Journal of Radiation Research, 2013, 54, 467–473
doi: 10.1093/jrr/rrs115 Advance Access Publication 28 November 2012

Radiotherapy concurrently with weekly cisplatin, followed by adjuvant chemotherapy, for N2–3 nasopharyngeal cancer: a multicenter trial of the Forum for Nuclear Cooperation in Asia

Tatsuya OHNO[1,*], Dang Huy Quoc THINH[2], Shingo KATO[3], C.R. Beena DEVI[4], Ngo Thanh TUNG[5], Kullathorn THEPHAMONGKHOL[6], Miriam Joy C. CALAGUAS[7], Juying ZHOU[8], Yaowalak CHANSILPA[6], Nana SUPRIANA[9], Dyah ERAWATI[10], Parvin Akhter BANU[11], Cho Chul KOO[12], Kunihiko KOBAYASHI[13], Takashi NAKANO[14] and Hirohiko TSUJII[15]

[1]Gunma University Heavy Ion Medical Center, Gunma University, Gunma, Japan
[2]Department of Radiation Oncology No. 3, Ho Chi Minh City Cancer Center, Ho Chi Minh City, Vietnam
[3]Department of Radiation Oncology, Saitama Medical University, Saitama, Japan
[4]Department of Radiation Oncology, Sarawak General Hospital, Malaysia
[5]Head and Neck Radiation Department, National Cancer Hospital, Hanoi, Vietnam
[6]Department of Radiology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand
[7]Department of Radiation Oncology, St. Luke's Medical Center, Quezon City, Philippines
[8]Department of Radiation Oncology, The First Affiliated Hospital of Soochow University, Suzhou, China
[9]Department of Radiotherapy, Dr Cipto Mangunkusumo General Hospital, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia
[10]Department of Radiotherapy, Dr Soetomo General Hospital, Surabaya, Indonesia
[11]Department of Radiation Oncology, Delta Hospitals Limited, Bangladesh
[12]Department of Radiation Oncology, Korea Cancer Center Hospital, Seoul, Korea
[13]Department of Respiratory Medicine, Saitama Medical University, Saitama, Japan
[14]Department of Radiation Oncology, Gunma University Graduate School of Medicine, Gunma, Japan
[15]Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan
*Corresponding author. Gunma University Heavy Ion Medical Center, Gunma University, 3-39-22 Showa, Maebashi, 371-8511, Japan. Tel: +81-027-220-8378; Fax: +81-027-220-8379; Email: tohno@gunma-u.ac.jp

(Received 31 August 2012; revised 31 October 2012; accepted 2 November 2012)

The purpose of this study was to evaluate the efficacy and toxicity of radiotherapy concurrently with weekly cisplatin, followed by adjuvant chemotherapy, for the treatment of N2–3 nasopharyngeal cancer (NPC) in Asian countries, especially regions of South and Southeast Asian countries where NPC is endemic. Between 2005 and 2009, 121 patients with NPC (T1–4 N2–3 M0) were registered from Vietnam, Malaysia, Indonesia, Thailand, The Philippines, China and Bangladesh. Patients were treated with 2D radiotherapy concurrently with weekly cisplatin (30 mg/m ^{2}), followed by adjuvant chemotherapy, consisting of cisplatin (80 mg/m^2 on Day 1) and fluorouracil (800 mg/m^2 on Days 1–5) for 3 cycles. Of the 121 patients, 56 patients (46%) required interruption of RT. The reasons for interruption of RT were acute non-hematological toxicities such as mucositis, pain and dermatitis in 35 patients, hematological toxicities in 11 patients, machine break-down in 3 patients, poor general condition in 2 patients, and others in 8 patients. Of the patients, 93% completed at least 4 cycles of weekly cisplatin during radiotherapy, and 82% completed at least 2 cycles of adjuvant chemotherapy. With a median follow-up time of 46 months for the surviving 77 patients, the 3-year locoregional control, distant metastasis-free survival and overall survival rates were 89%, 74% and 66%, respectively. No treatment-related deaths occurred. Grade 3–4 toxicities of mucositis, nausea/vomiting and leukopenia were observed in 34%, 4% and 4% of the patients, respectively.

In conclusion, further improvement in survival and locoregional control is necessary, although our regimen showed acceptable toxicities.

Keywords: nasopharyngeal cancer; chemoradiotherapy; adjuvant chemotherapy; developing country; 2D radiotherapy

INTRODUCTION

Radiotherapy (RT) is the mainstay treatment for nasopharyngeal cancer (NPC) because of the surgically inaccessible anatomic location and radiosensitive character. Although RT can cure most patients with early-stage disease, those with advanced disease often develop locoregional and distant failure. The 5-year overall survival (OS) rate is approximately 35% for Stage III–IV disease with RT alone in most reported series in the era of 2-dimensional RT [1–4]. The Intergroup 0099 trial was the first randomized clinical trial to show significant OS benefit by adding cisplatin concurrently with RT, followed by adjuvant cisplatin and 5-FU. Its outcome established the standard of care for locally advanced NPC in North America [5]. Since then, several randomized trials from Singapore, Hong Kong, Taiwan and South China have investigated the significance of concurrent chemoradiotherapy (CCRT), with or without adjuvant chemotherapy [6–12]. Meta-analyses have shown that CCRT significantly improves OS with a pooled hazard ratio of 0.48, corresponding to a survival benefit of 20% after 5 years [13–14].

The treatment paradigm is considered to be applicable to patients in other regions of South and Southeast Asian countries where NPC is endemic. However, much attention has been paid to its introduction because large randomized trials of CCRT have also demonstrated the cost of increased treatment-related toxicities and poor treatment compliance [5–12]. Especially in developing countries, the general condition of patients is compromised, further compounded by a lack of adequate supportive therapy for managing treatment-related toxicities [15]. Therefore, it remains unclear whether the evidence from the literature is adequate to justify the use of CCRT as standard care, especially in other regions of South and Southeast Asian countries where NPC is endemic.

The Forum for Nuclear Cooperation in Asia (FNCA) is a framework of regional cooperation among Asian countries with the aim of peaceful and safe application of nuclear science and technology. The medical project of the FNCA was launched in 1993, aiming to standardize RT and CCRT for common cancers in Asia with the participation of nine Asian countries: Bangladesh, China, Indonesia, Japan, Korea, Malaysia, The Philippines, Thailand and Vietnam. A multi-institutional clinical study on locally advanced NPC was conducted as one of the FNCA activities. The purpose of this study was to evaluate the efficacy and toxicities of CCRT followed by adjuvant chemotherapy for locally advanced NPC in Asian countries, especially regions of South and Southeast Asian countries where NPC is endemic.

MATERIALS AND METHODS

Patient eligibility

The multi-institutional prospective single-arm study was designed as a project of the FNCA. Patients fulfilling all the following criteria were eligible for this study: histologically confirmed World Health Organization (WHO) Type 2 or 3 carcinoma of nasopharynx, Stage III, IVA and IVB (UICC-TNM, 6th edition), age between 20 and 70 years, performance status (PS) 0–2, adequate bone marrow, hepatic and renal functions (WBC $\geq 3000/mm^3$, Hb $\geq$ 10g/dl, platelet $\geq 100\,000/mm^3$, total bilirubin $\leq$ 1.5 mg/dl, AST/ALT $\leq 2 \times$ upper limit of normal, serum creatinine $\leq$ 1.5 mg/dl). Exclusion criteria were WHO Type 1 carcinoma of nasopharynx, severe concomitant illness such as uncontrolled cardiovascular disease, uncontrolled diabetes mellitus, active peptide ulcer, severe infection, severe psychological illness, an active double cancer, prior radiotherapy or chemotherapy, pregnancy or lactation. Written informed consent was obtained from all patients.

All patients underwent nasopharyngoscopy and biopsy to obtain specimens for pathological diagnosis. Pretreatment evaluations included physical examination of the head and neck, computed tomography (CT) scan, chest radiography, a complete blood cell count with differential counts, and biochemistry profile. Due to the differences of availability among the participating institutes, abdominal ultrasonography and bone scans were used optionally, but their use was recommended if at all possible.

Radiotherapy

Patients were treated using a 6 or 10 MV linear accelerator, or a telecobalt unit, by conventional 2D RT technique. The superior margin of the initial radiation field ranged 2 cm beyond the visible tumor on CT scan, and included the entire base of the skull and the sphenoid sinus. Posteriorly, the field extended at least 1.5 cm beyond palpable nodes. Anteriorly, the field included the posterior ethmoidal sinus,

the posterior one-third of the maxillary antrum, or at least 1.5 cm beyond the visible tumor.

Patients received conventional fractionated RT of 1.8–2 Gy per fraction, with five daily fractions per week. Patients were treated in a supine position, usually with bilateral parallel opposing fields to the primary tumor and upper neck, and a single anterior field to the lower neck with a central shield. After 40–45 Gy, the primary tumor was boosted using bilaterally opposed reduced portals. The bulky nodal area was irradiated with posterio-anterio parallel opposing ports for the neck region or an electron beam with appropriate energy. The total dose planned was 65–70 Gy for T1–2 disease, 66–70 Gy for T3, 66–75 Gy for T4, and 60–70 Gy for the positive neck region, respectively.

RT was suspended if a patient developed Grade 4 hematological toxicities, Grade 4 radiation mucositis of the oral cavity or pharynx, Grade 4 radiation dermatitis, Grade ≥3 non-hematological toxicities (e.g. nausea, vomiting) except for mucositis and/or dermatitis, or PS 3–4. RT was resumed when the hematological and non-hematological toxicities were recovered to Grade 2.

Chemotherapy

Cisplatin at a dose of 30 mg/m^2 was administered weekly starting from Week 1 for 6 consecutive weeks during the course of RT. Patients were hydrated with more than 1500 ml of normal saline per session. Administration of cisplatin with RT was interrupted when patients developed a WBC count <3000/mm^3, a platelet count < 75 000/mm^3, fever > 38.0°C, PS 3–4, or Grade ≥3 non-hematological toxicities (e.g. emesis, loss of appetite, fatigue), or serum creatinine >1.5 mg/dl. Subsequent adjuvant chemotherapy, consisting of cisplatin 80 mg/m^2 plus 5-FU 1000 mg/m^2/day for four days were administered for 3 cycles. The first cycle of adjuvant chemotherapy was started three weeks after completion of RT. For prevention of emetics, 5-HT3 receptor antagonists and dexamethasone were given with the chemotherapy. Adjuvant chemotherapy was withheld if a patient developed WBC < 3000/mm^3, platelets < 75 000/mm^3, Grade ≥3 non-hematological toxicities, except for elevation of serum creatinine level (e.g. emesis, mucositis, loss of appetite), fever >38.0°C, or PS 3–4. If the serum creatinine level was >1.5 mg/dl, cisplatin was not given, but 5-FU was administered. If the serum creatinine level was >2.0 mg/dl, neither cisplatin nor 5-FU was given. According to the toxicities in the previous cycle, the doses of cisplatin and 5-FU were reduced, even though the toxicities had recovered. If a patient developed Grade 3 hematological toxicities, cisplatin was decreased to 60 mg/m^2 and 5-FU to 1000 mg/m^2/day for three days. If a patient developed Grade 4 hematological toxicities and/or Grade 3 non-hematological toxicities, cisplatin was decreased to 50 mg/m^2 and 5-FU to 800 mg/m^2/day for three days.

Assessment and follow-up

While undergoing CCRT, toxicity and tumor response were evaluated weekly. After CCRT treatment, toxicity and tumor response were evaluated at the completion of each cycle of adjuvant chemotherapy. The Common Terminology Criteria for Adverse Events v3.0 (CTCAE) was used for evaluation of toxicities.

After treatment, follow-up examinations were conducted at least every three months for the initial three years and then every 3–6 months for the subsequent two years. Disease status and toxicities were assessed by history-taking, physical examination, appropriate laboratory tests and chest radiography. Imaging modality such as ultrasonography, CT or magnetic resonance imaging was used if necessary. Locoregional control (LC) was defined as no evidence of tumor failure in the head and neck region.

Statistical analysis

The primary endpoint of the study was OS. The secondary endpoints included LC and toxicity. OS was measured from the date of initiation of therapy to the date of death from any cause, or the most recent follow-up visit. From the retrospective analysis of clinical data among the participating institutes of the FNCA project, the 3-year OS rate with 2D RT alone for patients with N2–3 and M0 NPC was 50%. The sample size evaluated in this study, which was calculated by the 3-year OS rate, was determined to be 113 patients. We chose a rate of 65% as a desirable target level and a rate of 50% as undesirable. Our design had a power in excess of 80% and less than 5% Type I error. Taking into account the decrease in power (e.g. loss to follow-up, entry of ineligible cases), this trial was designed to enrol 120 patients. The actual rates of LC, distant metastasis-free survival (DMFS), and OS were calculated using the Kaplan-Meier method. Differences between curves were tested by the log–rank test. A P value <0.05 was considered significant.

RESULTS

Patient characteristics

Between April 2005 and March 2009, 121 patients with N2–3 NPC were enrolled. Analysis was performed on all data entered at the FNCA data center as of December 25, 2010. The median follow-up was 38 months for all patients, and 46 months for the 77 surviving patients. For pretreatment evaluation, bone scans and ultrasonography of the upper abdomen were performed for 56 patients (46%) and 105 patients (87%), respectively. The patient characteristics are listed in Table 1.

Table 1. Patient characteristics ($n = 121$)

			n	%
Age	Median	46		
	Range	20–64		
Sex	Male		83	69%
	Female		38	31%
Country	Vietnam		75	62%
	Malaysia		25	21%
	Thailand		5	4%
	China		5	4%
	Indonesia		5	4%
	The Philippines		5	4%
	Bangladesh		1	1%
Performance status	0		52	43%
	1		65	54%
	2		4	3%
T classification	1		18	15%
	2a		30	25%
	2b		34	28%
	3		20	17%
	4		19	16%
N classification	2		81	67%
	3		40	33%
Stage	III		65	54%
	IVA		17	14%
	IVB		39	32%
Histology	Type 2		26	21%
	Type 3		95	79%

Table 2. Compliance of chemotherapy

No. of courses	Concurrent phase		Adjuvant phase	
	n	%	*n*	%
6	89	74		
5	18	15		
4	6	5		
3	4	3	68	56
2	3	2	31	26
1	1	1	4	3
0	0	0	18	15
total	121		121	

Dose modification of adjuvant chemotherapy was carried out in 12 patients.

Table 3. Reasons for incomplete (0–2 cycle) adjuvant chemotherapy

	0 cycle	1–2 cycle	Total
Tumor progression	1	0	1
Toxicities of CCRT	4	–	4
Poor general condition	5	1	6
Toxicities of adjuvant chemotherapy	–	28	28
Patient refusal	7	5	12
Financial problem	1	1	2
Total	18	35	53

CCRT = Concurrent chemoradiotherapy.

Treatment and compliance

A total of 99 patients (82%) were treated with the linear accelerator, and 22 patients (18%) with a telecobalt unit. The median overall treatment time of CCRT was 56 days. Of the 121 patients, 56 patients (46%) required interruption of RT. Twelve patients (10%) required interruption over 14 days, with the median duration being 14 days. The reasons for interruption of RT were acute non-hematological toxicities such as mucositis, pain and dermatitis in 35 patients, hematological toxicities in 11 patients, machine break-down in 3 patients, poor general condition in 2 patients, and others in 8 patients.

The compliance of concurrent and adjuvant chemotherapy is shown in Table 2. The reasons for incomplete concurrent chemotherapy were treatment-related toxicities in 26 patients, poor general condition in 2 patients, difficulty of hospital admission in 2 patients, and patient refusal in 2 patients. Adjuvant chemotherapy was carried out for 103 patients, and 12 patients had dose modification. Table 3 shows the reasons for incomplete adjuvant chemotherapy in 53 patients.

Toxicities

Hematological and non-hematological toxicities during the CCRT phase are listed in Table 4. The incidence of toxicities ≥Grade 3 in mucositis, nausea/vomiting and leucopenia was 34%, 4% and 4%, respectively. Hematological and non-hematological toxicities during the adjuvant chemotherapy phase are listed in Table 5.

Locoregional control, distant metastasis-free survival and overall survival

The 3-year LC, DMFS and OS rate for all 121 patients were 89%, 74% and 66%, respectively (Fig. 1–2).

Table 4. Toxicities of CCRT ($n = 121$)

Toxicity	Grade (CTCAE v.3)			
	1	2	3	4
Leukopenia	35	32	5	0
Neutropenia	39	12	3	0
Anemia	37	11	2	0
Thrombocytopenia	16	2	0	0
Dermatitis	40	48	33	0
Mucositis	21	59	41	0
Pain	24	56	18	0
Dry mouth	29	71	17	0
Nausea/Vomiting	52	20	5	0
Weight loss	47	36	14	1
Fatigue	54	48	7	0

Table 5. Toxicities of adjuvant chemotherapy ($n = 103$)

Toxicity	Grade (CTCAE v.3)			
	1	2	3	4
Leukopenia	27	34	6	2
Neutropenia	22	25	8	2
Anemia	56	15	0	0
Thrombocytopenia	30	6	1	0
Dermatitis	44	12	0	0
Mucositis	20	25	8	0
Pain	15	20	1	0
Dry mouth	27	58	16	0
Nausea	50	30	5	0
Weight loss	52	23	12	1
Fatigue	47	31	11	0

Subgroup analyses were performed for T- and N-diseases. For 82 patients with T1–2 disease, the 3-year LC, DMFS and OS were 91%, 74% and 68%, respectively. For 39 patients with T3–4 disease, the 3-year LC, DMFS and OS were 87%, 73% and 61%, respectively. No significant difference was found between the two groups in terms of LC ($P = 0.552$), DMFS ($P = 0.836$) or OS ($P = 0.239$).

For 81 patients with N2 disease, the 3-year LC, DMFS and OS were 91%, 74% and 65%, respectively. For 40 patients with N3 disease, the 3-year LC, DMFS and OS were 86%, 73% and 67%, respectively. No significant difference was found between the two groups in terms of LC ($P = 0.640$), DMFS ($P = 0.607$) or OS ($P = 0.851$).

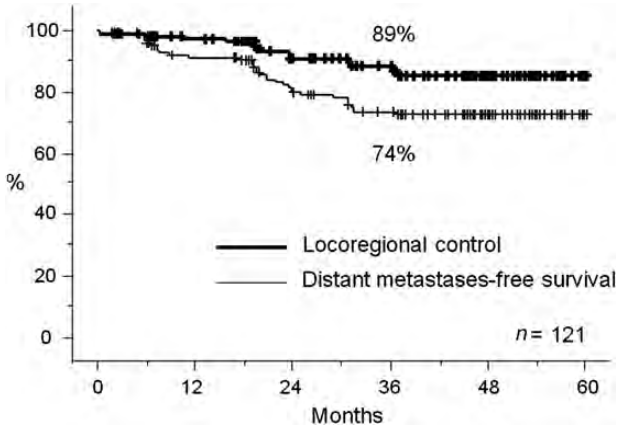

Fig. 1. Distant metastasis-free survival and locoregional control rates for all 121 patients.

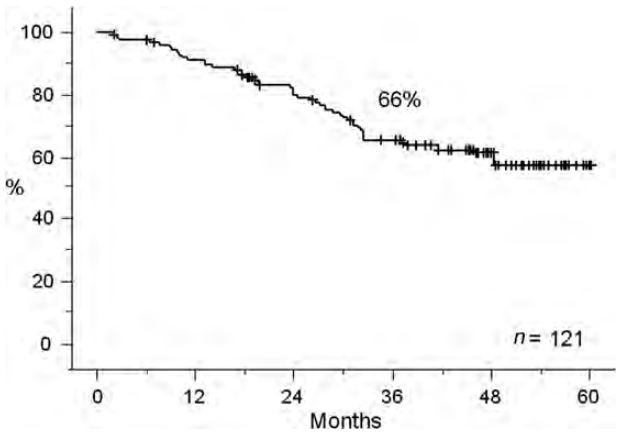

Fig. 2. Overall survival rate for all 121 patients.

In order to evaluate the impact of the bone scan on survival, patients were divided into two groups. The 3-year DMFS and OS were 73% and 66% for the 56 patients undergoing bone scans. The corresponding survivals were 75% and 65% for 65 patients not having bone scans. No significant difference was found between the two groups regarding DMFS ($P = 0.645$) or OS ($P = 0.965$).

DISCUSSION

NPC is a special type of head and neck cancer usually found in South and Southeast Asian and North African populations. Our study included patients from Vietnam, Malaysia, Thailand, China, Indonesia, The Philippines and Bangladesh. Despite the high prevalence of NPC in the region, only limited data on clinical outcomes after RT or CCRT is available. The present study showed that the 3-year locoregional control, distant metastasis-free survival

and OS rate for all 121 patients were 89%, 74% and 66%, respectively, and that 1% and 2% of the patients developed toxicities ≥Grade 4 in the CCRT and adjuvant chemotherapy phases, respectively. Thus, further improvement in survival and locoregional control would be necessary, although our regimen showed acceptable toxicities.

Survival after treatment for NPC depends on the extent of the disease, chemotherapy regimen, irradiation technique, doses delivered and the socio-economic conditions [15]. Recently published randomized clinical studies have demonstrated a 78–87% 3-year OS rates in the CCRT arm, while the present study showed a 66% 3-year OS [5, 7, 9–12]. There are several possible reasons for the differences. First, only patients with N2–3 disease were eligible in our study. Chua *et al*. analyzed the failure pattern of 324 patients with NPC after RT [16]. They demonstrated that the 5-year OS rate was 85% for T1–2 and N0–1, 82% for T3–4 and N0–1, 65% for T1–2 and N2–3, and 59% for T3–4 and N2–3, respectively, and that N2–3 disease indicated relatively high risk for distant failure. The proportion of N2–3 disease ranged between 54 and 100% in the published studies, indicating that our patient population included a greater patient proportion with unfavorable prognostic factors [5, 7, 9–12].

Second, all RT in our study was based on the 2D technique with conventional fractionation. On the other hand, the published studies partially used the 3D conformal technique, intensity-modulated RT (IMRT), and hyperfractionated accelerated RT, which are considered to increase the possibility of locoregional control [5, 9–10]. Lai *et al*. recently reported that the 5-year primary tumor control rates for T1, T2, T3 and T4 were 100%, 95%, 90% and 82% in patients treated with IMRT, and 94%, 93%, 88% and 72% in patients treated with 2D RT [17]. The improvement of disease-free survival with IMRT compared to 2D RT has been demonstrated, mainly by achieving a higher local tumor control rate. Since the locoregional control in our study was inferior, especially in the T3–4 or N3 disease group, the high locoregional failure with 2D RT might contribute to inferior survival. Third, a pretreatment bone scan was performed for only 46% of the patients, meaning that patients with undiagnosed bone metastasis could have been involved in the study. However, there were no significant differences in DMFS or OS between patients with or without bone scans.

Cisplatin is a very active drug in CCRT for locally advanced NPC. The current study used 30 mg/m^2 of weekly cisplatin for up to 6 cycles, and 93% of the patients completed at least 4 cycles of weekly cisplatin. Ho *et al*. also reported high compliance of this regimen, with 81% of the patients completing at least 7 cycles, in spite of patient age being >60 years [18]. In published studies on CCRT, daily low-dose (20–25 mg/m^2), weekly intermediate-dose (30–40 mg/m^2), or once-per-3 weeks high-dose (100 mg/m^2) cisplatin have been used [5, 6, 9–12, 19]. However, the optimal scheduling of cisplatin and RT has not been established. In the regimen of high-dose (100 mg/m^2) cisplatin, only 43–63% of patients completed the full cycles of chemotherapy concurrently with RT [5, 10, 19]. Chan *et al*. evaluated 40 mg/m^2 of weekly cisplatin up to 8 weeks concurrently with RT for locally advanced NPC [6–7]. In their study, the compliance of chemotherapy was 78% at 4 cycles and 44% at 6 cycles, which was considered unsatisfactory [6]. They also demonstrated that the progression-free survival for patients receiving less than 6 cycles was not statistically different from that of patients receiving at least 6 cycles [6].

Interruptions of RT were observed in 46% of the patients in the current study. The main reason was severe non-hematological toxicities such as mucositis, dermatitis, pain and dry mouth. In this regard, it must be cautioned that a higher incidence of acute toxicities could lead to inadvertent delays and extended overall treatment time. It is well known that prolongation of the overall treatment time results in poorer local control and lower survival rate in patients with head and neck cancer [20–21]. In other words, any therapeutic advantage that might be expected from CCRT could be eradicated by prolongation of the overall treatment time. Problems of this nature may be more evident in developing countries, as patients with advanced disease might be nutritionally compromised and have inadequate supportive therapy. Every effort should be made to provide adequate care and to minimize any extension of the overall treatment time in CCRT.

Based on the randomized studies, the role of adjuvant chemotherapy is still unclear because of the poor compliance. Our regimen of adjuvant chemotherapy, consisting of cisplatin 80 mg/m^2 plus 5-FU 1000 mg/m^2/day for four days was the same as that of the Intergroup 0099 study, and compliance was 55% at 3 cycles, 26% at 2 cycles, 3% at 1 cycle, and 15% at 0 cycles. The compliance of adjuvant chemotherapy in published studies, using a similar regimen to the Intergroup 0099 study, was 55–76% at 3 cycles, 5–6% at 2 cycles, 6% at 1 cycle, and 13–33% at 0 cycle [5, 10–12]. 'that a higher proportion of the patients received at least 2 cycles of adjuvant chemotherapy, compared with those in the published data, probably because of a relatively lower incidence of severe toxicities during the CCRT phase and/or a lower rate of patient refusal. However, in spite of the higher total dosage of adjuvant chemotherapy, distant metastasis control was still insufficient. A recent meta-analysis suggested an advantage for the use of neoadjuvant chemotherapy followed by CCRT [13]. Therefore, the impact of adjuvant/neoadjuvant chemotherapy in addition to CCRT on distant metastasis control and survival benefit should be further investigated, especially in patients with a high risk for distant metastasis.

FUNDING

This work was supported by the project of The Forum Nuclear Cooperation in Asia (FNCA), the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan, and a research project of the National Institute of Radiological Sciences, Japan.

ACKNOWLEDGMENTS

The authors thank the staff members of the Japan Atomic Industrial Forums (JAIF) Inc. and the Nuclear Safety Research Association (NSRA) for organizing a series of FNCA Workshops on Radiation Oncology. Pittaya Dankulchai, Conchitina Mendoza, Sheila Gonzales, Tomoko Takahashi and Michiko Yoshino are thanked for their assistance with data collection. We are grateful to Cao Jianping, Tang Tieng Swee, Nguyen Chan Hung and Nguyen Ba Duc for their support of this work.

REFERENCES

1. Teo P, Yu P, Lee WY *et al*. Significant prognosticators after primary radiotherapy in 903 nondisseminated nasopharyngeal carcinomas evaluated by computer tomography. *Int J Radiat Oncol Biol Phys* 1996;**36**:291–304.
2. Lee AW, Poon YF, Foo W *et al*. Retrospective analysis of 5,037 patients with nasopharyngeal carcinoma treated during 1976–1985: overall survival and patterns of failure. *Int J Radiat Oncol Biol Phys* 1992;**23**:261–70.
3. Fandi A, Altun M, Azli N *et al*. Nasopharyngeal cancer: epidemiology, staging, and treatment. *Semin Oncol* 1994;**21**: 382–97.
4. Sanguineti G, Geara FB, Garden AS *et al*. Carcinoma of the nasopharynx treated by radiotherapy alone: determinants of local and regional control. *Int J Radiat Oncol Biol Phys* 1997;**37**:985–96.
5. Al-Sarraf M, LeBlanc M, Giri PGS *et al*. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: Phase III randomized Intergroup Study 0099. *J Clin Oncol* 1998;**16**:1310–7.
6. Chan AT, Teo PML, Kgan RK *et al*. Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. *J Clin Oncol* 2002;**20**:2038–44.
7. 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* 2005;**97**:536–9.
8. Kwong DL, Sham JS, Au GK *et al*. Concurrent and adjuvant chemotherapy for nasopharyngeal carcinoma: a factorial study. *J Clin Oncol* 2004;**22**:2643–53.
9. 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 survival and progression-free survival. *J Clin Oncol* 2003;**21**:631–7.
10. Lee AW, Lau WH, Tung SY *et al*. Hong Kong Nasopharyngeal Cancer Study Group. Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: NPC-9901 Trial by the Hong Kong Nasopharyngeal Cancer Study Group. *J Clin Oncol* 2005;**23**:6966–75.
11. Wee J, Tan EH, Tai BC *et al*. 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. *J Clin Oncol* 2005;**23**:6730–8.
12. Chen Y, Liu MZ, Liang SB *et al*. Preliminary results of a prospective randomized trial comparing concurrent chemoradiotherapy plus adjuvant chemotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma in endemic regions of China. *Int J Radiat Oncol Biol Phys* 2008;**71**:1356–64.
13. Langendijk JA, Leemans Ch. R, 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* 2004;**22**:4604–12.
14. Thephamongkhol K, Zhou J, Browman G *et al*. Chemo-radiotherapy versus radiotherapy alone for nasopharyngeal carcinoma: a meta-analysis of 78 randomized controlled trials (RCTs) from English and non-English databases (abstr). *J Clin Oncol* 2004;**22**:5522.
15. Vikram B. Cancers of the head and neck region in developing countries. *Radiother Oncol* 2003;**67**:1–2.
16. Chua DTT, Sham JST, Wei WI *et al*. The predictive value of the 1997 American Joint Committee on cancer stage classification in determining failure patterns in nasopharyngeal carcinoma. *Cancer* 2001;**92**:2845–55.
17. Lai SZ, Li WF, Chen L *et al*. How does intensity-modulated radiotherapy versus conventional two-dimensional radiotherapy influence the treatment results in nasopharyngeal carcinoma patients? *Int J Radiat Oncol Biol Phys* 2011;**80**:661–8.
18. Ho HS, Su YC, Lee MS *et al*. A preliminary result of concurrent chemoradiation with weekly cisplatin in elderly nasopharyngeal carcinoma patients. *Acta Otolaryngol* 2008;**128**: 930–5.
19. Bahl M, Siu LL, Pond GR *et al*. Tolerability of the intergroup 0099 (INT 0099) regimen in locally advanced nasopharyngeal cancer with a focus on patient's nutritional status. *Int J Radiat Oncol Biol Phys* 2004;**60**:1127–36.
20. Nishimura Y, Nagata Y, Okajima K *et al*. Radiation therapy for T1,2 glottic carcinoma: impact of overall treatment time on local control. *Radiother Oncol* 1996;**40**:225–32.
21. Kwong DL, Sham JS, Chua DT *et al*. The effect of interruptions and prolonged treatment time in radiotherapy for nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 1997;**39**:703–10.