Long-term efficacy and adverse reactions of IMRT combined with Endostar versus IMRT combined with chemotherapy for locally advanced nasopharyngeal carcinoma: a retrospective study

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Background: This study aimed to analyze the long-term efficacy and late adverse reactions of intensity-modulated radiation therapy (IMRT) combined with recombinant human endostatin (Endostar) versus IMRT combined with concurrent chemotherapy (CCT) in patients with locoregionally advanced nasopharyngeal carcinoma (NPC).

Methods: This was a retrospective analysis of twenty-three NPC stage III-IVA patients treated with IMRT + Endostar or IMRT + CCT. Patients in the IMRT + Endostar group (n=10) received a total of 2 cycles of Endostar, while patients in the IMRT + CCT group (n=13) received a total of 3 cycles of concurrent cisplatin chemotherapy.

Results: The 5-year overall survival rates (OS) for the IMRT + Endostar group and the IMRT + CCT group were 90.0% and 61.5% ($P=0.123$), respectively. Local relapse-free survival (LRFS) rates were 90.0% and 76.9% ($P=0.396$), distant metastasis-free survival (DMFS) rates were 90.0% and 61.5% ($P=0.129$), and progression-free survival (PFS) rates were 90.0% and 53.8% ($P=0.074$) for the IMRT + Endostar group and the IMRT + CCT group. The incidence of grades 0, 1, and 2 xerostomia was 70.0%, 20.0%, and 10.0%, respectively, in the IMRT + Endostar group, and 15.4%, 76.9%, and 7.7% in the IMRT + CCT group, showing significant differences between the 2 groups ($P=0.020$). For the IMRT + Endostar group, the incidence of grades 0, 1, and 2 mouth-opening difficulty was 100.0%, 0%, and 0%, respectively, while for the IMRT + CCT group, the incidence was 53.8%, 38.5%, and 7.7%, with significant differences between the two groups ($P=0.044$). For the IMRT + Endostar group, the incidence of grades 0, 1, and 2 cervical and facial soft tissue fibrosis was 40.0%, 60.0%, and 0%, respectively, while for the IMRT + CCT group, the incidence was 0%, 76.9%, and 23.1%, showing significant differences between the two groups ($P=0.027$).

Conclusions: The difference in long-term efficacy between the IMRT + Endostar group and IMRT + CCT group was not significant for locally advanced NPC, but the IMRT + Endostar group had better efficacy and less severe late side effects. Further research involving a larger sample size and longer follow-up period are needed.

Keywords: Nasopharyngeal carcinoma (NPC); Endostar; intensity-modulated radiotherapy; long-term efficacy; late adverse effect

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Introduction

Nasopharyngeal carcinoma (NPC), which has a high incidence rate in East Asia and southeast China, is one of the most common malignant tumors of the head and neck in China (1). Radiotherapy (RT) is the predominant therapy for NPC patients. The progression of imaging, RT equipment, and technology has improved the prognosis of NPC patients significantly. However, distant metastasis remains one of the main reasons for treatment failure (2,3). According to the guidelines of the National Comprehensive Cancer Network (NCCN), intensity-modulated radiation therapy (IMRT) combined with concurrent chemotherapy (CCT) is the recommended standard treatment for patients with NPC. However, IMRT combined with CCT has poor compliance and significantly increases side effects, seriously affecting the quality of life for patients (4-7). Therefore, it is worth considering to find highly effective and less toxic alternatives to CCT for locally advanced nasopharyngeal carcinoma and reducing the risk of distant metastases from nasopharyngeal carcinoma.

Angiogenesis plays a crucial role in the growth and metastasis of NPC, and evidence for the use of antiangiogenic drugs has been widely reported in preclinical and clinical research (8). Endostar, independently developed in China, is a novel modified recombinant human endostatin with 9 amino acid residues added to the N-terminal, rendering it more stable against proteases, acid, and heat (8,9). Endostar suppresses tumor growth by blocking the formation of tumor neovascularization and reconstructing the disordered vascular network of a tumor to normalize its structure and function. It also improves the blood circulation and hypoxic state of tumors, and it increases the radiosensitivity of hypoxic cells. Endostar has been playing a key role in the treatment of refractory NPC (9-13). Many studies have also confirmed the therapeutic effects of Endostar on various other cancers, including non-small cell lung cancer, osteosarcoma, gastric cancer, and colorectal cancer (9,12,14-16). Further studies have shown that Endostar significantly improves the radiosensitivity of NPC by targeting tumor blood vessels *in vitro* and *in vivo* (10,13,17,18). However, there are few reports on the use of treatment for nasopharyngeal carcinoma IMRT combined with antiangiogenic drugs. The therapeutic value of IMRT combined with Endostar has not been fully evaluated. Our study explored the therapeutic potential of Endostar by investigating the difference between IMRT combined with Endostar and IMRT plus CCT in long-term efficacy and

late adverse reactions when treating locally advanced NPC. We present the following article in accordance with the STROBE reporting checklist (available at <https://dx.doi.org/10.21037/apm-21-3018>).

Methods

Subjects

This retrospective analysis in patients with locoregionally advanced nasopharyngeal carcinoma was designed to recruit patients at the RT Department of the Guangxi Medical University between January 2013 and December 2013. Patients were allocated to the IMRT + Endostar group or the IMRT + CCT group. Inclusion criteria were defined as follows: (I) a pathology diagnosis of NPC; (II) patients who had not previously received RT or chemotherapy; (III) patients with NPC stage III-IVA based on the 7th edition of the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC); (IV) measurable lesions observed according to Response Evaluation Criteria in Solid Tumors (RECIST); (V) creatinine clearance (Ccr) ≥ 60 mL/min or serum creatinine (Cr) level $\leq 1.25 \times$ upper normal limit (UNL); AST (SGOT) and ALT (SGPT) level $\leq 2.5 \times$ UNL, alkaline phosphatase level $\leq 5 \times$ UNL, serum bilirubin level $\leq 1.25 \times$ UNL, platelet count $\geq 100,000/\mu\text{L}$, serum hemoglobin level ≥ 10 gm/dL, and absolute neutrophil count $\geq 1,500/\mu\text{L}$; (VI) Karnofsky performance status (KPS) score > 70 ; and (VII) Estimated total survival > 6 months. Exclusion criteria were defined as follows: (I) cognitive impairment, bone marrow metastasis, symptomatic brain metastasis, or other distant metastasis; (II) lactation or pregnancy; (III) history of carcinoma or others; (IV) patients who had received RT, chemotherapy, or immunotherapy; (V) serious disorders of bone marrow function; (VI) bleeding disorders; (VII) drug abuse or alcohol abuse; (VIII) patients who did not follow the therapeutic schedule or complete more than 80%; and (IX) patients who violated the study protocol. Patients who did not complete the study because of side effects were not included in efficacy analysis. However, they were included in side effect analysis. Finally, when unacceptable toxicity, disease progression, use of other medications, or regrets participating in the study occurred in any patient, their participation in the trial was ended.

All patients underwent medical history review, physical examination, KPS score assessment, nasopharyngeal examination, magnetic resonance imaging (MRI) of the

rhinopharynx and neck with plain and enhanced scans, chest computed tomography (CT) or X-ray, upper abdominal CT, abdominal color Doppler, whole body bone scanning, liver and renal functions, electrocardiogram, blood routine, and electrolytes detection. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the committee of medical ethics institution of Guangxi Medical University [No. 2021 (KY-E-253)], and all patients signed written informed consent.

Treatment

A CT scan was performed on all patients, with a range of 3 cm from the top of the head to the subclavicle and a spacing of 3 mm. The scanned images were uploaded to the Eclipse treatment planning software system (Varian Medical Systems, Palo Alto, CA, USA). Nasopharynx gross tumor volume (GTVnx), lymph node gross tumor volume (GTVnd), clinical target volume-1 (CTV-1), clinical target volume-2 (CTV-2), and planned target volume (PTV) (CTV extension 3–5 mm) were outlined layer by layer, and the radiation doses were 7,030–7,400 CGy (PTVnx), 6,800–7,000 CGy (PTVnd), 6,000–6,600 CGy (PTV1), and 5,000–5,600 CGy (PTV2), respectively. Patients were treated using a 6 MV X-ray (IX-SN4948, Varian Medical Systems) five times a week.

Endostar targeted therapy or CCT was initiated at the same time as IMRT. Endostar (15 mg/day; Simcere, Yantai, China) was dissolved in 500 mL normal saline and injected intravenously for 3–4 hours from day 1, followed by continuous use for 14 days (1 cycle) and then withdrawal for 7 days. Patients received 2 cycles of treatment in total. For chemotherapy, cisplatin (80 mg/m², D 1–2) was administered for a total of 3–4 cycles, with 1 cycle defined as 21 days. Antiemetic, gastric care, hydration, and other adjuvant treatments were used during chemotherapy. The 10 patients in the IMRT + Endostar group received 2 cycles of Endostar, and the 13 patients in the IMRT + CCT group received 3 cycles of CCT.

Evaluation of treatment efficacy and side effects

As the primary endpoint, overall survival (OS) was regarded as the length of time from the start of treatment. Progression-free survival (PFS) was defined as the period from the date starting treatment until disease progressed. Local relapse-free survival (LRFS) was computed from the

start of treatment until relapse in the nasopharynx or neck. Distant metastasis-free survival (DMFS) was calculated as the period from the date starting treatment until detection of any distant metastasis. Evaluation criteria of late radiation responses was in line with the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC).

Follow-up

Follow-up frequency was set at every 3 months (within 2 years), every half year (within 3–5 years), and every year (beyond 5 years). At each follow-up visit, patients underwent physical examination, chest X-ray, chest CT, abdominal ultrasound, nasopharyngeal, and laboratory examination. RTOG/EORTC standards were used to detect late radiation injury. Head and neck MRI was performed every 6 months, and biopsies from patients with suspected recurrence were obtained. Patients with suspected distant metastasis received chest and abdomen CT, and radioisotope bone scan. Positron emission tomography (PET)/CT examination was performed when necessary. Follow-up was undertaken until March 9, 2020. The analysis parameters included OS, LRFS, DMFS, and PFS. Length of survival time was measured from the date of diagnosis.

Statistical analysis

Statistical analysis was performed by SPSS 25.0 software (IBM, Armonk, NY, USA). OS, LRFS, DMFS, and PFS were calculated with Kaplan-Meier methods and compared using the log-rank test. Cox proportional hazard model was conducted to determine the covariates for survival time. The reverse method was used in multivariate analysis. Chi square test was used for testing associations between categorical responses. The statistical significance level was defined as less than 0.05 ($P < 0.05$).

Results

Characteristics of patients

There were 23 eligible patients with NPC stage III–IVA were included and analyzed in our study. As shown in *Table 1*, patients were allocated to the IMRT + Endostar group ($n=10$) and the IMRT + CCT group ($n=13$). Among the IMRT + Endostar patients, there were 8 males and 2 females, and the median age was 59.2 (range, 40–77) years. Four patients in

Table 1 Clinical characteristics of nasopharyngeal carcinoma patients

Clinical data	Radiotherapy + Endostar (n=10)	Radiotherapy + chemotherapy (n=13)	P
Age (years)			0.830
Median	59	49	
Range	40–77	41–64	
Gender (No. of cases)			0.772
Male	8 (80.00)	11 (84.62)	
Female	2 (20.00)	2 (15.38)	
Pathological types			0.859
WHO I	0	0	
WHO II	2 (20.00)	3 (23.08)	
WHO III	8 (80.00)	10 (76.92)	
Tumor staging (No. of cases)			0.129
T1	0	0	
T2	0	2 (15.38)	
T3	7 (70.00)	4 (30.77)	
T4	3 (30.00)	7 (53.85)	
Node staging (No. of cases)			0.204
N0	2 (20.00)	1 (7.69)	
N1	2 (20.00)	0	
N2	4 (40.00)	10 (76.92)	
N3	2 (20.00)	2 (15.38)	
Clinical staging (No. of cases)			0.645
III	4 (40.00)	4 (30.77)	
IV	6 (60.00)	9 (69.23)	

WHO, World Health Organization.

this group were stage III and 6 were stage IVA. Two cases in this group were differentiated non-keratinizing carcinoma and the other 8 cases were undifferentiated non-keratinizing carcinoma. Among the IMRT + CCT patients, there were 11 males and 2 females, and the median age was 50.5 (range, 41–64) years. Four patients were stage III and 9 were stage IVA. Three cases in this group were differentiated non-keratinizing carcinoma and the other 10 cases were undifferentiated non-keratinizing carcinoma.

Long-term efficacy

The patients in this study were followed up from January

2013 to March 2020. The median follow-up period was 81 (range, 30–85) months, with a median follow-up period of 82 (range, 30–85) months for the IMRT + CCT group and 78 (range, 60–84) months for the IMRT + Endostar group. There was no significant difference in OS rate (90.0% *vs.* 61.5%, $P=0.123$), LRFS rate (90.0% *vs.* 76.9%, $P=0.369$), DMFS rate (90.0% *vs.* 61.5%, $P=0.129$), and PFS rate (90.0% *vs.* 53.8%, $P=0.074$) between the IMRT + Endostar group and the IMRT + CCT group, respectively (*Figure 1*). In total, 7 patients died during the follow-up period. In the experimental group, 1 patient died of local recurrence and 1 patient died as a result of a traffic accident. In the IMRT + CCT group, 3 patients died of local recurrence and 3

Figure 1 Cumulative survival curves of intensity-modulated radiation therapy combined with Endostar group versus intensity-modulated radiation therapy combined with concurrent chemotherapy group. (A) Kaplan-Meier curves of overall survival rates; (B) Kaplan-Meier curves of local relapse-free survival rates; (C) Kaplan-Meier curves of distant metastasis-free survival rates; and (D) Kaplan-Meier curves of progression-free survival rates of the two groups.

patients died of pulmonary metastasis.

Late adverse reactions

We evaluated the following late adverse reactions in subjects: xerostomia, cranial nerve palsy, subcutaneous soft-tissue fibrosis, deafness, difficulty in opening mouth, radiation-induced temporal lobe necrosis, visual loss, and headache. Regarding the late adverse effects of visual loss, there was 1 case of grade 4 in group IMRT + Endostar and 2 cases of grade 3 in group IMRT + CCT. Xerostomia was the most common late adverse reaction. For the IMRT + Endostar group, the incidence of xerostomia with grades 0, 1, and 2 was 70.0%, 20.0%, and 10.0%, respectively, whereas for the IMRT + CCT group, it was 15.4%, 76.9%, and 7.7%, respectively ($z=1.853$, $P=0.020$), showing significant differences. The incidence of mouth opening difficulties with grades 0, 1, and 2 in the IMRT + Endostar group was 100.0%, 0%, and 0%, respectively, while the incidence in the IMRT + CCT group was 53.8%,

38.5%, and 7.7%, respectively ($z=6.244$, $P=0.044$), showing significant differences. The incidence of cervical and facial soft tissue fibrosis with grades 0, 1, and 2 in the IMRT + Endostar group was 0%, 40.0%, and 60.0%, respectively, while the incidence in the IMRT + CCT group was 0%, 76.9%, and 23.1%, respectively ($z=7.202$, $P=0.027$). There was no significant difference between the IMRT + CCT group and IMRT + Endostar group in the incidence of pharyngeal pain ($P=0.244$), hearing loss ($P=0.372$), visual loss ($P=0.245$), and headache ($P=0.194$) (Table 2). In addition, except for xerostomia, difficulty in opening mouth, and cervical and facial soft tissue fibrosis, no significant differences were detected between the 2 groups in the grades of other advanced adverse reactions.

Discussion

In recent years, IMRT has been widely used in the treatment of NPC and achieved satisfactory results. A total of 333 patients with clinical stage III/IV M0 were reported

Table 2 Comparison of late adverse reactions in the 2 groups [No. of cases (%)]

Late adverse reaction	Radiotherapy combined with Endostar					Radiotherapy combined with chemotherapy					z	P
	0	1	2	3	4	0	1	2	3	4		
Throat pain	9 (90.0)	1 (10.0)	0 (0)	0 (0)	0 (0)	13 (100.0)	0 (0)	0 (0)	0 (0)	0 (0)	1.359	0.244
Hearing loss	5 (50.0)	4 (40.0)	1 (10.0)	0 (0)	0 (0)	10 (76.9)	2 (15.4)	1 (7.7)	0 (0)	0 (0)	1.976	0.372
visual loss	8 (80.0)	1 (10.0)	0 (0)	0 (0)	1 (10)	11 (84.6)	0 (0)	0 (0)	2 (15.4)	0 (0)	4.153	0.245
Headache	10 (100.0)	0 (0)	0 (0)	0 (0)	0 (0)	11 (84.6)	2 (15.4)	0 (0)	0 (0)	0 (0)	1.685	0.194
Xerostomia	7 (70.0)	2 (20.0)	1 (10.0)	0 (0)	0 (0)	2 (15.4)	10 (76.9)	1 (7.7)	0 (0)	0 (0)	1.853	0.02
Difficulty in mouth opening	10 (100.0)	0 (0)	0 (0)	0 (0)	0 (0)	7 (53.8)	5 (38.5)	1 (7.7)	0 (0)	0 (0)	6.244	0.044
Subcutaneous soft tissue fibrosis	4 (40.0)	6 (60.0)	0 (0)	0 (0)	0 (0)	0 (0)	11 (84.6)	2 (15.4)	0 (0)	0 (0)	7.202	0.027
Heart	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	–	–
Osteoradionecrosis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	–	–
Radiation brain damage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	–	–
Radiation caries	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	–	–

in the Cancer Hospital of Chinese Academy of Medical Sciences. The 5-year local control rate, 5-year OS rate, DFS rate and DMFS rate were 87.3%, 80.2%, 69.3% and 82% after IMRT alone (19). In Wang's study, 546 primary III-IVb stage patients were received pure IMRT, and the 5-year DMFS rate, LRRFS rate, PFS rate and OS rate were 85.61%, 89.79%, 77.99% and 85.97%, respectively (20). Xiao reported that after treating with IMRT alone, the 5-year OS rates of patients was 79.7% in stage III (243 patients), 67.9% in stage IVa (108 patients), and 75% in stage IVb (23 patients) (21). Yi, Zhao and Xiao's study showed that the factors influencing OS included gender, age, T stage and N stage. T stage affects local control rate, and both T stage and N stage affect disease-free survival rate and distant metastasis free survival rate (19,21,22). Some patients with locally advanced nasopharyngeal carcinoma undergo recurrence and metastasis after treatment, and the side effects of RT combined with chemotherapy decrease patient quality of life. RT combined with antiangiogenesis treatment is considered a promising strategy for locally advanced NPC.

Our previous studies showed that IMRT + Endostar had similar therapeutic effects to IMRT + CCT and its acute toxicity is relatively lower, which is conducive to improving quality of life for NPC patients (11). However, we only analyzed the 2-year OS, 2-year LRRFS, 2-year DMFS and 2-year PFS rates before. Acute toxicity, including

leucopenia, nausea/vomiting, weight loss, and oral mucositis were also observed in previous study. Differentially, this study evaluated long-term efficacy and late side effects in NPC patients. The results showed no statistical difference between the IMRT + Endostar group and IMRT + CCT group in 5-year OS, 5-year LRRFS, 5-year DMFS, and 5-year PFS. Although there was no difference shown between the two groups in survival, the survival curves of the two groups were separated, suggesting that the IMRT + Endostar group was trending towards achieving a better survival than the IMRT + CCT group. The insignificant statistical difference may be due to the small sample size. Xerostomia was the most common side effect in both the IMRT + Endostar group and IMRT + CCT group, but the incidence of xerostomia in the concurrent chemoradiotherapy group was significantly higher than that after IMRT + Endostar treatment. Meanwhile, difficulty of mouth opening and fibrosis of face and neck tissue were significantly reduced in the IMRT combined with Endostar group. However, there was no significant difference in side effects such as sore throat, hearing loss, vision loss, and headache ($P>0.05$), suggesting that the late toxicity of IMRT combined with Endostar was relatively mild.

In recent years, the quality of life of NPC patients with radiotherapy and chemotherapy is poor, accompanied by serious side effects such as bone inhibition. Targeted therapy can accurately identify and treat nasopharyngeal carcinoma

cells, with low toxicity and side effects, and has broad prospects in clinical treatment (23). EGFR and VEGFR are two major intervention targets for nasopharyngeal carcinoma. Currently, targeted therapies are mainly divided into monoclonal antibodies and small molecule compounds, including epidermal growth factor receptor (EGFR), angiogenic factor (VEGF) and angiogenic factor receptor (VEGFR) inhibitors (24). In the EGFR signaling pathway, targeted drugs enter the body, specifically bind the EGFR sites of tumor cells, interference EGFR signal transduction pathways, inhibit tumor cell proliferation, induce differentiation, promote apoptosis, inhibit tumor angiogenesis, and improve the efficacy of radiotherapy and chemotherapy (25). Tumor growth is related to angiogenesis (26,27), hence the inhibition of vascular supply can impede tumor growth (28-30). Endostatin has been proven to inhibit tumor growth, and as a human angiogenesis inhibitor, Endostar has an anticancer effect by restraining the function of endothelial cells and inhibiting angiogenesis of tumors. Furthermore, Endostar improves the disordered vascular network, blood circulation and hypoxia, and enhances the radiation sensitivity of hypoxic cells. Endostar promotes cell cycle redistribution and promotes the effects of Endostar and radiotherapy at different stages of the cell cycle (11). Therefore, Endostar plus RT is more effective than Endostar or RT alone. Studies have shown that antiangiogenic therapy combined with RT improves the local control rate (LCR) and long-term disease-free survival (DFS) rate. Zhou *et al.* (10) compared the antitumor efficacy of Endostar combined with radiation in an animal model of subcutaneous transplantation of NPC. The results showed that Endostar combined with RT had significant antitumor efficacy, with significantly improved RT sensitivity and LCR. The level of vascular endothelial growth factor (VEGF) in tumor tissues of the group receiving Endostar combined with RT was below that of the RT group and the Endostar group alone, suggesting that Endostar may have increased the radiosensitivity of nude mice with NPC by reducing the expression of VEGF. Teicher (31), Hansen-Algenstaedt (32), Luo (33), and Itasaka (34) *et al.* have also shown that Endostar plus RT could significantly inhibit the growth and metastasis of NPC cells.

In many clinical studies, Endostar has been shown to be effective against some tumors. Wang *et al.* (12) conducted a stratified double-blind, randomized phase III trial with 493 patients with stage IIIB and IV non-small cell lung cancer (NSCLC). The results showed that the total effective rate of Endostar combined with vinorelbine and

cisplatin (NP) was 35.4%, while for the group receiving NP alone, it was 19.5% ($P=0.0003$). The median time to progression (TTP) of the two groups was 6.3 and 3.6 months ($P<0.001$), respectively. The clinical benefit rate of the group receiving Endostar combined with NP was 73.3%, while for the group receiving NP alone, it was 64.0% ($P=0.035$). The effective rate, median TTP, and clinical benefit rate of Endostar combined with NP were significantly higher in advanced NSCLC patients than NP alone. Further, Endostar combined with CCT showed the advantages of synergistic activity and low toxicity in patients with advanced NSCLC. Guan (9) found that complete response (CR) rate, 1-year OS rate, and 2-year OS rate of patients who received Endostar plus IMRT were 90.9%, 93.3%, and 66.4%, respectively, which was significantly higher than those in previous studies (35-38). Radiation-induced apoptosis of endothelial cells can impair the barrier integrity of blood vessels, leading to edema and hypoxia of the tissues. Also, tissue hypoxia helps to upregulate VEGF, so the persistence of this condition may result in higher vasopermeability and tissue necrosis (17,39,40). Endostar combined with RT is able to effectively reduce the incidence and degree of nasopharyngeal mucosa necrosis by normalizing the abnormal blood vessels in the fields of RT and improving the poor blood supply to the necrotic tissues. Previous studies have shown that VEGF expression in NPC is directly related to tumor microvascular density (39). While Endostar upregulates endogenous antiangiogenesis and antitumor factor pigment epithelium-derived factor (PEDF), it downregulates VEGF activity, reduces immature blood vessel numbers and oxygen consumption, enhances hypoxia tolerance, reduces inflammatory ooze, and improves the ability to recover from necrotic tissue (17,40). Zhang *et al.* (41) found that Endostar enhanced RT sensitivity by downregulating vascular expression and normalizing blood vessels, and it attenuated the elevation of transforming growth factor (TGF)- β 1 expression after radiation-induced lung injury (RILI). Chen *et al.* (42) reported that liver inflammation and hepatocyte necrosis could be improved by Endostar in a carbon tetrachloride (CCL₄)-induced liver fibrosis model, suggesting that Endostar may have antagonized hepatocyte necrosis and hepatic fibrosis via the transduction pathways of TGF regulatory factors and VEGF.

Treating locally relapsed NPC patients with Endostar combined with IMRT can enhance patient tolerance and also reduce the incidence of side effects. Guan *et al.* (9) found that Endostar was used in combination with IMRT.

All patients completed the planned RT, and the incidence of grades 3–5 toxicities was 50% (11 out of 22), while the infection and/or necrosis rate of nasopharyngeal mucosa was 31.8%, significantly lower than those treated with IMRT plus CCT in 2 previous studies by Han *et al.* (35) and Qiu *et al.* (37), indicating that Endostar combined with IMRT effectively reduced the incidence of nasopharyngeal mucosal necrosis.

There are some limitations to this study. First of all, these findings are based on a small sample size. In the second place, recall bias may exist because this is a retrospective analysis. Finally, the observation period can be longer.

Conclusions

In conclusion, IMRT combined with Endostar is a more effective regimen for NPC patients compared to IMRT plus CCT. With fewer severe adverse reactions than IMRT plus CCT, IMRT combined with Endostar can better improve patient quality of life. Therefore, as a highly effective and low-toxicity potential treatment for NPC, this regimen is worthy of large-scale clinical studies to further evaluate its efficacy, safety, and toxic side effects.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the committee of medical ethics institution of Guangxi Medical University [No. 2021 (KY-E-253)] and informed consent was taken from all the patients.

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