Clinical outcomes of salvage endoscopic nasopharyngectomy in recurrent nasopharyngeal carcinoma

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Key points

***T** he purpose of this study was to explore the demographics, treatment outcomes, and prognostic factors of salvage endoscopic nasopharyngectomy in recurrent nasopharyngeal carcinoma (NPC).

***T** he overall 1-, 3- and 5-year survival rates were 82.2%, 59.5%, and 43.6%.

***I** n subjects over 50 years of age, diabetes, low BMI (<20 kg/m^2), increased NLR ([?]6), advanced T stage (rT3 and rT4), lymph node metastasis, and tumor necrosis are the independent prognostic factor for overall survival.

***T** umor necrosis was a better predictor for disease recurrence (area under the receiver operating curve [AUROC; 0.347; p <0.001) than other clinical features.

Keywords : Nasopharyngeal carcinoma, Recurrent, Endoscopic, Nasopharyngectomy, Prognostic factors, Tumor necrosis

Introduction

N asopharyngeal carcinoma (NPC) is a common malignant tumor in southern China.[1] Radiotherapy is the first choice of treatment for NPC owing to sensitivity of the tumor in early stages. However, approximately 10% of patients experience local recurrence of the tumor after radiotherapy.[2] After the first course of radiotherapy, patients often demonstrate hyperplasia of fibers in the nasopharynx and poor local circulation due to local vascular occlusion. Repeating radiotherapy may result in low efficacy and complications, which can seriously damage the quality of life of patients, sometimes leading to death. In addition, mutations may occur in the residual tumor after the first treatment or other mechanisms that may persist, resulting in tumor resistance to subsequent treatment sessions. Therefore, surgical treatment of residual and recurrent NPC is advocated. You et al. reported that salvage endoscopic nasopharyngectomy may be more effective for maximizing survival and quality of life benefits and minimizing treatment-related complications in patients with recurrent NPC, as compared with intensity modulated radiation therapy.[3]

E ndoscopic nasopharyngectomy is less invasive and does not result in facial scars as compared to conventional maxillary swing approach for resection of recurrent tumors.[4,5]Therefore, several institutions have started performing endoscopic nasopharyngectomy for the resection of residual and recurrent NPC. Salvage surgery for recurrent NPC is challenging due to the risk of damage to various neurovascular structures and

potentially the dura mater. Moreover, only few retrospective studies have been conducted to assess the survival and prognostic factors of salvage surgery in recurrent NPC. Wong et al. reported a 2-year overall survival rate of 66.7% during a median follow-up of 19.4 months in 15 patients with recurrent NPC (rT3 and rT4 tumors) who underwent endoscopic endonasal nasopharyngectomy.[6] In our study, we focused on the demographics, treatment outcomes, and prognostic factors associated with salvage endoscopic nasopharyngectomy in recurrent NPC.

Methods

W e performed a retrospective chart review of 189 patients who were diagnosed with recurrent NPC and treated at the Department of Otorhinolaryngology of the AEENTH at [Blinded for review] University from January 2006 to June 2018. Patients who had distant metastasis or missing data on important variables were excluded. All patients underwent Salvage endoscopic nasopharyngectomy performed by [Blinded for review].

C linical data were retrieved, including the age; sex; history of smoking and alcohol consumption; diabetes and hypertension; body mass index (BMI); number of radiotherapy sessions before surgery;preoperative chemotherapy; period between recurrence and the last session of radiotherapy; T/N-stage; pathological type; status of tumor necrosis; overall survival rate;and serological factors(hemoglobin (Hb) count, neutrophil to lymphocyte ratio (NLR),and serum levels of alkaline phosphatase (ALP). In addition, prognostic factors were assessed using the Kaplan-Meier method. Differences in survival distributions were evaluated with the log-rank test. The Cox regression model was used for multivariate survival analyses. The follow-up period was from the initial diagnosis at our institution to date of death or last contact.

Results

A summary of the patients included in this study is depicted in Table 1. A total of 189 patients were identified, of which 132 (69.8%) were male, and 57 (30.2%) were female. The median age was 51 years (range, 25–85 years). The number of patients with history of smoking and alcohol consumption, hypertension, and diabetes were 34, 22, 41, and 9, respectively. The normal range of body mass index (BMI) was set at 20 kg/m^2–26 kg/m^2, and the number of patients with high, normal, and low BMI was 25, 150, and 14, respectively. For serologic factors, the number of patients with low hemoglobin (Hb<120 g/l), high NLR ([?]6), and low ALP (<50 mmol/l) were 43, 52, and 9, respectively. According to rTNM staging system of the American Joint Committee on Cancer -AJCC/UICC,[7] the tumors were staged as follows: rT1, 55; rT2, 42; rT3, 64; and rT4, 28. Forty-five patients (23.8 %) had lymph node metastases. The histological subtype in most patients was World Health Organization (WHO) type III (n =119; 63.0%), followed by the WHO type II (n =70; 37.0 %). Tumor necrosis was observed in 70 patients (37.0%).

T he overall 1-, 3-, and 5-year survival rates were 82.2%, 59.5%, and 43.6%, respectively, during a median follow-up of 24 months (range, 2-111 months) in all patients (Fig. 1). The 5-year overall survival (OS) of rT1, rT2, rT3, and rT4 were 42.5%,54.4%,44.1%,and 32.5%, respectively (Fig. 2). Sixty-nine patients had died, out of which 38 patients died of tumor progression at the locoregional site (33) or brain (5); two of lung metastasis, one of liver metastasis; 22 of severe internal carotid hemorrhage, two of temporal lobe necrosis, and four patients died of other diseases or accident. The tumors were relieved by physical examination and imaging examination in 89 cases (47.1%), and 31 patients (16.4 %) remained alive with disease.

P rognostic factors for recurrent NPC are shown in Table 2. In patients over 50 years of age (Fig. 3A), diabetes (Fig. 3B) and low BMI (<20 kg/m^2, Fig. 3C) were associated with poor prognosis (P=0.039, P<0.001, P=0.011). Low hemoglobin (<120g/l, Fig. 3D) and increased NLR ([?]6, Fig. 3E) also adversely affected outcomes. Patients with stages rT3 and rT4 had a 40.0% five-year cumulative survival rate, whereas patients with rT1 and rT2 had an improved survival rate of 50.3% (p=0.001, Fig. 3F). Lymph node metastasis (Fig. 3G) and tumor necrosis (Fig. 3H) were associated with poor prognosis (p=0.029,P<0.001); however, sex, history of smoking and alcohol consumption, hypertension, low ALP (<50 mmol/l), number of sessions of radiotherapy, preoperative chemotherapy, pathological type, interval between recurrence and the last session of radiotherapy did not influence overall survival. Variables considered significant in the

univariate analyses were entered in the Cox multivariate analyses (Table 3). A total of seven variables, including age, BMI, NLR, diabetes, T stage, N stage or tumor necrosis, were proven independent prognostic factors in the multivariate Cox regression model (Table 3). Moreover, based on the factors affecting OS, the predictive values of tumor recurrence was also analyzed by ROC, which revealed that tumor necrosis was the best predictor for OS. The area under the ROC curve for tumor necrosis was 0.347 (95% confidence interval [CI], 0.264 to 0.429; p <0.001) for OS. The prognostic values determined for the other factors are listed in Figure 4.

Discussion

A lthough NPC is radiosensitive, recurrence of the tumor after radiotherapy is a common cause of treatment failure. It is generally recommend to perform actively salvage treatment for local recurrence of NPC, owing to high success rate of the procedure [8] The OS of patients receiving salvage treatment was significantly higher than patients who did not receive the treatment.[9]Re-irradiation is often accompanied by serious complications, such as radiation necrosis of bone, multiple cranial nerve dysfunction and brain necrosis, which damages the quality of life of patients and even leads to death.[10] In addition, Yu et al. reported that re-irradiation could only improve the survival rate of patients with tumor stages rT1 and rT2, while patients with rT3 and rT4 showed no significant change.[2] Wang et al. also concluded that NPCs with advanced recurrence (rT3, rT4, and bulky rT2) have poor re-irradiation effect, low control rate, and high incidence of complications.[11]

I n our study, the overall 3-year survival rates of salvage endoscopic nasopharyngectomy were 59.5%. However, Kong et al. demonstrated 46.0% 3-year survival rate after re-irradiation in 184 patients with recurrent NPC.[12] In addition, the five-year OS of patients with rT3 and rT4 tumors were 44.1% and 32.5% respectively in our institution, which were higher than that of salvage re-irradiation treatment reported in the literature (the 5-year OS for patients with rT3 and rT4 tumors was only 35.5–36 and 19–30.2 %, respectively).[11,13]Chua et al. also reported that patients who underwent salvage surgeries had higher survival rates compared to re-irradiation for rT1 and rT2 tumors.[14] Therefore, we hypothesize that salvage surgery may be associated with better survival prognosis than re-irradiation alone; however, more clinical case studies and prospective studies are needed to confirm this perspective.

P atients with tumor stages rT3 and rT4 have significantly worse prognosis for OS in univariate and multivariate analyses. This is because salvage surgery for recurrent rT3 and rT4 NPC is challenging, which could damage various neurovascular structures, base of the skull, dura, and possibly cause intracranial destruction. Chan et al. revealed that the probability of achieving clear resection margins during salvage nasopharyngectomy is significantly lower for late (rT3 and rT4) compared to early (rT1 and rT2) tumors.[15] Meanwhile, Bian et al. also supported the observations that tumors with high recurrence (rT3 and rT4) are associated with unfavorable survival after nasopharyngectomy.[8] In the present study, we chose another prognostic factor, metastatic lymph nodes, in univariate and multivariate analyses, because most patients with NPC have cervical lymph node metastasis at the time of initial diagnosis. New evidence suggests that lymph node metastasis increases the risk of distant organ metastasis and is associated with poor prognosis.[16,17]Consistent with previous reports, our study further supports the relationship between metastatic lymph nodes and poor clinical outcomes.

S ome studies have found that the pretreatment NLR independently affects the survival rate of patients with NPC undergoing radiotherapy.[18-20] In this study, we found for the first time that the serum NLR marker could be a potential prognostic indicator of recurrent NPC. NLR reflects the number of neutrophils and lymphocytes, which can be easily measured clinically by peripheral blood test. A previous study conducted on more than 12000 patients also supported the relationship between high NLR and poor OS in different types of cancer.[21] One possible reason is that neutrophils can inhibit the immunosuppression induced by activated T cells and NK cells, while lymphocytes can inhibit tumor cell proliferation and metastasis through anti-tumor reactions involving cytokine production and cytotoxic cell death.[22]

M ultivariate analyses in our previous study on 91 patients with residual and recurrent NPC who underwent

endoscopic nasopharyngectomy showed that tumor necrosis was an independent risk factor for OS.[4] In this study, ROC analysis also revealed that tumor necrosis was the best predictor for OS. The cause of necrosis in recurrent NPCs and the mechanism associated with adverse clinical outcomes remains unclear. The general assumption of development of tumor necrosis is the rapid growth of malignant cells, especially in more aggressive cancer types, increase in blood supply with subsequent creation of a hypoxic environment leading to necrosis of tissue. Immune factors, such as innate and adaptive immune systems, also play a role in necrosis; however, further studies are needed to elucidate their potential effects.[23,24]Atanasov et al. reported that assessment of tumor necrosis was a valuable additional prognostic tool for hilar cholangiocarcinoma, which may have implications for monitoring and planning more personalized multimodal treatment strategies.[25] Postoperative pathological examination done in other studies also reported that tumor necrosis was related to the decrease in survival rate of patients with different tumor entities.[26-28]

Conclusion

S alvage endoscopic nasopharyngectomy is a feasible treatment to improve patient survival for recurrent NPC. In patients over 50 years of age, diabetes, low BMI (<20),increased NLR ([?]6), advanced T stage (rT3 and rT4), lymph node metastasis, and tumor necrosis are the independent prognostic factors for overall survival. However, additional studies with long-term follow up and larger sample size are required.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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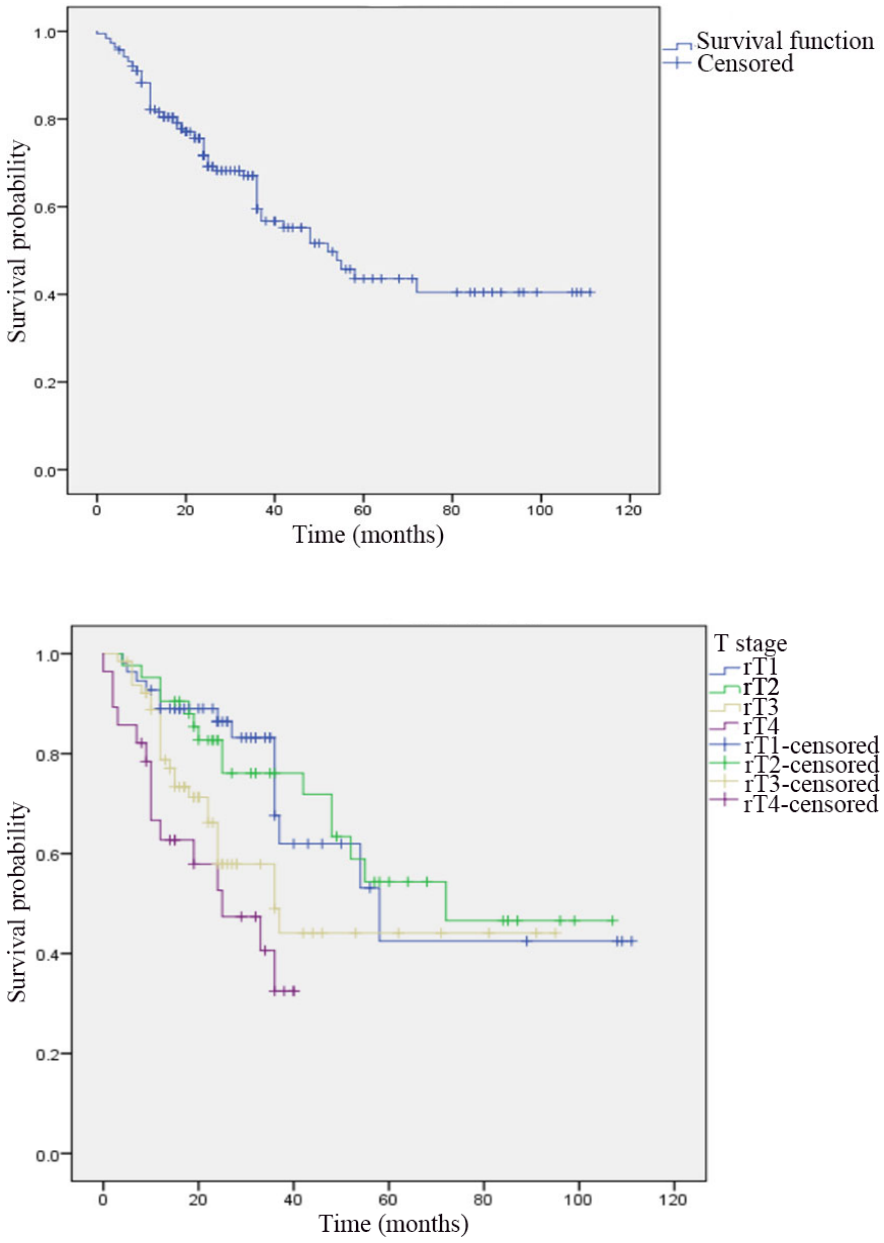
Figures

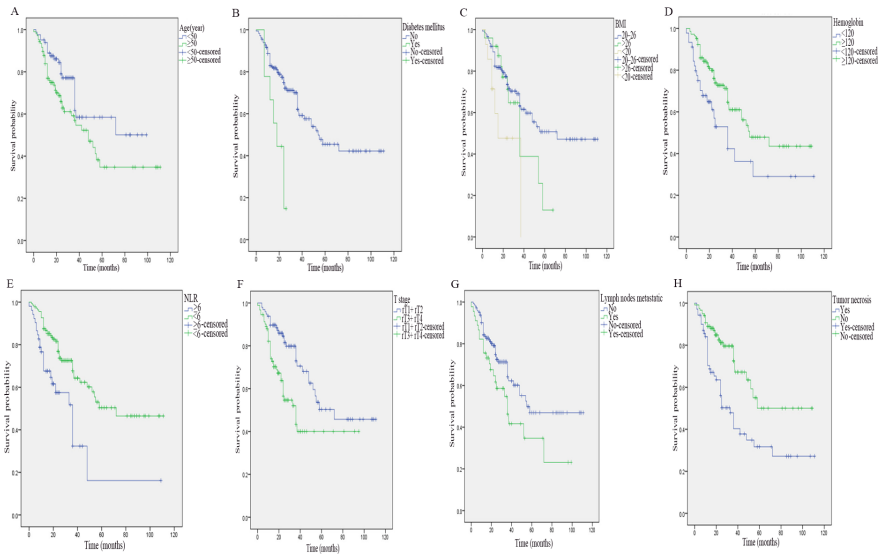
Figure 1. Kaplan–Meier curve of the overall survival probability of patients with recurrent NPC.

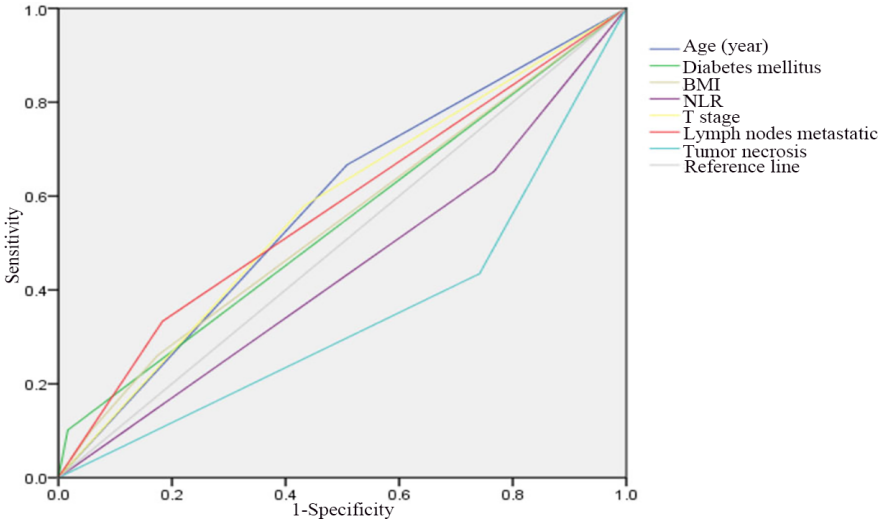
Figure 2. Kaplan–Meier curves for survival of patients with different rT stage (p = 0.002).

Figure 3. Kaplan–Meier curves for survival of patients in recurrent NPC. A: different age ([?]50 years vs. <50 years old), B: diabetes, C: BMI (<20 kg/m^2, 20 kg/m^2–26 kg/m^2, ¿26 kg/m^2), D: Low hemoglobin (<120 g/l vs. [?] 120 g/l), E: NLR ([?]6 vs. <6), F: rT stage (rT1, rT2 vs. rT3, rT4), G: lymph node metastasis, H: tumor necrosis.

Figure 4. Receiver operating characteristic analysis revealed that tumor necrosis was the best predictor for OS. The area under the ROC curve for tumor necrosis was 0.347 (95% confidence interval [CI], 0.264 to 0.429; p<0.001) for OS. AUC, area under the curve; SE, standard error.







Variables	AUC	SE	95% CI	P value
Age	0.579	0.043	0.495-0.663	0.070
Diabetes mellitus	0.542	0.044	0.455-0.629	0.332
BMI	0.544	0.044	0.458-0.631	0.312
NLR	0.443	0.044	0.357-0.529	0.190
T stage	0.573	0.043	0.488-0.658	0.094
Lymph nodes metastatic	0.575	0.044	0.489-0.661	0.086
Tumor necrosis	0.347	0.042	0.264-0.429	<0.001

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