Treating radiation-related nasopharyngeal necrosis with endostar in patient with nasopharyngeal carcinoma: A report of two cases and a literature review

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Abstract. Radiation-related nasopharyngeal necrosis (RRNN) is a rare and often fatal complication in patients with nasopharyngeal carcinoma (NPC). Currently, no standard treatments are recommended for RRNN. The effects of traditional conservative treatments are suboptimal, and surgery for RRNN cannot be performed by inexperienced doctors. In the present study, the use of Endostar in two patients with RRNN was evaluated. Two patients with RRNN were treated at the Department of Oncology, Panyu Central Hospital (Guangzhou, China). Endostar was administrated (15 mg/day from day 1 to day 7, every three weeks) intravenously for four and seven cycles in a male and a female patient, respectively. The effects of Endostar were assessed using magnetic resonance imaging (MRI) and a nasopharyngoscope. The symptoms of RRNN in both patients were relieved after treatment with Endostar. MRI and nasopharyngoscope analysis revealed that necrosis of the nasopharynx was substantially decreased and nasopharyngeal ulcers were healed. Endostar has the potential to be a novel, effective therapy for the treatment of patients with RRNN. However, clinical trials are required to confirm the results of the present study.

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Introduction

Nasopharyngeal carcinoma (NPC) is common in Southeast Asia and is less common in Europe and the United States. The incidence of NPC in endemic areas can reach 10-50 per 100,000 individuals (1). With the use of intensity-modulated radiation therapy (IMRT), the 5-year local recurrence-free survival rate and overall survival rate are approximately 90 and 80%, respectively (2,3). However, the extension of survival time leads to the occurrence of late adverse effects (AEs) of radiotherapy, which are associated with poor quality of life in patients with NPC. The most common AEs in patients with NPC treated with radiotherapy include hearing loss, tinnitus, subcutaneous fibrosis, and xerostomia (4). Radiation-related nasopharyngeal necrosis (RRNN) is a rare AE of radiotherapy, with an incidence of 1-2% in patients with primary NPC (5,6). However, in patients with recurrent NPC treated with reirradiation, the incidence of RRNN is 30-40% (7,8). Predominant symptoms caused by RRNN include foul nasal odor, persistent headache, and nasal hemorrhage. Most patients with RRNN succumb, as a result of massive nasopharyngeal bleeding due to internal carotid artery rupture (9).

There are currently no effective treatments for RRNN due to a lack of knowledge surrounding its pathophysiology. Conservative management includes nasal irrigation, systemic or topical antibiotics, intravenous nutritional supplements, hyperbaric oxygen, and debridement guided by nasal endoscopy; however, outcomes with these treatments remain suboptimal (9). Endoscopic or open surgery have also been suggested to remove necrotic tissue, followed by flap covering; however, these approaches are associated with high costs and can only be performed by few skilled surgeons in China (10-12). As such, there is a need to identify effective, low cost therapies that can effectively treat RRNN in patients with NPC.

Endostar, as a recombinant form of endostatin, exerts antitumor effects via inhibition of the VEGF pathway, similar to bevacizumab (13-16). Endostar, in combination with chemotherapy, was approved by the China Food and Drug Administration as first-line therapy for stage III-IV non-small cell lung cancer (NSCLC) (16). In addition to its anti-angiogenic effect, Endostar was also demonstrated to reduce radiation damage to normal tissues. Guan *et al* revealed that Endostar decreased the occruence of RRNN in patients with local recurrent NPC who were treated with radiotherapy (17). Xing *et al* also successfully treated patients with radiotherapy-induced brain necrosis, with Endostar (18). In addition, a pre-clinical study revealed that Endostar could reduce radiation-induced fibrosis (19).

Based on these studies, two patients with RRNN were treated with Endostar to determine its effectiveness. To the best of our knowledge, this is the first study of an anti-angiogenic approach for the treatment of RRNN.

Case report

The present study was approved (approval no. PYRC2023090) by the Ethics Committee of Panyu Central Hospital (Guangzhou, China). The patients agreed to participate in the present study and submitted written informed consent.

The first patient (case 1), was a 50-year-old man who in June 2019 presented to the Outpatient Department of Panyu Central Hospital (Guangzhou, China), with a headache and was diagnosed with undifferentiated non-keratinizing carcinoma of the nasopharynx [World Health Organization (WHO) type III], tumor stage III (T3N1M0) according to the eighth edition of the American Joint Committee on Cancer staging system (20,21). From June 26, 2019, the patient received two cycles of induction chemotherapy with docetaxel plus cisplatin, followed by concurrent chemoradiotherapy with IMRT, administered according to the following dosing schedule: Gross tumor volume (GTV), high risk area around primary tumor (CTV1), low risk area around tumor and bilateral cervical lymph node drainage area (CTV2), left positive lymph node and right positive lymph node were dosed with 70.4, 60, 54, 66 and 64 Gy, respectively. The fractionation number was 32. A complete response was revealed using MRI and a nasopharyngoscope on September 10, 2019. On July 3, 2020, the patient again presented to the hospital due to a refractory, severe headache. A nasopharyngoscope revealed a yellowish necrotic tissue on the left parietal-posterior wall of the nasopharynx, surrounded by purulent secretions (Fig. 1A). MRI revealed necrotic lesions on the left side of the nasopharynx (Fig. 1B). No tumor metastases were detected by contrast-enhanced CT of the chest and abdomen. The patient was negative for Epstein-Barr virus. Repetitive histological examination (10% formalin-fixed for 12 h at room temperature; embedded in paraffin; section thickness, 3 μm; staining, hematoxylin and eosin stain used for 15 min at room temperature; and visualized using a light microscope with a magnification of x100) of nasopharyngeal specimens showed no recurrent tumor (Fig. 1C). Initially, conservative treatments including nasal irrigations, systemic antibiotics and intravenous nutrition were used to treat the patient. However, the headache of the patient worsened one week later. The decision was made to use Endostar following approval (approval no. PYRC2023090) by the Ethics Committee of Panyu Central Hospital (Guangzhou, China). The headache of the patient was significantly relieved after one course of Endostar (15 mg per day, from day 1 to day 7, every three weeks), and oxycodone was not required for pain relief after four courses of treatment. MRI and a nasopharyngoscope revealed that the necrotic lesion had disappeared after two cycles of Endostar (Figs. 2 and 3). Due to financial constraints, the patient declined to return for examination and treatment after four cycles of Endostar. However, on August 20, 2022, the patient was revealed to be doing well without any discomfort such as headache, nasal odor, or nasal hemorrhage, upon examination at the Outpatient Department.

The second patient (case 2), was a 50-year-old woman who in November 2019 was diagnosed with undifferentiated non-keratinizing carcinoma of the nasopharynx (WHO type III), tumor stage IVA (T4N1M0) at Panyu Central Hospital (Guangzhou, China) according to the eighth edition of the American Joint Committee on Cancer staging system. The patient received three cycles of chemotherapy with gemcitabine, cisplatin, and sintilimab, followed by concurrent chemoradiotherapy as part of a randomized controlled trial for patients with local advanced nasopharyngeal carcinoma. IMRT was administered at 70, 60, 54, 66 and 64 Gy for the GTV, CTV1, CTV2, left positive lymph node and right positive lymph node, respectively. The fractionation number was 33. A total of six additional cycles of immunotherapy with sintilimab were administered after chemoradiotherapy and the last dose of sintilimab was administered on September 9, 2020. The patient was admitted to the Department of Oncology, Panyu Central Hospital (Guangzhou, China) on September 23, 2020 due to foul nasal odor and hearing loss. A nasopharyngoscope revealed a large amount of necrotic tissue and bone on the posterior wall of the nasopharynx (Fig. 4A). An endotoscope revealed bilateral middle ear effusion. MRI revealed osteonecrosis of the skull base and necrosis of the posterior wall of the nasopharyngx (Fig. 4B). No distant metastases were identified by CT scan of the chest and abdomen. The patient was negative for Epstein-Barr virus. Due to insufficient exposure of the nasopharynx with the use of the nasopharyngoscope, as well as severe necrosis and adhesion, a forceps biopsy was not permitted as there was a possibility of massive nasopharyngeal hemorrhage. The patient was eventually diagnosed with RRNN based on the results of MRI and the nasopharyngoscope and was treated with Endostar following approval (approval no. PYRC2023090) by the Ethics Committee of Panyu Central Hospital (Guangzhou, China). The patient received bilateral middle ear tube drainage and seven cycles of Endostar (15 mg per day, from day 1 to day 7, every three weeks) between September 30, 2020 and February 23, 2021. The symptoms of the patient were relieved after two courses of Endostar. The nasopharyngoscope and MRI showed that the nasopharyngeal necrotic lesions had disappeared and the nasopharyngx was filled with new tissue (Figs. 5 and 6). Pathological biopsy (10% formalin-fixed for 12 h at room temperature; embedded in paraffin; section thickness, 3 μm; staining, hematoxylin and eosin stain used for 15 min at room temperature; and visualized using a light microscope with a magnification of x100) of the posterior wall of the nasopharynx revealed that there was no tumor recurrence (Fig. 7).

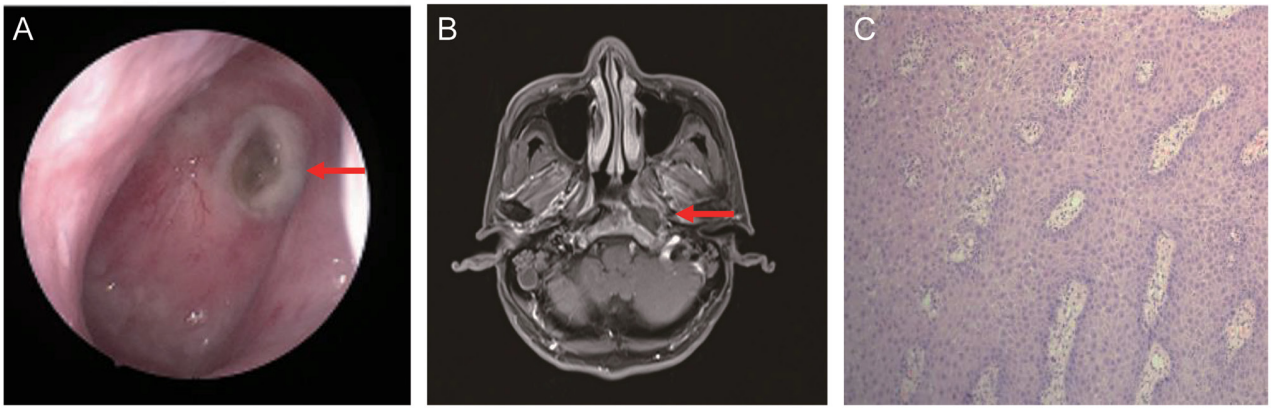

Figure 1. Images before treatment of case 1. (A) A nasopharyngoscope showed necrosis on the left side of the nasopharynx, with yellow dead tissue in the center of the lesion and purulent secretions (red arrow). (B) Transverse, contrast-enhanced, T1-weighted MRI revealed necrotic lesions (red arrow). (C) No tumor cells were identified in the lesion (magnification, x100).

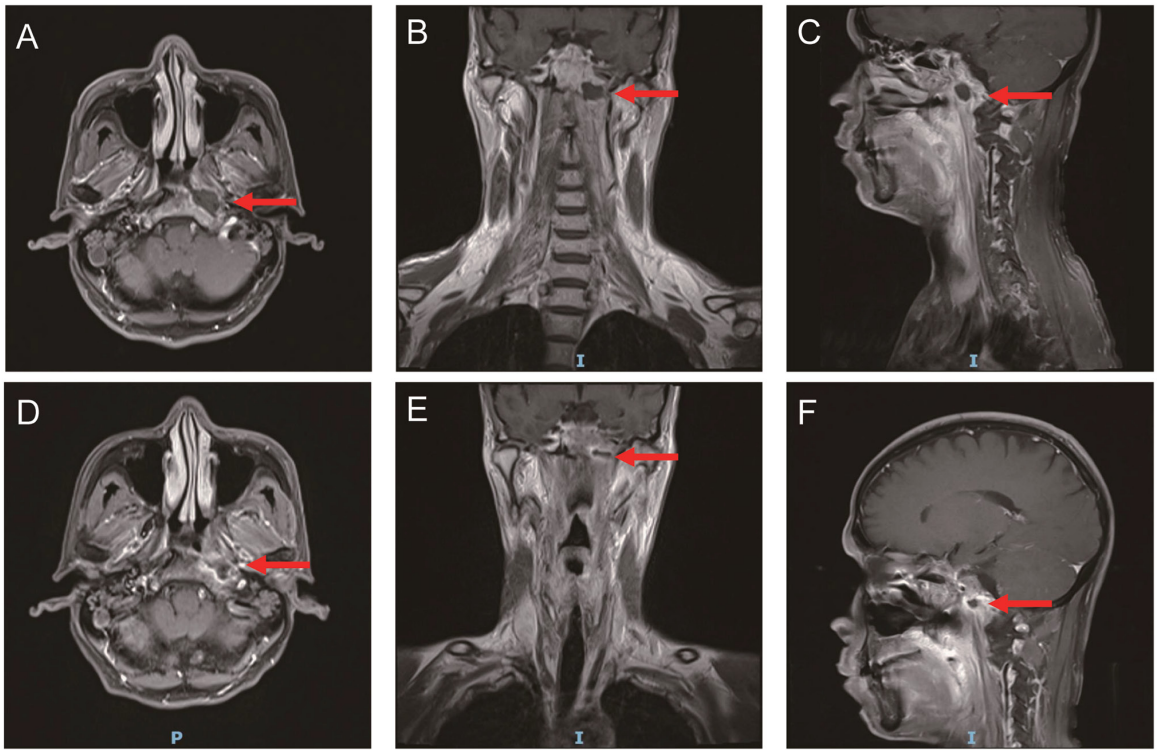

Figure 2. Comparison of the images obtained with MRI before and after treatment for case 1. (A-C) Pre-treatment images obtained with MRI and (D-F) post-treatment images obtained with MRI. By comparison, it was confirmed that the nasopharyngeal necrosis was replaced with new tissues with a high signal in the T1-enhanced sequence (red arrow).

Discussion

RRNN is defined as necrosis of the nasopharyngeal mucosa, adjacent muscles, or the skull base following exposure to high doses of radiation in patients with NPC (22). Reirradiation is the most important risk factor for the development of RRNN. Other risk factors include tumor stage, nutritional status during radiotherapy, and anemia (5). Patients with RRNN often present with headache, foul nasal odor, and recurrent epistaxis, which may occur alone or together (6,9,23). RRNN can significantly reduce the quality of life of the patient and is associated with mortality. The reported 2-year overall survival (OS) in patients with RRNN is 51.6% (11). In patients in whom necrosis or ulcers have eroded the skull base bone, survival rates are even worse (9). The diagnosis of RRNN can be achieved via a nasopharyngoscope and MRI of the nasopharynx; however, the gold standard of diagnosis is a pathological biopsy (11).

RRNN is challenging for physicians to treat. The mainstays of treatment include conservative and surgical management. The conservative approach consists of daily rinsing of the nasopharynx with 2% aqueous hydrogen peroxide solution or saline, hyperbaric oxygen, systemic antibiotics, intravenous nutrition and surgical debridement, which is associated with

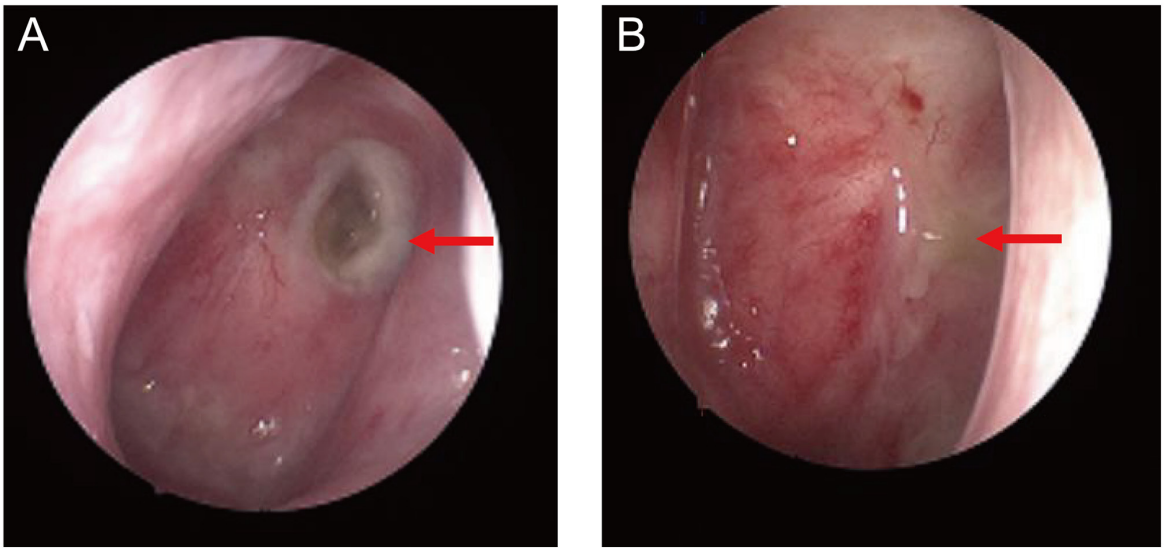

Figure 3. Comparison of the images obtained with a nasopharyngoscope before and after treatment for case 1. (A) The image obtained with the nasopharyngoscope before treatment. (B) The image obtained with the nasopharyngoscope after treatment. These results show that necrotic lesions disappeared and the original lesion was covered by new mucosal epithelium (red arrow).

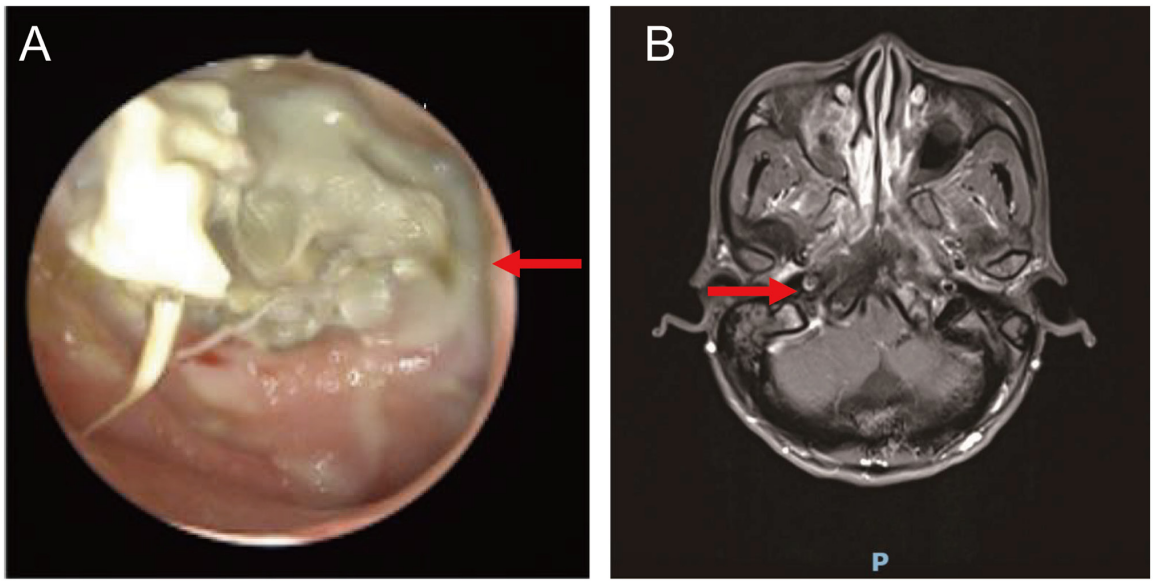

Figure 4. Images before treatment of case 2. (A) The image obtained with the use of a nasopharyngoscope showed a large amount of necrotic tissue on the posterior wall of the nasopharynx, surrounded by dead bone (red arrow). (B) Transverse, contrast-enhanced, T1-weighted MRI revealed necrotic lesions at the right side of the nasopharynx (red arrow).

a cure rate of only 13.4% (9). In addition, a combination of pentoxifylline, tocopherol, and clodronate, or PENTOCLO, was revealed to be effective for treating refractory osteoradionecrosis, which is a serious complication of RRNN (24,25). However, a study by Huang *et al* (12) revealed that only 9.5% of patients with mucosal defects caused by RRNN could be effectively treated with PENTOCLO, which is lower than the 59% cure rate reported by Robard *et al* (25). Surgical management, including complete resection of necrotic nasopharyngeal tissue under endoscopy, and maxillary swing or mandibulotomy with free vastus lateralis flap for reconstruction, may be effective methods for the treatment of RRNN (11,12). However, surgery is a complex and risky procedure that can only be performed by specific experts. Additionally, only 32% of patients with osteoradionecrosis were eligible for surgery in a study by Chen *et al* (11).

In the present study, the successful treatment of two patients with RRNN using the anti-angiogenic drug, Endostar was reported. As of October 8, 2022, neither patient reported headache, nasal odor, nasal bleeding or other symptoms and both patients did not require analgesic drugs.

The main mechanism underlying the development of RRNN is radiation-induced fibrosis (RIF) (26). This process can be divided into three phases; phase I involves the injury of endothelial cells by radiation leading to the generation of chemotactic cytokines that can trigger acute, non-specific

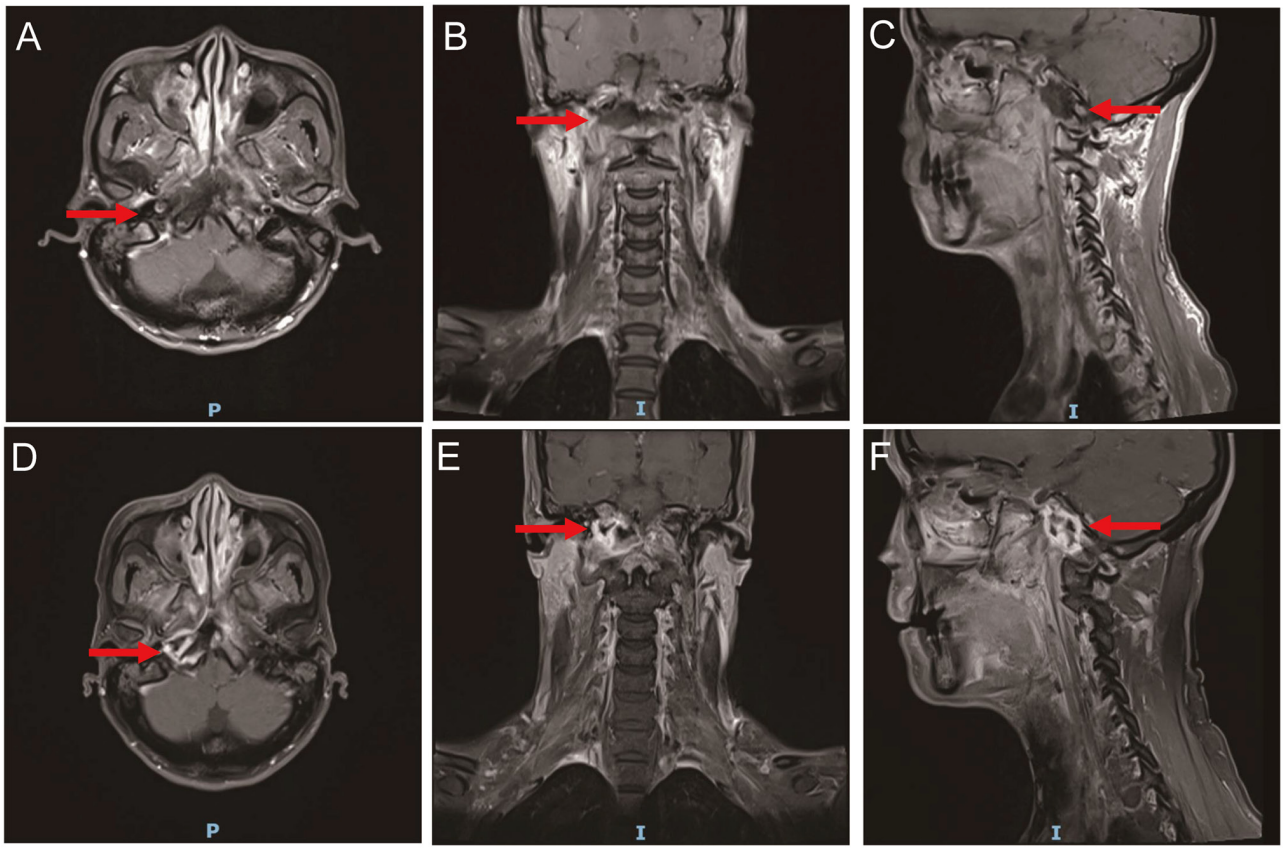

Figure 5. Comparison of the images obtained with MRI before and after treatment for case 2. (A-C) Pre-treatment images obtained with MRI and (D-F) post-treatment images obtained with MRI. MRI revealed that necrosis of the nasopharynx was replaced by new tissues that exhibited high signals on contrast enhanced T1-weighted CT (red arrow of D-F).

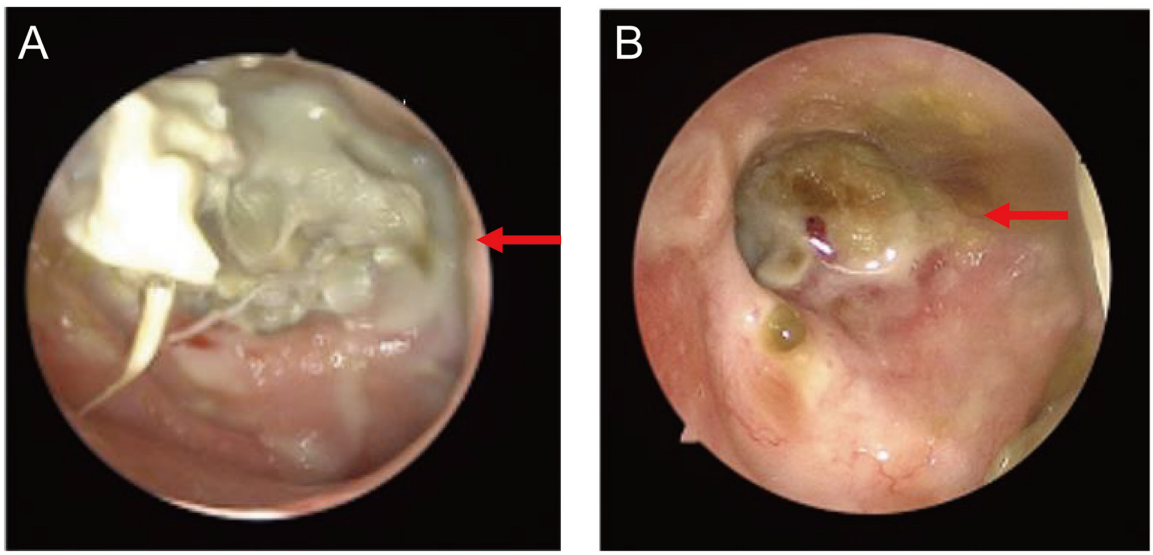

Figure 6. Comparison of the images obtained with a nasopharyngoscope before and after treatment for case 2. The red arrows indicate the necrotic lesions in the nasopharynx before and after treatment. (A) The image obtained with the nasopharyngoscope before treatment. (B) The image obtained with the nasopharyngoscope after treatment. The results showed that the purulent nasal discharge was significantly reduced after treatment, and there were new tissues in the posterior wall of the nasopharynx.

inflammation.This inflammation is characterized by increased vascular permeability, local edema formation and local ischaemia. This process is very similar to the changes observed in the vasculature of the blood-spinal cord barrier following radiotherapy, which may be due to upregulation of VEGF expression induced by radiotherapy. Phase II is characterized by the activation of fibroblasts by cytokines that seep into tissue from the micro vasculature and become myofibroblasts, leading

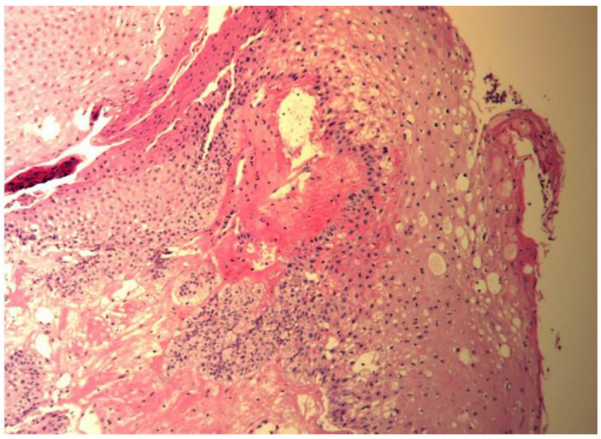

Figure 7. Images of a nasopharyngeal pathological biopsy after treatment for case 2. A biopsy of new tissues in the nasopharynx revealed that there were no recurrent tumor cells and an abundance of squamous cells (magnification, x100).

to the formation of RIF tissue in place of normal tissue. Among these cytokines, transforming growth factor β1 (TGF-β1) plays a predominant role. Finally, phase III involves the death of myofibroblasts in RIF tissue, which leads the tissue to become poorly vascularized, paucicellular, and unable to heal once it is subjected to trauma and is therefore prone to necrosis (26,27).

Endostatin was shown to exert antitumor effects by inhibiting tumor angiogenesis in xenografted mouse models (28-31). Endostar is a recombinant form of endostatin, which was approved by the China Food and Drug Administration in combination with vinorelbine and cisplatin, for the treatment of NSCLC in 2005 (16). However, a phase II study showed that Endostar alone did not cause tumor regression in highly vascular neuroendocrine tumors (32). These results indicate that the antitumor activity of Endostar is more complex than previously considered. Another study in a xenografted mouse model of human NPC demonstrated that Endostar can restore normal vasculature. The tumor vasculature had fewer sprouts and branches in the Endostar group compared with controls. In addition, Endostar significantly increased the pericyte coverage, and the percentage of basement membrane in the blood vessels. By contrast, Endostar decreased the permeability of the tumor vasculature and improved hypoxia in tumor tissue compared with controls in a xenografted mouse model of human NPC ($P<0.05$). These effects are attributable to the antiangiogenic activity of Endostar (33). Wang *et al* demonstrated that Endostar could significantly increase the blood volume and blood flow velocity in the tumors of patients with NPC (34). Thus, Endostar may treat RRNN by downregulating the VEGF pathway, leading to decreased vascular permeability in irradiated tissue. Additionally, Endostar may also downregulate TGF-β1 to treat RRNN (19).

Guan *et al* demonstrated that treatment with Endostar decreased the incidence of RRNN in patients with recurrent NPC who received radiotherapy (17). In the present study, the effect of Endostar in the treatment of RRNN was investigated. In case 1, T1-enhanced imaging showed that the signal intensity of the skull base bone significantly decreased after treatment. This may be due to reduced vascular permeability following treatment with Endostar. In both cases, new tissue was observed in the nasopharynx, which presented with a high signal in T1-enhanced images. Pathological biopsy from the posterior wall of the nasopharynx in case 2 revealed that the tissue was full of squamous cells, which is in contrast to RIF tissue decribed in a previous study (26).

Endostar is generally dosed at 7.5 mg/m^2/day for 14 consecutive days (13,16). However, clinical trials have evaluated different doses, including 15 mg/day for 14 days or 45 mg/day on days 1, 3, and 4 (35,36). In the present study, a treatment regimen of 15 mg daily for 7 days was evaluated. Total therapeutic dosage was determined based on the response of each patient to treatment. After each cycle of treatment, the patient was evaluated for symptoms, and underwent a nasopharyngoscope examination and MRI every two cycles. If the following criteria were met, treatment was discontinued: Resolution or significant improvement of symptoms; signs of ulcer repair with the use of the nasopharyngoscope; no infectious secretions in the nasopharynx; resolution of necrotic lesions observed with MRI. However, given the limited clinical experience of the authors, further studies are required to explore the optimal total dosage.

Previous clinical research has reported several AEs associated with Endostar including arrhythmia, prolonged or shortened Q-T interval, hematological adverse reactions such as anemia and prolonged thrombin time, and digestive adverse reactions such as transaminase elevation (37). In the present study, no Endostar-related AEs were observed. Morevover, previous pharmacokinetic studies have shown that the maximum total dose of Endostar in humans can reach 240 mg/m^2/day for 168 days (38), which demonstrates the favorable safety profile of Endostar.

In conclusion, in the present study it was revealed that two patients with RRNN were cured with Endostar, suggesting that it may be a promising treatment for this intractable disease. However, large-scale, prospective, controlled trials are required to confirm the effectiveness of Endostar for the treatment of RRNN.

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Availability of data and materials

The data generated in the present study are included in the figures of this article.

Authors' contributions

JT, XWL and YW contributed to the design of the study. YHL, ZS and XLC contributed to the conception of the study. JT,

XWL, GRZ, YHL, ZS, and XLC performed the extraction of images. JT, BCW, XWS, YH and XWL performed the analysis of the images. JT and BCW wrote the manuscript. GRZ, YW and JT edited the manuscript. JT and BCW confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved (approval no. PYRC2023090) by the Ethics Committee of Panyu Central Hospital (Guangzhou, China). The patients agreed to participate in the present study and submitted written informed consent.

Patient consent for publication

The patients provided consent for their information to be published.

Competing interests

The authors declare that they have no competing interests.

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