International Journal of Clinical Oncology (2019) 24:248–255
https://doi.org/10.1007/s10147-018-1354-8

ORIGINAL ARTICLE

Endoscopic sequestrectomy for skull base osteoradionecrosis in nasopharyngeal carcinoma patients: a 10-year experience

Juan Liu[1] · Xianhui Ning[1] · Xicai Sun[1] · Hanyu Lu[1] · Yurong Gu[1] · Dehui Wang[1]

Received: 4 May 2018 / Accepted: 3 October 2018 / Published online: 9 November 2018

Abstract

Background Skull base osteoradionecrosis is a devastating post-irradiation complication in nasopharyngeal carcinoma patients. We conducted a retrospective analysis to assess the long-term survival and prognostic factors of patients with skull base osteoradionecrosis treated with endoscopic sequestrectomy.

Methods We enrolled 59 nasopharyngeal carcinoma patients with skull base osteoradionecrosis who underwent endoscopic nasopharyngectomy. The clinical characteristics and outcome at the last follow-up visit were collected. The survival curve and univariate and multivariate survival analysis were analyzed by Kaplan–Meier and Cox proportional hazards model to analyze the potential prognostic factors of overall survival, including age, gender, number of radiation, number of operations, extension of disease (local or extensive), whether the ICA is exposed to the procedure (yes or no) and the hypha status (yes or no) at postoperative pathological examination.

Results The predilection sites of skull base osteoradionecrosis in osteoradionecrosis patients are as follows: the base of the sphenoid bone and sphenoid sinus region, the clivus and petrous apex region including the internal carotid canal and the pterygoid process region (including its medial and lateral pterygoid plates). After surgery, clinical symptoms were alleviated in most patients to varying degrees. By the last follow-up visit, 26 patients had died. Most deaths (24) in the study occurred during the first 2 years. Most patients (24) died of sudden severe hemorrhage. The follow-up period ranged from 1 to 108 months, with a median of 27 months. The 2-year overall survival rate was 54.2%. Multivariate Cox regression analysis showed that the number of radiation ($P=0.026$) and age ($P=0.002$) were independent risk factors for the overall survival.

Conclusions Endoscopic sequestrectomy with minimal complications and clear vision is a valuable option for the therapy of skull base osteoradionecrosis in nasopharyngeal carcinoma patients.

Keywords Nasopharyngeal carcinoma · Osteoradionecrosis · Endoscope · Complication · Radiotherapy

Introduction

The current mainstay treatment for nasopharyngeal carcinoma (NPC) is radiotherapy [1]. However, post-irradiation complications of NPC are very common. Osteoradionecrosis (ORN) is one of the devastating late complications with an incidence rate of 10.1% [2]. Because of the tumor's location and radiation technique, the skull base has to be included inevitably in radiation treatment portals. Therefore, skull base ORN occurs at times in NPC patients. The most likely affected bones of the skull base are the sphenoid bone, clivus and temporal bone. The main symptoms of skull base ORN in NPC patients are headache, foul odor and intermittent bleeding [3, 4].

Skull base ORN not only severely impacts quality of life, but also endangers patients' life. Treatments of skull base ORN basically include surgical debridement and conservative treatments such as antibiotics, daily nasopharynx irrigation and hyperbaric oxygen therapy. Although a standard treatment protocol for skull base ORN has not been developed, surgical approaches, especially endoscopic sequestrectomy, seem to lead to a better survival than conservative management in most of the patients [5, 6]. With appropriate

Juan Liu, Xianhui Ning and Xicai Sun are equal contributors.

✉ Dehui Wang
wang_dehuient@126.com

[1] Department of Otolaryngology, Eye Ear Nose and Throat Hospital, Shanghai Medical College, Fudan University, 83 Fenyang Road, Shanghai, People's Republic of China

surgical management, the necrotic tissue may be removed and the necrotic procedure slowed down or stopped.

In recent years, the skull base ORN in post-radiation NPC patients has been reported in some small series [3, 7–9]. The results showed that the outcome of the endoscopic sequestrectomy for skull base ORN in NPC patients was excellent with minimal complications and clear vision. Nevertheless, the numbers of patients included in their studies were small and the patients' follow-up time was short. In the present study, we report the outcomes of endoscopic sequestrectomy performed on a large series of patients with skull base ORN in NPC patients.

Patients and methods

The study was approved by the institutional review board of Fudan University. We enrolled 59 NPC patients with skull base ORN who underwent endoscopic nasopharyngectomy at the Eye Ear Nose and Throat Hospital of Fudan University in Shanghai, from June 2007 to June 2017. Clinical and demographic characteristics including gender, age, medical history, interval between irradiation completion and skull base ORN onset, symptoms, radiographic findings, treatment modalities, recurrence time, postoperative pathological examination findings, complications and outcome at the last follow-up visit were collected. The extent of disease was evaluated during endoscopic surgery together with computed tomography (CT) scan and/or magnetic resonance imaging (MRI). Duration was calculated from the date of first surgery to the date of each event or the last follow-up visit. The survival curve and univariate and multivariate survival analysis were analyzed by Kaplan–Meier and Cox proportional hazards model to analyze the potential prognostic factors of overall survival, including age, gender, number of radiations, number of operations, extension of disease (local or extensive), whether the ICA is exposed to the procedure (yes or no) and the hypha status (yes or no) at postoperative pathological examination.

Surgical procedures (Fig. 1, the schema of the surgical procedures and the fields of necrotic skull base)

The patient lay supine and received general anesthesia. At the beginning of the procedure, the posterior third of the septum was removed to visualize the entire nasopharyngeal cavity and to facilitate a bi-nostril four-handed surgical technique if necessary. Surgical procedures extend in three directions according to the extension of disease. Superiorly, a wide endoscopic sphenoidotomy including the removal of anterior and base walls of the sphenoid sinus is performed in most patients, which makes a connection between the sphenoid sinus and the nasopharynx. When finished, sequestra in the most local ORN cases can be curetted along the course of enlargement of the operative field. In the extensive ORN cases, more procedures were needed to obtain an adequate surgical field. Posteriorly, surgical resection could reach deep into the periosteum of the skull base, and the ventral portion of the clivus could also be drilled out if involved with disease. Laterally, the necrotic posterolateral nasopharynx could be removed together with the cartilaginous tube, the peritubaric muscles and the upper portion of the pterygoid muscles. Clinically, the disease could involve one or more or all the regions at the same time, and the surgical procedures should be performed accordingly. To provide additional maneuvering room, an ipsilateral labiogingival incision could be performed if necessary. When required, the floor of the middle cranial fossa and the lateral foramina (rotundum and ovale) can be reached with an extended transpterygoidal approach. The necrotic bones including the sphenoid sinus, clivus, petrous bone, pterygoid process and its medial, lateral pterygoid plate should be drilled as much as possible. A pedicled middle turbinate or nasoseptal flap could be used to resurface the surgical field. In the procedure, care must be taken to avoid damage to the optic nerve, cavernous sinus, internal carotid artery (ICA) and brainstem.

After surgery, nasopharynx irrigation was recommended to maintain hygiene and restore the wound healing process. Patients must be reexamined every 2 weeks for 1–3 months after surgery. It took approximately 1 month to be epithelialized and the follow-up interval was 3–6 months after epithelialization of the wound.

Results

Clinical manifestations (Table 1)

There were 44 males and 15 females enrolled in our study with a median age of 53 years ranging from 36 to 79 years. All patients had received radiotherapy for NPC previously. There were 36 patients with a single course of radiotherapy and 23 patients with two courses. The interval between the last irradiation completion and skull base ORN onset for patients with a single course ranged from 0.5 to 42 years, with a mean of 8 years. But the interval for the patients with two courses was much smaller, ranging from 1 month to 14 years with a mean of 3 years. 31 (52.5%) cases occurred during the first 2 years after the last irradiation completion. Two patients with recurrent NPC underwent endoscopic nasopharyngectomy. Four patients with recurrently occurring (three patients) or nasopharyngeal granulomatous mass (one patient) underwent nasopharyngectomy after second radiotherapy.

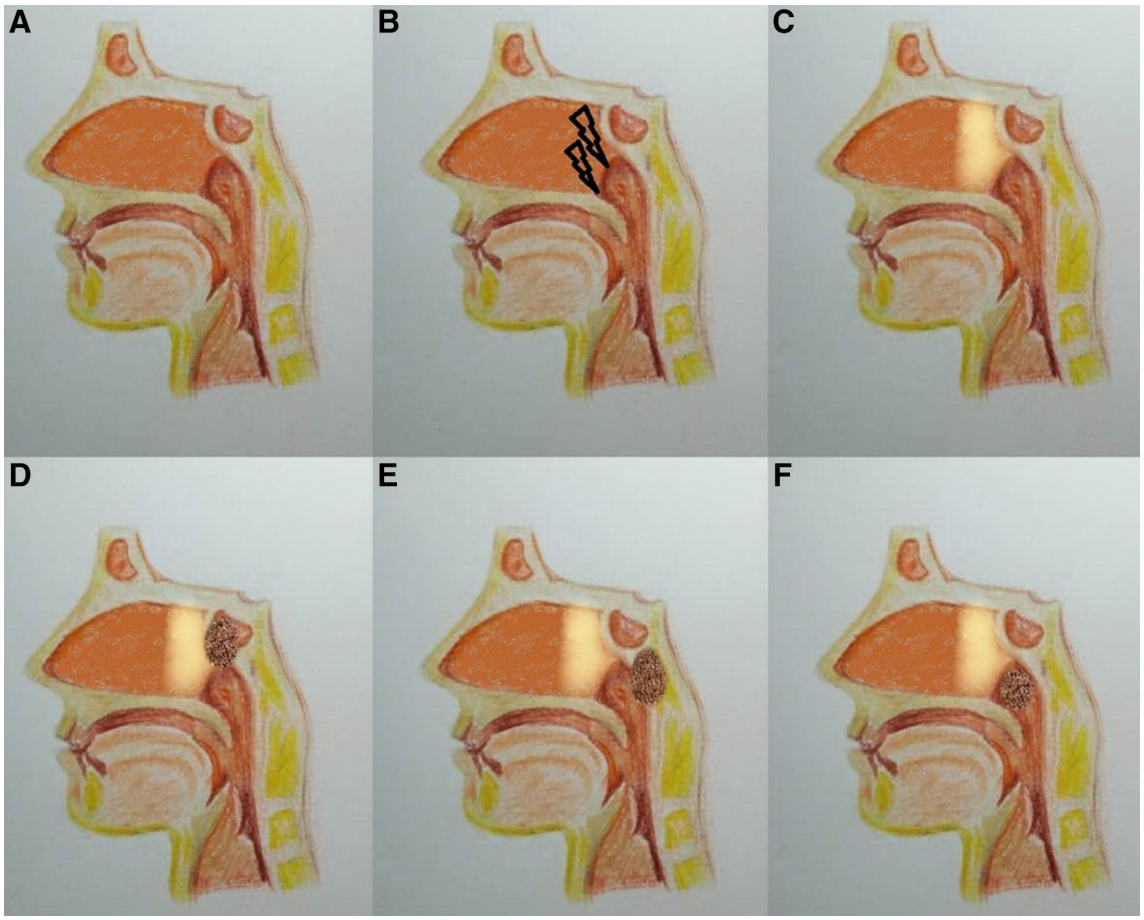

Fig. 1 The schema of the surgical procedures and the fields of the necrotic skull base. **a** The normal nasopharynx. **b** The posterior third of the septum was removed to visualize the entire nasopharyngeal cavity and to facilitate a bi-nostril four-handed surgical technique if necessary. **c** After removing the posterior third of the septum. **d** If the disease was in the base of the sphenoid bone and the sphenoid sinus region, a wide endoscopic sphenoidotomy including the removal of anterior and base walls of the sphenoid sinus should be performed to make a connection between the sphenoid sinus and the nasopharynx. **e** If the disease was in the posterior wall of the nasopharynx and the clivus, the longus capitis and the ventral portion of the clivus should be removed. **f** If the disease was in the lateral wall of the nasopharynx, the necrotic cartilaginous tube, the peritubaric muscles and the upper portion of the pterygoid muscles should be removed together. Clinically, the disease could involve one or more or all the regions at the same time. The surgical procedures should be performed accordingly

Most patients reported different degrees of the following symptoms: headache, foul odor and recurrent bleeding. A patient mainly manifested one, two or all of three symptoms. Ten patients had cranial nerve palsy as follows: facial numbness in eight patients, abducens paralytic strabismus in three patients, choking and hoarseness in three patients, tongue hemiparesis in two patients and dysphagia in one patient. Physical examination showed crusts or necrotic tissue in the nasopharynx.

Two representative cases

A 68-year-old male patient was admitted to our hospital with right-sided severe headache and foul odor for 2 months. He had undergone successful curative radiotherapy for NPC 20 years earlier. Nasal endoscopy showed profuse purulent secretion and foul necrotic tissue in the nasopharynx. Contrast-enhanced MRI demonstrated that there was no evidence of tumor recurrence. And it revealed soft tissue incrassation of the nasopharyngeal posterior wall and right lateral wall combined with center liquefactive necrosis (Fig. 2a, b). Additionally, the biopsy also confirmed no recurrence of malignant disease. He was diagnosed with skull base ORN and received endoscopic sequestrectomy to remove the necrotic tissues (Fig. 2c). In the surgery, the necrotic tissue in the nasopharyngeal posterior wall was reach the longus capitis muscle deeply. With the resection of the necrotic tissues (including part of the longus capitis muscle), the clivus was exposed. The necrotic tissue in the right lateral wall was very deep and extensive. The right parapharyngeal space

Table 1 Patient characteristics ($N=59$) and univariate analysis

Factor	Characteristic	N (%)	P
Sex	Male	44 (74.6%)	0.823
	Female	15 (25.4%)	
Age (years)	Median	53	0.007
	Range	36–79	
The number of radiations	1 course	36 (61%)	0.121
	2 courses	23 (39%)	
Interval	1 course	0.5–42 years with a mean of 8 years	
	2 courses	1 month to 14 years with a mean of 3 years	
Interval	≤ 2 years	31 (52.5%)	
	> 2 years	28 (47.5%)	
The number of surgeries	1	53 (89.8%)	0.709
	2	6 (10.2%)	
Extension	Local	14 (23.7%)	0.116
	Extensive	45 (76.3%)	
Status of ICA	Exposed group	29 (49.2%)	0.214
	Unexposed group	30 (50.8%)	
Status of hypha	Yes	21 (35.6%)	0.984
	No	38 (64.4%)	
Follow-up (months)	Median	27	
	Range	1 to 108	
Status of follow-up	Alive	33 (55.9%)	
	Died	26 (44.1%)	
Time to death	≤ 2 years	24 (92.3%)	
	> 2 years	2 (7.7%)	
Cause of death	Severe hemorrhage	24 (92.3%)	
	Others	2 (7.7%)	

was full of the necrotic tissue. After removing the necrotic tissue, the right parapharyngeal ICA sheath was exposed. The necrotic part of the right pterygoid process was also drilled. The severe headache and foul odor gradually disappeared after surgery. There was no evidence of recurrence according to the contrast-enhanced MRI postoperatively at the 6-month follow-up (Fig. 2d, e). The endoscopic examination demonstrated that the wound would be well epithelized at the 1-month follow-up (Fig. 2f). At the 10-month follow-up, the patient was alive without complications.

A 63-year-old female patient was diagnosed with skull base ORN. She had been given radiotherapy for NPC 32 years ago. She complained of having intense headache for 3 months. Twenty-two days ago, she sought medical advice due to repeated massive nasal hemorrhage. Nasal endoscopy showed the foul necrotic tissue with yellow purulent secretion in the nasopharynx. Contrast-enhanced CT demonstrated that the soft tissue of the nasopharyngeal posterior wall and the lateral wall all showed incrassation with necrosis (Fig. 3a). It clearly depicted extensive bone destruction in the skull base, including the basilar clivus, the apex of the left petrous bone, sphenoid bone and the pterygoid process (Fig. 3a). The CT also revealed a pseudoaneurysm of the left ICA (Fig. 3b). The pseudoaneurysm was then confirmed by MRA (Fig. 3c, d). Monitored by the urgent DSA, balloon angioplasty and 2 PTFE-covered stents were released in the left ICA (Fig. 3e, f). After the patient's condition was stable, she received endoscopic sequestrectomy. During the operation, there was a lot of necrotic tissue in the nasopharynx (Fig. 3g). The extent was much larger than that in case 1. The whole nasopharyngeal posterior wall and the left lateral wall were necrotic. The necrotic soft tissues in the posterior wall was removed. The skull base including the basilar clivus and the sphenoid bone was exposed. Then the dead bone was drilled. In the left lateral wall, part of the eustachian tube and the soft tissues in the Rosenmuller fossa and parapharyngeal space were obviously necrotic. The necrotic tissues were removed as far as possible. But they could not be cleared completely. The apex of the left petrous bone was drilled to remove the dead bone. After removing most of the necrotic tissue, the left ICA sheath was exposed and the pulse could also be seen. At the end of the surgery, a large deep ulcer was found in the nasopharynx (Fig. 3h). After the surgery, the headache and nasal hemorrhage were significantly alleviated within 2 months, but then recurred. Finally, she died of severe hemorrhage about 4 months later.

Treatment outcomes of ORN

Three patients with severe trismus were anesthetized with the assistance of flexible fiber-optic bronchoscopy. Other patients were orally intubated except for one case, who was intubated by tracheostomy due to extremely severe trismus. All patients received endoscopic sequestrectomy. Six patients accepted reoperation. The necrotic tissues could not be removed completely in five cases, of which three received further resection. In this series, ICA was occluded by coil in two cases before surgery and then removed during surgery. Extracranial–intracranial vascular (EC–IC) bypass and ICA ligation were performed on another patient, which was an effective procedure for the prevention of massive nasopharyngeal bleeding and was also to thoroughly remove the necrotic tissue. Balloon angioplasty and 2 PTFE-covered stents were released in another patient. A pedicled middle turbinate or nasoseptal fap was used to resurface the surgical field in five patients. Blood loss during the operation was not much. Only two patients required blood transfusion because of massive nasal bleeding before surgery. No serious complication or operation-related mortality was observed.

The predilection sites of skull base ORN in NPC patients are as follows: the base of the sphenoid bone and the

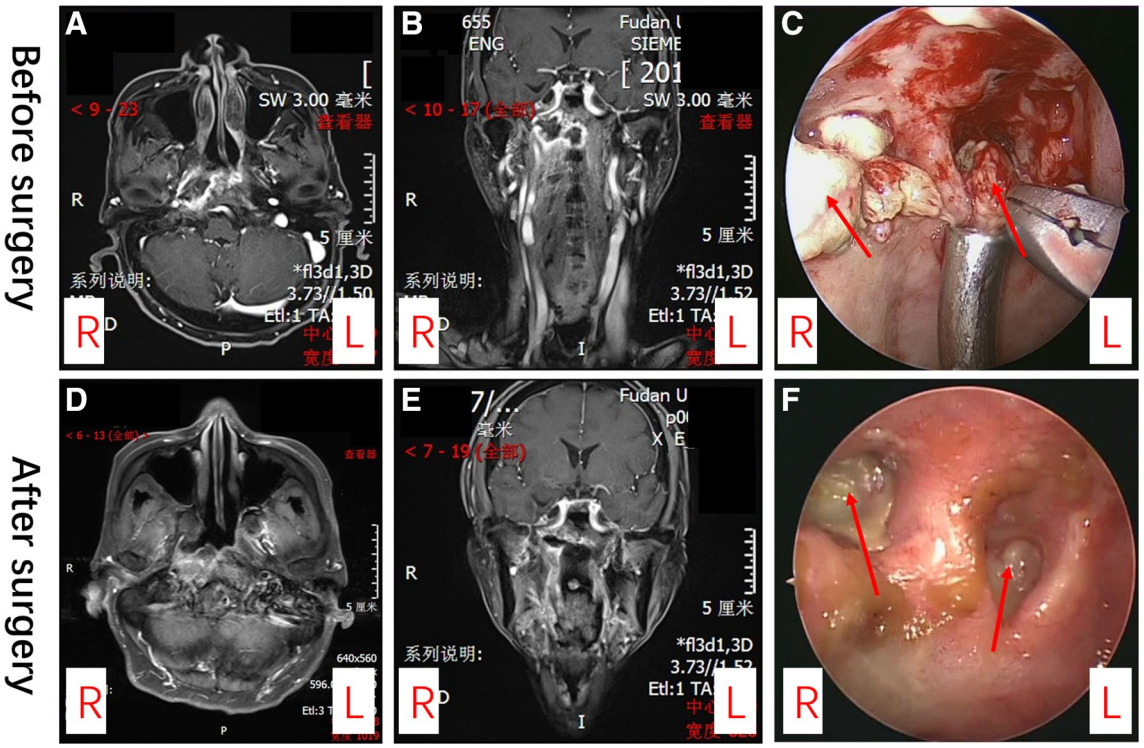

Fig. 2 **a**, **b** The preoperative image examinations (MRI) of the first representative case. **c** The necrotic tissues in the surgery. **d, e** The postoperative image examinations (MRI) at the 6-month follow-up. **f** The epithelization of the wound

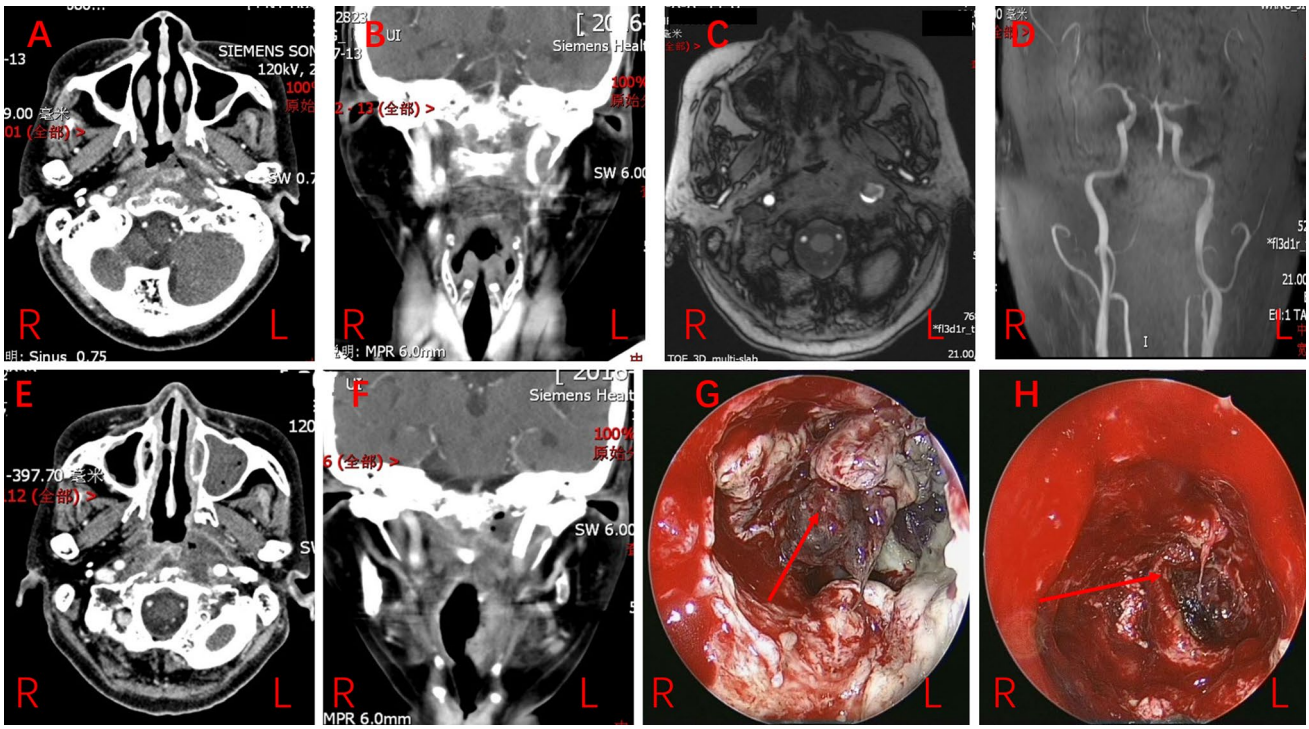

Fig. 3 **a**–**d** The necrotic tissues and a pseudoaneurysm of the left ICA by CT and MRA. **e, f** Images of CT after balloon angioplasty and implantation of 2 PTFE-covered stents in the ICA. **g, h** The necrotic tissues in the surgery

sphenoid sinus region, the clivus and the petrous apex region including the internal carotid canal, the pterygoid process region (including its medial, lateral pterygoid plates). In some cases, the lesions even involved the atlas, axis and hypoglossal canal. According to the extension of the second surgery, surgeries were divided into local (14) and extensive groups (45). They also fell into two categories depending on whether the ICA was exposed to the procedure: the exposed (29) and unexposed groups (30). Hypha in the ORN specimen at postoperative pathological examination was identified in 21 of 59 patients.

Follow-up and prognosis

The follow-up information until September 2017 was obtained from the patients' medical records. Additional phone calls were also made to some of the patients to verify the follow-up data. After surgery, clinical symptoms were alleviated in most patients to varying degrees. Many patients after surgery were either symptom free (18 patients) or significantly improved (15 patients). In a few patients, the symptoms were not ameliorated (2 patients) or ameliorated for only a short term (3 patients).

At the last follow-up, 21 patients were alive without symptoms, 7 were alive with the symptoms improved significantly, 3 patients were alive with the symptoms improved slightly, and 1 was alive with stroke at 4 years postoperatively. One patient with symptom (headache) ameliorated for only a short term received endovascular embolization after 1 month because of massive hemorrhage. By the last follow-up visit, 26 patients had died. Most deaths (24/26, 92%) in the study occurred during the first 2 years. Most patients (24) died of sudden severe hemorrhage; the other two patients died of cerebral infarction or pulmonary infection.

The follow-up period ranged from 1 to 108 months, with a median of 27 months. The survival curve related to overall survival (OS) is shown in Fig. 4. At 2 years, the OS rate was 54.2%. In addition, it hardly decreased after 2 years. The results of Cox regression analysis showed that the number of radiations before surgery ($P=0.026$) and age ($P=0.002$) were independent risk factors for the OS of skull base ORN in NPC patients treated by endoscopic nasopharyngectomy (Table 2).

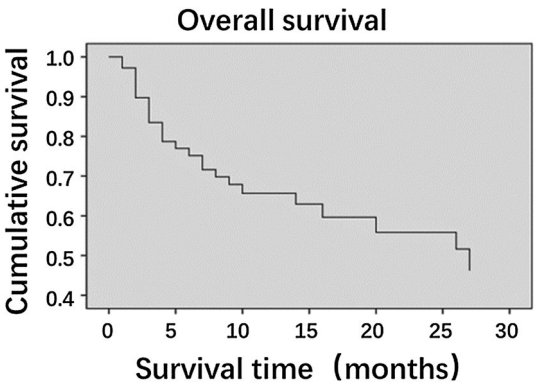

Fig. 4 Kaplan–Meier survival curve related to overall survival

Discussion

Patients with skull base ORN had intense headache, foul odor and repeated bleeding, which decreased their quality of life severely. Unbearable headache made sufferers often use painkillers for controlling the pain. In our study, some of them still had headache with oral analgesic drugs. They had to resort to strong painkillers like morphine. Foul odor was strong and persistent, which affected patients' communication seriously. Repeated bleeding might deteriorate into life-threatening sudden massive bleeding at any moment, which was the biggest worry for patients and their relatives. In this study, most cases (24 patients) died of sudden fatal massive bleeding. Many patients (not included in the study) died in similar incidents in our emergency room without prompt treatments. Skull base ORN is a rare, but potentially lethal late complication in patients with NPC after radiation therapy.

Skull base ORN was initially diagnosed by radiotherapy history, clinical symptoms, nasopharyngeal endoscopy and radiographic findings. Endoscopy showed foul necrotic tissue with gray or yellow-green purulent secretion in the nasopharynx. Sequestra could be seen directly or after removal

Table 2 Cox multiple regression analysis: prognostic factors

	B	SE	Wald	*df*	Sig.	Exp(*B*)
Sex	0.408	0.559	0.533	1	0.465	1.503
Age	0.072	0.023	9.611	1	0.002	1.075
The number of radiations	1.029	0.462	4.966	1	0.026	2.797
The number of surgeries	−0.890	0.725	1.508	1	0.219	0.411
Extension	0.919	0.672	1.869	1	0.172	2.506
Status of ICA	0.484	0.509	0.906	1	0.341	1.623
Status of hypha	−0.336	0.458	0.537	1	0.464	0.715

of secretion. In some patients, the endoscopy could not provide a trusty means for the medical diagnosis of disease, because the lesion site was very deep (Fig. 5a). In this condition, radiographic findings play important roles in the site and range of the lesion, especially contrast-enhanced MRI (Fig. 5b, c).

The management of skull base ORN is quite challenging. In the study, most patients received conservative management including nasopharynx irrigation and antibiotic treatment before surgery. But the clinical symptoms were not improved obviously. In a study about ORN of the temporal bone, the authors observed that conservative treatment has no effect, and symptoms frequently recurred [10]. Huang et al. reported that the cure rate of endoscopic sequestrectomy (100%, 9/9) was much higher than that of conservative therapy (16.7%, 1/6) [3]. In another study, endoscopic sequestrectomy in six patients for skull base ORN obtained good results with five patients cured and one patient improved [4]. Some scholars held that once there was sequestra, dead bone could not be revitalized and should be removed surgically [4, 11]. If not treated on time, the situation would become increasingly worse and more troublesome to handle over time. Hua et al. described skull base ORN as a severe stage of the three stages of nasopharyngeal necrosis [5]. They believed surgery appeared to be the only effective treatment in some circumstances [5]. The recent reviews of the literature also found that the use of nonsurgical measures in skull base ORN would only delay the treatment [12, 13]. Therefore, endoscopic debridement of the necrotic tissues has been considered the gold standard in skull base ORN patients. In this series, all the patients received debridement guided by nasopharyngeal endoscopy. We agreed with that once a diagnosis of ORN was made, aggressive treatment with endoscopic debridement was recommended as soon as possible [14].

The main fatal cause of the NPC patients with skull base ORN was nasopharyngeal excessive bleeding (24/26, 92%), which was in accordance with other studies [3, 5]. The massive bleeding was supposedly caused by rupture of the ICA, which was also the biggest risk in surgery. The risk of ICA rupture and its perioperative management have become particularly important. Radiation can induce various vascular changes including premature atherosclerosis with stenosis, adventitial fibrosis and weakening of the arterial wall caused by obliteration of the vasa vasorum [15, 16]. These changes can lead to sudden rupture of the ICA, resulting in death. If patients had severe epistaxis, or if the disease involved the ICA, or if it revealed a pseudoaneurysm of the ICA by image examination, we strongly recommend the endovascular coiling embolization of the ICA. In these cases, the artery may be exposed to the nasopharyngeal cavity during surgery, and the risk of blood vessel burst increases. For these patients, endovascular coiling embolization of the ICA is necessary, and whether the ICA can be safely occluded without cerebral ischemia is decided by balloon occlusion test (BOT). A negative result indicated permanent occlusion with low risk of a delayed stroke. If the result was positive, EC–IC bypass was performed in advance to allow embolization of the ICA without jeopardizing cerebral perfusion. Some authors have suggested that it would be better to remove the ICA to avoid artery blow-out in patients who had received greater than 70 Gy irradiation [17]. ICA management can both decrease the incidence of massive nasopharyngeal hemorrhage efficiently and facilitate the radical nasopharyngectomy of necrotic tissues thoroughly. In the series, the ICA was endovascular coiling embolized or ligated in four cases before endoscopic sequestrectomy, one of which underwent EC–IC bypass in advance.

The prognosis of skull base ORN is frustrating. In this study, nearly half (26/59) of the patients had died. The

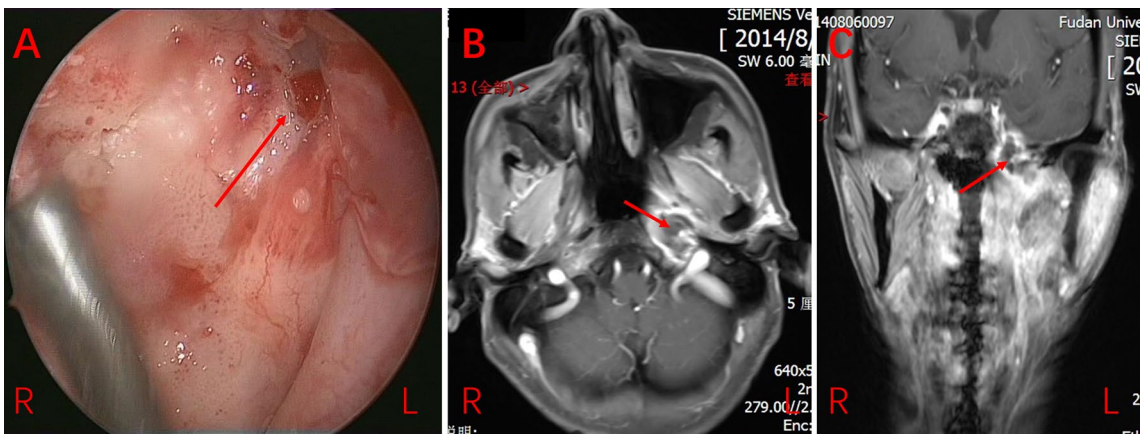

Fig. 5 **a** The endoscopic examination of one patient with skull base ORN which did not show the necrotic tissues. **b, c** The necrotic tissues by contrast-enhanced MRI

estimated median survival time was 27 months as provided by the Kaplan–Meier method. Most deaths in the study occurred during the first 2 years (24/26, 92%), especially in the first year (21/26, 81%). The poor prognosis we concluded was because endoscopic sequestrectomy could not stop the development of skull base ORN in some cases. But the exciting thing was that with the extension of time, the death rate decreased and then plateaued after 2 years follow-up. Although 26 patients were dead, the necrotic processes after surgery were slowed down and the symptoms were relieved in most patients to varying degrees, which led to improved quality of life.

In this study, multivariate analysis indicated that the number of radiations before surgery ($P = 0.026$) and age ($P = 0.002$) were independent factors for prognosis. Radiation was the fundamental cause of skull base ORN. The result showed that the mortality rate for skull base ORN patients with two courses of radiotherapy was 3.188 times higher than those with a single course. One previous study showed that reradiation for recurrent patients increased the risk of major complications. It was reported that 17% (6/36) of the recurrent NPC developed ORN involving the skull base. [18] In our study, 23 patients with local recurrence received a second course of radiotherapy and the mean interval between radiotherapy and skull base ORN onset shortened from 8 to 3 years compared with the patients with a single course. In addition, we found that the age which elevated the mortality risk by 7.4% for every 1 year was an independent factor for prognosis. We speculated that the ability of mucosal repair may decrease with age. In this study, whether the ICA was exposed to the procedure and the extension of disease had showed trends of death rate by the Kaplan–Meier method, but the difference was not significant. Maybe, we need more practice and further research to allow more analyses.

Conclusions

Skull base osteoradionecrosis is a devastating post-irradiation complication in nasopharyngeal carcinoma patients. It not only severely impacts quality of life, but also endangers patients' life. Endoscopic sequestrectomy provides direct access to remove the necrotic tissues by passing through the nasal fossae. With minimal complications and clear vision, it is a valuable option for the therapy of skull base osteoradionecrosis in nasopharyngeal carcinoma patients. The surgery can relieve symptoms and improve the life quality in most patients.

Acknowledgements We thank all participating patients for their contributions to this study.

Compliance with ethical standards

Conflict of interest No conflict.

References

1. Lin S, Lu JJ, Han L et al (2010) Sequential chemotherapy and intensity-modulated radiation therapy in the management of locoregionally advanced nasopharyngeal carcinoma: experience of 370 consecutive cases. BMC Cancer 10:39
2. Lee CC, Ho CY (2012) Post-treatment late complications of nasopharyngeal carcinoma. Eur Arch Otorhinolaryngol 269(11):2401–2409
3. Huang XM, Zheng YQ, Zhang XM et al (2006) Diagnosis and management of skull base osteoradionecrosis after radiotherapy for nasopharyngeal carcinoma. Laryngoscope 116(9):1626–1631
4. Chang KP, Tsang NM, Chen CY et al (2000) Endoscopic management of skull base osteoradionecrosis. Laryngoscope 110(7):1162–1165
5. Hua YJ, Chen MY, Qian CN et al (2009) Postradiation nasopharyngeal necrosis in the patients with nasopharyngeal carcinoma. Head Neck 31(6):807–812
6. Yang Q, Zou X, You R et al (2017) Proposal for a new risk classification system for nasopharyngeal carcinoma patients with postradiation nasopharyngeal necrosis. Oral Oncol 67:83–88
7. Choi NY, Kim HJ, Baek CH (2017) Surgical management of extensive osteoradionecrosis in nasopharyngeal carcinoma patients with the maxillary swing approach and free muscular flaps. Clin Otolaryngol 42(5):1100–1104
8. Adel M, Chang KP (2016) Using a nasoseptal flap for the reconstruction of osteoradionecrosis in nasopharyngeal carcinoma: a case report. J Otolaryngol Head Neck Surg 45:27
9. Chen Z, Qiu QH, Zhan JB et al (2016) Endoscopic surgery and reconstruction for extensive osteoradionecrosis of skull base after radiotherapy for nasopharyngeal carcinoma. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 51(12):881–886
10. Xu YD, Ou YK, Zheng YQ et al (2008) Surgical treatment of osteoradionecrosis of the temporal bone in patients with nasopharyngeal carcinoma. J Laryngol Otol 122(11):1175–1179
11. Hao SP, Chen HC, Wei FC et al (1999) Systematic management of osteoradionecrosis in the head and neck. Laryngoscope 109(8):1324–1327 **(discussion 1327–1328)**
12. Rice N, Polyzois I, Ekanayake K et al (2015) The management of osteoradionecrosis of the jaws—a review. Surgeon 13(2):101–109
13. Marwan H, Green JM, Tursun R et al (2016) Recurrent malignancy in osteoradionecrosis specimen. J Oral Maxillofac Surg 74(11):2312–2316
14. Chen KC, Yen TT, Hsieh YL et al (2015) Postirradiated carotid blowout syndrome in patients with nasopharyngeal carcinoma: a case-control study. Head Neck 37(6):794–799
15. Swain RE, Biller HF, Ogura JH et al (1974) An experimental analysis of causative factors and protective methods in carotid artery rupture. Arch Otolaryngol 99(4):235–241
16. Soria JC, Deutsch E (2011) Hemorrhage caused by antiangiogenic therapy within previously irradiated areas: expected consequence of tumor shrinkage or a warning for antiangiogenic agents combined to radiotherapy. Ann Oncol 22(6):1247–1249
17. Shu CH, Cheng H, Lirng JF et al (2000) Salvage surgery for recurrent nasopharyngeal carcinoma. Laryngoscope 110(9):1483–1488
18. Low JS, Chua ET, Gao F et al (2006) Stereotactic radiosurgery plus intracavitary irradiation in the salvage of nasopharyngeal carcinoma. Head Neck 28(4):321–329