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

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BACKGROUND. The aim of this trial was to compare the outcome achieved with neoadjuvant chemotherapy followed by radiotherapy to that achieved with radiotherapy alone for patients with locoregionally advanced undifferentiated or poorly differentiated nasopharyngeal carcinoma (NPC) meeting one of the following criteria: Ho's T3 disease, Ho's N2–N3 disease, or lymph node size $\geq$3 cm.

METHODS. Between September 1989 and August 1993, 334 patients were enrolled in the study, with equal numbers of patients randomized to the neoadjuvant chemotherapy arm (CT arm) and the radiotherapy arm (RT arm). Neoadjuvant chemotherapy consisting of 2–3 cycles of cisplatin (60 mg/m^2 on Day 1) and epirubicin (110 mg/m^2 on Day 1) followed by radiotherapy was given to the CT arm. For radiotherapy, a dose of 66–74 gray (Gy) (median, 71 Gy) was delivered to the primary tumor and 60–76 Gy (median, 66 Gy) to the neck. Two hundred eighty-six eligible patients completed the treatment and were evaluable for treatment response (134 in the CT arm, 152 in the RT arm). All patients were included in the survival analysis based on the intention to treat. The median follow-up was 30 months for the whole cohort and 41 months for the surviving patients.

RESULTS. Analysis of the 334 patients based on the intention to treat showed no significant difference in relapse free survival (RFS) or overall survival (OS) between the 2 treatment arms (3-year RFS rate: 48% in the CT arm vs. 42% in the RT arm, $P = 0.45$; 3-year OS rate: 78% vs. 71%, $P = 0.57$). In an efficacy analysis based on only the 286 evaluable patients, a trend of improved RFS favoring the CT arm was observed (3-year RFS rate: 58% vs. 46%, $P = 0.053$), with again no significant difference in OS (3-year OS rate: 80% vs. 72%, $P = 0.21$). In the subgroup of 49 patients with bulky neck lymph nodes >6 cm, improved RFS (3-year RFS rate: 63%

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vs. 28%, $P = 0.026$) and OS (3-year OS rate: 73% vs. 37%, $P = 0.057$) were observed, favoring the CT arm.

CONCLUSIONS. This multicenter randomized study did not demonstrate any benefit with the addition of cisplatin-epirubicin neoadjuvant chemotherapy for patients with locoregionally advanced nasopharyngeal carcinoma; therefore routine administration of neoadjuvant chemotherapy to this target group cannot be recommended. Although the overall incidence of recurrence was reduced with the addition of chemotherapy in the efficacy analysis, the overall survival was not affected. A more effective chemotherapy regimen, the selection of an appropriate target group, and the use of an alternative strategy for combining chemoradiotherapy should be explored in future trials. [See editorial on pages 2255–8, this issue.] ***Cancer* 1998;83:2270–83.**

KEYWORDS: nasopharyngeal carcinoma, neoadjuvant chemotherapy, radiotherapy, relapse free survival, overall survival, recurrence, distant metastasis, cisplatin, epirubicin.

Nasopharyngeal carcinomas (NPCs) have a natural history distinct from that of other squamous cell carcinomas of the head and neck. Up to 80% of patients with NPC have evidence of cervical lymph node metastases at presentation.[1–2] A higher incidence of distant metastases has also been observed among patients with NPC, with a substantial number eventually experiencing distant failure despite lasting local control. Between 5% and 10% of the patients have distant metastases at presentation.[3–5] In one large series of NPC patients, the distant failure rate was 29%; in 17%, distant metastases were the only sites of failure.[3] The incidence of distant failure was even higher in patients with advanced stage disease. Another large series reported a 5-year distant failure rate of 30% for patients with locoregional control.[6] Both the advanced primary and lymph node diseases are significant predictors of distant failure.[3,5–6]

NPC is both radiosensitive and chemosensitive, yet standard treatment of NPC is still radiotherapy, with the role of chemotherapy still uncertain. Despite improvements in imaging and radiotherapy, treatment results for patients with locoregionally advanced disease after radiotherapy alone remain poor.[7–10] Numerous Phase I/II studies have demonstrated high response rates of NPC to a variety of chemotherapeutic agents.[11–18] High rates of response to chemotherapy were also commonly observed for patients with recurrent and metastatic disease, and long term survival after chemotherapy for distant metastases has been reported.[19–21] Thus, it is logical to test the benefit of adding neoadjuvant chemotherapy to radiotherapy in the treatment of patients with locoregionally advanced NPC.

Active chemotherapeutic agents in NPC include cisplatin, 5-fluorouracil (5-FU), doxorubicin, epirubicin, bleomycin, mitoxantrone, methotrexate, and Vinca alkaloids.[19–27] Rossi et al. reported a randomized study of 229 patients comparing radiotherapy alone and radiotherapy followed by 6 cycles of adjuvant chemotherapy consisting of vincristine, cyclophosphamide, and doxorubicin, and noted no significant differences in relapse free survival or overall survival.[28] However, the regimen did not include cisplatin, which remains the most active single agent in NPC. Other single-institution, randomized studies using cisplatin-based regimens were limited by the relatively small numbers of patients in their cohorts.[29–30] To define the role of chemotherapy in NPC, a large scale clinical trial with sufficient power to test a highly effective chemotherapy regimen is needed, because any survival benefit associated with the addition of chemotherapy is likely to be modest.

The combination of epirubicin and cisplatin as neoadjuvant chemotherapy was studied in a Phase II trial by the Asian-Oceanian Clinical Oncology Association. A high response rate was observed after chemotherapy prior to the beginning of radiotherapy, with an overall response rate of 89% and a complete response rate of 26%, and mild toxicity (data not published). High response rates similar to that achieved with the cisplatin-epirubicin combination, and acceptable toxicity, were also reported by other authors.[31–32] Based on these preliminary results, we decided to carry out a multicenter Phase III study comparing this combination chemotherapy as neoadjuvant treatment prior to radiotherapy with standard radiotherapy alone for patients with locoregionally advanced NPC. The objective of the current study was to determine whether treatment outcomes for patients with locoregionally advanced NPC could be improved with the addition of cisplatin-based neoadjuvant chemotherapy.

TABLE 1
Comparison of Ho's and UICC/AJCC Stage Classifications for Nasopharyngeal Carcinoma

Ho's stage classification	UICC/AJCC stage classification
T1: tumor confined to the nasopharynx	T1: tumor limited to one subsite of nasopharynx T2: tumor invades more than one subsite of nasopharynx T3: tumor invades nasal cavity and/or oropharynx
T2: tumor extended to the nasal fossa, oropharynx, or adjacent muscles or nerves below the base of the skull	
T3: tumor extended beyond T2 limits	T4: tumor invades skull base and/or cranial nerves
N0: no palpable neck lymph nodes	N0: no regional lymph node metastasis
N1: lymph nodes wholly in the upper cervical level, limited below by the neck crease extending laterally and backwards from or just below the thyroid notch	N1: metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2: palpable lymph nodes between the crease and the supraclavicular fossa, the upper limit being a line joining the upper margin of the sternal end of the clavicle and the apex of an angle formed by the lateral surface of the neck and the superior margin of the trapezius	N2: metastasis in a single ipsilateral node, >3–6 cm in greatest dimension; or in multiple ipsilateral nodes, none >6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension N3: metastasis in a lymph node >6 cm in greatest dimension
N3: palpable lymph nodes in the supraclavicular fossa and/or skin involvement in the form of carcinoma en cuirasse or satellite nodules above the clavicle	
M1: hematogenous metastasis and/or involvement of the skin or lymph nodes extending below the clavicles	M1: presence of distant metastasis
Stage grouping:	
Stage I T1N0M0	Stage I T1N0M0
Stage II T2 and/or N1, M0	Stage II T2N0M0
Stage III T3 and/or N2, M0	Stage III T3 and/or N1, M0
Stage IV T1–3 and N3, M0	Stage IV T4, any N, M0, any T, N2 or N3, M0, any T, any N, M1
Stage V any T, any N, M1	

UICC: International Union Against Cancer; AJCC: American Joint Committee on Cancer.

PATIENTS AND METHODS

This was a multicenter, prospective, randomized, open-labeled Phase III study comparing neoadjuvant chemotherapy with radiotherapy alone for patients with locoregionally advanced NPC. A total of 334 patients at 6 participating treatment centers were enrolled, as follows: Hong Kong (1 center, 183 patients); Thailand (3 centers, 128 patients); Malaysia (1 center, 13 patients); and Indonesia (1 center, 10 patients). Patients were staged according to Ho's stage classification.[33] A comparison of Ho's system and the International Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC)[34] stage classification system for NPC is shown in Table 1.

Eligibility Criteria

Eligibility criteria for entry into the trial included Ho's Stage III/IV disease, or any stage with a neck lymph node ≥3 cm in greatest dimension. Only patients with histologically proven undifferentiated or poorly differentiated carcinoma were eligible. Patients should not have had previous treatment for their disease and were required to have a pretreatment Eastern Cooperative Oncology Group performance status of ≤2. Adequate bone marrow reserve was required, with a leukocyte count of at least 4000/μL and a platelet count of at least 100,000/μL. Serum bilirubin less than 1.5 mg/dL, serum creatinine less than 1.5 mg/dL, and creatinine clearance greater than 60 mL/min were also required. Patients also had to have a normal electrocardiograph. Patients with a history of cardiac or renal disease were excluded. All patients gave written consent prior to treatment.

Pretreatment Evaluation

Pretreatment evaluation included complete physical examination, complete blood count, biochemical profile, creatinine clearance, and electrocardiograph. All patients had fiberoptic endoscopy and biopsy of the nasopharynx and computed tomography of the nasopharynx and neck for staging of the primary disease. Magnetic resonance imaging was not performed because of limited accessibility. Metastatic workup included chest radiograph and imaging of liver by ultrasound or computed tomography in all patients. Bone scan was not routinely performed and was restricted to those with bone pain, elevated serum alkaline phosphatase, or lymph node size ≥8 cm. As a result, only 43 patients (24 in the CT arm and 19 in the RT arm) had bone scan performed as part of their metastatic workup.

Treatment Arms

Eligible patients were randomized into two arms: neoadjuvant chemotherapy, consisting of 2–3 cycles of epirubicin and cisplatin, followed by radiotherapy (CT arm), and radiotherapy alone (RT arm). In the CT arm, reassessment was performed at the end of two cycles; patients with at least partial response were given one more cycle of chemotherapy followed by radiotherapy, whereas further chemotherapy was omitted for patients with less than partial response. If progressive disease was documented at any time during chemotherapy, further cycles were omitted.

Randomization

Randomization was performed in a central office, using a computer-generated randomization code. A separate randomization code was generated for each participating center. Randomization was also stratified into three groups, according to the greatest dimension of neck lymph nodes measured at baseline: ≤3 cm, >3–6 cm, and >6 cm.

Neoadjuvant Chemotherapy

The chemotherapy regimen consisted of cisplatin at a dose of 60 mg/m^2 on Day 1 and epirubicin 110 mg/m^2 on Day 1, repeated every 21 days. All patients had prehydration with intravenous fluids for 1 day prior to chemotherapy. Cisplatin was administered as an infusion over 4 hours, and epirubicin was administered as a bolus injection. Antiemetic prophylaxis was routinely given and usually consisted of metoclopramide 1 mg/kg i.v., dexamethasone 10–20 mg i.v., and diphenhydramine 50 mg i.v. given prior to chemotherapy and repeated every 2 hours for 2 more doses.

A pretreatment white blood cell count (WBC) of at least 4000/μL and a platelet count of at least 100,000/μL were required before the first cycle of chemotherapy, and a WBC of at least 3000/μL and a platelet count of at least 70,000/μL were required before subsequent cycles. For subsequent cycles, if a pretreatment WBC of 3000 to less than 4000/μL or a platelet count of 70,000 to less than 100,000/μL was observed, then the dose of chemotherapy was reduced by 50%. If the bone marrow function remained inadequate (WBC <3000/μL or platelet count <70,000/μL), then chemotherapy was postponed for 7 days, up to a maximum delay of 14 days. In patients who had inadequate bone marrow function even after a delay of 14 days, further chemotherapy was omitted and radiotherapy was instead administered.

When hepatic dysfunction occurred, the dose of epirubicin was modified as follows: for serum bilirubin <2 mg/dL or liver enzymes (serum glutamic–oxaloacetic transaminase/serum glutamic–pyruvic transamiase) less than twice normal, there was no dose reduction; for bilirubin 2–3 mg/dL or liver enzymes 2–5 times normal, the dose of epirubicin was decreased by 50%; for bilirubin >3 mg/dL or liver enzymes >5 times normal, epirubicin was withheld.

The dose of cisplatin was modified according to serum creatinine level, as follows: for serum creatinine <1.5 mg/dL, there was no dose reduction; for creatinine 1.5–2 mg/dL, the cisplatin dose was reduced by 50%; for creatinine >2 mg/dL, cisplatin was withheld.

Radiotherapy

Radiotherapy began within 3 weeks of randomization in the RT arm and within 3 weeks of completion of the last cycle of chemotherapy in the CT arm. Irradiation fields were chosen according to extension of the tumor. Neck irradiation was given to all patients irrespective of T and N classification. Megavoltage photons (4 MV or cobalt-60) were used to treat the primary tumor and neck lymph nodes. Of those who completed the radiotherapy per protocol, 110 were treated with 5 fractions per week of a conventional fraction dose of 2 Gy, whereas 176 were treated with a hypofractionated regimen, and the latter employed different fractionation in a 2-phase treatment: 2.5 Gy per fraction and 4 fractions per week in Phase I, followed by 3.5 Gy per fraction and 3 fractions per week in Phase II. The conventional dose to the nasopharynx calculated by TDF ranged from 66 to 74 Gy (median, 71 Gy), with 36% receiving a dose between 66 and 70 Gy and 64% receiving >70 to 74 Gy. The dose to the neck ranged from 60 to 76 Gy (median, 66 Gy), with 82.5% receiving a dose between 60 and 66 Gy and 17.5% receiving >66 to 76 Gy; the latter included an additional boost dose to palpable residual lymph nodes at the end of radiotherapy. At least 60 Gy was delivered to cover the cervical lymphatic chain irrespective of N classification. During the initial design of the study, it was decided that instead of using a standard radiotherapy protocol for all the treatment centers, each would instead be allowed to follow their usual practice of radical radiotherapy for NPC. Although the radiation technique, dose, and fractionation differed from one center to another, each center was consistent in its own radiation treatment protocol, so that patients from the same center were treated using the same protocol irrespective of the treatment arm to which they were assigned. In addition, randomization was performed separately for each center to ensure comparability between the two arms.

Response Assessment and Follow-Up

Criteria for response were as follows: Complete response was defined as complete regression of all evidence of tumor. Partial response was defined as an estimated decrease in tumor size of 50% or more. In measurable disease, this represented a 50% decrease in the sum of the products of the two longest diameters of all measurable lesions. No change was defined as no significant change or any change in tumor size that was less than a partial response but not large enough to be considered progressive disease. Progressive disease was defined as the appearance of any new lesions or an increase of 25% or more in existent lesions.

Response to chemotherapy was assessed by clinical examination at the end of each cycle. Computed tomography was not performed for the assessment of chemotherapy response. During each assessment, the nasopharynx was examined and any palpable lymph nodes measured. As tumor size in the nasopharynx could not be reliably measured by mirror examination, the assessment of the primary tumor response was rather limited, and only a crude estimation was possible; thus, the reported response rate of primary tumor to chemotherapy should be interpreted as such. Responses in the nasopharynx and the neck were documented separately. In patients with assessable disease in both the primary site and cervical lymph nodes, the worst response was recorded as the overall response to chemotherapy.

Response after radiotherapy was assessed at 3 months after completion of the treatment. This required endoscopy and biopsy of the nasopharynx, as well as computed tomography if it was indicated. Patients with complete response to treatment were followed up at least every 3 months. Follow-up clinical examinations included a mirror examination of the nasopharynx. Endoscopy was reserved for those with inadequate mirror examination or suspicious findings. Chest radiographs were taken yearly, whereas computed tomography and other investigations such as bone scans were performed when clinically indicated.

Salvage Treatment

Whenever possible, salvage treatments were given to patients after documented relapse or when disease was persistent. The treatments employed included a second course of external radiotherapy, brachytherapy using transpalatal gold grain implantation, intubation or iridium wire implants, chemotherapy, and surgery.

Statistical Analysis

The following endpoints were used for assessment in the current analysis: chemotherapy response, overall treatment response, relapse free survival (RFS), and overall survival (OS). Chemotherapy response and overall treatment response in both arms were compared using the chi-square test. RFS and OS rates were calculated according to the Kaplan–Meier product-limit method.[35] Time was measured from the date of randomization until the time of first failure, or the most recent follow-up if no relapse was detected. Patients who relapsed but for whom salvage therapy was successful were still considered to have experienced failure at the time of event occurrence. For patients with persistent disease, the length of relapse free survival was defined as zero. Significance of differences between survival curves was calculated by the log rank test; a P value of 0.05 or less was considered statistically significant. It was determined that in order to detect a 15% RFS or OS gain from neoadjuvant chemotherapy with 0.9 power and 0.05 α-type error, a total of 320 patients (160 in each arm) would be required.

RESULTS

Patient Population

Between September 1989 and August 1993, 334 patients were enrolled in the study, with 167 patients randomized to each treatment arm. Forty-eight patients were considered inevaluable for treatment response because they had had no treatment, incomplete treatment, or a major protocol violation. Of these, 18 patients (9 in the CT arm, 9 in the RT arm) did not receive any treatment: 2 patients died before treatment was started, and 16 patients were lost before the assigned treatment was started. Twenty patients (17 in the CT arm, 3 in the RT arm) did not complete their treatment: 2 patients died during chemotherapy, 12 patients discontinued treatment during chemotherapy, and 6 discontinued treatment during radiotherapy. Ten patients (5 in the CT arm, 5 in the RT arm) had major protocol violations: 2 had ineligible stage and 8 had radiation treatments that were considered inadequate. Thus, 134 patients (80%) in the CT arm and 152 patients (91%) in the RT arm had completed the treatment in accordance with the protocol and were considered evaluable for treatment response. All of the 334 patients enrolled in the study were included in the analysis of RFS and OS based on the intention to treat. An efficacy analysis was also performed, including only the 286 evaluable patients. One hundred fifty-five patients were evaluable for chemotherapy response and toxicity, and 302 patients were evaluable for radiation toxicity.

TABLE 2
Pretreatment Characteristics

	All patients (n = 334)		Evaluable patients (n = 286)	
	CT arm	RT arm	CT arm	RT arm
	No. of patients (%)		No. of patients (%)	
Total	167	167	134	152
Age (yrs)				
≤40	52 (31)	51 (30.5)	44 (33)	44 (29)
>40	115 (69)	116 (69.5)	90 (67)	108 (71)
Median	47	46	47	47
Gender				
Male	122 (73)	121 (72.5)	100 (75)	109 (72)
Female	45 (27)	46 (27.5)	34 (25)	43 (28)
Ho's stage				
II	11 (7)	12 (7)	8 (6)	11 (7)
III	124 (74)	123 (74)	103 (77)	116 (76)
IV	32 (19)	32 (19)	23 (17)	25 (17)
T-classification				
T1	48 (29)	44 (26)	42 (31)	40 (26)
T2	41 (24)	48 (29)	29 (22)	43 (28)
T3	78 (47)	75 (45)	63 (47)	69 (45)
N-classification				
N0	16 (10)	11 (7)	15 (11)	11 (7)
N1	24 (13)	24 (14)	18 (14)	21 (14)
N2	96 (58)	100 (60)	78 (58)	95 (62.5)
N3	31 (19)	32 (19)	23 (17)	25 (16.5)
Lymph node size				
≤3 cm	46 (28)	46 (28)	38 (28)	40 (26)
>3–6 cm	87 (52)	87 (52)	74 (55)	85 (56)
>6 cm	34 (20)	34 (20)	22 (17)	27 (18)
ECOG PS				
0	134 (80)	136 (81)	110 (82)	126 (83)
1	29 (17)	28 (17)	21 (16)	23 (15)
2	4 (3)	3 (2)	3 (2)	3 (2)

CT arm: neoadjuvant chemotherapy followed by radiotherapy; RT arm: radiotherapy alone; ECOG PS: Eastern Cooperative Oncology Group performance status.

Both treatment arms were well balanced in terms of patient characteristics and disease stage (Table 2). The median duration of follow-up was 30 months (range, 0.1–77 months). The median duration of follow-up for living patients was 41 months (range, 5–77 months).

Neoadjuvant Chemotherapy

One hundred fifty-five patients received chemotherapy. Eleven patients received 1 cycle of chemotherapy only, 24 patients received 2 cycles, and 120 patients received 3 cycles. The responses to chemotherapy are summarized in Table 3. An overall response rate of 84% was observed, with a complete response rate of 18%. Neck lymph node disease had a higher complete response rate to chemotherapy (38%) compared with the primary tumor (26%). Only 16% of patients had no documented response to chemotherapy. No patients had a complete response after 1 cycle of chemotherapy, whereas 3% and 24% of patients had a complete response after 2 and 3 cycles of chemotherapy, respectively.

TABLE 3
Response to Chemotherapy (n = 155)

	No. (%) of patients		
Response	Nasopharynx	Neck nodes	Nasopharynx + neck lymph nodes
Not assessable	24	23	38
Assessable	131	132	117
Complete response	34 (26%)	50 (38%)	21 (18%)
Partial response	86 (66%)	64 (49%)	77 (66%)
No change	9 (7%)	16 (12%)	16 (14%)
Progression	2 (1%)	2 (1%)	3 (2%)

TABLE 4
Toxicity of Chemotherapy (WHO Grading, Using the Worst Toxicity Recorded per Patient)

	No. of patients			
Type of toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Hair loss	6	94	40	1
Nausea/vomiting	16	84	42	—
Infection	4	3	1	1
Anemia	53	25	3	—
Thrombocytopenia	1	1	—	—
Leukopenia	24	13	3	1

WHO: World Health Organization.

Toxicity

The toxicity of chemotherapy is summarized in Table 4. The main nonhematologic toxicities were alopecia and nausea/vomiting, with 28% of patients experiencing Grade 3–4 hair loss or Grade 3 nausea/vomiting. Hematologic toxicity was mild; only 2% of the patients developed Grade 3 leukopenia and 1% developed Grade 4 leukopenia. Febrile neutropenia occurred in 3% of the patients, reflecting a generally mild myelotoxicity, although there were 2 toxic deaths (1%), both due to neutropenic sepsis.

The incidence of acute radiation toxicities did not differ significantly between the two treatment arms. Grade 2–3 mucositis occurred in 29% of patients in the CT arm compared with 26% in the RT arm. Grade 2–3 skin reaction affected 6% of patients in the CT arm compared with 11% in the RT arm. There were no Grade 4 cases of mucositis or skin reactions in either treatment arm. No significant differences in acute radiation toxicities were observed between those treated

by conventional fractionation and those who received a hypofractionated regimen.

Overall Treatment Response

At 3 months after completion of treatment, 126 patients in the CT arm and 132 patients in the RT arm achieved complete response. The complete response rate was higher in the CT arm (94% vs. 87%), the difference being statistically significant ($P = 0.041$).

Relapse Free Survival

The median RFS for the whole group of patients was 26 months, and the 3-year RFS rate was 45%. There was no significant difference in RFS between the 2 treatment arms: for the CT arm, the median RFS was 27 months, and the 3-year rate was 48%. For the RT arm, the median RFS was 26 months, and the 3-year rate was 42% ($P = 0.45$, Fig. 1).

Overall Survival

The median OS for the whole group had not been reached at the time of analysis. The 3-year OS rate for the whole group was 69%. A 3-year OS rate of 78% was observed in the CT arm compared with 71% in the RT arm (Fig. 2); the difference was not statistically significant ($P = 0.57$). Sixty-three patients (22%) had died of NPC at the time of analysis.

Subgroup Analysis

As more patients in the CT arm did not complete the treatment (16% in the CT arm vs. 7% in the RT arm), an efficacy analysis was performed that included only the 286 patients who were evaluable for treatment response. In this subgroup analysis, the median RFS was 50 months in the CT arm compared with 29 months in the RT arm, and the 3-year RFS rate was 58% in the CT arm compared with 46% in the RT arm (Fig. 3); this difference was of marginal statistical significance ($P = 0.053$). Sixty patients (45%) in the CT arm had relapsed at the time of analysis, compared with 85 patients (56%) in the RT arm. No significant difference in OS was observed between the two treatment arms. For the CT arm, the 3-year OS rate was 80%, compared with 72% in the RT arm ($P = 0.21$, Fig. 4).

Analysis was also performed according to the size of neck lymph nodes: ≤3 cm, >3–6 cm, and >6 cm. No significant differences in RFS and OS were observed between the 2 treatment arms among those with lymph size ≤3 cm or >3–6 cm. In the subgroup with lymph node size >6 cm, however, significantly improved RFS favoring the CT arm was observed. In this subgroup of 49 patients, a median RFS of 48 months and a 3-year RFS rate of 63% were observed in the CT arm, compared with a median RFS of 11 months and a 3-year RFS rate of 28% in the RT arm ($P = 0.026$, Fig. 5). Patients in the CT arm also had better overall survival, with a 3-year OS rate of 73% compared with 37% in the RT arm; this difference was marginally significant ($P = 0.057$, Fig. 6). The median OS was 27 months in the RT arm, whereas the median OS in the CT arm had not been reached at the time of analysis. Examination of this subgroup revealed comparability of the distribution of major prognostic factors in the 2 treatment arms (T and N classification, Ho's stage, gender, and performance status), except that more patients in the CT arm were age ≤40 years (46% vs. 19%).

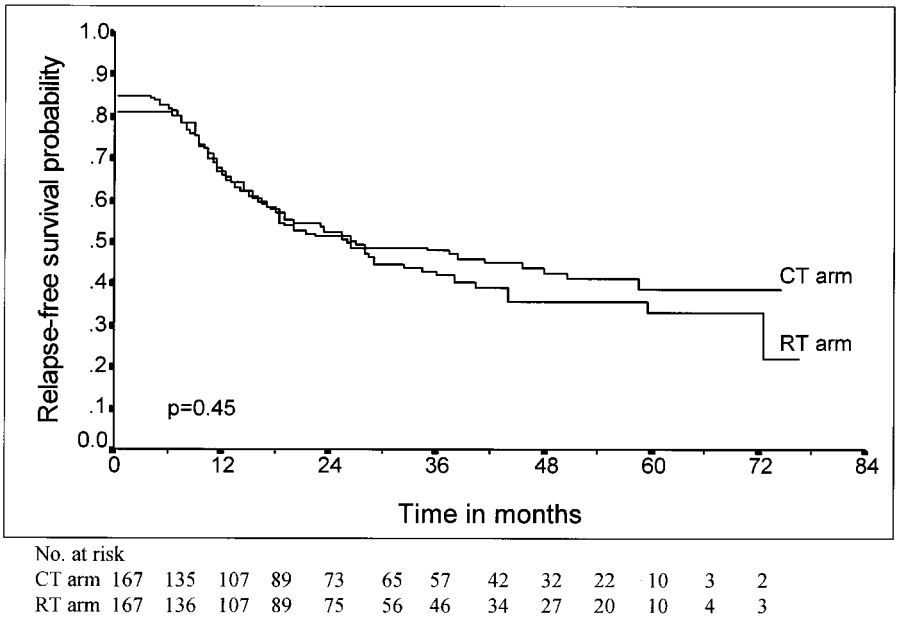
Patterns of Treatment Failure

The patterns of treatment failure are summarized in Table 5, which lists the first failure site for both treatment arms. The figures for failure in the nasopharynx and the neck include those patients with persistent locoregional disease. Table 5a summarizes the failure pattern for the 286 evaluable patients. The incidence of local, lymph node, and distant failure were all reduced in the CT arm, although the differences were not statistically significant. There was also no significant difference in the distribution of failure sites between the two treatment arms, with both locoregional and distant failure occurring in approximately the same proportion. With respect to distant metastases, the most common site involved was bone (40%), followed by lung (33%) and liver (26%). Again, no difference was found in the distribution of distant failure sites between the two treatment arms. The median time to development of distant metastasis in the CT arm was 11.4 months, which was not significantly different from the 12.5 months observed in the RT arm ($P = 0.57$).

Table 5b summarizes the failure pattern in the subgroup with bulky neck lymph nodes (>6 cm), again including only the evaluable patients. Within this subgroup, there was no significant difference in the incidence of lymph node or distant failure. The median time to distant metastasis was 11.1 months in CT arm compared with 12.1 months in RT arm. On the other hand, the incidence of local failure was significantly lower in the CT arm (8%) compared with the RT arm (34.5%). Thus, the improved survival observed in this subgroup was mainly due to the improvement of local control rather than a decline in distant failure.

DISCUSSION

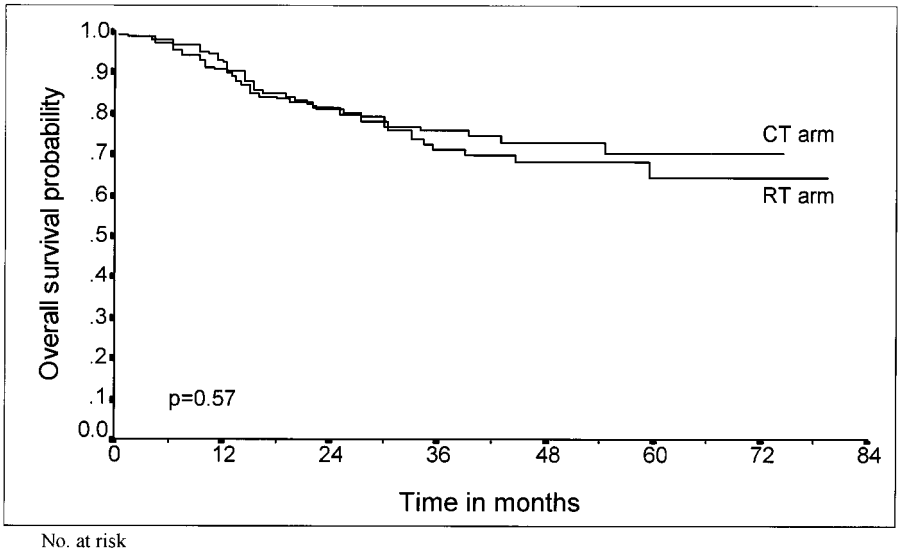
The chemotherapy regimen used in the current study was effective. The 84% response rate to chemotherapy was consistent with the best results obtained in other



No. at risk

CT arm	167	135	107	89	73	65	57	42	32	22	10	3	2
RT arm	167	136	107	89	75	56	46	34	27	20	10	4	3

FIGURE 1. Relapse free survival, according to treatment arm, for all enrolled patients is shown (CT arm: neoadjuvant chemotherapy followed by radiotherapy, n = 167; RT arm: radiotherapy alone, n = 167).



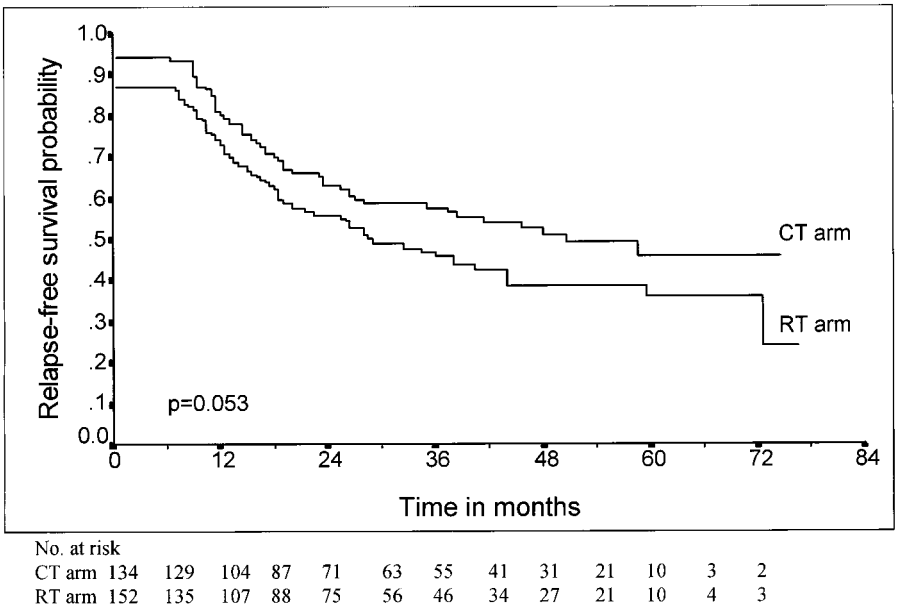
No. at risk

CT arm	167	141	129	107	92	76	65	50	38	27	12	3	2
RT arm	167	148	128	107	92	76	55	44	37	27	13	5	3

FIGURE 2. Overall survival, according to treatment arm, for all enrolled patients is shown (CT arm:neoadjuvant chemotherapy followed by radiotherapy, n = 167; RT arm: radiotherapy alone, n = 167).

studies using cisplatin-based regimens, although the 18% complete response rate was lower than in our previous Phase II study using the same regimen. Lymph node disease was associated with a higher complete response rate (38%) than the primary tumor (26%); both responses were assessed by clinical examination alone without the use of CT. The combination of cisplatin and epirubicin as neoadjuvant chemotherapy has also been studied by other authors. Using a higher dose intensity than ours, Rahal et al. and Lage et al. reported a higher response rate (96–98%), though the complete response rate was quite variable (4–58%), the latter being dependent on the extent of assessment for definition of complete response. Although clinical examination alone is often accurate enough to detect response in lymph node disease, the same does not apply to the primary tumor; thus, if CT assessment of response to chemotherapy were performed, the complete response rate in the primary tumor could be lower than with clinical examination alone.

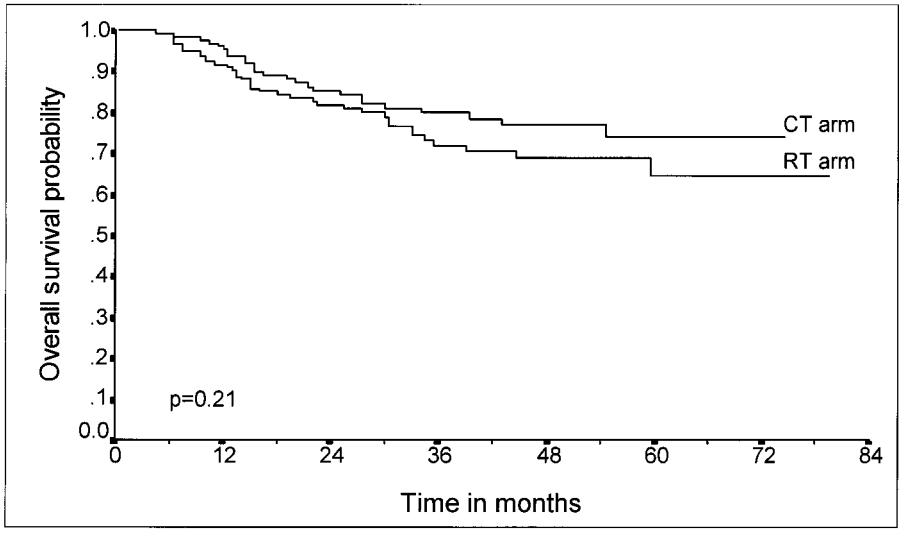
Our data show that twice as many patients in the RT arm had persistent disease at the end of treatment compared with those in the CT arm. This is perhaps



No. at risk

CT arm	134	129	104	87	71	63	55	41	31	21	10	3	2
RT arm	152	135	107	88	75	56	46	34	27	21	10	4	3

FIGURE 3. Relapse free survival, according to treatment arm, for evaluable patients is shown (CT arm: neoadjuvant chemotherapy followed by radiotherapy, n=134; RT arm: radiotherapy alone, n=152).



No. at risk

CT arm	134	133	123	104	89	74	63	49	37	26	12	3	2
RT arm	152	147	128	106	92	76	55	44	37	28	13	5	3

FIGURE 4. Overall survival, according to treatment arm, for evaluable patients is shown (CT arm: neoadjuvant chemotherapy followed by radiotherapy, n=134; RT arm: radiotherapy alone, n=152).

not surprising given the observed high rate of response to neoadjuvant chemotherapy. A high complete response rate after radiotherapy was achieved in both arms, a result which may have been related in part to the administration of high radiation doses at some treatment centers. On the other hand, the reported complete response rate may have been falsely high, as the posttreatment computed tomography very often did not become completely normal, and complete response was sometimes defined only by negative fiberoptic endoscopy and biopsy as well as by the absence of palpable neck lymph nodes.

In the current study, a substantial number of enrolled patients did not receive or complete the treatment, and this occurred more frequently in the CT arm. In fact, 14% of patients in CT arm did not receive radiotherapy compared with 5% in the RT arm. Although no significant difference in the treatment outcome was evident in survival analysis when all enrolled patients were included, the fact that a relatively higher proportion of patients in the CT arm did not complete the treatment would dilute any beneficial effect associated with neoadjuvant chemotherapy. An efficacy analysis based on a subgroup of evaluable

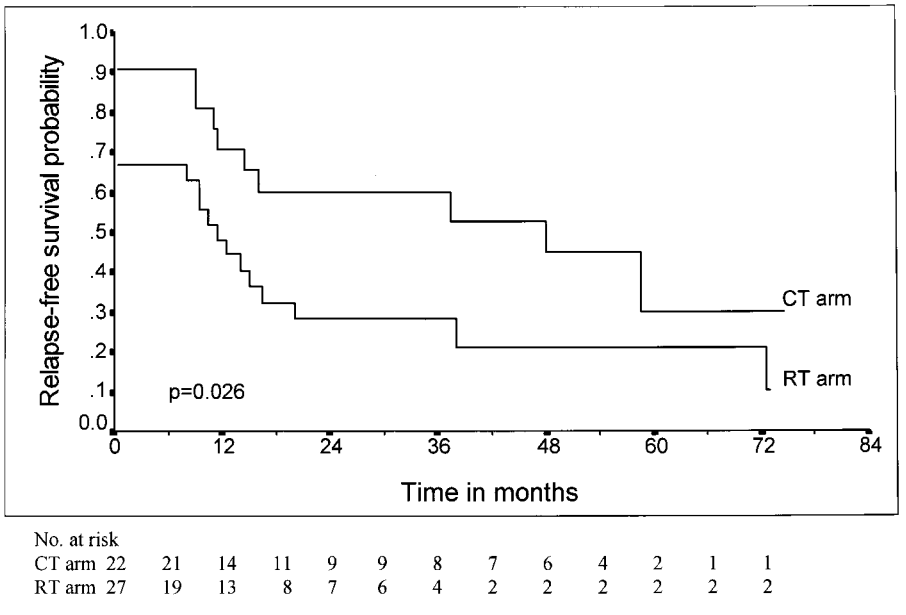


FIGURE 5. Relapse free survival, according to treatment arm, is shown for the subgroup with lymph node size >6 cm (CT arm: neoadjuvant chemotherapy followed by radiotherapy, n = 22; RT arm: radiotherapy alone, n = 27).

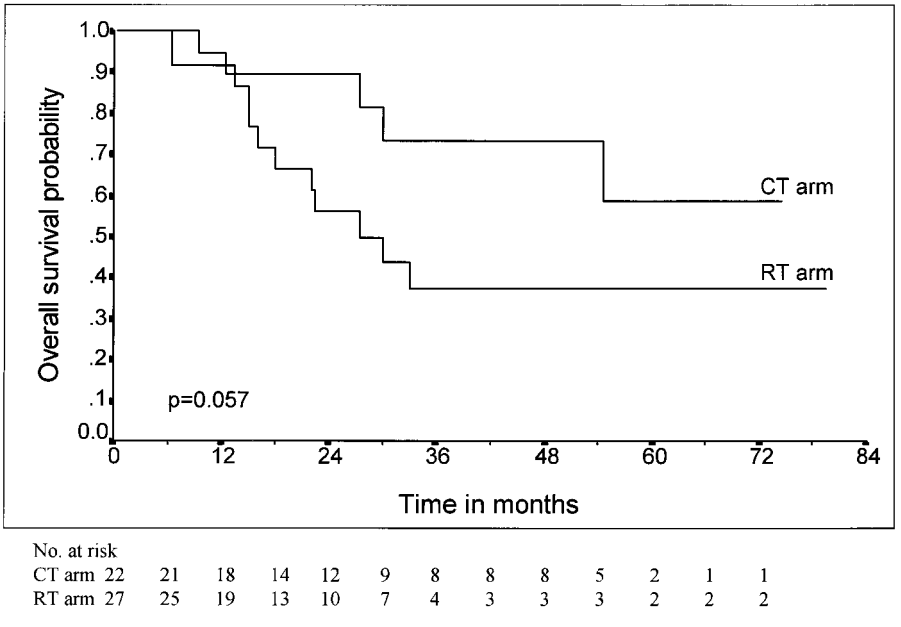


FIGURE 6. Overall survival, according to treatment arm, is shown for the subgroup with lymph node size >6 cm (CT arm: neoadjuvant chemotherapy followed by radiotherapy, n = 22; RT arm: radiotherapy alone, n = 27).

patients was therefore performed to investigate further the efficacy of chemotherapy, though the result has to be interpreted in this context. Although this may have introduced bias, the remaining evaluable patients in the two treatment arms were still comparable in terms of pretreatment characteristics and prognostic factors. Our findings, from the subgroup analysis, suggest that the addition of chemotherapy does reduce the overall incidence of recurrence and that disease tends to relapse at a later time after chemotherapy. These gains, however, do not translate into an overall survival benefit. One possible explanation is the fairly high success rate of salvage treatment, which indicates that patients with disease in the nasopharynx or neck may still be amenable to salvage treatment with either reirradiation or surgery. Furthermore, patients with locoregional disease tend to survive longer than those with distant failure, and a longer follow-up with enough events is needed to study the survival outcome. Our findings also point to the importance of defining a high risk patient group that may benefit from the combined modality treatment. It is not uncommon for NPC patients to have advanced T classification but no or early stage cervical

TABLE 5
Patterns of Failure in the Two Treatment Arms

a) Evaluable patients (n = 286)

	CT arm (n = 134)	RT arm (n = 152)	
	No of patients (%)		*P* value
Nasopharynx	19 (14%)	27 (18%)	0.35[a]
Neck lymph nodes	12 (9%)	18 (12%)	0.38[a]
Distant	27 (20%)	38 (25%)	0.27[a]
Multiple	2 (1.5%)	2 (1.3%)	0.65[b]

b) Subgroup with neck lymph nodes >6 cm (n = 53)

	CT arm (n = 24)	RT arm (n = 29)	
	No. of patients (%)		*P* value
Nasopharynx	2 (8%)	10 (34.5%)	0.024[a]
Neck lymph nodes	1 (4%)	4 (14%)	0.24[b]
Distant	7 (29%)	7 (24%)	0.68[a]
Multiple	0	1 (3%)	0.55[b]

CT arm: neoadjuvant chemotherapy followed by radiotherapy; RT arm: radiotherapy alone.
[a] Pearson chi-square test.
[b] Fisher's exact test.

lymph node metastases, and for patients with advanced N classification but early T classification. The natural history and patterns of failure are quite different between those with predominantly advanced local disease and those with advanced lymph node disease; patients in the former group usually experience local failure, whereas patients in the latter experience distant failure. Thus, different treatment strategies should be applied to different patient subgroups, depending on their failure patterns.

The main advantage of neoadjuvant chemotherapy is the early eradication of distant micrometastases, and, given the high distant failure rate associated with NPC, it is logical to expect a decline in distant failure with the use of neoadjuvant chemotherapy. There are several possible reasons why neoadjuvant chemotherapy was not effective in reducing distant metastasis in the current study. First, three cycles of neoadjuvant chemotherapy may not have been sufficient to eradicate all the distant micrometastases, and prolonged chemotherapy may have been needed to reduce the incidence of distant metastasis. The use of more cycles in the neoadjuvant setting, on the other hand, would probably have allowed too much accelerated repopulation of surviving tumor cells and compromised the local control that could be achieved with subsequent radiotherapy. The addition of chemotherapy during or after radiotherapy may have overcome this limitation. Second, the chemotherapeutic agents and the dose we administered may have been inadequate. In this study, we elected the use of a lower dose of cisplatin (60 mg/m^2; total dose, 180 mg/m^2) in combination with a higher dose of epirubicin (110 mg/m^2), hoping that the tested regimen would be at least as effective as the standard regimen of cisplatin and 5-FU but less toxic due to a lower total cisplatin dose. Given that the combination of cisplatin and 5-FU still represents the standard chemotherapy regimen for metastatic NPC, and that the usual dose of cisplatin is 100 mg/m^2 per cycle instead of 60 mg/m^2 as in our study, one may question whether the combination of chemotherapeutic agents as well as the dosage we administered are indeed adequate. The high response rate to neoadjuvant chemotherapy observed in the current study was, however, in agreement with results achieved with other cisplatin-based regimens, and reports from other studies using a higher dose of cisplatin (total dose, 200–300mg/m^2) in combination with epirubicin or 5-FU also failed to demonstrate any survival benefit or reduction in distant metastasis.[29,36] Third, many of our patients had both advanced T and N classifications, and the subsequent clinical course may have been dominated by the status of local disease. Thus, the benefit of chemotherapy in the treatment of distant metastasis, if any, may be more easily demonstrated in patients with a predominant high risk of distant failure (early T classification but advanced N classification). This may also partly explain why our patients with bulky neck lymph nodes, many of whom also had advanced T classification, had improved outcome, mainly due to improved local control rather than reduced incidence of distant failure after chemotherapy.

In another large multicenter Phase III trial conducted by the International Nasopharynx Cancer Study Group, which also studied the role of neoadjuvant chemotherapy in NPC, a significantly better 3-year disease free survival rate (58% vs. 35%) was observed in the chemotherapy arm.[36] In that study, only patients with advanced lymph node disease (classified as N2 or N3, according to UICC/AJCC criteria) were included, with no restriction on T classification. The chemotherapy regimen used was different from that in the current study and consisted of bleomycin in addition to cisplatin and epirubicin. This regimen was associated with a higher treatment toxicity and mortality (8% treatment-related death) compared with ours. Despite the use of a more toxic regimen in a study population with a higher risk of distant metastasis, no survival benefit could be demonstrated with the addition of neoadjuvant chemotherapy.

In a single-institution randomized trial reported by Chan et al., neoadjuvant and adjuvant chemother-

TABLE 6
Results of the Three Large Multicenter Randomized Trials Comparing Combined Chemotherapy and Radiotherapy versus Radiotherapy Alone for Patients with Nasopharyngeal Carcinoma

Study	Eligibility criteria	No. of patients analyzed/enrolled	Treatment regimen in the study arm	Results
International Nasopharynx Cancer Study Group: VUMCA I[36]	UICC/AJCC N2–3, M0, any T; undifferentiated carcinoma only	339/339	Bleomycin + epirubicin + cisplatin × 3 cycles followed by radiotherapy	Improved progression free survival ($P < 0.01$), no effect on overall survival
Intergroup Study 0099[37]	UICC/AJCC Stage III–IV	146/193	Cisplatin × 3 cycles concurrent with radiotherapy followed by cisplatin + 5-FU × 3 cycles	Improved progression free survival ($P = 0.0001$) and overall survival ($P = 0.0014$)
Asian-Oceanian Clinical Oncology Association: HEPI/003 (current report)	Ho's T3 or N2–3 or any stage with lymph node size ≥3 cm; poorly or undifferentiated carcinoma only	334/334	Cisplatin + epirubicin × 2–3 cycles followed by radiotherapy	No difference in relapse free and overall survival; improved relapse free survival ($P = 0.053$) in subgroup of evaluable patients, but no effect on overall survival

UICC: International Union Against Cancer; AJCC: American Joint Committee on Cancer; 5-FU: 5-fluorouracil.

apy using cisplatin and 5-FU in addition to radiotherapy was compared with radiotherapy alone in the treatment of 77 patients with advanced lymph node disease (Ho's N3 or lymph node size ≥4 cm).[29] After a short median follow-up of 28.5 months, no significant differences in survival, locoregional control, or distant failure rates could be demonstrated. That study was limited by a relatively small cohort of patients and the finding that only 54% of patients completed the adjuvant chemotherapy. It is noteworthy, however, that the aggressive radiation treatment used (external radiotherapy ± parapharyngeal boost ± intracavitary boost) resulted in a high locoregional control and survival, even in the arm that received radiotherapy alone.

A different strategy of combining chemotherapy and radiotherapy with the use of concomitant chemoradiotherapy followed by adjuvant chemotherapy was tested in a multicenter Phase III study (Intergroup Study 0099). Patients were randomized to receive cisplatin for 3 cycles concurrent with radiotherapy followed by adjuvant chemotherapy with cisplatin and 5-FU or radiotherapy alone. The eligibility criteria of the Intergroup Study required patients to have locally advanced disease and/or lymph node involvement; 41% of the patients had undifferentiated carcinoma, and the rest had squamous cell carcinoma. An interim analysis of the 146 evaluable patients revealed significant progression free and overall survival favoring the chemotherapy arm, and the study was closed early.[37] However, the reported treatment outcome for the arm in that study that received radiotherapy alone was considerably worse than in other series, which is not surprising because of the inclusion of a large proportion of patients with squamous cell carcinoma of the nasopharynx.

Table 6 summarizes the results of three large multicenter trials comparing combined chemotherapy and radiotherapy versus radiotherapy alone for patients with locally and/or regionally advanced NPC. No survival benefit could be demonstrated with the addition of neoadjuvant chemotherapy in the current study or in the International Nasopharynx Cancer Study Group trial, which represent the two largest randomized trials that have tested the role of cisplatin-based neoadjuvant chemotherapy in NPC. Our observation of improved RFS in the subgroup of evaluable patients, even if valid, was not associated with improvement in overall survival. On the other hand, significant improvement in survival was observed with the use of concurrent chemoradiotherapy and adjuvant chemotherapy in the Intergroup Study, although the impact of such treatment on patients with undifferentiated carcinoma is still uncertain. Currently, several centers in Asia are conducting clinical trials testing concurrent chemoradiotherapy for locoregionally advanced undifferentiated carcinoma of the nasopharynx, using the same protocol of the Intergroup Study, or a modification of it.

In conclusion, no survival benefit was demonstrated in the current study with the addition of neoadjuvant cisplatin-epirubicin in the treatment of patients with locoregionally advanced NPC, and routine administration of neoadjuvant chemotherapy in this target group is not recommended. Future studies should aim at defining a high risk patient group that would be likely to benefit from combined modality treatments, optimizing the dose intensity and toxicity

of combined treatments, and comparing different strategies for combining treatment modalities.

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