

ORIGINAL ARTICLE

Assessment of radiotherapy combined with adjuvant chemotherapy in the treatment of patients with advanced nasopharyngeal carcinoma: a prospective study

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Summary

Purpose: To explore the clinical efficacy of radiotherapy combined with concurrent combination chemotherapy in the treatment of patients with advanced nasopharyngeal carcinoma (NPC).

Methods: Two hundred patients with stage III/IV NPC were randomly allocated into the treatment group (N=100) and the control group (N=100). Patients in the control group received conventional fractionated radiotherapy, while patients in the treatment group received conventional fractionated radiotherapy combined with concurrent combination chemotherapy with cisplatin and 5-fluorouracil (5-FU). Short-term efficacy, radiotherapy toxicity, short- and long-term survival were compared.

Results: The short-term response rate of the treatment

group was 96%, which was significantly higher than that of the control group (87%, $p < 0.05$). The local radiation toxicity of the treatment group was similar to that of the control group ($p > 0.05$), but the hematological and gastrointestinal toxicities were significantly higher in the treatment group ($p < 0.05$). The 1-, 3- and 5-year overall survival rates were 87, 80, and 76%, respectively, in the treatment group and 74, 64, and 51%, respectively, in the control group, significantly favoring the treatment group ($p < 0.05$).

Conclusion: Radiotherapy with concurrent combination chemotherapy can improve the prognosis of patients with advanced NPC but at the cost of significant toxicity.

Key words: chemotherapy, efficacy, nasopharyngeal carcinoma, radiotherapy, survival

Introduction

Although the incidence of NPC is less than 1 in 10^5 in general, it is greater in races with xanthoderma, such as Southeast Asians [1]. In China, some cities have a higher incidence of NPC, such as Zhaoqing, Foshan, and Guangzhou in the Guangdong province, where the incidence rate can be 20-fold or more higher than normal. The prognosis of NPC differs according to clinical stage. More than 70% of early NPC can be cured by radiotherapy, which is the standard therapy, while the prognosis is poor in advanced NPC. A recent report focused on the prognostic factors of advanced NPC. There, the authors reported that age or tumor size were not a determinant of survival, while TNM stage, especially lymph node in-

volvement, was a significant prognostic factor [2]. Another study pointed out that the intensity-modulated radiation therapy (IMRT) could improve the prognosis of patients with NPC [3]. Some NPC patients have poor prognosis due to their insensitivity to radiotherapy [4]. At present, combined therapy based on radiotherapy and chemotherapy has become the main treatment for NPC. Radiotherapy concurrent with chemotherapy is a more classical treatment for those patients who tolerate radiotherapy. However, induction chemotherapy followed by concomitant chemoradiotherapy also showed excellent activity in locally advanced NPC [5]. It has been confirmed that IMRT and platinum-based chemotherapy improve prognosis of locally advanced NPC [6]. In order to treat patients who are insensitive to chemotherapy

Table 1. The clinical characteristics of the subjects in the two groups

Groups	Patients, N (%)	Age, years Mean \pm SD	Gender		Tumor stage	
			Male N (%)	Female N (%)	Stage III N (%)	Stage IV N (%)
Treatment	100 (100)	50 \pm 19.4	63 (63.0)	37 (37.0)	77 (77.0)	23 (23.0)
Control	100 (100)	52 \pm 16.7	61 (61.0)	39 (39.0)	69 (69.0)	31 (31.0)
χ^2		1.26		1.19		0.82
p value		>0.05		>0.05		>0.05

SD: standard deviation

and radiotherapy, drugs with sensitizing effects are now being used in chemoradiotherapy. Considering the toxicity and side effects of radiotherapy, single-agent chemotherapy is commonly used. However, it has been noted that multi-drug chemotherapy can improve the therapeutic efficacy, compared with single-agent chemotherapy [7].

Our study was conducted to explore the clinical efficacy of radiotherapy combined with concurrent combination chemotherapy using cisplatin and 5-FU. The curative effect and safety were the primary endpoints.

Methods

Clinical data

Written informed consent was obtained from each of the 200 patients with advanced NPC who were hospitalized in our hospital's Department of Radiotherapy and who were subsequently enrolled in this study from January 2006 to December 2006. The patient gender included 124 men and 76 women aged between 18 and 78 years. All patients were pathologically diagnosed with NPC stage III (N=146) and stage IV (N=54), according to the diagnostic and treatment practices for NPC established by the Ear, Nose and Throat branch of the Chinese Medical Association in 1992. Patients with contraindications to chemoradiotherapy or with other carcinomas were excluded from this study. Patients were randomly allocated into the treatment and control groups (N=100 each), and their clinical characteristics are listed in Table 1. This study was conducted in accordance with the declaration of Helsinki and after approval from the Ethics Committee of Hainan Provincial People's Hospital.

Radiotherapy

Patients underwent computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) before they received treatment in order to exclude distant metastasis to other organs, including brain and bones. They received conventional fractionated radiotherapy using Siemens Type 6740 Medical Linear Accelerator (Munich, Germany), while supine on bed. A thin-slice CT scan was used to delin-

eat the target outlines of the primary lesion and the metastatic lymph node. The target regions for irradiation were the gross tumor volume plus 5-10 mm margin for the primary lesion and 3 mm margin for the lymphatic drainage area. Then, the treatment planning system was used to deliver radiotherapy as well as the correct dosage to the target regions. The primary program was as follows: 66-75 Gy to the primary lesion, 60-70 Gy to the metastatic lymph nodes, and 50 Gy prophylactic dose to the neck. First, the faciocervical united field and the anterior tangential field were irradiated with 36 Gy, followed by the small faciocervical united field, the upper hind neck β -ray field, and the anterior tangential field or the faciocervical split field. According to the range of the nasal lesions, additional fields such as the nasal anterior field, preauricular field, basilar field, antral ethmoidal field, small cervical field, and other auxiliary fields, could be irradiated for individualized treatment. Radiation dose for the subclinical lesions was 50-55 Gy with conventional fractionation of 1.8-2.0 Gy/day, 5 times a week. Radiotherapy was carried out continuously with the non-target area and the organs at risk (OAR) were blocked. OARs should not receive more radiation than their tolerated doses, which are as follows: 50 Gy for the brainstem, 40 Gy for the spinal cord, 50 Gy for the optic chiasm, 6 Gy for the crystal, 55 Gy for the temporal lobe, and 26 Gy for the parotid gland. After a 2-week radiotherapy, patients underwent a CT scan for evaluation of the therapeutic efficacy to determine the new scope of radiotherapy and the radiation dose. The total duration of radiotherapy was 7-7.5 weeks.

Chemotherapy

Patients in the treatment group received concurrent combination chemotherapy while they were receiving radiotherapy. The chemotherapy program was cisplatin 20 mg/m², days 1-5 plus 5-FU 750 mg/m² by i.v. infusion. Cycle repetition was every 21 to 28 days. After the end of radiotherapy, chemotherapy was continued for 1-2 additional cycles. During the whole course of chemotherapy, liver and renal function tests, and routine blood examination were performed.

Evaluation of the therapeutic effect

The therapeutic effect was characterized as com-

Table 2. Short-term efficacy of the two groups

Groups	Patients, N (100)	CR N (%)	PR N (%)	SD N (%)	PD N (%)	RR N (%)
Control	100 (100)	34 (34.0)	53 (53.0)	6 (6.0)	7 (7.0)	87 (87.0)
Treatment	100 (100)	46 (46.0)	50 (50.0)	2 (2.0)	2 (2.0)	96 (96.0)
χ^2						11.64
p value						<0.05

For abbreviations see text

Table 3. Toxicity-related complications in the two groups

Groups	Neck skin damage					Oral mucosal lesions					Nasal mucosal damage				
	0	I	II	III	IV	0	I	II	III	IV	0	I	II	III	IV
Treatment	15	16	46	16	7	8	36	20	17	19	0	27	29	26	18
Control	17	21	38	19	5	5	29	24	24	18	0	29	33	22	16
U value			6.92					5.07					11.73		
p value			0.914					0.925					0.575		

Table 4. Systemic toxicity in the two groups

Groups	Leucopenia					Thrombocytopenia					Gastrointestinal reactions*				
	0	I	II	III	IV	0	I	II	III	IV	0	I	II	III	IV
Treatment	4	31	44	11	10	4	32	30	25	11	2	26	52	15	5
Control	12	45	31	9	3	16	38	33	7	6	12	42	36	8	2
U value			3.21					2.06					2.52		
p value			0.076					0.092					0.081		

*anorexia, nausea, vomiting, abdominal distension etc

plete response, partial response, stable disease, and progressive disease based on the response evaluation criteria for solid tumors (RECIST). Response rate was equal to complete plus partial response.

Toxicity evaluation

Toxicity evaluation of radiotherapy was performed according to the toxicity classification methods for radiotherapy established by the World Health Organization and was graded from grade 0 to grade IV.

Statistics

Statistical analyses were performed using the SPSS software program v11.5 (SPSS Inc., Chicago, ILL, USA). Comparisons of the frequency of data between groups were carried out using the chi-square test, whereas ranked data was analyzed using the rank sum test. The patient survival rates were compared using the Kaplan-Meier method with log-rank test. P values less than 0.05 were considered statistically significant.

Results

Short-term efficacy

The short-term clinico-imaging response rate of the treatment group was 96%, which was significantly higher than that of the control group (87%, $p < 0.05$; Table 2).

Local radiation toxicity

The radiation toxicity-related complications in the treatment group, including neck skin damage, oral mucosal lesions and nasal mucosal damage, were no more serious than those in the control group ($p > 0.05$, Table 3).

Systemic toxicity

Comparisons of hematological and gastrointestinal toxicities between the two groups were also carried out. The grades of leukopenia, thrombocytopenia, and gastrointestinal reactions in the

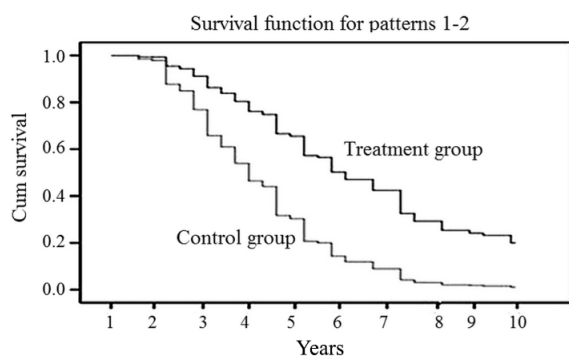


Figure 1. Kaplan-Meier estimates of overall survival of patients in the two groups ($p < 0.05$).

treatment group were all remarkably higher than those in the control group ($p < 0.05$, Table 4).

Short and long-term survival

The 1-, 3- and 5-year overall survival rates in the treatment group ($N=100$) were 87, 80, and 76%, respectively, and those in the control group ($N=100$) were 74, 64, and 51%, respectively, favoring significantly the treatment group ($p < 0.05$) (Figure 1).

Discussion

NPC is a highly malignant neoplasm. Several studies have shown that the prevalence of NPC is associated with Epstein-Barr virus infection [8]. Local invasion and lymph node metastasis are very common in advanced NPC. Unfortunately, most patients with NPC are not particularly sensitive to chemotherapy [9], and radiotherapy still remains the main treatment modality. It has been reported that the majority of NPC patients can achieve better therapeutic results with radiotherapy and obtain complete tumor remission or considerable symptom relief and some patients can even achieve long-term survival [10]. However, some authors reported a considerable local recurrence and distant metastasis rate after radiotherapy [11], which is one of the major causes of patients' death. Therefore, for some patients with advanced NPC, radiotherapy alone cannot completely kill the tumor cells.

In recent years, treatment of NPC using radiotherapy along with chemotherapy and psychological support has resulted in better clinical outcomes and an improved quality of life [12]. In addition, some traditional Chinese medicines such as curcumin and quercetin were also shown to

process inhibitory effects on NPC [13]. One study showed that quercetin and cisplatin exhibited a synergistic effect on NPC cells [14]. Cisplatin is an alkylator that can inhibit the proliferative activity of several tumor cells [15,16]. Cisplatin can inhibit the proliferation of the NPC cell line CNE-2 in a concentration-dependent manner, with low cisplatin concentration having almost no inhibitory effect on cell invasion and migration [17]. Cisplatin also has a unique radiosensitization effect [18], which is similar to the role of glycodidazolium sodium. Its conventional dose has little impact on bone marrow function [19]. When used simultaneously with radiotherapy, it does not add to the radiation toxicity. Thus, cisplatin is considered a relatively good drug for chemotherapy concurrent with radiotherapy [20]. A recent study [21] has also shown that if chemotherapy was used concurrently with radiotherapy, hypoxia in the tumor, which is one of the main reasons for resistance to radiotherapy, improved and the tumor shrank.

It was found that the high expression of caspase recruitment domain in tumor tissues played an important role in the pathogenesis of NPC and led to radiation and cisplatin resistance [22].

Gu et al. reported that radiotherapy combined with cisplatin and gemcitabine (GP) or with cisplatin and 5-FU (PF) can both significantly increase patients' overall survival, disease-free survival, and distant metastasis-free survival [23]. Carboplatin/5-FU is not inferior to PF with regard to its efficacy [24]. Wang et al. showed that although radiotherapy combined with concurrent cisplatin-based chemotherapy for the treatment of locally advanced NPC can produce satisfactory results, tumor recurrence and metastasis are still the main obstacles to positive therapeutic effects [25]. Jin et al. compared the response rate, toxicity, and long-term survival of PF, paclitaxel + cisplatin (TP), GP, paclitaxel + cisplatin + 5-FU, and bleomycin + cisplatin + 5-FU. The response rates in the GP and paclitaxel + cisplatin + 5-FU regimens were higher than in PF and TP, but there were no significant differences in progression-free survival and overall survival among different groups. PF/TP/GP regimens were all effective as first-line chemotherapy for metastatic NPC and were well tolerated [26].

5-FU specifically targets the S-phase of the cell cycle. It can be converted into 5-FU oligodeoxynucleotides in tumor cells and inhibits the functions of tetrahydrofolic acid and thymine nucleotides, thereby inhibiting cell proliferation. A

study focused on recurrent and metastatic NPC showed that the objective response rate reached 77.8% with the combination of sorafenib, cisplatin, and 5-FU, and was both tolerable and feasible [27]. Thus, this regime has good clinical results in the treatment of NPC [28].

In this study, we used fractionated radiotherapy combined with 5-FU and cisplatin for the treatment of advanced NPC. The results showed that the short-term response rate of patients in the treatment group was significantly higher than that in the control group, indicating that concurrent chemoradiotherapy can improve the efficacy of radiotherapy [29]. On comparing the patient survival rates we also found that the 5-year overall survival of patients in the treatment group reached 76%, showing a quite satisfactory efficacy. The 1-, 3- and 5-year survival rates of patients in the treatment group were all significantly higher than those in the control group, suggesting that radiotherapy combined with concurrent chemotherapy can improve the long-term efficacy of patients with NPC. During the course of radiotherapy, combination chemotherapy with 5-FU and cisplatin did not increase the local toxic effects of

radiotherapy. The local radiation complications of the 2 groups were not significantly different from each other.

However, systemic toxicity in the treatment group was higher compared with the control group and manifestations such as thrombocytopenia, leukopenia and other signs of bone marrow dysfunction were seen. One study recruited 2829 NPC patients, where the risk of treatment-related mortality increased from 0.8% in the radiotherapy alone group to 1.7% in the radiotherapy plus cisplatin-based chemotherapy group, while severe acute myelotoxicity also increased [30].

The results of the present and of others studies discussed above suggest that when radiotherapy is combined with concurrent combination chemotherapy, the toxic and adverse reactions of chemotherapy should be kept in mind in order to increase the safety of the treatment.

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