RESEARCH ARTICLE

Editorial Process: Submission:11/11/2017 Acceptance:05/22/2018

Concurrent Chemoradiotherapy for Loco-regionally Advanced Nasopharyngeal Carcinoma: Treatment Outcomes and Prognostic Factors

Moonkyoo Kong*, Yu Jin Lim, Youngkyong Kim

Abstract

Background: We conducted this study to contribute to resolving some controversial issues on management of nasopharyngeal carcinoma. **Methods:** Thirty-two patients with stage III-IVB nasopharyngeal carcinoma were included in this retrospective study. All patients received concurrent chemoradiotherapy with either 3D conformal radiotherapy or intensity-modulated radiotherapy. We retrospectively analyzed the survival outcome, prognostic factors for survival, and toxicity outcome. **Results:** The 2- and 5-year overall survival rates were 89.9% and 82.6%. The 2- and 5-year distant metastasis-free survival rates were 83.2% and 79.4%. The 2- and 5-year loco-regional recurrence-free survival rates were 83.3% and 79.5%. Addition of induction chemotherapy to concurrent chemoradiotherapy did not improve survival outcomes. The survival benefit of intensity-modulated radiotherapy over 3D conformal radiotherapy was not clear. Intensity-modulated radiotherapy significantly decreased the development of late toxicities compared with 3D conformal radiotherapy. Total RT dose was prognostic factor for overall, loco-regional recurrence-free, and distant metastasis-free survival. Temporary RT interruption was prognostic factor for overall survival. Daily RT dose was prognostic factor for distant metastasis-free survival. **Conclusions:** Concurrent chemoradiotherapy resulted in high survival rates with an acceptable level of toxicities in patients with loco-regionally advanced nasopharyngeal carcinoma. To confirm the results of this study, well-designed randomized prospective trials are warranted**.**

Keywords: Nasopharyngeal carcinoma- radiotherapy- survival

Asian Pac J Cancer Prev, **19 (6)**, 1591-1599

Introduction

Definitive radiotherapy (RT) with concurrent chemotherapy is the standard treatment for patients with loco-regionally advanced nasopharyngeal carcinoma. Several phase III randomized trials have confirmed concurrent chemo-RT as the standard of care for loco-regionally advanced nasopharyngeal carcinoma (Al-Sarraf et al., 1998; Lin et al., 2003; Chan et al., 2005; Wee et al., 2005; Zhang et al., 2005; Chen et al., 2008). However, several debates still exist. Because RT fractionation and concurrent chemotherapy schedules varied from trial to trial, the optimal RT dose fractionation and concurrent chemotherapy schedules remain to be defined. Also, the role of induction or adjuvant chemotherapy in addition to chemo-RT is controversial. Several clinical studies have been conducted to investigate the potential survival benefit conferred by the use of induction or adjuvant chemotherapy over concurrent chemo-RT alone (Chan et al., 2005; Wee et al., 2005; Hui et al., 2009; Chen et al., 2012; Fountzilas et al., 2012; Sun et al., 2016). However, the results of these trials were in conflict with each other. In addition, results showing the clear survival benefit of intensity-modulated RT over 3D conformal RT in patients with nasopharyngeal carcinoma are still limited (Fang et al., 2008; Lee et al., 2014; Moon et al., 2016).

In this study, to contribute to resolving some controversial issues regarding the management of nasopharyngeal carcinoma, we retrospectively analyzed the clinical outcomes and prognostic factors for survival in patients with loco-regionally advanced nasopharyngeal carcinoma treated with concurrent chemo-RT.

Materials and Methods

Inclusion criteria were histologically proven stage III-IVB nasopharyngeal carcinoma, receipt of definitive concurrent chemo-RT, receipt of >80% of the planned RT dose, Eastern Cooperative Oncology Group performance status ≤2, no previous history of head and neck area irradiation, no distant metastasis, no previous or concurrent illness that would compromise completion of treatment, and available follow-up data. From January

*Department of Radiation Oncology, Kyung Hee University Medical Center, Kyung Hee University School of Medicine, Seoul, Republic of Korea. *For Correspondence: kongmoonkyoo@khu.ac.kr*

2007 to December 2015, 89 patients with nasopharyngeal carcinoma received RT at our institution. Of these patients, 32 met the inclusion criteria and were included in this retrospective study.

Pretreatment evaluation consisted of a complete history and physical examination, nasopharyngeal fiberscopy, complete blood and biochemical tests, tests to assess liver and renal function, a chest X-ray, dental evaluation, computed tomography (CT) scan and magnetic resonance imaging (MRI) of the head and neck region, and positron emission tomography (PET). A bone scan and CT scans of the chest and/or abdomen were performed when clinically indicated. Each cancer was restaged according to the 7th edition of the American Joint Committee on Cancer staging system. Biopsy specimens were histologically classified according to the World Health Organization system. We retrospectively reviewed hospital records, laboratory records, and imaging studies. The Institutional Review Board of our institution approved this study, and all research was carried out in compliance with the Declaration of Helsinki.

All patients received CT-planned RT with either 3D conformal RT or intensity-modulated RT. The choice between 3D conformal RT and intensity-modulated RT was determined by the physician based on tumor spread, and the patient's preference and general condition. Gross tumor volume (GTV) included the gross extent of the primary tumor and involved cervical lymph nodes based on CT, MRI, and/or PET, as well as suspicious areas on physical and/or endoscopic examinations. High-risk clinical target volume (CTV) was defined as the GTV plus a 1- to 1.5-cm margin in order to account for subclinical tumor spread. CTV -> High-risk CTV usually encompassed the entire nasopharyngeal mucosa and suspicious areas at risk in the skull base, parapharyngeal spaces, inferior sphenoid sinuses, posterior nasal cavity, and posterior maxillary sinuses. Low-risk CTV was defined by the total volume of prophylactically treated neck lymph nodes. Planning target volume (PTV) was created by adding an additional 5-mm margin to the CTV. Prescription dose was determined by the physician based on tumor stage, patient's general condition, and probability of RT-induced toxicity. High-risk PTV was treated with a daily dose of 1.8-2.2 Gy and a total dose of 63-73.5 Gy. Low-risk PTV was treated with a daily dose of 1.65-2 Gy and a total dose of 45-54 Gy. For standard comparison of different RT dose schedules, biologically equivalent doses were calculated using a linear quadratic model with an α/β ratio of 10. The 3D conformal RT was performed with a Clinac iX (Varian Medical System Inc., Palo Alto, CA, USA) and intensity-modulated RT was conducted using a TomoTherapy (Accuray Inc., Madison, WI, USA) with a simultaneous integrated boost technique. An individual RT plan was tailored according to patient anatomy and disease extent. Treatment plans were evaluated using dose-volume histograms and isodose curves. In general, we considered plans to be acceptable if the PTV was covered by 95% isodose curves, if the inhomogeneity for PTV ranged from 95% to 110%, and if the doses to critical normal organs were limited in their tolerances.

All patients received concurrent chemotherapy during the course of the RT with intravenous administration of 100 mg/m^2 cisplatin every 3 weeks or 30-40 mg/m^2 weekly, starting on the day of RT initiation. The decision to use induction chemotherapy before concurrent chemo-RT was made by a multidisciplinary team after discussion among radiation, surgical, and medical oncologists. The induction chemotherapy regimen was a combination of docetaxel/cisplatin/5-fluorouracil every 3 weeks for 2-4 cycles. The regimen of chemotherapy was individualized based on the patient's general condition and compliance. During the study period, no patient received adjuvant chemotherapy at our institution.

The primary endpoint of this study was overall survival. The secondary endpoints were loco-regional recurrence-free survival, distant metastasis-free survival, and incidence of treatment-induced toxicities. Patients were examined at least weekly during chemo-RT to monitor the presence of treatment-induced acute toxicities. After completion of chemo-RT, patients were evaluated every 2 to 4 weeks until the acute toxicities subsided. For routine follow-up evaluation, patients were examined at least a 3 months interval during the first 2 years, and subsequently every 6 months until death. Each follow-up evaluation included a complete history and physical examination, nasopharyngeal fiberscopy, and CT or MRI of the head and neck region. When patients had potential loco-regional recurrence or distant metastasis, additional examinations were performed at the discretion of the treating physician to confirm disease progression. Loco-regional recurrence was defined as increased size of target lesions (in-field loco-regional recurrence) or the appearance of new lesions in the head and neck region (out-field loco-regional recurrence). Distant metastasis was defined as evidence of tumor in any other area. The patients who experienced loco-regional recurrence or distant metastasis received salvage treatment, such as RT, surgery, and/or chemotherapy, if possible. Acute and late toxicities were graded according to the Radiation Therapy Oncology Group (RTOG)/ European Organization for Research and Treatment of Cancer (EORTC) toxicity criteria. Acute toxicity was defined as toxicity that occurred during chemo-RT or within 3 months after completion of treatment. Toxicity that occurred thereafter was graded as late toxicitiy.

Actuarial survival rates were estimated using the Kaplan-Meier method, and comparisons between groups were performed using log-rank tests. Survival times were calculated from the date of nasopharyngeal carcinoma diagnosis to the date of an endpoint event or the final follow-up visit. Parameters with a P-value <0.50 on univariate analysis were further assessed with multivariate analysis using a Cox proportional regression hazard model. The chi-square test was used to compare toxicity rates between treatment groups. All tests were two-sided and a $P<0.05$ was considered to be statistically significant. All analyses were performed using SPSS version 20.0 (IBM corporation, Armonk, NY, USA).

Results

Patient and tumor characteristics are summarized in

Table 1. The most commonly prescribed RT fractionation schedule was total 70 Gy with daily 2 Gy; 11 patients (34.4%) were treated with this fractionation schedule. Twelve patients (37.5%) experienced temporary RT interruption because of either acute treatment toxicities or refusal of treatment. The median duration of RT interruption was 13 days (range, 1-38 days). Due to treatment toxicities, four (12.5%) and three (9.3%) patients received incomplete concurrent and induction chemotherapy, respectively. One patient died of treatment toxicity after 45 days of concurrent chemo-RT completion. The dead patient received induction chemotherapy followed by concurrent chemo-RT. In all patients, the median follow-up period was 54.5 months (range, 1.5-158.1 months).

During the follow-up period, 27 patients (84.4%) remained alive. The 2- and 5-year overall survival rates were 89.9% and 82.6%, respectively. Distant metastases developed in six patients. The most common metastatic site was a lung. Among the six patients who experienced distant metastases, three patients experienced distant metastases in the lung, one patient in bone, one patient in the liver, and one patient in both the brain and bone. The 2- and 5-year distant metastasis-free survival rates were 83.2% and 79.4%, respectively. Six patients experienced loco-regional recurrences. Among the patients who experienced loco-regional recurrences, three experienced both in- and out-field loco-regional recurrences, two experienced out-field loco-regional recurrence. One patient experienced in-field loco-regional recurrence only. The 2- and 5-year loco-regional recurrence-free survival rates were 83.3% and 79.5%, respectively (Table 2). Among the patients who experienced disease recurrences, three experienced both loco-regional recurrence and distant metastasis. All patients with distant metastases were salvaged with systemic chemotherapy. Among the three patients who experienced loco-regional recurrence alone, two were salvaged with re-irradiation, and one patient underwent surgical resection.

In all patient groups, univariate and multivariate analyses were performed to identify prognostic factors for survival. The analysis of prognostic factors for overall survival is summarized in Table 3. Univariate analysis revealed that total RT dose (P=0.026) and temporary RT interruption (P=0.046) were significant prognostic factors for overall survival. Lower radiation dose and temporary RT interruption were significantly associated with worse overall survival. However, these associations were not statistically significant in multivariate analysis. Prognostic factors for loco-regional recurrence-free survival are summarized in Table 4. Total RT dose (P=0.010) was significantly associated with loco-regional recurrence-free survival in univariate analysis. However, there was no significant prognostic factor for loco-regional recurrence-free survival in multivariate analysis. Prognostic factors for distant metastasis-free survival were also analyzed and the results are summarized in Table 5. In univariate analysis, total RT dose (P=0.008) was a significant prognostic factor for distant metastasis-free survival. In multivariate analysis, daily RT dose (P=0.040; hazard ratio, 6.739; 95% confidence interval, 0.869-68.462) was significantly associated with distant metastasis-free survival. Patients who received lower daily radiation dose exhibited worse distant metastasis-free survival. However, the statistically significant association between total RT dose and distant metastasis-free survival was lost on multivariate analysis.

Acute toxicities occurred in almost all patients. Commonly observed acute toxicities were mucositis, dermatitis, dysphagia, and xerostomia. The incidences of acute toxicities are summarized in Table 6. There were no significant differences in acute toxicities between patients who underwent 3D conformal RT and those who underwent intensity-modulated RT. Because one patient died after 45 days of concurrent chemo-RT completion, late toxicities were evaluated in 31 patients except the dead patient. Frequently occurring late toxicities were xerostomia, dysphagia, and hearing loss. The incidences of late toxicities are summarized in Table 7. Patients who received 3D conformal RT experienced

Table 1. Patient and Tumor Characteristics (n=32)

Characteristics	n (%)
Age (years)	Median 53.2 (range, 34.5-70.5)
Sex	
Male/female	25 (78.1)/7 (21.9)
ECOG performance status	
0/1/2	6 (18.7)/21 (65.6)/5 (15.7)
Alcohol status	
Current/previous/never	22 (68.7)/2 (6.3)/8 (25)
Smoking status	
Current/previous/never	18 (56.3)/5 (15.6)/9 (28.1)
WHO histology[a]	
I / II / III	12 (37.5)/5 (15.6)/15 (46.9)
T stage	
1/2/3/4	3 (9.4)/12 (37.5)/9 (28.1)/8 (25)
N stage	
0/1/2/3	2 (6.3)/6 (18.8)/21 (65.5)/3 (9.4)
AJCC stage	
III / IVA / IVB	22 (68.8)/7 (21.9)/3 (9.3)
GTV (cc)	Median 56.5 (range, 25.1-95.4)
RT technique	
IMRT/3D-CRT	15 (46.9)/17 (53.1)
Total RT dose (BED, Gy_{10})	Median 82.7 (range, 68.7-88.9)
RT duration (weeks)	Median 7.5 (range, 6.2-13.2)
RT interruption	
Yes/no	12 (37.5)/20 (62.5)
Induction chemotherapy	
Yes/no	15 (46.9)/17 (53.1)

ECOG, Eastern Cooperative Oncology Group; WHO, World Health Organization; AJCC, American Joint Committee on Cancer Staging; GTV, gross tumor volume; RT, radiotherapy; IMRT, intensity-modulated radiotherapy; 3D-CRT, 3-dimensional conformal radiotherapy; BED, biologically equivalent dose; [a]WHO histology I, keratinizing squamous cell carcinoma; II, non-keratinizing carcinoma, differentiated type; III, non-keratinizing carcinoma, undifferentiated type.

Table 2. Survival Outcomes of 32 Patients with Loco-regionally Advanced Nasopharyngeal Carcinoma Receiving Concurrent Chemoradiotherapy

	2-year (%)	5-year (%)	Details
Loco-regional recurrence-free survival	83.3	79.5	Loco-regional recurrence developed in 6 patients
			3: both in- and out-field recurrence
			2: out-field recurrence
			1: in-field recurrence
Distant metastasis-free survival	83.2	79.4	Distant metastasis developed in 6 patients
			3: lung
			1: bone
			1: liver
			1: both brain and bone
Overall survival	89.9	82.6	27 patients alive

Table 3. Analysis of Prognostic Factors for Overall Survival

Variables	3-year overall survival (%)	P-value	
		Univariate	Multivariate
RT technique			
IMRT vs. 3D-CRT	87.5 vs. 76.0	0.391	0.244
Age (years)			
<50 vs. ≥50	72.7 vs. 94.1	0.186	0.178
Gender			
Male vs. female	81.6 vs. 85.7	0.875	
Smoking status			
Current or previous vs. never	79.7 vs. 88.9	0.611	
Alcohol status			
Current or previous vs. never	80.4 vs. 87.5	0.759	
WHO histology[a]			
1 vs. 2-3	82.5 vs. 82.7	0.974	
T stage			
1-2 vs. 3-4	93.3 vs. 70.0	0.147	0.126
N stage			
0-1 vs. 2-3	85.7 vs. 81.2	0.816	
AJCC stage			
3 vs. 4	90.7 vs. 59.3	0.074	0.070
GTV (cc)			
≤55 vs. >55	92.9 vs. 73.9	0.253	0.571
Total RT dose (BED, Gy_{10})			
≤82.5 vs. >82.5	67.6 vs. 100	0.026	0.255
Daily dose (Gy)			
≤2 vs. >2	86.1 vs. 72.9	0.467	0.443
RT duration (weeks)			
≤7.5 vs. >7.5	92.9 vs. 73.7	0.209	0.327
RT interruption			
Yes vs. no	64.2 vs. 94.4	0.046	0.075
Induction chemotherapy			
Yes vs. no	79.4 vs. 85.7	0.522	

RT, radiotherapy; IMRT, intensity-modulated radiotherapy; 3D-CRT, 3-dimensional conformal radiotherapy; WHO, World Health Organization; AJCC, American Joint Committee on Cancer Staging; GTV, gross tumor volume; BED, biologically equivalent dose. [a]WHO histology I, keratinizing squamous cell carcinoma; II, non-keratinizing carcinoma, differentiated type; III, non-keratinizing carcinoma, undifferentiated type

Table 4. Analysis of Prognostic Factors for Loco-regional Recurrence-free Survival

Variables	3-year loco-regional recurrence-free survival (%)	P-value	
		Univariate	Multivariate
RT technique			
IMRT vs. 3D-CRT	82.4 vs. 73.5	0.714	0.415
Age (years)			
<50 vs. ≥50	66.0 vs. 93.8	0.077	0.053
Gender			
Male vs. female	82.2 vs. 71.4	0.546	
Smoking status			
Current or previous vs. never	80.5 vs. 77.8	0.879	
Alcohol status			
Current or previous vs. never	72.8 vs. 100	0.138	0.421
WHO histology[a]			
1 vs. 2-3	66.7 vs. 87.4	0.120	0.478
T stage			
1-2 vs. 3-4	85.7 vs. 75.5	0.353	0.273
N stage			
0-1 vs. 2-3	87.5 vs. 76.8	0.650	
AJCC stage			
3 vs. 4	85.2 vs. 68.6	0.186	0.181
GTV (cc)			
≤55 vs. >55	91.7 vs. 70.9	0.134	0.377
Total dose (BED, Gy_{10})			
≤82.5 vs. >82.5	60.4 vs. 100	0.010	0.201
Daily dose (Gy)			
≤2 vs. >2	86.1 vs. 61.0	0.167	0.094
RT duration (weeks)			
≤7.5 vs. >7.5	85.9 vs. 73.3	0.385	0.576
RT interruption			
Yes vs. no	81.8 vs. 78.7	0.917	
Induction chemotherapy			
Yes vs. no	78.3 vs. 80.1	0.878	

RT, radiotherapy; IMRT, intensity-modulated radiotherapy; 3D-CRT, 3-dimensional conformal radiotherapy; WHO, World Health Organization; AJCC, American Joint Committee on Cancer Staging; GTV, gross tumor volume; BED, biologically equivalent dose. [a]WHO histology I, keratinizing squamous cell carcinoma; II, non-keratinizing carcinoma, differentiated type;III, non-keratinizing carcinoma, undifferentiated type

significantly higher incidence of late toxicities compared with those who received intensity-modulated RT (P=0.021 for dysphagia, P=0.032 for xerostomia, and P=0.039 for hearing loss).

Discussion

Several studies have reported the treatment outcomes of concurrent chemo-RT in patients with nasopharyngeal carcinoma, and the reported 5-year overall survival rates range from 73% to 83.2%, the loco-regional recurrence-free survival rates range from 81.1% to 91.8%, and the distant metastasis-free survival rates range from 66% to 81% (Lin et al., 2009; Wong et al., 2010; Siti-Azrin et al., 2014; Sun et al., 2014; Shi et al., 2015; Wee et al., 2015; Zheng et al., 2015; Maklad et al., 2016; Tao et al., 2016). In our study, the 5-year overall, loco-regional recurrence-free, and distant metastasis-free survival rates were 82.6%, 79.5%, and 79.4%, respectively. Due to heterogeneous tumor characteristics, various RT fractionation and chemotherapy schedules, and an imbalance in risk factors, it is hard to compare treatment outcomes between previously published studies and our study. It is also important to note that there are ethnic differences in the patient populations in these studies, because diseases can behave differently among different nationalities. In Korea, Wee et al., (2015) reported the oncologic outcomes of loco-regionally advanced nasopharyngeal carcinoma in patients treated with concurrent chemo-RT in 2015. In that retrospective study, 83 patients with stage III-IVB nasopharyngeal carcinoma were included for evaluation, and the 5-year overall, loco-regional recurrence-free, and distant metastasis-free survival rates were 81.8%, 89.3%, and 77.8%, respectively. Compared with Wee's study, our study showed comparable overall (82.6% vs. 81.8%) and distant metastasis-free survival rates (79.4% vs. 77.8%).

Table 5. Analysis of Prognostic Factors for Distant Metastasis-Free Survival

Variables	3-year distant metastasis-free survival (%)	P-value	
		Univariate	Multivariate
RT technique			
IMRT vs. 3D-CRT	81.9 vs. 77.1	0.656	0.275
Age (years)			
<50 vs. ≥50	73.3 vs. 83.9	0.334	0.270
Gender			
Male vs. female	81.4 vs. 71.4	0.433	0.375
Smoking status			
Current or previous vs. never	79.4 vs. 77.8	0.769	
Alcohol status			
Current or previous vs. never	72.8 vs. 100	0.142	0.442
WHO histology[a]			
1 vs. 2-3	74.1 vs. 82.9	0.558	
T stage			
1-2 vs. 3-4	85.7 vs. 73.3	0.435	0.417
N stage			
0-1 vs. 2-3	81.9 vs. 72.9	0.627	
AJCC stage			
3 vs. 4	80.4 vs. 78.8	0.798	
GTV (cc)			
≤55 vs. >55	83.9 vs. 76.6	0.594	
Total dose (BED, Gy_{10})			
≤82.5 vs. >82.5	59.6 vs. 100	0.008	0.197
Daily dose (Gy)			
≤2 vs. >2	64.8 vs. 85.6	0.142	0.040
RT duration (weeks)			
≤7.5 vs. >7.5	80.2 vs. 79.4	0.945	
RT interruption			
Yes vs. no	71.6 vs. 84.0	0.512	
Induction chemotherapy			
Yes vs. no	78.6 vs. 80.1	0.762	

RT, radiotherapy; IMRT, intensity-modulated radiotherapy; 3D-CRT, 3-dimensional conformal radiotherapy; WHO, World Health Organization; AJCC, American Joint Committee on Cancer Staging; GTV, gross tumor volume; BED, biologically equivalent dose. [a]WHO histology I, keratinizing squamous cell carcinoma; II, non-keratinizing carcinoma, differentiated type; III, non-keratinizing carcinoma, undifferentiated type

Table 6. Acute Toxicities after Concurrent Chemo-RT for Nasopharyngeal Carcinoma

RT technique	Grade	Mucositis	Dermatitis	Dysphagia	Xerostomia	Hematologic
3D-CRT (n=17)	0	0	0	0	0	0
	1	1 (5.9)	2 (11.8)	5 (29.4)	9 (52.9)	7 (41.1)
	2	5 (29.4)	5 (29.4)	6 (35.3)	6 (35.3)	7 (41.1)
	3	11 (64.7)	10 (58.8)	6 (35.3)	2 (11.8)	2 (11.8)
	4	0	0	0	0	0
	5	0	0	0	0	1 (6)
IMRT (n=15)	0	0	0	0	1	0
	1	1 (6.7)	1 (6.7)	5 (33.3)	7 (46.6)	7 (46.6)
	2	5 (33.3)	5 (33.3)	5 (33.3)	6 (40)	7 (46.6)
	3	9 (60)	9 (60)	5 (33.3)	2 (13.4)	1 (6.7)

RT, radiotherapy; 3D-CRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy. Data are presented as number of patients (%)

Table 7. Late Toxicities after Concurrent Chemo-RT for Nasopharyngeal Carcinoma

RT technique	Grade	Dysphagia	Xerostomia	Hearing loss
3D-CRT (n=16)	0	4 (25)	0	4 (25)
	1	5 (31.3)	5 (31.3)	5 (31.3)
	2	5 (31.3)	7 (43.8)	5 (31.3)
	3	2 (12.4)	4 (25)	2 (12.4)
IMRT (n=15)	0	7 (46.7)	0	8 (53.3)
	1	4 (26.6)	8 (53.3)	5 (33.3)
	2	4 (26.6)	7 (46.7)	2 (13.4)
	3	0	0	0

RT, radiotherapy; 3D-CRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy. Data are presented as number of patients (%)

However, the loco-regional recurrence-free survival rate in our study was lower than that reported in Wee's study (79.5% vs. 89.3%). One possible explanation for the inferior loco-regional recurrence-free survival found in our study is the different RT techniques used. While 53% of patients received 3D conformal RT in our study, all patients received intensity-modulated RT in Wee's study. In our study, patients treated with intensity-modulated RT showed a higher loco-regional recurrence-free survival rate compared to patients treated with 3D conformal RT, although this difference was not statistically significant (Table 4). In addition, while all patients were treated with a homogeneous RT fractionation schedule (total 67.5 Gy in 30 daily fractions) in Wee's study, the prescription RT doses were heterogeneous in our study; consequentially, 50% of patients were treated with a lower biologically equivalent dose than that used in Wee's study. Lastly, while 14.5% of patients received adjuvant chemotherapy after concurrent chemo-RT in Wee's study, no patient received adjuvant chemotherapy in our study. These factors might have affected the lower loco-regional recurrence-free survival rate in our study. However, despite the lower loco-regional recurrence-free survival, our study showed comparable overall and distant metastasis-free survival rates compared with previous studies. To date, the direct association between local tumor control and survival is not yet clear in cases of nasopharyngeal carcinoma. Whether improvement of local control will translate to better distant metastasis-free and/or overall survival rates must be evaluated in further randomized trials.

The survival benefit of induction chemotherapy for the management of nasopharyngeal carcinoma has not yet been proven. Two phase II randomized trials compared induction chemotherapy plus concurrent chemo-RT with concurrent chemo-RT alone; however, the results were contradictory (Hui et al., 2009; Fountzilas et al., 2012). Moreover, the reported 3-year overall survival rates from those trials (67.7% and 71.8%) were considerably lower than the 5-year overall survival rate found in our study. These contradictions make difficult to interpret the obtained results. A previous Korean retrospective study conducted by Wee et al., (2015) also compared the oncologic outcomes of induction chemotherapy plus concurrent chemo-RT with those of concurrent chemo-RT alone. In that study, the addition of induction chemotherapy did not improve any measured clinical endpoint. Moreover, concurrent chemo-RT alone resulted in better treatment outcomes in all endpoints, although the differences were not statistically significant. In this study, we also compared the clinical outcomes of induction chemotherapy plus concurrent chemo-RT with those of concurrent chemo-RT alone. The addition of induction chemotherapy did not improve any survival outcomes in our study. In addition, similar to the previous Korean retrospective study, patients who were treated with concurrent chemo-RT alone showed better loco-regional recurrence-free, distant metastasis-free, and overall survival rates compared with patients who were treated with induction chemotherapy followed by concurrent chemo-RT. Recently, Sun et al reported interim analysis results of an ongoing Chinese phase III multicenter randomized trial (NCT01245959) that compared induction chemotherapy plus concurrent chemo-RT with concurrent chemo-RT alone in the management of loco-regionally advanced nasopharyngeal carcinoma (Sun et al., 2016). According to their interim analysis results, induction chemotherapy using a combination of docetaxel/cisplatin/5-fluorouracil significantly improved the failure-free, distant failure-free, and overall survival rates compared with those associated with concurrent chemo-RT alone. However, because of the short follow-up period reported in Sun's study (median 45 months), long-term follow-up is needed to fully assess the efficacy of induction chemotherapy in treating loco-regionally advanced nasopharyngeal carcinoma. At present, four phase III randomized trials for comparing the efficacy of induction chemotherapy plus concurrent chemo-RT with that of concurrent chemo-RT alone are ongoing. We expect the final results of the ongoing randomized trials to help determine the role of induction chemotherapy in the treatment of loco-regionally advanced nasopharyngeal carcinoma.

The survival benefit of intensity-modulated RT over 3D conformal RT in patients with nasopharyngeal carcinoma has been also debated. Some studies have reported no significant difference in survival outcomes between patients who undergo intensity-modulated RT and those treated with 3D conformal RT (Wolden et al., 2006; Fang et al., 2008; Lee et al., 2014). In another Korean retrospective study, Moon et al., (2016) compared treatment outcomes of 2D RT, 3D conformal RT, and intensity-modulated RT in 1237 patients with nasopharyngeal carcinoma. In that study, intensity-modulated RT did not significantly

improve any survival outcome. However, in the T3-4 subgroup, the intensity-modulated RT group showed a significantly higher 5-year overall survival rate compared with the 3D conformal RT group (70.7% vs. 57.8%). In our study, we also compared the survival outcomes of patients treated with intensity-modulated RT and those treated with 3D conformal RT. Patients who were treated with intensity-modulated RT showed higher loco-regional recurrence-free, distant metastasis-free, and overall survival rates; however, these differences were not statistically significant. We previously conducted a study to compare the survival outcomes between intensity-modulated RT and 3D conformal RT in patients with head and neck cancer (Kong et al., 2013). In that study, intensity-modulated RT significantly improved the loco-regional recurrence-free survival rates compared with 3D conformal RT. However, patients with oral cavity or oropharynx cancer were also included in the patient population in that previous comparative study. In the current study, which included only nasopharyngeal carcinoma patients, we could not find the survival benefit of intensity-modulated RT over 3D conformal RT. However, even if the survival benefit of intensity-modulated RT is not yet clear, intensity-modulated RT significantly decreased the incidence of late toxicities compared with 3D conformal RT (Table 7). This benefit of intensity-modulated RT over 3D conformal RT has been reported in several other studies (Wolden et al., 2006; Fang et al., 2008; Kong et al., 2013; Qu et al., 2015; Moon et al., 2016; Radhakrishnan et al., 2017). Although prospective randomized trials are warranted to confirm the survival benefit of intensity-modulated RT over 3D conformal RT, we believe that intensity-modulated RT should be actively conducted to decrease the incidence of treatment-related toxicities.

This study had some limitations. First, the retrospective design might have resulted in inadvertent inherent biases. For instance, the RT fractionation schedules and the implementation of induction chemotherapy were decided by physicians rather than based on established protocols. Second, the patient characteristics were heterogeneous. Third, the sample size was small, which might have resulted in our study being underpowered to detect existing significant differences in our statistical analyses. Nonetheless, we believe that this study provides valuable information regarding oncologic outcomes of patients with loco-regionally nasopharyngeal carcinoma treated with concurrent chemo-RT in a community clinical setting and contributes toward the resolution of some controversial issues regarding the management of nasopharyngeal carcinoma.

In conclusion, the use of concurrent chemo-RT resulted in high survival rates with an acceptable level of associated toxicities in patients with loco-regionally advanced nasopharyngeal carcinoma. The addition of induction chemotherapy to concurrent chemo-RT did not improve survival outcomes. The survival benefit of intensity-modulated RT over 3D conformal RT was not clear. Intensity-modulated RT significantly decreased the development of late toxicities compared with 3D conformal RT. To confirm the results of this study, well-designed randomized prospective trials are warranted.

Acknowledgments

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (Ministry of Science, ICT & Future Planning) (2017R1C1B5015640).

References

Al-Sarraf M, LeBlanc M, Giri PG, et al (1998). Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol*, **16**, 1310-7.

Chan AT, Leung SF, Ngan RK, et al (2005). Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. *J Natl Cancer Inst*, **97**, 536-9.

Chen L, Hu CS, Chen XZ, et al (2012). Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial. *Lancet Oncol*, **13**, 163-71.

Chen Y, Liu MZ, Liang SB, et al (2008). 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*, **71**, 1356-64.

Fang FM, Chien CY, Tsai WL, et al (2008). Quality of life and survival outcome for patients with nasopharyngeal carcinoma receiving three-dimensional conformal radiotherapy vs. intensity-modulated radiotherapy-a longitudinal study. *Int J Radiat Oncol Biol Phys*, **72**, 356-64.

Fountzilas G, Ciuleanu E, Bobos M, et al (2012). Induction chemotherapy followed by concomitant radiotherapy and weekly cisplatin versus the same concomitant chemoradiotherapy in patients with nasopharyngeal carcinoma: a randomized phase II study conducted by the Hellenic Cooperative Oncology Group (HeCOG) with biomarker evaluation. *Ann Oncol*, **23**, 427-35.

Hui EP, Ma BB, Leung SF, et al (2009). Randomized phase II trial of concurrent cisplatin-radiotherapy with or without neoadjuvant docetaxel and cisplatin in advanced nasopharyngeal carcinoma. *J Clin Oncol*, **27**, 242-9.

Kong M, Hong SE, Choi J, et al (2013). Comparison of survival rates between patients treated with conventional radiotherapy and helical tomotherapy for head and neck cancer. *Radiat Oncol J*, **31**, 1-11.

Lee AW, Ng WT, Chan LL, et al (2014). Evolution of treatment for nasopharyngeal cancer--success and setback in the intensity-modulated radiotherapy era. *Radiother Oncol*, **110**, 377-84.

Lin JC, Jan JS, Hsu CY, et al (2003). Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival. *J Clin Oncol*, **21**, 631-7.

Lin S, Pan J, Han L, et al (2009). Nasopharyngeal carcinoma treated with reduced-volume intensity-modulated radiation therapy: report on the 3-year outcome of a prospective series. *Int J Radiat Oncol Biol Phys*, **75**, 1071-8.

Maklad AM, Bayoumi Y, Senosy Hassan MA, et al (2016). Patterns of failure and survival in patients with nasopharyngeal

carcinoma treated with intensity-modulated radiation therapy in Saudi Arabia. *Onco Targets Ther*, **9**, 6561-7.
Moon SH, Cho KH, Lee CG, et al (2016). IMRT vs. 2D-radiotherapy or 3D-conformal radiotherapy of nasopharyngeal carcinoma : Survival outcome in a Korean multi-institutional retrospective study (KROG 11-06). *Strahlenther Onkol*, **192**, 377-85.
Qu S, Liang ZG, Zhu XD (2015). Advances and challenges in intensity-modulated radiotherapy for nasopharyngeal carcinoma. *Asian Pac J Cancer Prev*, **16**, 1687-92.
Radhakrishnan S, Chandrasekaran A, Sarma Y, et al (2017). Dosimetric comparison between single and dual arc-volumetric modulated arc radiotherapy and intensity modulated radiotherapy for nasopharyngeal carcinoma using a simultaneous integrated boost technique. *Asian Pac J Cancer Prev*, **18**, 1395-402.
Shi RC, Meng AF, Zhou WL, et al (2015). Effects of home nursing intervention on the quality of life of patients with nasopharyngeal carcinoma after radiotherapy and chemotherapy. *Asian Pac J Cancer Prev*, **16**, 7117-21.
Siti-Azrin AH, Norsa'adah B, Naing NN (2014). Five-year survival and median survival time of nasopharyngeal carcinoma in Hospital Universiti Sains Malaysia. *Asian Pac J Cancer Prev*, **15**, 6455-9.
Sun X, Su S, Chen C, et al (2014). Long-term outcomes of intensity-modulated radiotherapy for 868 patients with nasopharyngeal carcinoma: an analysis of survival and treatment toxicities. *Radiother Oncol*, **110**, 398-403.
Sun Y, Li WF, Chen NY, et al (2016). Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial. *Lancet Oncol*, **17**, 1509-20.
Tao H, Wei Y, Huang W, et al (2016). Comparison of long-term survival and toxicity of simultaneous integrated boost vs conventional fractionation with intensity-modulated radiotherapy for the treatment of nasopharyngeal carcinoma. *Onco Targets Ther*, **9**, 1865-73.
Wee CW, Keam B, Heo DS, et al (2015). Locoregionally advanced nasopharyngeal carcinoma treated with intensity-modulated radiotherapy plus concurrent weekly cisplatin with or without neoadjuvant chemotherapy. *Radiat Oncol J*, **33**, 98-108.
Wee J, Tan EH, Tai BC, et al (2005). 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*, **23**, 6730-8.
Wolden SL, Chen WC, Pfister DG, et al (2006). Intensity-modulated radiation therapy (IMRT) for nasopharynx cancer: update of the Memorial Sloan-Kettering experience. *Int J Radiat Oncol Biol Phys*, **64**, 57-62.
Wong FC, Ng AW, Lee VH, et al (2010). Whole-field simultaneous integrated-boost intensity-modulated radiotherapy for patients with nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*, **76**, 138-45.
Zhang L, Zhao C, Peng PJ, et al (2005). Phase III study comparing standard radiotherapy with or without weekly oxaliplatin in treatment of locoregionally advanced nasopharyngeal carcinoma: preliminary results. *J Clin Oncol*, **23**, 8461-8.
Zheng W, Xu YJ, Qiu SF, et al (2015). Analysis on clinical characteristics and influencing factors of patients with locoregionally advanced nasopharyngeal carcinoma. *Asian Pac J Cancer Prev*, **16**, 4393-9.