	3	10	9	3	3
Overall response, complete + partial	96	87	101	91	96	87	106	95	95	86	100	90

*Composite response is defined as the worst response at primary or neck site when both were considered together.

13% for CRT (Fig 2), and this difference of 17% was statistically significant (95% CI, 14% to 20%; $P = .0029$).

DFS

Altogether, there were 55 treatment failures in the RT alone arm and 35 in CRT arm. These failures include persistent disease and death as a result of other causes. The Kaplan-Meier DFS curves are shown in Figure 3. The 2- and 3-year DFS rates were 57% and 75% and 53% and 72% for RT alone and CRT patients, respectively. Thus, patients who were randomly assigned to receive CRT had a lower risk of relapse. The hazard ratio (HR) was 0.57 (95% CI, 0.38 to 0.87; $P = .0093$) and accounting for the strata of nodal status (N0-2 and N3) and tumor size (TNM staging) made no appreciable difference to this estimate.

OS

Sixty-eight deaths (44 in the RT alone arm and 24 in the CRT arm) were reported, of which 60 (39 in the RT alone arm and 21 in the CRT arm) were disease related (Table 6). Other causes of death in the RT alone arm included disseminated intravascular coagulation, pneumonia, neutropenic sepsis (which occurred during subsequent treatment for metastases), multiple injuries, and a second malignancy at the lung. Other causes of death in the CRT arm included suicide, pneumonia, and neutropenic sepsis (treatment related).

Figure 4 compares the Kaplan-Meier OS curves of the two treatment groups. The 2- and 3-year survival rates were 78% and 85% and 65% and 80% for RT alone and CRT, respectively. Thus, patients who were randomly assigned to receive CRT had a reduced risk of death, with an HR of 0.51 (95% CI, 0.31 to 0.81; $P = .0061$). This result remained unaltered with a stratified analysis for nodal status (and adjusting for tumor size, TNM staging).

Table 5. Site of First Relapse

Site	No. of Patients		
	Radiotherapy Alone	Chemoradiotherapy	Total
Local	8	4	12
Neck	2	3	5
Local + neck	—	2	2
Distant	38	18	56

DISCUSSION

In recent years, the addition of chemotherapy to standard RT has yielded superior results in the treatment of locally advanced cancers in a variety of tumor types.[23-26] Cancers at high risk of recurrence after surgical resection have also benefited from combined CRT.[27,28] The treatment seemed to achieve greatest benefit when chemotherapy was administered concurrently with RT.[24,29]

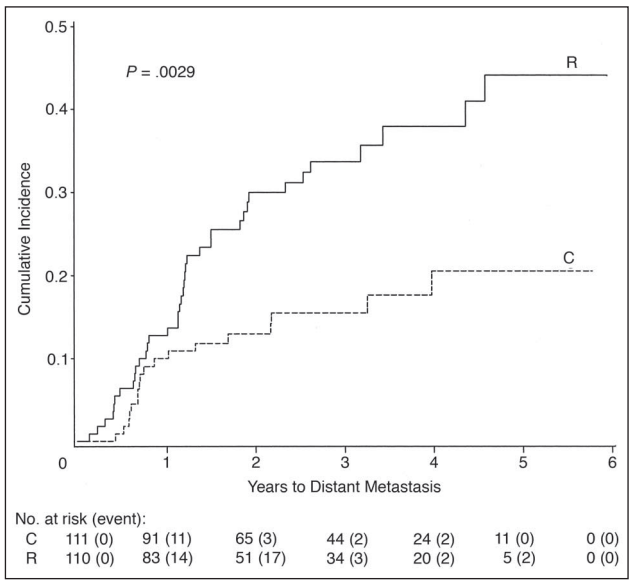

Fig 2. Cumulative incidence of distant metastasis.

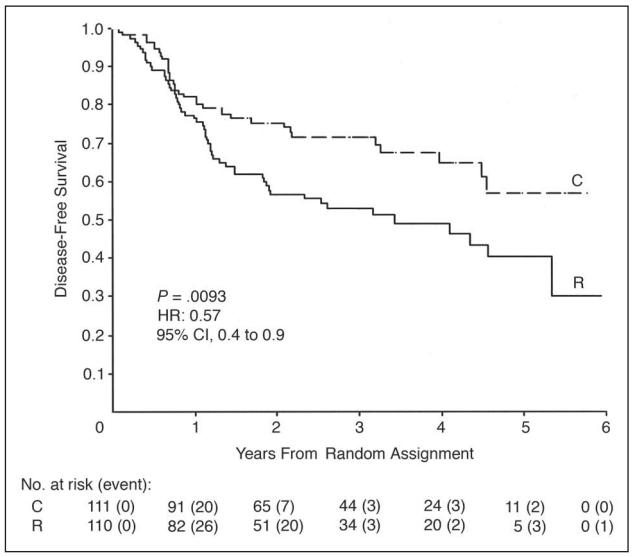

Fig 3. Disease-free survival by treatment.

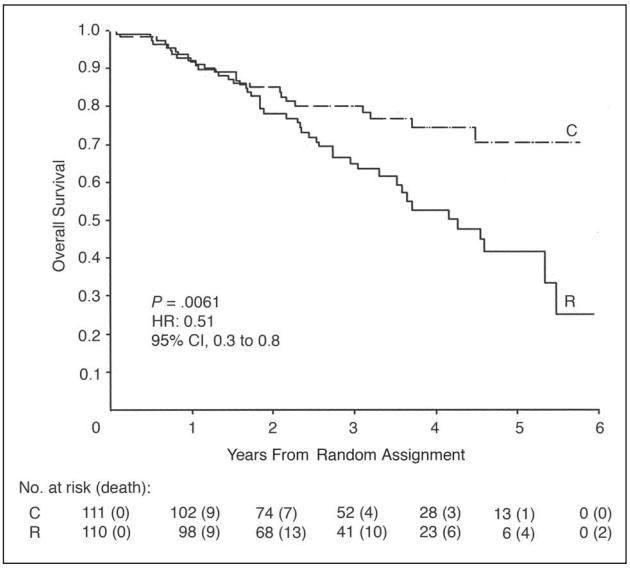

Fig 4. Overall survival by treatment.

However, NPC is extremely sensitive to RT, and RT alone can achieve 5-year survival rates of 75% or higher in stage I and II disease.[2,30] Thus, the benefit of adding chemotherapy becomes more debatable. This was the case until the landmark study Intergroup Trial 00-99 demonstrated a clear benefit for patients with stage III and IV NPC in the combined treatment arm.

The current study tested the same hypothesis but in patients with endemic NPC (only WHO types II and III). Our results showed that the addition of chemotherapy significantly improved 2-year distant metastasis–free, DFS, and OS rates of patients with locally advanced NPC, confirming the results of the Intergroup 00-99 Trial in our patients with endemic NPC. The overall 2- and 3-year survival rates for the CRT arm in both trials were comparable (2- and 3-year rates, 85% *v* 82% and 80% *v* 78% for the present trial and the 00-99 Trial, respectively). Both trials showed that the CRT regimen reduced the risk of death compared with standard RT. The magnitude of risk reduction was similar, with HRs of 0.51 (95% CI, 0.31 to 0.81) in our study and 0.40 (95% CI, 0.21 to 0.78) in the 00-99 Trial.[10]

Table 6. Primary Outcome by Treatment

Survival Status	Radiotherapy Alone Patients (No.)	Chemoradiotherapy Patients (No.)	All Patients (No.)
Alive	65	86	151
Lost to follow-up	1	1	2
Death			
Disease related	39	21	60
Treatment related	0	1	1
Other cause	5	2	7

Although RT was not compromised, the compliance with treatment for the CRT arm was at best fair, with 71% of patients receiving the planned three cycles of concurrent chemotherapy during RT and 57% of patients completing all three cycles of adjuvant chemotherapy. This was probably multifactorial and contributed to, in part, by the toxicities of chemotherapy and by the accentuated mucositis from radiosensitization. However, fractionation of CDDP over a period of 4 days did result in lower incidences of grade 3 or 4 emesis and may have accounted for the slightly higher percentage of patients receiving three cycles of concurrent chemotherapy compared with the Intergroup trial (63% in the 00-99 Trial).

Oropharyngeal mucositis remained a significant problem, especially for the CRT arm. The RT portal required was wide, extending from the skull base to the root of the neck. The presence of bulky primary or cervical nodes, which are common in NPC, often resulted in significant doses of RT being delivered to the mucosal surfaces, which, in turn, caused extensive mucositis. The incidence of grade 3 or 4 mucositis was 48% for the CRT arm and 32% for the RT alone arm; these figures were much higher than those reported in the 00-99 Trial (37% and 28%, respectively) probably because of the difference in RT techniques and possibly because of the split-dose scheduling of CDDP. It remains to be seen whether there will be long-term sequelae of these differences. Follow-up of the chronic toxicities in patients who received concurrent CRT compared with RT would be important. The use of newer technologies, like intensity-modulated RT,[31] would likely reduce these toxicities and improve compliance with treatment.

Although much has been achieved in way of improving DFS and OS by administering chemotherapy concurrently

with RT, more is to be desired, especially concerning reduction of distant failure. Different scheduling of chemotherapy and RT has been assessed by many investigators, including regimens of neoadjuvant chemotherapy followed by definitive RT[4,32] or RT with adjuvant chemotherapy.[8,9] Aggregate results[33] seem to indicate that concomitant chemotherapy is probably still the most effective way of improving survival outcome, as has been shown in our study and two other recent studies conducted in the region.[34,35] The latter studies from Taiwan and Hong Kong looked specifically at concurrent CRT in a randomized setting.

Lin et al[34] used a combination of CDDP at 20 mg/m^2/d and FU at 400 mg/m^2/d over a 96-hour infusion in their study. Patients randomly assigned to CRT would receive two cycles of the chemotherapy regimen during weeks 1 and 5 of the RT. Two hundred eighty-four patients were randomly assigned over a 5-year period from December 1993 to April 1999. Despite the expected higher acute toxicities with concurrent chemotherapy, the compliance with RT was not reduced, and the number of patients requiring delay in RT was not increased when compared with the RT alone arm (11 patients in the CRT arm *v* 16 patients in the RT alone arm). The compliance with chemotherapy was also good, with 93.6% of the patients completing the planned two cycles, with a delay of $\geq$ 1 week of the second cycle in only nine patients. At a median follow-up of 65 months (range, 36 to 100 months), there was significant improvement in the 5-year OS and progression-free survival rates in the CRT arm compared with the RT alone arm (72.3% *v* 54.2% and 71.6% *v* 53%, respectively). This was mainly attributable to the significant improvement in local control rates at 5 years (89.3% in the CRT arm *v* 72.6% in the RT alone arm, $P = .0009$), although there was also a nonsignificant trend towards improved distant control (78.7% in the CRT arm *v* 69.9% in the RT alone arm, $P = .0577$).

Chan et al[35] used weekly CDDP at 40 mg/m^2 during the RT in their study, and 350 patients were randomly assigned between April 1997 and November 1999, with OS (progression-free survival) as the end point. As expected, toxicities were higher in the CRT arm, and 78% of the patients were able to receive at least 4 weekly doses of CDDP. Only 44% of the patients were able to complete at least 6 weekly doses of CDDP. At a median follow-up of 5.5 years, the 5-year OS rate was 58.6% (95% CI, 50.9% to 66.2%) for the RT arm and 70.3% (95% CI, 63.4% to 77.3%) for the CRT arm. This difference was statistically significantly in favor of concurrent CRT ($P = .049$; HR = 0.71; 95% CI, 0.5 to 1.0).

Although the designs of the Taiwan and Hong Kong studies differ from the design of our study, it is quite clear that the administration of effective cytotoxic(s) and RT concurrently is a major contributor to the improved survival outcome. The radiosensitization effect of this schedule contributes to a high rate of locoregional control, which, in turn, leads to significant improvement in OS. Does the additional administration of chemotherapy after completion of the concurrent CRT phase, as in the 00-99 Trial and our study, add any benefit to this group of patients? We believe that it does. This is shown in the significant reduction in distant metastasis rate in both the 00-99 Trial and our study. Given that the major cause of treatment failure in the concurrent CRT arm was distant metastases,[31] more should be done to improve on the efficacy of the adjunct chemotherapy that is administered. Although one can consider adding more cytotoxics in combination during the concurrent CRT phase, the expected increased oropharyngeal mucositis will limit both the number of cytotoxics and the dose that can be administered.

The past decade has seen results from newer active agents,[36-39] and a recent study has shown promising results with the use of a triplet combination of these drugs in disseminated NPC.[40] The recent advent of targeted therapies[41-43] could add to the armamentarium of oncologists for the treatment of NPC. It is possible that using novel combinations of newer agents as an adjunct and perhaps administering them before, rather than after, CRT to improve compliance may result in further improvement in systemic control. Future trials looking at this issue are currently being planned.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

REFERENCES

1. Chia KS, Lee HP, Seow A, et al: Trends in cancer incidence in Singapore 1968-1992. Singapore Cancer Registry Report 4:70-71, 1996

2. Heng DM, Wee J, Fong KW, et al: Prognostic factors in 677 patients in Singapore with nondisseminated nasopharyngeal carcinoma. Cancer 86:1912-1920, 1999

3. Lee AW, Law SC, Foo W, et al: Retrospective analysis of patients with nasopharyngeal carcinoma treated during 1976-1985: Survival after local recurrence. Int J Radiat Oncol Biol Phys 26:773-782, 1993

4. Chan AT, Teo PM, Leung TW, et al: A prospective randomized study of chemotherapy adjunctive to definitive radiotherapy in advanced nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 33:569-577, 1995

5. International Nasopharynx Cancer Study Group: 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: VUMCA I trial. Int J Radiat Oncol Biol Phys 35:463-469, 1996

6. Ma J, Mai HQ, Hong MH, 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 19:1350-1357, 2001

7. Chua DT, Sham JS, Choy D, 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 83:2270-2283, 1998

8. Rossi A, Molinari R, Boracchi P, 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 6:1401-1410, 1988

9. Chi KH, Chang YC, Guo WY, et al: A phase III study of adjuvant chemotherapy in advanced nasopharyngeal carcinoma patients. Int J Radiat Oncol Biol Phys 52:1238-1244, 2002

10. Al-Sarraf M, LeBlanc M, Giri PG, et al: Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: Phase III randomized Intergroup study 0099. J Clin Oncol 16:1310-1317, 1998

11. Chan AT, Teo PM, Johnson PJ: Controversies in the management of locoregionally advanced nasopharyngeal carcinoma. Curr Opin Oncol 10:219-225, 1998

12. Shanmugaratnam K, Chan SH, de-The G, et al: Histopathology of nasopharyngeal carcinoma: Correlations with epidemiology, survival rates and other biological characteristics. Cancer 44:1029-1044, 1979

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

14. Tan EH, Chua ET, Wee J, et al: Concurrent chemoradiotherapy followed by adjuvant chemotherapy in Asian patients with nasopharyngeal carcinoma: Toxicities and preliminary results. Int J Radiat Oncol Biol Phys 45:597-601, 1999

15. Machin D, Campbell MJ, Fayers PM, et al: Sample Size Tables for Clinical Studies. Oxford, United Kingdom, Blackwell, 1997

16. Ho JH: An epidemiologic and clinical study of nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 4:182-198, 1978

17. Wee JTS, KhooTan HS, Chua EJ: Radiotherapy, in Chong VH, Tsao SY (eds): Nasopharyngeal Cancer. Singapore, Armour Publishing, 1997, pp 90-102

18. Kalbfleisch JD, Prentice RL: The Statistical Analysis of Failure Time Data. New York, NY, Wiley, 1980

19. Tai BC, Machin D, White I, et al: Competing risks analysis of patients with osteosarcoma: A comparison of four different approaches. Stat Med 20:661-684, 2001

20. Gray R: A class of k-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 16:1141-1154, 1988

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

22. Peto R, Pike MC, Armitage P, et al: Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Br J Cancer 35:1-39, 1977

23. Dillman RO, Herndon J, Seagren SL, et al: Improved survival in stage III non-small-cell lung cancer: Seven-year follow-up of Cancer and Leukemia Group B (CALGB) 8433 Trial. J Natl Cancer Inst 88:1210-1215, 1996

24. Forastiere AA, Goepfert H, Maor M, et al: Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 349:2091-2098, 2003

25. Herskovic A, Martz K, Al-Sarraf M, et al: Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med 326: 1593-1598, 1992

26. Morris M, Eifel PJ, Lu J, et al: Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med 340: 1137-1143, 1999

27. Cooper JS, Pajak TF, Forastiere AA, et al: Postoperative concurrent radiotherapy and chemotherapy for high risk squamous-cell carcinoma of the head and neck. N Engl J Med 350:1937-1944, 2004

28. Bernier J, Domenge C, Ozsahin M, et al: Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 350:1945-1952, 2004

29. Furuse K, Fukuoka M, Kawahara M, et al: Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol 17:2692-2699, 1999

30. Fong KW, Chua EJ, Chua ET, et al: Patient profile and survival in 270 computer tomography-staged patients with nasopharyngeal cancer treated at the Singapore General Hospital. Ann Acad Med Singapore 25:341-346, 1996

31. Lee N, Xia P, Quivey JM, et al: Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: An update of the UCSF experience. Int J Radiat Oncol Biol Phys 53:12-22, 2002

32. Hareyama M, Sakata K, Shirato H, et al: A prospective trial comparing neoadjuvant chemotherapy with radiotherapy alone in patients with advanced nasopharyngeal carcinoma. Cancer 94: 2217-2223, 2002

33. Langendijk KA, Leemans ChR, Buter J, et al: The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma: A meta-analysis of the published literature. J Clin Oncol 22:4604-4612, 2004

34. Lin JC, Jan JS, Hsu CY, et al: Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: Positive effect on overall and progression-free survival. J Clin Oncol 21:631-637, 2003

35. Chan AT, Leung SF, Ngan RK, et al: Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. J Natl Cancer Inst 97:536-539, 2005

36. Au E, Tan EH, Ang PT: Activity of paclitaxel by three-hour infusion in Asian patients with metastatic undifferentiated nasopharyngeal cancer. Ann Oncol 9:327-379, 1998

37. Foo KF, Tan EH, Leong SS, et al: Gemcitabine in metastatic nasopharyngeal carcinoma of the undifferentiated type. Ann Oncol 13:150-156, 2002

38. Chua DT, Sham JS, Au GK: A phase II study of capecitabine in patients with recurrent and metastatic nasopharyngeal carcinoma pretreated with platinum-based chemotherapy. Oral Oncol 39:361-366, 2003

39. Poon D, Chowbay B, Cheung YB, et al: Phase II study of irinotecan (CPT-11) as salvage therapy for advanced nasopharyngeal carcinoma. Cancer 103:576-587, 2005

40. Leong SS, Wee J, Tay MH, et al: Paclitaxel, carboplatin, and gemcitabine in metastatic nasopharyngeal carcinoma. Cancer 103:569-575, 2005

41. Bonner JA, Giralt J, Harari PM, et al: Cetuximab prolongs survival in patients with locoregionally advanced squamous cell carcinoma of head and neck: A phase III study of high dose radiation therapy with or without cetuximab. J Clin Oncol 22:489, 2004 (suppl, abstr 5507)

42. Chan AT, Hsu MM, Goh BC, et al: Multicenter, phase II study of cetuximab in combination with carboplatin in patients with recurrent or metastatic nasopharyngeal carcinoma. J Clin Oncol 23:3568-3576, 2005

43. Soo R, Putti T, Tao Q, et al: Overexpression of cyclooxygenase-2 in nasopharyngeal carcinoma and association with epidermal growth factor receptor expression. Arch Otolaryngol Head Neck Surg 131:147-152, 2005