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Radiotherapy alone and with concurrent chemotherapy for nasopharyngeal carcinoma

A retrospective study

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Abstract

We sought to evaluate clinical outcomes and toxicities of radiation therapy (RT) alone compared to RT with concurrent chemotherapy (CCT) for nasopharyngeal carcinoma (NPC) treatment.

We conducted a retrospective review of consecutive patients with biopsy-proven nonmetastatic NPC who underwent RT at our institution. From May 2001 to April 2015; 62 newly diagnosed NPC patients were treated with three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT) with or without CCT. The patients were classified as follows: 8% stage I, 15% stage II, 32% stage III, and 45% stage IVA/IVB. A total of 76% of tumors were World Health Organization types II or III. Acute and late toxicities were graded according to the Common Terminology Criteria for Adverse Events version 3.0. Overall survival (OS), progression-free survival (PFS), locoregional progression-free survival (LRPFS), and distant metastasis-free survival (DMFS) were analyzed.

The median follow-up period for living patients was 53 months. The median actual delivered dose was 70 Gy with a range of 28 to 70 Gy in fraction sizes of 2 Gy. The estimated 5-year OS, PFS, LRPFS, and DMFS rates were 72.7%, 59.8%, 77.9%, and 84.2%, respectively. The use of CCT was a predictive factor of significantly better OS and PFS, whereas stage IV was a significant predictor of poor OS and PFS. The most severe acute toxicities included Grade 3 mucositis in 56% and Grade 3 dermatitis in 8%. Subset analysis revealed that Grade 2 xerostomia was significantly lower in the IMRT (23%) group than in the 3D-CRT (52%) group ($P = .02$).

RT yielded favorable outcomes. CCT was associated with longer PFS and OS than RT alone.

Abbreviations: 3D-CRT = three-dimensional conformal radiotherapy, AEs = adverse events, CCT = concurrent chemotherapy, CI = confidence intervals, CT = computed tomography, DMFS = distant metastasis-free survival, HR = hazard Ratio, IMRT = intensity-modulated radiotherapy, KPS = Karnofsky Performance Status, LRPFS = locoregional progression-free survival, MRI = magnetic resonance imaging, NPC = nasopharyngeal carcinoma, OS = overall survival, PFS = progression-free survival, PTV = planning target volume, RT = radiation therapy, VMAT = volumetric modulated arc therapy, WHO = World Health Organization.

Keywords: chemoradiotherapy, nasopharyngeal carcinoma, prognosis, radiotherapy, retrospective studies

1. Introduction

Nasopharyngeal carcinoma (NPC) is a relatively rare disease in Japan, with an incidence of <1 case per 100,000 population per year.[1] This cancer displays a unique geographic and ethnic pattern of incidence, with particularly high rates in natives of south China, Southeast Asia, the Arctic, and the Middle East, and northern Africa.[2] In low-risk NPC regions, such as Japan, the age-incidence curves exhibit a bimodal pattern, with the first peak occurring in late adolescence/early adulthood followed by a second peak in the elderly; in contrast, there is no late adolescence/early adulthood peak in high-risk regions.[3] The male-to-female age-standardized ratio varies from 2 to 3 in both high- and low-risk areas.[4]

The most common site of primary NPC is the lateral wall of the nasopharynx, especially the fossa of Rosenmüller. NPC usually presents with nonspecific signs and symptoms, including nasal obstruction, headache, auditory abnormalities, and cranial nerve palsies, especially of nerves III, V, VI, and XII.[5] A meta-analysis of 2920 cases reported that 85% of patients presented with regional lymphadenopathy.[6] The most commonly involved regions include the retropharynx (69%) and level II lymph nodes (70%). Distant metastases are found at presentation in 5% to 11% of patients.

According to the World Health Organization (WHO) classification,[7] NPCs are classified pathologically as keratinizing squamous cell carcinoma (type I), differentiated non-keratinizing carcinoma (type II), and undifferentiated carcinoma (type III). Type I NPC may be associated with oncogenic human papilloma

Editor: Martin S. Staege.

The authors report no conflicts of interest regarding the publication of this paper.

Supplemental Digital Content is available for this article.

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Medicine (2018) 97:18(e0502)

Received: 30 October 2017 / Received in final form: 3 January 2018 / Accepted: 28 March 2018

http://dx.doi.org/10.1097/MD.0000000000010502

virus.[8] In general, type II and III are associated with Epstein-Barr virus infection and are considered to be more radiosensitive than type I.[9] Multivariate analysis using data from the Surveillance, Epidemiology, and End Results program revealed a better prognosis among type III NPC patients compared with type I NPC patients (hazard ratio [HR]: 0.67; $P < .001$).[10]

Although many large-scale studies have been published from NPC endemic regions,[11,12] their data may not be applicable to our country.[13] The purpose of this retrospective study was to evaluate the feasibility and efficacy of radiation therapy (RT) with or without concurrent chemotherapy (CCT) for NPC patients treated at our institution and to determine whether the adverse events (AEs) were comparable to those reported in the past. We investigated independent predictors of survival among patients using multivariate analysis.

2. Methods

2.1. Case eligibility

We included 62 consecutive cases of NPC treated by definitive RT with or without CCT at our hospital from May 2001 to April 2015. This study was performed in accordance with the guidelines approved by the institutional review board at the University of Tokyo Hospital. Written informed consent was obtained from all the patients. Clinical staging was performed according to the 6th edition of the American Joint Committee on Cancer staging manual.[14] The staging procedure basically includes physical examination, nasal endoscopy, contrast-enhanced computed tomography (CT), and contrast-enhanced magnetic resonance imaging (MRI). Positron-emission tomography was used in some patients. All cases collected in this study satisfied the following eligibility criteria: biopsy-proven NPC; no evidence of distant metastasis; and no history of previous radiotherapy to the neck. The medical follow-up included medical history with toxicity evaluation, physical examination, and imaging studies, scheduled as follows: every week during RT, every month for the first year, every 2 months for the second year, every 3 months for the third year, and every 6 months for the fourth and fifth years. Local control was defined as no signs of tumor progression on endoscopy, CT, or MRI scans. Acute and late AEs were graded according to the criteria of the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0.

2.2. Radiotherapy

The planning CT dataset was acquired using a 16-detector scanner (Toshiba Aquilion LB, Toshiba Medical Systems, Otawara, Japan). All patients underwent RT with 6 to 10 MV photon linear accelerators using either three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT) using step-and-shoot or volumetric modulated arc therapy techniques. CT image data were reconstructed as 5-mm sections for 3D-CRT and 2-mm sections for IMRT. These data were then sent to a treatment planning system, either Pinnacle (Philips), Monaco (Elekta CMS), or Xio (Elekta CMS). We adopted a 2-step RT method[15] that consists of whole-neck irradiation including bilateral level II–V and retropharyngeal lymph nodes of 40 to 46 Gy in 20 to 23 fractions using 3D-CRT (or of 46 Gy in 23 fractions using IMRT), followed by boost irradiation (outlined with a second planning CT acquired during the third week of RT) to the high-risk clinical target volume (including the primary tumor and positive lymph nodes), for a total dose of 60 to 70 Gy per 30 to 35 fractions (Supplemental Figure 1, http://links.lww.com/MD/C215). IMRT dose constraints for the planning target volume (PTV) and organs at risk (OARs) were: median values of D2% (maximum dose received by 2% of the PTV), D10%, and D50% were <120%, 110%, and 105% of the prescribed dose, respectively. The maximum dose to the brainstem was <54 Gy; the maximum dose to the spinal cord was <48 Gy; the maximum dose to the parotid gland at contralateral side was <26 Gy.

Table 1

Treatment characteristics.

Treatment type	N	Percentage
Radiation therapy		
3D-CRT	17	27
3D-CRT and IMRT	7	11
IMRT	38	61
Chemotherapy		
Concurrent	31	50
Adjuvant only	1	3
Concurrent and adjuvant	21	34
None	9	15
Concurrent chemotherapy agent		
Docetaxel + cisplatin/nedaplatin + 5-FU (DCF/DNF)	18	29
Cisplatin/Nedaplatin + 5-FU (CF/NF)	16	26
Cisplatin (CDDP) or nedaplatin (NDP)	17	27
Pirarubicin + cisplatin + 5-FU (THP+FP)	1	2
Adjuvant chemotherapy agent		
Docetaxel + Cisplatin + 5-FU (DCF)	4	
Docetaxel + cisplatin/nedaplatin (DC/DN)	3	5
Cisplatin + 5-FU (CF)	1	2
Cisplatin (CDDP) or nedaplatin (NDP)	10	16
S-1	4	6

3D-CRT = three-dimensional conformal radiation therapy, IMRT = intensity-modulated radiation therapy.

2.3. Chemotherapy

A total of 52 patients (84%) underwent CCT, which consisted of a DCF (docetaxel, platinum plus 5-fluorouracil) regimen (29%), CF (platinum plus 5-fluorouracil) regimen (26%), a single-agent platinum regimen (27%), and other regimens. A total of 22 patients (36%) underwent adjuvant chemotherapy, which consisted of a single-agent platinum regimen (16%), a DCF (platinum plus 5-fluorouracil) regimen (6%), an oral S-1 administration (6%), and other regimens (Table 1). One patient received adjuvant therapy without CCT.

2.4. Statistics

All statistical analyses were performed with the R statistical package (The R Foundation for Statistical Computing, Vienna, Austria). Overall survival (OS), progression-free survival (PFS), locoregional progression-free survival (LRPFS), and distant metastasis-free survival (DMFS) were measured from the first day of initial therapy and calculated by the Kaplan-Meier method. Comparisons between the 3D-CRT and IMRT groups were calculated with Fisher exact test for qualitative data. We conducted a multivariate Cox proportional hazard analysis with a stepwise selection process using the following covariates: sex, age, smoking history, clinical stage, WHO histology, Karnofsky Performance Status (KPS), and administration of CCT. A P value <.05 was considered statistically significant.

Table 2

Patient and tumor characteristics.

Characteristics		N	Percentage
Sex	Male	50	81
	Female	12	19
KPS	100%	3	5
	90%	42	68
	80%	10	16
	70%	6	10
	50%	1	2
Smoking history	Never	18	29
	Previous	18	29
	Current	26	42
Alcohol history	None	15	24
	Previous	2	3
	Current	45	73
WHO histology	Type I	15	24
	Type II and III	47	76
PEG before RT	Yes	36	58
	No	26	42

KPS = Karnofsky Performance Status, PEG = percutaneous endoscopic gastrostomy, RT = radiation therapy, WHO = World Health Organization.

3. Results

3.1. Patient and tumor characteristics

Patient and tumor characteristics are summarized in Table 2. A total of 77% of the patients were considered locally advanced (Supplemental Table 1, http://links.lww.com/MD/C215). The median actual delivered dose was 70 Gy with a range of 28 to 70 Gy in fraction sizes of 2 Gy.

3.2. Survival

The median follow-up was 40 months (range: 1–173 months) for all patients, and 53 months (range: 7–173 months) for survivors. The OS and PFS rates at 5 years were 72.7% (95% confidence interval [CI]: 57.8–83.1%) and 59.8% (95% CI: 45.3–71.6%), respectively (Fig. 1A and B). The 5-year OS and PFS rates were significantly worse in the advanced clinical stage group (OS: $P = .039$, PFS: $P = .036$) by the log-rank test in univariate analysis (Table 3). The log-rank tests also indicated a significant improvement of OS in the CCT group ($P = .025$). Multivariate analysis revealed that clinical stage and administration of CCT were independent predictors for both OS and PFS, regardless of other factors (Table 4).

Following completion of RT, 18 patients developed recurrent disease. The median time to first recurrence was 16 months, ranging from 4–66 months. The LRPFS and DMFS rates at 5 years were 77.9% (95% CI: 63.2%–87.3%) and 84.2% (95% CI: 70.6%–91.8%), respectively (Fig. 1C, D). LRPFS was significantly worse in patients treated with RT alone compared with patients treated with CCT ($P = .0489$), beside DMFS was not ($= .835$). Supplemental Table 2, http://links.lww.com/MD/C215 represents a schema of the first recurrence site. In the cases

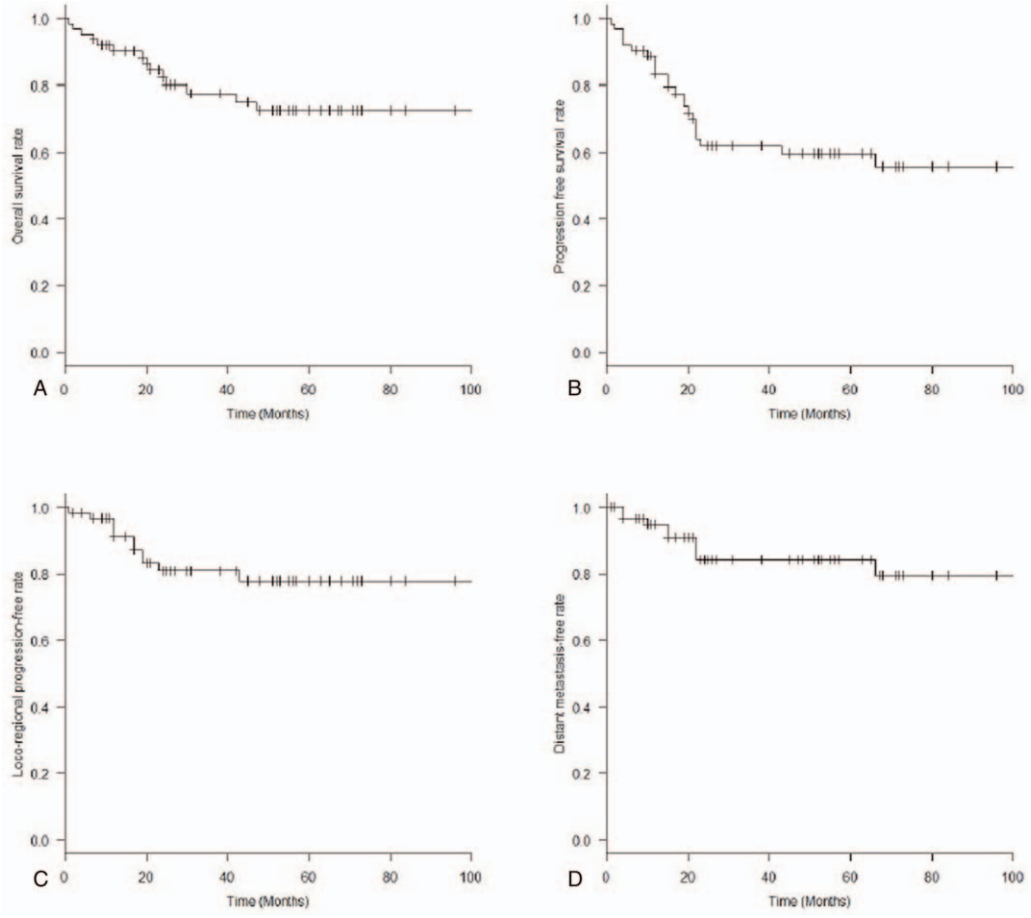

Figure 1. Kaplan-Meier curves for (A) overall survival, (B) progression-free survival, (C) loco-regional progression free, and (D) distant metastasis free. A vertical bar indicates a censored case.

Table 3

Univariate Cox regression analysis of prognostic factors.

Covariables		N	5-year OS rate (95% CI)	P	5-year PFS rate (95% CI)	P
Sex	Male	50	0.704 (0.531–0.823)	.352	0.566 (0.405–0.699)	.285
	Female	12	0.825 (0.461–0.953)		0.714 (0.337–0.901)	
Age	≤60 y	38	0.805 (0.613–0.909)	.068	0.666 (0.475–0.801)	.100
	>60 y	24	0.593 (0.333–0.780)		0.488 (0.263–0.679)	
KPS	<90%	17	0.600 (0.309–0.801)	.182	0.557 (0.286–0.761)	.565
	≥90	45	0.777 (0.597–0.883)		0.612 (0.437–0.747)	
Smoking history	No	19	0.685 (0.393–0.858)	.866	0.591 (0.322–0.784]	.760
	Yes	43	0.746 (0.563–0.861)		0.597 (0.420–0.736))	
Clinical stage	123	34	0.840 (0.621–0.938)	.039	0.714 (0.505–0.847)	.036
	4	28	0.596 (0.372–0.762)		0.460 (0.261–0.639)	
Concurrent chemotherapy	No	10	NA*	.025	NA	.050†
	Yes	52	0.759 (0.594–0.864)		0.628 (0.468–0.751)	
WHO classification	I	15	0.630 (0.319–0.830)	.095	0.485 (0.209–0.716)	.138
	II, III	47	0.761 (0.586–0.870)		0.633 (0.462–0.762)	

KPS = Karnofsky Performance Status, NA = not available, OS = overall survival, PFS = progression–free survival, WHO = World Health Organization.

* The follow-up duration of all patients treated with RT alone was I<5 years.

† 0.05004155 in detail.

with distant metastases, there was a wide variety of metastatic sites: four to lung, one to liver, two to both lung and liver, one to thyroid, and one to bone.

3.3. AEs

One patient treated by RT with CCT died from hemorrhage. The patient felt fatigue and pharyngodynia with fever, one month after the administration of 70Gy radiotherapy. Two months after RT, the patient was died from a sudden profuse hemorrhage from the nasopharynx. There were no Grade 4 AEs (Supplemental Table 3, http://links.lww.com/MD/C215). Five patients developed acute severe dermatitis (Grade 3). Moderate-severe mucositis was found in all patient (Grade 2: 27 patients, Grade 3: 35 patients). Acute severe AEs (grade 3) of any kind was experienced by 63% (33/52) of the patients receiving RT with CCT group and by 20% (2/10) of the patients in RT alone group. This gave a significant difference of incidence of severe AEs between these 2 groups ($P = .0156$). The most common late AEs were mild xerostomia (38 patients) and dysgeusia (45 patients). Grade 2 to 4 late AEs occurred more frequently among patients receiving CCT than RT alone (CCT 37% vs. RT alone 13%, $P = .249$). Incidence of grade 2 chronic xerostomia was significantly lower after IMRT (23%) than 3D-CRT (52%) ($P = .027$). One patient had a central nervous system disorder as a late AE.

4. Discussion

We reviewed the results of treatment of 62 patients with NPC treated in a single institution by definitive RT with or without CCT. Our 5-year OS, PFS, and LRPFS are comparable to those in previous reports [15–17]

Table 4

Multivariate Cox regression analysis of prognostic factors.

Covariables		Overall survival		Progression-free survival	
		Hazard ratio (95% CI)	P	Hazard ratio [95% CI)	P
Clinical stage	1, 2, 3 vs. 4	5.458 (1.559–19.100)	.008	3.660 (1.421–9.427)	.007
Concurrent chemotherapy	No vs. yes	0.146 (0.036–0.593)	.007	0.231 (0.074–0.720)	.011
WHO classification	I vs. II, III	0.379 (0.131–1.102)	.075	0.473 (0.197–1.133)	.093

CI = confidence interval, WHO = World Health Organization.

Our results of multivariate analysis showed that CCT was an independent prognostic factor for both OS and PFS. Chen et al[18] reported a phase III randomized study comparing CCT and RT arms and revealed that the 5-year OS rates were 70.3% (95% CI: 63.4%–77.3%) and 58.6% (95% CI: 50.9%–66.2%), respectively. Lin et al also reported on CCT consisting of a cisplatin and 5-fluorouracil (CF regimen) in their phase III study. They revealed that the 5-year OS rates were 72.3% for the CCT arm and 54.2% for the RT arm ($P=.0022$).[19]

According to a meta-analysis of 19 clinical trials, the addition of chemotherapy to RT significantly improved OS (HR: 0.79, 95% CI: 0.73–0.86).[20] CCT plus adjuvant chemotherapy (HR: 0.65, 95% CI: 0.56–0.76) and CCT alone (HR: 0.80, 95% CI: 0.70–0.93) significantly improved OS, but not adjuvant chemotherapy alone (HR: 0.87, 95% CI: 0.68–1.12) or induction chemotherapy alone (HR: 0.96, 95% CI: 0.80–1.16). A multicenter phase III randomized controlled trial reported that adjuvant cisplatin and fluorouracil chemotherapy did not significantly improve failure-free survival after CCT in locoregionally advanced NPC.[21] No definitive conclusion has been reached on the necessity of adjuvant chemotherapy with RT for NPC. The present study also revealed no significant improvement by using adjuvant chemotherapy ($P=.5656$).

The most common acute AEs of grade 3 were mucositis, occurred in 56.5% (35/62) of the patients. The incidence rate of these severe AEs was not in contradiction to previous reports. Meta-analysis of 33 studies has reported grade 3 and 4 incidence of mucositis in 39% to 80% of head and neck cancer patients treated by RT with CCT.[22] The incidence of grade 2 chronic xerostomia was significantly lower after IMRT (23%) than 3D-CRT (52%), although there were no significant differences in terms of OS and PFS ($P=.604$ and $P=.130$, respectively). Nutting et al[23] also reported that Grade 2 or worse xerostomia at 12 months was significantly lower with IMRT (38%) than with conventional RT (74%). One of our patients had a central nervous system disorder as a late AE. In the report of Lee et al,[24] CCT using cisplatin and 5-FU was used, and a central nervous system disorder occurred in 3.9% of cases as a late AE. Although the incidence is very low, it is considered to be a serious AE requiring long-term follow-up. Hunt et al[25] compared IMRT and conventional treatment plans for primary nasopharynx cancer radiotherapy. In the IMRT plan, the volume of mandible and temporal lobes receiving >60 Gy decreased by 10% to 15%.

In a multi-institutional Japanese study, 19% of the 333 NPC cases were diagnosed as type I and patients with types II and III were found to have significantly higher 5-year OS rates.[26] It is well known that the incidence of type I is relatively high in low-risk NPC regions, in contrast to the usually <5% in the endemic NPC populations.[27] Our study showed that 24% of our patients were WHO classification type I (keratinizing). Nevertheless, in the present study, the nonkeratinizing types II and III patients showed no significant difference in OS and PFS compared to type I patients ($P=.071$ and $P=.084$, respectively). This may be because of the small number of cases.

Several limitations of our study warrant mention. First, this was a retrospective review with a limited number of cases because of the low incidence of NPC in Japan. Second, large variety of treatment modality regarding radiation technique and chemotherapy regimens were used because of retrospective data collection. Third, limited information was available regarding quality of life through and after treatment. We need further consideration to optimize the treatment of distress, and improve quality of life of the patient. These limitations can be overcome by further prospective studies that include long-term results.

In summary, our retrospective study found that RT alone and advanced clinical stage were associated with poor PFS and OS in patients with NPC. In Japan, the Radiation Therapy Study Group of the Japan Clinical Oncology Group has started a multicenter phase II study of IMRT with chemotherapy for locoregionally advanced NPC,[28] accompanied by strict quality control and quality assurance. Interim analysis presented at the American Society for Radiation Oncology 2016 Annual Meeting revealed that acute toxicity was acceptable and that the incidence of Grade 2 or more xerostomia at 1 year was satisfactorily low (26% of patients). The final result will be critical to elucidating the efficacy and feasibility of 2-step IMRT with CCT in the treatment of NPC.

Author contributions

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