



Phase II trial

Comparison of weekly versus triweekly cisplatin delivered concurrently with radiation therapy in patients with locally advanced nasopharyngeal cancer: A multicenter randomized phase II trial (KCSG-HN10-02)



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ABSTRACT

Purpose: Triweekly delivery of cisplatin concurrent with a course of radiation therapy (RT) has been the standard regimen for treatment of locally advanced nasopharyngeal carcinoma (NPC) despite a high level of concern regarding treatment-related complications. We conducted a randomized phase II study to compare weekly and triweekly cisplatin delivery during RT with respect to efficacy and toxicity profiles. **Material and methods:** Patients with locally advanced NPC (stage II–IVb) were randomly assigned to a regimen of either seven doses of cisplatin (40 mg/m²) given once a week or three doses of cisplatin (100 mg/m²) given every 3 weeks concurrently during RT.

Results: Of 109 eligible patients, 53 were assigned to the weekly regimen and 56 to the triweekly regimen. The two groups were comparable with respect to demographic and clinical characteristics. There were no significant differences in mean RT dose (68.3 Gy vs. 67.3 Gy, $p = 0.559$) and mean cisplatin dose (248.9 mg/m² vs. 256.6 mg/m², $p = 0.433$) between the two regimens. The primary endpoint was 3-year progression-free survival, which was not different between the regimens (64.9% vs. 63.8%, $p = 0.074$). Overall, the occurrence of grade 3–4 toxicities was similar between the two arms (47.2% vs. 39.3%, $p = 0.443$). Quality of life (QoL) related to functional outcomes 3 weeks after treatment completion was better for the weekly regimen.

Conclusions: Although no definitive conclusions can be made, a once-weekly cisplatin regimen appears to be associated with improved QoL and is not inferior to the standard triweekly regimen with respect to efficacy and toxicity profiles.

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Locally advanced nasopharyngeal carcinoma (NPC) has a relatively poor prognosis if treated with radiation therapy (RT) alone, with a 5-year overall survival (OS) rate of 50–60% [1,2]. The Intergroup-0099 study (INT-0099) substantiated the benefit of concurrent chemoradiotherapy (CCRT) followed by adjuvant chemotherapy, with an improved 3-year OS compared to RT alone (78% vs. 47%, $p < 0.01$) [3]. However, concerns have been raised over toxicity and compliance when delivering the standard schedule of cisplatin (every 3 weeks) concurrently with RT. In fact, poor

compliance with the triweekly cisplatin regimen during CCRT was reported in the INT-0099 trial (63%) [3] and by Bahl et al. (43%) [4], and resulted in discontinuation of therapy in the majority of patients due to toxicity.

To date, there are several reports showing benefits in locoregional disease control and/or survival with an alternative schedule of cisplatin with concurrent radiotherapy for head and neck cancer [5–8]. These data suggest that smaller cisplatin doses administered more frequently may result in acceptable acute toxicities without compromising efficacy [5–8]. With regard to acute cisplatin-induced nephrotoxicity, vigorous pre- and post-chemotherapy hydration is not necessary in the weekly low-dose cisplatin regimen, which makes it easier to apply in an outpatient setting [8,9]. In a retrospective study by Ho et al., more than 80% of elderly patients with NPC were able to receive more than seven doses of weekly cisplatin during the RT course with promising survival outcomes [10].

Although several investigations have been undertaken to reduce toxicity while maintaining efficacy [11–16], no randomized controlled trial has been conducted to compare the efficacy and toxicity profiles of two different schedules of cisplatin as part of CCRT in the treatment of locally advanced NPC. We therefore conducted a multicenter randomized phase II trial to evaluate the efficacy, toxicity, and tolerability of a weekly versus triweekly cisplatin regimen in the CCRT setting.

Patients and methods

Patients

This was a prospective, multicenter, randomized phase II trial conducted at 19 centers in Korea. Patients with histologically confirmed WHO type I–III NPC that was locally advanced (Stage II–IVb) by AJCC/UICC-5 staging system without evidence of systemic metastasis were eligible to participate. Other inclusion criteria included age 19 years or older, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, and adequate organ function. Patients were not eligible if they had received prior chemotherapy and/or radiotherapy.

The current study was approved by the Institutional Review Board for Human Research at each participating institute. All patients were required to sign a written informed consent form before enrollment to the study. This study was coordinated by an independent central committee, the Korean Cancer Study Group (KCSG), for monitoring and data collection.

Concurrent and adjuvant chemotherapy

The patients were randomly assigned in a 1:1 ratio to a weekly cisplatin regimen (cisplatin 40 mg/m² infusion over 1 h on days 1, 8, 15, 22, 29, 36, and 43) or to a triweekly cisplatin regimen (cisplatin 100 mg/m² infusion over 1 h on days 1, 22, and 43). Both regimens were to be delivered concurrent with the RT course. Subsequent adjuvant chemotherapy using a combination of cisplatin 80 mg/m² intravenously and 5-fluorouracil 1000 mg/m²/day by 96-h infusion was given every 3 weeks for a total of three cycles, beginning 3 weeks after completion of CCRT.

Radiation therapy

Patients were stratified by RT technique (3-dimensional conformal RT [3D-CRT] vs. intensity-modulated RT [IMRT]). Delineation of gross tumor volume (GTV) and clinical target volume (CTV) was based on all available clinical and diagnostic image information. The GTV was designated to include all clinically evident gross disease and the CTV was designed to cover the clinically

uninvolved adjacent soft tissues or lymphatics that were suspected to harbor subclinical micrometastasis. Radiation dose was prescribed to the planning target volume, which extended the CTV by a few millimeters to consider the neighboring structures. The typical radiation dose schedule when using 3D-CRT was to deliver 70 Gy to the GTV over 7 weeks by daily administration of 2 Gy (50–60 Gy to the CTV followed by 10–20 Gy boost to the GTV). When using IMRT, the dose schedule was not strictly unified among the participating institutes and planned to deliver biologically equivalent doses to those used in 3D-CRT: 66–68.4 Gy to the GTV by daily administration of 2.2–2.4 Gy and 50–60 Gy to the CTV by daily administration of 1.8–2.0 Gy over 6–7 weeks. During the RT course, all patients were examined weekly to assess treatment-related toxicities, which were recorded using the Radiation Therapy Oncology (RTOG) acute morbidity scoring criteria.

Dose modification and discontinuation of chemotherapy

If the nadir of absolute neutrophil count (ANC) was <1000/μL and/or that of platelets was <100,000/μL, chemotherapy was delayed for up to 2 weeks until the ANC and platelet counts recovered to greater than 1000/μL and 100,000/μL respectively. For renal toxicities, if serum creatinine was between 1.5 and 2.0 times the upper normal limit (UNL) and calculated creatinine clearance rate (Ccr) was <60 mL/min, the cisplatin dosage was reduced to 50% for the next cycle. If serum creatinine was >2.0 × UNL or calculated Ccr was <45 mL/min, no further cisplatin was given.

Chemotherapy treatment was discontinued for the following reasons: disease progression, serious adverse events requiring other rescue therapies, delay of longer than 2 weeks for blood count recovery or renal toxicity, or at the request of the patient.

Patient assessment and follow-up

Clinical assessment following CCRT was scheduled 3 weeks after CCRT completion and included physical examination, blood tests, chest X-ray, and neck computed tomography (CT). Further clinical assessments were scheduled regularly at 3-month intervals for the first year and at 6-month intervals thereafter until disease progression and/or death. Treatment response was assessed according to Response Evaluation Criteria In Solid Tumor 1.1. All patients were asked to complete quality of life (QoL) questionnaires using the European Organization for Research and Treatment of Cancer (EORTC) Core Questionnaire Version 30 (EORTC QLQ-C30) [17] and the EORTC Head and Neck Cancer Module (EORTC QLQ-HN35) [18] at four time points: before the start of CCRT and at 3 weeks, 3 months, and 1 year after CCRT completion.

Statistical analysis

The primary endpoint of the current study was 3-year progression-free survival (PFS), defined as the time from the first date of CCRT until the date of first failure at any site or death from any cause. The secondary endpoints included OS, overall response rate (ORR), toxicity profile, and QoL changes. We compared the weekly regimen with the triweekly regimen by assessing whether the one-sided 80% confidence limit for the hazard ratio (HR) in PFS excluded a predefined margin of 1.5 for the HR [19]. Predicated on the INT-0099 trial [3], we expected a 3-year PFS of 75% with the triweekly regimen. For 80% power using a one-sided type I error of 20%, the test required at least 98 patients (49 patients per arm). All analyses were performed for the per-protocol population, excluding patients who withdrew before starting treatment. A χ^2 -test was used to assess the association of two categorical variables. Survival estimates were calculated according to the Kaplan–Meier method. Statistical analysis was performed using

SAS 9.4 (SAS Institute Inc., Cary, NC) and R version 3.1.2 (Vienna, Austria; <http://www.R-project.org/>). A two-sided *P*-value <0.05 was considered statistically significant.

Results

Patient characteristics

From September 2009 to December 2013, 111 eligible patients were enrolled from 19 Korean institutes. Two patients (one from each regimen) withdrew their consent before starting CCRT, and the remaining 109 patients (53 in the weekly regimen and 56 in the triweekly regimen) formed the per-protocol population (Fig. 1). The baseline characteristics of the patients were comparable between the regimens (Table 1). The median age of all patients was 53.6 years and 78.9% were male. The majority of the patients had stage III–IVb (77.1%) and WHO type 2 histology (71.6%) and 84.4% of the patients received IMRT.

Treatment and compliance

Table 2 shows the dose intensity and compliance in each regimen. The mean total dose of cisplatin and RT given were similar between the weekly and triweekly regimens (cisplatin, 248.9 mg/m² vs. 256.6 mg/m², *p* = 0.433; RT, 68.3 Gy vs. 67.3 Gy, *p* = 0.559). During CCRT, 31 patients (58.5%) completed the planned seven cycles of chemotherapy in the weekly regimen and 37 patients (66.1%) completed the planned three cycles of cisplatin in the triweekly regimen (*p* = 0.414). Thirteen patients (11.9%) could not complete CCRT and dropped out of the study due to toxicity and/or patient refusal: seven in the weekly regimen (13.2%) vs. six in the triweekly regimen (10.7%) (Fig. 1).

Adjuvant chemotherapy following CCRT was not delivered in 69 patients: 29 patients in the weekly regimen and 40 in the triweekly regimen (54.7% vs. 71.4%, *p* = 0.070). The main reason was poor performance status following CCRT in the triweekly regimen and refusal in the weekly regimen; however, this difference was not statistically significant (*p* = 0.434).

Efficacy

Response to the treatment protocol at 3 weeks after completion of CCRT could not be evaluated for five patients. The ORR was

98.1% with the weekly regimen and 96.2% with the triweekly regimen; complete response rates were 21.6% and 20.7%, respectively. The median follow-up was 30.0 months (range, 0.3–55.5). By February 6 2015, 29 patients (26.6%) had developed relapse (16 [30.2%] in weekly and 13 [23.2%] in triweekly regimen) and 14 patients (12.8%) had died (seven [13.2%] in weekly and seven [12.5%] in triweekly regimen). The 3-year PFS rate, which is the primary endpoint of the current study, was not inferior with the weekly regimen compared to the triweekly regimen (64.9% vs. 63.8%; HR 0.912, 95% CI, 0.68–1.22, *p* = 0.074) (Fig. 2A). The major failure pattern was local relapse in the triweekly regimen and distant metastasis in the weekly regimen; however, this difference was not statistically significant (Supplementary Table 1). The 3-year OS rates were 90.8% for weekly vs. 91.0% for triweekly regimen (HR 0.935, 95% CI, 0.33–2.67, *p* = 0.900) (Fig. 2B).

Subset analyses for RT technique (IMRT vs. 3D-CRT) showed that a significantly better 3-year PFS rate was achieved with IMRT than with 3D-CRT (69.3% vs. 41.8%, *p* = 0.027) (Supplementary Table 2). The addition of adjuvant chemotherapy was not a significant determinant with respect to survival outcome (*p* = 0.910 for PFS, *p* = 0.993 for OS). Subgroup analyses were consistent with those of the overall study population (Supplementary Fig. 1).

Toxicity

Toxicities after completion of CCRT that occurred in ≥10% of patients in either arm are listed in Table 3. There was no incidence of treatment-related mortality, and the most frequent toxicities were anemia, neutropenia, thrombocytopenia, stomatitis, nausea, and vomiting. Grade 3–4 toxic events of any type were observed in 25 patients (47.2%) in the weekly and 22 patients (39.3%) in the triweekly regimen (*p* = 0.443). In terms of grade 3–4 hematologic toxicity, neutropenia and thrombocytopenia were more common with the weekly regimen, whereas anemia was more frequent with the triweekly regimen. Grade 3–4 nephrotoxicity was not observed in either regimen. Two patients (one in each regimen) developed hearing loss following CCRT.

Quality of life

Baseline symptom score questionnaires were collected from all 109 patients. Overall, compliance of QoL assessment declined over

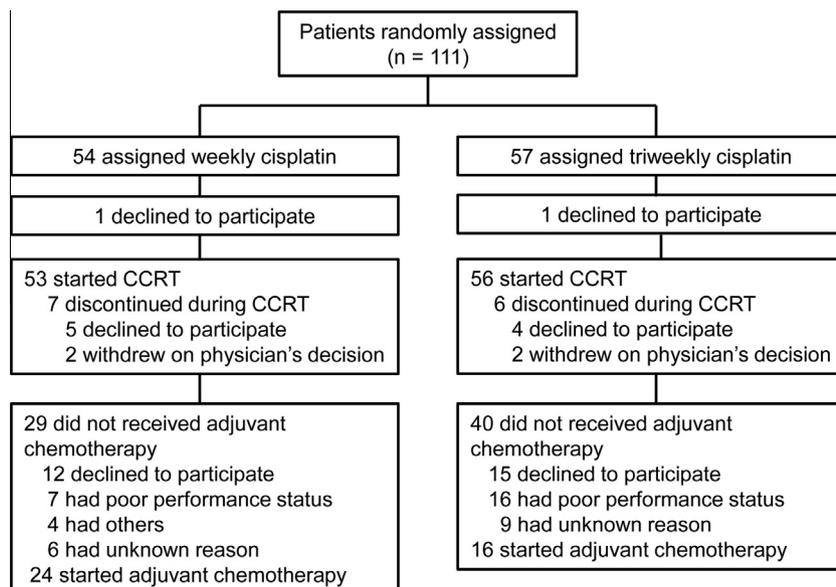


Fig. 1. Trial profile.

Table 1
Baseline characteristics.

Characteristics	Weekly arm (n = 53)		Triweekly arm (n = 56)		Total (n = 109)		p
	No.	%	No.	%	No.	%	
Age, years							
Median (range)	53.6 (18.7–73.9)		52.7 (19.2–77.7)		52.6 (18.7–77.7)		0.848
Sex							
Male	39	73.6	47	83.9	86	78.9	0.186
Female	14	26.4	9	16.1	23	21.1	
ECOG PS							
0	6	11.3	4	7.1	10	9.2	0.214
1	47	88.7	50	89.3	97	89.0	
2	0	0	2	3.6	2	1.8	
T stage (1997 AJCC)							
T1–T2	28	52.8	26	46.4	54	49.5	0.568
T3–T4	25	47.2	30	53.6	55	50.5	
N stage (1997 AJCC)							
N0–N1	29	54.7	28	50.0	57	52.3	0.689
N2–N3	24	45.3	28	50.0	52	47.7	
Stage (1997 AJCC)							
II	15	28.3	10	17.9	25	22.9	0.435
III	24	45.3	32	57.1	56	51.4	
IVa–IVb	14	26.4	14	25.0	28	25.7	
Histology							
WHO type 1	7	13.2	10	17.9	17	15.6	0.407
WHO type 2	37	69.8	41	73.2	78	71.6	
WHO type 3	9	17.0	5	8.9	14	12.8	
RT parameter							
3D-CRT	8	15.1	9	16.1	17	15.6	0.888
IMRT	45	84.9	47	83.9	92	84.4	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; RT, radiotherapy; 3D-CRT, 3-dimensional conformal RT; IMRT, intensity-modulated radiation therapy.

Table 2
Treatment and response.

	Weekly arm (n = 53)		Triweekly arm (n = 56)		p
	No.	%	No.	%	
Total dose given during CCRT					
Cisplatin, mg/m ²					
Mean (SD)	248.9 (46.5)		256.6 (56.0)		0.433
Radiotherapy, Gy					
Mean (SD)	68.3 (8.1)		67.3 (10.0)		0.559
Intended cycles completed during CCRT					
Yes	31	58.5	37	66.1	0.414
No	22	41.5	19	33.9	
Dosage alterations					
Dose reduction	1	1.9	3	5.4	0.619
Dose delay	10	18.9	18	32.1	0.113
Dose omission	27	50.9	22	39.3	0.221
Subsequent systemic adjuvant chemotherapy					
Yes	24	45.3	16	28.6	0.070
No	29	54.7	40	71.4	
Reason skip adjuvant chemotherapy*					
Poor performance status	7	30.4	16	51.6	0.434
Refusal	12	52.2	15	48.4	
Other	4	17.4	0	0	
Tumor control after completion of CCRT [†]					
Complete response	11	26.6	11	20.7	1.000
Partial response	39	76.5	40	75.5	
Stable disease	1	1.9	2	3.8	

Abbreviations: CCRT, concurrent chemoradiation; SD, standard deviation.

* Out of 69 patients who did not received adjuvant chemotherapy, 54 patients were able to further analysis.

[†] Of a total 109 patients, 104 patients were evaluable for tumor response.

the course of the study in both groups. The compliance rate of QoL assessment between the weekly and triweekly regimens was different at each time point: 83.0% and 67.9% at 3 weeks ($p = 0.067$); 67.9% and 60.7% at 3 months ($p = 0.433$); 58.5% and 37.5% at 1 year ($p = 0.028$). Overall, QoL decreased 3 weeks after completing CCRT and gradually improved thereafter for both regimens. According to the EORTC QLQ-C30 at 3 weeks after CCRT, patients on the weekly regimen showed better physical ($p = 0.039$), emotional ($p = 0.019$), and social functioning ($p = 0.008$) than those on the triweekly regimen (Fig. 3A). Patients on the triweekly regimen reported more appetite loss than those on the weekly regimen ($p = 0.006$) (Fig. 3A). EORTC-QLQ-HN35 scoring at 3 weeks after CCRT revealed that patients on the triweekly regimen had more problems with speech ($p = 0.003$), social contact ($p = 0.043$), and sticky saliva ($p = 0.019$) than those on the weekly regimen (Fig. 3B). There were no significant differences in QoL parameters compared to the baseline scores at other time points (3 months and 1 year after CCRT) except for dry mouth at 3 months and social functioning at 1 year after CCRT (Supplementary Table 3 and Supplementary Fig. 2).

Discussion

The mainstay of treatment for locally advanced NPC is cisplatin-based CCRT. Although several randomized studies have been conducted in patients with locally advanced NPC, the optimal CCRT regimen with regard to efficacy and safety remains to be determined. To our knowledge, this is the first randomized trial to evaluate the efficacy, toxicity, and tolerability of weekly administration of cisplatin (40 mg/m²) compared with triweekly administration of

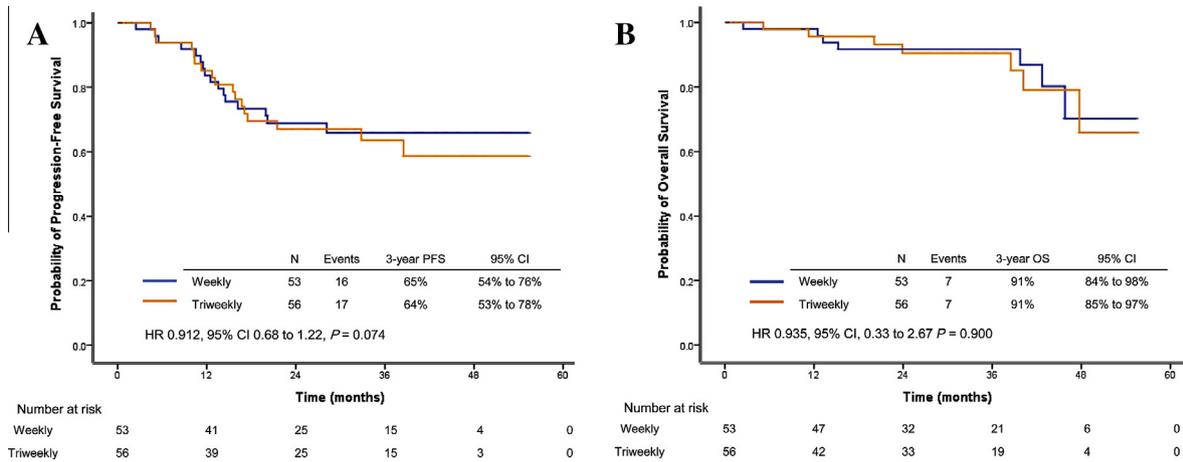


Fig. 2. Kaplan–Meier curves for progression-free survival (A) and overall survival (B) according to treatment regimen.

Table 3
Adverse events.

Toxicity	Weekly arm (n = 53)	Triweekly arm (n = 56)	p
Hematologic			
Anemia, n (%)			
<G3	52 (98.1)	51 (91.1)	0.207
≥G3	1 (1.9)	5 (8.9)	
Neutropenia, n (%)			
<G3	38 (71.7)	47 (83.9)	0.124
≥G3	15 (28.3)	9 (16.1)	
Thrombocytopenia, n (%)			
<G3	49 (82.5)	55 (98.2)	0.198
≥G3	4 (7.5)	1 (1.8)	
Non-hematologic			
Nausea/vomiting, n (%)			
<G3	49 (92.5)	50 (89.3)	0.743
≥G3	4 (7.5)	6 (10.7)	
Stomatitis, n (%)			
<G3	45 (84.9)	49 (87.5)	0.694
≥G3	8 (15.1)	7 (12.5)	
Rash, n (%)			
<G3	53 (100)	55 (98.2)	1.000
≥G3	0	1 (1.8)	
Neuropathy [†] , n (%)			
G0	51 (96.5)	52 (92.9)	0.679
G1	2 (3.8)	4 (7.1)	

Abbreviation: G, grade.

[†] There was no grade 2–4 toxicities in two groups.

cisplatin (100 mg/m²) under a CCRT setting in the treatment of locally advanced NPC.

The current study confirmed that the primary endpoint of 3-year PFS with the weekly cisplatin regimen was not inferior to that with the triweekly cisplatin regimen (HR 0.912). The 3-year PFS rate achieved with the weekly regimen (64.9%) was comparable to that with the triweekly regimen (63.8%), which in turn was comparable to previous reports [14,20,21]. At 3 weeks after completion of CCRT, the ORR was similar between the two arms (98.1% vs. 96.2%). As in previous reports [22,23], the current study showed better PFS with the IMRT technique than with the 3D-CRT technique; however, subset analysis according to RT technique demonstrated no difference between weekly and triweekly regimens.

In the current study, more than 85% of the planned cisplatin dose was administered during the RT course for both regimens. This high compliance rate in both regimens could in part be explained by the high rate of IMRT adoption (greater than 85%)

as CCRT using the IMRT technique is known to be associated with improved toxicity profiles and QoL [23–25]. When we compared the compliance of CCRT between weekly and triweekly regimens, the mean cisplatin dose was not significantly different between the two groups (248.9 mg/m² vs. 256.6 mg/m²), consistent with the study by Ho et al. [8]. Almost two-thirds of the patients in the current study did not receive adjuvant chemotherapy following CCRT completion, and this proportion was higher with the triweekly regimen. Whether the addition of adjuvant chemotherapy provides additional survival benefit over CCRT alone in NPC remains controversial [26–28]. In the current study, the overall clinical outcome of patients who did not receive adjuvant chemotherapy was comparable to that of those treated with adjuvant chemotherapy, although this may reflect the high prevalence of favorable histologic types in our study population. It is interesting that poor performance status after CCRT was the main reason for omission of adjuvant chemotherapy in patients treated with the triweekly regimen. It appears that cisplatin-based CCRT is less tolerable in a triweekly regimen than in a weekly regimen.

The concept of a once-weekly regimen is based on the hypothesis that smaller cisplatin doses administered more frequently will produce a better toxicity profile while maintaining efficacy. It is notable that the incidence of grade 3–4 toxic events of any type was not decreased in the patients on the weekly regimen, similar to findings of the study by Ho et al. [8]. Uygun et al. demonstrated that grade 3–4 toxic events were observed more often with a triweekly regimen (53.3%) compared with a weekly regimen (40%), but this difference was not significant [29]. In contrast, Geeta et al. [30] and Tsan et al. [31] found that a once-weekly cisplatin regimen had a higher rate of severe mucositis. In the current study, per protocol toxicity assessment was once a week, but assessment every 3 weeks was allowed according to the investigator's decision. The proportion of patients who were evaluated four or more times for toxicity assessment was significantly higher among the patients on the weekly regimen compared with the triweekly regimen (56.6% vs. 7.1%, $p < 0.001$). This finding might represent an undefined bias regarding toxicity profiles.

To the best of our knowledge, this is the first study that evaluates QoL prospectively using EORTC QLQ-C30 and QLQ-H&N35 using a longitudinal design in randomly assigned patients with NPC. All patients completed the baseline QoL measurement, but low compliance was noted with follow-up assessments. It is noteworthy that the compliance rate of the QoL questionnaire was consistently higher in the weekly regimen arm across all time points. The results indicated an inverse relationship between QoL scores and the probability of dropout. At 3 weeks after CCRT completion a majority

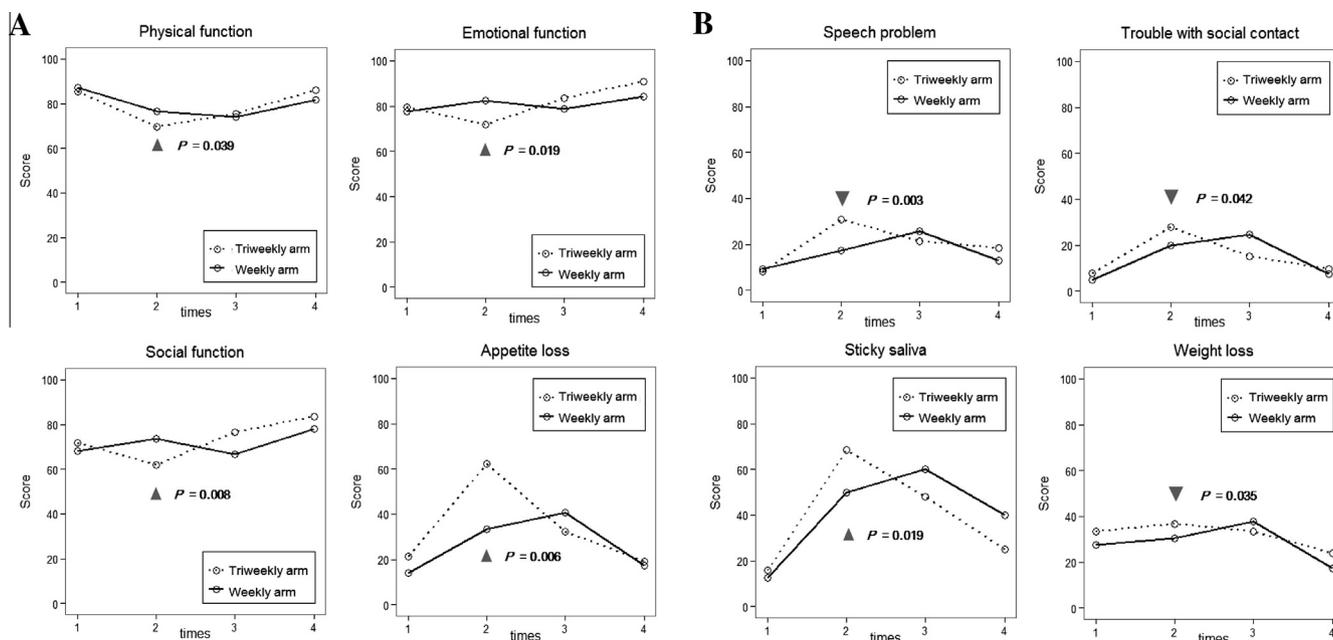


Fig. 3. Time trend for responses to EORTC QLQ-C30 (A) and EORTC-QLQ-HN35 (B) questionnaires according to treatment regimen.

patients in each regimen reported temporary worsening of QoL; however, most scores returned to near baseline levels over the course of follow-up. Intriguingly, patients on the weekly regimen reported better physical, emotional, and social functioning and less worsening of symptom scales including appetite loss, speech problems, and sticky saliva. Recently, Tsan et al. [31] demonstrated that the triweekly cisplatin regimen resulted in better physical well-being than the weekly regimen. These contradictory results might be attributed to differences in the study populations.

This study has several limitations. Given the low incidence of locally advanced NPC in Korea, we chose a relatively large alpha value and a large hazard ratio to attain a reasonable sample size for this phase II trial, resulting in low statistical power. Unbalanced assessment of toxicity profiles between the two regimens is a potentially undefined bias regarding safety. Therefore, a large randomized phase III trial is warranted to confirm the safety and efficacy of the weekly regimen. Considering the favorable prognosis of NPC, further follow-up is needed to fully evaluate the long-term survival and late toxicities.

Although not conclusive, our data indicate that once-weekly cisplatin combined with radiation for the treatment of locally advanced NPC has comparable efficacy and safety with improved QoL compared to a triweekly regimen.

Conflicts of interest statement

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.radonc.2015.11.030>.

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