Concurrent Chemoradiotherapy with Docetaxel, Cisplatin and 5-Fluorouracil (TPF) in Patients with Nasopharyngeal Carcinoma

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Abstract. *Background/Aim: Several randomized trials have shown that concurrent chemoradiotherapy (CCRT) either with or without adjuvant chemotherapy is more effective than radiotherapy-alone for treating nasopharyngeal carcinoma (NPC). The present study retrospectively evaluated the efficacy and toxicity of CCRT with docetaxel, cisplatin, and 5-fluorouracil (TPF) chemotherapy in patients with NPC. Patients and Methods: The study regimen consisted of two cycles of TPF chemotherapy [docetaxel (90 mg/m^2), cisplatin (60 mg/m^2), and continuous 5-fluorouracil (600 mg/m^2/day: 5 days)] during definitive radiotherapy. Radiotherapy was performed 5 days a week with a single daily fraction of 1.8 or 2.0 Gy totalling to 70-Gy doses. A total of 24 patients with NPC were enrolled and evaluated. Results: Treatment completion rate was 70.8%, with an overall response rate of 100%. The 5-year overall survival rate was 82.4%, and 5-year progression-free survival rate was 78.3%. Conclusion: CCRT with TPF resulted in excellent survival rates for patients with NPC.*

Nasopharyngeal carcinoma (NPC) is an extremely rare form of cancer in Japan. NPC is considered unresectable due to its unique anatomical location, and radiotherapy (RT) is the standard treatment modality. This cancer is not only radiosensitive but also chemosensitive and, based on these characteristics, several randomized trials using RT plus chemotherapy for the treatment of NPC have been conducted (1-8). Results of these trials showed that concurrent chemoradiotherapy (CCRT) either with or without adjuvant chemotherapy (AC) is more effective than RT alone.

Recently, CCRT with 3 courses of 100 mg/m^2 cisplatin (CDDP) followed by AC [3 courses of CDDP 80 mg/m^2 and 5-fluorouracil (5-FU) 1,000 mg/m^2] has become standard therapy for NPC in the US and Europe. However, several randomized trials have demonstrated that a regimen of docetaxel plus CDDP and 5-FU (TPF) leads to a significantly greater survival rate in patients with squamous cell carcinoma of the head and neck (SCCHN) than a regimen of CDDP and 5-FU (PF) in an induction chemotherapy (IC) setting (9-11).

We previously conducted a phase I study of CCRT with TPF in locally advanced patients with SCCHN (12, 13). We compared IC with TPF followed by definitive RT and CCRT with TPF (14), and found that patients in the CCRT group had a significantly better overall survival rate than patients in the IC group, despite similar CR rates (IC group: 87% *vs.* 84%: CCRT group). Furthermore, our phase II trial showed that the 3-year survival rate in patients who received CCRT with TPF was superior to that in patients who received modified PF, although the overall response and CR rates in the two groups were similar (15). We, therefore, report that the regimen of CCRT with TPF provided excellent long-term survival and organ preservation in patients with locally advanced SCCHN (16).

Since 2005, we have administered TPF-CCRT in patients with NPC same as other-site SCCHN. In the present study, we retrospectively evaluated the efficacy and toxicity of CCRT in combination with TPF in patients with NPC.

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Furthermore, the role of chemotherapy in the treatment of NPC through examination of chemotherapy courses and administration of AC in these patients is discussed.

Patients and Methods

Records from the Yokohama City University Hospital (Yokohama, Japan) were retrospectively reviewed to identify patients who had received CCRT in combination with TPF for histologically-proven, previously untreated squamous cell carcinoma of the nasopharynx between 2005 and 2013. To be eligible, each patient had to have at least one dimensionally-measurable lesion, with no distant metastasis and no concurrent malignancies.

Patients were further required to meet the following criteria: age under 75 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; life expectancy of at least 3 months; WBC count ≥4,000 cells/μl; absolute neutrophil count (ANC) ≥2,000 cells/μl; platelet count ≥100,000/μL; hemoglobin level ≥9.5 g/dl; AST, ALT, and alkaline phosphatase levels below 2.5-times the upper limit of normal (ULN); total bilirubin and creatinine levels lower than 1.5-times the ULN; BUN level below the ULN; and 24-h creatinine clearance rate ≥65 ml/min. Patients with significant cardiac arrhythmias or heart failure were excluded. All patients provided their written informed consent prior to study enrollment.

We previously conducted a phase I study of CCRT with TPF in patients with laryngeal, oropharyngeal and hypopharyngeal squamous cell carcinomas (12, 13). Based on results of that study, we administered docetaxel (50 mg/m^2) intravenously over 1 h on day 1. On days 1-5, 5-FU (600 mg/m^2/day) was administered by continuous intravenous infusion with 3.5 l of normal saline per day for at least 1 h after completion of the intravenous administration of docetaxel. CDDP (60 mg/m^2) was administered intravenously on day 4. Two cycles of this regimen were administered every 4 weeks during RT.

Patients were treated using a 6-MV linear accelerator *via* a conventional 2D-RT technique. The use of computed tomography (CT), magnetic resonance imaging (MRI), and nasopharyngoscopy is recommended for the accurate definition of the gross tumor. The superior margin of the initial radiation field ranged 2 cm beyond the visible tumor on CT scans and included the entire base of the skull and sphenoid sinus. Posteriorly, the field extended at least 1.5 cm beyond the palpable nodes. Anteriorly, the fialpable nodes. Anteriorly, the the skull a and the posterior one-third of the maxillary antrum, or at least 1.5 cm beyond the visible tumor. Patients received conventional fractionated RT (1.8-2 Gy) per fraction, for 5 daily fractions per week). Patients were treated in a supine position, usually with bilateral, parallel opposing fields at the primary tumor and upper neck and a single anterior field at the lower neck with a central shield. After delivery of 40-45 Gy of radiation, the primary tumor was boosted using bilaterally opposed reduced portals. The total planned dose was 70 Gy, and no patients in the study received intensity-modulated radiation therapy.

Re-treatment on day 29 was based on the following criteria: ANC ≥2,000 cells/μl; platelet count ≥100,000/μl; hemoglobin level ≥9.5 g/dl; AST, ALT, and alkaline phosphatase levels less than 2.5-times the ULN; 24-h creatinine clearance rate ≥65 ml/min; and resolution of all non-hematological toxicities (except alopecia, musculoskeletal pain and fatigue) such that they were baseline or below Grade 1. Every effort was made to continue radiation on schedule. Subcutaneous granulocyte colony-stimulating factor (G-CSF; 150 μg/day) was injected if the neutrophil count was <1,000 cells/μl after chemotherapy, and irradiation was continued during the G-CSF injections. When toxicities ≥grade 3 persisted for more than 7 days, the second cycle of chemotherapy was delayed for approximately 7 days. If severe toxicities continued for more than 14 days, radiation alone or CCRT with another chemotherapy regimen (*e.g.*, oral administration of S-1) was delivered. When patients could not maintain oral intake because of oral or pharyngeal pain induced by CCRT, a gastric tube was inserted to maintain patients' nutrition.

Toxicity was assessed once per cycle according to the 2009 Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0). Resolution of side-effects (*e.g.*, myelosuppression, mucositis, or fever >38.0˚C) and other disorders was required prior to initiation of the second treatment cycle.

For each patient, clinical response was assessed according to the combined CT, MRI PET-CT, and ultrasonic examinations findings at 4-6 weeks after CCRT completion. The definitions of complete response (CR), partial response (PR), no-change (NC) and progressive disease (PD) were based on the standard definitions established by the World Health Organization (17).

With regard to adjuvant chemotherapy, the S-1 and uracil-tegafur regimens were planned before 2009, and the TPF regimen was planned from 2010. The decision to administer AC and the selection of the regimen were finally determined by each patient's treating doctor considering the patient's general status and toxicities during CCRT.

After treatment, follow-up examinations were conducted at least every 2 months for the initial 2 years and then every 3-6 months for the subsequent 3 years. The follow-up period of survivors ranged from 9.9 to 97.2 months (median=41.8 months). Disease status and toxicities were assessed by physical examination, laboratory tests, and chest radiography. Imaging modalities, such as ultrasonography, CT or MRI, were used where necessary. Overall survival (OS) times were calculated as the time from the beginning of RT until death. Disease-specific survival (DSS) times were calculated as the time from beginning of RT until death, with patients who died from causes other than the disease not being included in the DSS calculations. Progression-free survival (PFS) time was defined as the interval from the beginning of RT until the date of disease progression or death. OS, DSS and PFS curves were estimated using the Kaplan-Meier method. Differences in survival were analyzed according to the log-rank criteria. Differences with $p<0.05$ were considered statistically significant.

Results

Patients' characteristics. Twenty-four patients with NPC received CCRT with TPF chemotherapy. Patients' characteristics and tumor staging are shown in Table I.

Toxicity. Table II presents the toxicities observed in the study population. No deaths resulted from treatment. Mucositis was the most common adverse reaction, with grade 3 and grade 4 toxicities observed in 58.3% (n=14) and 8.3% (n=2) of patients, respectively. Sixteen patients required tube feeding during CCRT. Neutropenia was the second most common adverse event, with 33.3% (n=8) and 8.3% (n=2) of the patients experiencing grade 3 or grade 4 toxicities, respectively.

Table I. *Patients' characteristics.*

Age (Years)	Median (Range)	49 (16-66)
Gender	Male	18 (75.0%)
	Female	6 (25.0%)
T	1	3 (12.5%)
	2	14 (58.3%)
	3	5 (20.8%)
	4	2 (8.3%)
N	0	5 (20.8%)
	1	8 (33.3%)
	2	10 (41.7%)
	3	1 (4.2%)
Stage	I	1 (4.2%)
	II	7 (29.2%)
	III	13 (54.2%)
	IVA	2 (8.3%)
	IVB	1 (4.2%)
Histology	WHO type I	4 (16.7%)
	WHO type II	15 (62.5%)
	WHO type III	5 (20.8%)

Table II. *Toxicities during concurrent chemoradiotherapy.*

	Grade1/2	Grade 3	Grade 4
Hematological toxicities			
Anemia	21 (87.5%)	1 (4.2%)	2 (8.3%)
Neutropenia	14 (58.3%)	8 (33.3%)	2 (8.3%)
Thrombocytopemia	14 (58.3%)	2 (8.3%)	0 (0%)
Non-hematological toxicities			
Mucositis	8 (33.3%)	14 (58.3%)	2 (8.3%)
Liver impairment	13 (54.2%)	0 (0%)	0 (0%)
Renal impairment	7 (29.2%)	0 (0%)	0 (0%)
Nausea/vomiting	13 (54.2%)	10 (41.7%)	0 (0%)

Treatment compliance. Seventeen patients (70.8%) completed the scheduled CCRT. The second course of chemotherapy was discontinued in 7 cases. The most common causes of chemotherapy discontinuation were myelosuppression (4/7, 57.1%) and renal dysfunction (2/7, 28.6%). Among patients who received only one course of TPF, 2 patients received an oral administration of S-1, and 5 patients did not receive any additional chemotherapy. The median radiation dose was 70.2 Gy (range=66.0-70.2 Gy). The median RT duration was 55.5 days (range=45-64 days). RT was delayed for 3 days in one patient (4.2%) due to infection.

Response. The overall response rate for primary tumors was 100% (21 CR and 3 PR). Among cases with lymph-node involvement, the lymph-node response was also 100% (16 CR and 3 PR).

Survival. After CCRT, tumors persisted in 3 patients (12.5%). Among these patients, one patient received 6 courses of TPF chemotherapy as AC. Complete response was observed after AC and the patient survived for 46.9 months. The other 2 patients died of the disease.

Four patients (16.7%) experienced tumor relapse after CCRT. Three of these patients had locoregional relapse and one patient had distant metastasis. Among these patients, one patient underwent salvage surgery (neck dissection), one patient received cyber-knife therapy for local relapse, and the other 2 patients received palliative support care. The patient who underwent salvage surgery was alive with no evidence of disease at the latest follow-up (4 months after salvage surgery). One patient died of disease, and 2 patients remained alive with disease.

At the end of follow-up, 19 patients (79.2%) remained alive with no evidence of disease. Three patients (12.5%) had died of the disease, and 2 patients (8.3%) were alive with disease. Among the total study sample of 24 patients, the 3- and 5-year OS rates were both 82.4%, with the 3- and 5-year DSS rates both 82.4%, and the 3- and 5-year PFS rates both 78.3% (Figure 1).

Stratification by clinical stage revealed that the 3-year DSS rates were 83.3% for patients with stage I and II disease, 90.9% for patients with stage III disease, and 50.0% for patients with stage IV disease (Table III). The 3-year PFS rates were 87.5% for stage I and II cases, 75.5% for stage III cases, and 66.7% for stage IV cases (Table III). Patients with stage IV disease had a tendency towards a reduced survival rate, but there were no significant differences observed according to staging.

Courses of chemotherapy. We compared survival rates for different courses of chemotherapy (Figure 2). No significant differences in sex, age, WHO classification, T stage, N stage or M stage were observed between the two groups. Among patients receiving two courses of TPF chemotherapy, the 3-year DSS and PFS rates were 100% and 94.1%, respectively. Among patients receiving only one course of TPF chemotherapy, the 3-year DSS and PFS rates were 44.4% and 42.9%, respectively, indicating that there were significant differences in survival rates according to the number of courses of chemotherapy ($p<0.001$).

Adjuvant chemotherapy. After CCRT, AC was administered in 20 patients (83.3%). Eight patients (CR/PR: 7/1) received AC with daily oral administration of uracil-tegafur, 7 patients (CR/PR: 5/2) received the TPF regimen, and 5 patients (CR/PR: 5/0) received the S-1 regimen as an oral administration. No significant difference in the number of patients according to AC regimen was observed between the CR and PR groups. Stratification by AC regimen revealed that

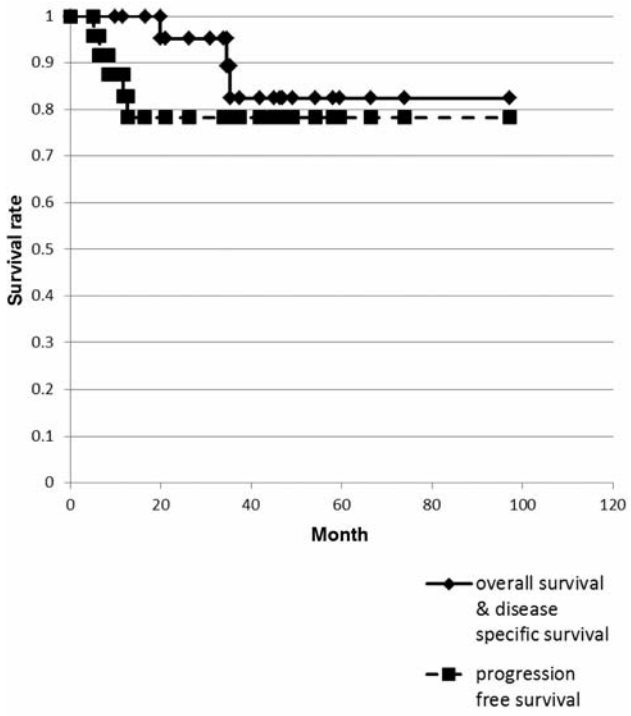

Figure 1. *Kaplan-Meier survival curves (months) for all patients who received CCRT with TPF. The 5-year OS and DSS were both 82.4%. The 5-year PFS was 78.3%.*

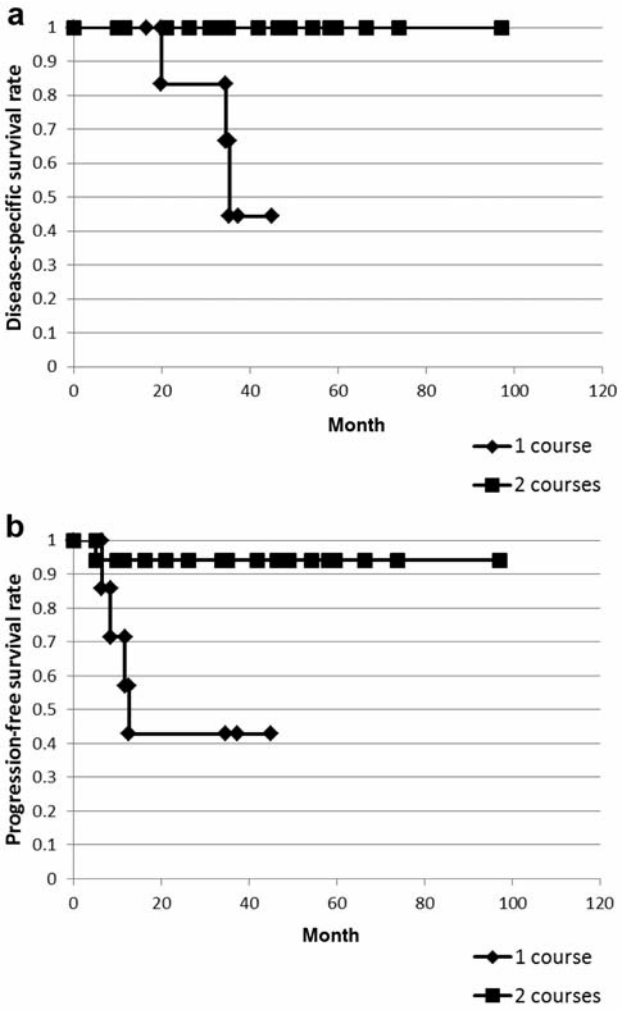

Figure 2. *Kaplan-Meier curves (months) by the number of courses of chemotherapy. (a) Disease-specific survival curve. There was a significant difference between the two groups (p=0.005). (b) Progression-free survival curve. A significant difference was observed between the two groups (p=0.008).*

the 3-year DSS rates were 100% for patients in both the S-1 and TPF groups, 55.6% for those in the uracil-tegafur group, and 75% for those in the group not receiving AC (Figure 3a). The 3-year PFS rates were 100% for patients in the S-1 and TPF groups, 58.3% for those in the uracil-tegafur group, and 50% for those in the group not receiving AC (Figure 3b). There was a significant difference in PFS rates between the TPF group and the group not receiving AC (p=0.045).

Discussion

The efficacy of chemoradiotherapy for NPC has been previously reported in three meta-analyses (18-20). Each report showed that the combination of chemotherapy with RT improved survival, and that CCRT was more effective than IC or AC.

The efficacy of CCRT with or without AC was also supported by certain randomized phase III studies. In 1998, Al-Sarraf *et al*. reported the superiority of CCRT followed by AC over RT alone with a significant improvement in 3-year OS for the patients treated with CCRT (78% *vs*. 47%, p<0.001) (1). In addition, decreases in both loco-regional failure and distant metastases were observed in patients treated with CCRT. Wee *et al*. conducted a similar study, and reported that prognosis significantly improved in patients treated with CCRT compared to those treated with RT alone (5-year OS rates: 80% *vs*. 65%) (7).

Lin *et al*. reported the result of a phase III randomized study on CCRT without AC (5). Comparison of patients receiving CCRT with the regimen PF (4 days continuous infusion of CDDP 20 mg/m^2/day and 5-FU 400 mg/m^2/day, every 4 weeks) and those receiving RT-alone showed that the OS rates and PFS rates were significantly better in the group receiving CCRT. In our study, the 5-year OS and PFS rates were excellent at 82.4% and 78.3% of patients, respectively, similarly to those of previous reports (1-8).

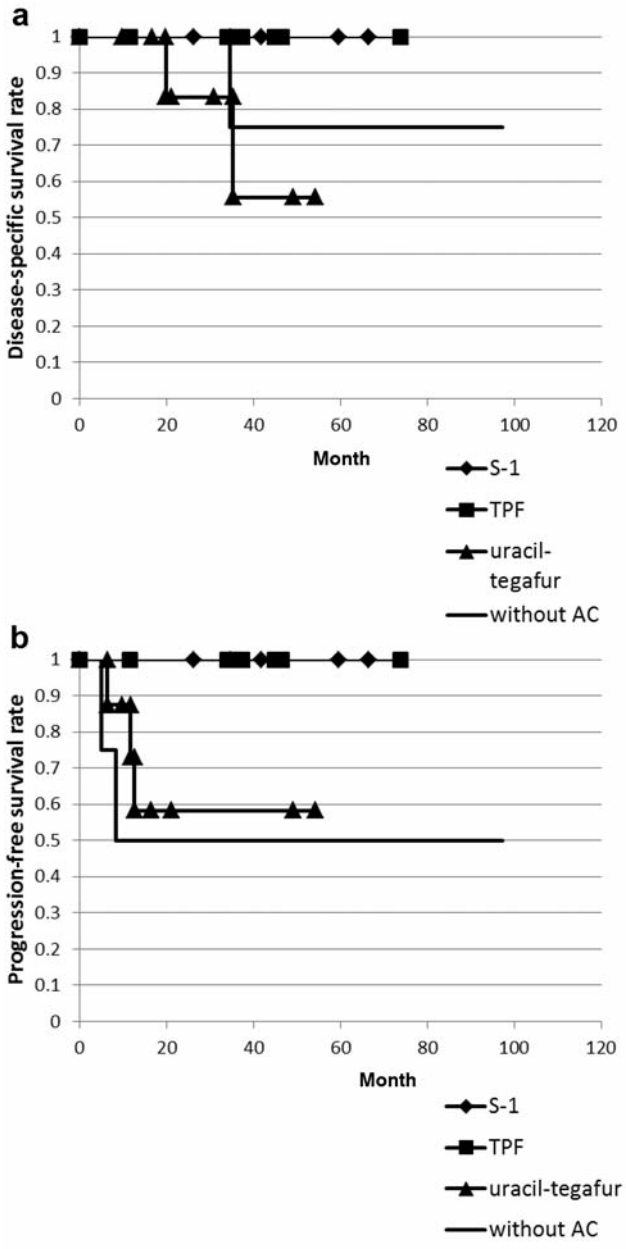

Figure 3. *Kaplan-Meier curves (months) by adjuvant chemotherapy regimen. (a) Disease-specific survival curve. (b) Progression-free survival curve. A significant difference was observed between the group receiving TPF and the group not receiving AC (p=0.045).*

In the present study, mucositis was the most common adverse effect, followed by neutropenia. Although severe myelosuppression and mucositis were also observed in our study, 70.8% of patients received the planned CCRT. Thus, CCRT with TPF chemotherapy is considered acceptable, and these acute toxicities could be appropriately managed by timely G-CSF or by nutritional support.

Table III. *Three- and 5-year OS, DSS and PFS rates by cancer staging.*

	OS and DSS		PFS	
	3-year	5-year	3-year	5-year
Stage I/II (n=8)	83.3%	83.3%	87.5%	87.5%
Stage III (n=13)	90.9%	90.9%	75.5%	75.5%
Stage IV (n=3)	50.0%	not reached	66.7%	not reached

OS: Overall survival, DSS: disease-specific survival, PFS: progression-free survival.

A comparison of patients receiving one course of chemotherapy to those receiving two courses showed that the latter group showed significantly better survival rates. Among patients with cancer of the oropharynx, hypopharynx and larynx, no significant differences in DSS were observed for the different number of courses of chemotherapy as part of the TPF regimen (16). As the number of chemotherapy courses is strongly related to the prognosis of patients with NPC, unlike to patients with cancer of the oropharynx, hypopharynx, or larynx, it is likely that the high sensitivity of NPC to chemotherapy and/or the high risk of distant metastasis in NPC contributed to the differences in survival rates. Selection of patients who can undertake administration of two courses of chemotherapy before commencement of treatment may be considered in a future study. For patients on whom 2 courses of chemotherapy are difficult, it is thought that additional chemotherapy, for example AC, should be considered. Furthermore, it is thought that improvement in treatment completion rate through use of a regimen with less toxicity should also be considered.

The current standard treatment is CCRT followed by AC, but the effectiveness of AC is still controversial. Chen, *et al*. reported that there was no significant difference in failure-free survival rates between patients who received CCRT-alone (weekly CDDP: 40 mg/m^2) and those who underwent CCRT followed by 3 courses of AC (CDDP: 80 mg/m^2: day 1, 5-FU: 800 mg/m^2/day: day 1-5) (21). Furthermore, a recent meta-analysis reported the superiority of CCRT followed by AC or CCRT alone over radiation-alone in terms of survival rate, but there was no significant difference between CCRT followed by AC and CCRT alone in terms of OS, locoregional recurrence-free survival, or distant metastasis-free survival (22). In our study, there was a significant advantage in progression-free survival for patients receiving the TPF regimen as AC over patients without AC. However, because our study was not randomized and not designed to examine the effect of the AC regimen, these results should not be used to conclude that AC was necessary, though they do suggest that additional chemotherapy may be important for the treatment of NPC.

In conclusion, CCRT with TPF showed excellent survival rates and manageable toxicity when used for NPC patients. Furthermore, it is proven and understood that a sufficient dosage of chemotherapy is important in the treatment of NPC.

References

1 Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, Forastiere AA, Adams G, Sakr WA, Schuller DE and Ensley JF: Chemoradiotherapy *versus* radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized intergroup study 0099. J Clin Oncol *16*: 1310-1317, 1998.

2 Ma J, Mai HQ, Hong MH, Min HQ, Mao ZD, Cui NJ, Lu TX and Mo HY: Results of a prospective randomized trial comparing neoadjuvant chemotherapy plus radiotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma. J clin Oncol *19*: 1350-1357, 2001.

3 Hareyama M, Sakata K, Shirato H, Nishioka T, Nishio M, Suzuki K, Saitoh A, Oouchi A, Fukuda S and Himi T: A prospective, randomized trial comparing neoadjuvant chemotherapy with radiotherapy alone in patients with advanced nasopharyngeal carcinoma. Cancer *15*: 2217-2223, 2002.

4 Chi KH, Chang YC, Guo WY, Leung MJ, Shiau CY, Chen SY, Wang LW, Lai YL, Hsu MM, Lian SL, Chang CH, Liu TW, Chin YH, Yen SH and Perng CH, Chen KY: A phase III study of adjuvant chemotherapy in advanced nasopharyngeal carcinoma patients. Int J Radiat Oncol Biol Phys *52*: 1238-1244, 2002.

5 Lin JC, Jan JS, Hsu CY, Liang WM, Jiang RS and Wang WY: Phase III study of concurrent chemoradiotherapy *versus* radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival. J Clin Oncol *15*: 631-637, 2003.

6 Chan AT, Leung SF, Ngan RK, Teo PM, Lau WH, Kwan WH, Hui EP, Yiu HY, Yeo W, Cheung FY, Yu KH, Chiu KW, Chan DT, Mok TS, Yau S, Yuen KT, Mo FK, Lai MM, Ma BB, Kam MK, Leung TW, Johnson PJ, Choi PH and Zee BC: Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. J Natl Cancer Inst *97*: 536-539, 2005.

7 Wee J, Tan EH, Tai BC, Wong HB, Leong SS, Tan T, Chua ET, Yang E, Lee KM, Fong KW, Tan HS, Lee KS, Loong S, Sethi V, Chua EJ and Machin D: 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 VI nasopharyngeal cancer of the endemic variety. J Clin Oncol *23*: 6730-6738, 2005.

8 Lee AW, Tung SY, Chua DT, Ngan RK, Chappell R, Tung R, Siu L, Ng WT, Sze WK, Au GK, Law SC, O'Sullivan B, Yau TK, Leung TW, Au JS, Sze WM, Choi CW, Fung KK, Lau JT and Lau WH: Randomized trial of radiotherapy plus concurrent-adjuvant chemotherapy *vs*. radiotherapy alone for regionally advanced nasopharyngeal carcinoma. J Natl Cancer Inst *102*: 1188-1198, 2010.

9 Pignon JP, Syz N, Posner M, Olivares R, Le Lann L, Yver A, Dunant A, Lewin F, Dalley DN, Paccagnella A, Taylor SG, Domenge C, Bourhis J and Mazumdar M: Adjusting for patient selection suggests the addition of docetaxel to 5-fluorouracil-cisplatin induction chemotherapy may offer survical benefit in squamous cell cancer of the head and neck. Anticancer Drugs *15*: 331-340, 2004.

10 Vermorken JB, Remenar E, van Herpen C, Gorlia T, Mesia R, Degardin M, Stewart JS, Jelic S, Betka J, Preiss JH, van den Weyngaert D, Awada A, Cupissol D, Kienzer HR, Rey A, Desaunois I, Bernier J, Lefebvre JL; EORTC 24971/TAX 323 Study Group: Cisplatin, fluorouracil, and decetaxel in unresectable head and neck cancer. N Eng J Med *357*: 1695-1704, 2007.

11 Posner MR, Hershock DM, Blajman CR, Mickiewicz E, Winquist E, Gorbounova V, Tjulandin S, Shin DM, Cullen K, Ervin TJ, Murphy BA, Raez LE, Cohen RB, Spaulding M, Tishler RB, Roth B, Viroglio Rdel C, Venkatesan V, Romanov I, Agarwala S, Harter KW, Dugan M, Cmelak A, Markoe AM, Read PW, Steinbrenner L, Colevas AD, Norris CM Jr., Haddad RI; TAX 324 Study Group: Cisplatin and fluorouracil alone or with decetaxel in head and neck cancer N Eng J Med *357*: 1705-1715, 2007.

12 Tsukuda M, Mikami Y, Tanigaki Y, Katori H, Horiuchi C, Ikeda Y, Taguchi T, Ono M, Yoshida T, Sakuma Y and Aikoh K: Phase I trial of combined chemotherapy with docetaxel, cisplatin and 5-fluorouracil (TPF) for patients with locally advanced squamous cell carcinoma of the head and neck. Int J Clin Oncol *9*: 161-166, 2004.

13 Katori H, Tsukuda M, Mochimatu I, Ishitoya J, Kawai S, Mikami Y, Matsuda H, Tanigaki Y, Horiuchi C, Ikeda Y, Taguchi T, Ono M, Yoshida T, Hirose S, Sakuma Y and Yamamoto K: Phase I trial of concurrent chemoradiotherapy with docetaxel, cisplatin and 5-fluorouracil (TPF) in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN). Br J Cancer *90*: 348-352, 2004.

14 Katori H and Tsukuda M: Comparison of induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil (TPF) followed by radiation *vs*. concurrent chemoradiotherapy with TPF in patients with locally advanced squamous cell carcinoma of the head and neck. Clin Oncol (R Coll Radiol) *17*: 148-152, 2005.

15 Tsukuda M, Ishitoya J, Matsuda H, Horiuchi C, Taguchi T, Takahashi M, Nishimura G, Kawakami M, Watanabe M, Niho T, Kawano T, Ikeda Y, Sakuma Y, Shiono O and Komatsu M: Randomized controlled phase II comparison study of concurrent chemoradiotherapy (CCRT) with docetaxel, cisplatin, and 5-Fluorouracil *versus* CCRT with cisplatin, 5-Fluorouracil, methotrexate and leucovorin in patients with locally advanced squamous cell carcinoma of the head and neck. Cancer Chemother Pharmacol *66*: 729-736, 2010.

16 Komatsu M, Shiono O, Taguchi T, Sakuma Y, Nishimura G, Sano D, Sakuma N, Yabuki K, Arai Y, Takahashi M, Isitoya J and Oridate N: Concurrent chemoradiothrapy with docetaxel, cisplatin and 5-fluorouracil (TPF) in patients with locally advanced squamous cell carcinoma of the head and neck. Jpn J Clin Oncol *44*: 416-421, 2014.

17 World Health Organization. (1979) WHO Handbook for reporting results of cancer treatment. WHO offset publication No. 48. Geneva, Switzerland: World Health Organization.

18 Langendijk JA, Leemans CR, Buter J, Berkhof J and Slotman BJ: The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma : a meta-analysis of the published literature. J Clin Oncol *22*: 4604-12, 2004.

19 Baujat B, Audry H, Bourhis J, Chan AT, Onat H, Chua DT, Kwong DL, Al-Sarraf M, Chi KH, Hareyama M, Leung SF, Thephamongkhol K, Pignon JP; MAC-NPC Collaborative Group: Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. Int J Radiat Oncol Biol Phys *64*: 47-56, 2006.

20 Zhang L, Zhao C, Ghimire B, , Hong MH, Liu Q, Zhang Y, Guo Y, Huang YJ and Guan ZZ: The role of concurrent chemoradiotherapy in the treatment of locoregionally advanced nasopharyngeal carcinoma among endemic population: a meta-analysis of phase III randomized trials. BMC Cancer *10*: 558, 2010.

21 Chen L, Hu CS, Chen XZ, Hu GQ, Cheng ZB, Sun Y, Li WX, Chen YY, Xie FY, Liang SB, Chen Y, Xu TT, Li B, Long GX, Wang SY, Zheng BM, Guo Y, Sun Y, Mao YP, Tang LL, Chen YM, Liu MZ and Ma J: Concurrent chemoradiotherapy plus adjuvant chemotherapy *versus* concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomized controlled trial. Lancet Oncol *13*: 163-71, 2012.

22 Chen YP, Wang ZX, Chen L, Liu X, Tang LL, Mao YP, Li WF, Lin AH, Sun Y and Ma J: A Bayesian network meta-analysis comparing concurrent chemoradiotherapy followed by adjuvant chemotherapy, concurrent chemoradiotherapy alone and radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma. Ann Oncol *26*: 205-11, 2015.

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