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

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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/m²), followed by adjuvant chemotherapy, consisting of cisplatin (80 mg/m² on Day 1) and fluorouracil (800 mg/m² 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 ≥ 3000/mm³, Hb ≥ 10g/dl, platelet ≥ 100 000/mm³, total bilirubin ≤ 1.5 mg/dl, AST/ALT ≤ 2 × upper limit of normal, serum creatinine ≤ 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 peptic 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 posterior-anterior 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/m² 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/mm³, a platelet count <75 000/mm³, 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/m² plus 5-FU 1000 mg/m²/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/mm³, platelets <75 000/mm³, 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/m² and 5-FU to 1000 mg/m²/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/m² and 5-FU to 800 mg/m²/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 ultrasoundography, 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.
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 leukopenia 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).
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).

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/m² 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/m²), weekly intermediate-dose (30–40 mg/m²), or once-per-3 weeks high-dose (100 mg/m²) 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/m²) cisplatin, only 43–63% of patients completed the full cycles of chemotherapy concurrently with RT [5, 10, 19]. Chan et al. evaluated 40 mg/m² 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/m² plus 5-FU 1000 mg/m²/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.
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