Dosimetric comparison and observation of three-dimensional conformal radiotherapy for recurrent nasopharyngeal carcinoma

RONGQIANG PAN[1], JINGMING WANG[2], FENG QI[3] and RUIZHEN LIU[3]

[1]Cancer Center, Nanchong Central Hospital, Nanchong, Sichuan 637000;
[2]Department of Ear, Nose and Throat, Gansu Provincial Maternity and Child Care Hospital, Lanzhou, Gansu 730050;
[3]Department of Radiotherapy, The First People's Hospital of Shangqiu, Shangqiu, Henan 476100, P.R. China

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Abstract. The aim of the study was to investigate the effect of three-dimensional conformal radiation therapy (3D-CRT) on nasopharyngeal carcinoma (NPC) and the incidence of complications. Between May 2010 and June 2012, 141 patients diagnosed with local recurrence of NPC due to cranial base lesions or cranial nerve symptoms, confirmed by pathology biopsy and/or by CT/MRI, were included in the present study. In accordance with the principle of randomized control, the patients were divided into three groups and treated with three different doses of 3D-CRT. The planned radiotherapy doses of 3D-CRT were 58/1.8-2 Gy, 62/1.8-2 Gy and 68/1.8-2 Gy, respectively. The survival rate, disease-free survival (DFS) rate and local control rate of the three groups of patients were compared as well as the adverse reactions observed after radiotherapy. The prognoses of NPC patients were analyzed by univariate and multivariate analyses. The follow-up rate of the study was 100%. The 5-year overall survival, DFS, and locoregional recurrence-free survival rates were: 43.2 vs. 64.53 vs. 75%, 29.13 vs. 42.82 vs. 39.7% and 30.76 vs. 44.19 vs. 45.4%, respectively. In addition, 62/1.8-2 Gy was similar in treatment effects to 68/1.8-2 Gy, but 68/1.8-2 Gy showed more adverse reactions than 62/1.8-2 Gy. Thus, 62/1.8-2 Gy can be used as a safe and effective dose for 3D-CRT treatment of NPC. Univariate and multivariate analyses showed that age may be the main prognostic factor of patients with NPC. In conclusion, 3D-CRT with a dose of 62/1.8-2 Gy is a safe, effective and tolerable treatment for NPC patients with good clinical value.

Introduction

Nasopharyngeal carcinoma (NPC) is a common head and neck cancer. Owing to its sensitivity to radiation, radiotherapy is the most important method used to treat NPC (1,2). Since the site where NPC occurs usually has limited space and the head and facial nerve distribution is widespread, there are only limited treatments for NPC.

Commonly used methods of treatment include surgery, posterior implantation or implantation of radiation therapy as well as stereotactic radiotherapy and external irradiation (3-5). Due to the wide spread of nasopharyngeal mass, surgery, endovascular grafting, implantation of radiotherapy and stereotactic radiotherapy are often limited, which causes a high recurrence of NPC. High-dose external irradiation is the main treatment for patients with relapse, especially for those with large local masses or a wide range attack when recurrence occurs (6,7). As conventional radiotherapy can often lead to serious complications and sequelae, including nasopharyngeal ulcers, hearing loss, temporal lobe necrosis, radiation encephalopathy, posterior cranial nerve injury and/or difficulty in mouth opening (7), in recent years we have continued to explore new radiotherapy treatments that can reduce the incidence of adverse reactions.

Three-dimensional conformal radiation therapy (3D-CRT) is an advanced treatment technique that can irradiate the target area through multiple fields (usually 5-7 fields) to align the tumor with the radiation target through three-dimensional directions. It makes the target dose distribution more reasonable and reduces exposure to adjacent normal tissue (8). To the best of our knowlegde, few studies have focused on the treatment of recurrent NPC by 3D-CRT. Therefore, the aim of the present study is to analyze the efficacy of 3D-CRT in the treatment of recurrent NPC and long-term adverse effects after radiotherapy.

Materials and methods

Materials. Between May 2010 and June 2012, 141 patients with NPC who had been diagnosed with local recurrence by biopsy and/or computed tomography/magnetic resonance imaging (CT/MRI) imaging of bone destruction or cranial nerve symptom progression received 3D-CRT treatment. The median relapse interval was 27.5 months (range, 3-156 months). Chest X-ray, abdominal B-ultrasound, head and neck CT/MRI, electrocardiogram, bone scan and oral, and other tests were performed. Since July 2005, CT was replaced with MRI in the head and neck exam (CT before July and MRI after July).

Correspondence to: Dr Jingming Wang, Department of Ear, Nose and Throat, Gansu Provincial Maternity and Child Care Hospital, 143 Qilihe North Street, Lanzhou, Gansu 730050, P.R. China
E-mail: wangjingming17@163.com

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Table I. Comparison of the general clinical situation of patients enrolled.

Factors	No.	Groups			χ^2 value	P-value
		58/1.8-2 Gy n=47	62/1.8-2 Gy n=47	68/1.8-2 Gy n=47		
Sex					0.473	0.556
Male	70	26	24	20		
Female	71	21	23	27		
Age (years)					0.102	0.732
≤50	68	24	21	23		
>50	73	23	26	24		
T stage					0.027	0.973
T1	31	13	10	8		
T2	50	14	17	19		
T3	30	9	11	10		
T4	30	11	9	10		
Combined chemotherapy						
No	87	27	32	28		
Yes	54	20	15	19		
Nasopharyngeal tumor	55	19	22	14	0.483	0.567
invasion to both sides	86	28	25	33		
Time of relapse					0.465	0.587
<24 months	67	17	24	26		
24-36 months	28	8	9	11		
>36 months	46	16	17	13		

PET/CT examination was performed based on the physician's judgement depending on the condition of the patient. No neck biopsy was performed in 10 patients with recurrence in neck. All the patients were re-staged according to the AJCC (5th edition, 1997).

Signed written informed consent was obtained from patients enrolled in the study. The study was approved by the Ethics Committee of the Nanchong Central Hospital (Nanchong, China).

3D-CRT radiotherapy treatment plan. The patients were placed in a supine position and wore a thermoplastic mask. CT was performed from the head to 2 cm below the clavicle, with a scanning layer of 3 mm and an enhanced scan. From July 2005 onwards, the MRI/CT image was produced using MasterPlan® version 1.5, Nucletron BV software analysis and image fusion.

Gross tumor volume (GTV), such as GTV-P (planned target area of primary tumor area) and GTV-N (unplanned target area of primary tumor area), including masses visible on CT/MRI images as well as clinical target volume (CTV), including CTV-P and CTV-N received external radiation of 8-10 mm. If the mass was close to the brain stem or spinal cord, the exposure of the radiation boundary was smaller, with the smallest distance being 3 mm, to protect the brain stem and spinal cord from receiving more than the allowable tolerated dose. Cervical lymphatic drainage area did not receive prophylactic irradiation. Considering the system and positioning errors, 3 mm beyond CTV was considered as planning target volume (PTV). Organs affected included brain stem, spinal cord, optic nerve, optic chiasm, temporal lobe, pituitary, temporomandibular joint, eyeball, crystal and parotid gland. The dose received by affected organs was limited and individualized based on the first dose of radiotherapy, but within the tolerances specified by RTOG.

The treatment plan involved Plato® preparation planning software system (RTS® version 2.6.4), using isocentric coplanar or non-coplanar techniques; the isocenter is placed at the center of GTV-P. The irradiation of primary focus and neck involved 5-9 coplanar static intensity control technology. The prescribed doses were PTV-GTVnx, 70 Gy; PTV-GTVnd, 64-66 Gy; PTV-GTVnd, 64-66 Gy; PTV-CTVnx60, 60-64 Gy; PTV-CTVx50, 54 Gy; and PTV-CTVnd, 54 Gy; 31-32 times of segmentation irradiation. The mean radiotherapy dose of 3D-CRT for three groups of patients were 58/1.8-2 Gy, 62/1.8-2 Gy and 68/1.8-2 Gy respectively (single segmentation 2/1.8 Gy, once a day, 5 days/week). Five to seven coplanar irradiation fields were designed and a medical accelerator and a multi-leaf grating were used.

Radiotherapy. Due to the absence of current standard chemotherapy regimens for local recurrence of NPC, clinicians can consider whether to prescribe a combined chemotherapy

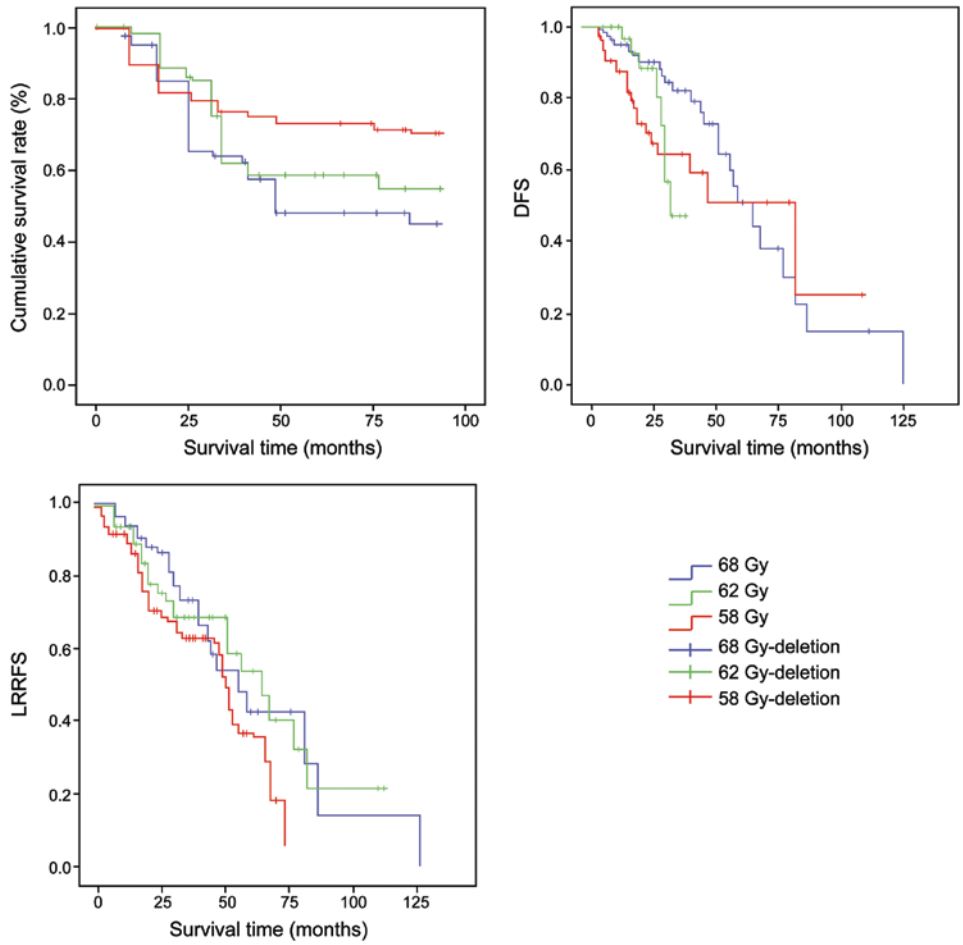

Figure 1. Kaplan-Meier survival analysis. OS, overall survival; DFS, disease-free survival; LRRFS, locoregional recurrence-free survival.

based on the overall state of health of patients. In our study, 65 patients received 2-6 cycles of platinum-based monotherapy or combinations of chemotherapy with neoadjuvant and/or concurrent adjuvant chemotherapy.

Follow-up. Patients were enrolled in a weekly check up for clinicians to evaluate the retraction of their lumps. Patients administered chemotherapy received routine blood, liver and kidney tests weekly. The patients were followed up every 3 months within 2 years after the treatment, every 6 months 3 years after the treatment and every year 5 years after the treatment. Each follow up included systemic examination, blood, VCA-IgA, VCA-EA, nose pharyngeal fibrobronchoscopy, chest X-ray, abdominal B-ultrasound, and head and neck MRI. Adverse reactions and sequelae were recorded according to the RTOG/EORTC assessment of adverse reactions of radiation therapy.

Statistical analysis. SPSS 19.0 software (IBM, Armonk, NY, USA) was used for statistical analysis. The time at which a local region relapses or shifts was calculated from the end of the 3D-CRT. Overall survival (OS) was defined as the time between the diagnosis of relapse and death or the last follow up. Locoregional recurrence-free survival (LRRFS), disease-free survival (DFS) and OS were calculated using the Kaplan-Meier method. The log-rank test was used for univariate analysis of different prognostic factors. The Cox regression model was used for multivariate analysis. $P<0.05$ was considered to indicate a statistically significant difference.

Table II. Comparison of adverse reaction rate.

Groups	Nasopharyngeal ulcer	Cranial nerve injury	Mouth opening difficulties	Hearing loss
58/1.8-2 Gy	2	1	3	2
62/1.8-2 Gy	0	1	2	4
68/1.8-2 Gy	15	10	3	8
χ^2 value		32.8		
P-value		0.001		

Results

Comparison of the general clinical situation of patients enrolled. The general clinical conditions of the patients were compared, including age, sex, T stage, whether to receive chemotherapy, time of recurrence and tumor invasion. The patient's age ranged from 26 to 71 years with an average age of 45 years. There was no statistically significant difference between the three groups in general clinical baseline data ($P>0.05$) (Table I).

Table III. Univariate prognostic analysis.

		OS		DFS		LFS	
Factors	n	t	P-value	t	P-value	t	P-value
Sex			0.387		0.583		0.387
Male	70	52.4±5.5		48.4±5.3		52.3±5.5	
Female	71	42.3±7.1		40.3±7.2		40.1±7.1	
Age (years)			0.027		0.016		0.008
<50	68	64.2±7.3		60.3±6.6		62.4±7.1	
≥50	73	55.4±7.2		38.7±4.5		38.6±5.2	
rT stage			0.276		0.078		0.271
1+2	81	57.3±7.2		58.7±7.2		57.5±8.2	
3+4	60	45.5±5.1		40.2±5.9		31.2±5.4	
Recurrence time			0.478		0.228		0.271
<24 months	67	57.6±7.1		55.1±6.7		57.3±7.2	
24-36 months	28	43.6±7.2		41.2±6.6		43.4±7.7	
>36 months	46	44.9±8.1		39.7±7.1		41.7±7.2	
Radiation dose			0.323		0.227		0.863
<60 Gy	47	47.3±5.5		57.2±9.1		49.3±5.5	
62 Gy	47	49.7±5.3		44.5±4.4		48.4±6.7	
68 Gy	47	48.3±4.3		46.5±4.3		48.1±5.3	

OS, overall survival; DFS, disease-free survival.

Table IV. Multivariate prognostic analysis.

							95% CI Exp (B)	
Factor	B	SE	WALD	df	Sig	Exp (B)	Lower	Upper
Age	0.538	0.215	6.218	1	0.014	1.701	1.121	2.598
T stage	0.368	0.206	3.187	1	0.076	1.453	0.956	2.156
Age	0.494	0.207	5.721	1	0.016	1.635	1.004	2.448
Age	0.552	0.212	6.798	1	0.009	1.747	1.165	2.628

Survival prognosis. The prognosis of the three groups of patients were analyzed. The OS, DFS and LRRFS of the 3 groups of patients were: 43.2 vs. 64.53 vs. 75%, 29.13 vs. 42.82 vs. 39.7%, 30.76 vs. 44.19 vs. 45.4%, respectively (Fig. 1).

Comparison of the incidence of adverse reactions. Adverse reactions mainly included nasopharyngeal ulcer, cranial nerve injury, mouth opening difficulties and hearing loss. The overall adverse reaction rate of the 68/1.8-2 Gy group was higher than that of the other two groups and the difference was statistically significant (P<0.05) (Table II).

Univariate prognostic analysis. The prognostic factors of the patients were analyzed by a univariate analysis. The prognostic factors included sex, age, treatment regimen (with or without chemotherapy), total radiation dose, primary T stage, recurrence T stage and recurrence interval. The results showed that age ≥50 years of age was a risk factor for poor prognosis (Tables III and IV).

Discussion

Nasopharyngeal carcinoma, after a timely and standardized radical radiotherapy or integrated radiotherapy and chemotherapy, can lead to local and/or regional recurrence in 20-30% of patients. Local nasopharyngeal and skull-based recurrence are the main reasons for the failure of local treatment of NPC after radiotherapy (9-11). Retrospective studies have shown that salvage therapy can improve survival in patients with a single local recurrence (especially those with local recurrence of T1-2) (12). For nasopharyngeal local recurrence of T1-2, surgery or follow-up treatment is an effective means of NPC (13). Some radiotherapy centers reported treatment results showing that intraluminal or interstitial brachytherapy was also feasible for

patients with local recurrence of NPC (14,15). Accordingly, Law *et al* (16) showed that, the use of ^{192}Ir interstitial particles DT50-55 Gy could lead to a 5-year local control rate of 85% and moderate as well as severe complications occurrence rate of 47%. Leung *et al* used high-dose rate of intracavitary and external irradiation treatment for recurrent NPC (17). The results showed that although the high dose of radiation was strong enough to kill local cancer cells, it could also cause local early recurrence due to normal tissue damage and interstitial cell damage.

In the present study, the patients with NPC were treated with different doses of radiation ranging from 58 to 68 Gy. The results showed that the three groups of patients had 5-year OS, DFS and regional recurrence-free survival rates as 43.2 vs. 64.53 vs. 75%, 29.13 vs. 42.82 vs. 39.7% and 30.76 vs. 44.19 vs. 45.4%. The treatment effect of 62/1.8-2 Gy was similar to that of 68/1.8-2 Gy, but 68/1.8-2 Gy showed more adverse reactions than 62/1.8-2 Gy. Therefore, we believe that 62/1.8-2 Gy can be used as a safe and effective dose for 3D-CRT treatment of NPC. Age may be the main prognostic risk factor for patients with NPC (18). Previous findings have shown that radiation dose in the treatment of cancer may be positively correlated with an increase in side effects. Chang *et al* treated 35 patients with recurrent NPC using 3D-CRT (19). The results showed that the median survival rates of radiotherapy after 1, 2 and 3 years were 54.9, 30.2 and 22.9%, respectively. Additionaly, long-term adverse reactions included hearing loss and difficulty in mouth opening compared to the conventional group, albeit no brain necrosis was found. Our study further explored the dose and safety of three-dimensional radiotherapy, and further determined 62/1.8-2 Gy as a therapeutic dose with certain clinical applicability. Teo *et al* reported that more than 900 patients with recurrences showed better therapeutic effects when the radiation dose was ≥60 Gy (20). Those authors, however, did not explore in-depth the radiation dose ≥60 Gy, and the DFS and OS rates of patients. In this study, the 62 and 68 Gy radiation doses were further categorized and explored because of differences in the patient population and the number of patients enrolled in the study. We found that 62/1.8-2 Gy was safer and more effective as a three-dimensional radiotherapy dose and could lead to longer OS and DFS.

In conclusion, we believe that the dose of 62/1.8-2 Gy of 3D-CRT is a safe, effective and adverse-reaction-tolerable NPC treatment with good clinical values.

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