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ORIGINAL RESEARCH

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Prognostic factors of palatal adenoid cystic carcinoma: A single-center analysis of 85 cases

Baoxin Gu DDS[1,2,3] | Yanting Chi MDS[2,3,4] | Wenjie Wu DDS[1,2,3] | Yiwei Zhong DDS[1,2,3] | Jianyun Zhang DDS[2,3,4] | Jie Zhang DDS, MD[1,2,3]

[1]Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, Beijing, China

[2]National Center of Stomatology, Beijing, China

[3]National Clinical Research Center for Oral Diseases, Beijing, China

[4]Department of Oral Pathology, Peking University School and Hospital of Stomatology, Beijing, China

Correspondence
Jie Zhang, Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, No.22, Zhongguancun South Avenue, Haidian District, Beijing 100081, China.
Email: zhangjie06@126.com

Abstract

Objective: The purpose of this retrospective study was to describe the clinicopathological characteristics of primary adenoid cystic carcinoma (ACC) of the palate and to identify the factors affecting prognosis.

Methods: The medical records of 85 patients with primary ACC of the palate treated with surgery, with or without adjuvant radiotherapy/chemotherapy, from 2009 to 2019 were reviewed. The relationship of different clinical parameters with locoregional recurrence (LR), distant metastasis (DM), and overall survival (OS) were analyzed.

Results: Median follow-up time was 44.6 months. LR and DM rates were 24.7% and 25.9%, respectively, and the 5-year OS and disease-free survival (DFS) rates were 85.9% and 55.1%, respectively. Multivariate analysis showed that positive margins were independently associated with the risk of LR ($p < .001$). Positive margins ($p = .001$) and high histological grade ($p = .031$) were significantly associated with shorter OS.

Conclusion: Positive surgical margins are a strong adverse prognostic factor affecting LR and OS in patients with ACC; apart from that, high histopathological grade is an independent predictor of poor OS.

Level of Evidence: Level 3 (Prognosis – Cohort study).

KEYWORDS

adenoid cystic carcinoma, margins of excision, palate, prognosis, salivary gland neoplasms

1 | INTRODUCTION

Adenoid cystic carcinoma (ACC) is a rare malignancy that accounts for about 1% of all head and neck cancers and 10%–20% of all salivary neoplasms.[1,2] It most commonly arises in the parotid or minor salivary glands, with a predominant occurrence in the palatal region among the minor salivary glands.[3–8] ACC is characterized by sluggish growth, unusual regional metastases, and high risk of local recurrence and hematogenous dissemination, most commonly to the lungs.[9] These characteristics result in a relatively high 5-year survival rate (>65%) but poor 10-year survival.[4,10]

The best treatment approach for ACC is still unclear.[11] Surgical excision is the mainstay of treatment, but the cancer is relatively challenging to clear surgically since the true extent of ACC tumors is often underestimated.[3] Addition of radiotherapy to surgery can improve outcomes.[12] In clinical practice, adjuvant radiotherapy is frequently used because of positive surgical margins and infiltration by the tumor, but the actual value of radiotherapy remains uncertain.[11]

Because of the rarity of ACC, most previous reports have been on small numbers of patients with tumors in a variety of locations in the head and neck region; this made analysis of the characteristics of ACC at specific sites difficult.[13] Surgical difficulty and patient survival vary depending on the site of the lesion.[14] The aim of this study is to identify the characteristics of palatal ACC, to evaluate treatment effect, and determine the factors associated with prognosis.

2 | MATERIALS AND METHODS

Patients with ACC of the palate treated at the Peking University School of Stomatology Hospital between 2009 and 2019 were retrospectively enrolled. Patients with recurrent lesions or incomplete medical records were excluded. A total of 85 patients met the eligibility criteria. All patients underwent primary surgery with or without adjuvant radiotherapy or chemotherapy.

The medical records of the selected patients were reviewed to collect data on clinical and pathological characteristics, treatment, and disease outcomes. Postoperative maxillary defects were classified according to the Brown classification system described in 2010.[15] (The vertical classification is as follows: I, maxillectomy without oronasal fistula; II, not involving the orbit; III, involving the peri-orbital area or with orbital floor; IV, with orbital enucleation or exenteration; V, orbitomaxillary defect; VI, nasomaxillary defect. The horizontal classification is as follows: 'a,' palatal defect only; 'b,' 1/2 unilateral; 'c,' 1/2 bilateral or transverse anterior; 'd,' >1/2 maxillectomy).

Two pathologists specializing in head and neck cancers reviewed the pathological specimens and staged the lesions according to the American Joint Committee on Cancer 8th edition TNM classification system.[16] Tumor subtype (cribriform, tubular, or solid), presence of perineural/nerve invasion, and nodal status were recorded. If the solid component was ≥30%, the tumor was categorized as solid.[17,18] Margin status was recorded as positive, negative, or close (<5 mm).

The Ethics Committee of Peking University School of Stomatology Hospital approved this study, with waiver of the need for informed consent.

2.1 | Statistical analysis

Statistical analysis was performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 9.3.1 (GraphPad Software Inc., San Diego, CA, USA). Survival curves were generated by the Kaplan–Meier method and compared using the log-rank test. Association between clinicopathological factors and outcomes was analyzed using a Cox proportional hazards regression model. Two-tailed $p < .05$ was considered significant.

3 | RESULTS

The 85 patients (32 males and 53 females; male to female ratio, 1:1.7) had a median age of 51 years (range, 21–78 years). The peak incidence was during the fourth decade of life (19/85 patients, 22.4%). Almost half the patients (41/85, 48.2%) presented with a gradually growing mass. Other symptoms at presentation included pain, ulceration, denture discomfort, nasal obstruction, difficulty in swallowing, and so on.

Table 1 lists the clinicopathological features, and Table 2 lists the treatment modalities. The tumor site was the hard palate in 40 patients (47.1%), the junction of the hard palate and soft palate in 34 patients (40%), and the soft palate in 11 patients (12.9%). While 10 patients (11.8%) were treated with surgery alone, 75 patients (88.2%) were treated with surgery plus adjuvant radiotherapy, including 14 patients (16.5%) with ^{125}I seeds brachytherapy, 57 patients (67.1%) with external beam radiotherapy (EBRT) only, and another 4 patients (4.7%) treated with external beam radiotherapy who also received chemotherapy (EBCRT). The majority of patients (50/61, 82.0%) received a dose of EBRT that was at least 60 gy. According to the Brown classification system,[15] the most common class among patients was 'IIb' (44/85, 51.8%), followed by 'a' ($n = 16$, 18.8%).

While 21 patients (24.7%) had T1, T2, or T3 disease, 64 patients (75.3%) were diagnosed with T4 due to tumor extension through the palate into adjacent structures. At the time of staging, 2 patients (2.4%) had cervical lymph node metastasis, and 3 patients (3.5%) had distant metastases. Positive margins were identified in 30 patients (35.3%), and perineural invasion in 56 patients (65.9%). The cribriform or tubular pattern was identified in 65 patients (76.5%), the solid

TABLE 1 Tumor clinicopathological features.

Variable	Value	%
Primary site ($n = 85$)		
Hard palate	40	47.1
Soft palate	11	12.9
Junction of hard & soft palate	34	40.0
pT classification ($n = 85$)		
T1–3	21	24.7
T4	64	75.3
pN classification ($n = 85$)		
N0	83	97.6
N+	2	2.4
M classification ($n = 85$)		
M0	82	96.5
M1	3	3.5
Stage		
I–III	20	23.5
IV	65	76.5
Perineural invasion ($n = 85$)	56	65.9
Bone invasion ($n = 85$)	64	75.3
Skull base invasion ($n = 85$)	21	24.7
Histologic pattern ($n = 85$)		
Cribriform or tubular	65	76.5
Solid	19	22.4
High-grade transformation	1	1.2

TABLE 2 Treatment performed.

Variable	Value	%
Treatment ($n = 85$)		
Surgery alone	10	12.9
Surgery + Brachytherapy	14	15.3
Surgery + EBRT	57	67.1
Surgery + EBCRT	4	4.7
Rad Dose, GY ($n = 61$)		
<60	11	12.9
≥60	50	58.8
Margin status ($n = 85$)		
Negative/close	55	64.7
Positive	30	35.3
Neck dissection ($n = 85$)		
No	46	54.1
I–IIa	29	34.1
I–III	10	11.8
Maxillectomy defect classification ($n = 85$)		
0/a	7/16	8.2/18.8
IIa/IIb/IIc/IId	2/44/2/10	2.4/51.8/2.4/11.8
IIIb/IIId	1/3	1.2/3.5

TABLE 3 Follow-up results with recurrence and metastasis information.

Variable	Value	%
Recurrence time, m ($n = 21$)	44 (2–98)	
Locoregional recurrence	21	24.7
Local only	17	20
Local&regional nodal disease	4	4.7
Metastasis time, m ($n = 22$)	22 (0–106)	
Distant metastasis	22	25.9
Lungs	21	24.7
Bone	3	3.5
Liver	2	2.4
Status at last contact ($n = 85$)		
Death	13	15.3
Death from recurrence	4	4.7
Death from metastasis	1	1.2
Death from both	7	8.2
Death from others	1	1.2
Alive	72	84.7

pattern in 19 patients (22.4%), and high-grade transformation in 1 patient (1.2%).

Over median follow-up of 44.6 months (range, 11–128 months), 21 patients (24.7%) developed LR. Recurrence occurred at a median of 44 months (range, 2–98 months) after the initial treatment (Table 3). Local failure was registered in T1 3 cases ($n = 9$, 33.3%), T2 2 cases ($n = 11$, 18.2%), T4a 13 cases ($n = 54$, 24.1%), and T4b 3 cases ($n = 10$, 30%), of which 4 cases ($n = 21$, 19.0%) were accompanied by regional failure. In a cohort of sixty-one patients who underwent surgery plus EBRT/EBCRT,nine(14.8%) experienced LR. Among fourteen patients who underwent surgery plus brachytherapy, seven(50%) experienced LR, whereas in the subgroup of ten patients who underwent surgery only, five(50%) experienced LR. Positive margins were identified in 16 out of 21 patients who had LR.

In univariate analysis, the factors significantly associated with local control were margin status ($p < .001$) and postoperative radiotherapy (surgery alone vs. surgery plus brachytherapy/EBRT/EBCRT, $p = .037$; surgery alone vs. surgery plus EBRT/EBCRT, $p = .010$; Figure 1). In multivariate analysis, margin status ($p < .001$) was an independent predictor of LR (Table 4 and Figure 2).

A total of 19 patients (22.4%) had DM at 6–106 months after treatment of the primary disease, including the 3 patients (3.5%) who already had lung metastasis at diagnosis. Thus, the total DM rate was 25.9% (Table 3). The most common site of DM was the lung (21/22, 95.5%). No significant factors were found to be associated with DM in the multivariate analysis.

At the end of the follow-up period, 13 patients (15.3%) were dead; 12 patients died of the tumor (4 patients with LR only, 1 patient with DM only, and 7 patients with both LR and DM), and 1 patient died of other causes. 1 patient with DM was lost to follow-up 16 months after the beginning of the treatment. The 5-year locoregional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), and disease-free survival (DFS) rates in the entire cohort were 74.6%, 65.5% and 55.1%, respectively. Figure 1 and Table 4 show the results of univariate and multivariate analyses.

The 5- and 10-year overall survival (OS) rates were 85.9% and 70.2%, respectively (Figure 3). In both univariate and multivariate analyses, positive margins ($p = .001$) and high histopathological grade ($p = .031$) were significantly associated with shorter OS (Table 4 and Figure 3).

4 | DISCUSSION

The palate, especially the hard palate, is the most frequent site of salivary gland ACC.[3] In this study, the tumor was located in the hard palate or junction of the hard and soft palate in >80% of patients. In general, palate tumors are slow growing and without obvious symptoms. ACC should be suspected if symptoms such as pain, ulceration, numbness, or nasal congestion occur. ACC is characterized by high risk of recurrence and distant metastasis. In previous reports, the 5-year OS rates has been in the range of 75%–80% and the 15- to 20-year OS rates only 10%–30%.[5] In this study, the 5-year OS rate was 85.9%, but the 5-year DFS rate dropped to 55.1%.

According to previous studies, the factors affecting prognostic of patients with ACC include tumor location, treatment method, surgical margin, pathological grade, recurrence, lymph node metastasis, distant metastasis, and age.[13,19] In this study, positive margins were

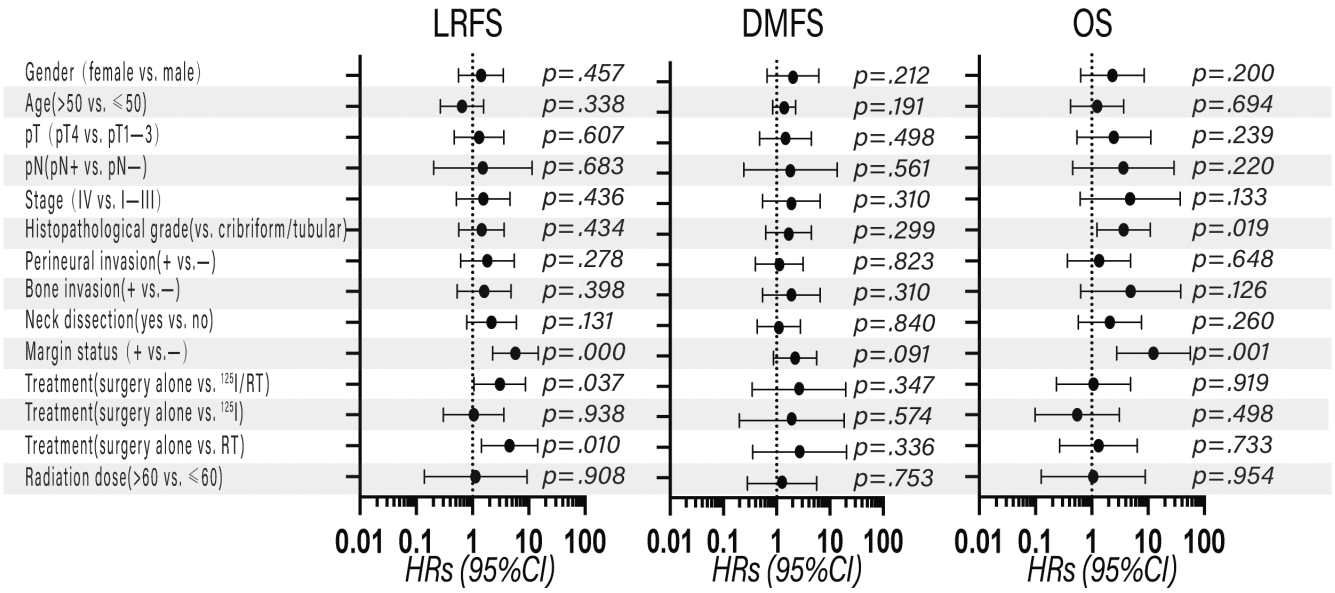

FIGURE 1 Impact of prognostic factors on treatment results by univariate analysis. 95% CI, 95% confidence interval; DMFS, distant metastasis-free survival; HRs, hazard ratio; ^{125}I, ^{125}I seed brachytherapy; LRFS, locoregional recurrence-free survival; OS, overall survival; RT, external beam radiotherapy combined with or without chemotherapy.

TABLE 4 Impact of prognostic factors on treatment results by multivariate analysis.

Endpoint	Items	HR	95% CI	*p*
OS	Margin status (positive vs. negative/close)	12.156	2.659–55.580	.001
	Histological grade (solid/HGT vs. cribriform/tubular)	3.361	1.117–10.110	.031
LRFS	Margin status (positive vs. negative/close)	1.117	2.265–14.678	.000

Abbreviations: 95% CI, 95% confidence interval; HGT, high-grade transformation; HR, hazard ratio; LRFS, locoregional-free survival; OS, overall survival.

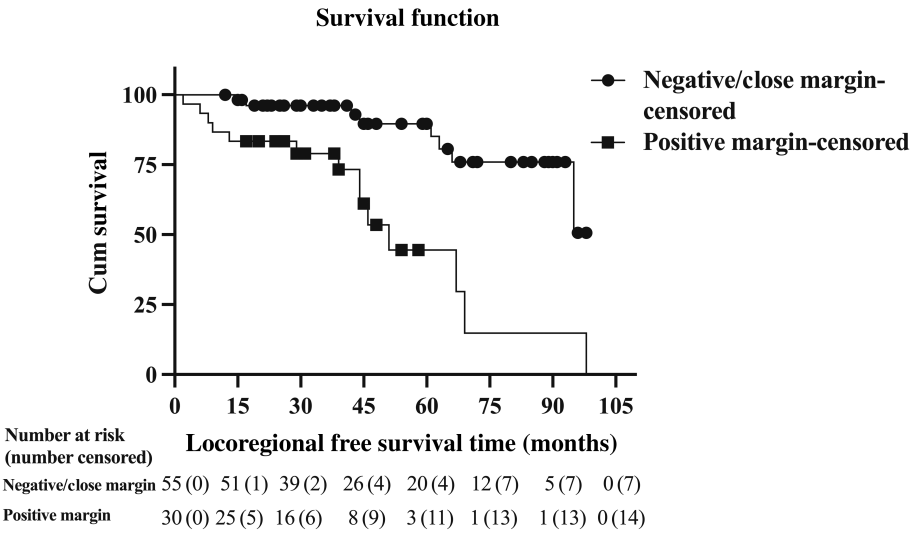

FIGURE 2 Locoregional-free survival (LRFS) rates calculated by the Kaplan–Meier method in patients by margin status.

associated with high risk of LR and poor OS but not with risk of DM. If a palatal ACC does not erode the hard plate and reaches the nasal side of the palate, the resection margins, except for the upper margin, can be easily identified. Palatal ACC is generally located close to the palatal nerve, and the neurotropic growth characteristics of this tumor make rapid upward growth extremely likely,[20] which is one of the reasons that explain the recurrence of early adenoid cystic carcinoma. Therefore, even if the hard plate is not invaded, it is advisable to perform hard palate resection and inspect the palatal nerve for involvement. In this study, perineural invasion emerged as a prevalent

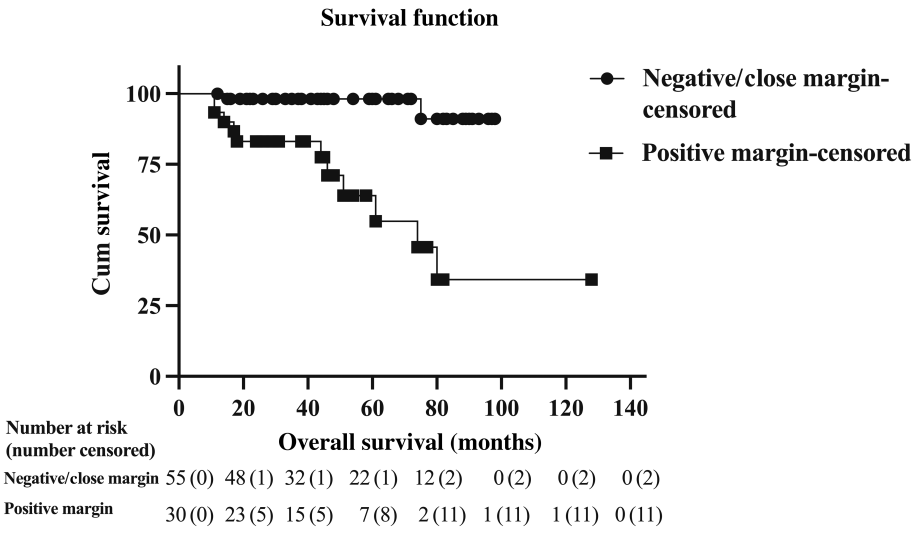

FIGURE 3 Overall survival (OS) rates calculated by the Kaplan–Meier method in patients by margin status.

phenomenon in the pathologic manifestations of adenoid cystic carcinoma, affecting 56 patients.

As the tumor has destroyed the hard plate and extended upwards, it is challenging to obtain a satisfactory upper resection margin due to the complex anatomy of the region, which includes the pterygoid plate, the pterygoid process, the attached muscles, the nasal mucosa, and the palatal nerve. Thus, local failure in this area is high likely.[3] In this study, 8 out of the 21 patients who underwent LR experienced a recurrence in the upper boundary, including the base of the skull, floor of the orbit, and even the middle fossa of the skull, resulting in a loss of opportunities for reoperation. Therefore, great attention should be paid to resection of the upper part of the tumor during surgery. The positive margin rate in this study (35.3%) was close to that in previous reports (38.6%–54.4%) on ACC of the head and neck.[11,21,22] Tabrizi et al.[3] showed that, in ACC of the palate, close surgical margins—especially superior and posterior margins—influence local recurrence rate.

Achieving negative margins can be challenging due to the growth characteristics of ACC and the complex anatomy of the palatal region.[3] Because evaluation of the resection margin of head and neck tumors is selective and ACC have a unique growth and invasion pattern, even if the margins are reported as negative, it does not mean that the tumor is completely removed. The National Comprehensive Cancer Network guidelines recommend the combination of surgery and radiotherapy to improve the local control rate in patients with ACC.[23] In view of the uncertainty regarding the upper margin status, the target area for postoperative radiotherapy must include the skull base.[24,25] Patients treated with EBRT presented with a more severe baseline tumor profile, yet the recurrence rate was significantly lower than the other two groups, indicating that EBRT is an efficient way of increasing the local control rate. We found no correlation between EBRT dose and prognosis, which is contrary to what other studies have found.[11]

Consistent with previous studies, positive margins were found to be an independent predictor of low LRFS and OS in this study.[3] In both univariate and multivariate analyses, positive margins were significantly associated with lower OS and LRFS. Furthermore, high histopathological grade is an independent predictor of poor overall survival.

Histopathological grading systems are based on the proportion of solid component present in the tumor.[17,18] Consistent with previous reports,[6,26] this study found that histopathological subtype is a significant predictor of survival. The solid-type tumor has significantly worse prognosis due to its more aggressive growth pattern and propensity for early distant metastases and should, therefore, be considered a high-grade tumor.[27] The most aggressive component of ACC is generally considered the high-grade transformation component, as a synonym for asexual reproduction or dedifferentiation, which was first formally described by Cheok et al.[28]

Surprisingly, this study showed no significant effect of perineural invasion on recurrence, metastasis, and survival. Some authors have suggested that perineural invasion loses prognostic significance due to the use of postoperative radiotherapy to eradicate residual microscopic tumors.[22] Amit et al.[26] found that intraneural, but not perineural, invasion was a poor prognostic factor. Garden et al.[29] reported that perineural invasion was a poor prognostic factor only when a major (named) nerve was invaded. It is an established fact that adenoid cystic carcinoma unquestionably spreads through nerves, resulting in skull base invasion and increased margin positivity. However, the prognostic significance of perineural invasion remains controversial.

Cervical lymph node metastasis rate of ACC is low.[30] In this study, of the 39 patients who underwent cervical lymph node dissection, only 2 patients were found to have cervical lymphatic metastases. If a neck lymph node is no significant characteristic metastatic in imaging, neck dissection cannot be performed.[9] The defect after resection needs repair by a soft flap. For patients in this study, when the blood vessels of the neck were prepared for flap repair, lymph nodes in areas I and IIa were examined by intraoperative frozen section pathology. If no metastasis was found, neck dissection was not performed. Cervical lymph node dissection is not recommended for cN0 patients.[31] In this study cohort, chest radiography at the time

of initial treatment revealed lung metastases in 3 patients; however, due to the limited amount of N+ and M1 patients, N stage and M stage were not taken into consideration for multivariate analysis. In previous studies, N stage has been identified as an important prognostic factor.

This study has certain limitations. First, this was a review of data from a single institution, and the follow-up period had to be lengthened to account for the long-term progression of the disease. Second, the research was conducted in a large tertiary care oncology hospital, a setting which only receives a small number of early-stage ACC patients. Although this may have biased the sample, this study presents the largest cohort of palatal primary ACC cases treated at a single institution.

In conclusion, the main prognostic factors for survival of patients with ACC are margin status and histopathological grade. Positive margins are also an independent prognostic factor for locoregional recurrence. For palatal primary ACC patients, surgical resection with a negative margin is the primary treatment. Postoperative radiotherapy planning should consider preoperative imaging findings, clinical symptoms, extent of resected disease, margin status, and the complex anatomy of the area to prevent local failure, extracranial skull base recurrence, and intracranial progression.

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

ORCID

Baoxin Gu https://orcid.org/0000-0002-0141-3056

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