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ORIGINAL ARTICLE

Concurrent chemoradiation followed by adjuvant chemotherapy in patients with locoregionally advanced nasopharyngeal carcinoma in Korea

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Abstract
Purpose Concomitant approach using cisplatin and 5-fluorouracil (5-FU) has shown an excellent local control rate and significantly reduced distant metastasis in patients with locally advanced nasopharyngeal carcinoma (NPC). However, optimal schedule and dosing of chemotherapy still need to be developed to reduce distant metastasis. This retrospective study was conducted to evaluate the efficacy, toxicity, and tolerability of a concurrent chemoradiation therapy (CCRT) regimen using cisplatin and 5-FU followed by adjuvant chemotherapy (AC) in patients with locoregioanlly advanced NPC.
Methods Forty-three NPC patients who had AJCC stage T3/T4 or N2/N3 and M0 disease were evaluated. The chemotherapy during CCRT consisted of cisplatin (75 mg/m^2 on day 1) plus 5-FU (750 mg/m^2/day on day 1–5), delivered every 4 weeks for two cycles. Three cycles of AC were given with cisplatin (75 mg/m^2), epirubicin (37.5 mg/m^2) on day 1, and bleomycin (7.5 mg/m^2 bolus iv. on day 1 followed by 9 mg/m^2 on day 1–5 by continuous infusion) every 3 weeks.
Results The overall response rate after CCRT was 95% (22 CRs and 19 PRs in 43) and 100% (16 CRs and 8 PRs in 24) after AC. Grade 3/4 neutropenia, mucositis, and weight loss were observed during CCRT phase in 18, 44, and 26% of patients, respectively. AC caused grade 3/4 neutropenia and emesis in 12.5 and 20.8% of patients, respectively.
Conclusions CCRT regimen using cisplatin and 5-FU followed by three cycles of BEC chemotherapy was effective in locally advanced NPC patients, with acceptable and reversible acute toxicities.

Keywords Nasopharyngeal carcinoma · Concomitant chemoradiation · Adjuvant chemotherapy · Retrospective analysis · Korea

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Introduction

Locally advanced nasopharyngeal cancer (NPC) is a clinical challenge in spite of its unique sensitivity to chemotherapy and radiotherapy. The risk for recurrence of locoregionally advanced disease has been reported to be greater than 50% after radiation therapy alone, and approximately half of all recurrences are distant failure [1–3]. Over the last two decades, there have been several attempts to combine chemotherapy before [4–6] and after [7] the radiation to improve the treatment results in this clinical setting, but the results were not successful. More recently, the Intergroup Trial 00-99 demonstrated that the administration of effective cytotoxic chemotherapy during and after radiation therapy (RT) can clearly improve survival outcome [8, 9], and this was

confirmed in the studies from Taiwan and Hong Kong [10, 11]. In these studies, nevertheless, distant metastasis still represented more important treatment failure factor than locoregional factor in concurrent chemoradiation arm. Therefore, development of optimal treatment schedule combining effective chemotherapy with RT is warranted for better clinical outcome in those patients.

Investigators in the intergroup study used cisplatin during the RT and added three cycles of cisplatin and 5-FU as adjuvant chemotherapy [8]. Since then, incorporation of cisplatin single agent during concurrent chemoradiation therapy (CCRT) has widely been accepted as a standard in locoregionally advanced NPC patients [10–14]. Thus, only a limited number of cytotoxic agents have been tested during CCRT as a single or in combination for treatment of NPC [15]. The combination of cisplatin and 5-FU has been considered as standard adjuvant chemotherapy (AC) after CCRT based on the results from the randomized trials [8, 12]. Lin et al. [10], however, used a combination of cisplatin and 5-FU over a 96-h infusion during RT and showed a clear survival benefit in the CCRT arm over RT alone in a randomized trial. Despite the expected higher acute toxicities with the addition of 5-FU to cisplatin, the compliance with RT was not compromised, and the delay of RT was not increased when compared with RT alone arm. These results suggest that the combination of cisplatin and 5-FU can safely be incorporated to RT in locally advanced NPC patients.

A combination of bleomycin, epirubicin, and cisplatin (BEC) has been reported to have excellent clinical results with 66% of complete response as neoadjuvant chemotherapy in locally advanced NPC patients [16]. Also, in patients with recurrent or metastatic disease, bleomycin and cisplatin-based combination chemotherapy achieved a response rate of 45–79% [17, 18]. Nevertheless, the high level of toxicity has been a limiting factor for the routine use of this effective regimen in clinical practice. For these reasons, we adopted three cycles of BEC regimen after dose modification as AC to improve prognosis of patients with locally advanced NPC.

In the current study, based on the experience at the Korea University Medical Center, we evaluated the toxicity and efficacy of BEC AC after CCRT using 5-FU and cisplatin in the locally advanced NPC. Specifically, we focused our emphasis on whether the systemic chemotherapy could be added to CCRT without significantly increasing morbidity.

Materials and methods

Patients

All patients, who had received concurrent chemoradiation followed by chemotherapy for histologically proven, previously untreated NPC with AJCC stage T3/T4 or N2/N3 and M0 disease at the Korea University Medical Center between September 1998 and December 2008, were retrospectively reviewed in this study. All eligible patients were required to have measurable diseases, including at least one bidimensionally measurable lesion, no previous anticancer treatment, a life expectancy of at least 3 months, ECOG performance status $\leq$1, absolute neutrophil count $\geq$1,500/μl, platelet count $\geq$100,000/μl, no abnormalities in the liver, kidneys, heart, and lungs (renal function: 24 h creatinine clearance $\geq$60 ml/min), and no double primary cancer, and to give an informed consent for treatment.

Patients were evaluated by a multidisciplinary team before treatment. Pretreatment evaluation included a medical history, physical examination, and assessment of performance status. A fiberoptic examination of upper aerodigestive tract was completed before treatment. A computerized tomography (CT) or magnetic resonance imaging (MRI) scan of nasopharynx and neck, including cervical and supraclavicular lymph node area, was used to evaluate the primary tumor and nodal status before and after the chemoradiation, and at the end of the AC. CT scan of chest or liver, and bone scan were used when any of the initial investigation suggested metastasis. Patients were required to have a dental examination before treatment. Individual patient consent was not required for this study.

Chemotherapy and dose modification

For CCRT, initial course of chemotherapy using cisplatin at a dose of 75 mg/m^2 intravenously on day 1 followed by continuous intravenous administration of 5-FU at a dose of 750 mg/m^2/24 h for 5 days (day 1–5) was performed during the course of RT. The chemotherapy was repeated for the second course 4 weeks after the first chemotherapy when patients met the following criteria: absolute neutrophil count $\geq$1,500/μl, platelet count $\geq$100,000/μl, and 24 h creatinine clearance $\geq$60 ml/min. The doses of cisplatin and 5-FU were decreased by 25% when the absolute neutrophil count was $\leq$500/μl or platelet count was $\leq$20,000/μl after the first chemotherapy. When the 24 h creatinine clearance was between 40 and 60 ml/min, the dosage of next cisplatin was decreased by 25%.

Adjuvant chemotherapy was performed at least 3 weeks after the completion of concurrent chemoradiation only for patients who accepted the rationale for further treatment. The dosage and schedule of the protocol were modified from the three-drug combination of BEC previously reported [16]. It consisted of three cycles of intravenous cisplatin (75 mg/m^2 intravenously on day 1), epirubicin (37.5 mg/m^2 intravenously on day 1), and bleomycin (7.5 mg/m^2 intravenous bolus on day 1 followed by 9 mg/m^2 on day 1–5 by continuous infusion) repeated every 3 weeks. A 25% dose

reduction for all of the chemotherapeutic agents was required with the occurrence of either absolute neutrophil count $\leq$500/μl for more than 5 days or platelet count $\leq$20,000/μl or febrile neutropenia.

Radiation treatment

Radiotherapy started concurrently with chemotherapy, using four or six MV photon beam produced by a linear accelerator. The nasopharynx, the base of the skull, and the upper part of the neck were irradiated by two lateral shaped, parallel opposing fields. The lower neck was irradiated by anterior single field with midline shielding. The total dose to primary site and gross neck node was 72 Gy, which was delivered in daily dose of 1.8 Gy for 5 days per week. At a dose of 40–45 Gy, shrinking fields were done to exclude the spinal cord. At a dose of 60–63 Gy, the second modification of the field was done to reduce the toxicity and to adjust the change of tumor volume. All treatment plans were designed in accordance with CT/MRI images (pre-radiotherapy and during radiotherapy) and physical examination, including nasopharyngoscopic findings.

Patient assessments and follow-up

Primary disease in nasopharynx and lymph node sites was evaluated 3 weeks after the completion of CCRT and 4–6 weeks after the AC by using CT or MRI scan of the head and neck, and nasopharyngoscopy. Final response in patients with CCRT alone was evaluated 3 months after the RT. Response to treatment was assessed by RECIST criteria [19]. Patients were seen every 2 months during the first year, every 3 months for the subsequent year, and then every 6 months thereafter. Local recurrences were diagnosed by endoscopic biopsy, CT, or MRI of the nasopharynx. Distant metastases were diagnosed by clinical symptoms, physical examinations, bone scan, chest X-ray, and CT scan.

Chemotherapy-related toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC). RT-related toxicities were graded according to the radiation morbidity scoring criteria of the RT oncology group.

Statistical analysis

This study was primarily a retrospective analysis to evaluate efficacy and safety; therefore, no formal estimation of the sample size was done. Survival times were calculated from the start of the study treatment until death. Progression-free survival was calculated from the first day of the chemotherapy until the date of progression or the date of last follow-up for any other reasons. Progression-free survival and overall survival curves were obtained using the Kaplan–Meier method. Differences in survival were examined according to criteria of log-rank. The Fisher's exact test was used for the comparison of categorical data. The statistical significance was established as $P < 0.05$.

Results

Patient characteristics

Patient characteristics are listed in Table 1. Forty-three patients were initially enrolled in this protocol, and 24 of the patients finished three courses of AC, whereas the rest of the patients refused to receive further treatment. The patient series presented herein had similar characteristics between the two treatment groups with regard to patient characteristics and tumor stage. The median follow-up times for CCRT only group and CCRT plus AC group were 42.5 months (range: 9.0–60.0 months) and 26.0 months (range: 5.0–82.0 months), respectively.

Treatment delivery and compliance

The median duration of concurrent chemoradiation was 8.5 weeks (range: 8–13 weeks). The entire patient series presented herein received two cycles of chemotherapy during the radiation. Four patients received a 25% reduced dose of chemotherapy due to grade 4 oral mucositis. Three cycles of the AC were delivered to 24 patients after the CCRT phase. Dose reduction by 25% of the planned dose was required due to grade 4 febrile neutropenia in two patients. Otherwise, all of patients who started the AC successfully finished three cycles of planned treatment. There was no treatment-related mortality in the adjuvant phase.

Treatment response, recurrence, and survival

After CCRT, 41 of 43 patients achieved an objective response rate of 95% (22 CRs and 19 PRs) when the patients were evaluated 3 weeks after the completion of CCRT. Nineteen patients who did not receive further chemotherapy achieved an objective response rate of 94% (16 CRs and 2 PRs) at 3 months after treatment completion (Table 2). Twenty-four patients subsequently received adjuvant BEC chemotherapy, and 16 of them achieved a complete response. Eight patients still remained in partial response (residual cervical lymph nodes) after the AC; however, residual lymph nodes regressed spontaneously in six patients with follow-up. One patient who had residual tumor in the neck lymph node received booster radiation.

As of June 2009 and with a median follow-up of 28 months (range: 5.0–85.0 months), 20 out of the 24

Table 1 Clinical characteristics of patients

Characteristics	All patients ($n = 43$)	Chemoradiotherapy and adjuvant chemotherapy patients ($n = 24$)	Chemoradiotherapy alone patients ($n = 19$)	P[a]
Age, years median (range)	48 (14–70)	46 (14–64)	49 (26–70)	0.24
Gender				0.70
Male	34	18	16	
Female	9	6	3	
Performance status				1.0
ECOG 1	43	24	19	
Histology, WHO				0.71
I	10	4	6	
II	5	2	3	
III	28	18	10	
Tumor size				0.89
T1	7	4	3	
T2	12	5	7	
T3	10	9	1	
T4	14	6	8	
Nodal status				0.17
N0	2	2	0	
N1	8	1	7	
N2	27	16	11	
N3	6	5	1	
TNM staging				0.70
Stage III	19	9	10	
Stage IV	24	15	9	

ECOG European cooperative oncology group
WHO World health organization
TNM tumor, node, metastasis
[a] *P* denotes statistical difference between the treatment groups

Table 2 Tumor response to treatment

	After concurrent chemoradiation ($n = 19$)			After adjuvant chemotherapy ($n = 24$)		
	Primary	Neck	Composite	Primary	Neck	Composite
Complete	12	12	12	18	22	16
Partial	7	6	6	6	2	8
Stable	0	1	1	0	0	0
Progression	0	0	0	0	0	0
Overall	19/19	18/19	18/19	24/24	24/24	24/24

patients who received AC were still alive with no evidence of disease, whereas 12 out of the 19 patients who were treated by CCRT only were in complete remission. The median progression-free survival time has not yet been reached in both patient groups, and 3-year progression-free survival rates of all patients, CCRT only, CCRT and AC groups were 65, 54, and 70%, respectively. The Kaplan–Meier progression-free survival curves are shown in Figs. 1a and 2. The difference between the treatment groups could not reach any statistically significant level in the log-rank test ($P > 0.05$). The overall survival for all the patients and two treatment groups is shown in Figs. 1b and 3. Overall survivals of 3 years for all the patients, CCRT group, and CCRT followed by AC group were 76, 71, and 82%, respectively. The difference in overall survival time between the treatment groups was not statistically significant either. Table 4 shows the patterns of disease failure in both groups. Distant failure was more common among the patients in CCRT only group than those with CCRT followed by AC group (26.3 vs. 4.2%, Fisher's exact test, $P = 0.008$). However, no significant differences in the cumulative incidence of distant metastasis were found between the two treatment groups (Fig. 4).

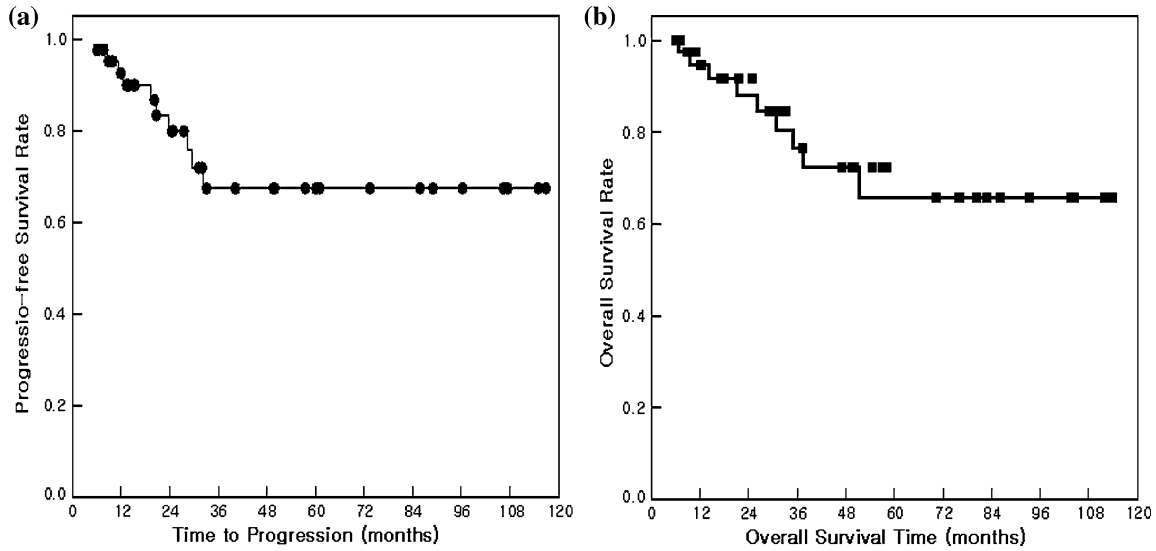

Fig. 1 Kaplan–Meier estimate of progression-free survival (**a**) and overall survival (**b**) in months for all patients

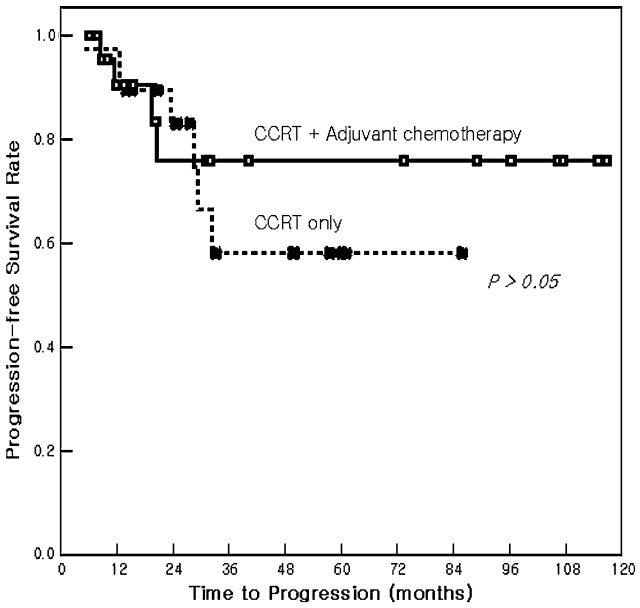

Fig. 2 Kaplan–Meier estimate of progression-free survival in months for patients with CCRT and adjuvant chemotherapy in comparison with CCRT only patients

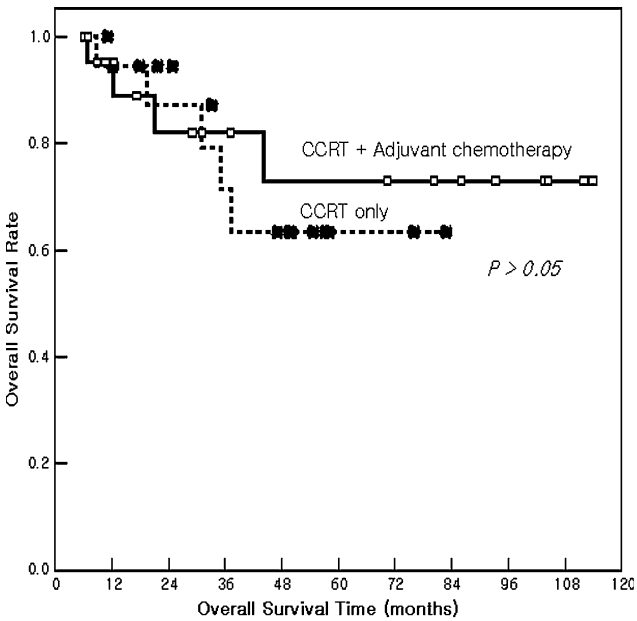

Fig. 3 Kaplan–Meier estimate of overall survival in months for patients with CCRT and adjuvant chemotherapy in comparison with CCRT only patients

Toxicity

There was no treatment-related death. Table 3 lists acute toxicities in the CCRT and AC phase. The most significant toxicities associated with CCRT were grade 3/4 oral mucositis and neutropenia. Eleven of the patients (25%) needed admission for the management of mucositis during the CCRT phase. The mean percent of weight change during CCRT was −6.5%. Eleven patients (25%) lost more than 10% of baseline body weight. During the course of AC, grade 3 or 4 neutropenia and thrombocytopenia were observed in three (12.5%) and four (16.7%) patients out of the 24 patients, respectively. Nausea and vomiting were the most common non-hematologic toxicities during the adjuvant treatment, developing in five (21.6%) patients. One patient lost his weight significantly further during the adjuvant treatment, whereas 19 of the 24 patients maintained or gained weight. There was no patient in this study who developed pulmonary toxicity in association with bleomycin treatment.

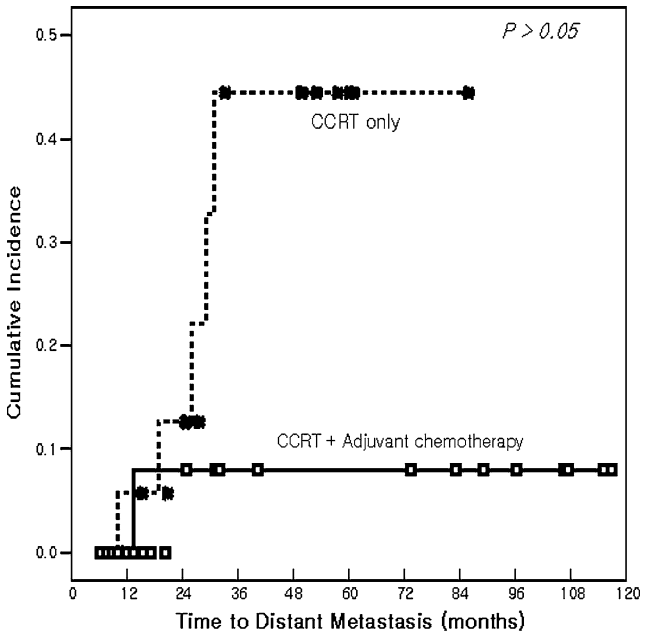

Fig. 4 Kaplan–Meier estimate of time to distant metastasis in months for patients with CCRT and adjuvant chemotherapy in comparison with CCRT only patients

Discussion

In the earlier randomized studies, cisplatin-based CCRT has been demonstrated to have higher efficacy than RT alone in patients with locally advanced NPC [8, 10, 11]. Concomitant chemotherapy during RT has been shown to improve local disease control by radiosensitizing effect and also found to significantly reduce distant metastasis [20]. However, the patterns of failure for locally advanced NPC show both locoregional recurrence and distant metastasis even after the concomitant chemoradiation [12, 21]. Therefore, incorporation of more effective cytotoxic agent than cisplatin single agent during CCRT seems to be needed. In this study, we adopted a combination of cisplatin and 5-FU regimen during RT based on experiences on other head and neck cancers [22, 23]. Both agents have been shown to have radiosensitizing effects in head and neck cancers, including nasopharyngeal cancer [22]. Lin et al. [10] used a combination of cisplatin at 20 mg/m^2/day and 5-FU at 400 mg/m^2/day over a 96-h infusion during RT for patients with locally advanced NPC and reported that the compliance with RT was not compromised from the chemotherapy and that delay in RT was not increased compared with the RT alone group. Furthermore, there was significant improvement in the 5-year overall survival and progression-free survival rates in the CCRT arm compared with RT alone. In our present study, we used cisplatin at a dose of 75 mg/m^2 intravenously on day 1, followed by continuous intravenous administration of 5-FU at a dose of 750 mg/m^2/24 h for 5 days (day 1–5). Even with higher dose of 5-FU, the incidence of grade 3 or 4 mucositis (44%) was comparable to that in the previous study (45.4%) of Lin et al. [10]. Considering the fact that the rate of grade 3/4 mucositis ranges from 28 to 48% in the studies with cisplatin-based CCRT, mucositis in this study is acceptable and manageable. In the current study, the median duration of RT was 8.5 weeks, and RT interruption for $\geq$1 week occurred in 13 patients. Using proactive measures, such as judicious hydration and antiemetics, for the prevention of renal or skin toxicities and emesis, more than 95% of the patients in the present study who started this treatment could finish full course of CCRT. Nonetheless, 28% of the patients lost more than 10% of body weight during CCRT in this study due to oral mucositis.

Table 3 Toxicities during the CCRT and adjuvant chemotherapy

	Concurrent chemoradiation (n = 43)		Adjuvant chemotherapy (n = 24)	
	Grade 1/2 *N* (%)	Grade 3/4 *N* (%)	Grade 1/2 *N* (%)	Grade 3/4 *N* (%)
Hematologic toxicity				
Anemia	24 (56)	0 (0)	12 (50)	0 (0)
Neutropenia	11 (25)	8 (18)	13 (54)	3 (12.5)
Thrombocytopenia	3 (7)	2 (5)	10 (42)	4 (16.7)
Non-hematologic toxicity				
Anorexia	31 (72)	3 (3)	9 (37.5)	2 (8.3)
Nausea/Vomiting	30 (70)	3 (7)	9 (37.5)	5 (20.8)
Diarrhea	0 (0)	0 (0)	1 (4)	2 (8.3)
Mucositis	19 (44)	19 (44)	14 (58)	3 (12.5)
Weight loss	24 (56)	11 (26)	4 (17)	1 (4)
Skin toxicity	25 (58)	2 (5)	NA	NA

NA not associated

Therefore, development of better CCRT protocol using more sophisticated RT techniques is still needed.

Recently, European society of medical oncology recommended that AC following CCRT may be beneficial [14], even though its own survival advantage has not been documented. In this study, three cycles of BEC after dose modification were given as AC to reduce the incidence of distant metastasis. Among 43 patients who completed CCRT, 24 (56%) patients agreed to receive AC. The most common reason for stopping treatment after CCRT was patient's refusal, because of perceived toxicities in the treatment and no confirmed benefit from AC prior to the published results from the intergroup study, but not because of severe toxicities. However, the treatment after CCRT has lately less frequently been refused with recent development of supportive care modalities such as better antiemetics, use of recombinant epidermal growth factor spray [24], and proactive education about the side effects. The compliance for the AC with our protocol was not inferior to those in other randomized studies. In the randomized studies from China [21] and Singapore [25], about 62 and 52% of patients in CCRT and AC arm were able to complete the planned treatment, whereas 56% of patients in this study were compliant.

For AC, the combination of cisplatin and 5-FU for three cycles has most commonly been used in the previous studies [8, 12, 21, 25]. However, a limited number of studies have so far been published on the best combination of chemotherapeutic agents after CCRT in patients with locally advanced NPC. There is an evidence to indicate that administration of sufficient amount of cytotoxic agent is required to control distant metastasis [26]. On the other hand, Kwong et al. [2] showed that even six cycles of chemotherapy using PF (cisplatin and 5-FU) and VBM (vincristine, bleomycin, and methotrexate) failed to improve overall survival because of severe toxicities. Therefore, the most pertinent issues confronting clinicians at this point of time may be to define an optimal combination and dosing of AC and to select patients who might benefit from more aggressive AC. In this current study, we used the combination of BEC that has been used in the neoadjuvant or metastatic setting in other studies because of an excellent efficacy of the regimen [5, 27]. Since the regimen has been known to have severe toxicities, including 8% of treatment-related deaths in a study [5], we modified the dosage of the drugs by 25% in this study. With careful dosing and development of supportive care, therefore, the toxicities during the AC were fairly acceptable in the current study. Although bleomycin is known to cause fatal pulmonary fibrosis even with a low dose [17], fortunately no patient in our present study experienced any clinically significant lung fibrosis. However, physicians should always pay special attention to the patients who are receiving bleomycin for potentially curable disease. It is important to note in our series that grade 3 or 4 toxicities occurred in less than 20% of the patients and that only one patient experienced febrile neutropenia that required admission during AC. Moreover, about 80% of the patients maintained or gained weight during AC, implying that the BEC regimen with dose modification is very safe and does not add any significant toxicity to the toxicities from CCRT.

After a median 28 months of follow-up, the 3-year progression-free survival rate was 65% in all the patients, 70% in CCRT followed by AC group, and 54% in CCRT group. Disease progression in the patients in CCRT plus AC group was mostly from local recurrence, whereas distant metastasis and local recurrence equally contributed in CCRT only group. Accordingly, the patterns of treatment failure were significantly different between the two treatment groups (Table 4, $P = 0.008$). Nonetheless, we failed to observe any significant difference in progression-free or distant metastasis-free survival time in the two groups. The possible reasons include small number of patients and insufficient events in order to reach median survival time. In addition, patients in this study were not randomized for the AC. Thus, it is difficult to demonstrate any difference between the treatment groups, even though clinical characteristics of patients in the two treatment groups were quite similar (Table 1). In the current analysis, local recurrence was a still important pattern of treatment failure in both of the treatment groups (17% of CCRT plus AC group and 21% of CCRT only group) with this protocol. Considering the fact that RT interruption can compromise local control in head and neck cancers [28], the number of patients (13/43; 27%) who had RT break for $\geq$1 week

Table 4 Site of recurrence

Site of recurrence	Chemoradiotherapy and adjuvant chemotherapy patients (n = 5/24)	Chemoradiotherapy alone patients (n = 7/19)
Local	4 (16.6%)	4 (21%)
Distant	1 (4.2%)	5 (26.3%)
Lung	0	1
Bone	1	3
Liver	0	1

might be an explanation for local relapses in this study. With recent advances in intensity-modulated RT (IMRT) techniques [29, 30], better local control as well as higher compliance may be achieved in future.

Since this is a retrospective study, a number of factors in terms of patients and tumor characteristics could not be controlled. Furthermore, the small number of patients and short follow-up time are limiting factors of this study. Nevertheless, we herein presented an evidence to indicate that a novel scheduling of cytotoxic agents (cisplatin and 5-FU) during CCRT, followed by three cycles of reduced dose BEC, is effective with acceptable toxicity in locally advanced NPC patients. Furthermore, there was a trend for reduction in distant metastasis with the addition of BEC AC even after the dose modification. More importantly, all the patients who started to receive AC were able to complete three cycles of treatment because of the mild toxicity profile. Finally, the treatment efficacy with our protocol in terms of 3-year progression-free and overall survival rates was similar to those from other randomized studies that used the protocol for the multimodal treatment of the intergroup study; 3-year progression-free survival rates were 65–70% in our study and 62–80% in the randomized studies [3, 8, 21].

In conclusion, the present study demonstrated that CCRT using cisplatin and 5-FU, followed by BEC AC, in patients with locally advanced NPC is efficient and has acceptable and manageable toxicity. Further prospective study is needed to confirm our results.

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