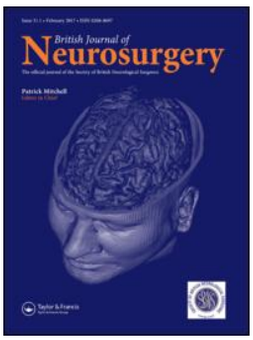

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ORIGINAL ARTICLE

Clinical study of salivary gland malignant tumor with skull base metastasis

Lin Yao[a,b], Ming Feng[a], Xue-Tao Li[a], Wen-Juan Gan[c], Xiao-Ting Xu[d] and You-Xin Zhou[e]

[a]Department of Neurosurgery, The First Hospital Affiliated to SooChow University, Suzhou, Jiangsu, China; [b]Department of Neurosurgery, The First Affiliated Hospital of Wannan Medical College (Yijishan Hospital of Wannan Medical College), Wuhu, Anhui, China; [c]Department of Pathology, The First Hospital Affiliated to SooChow University, Suzhou, Jiangsu, China; [d]Department of Radiotherapy, The First Hospital Affiliated to SooChow University, Suzhou, Jiangsu, China; [e]Department of Neurosurgery and Brian and Nerve Research Laboratory, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China

ABSTRACT

Purpose: To investigate the clinical performance, pathological characteristics, treatment and prognosis of salivary gland malignant tumor (SGMT) with skull base metastasis.

Methods: Five SGMT patients with skull base metastasis were retrospectively studied. Major clinical symptoms included headache, facial paralysis, and ear hearing loss. Three patients had previous history of SGMT resection. All patients underwent preoperative computed tomography (CT) and magnetic resonance imaging (MRI). Craniotomy was performed in three patients, and all the five patients underwent radiotherapy and chemotherapy.

Results: Two patients were confirmed as having adenocarcinoma, one patient was pathologically confirmed to have squamous cell carcinoma, one patient had ductal carcinoma, and one patient had acinar cell carcinoma. One patient died after 2 years of treatment, and the remaining 4 patients were followed up for 6 ~ 24 months, suggesting that the tumor size was not enlarged or showed no local recurrence.

Conclusion: SGMT with skull base metastasis is extremely rare, and due to similar imaging characteristics, it can be easily misdiagnosed as meningioma or schwannoma. Early diagnosis, extent of invasion, surgery and combination of chemotherapy and radiotherapy are the prognostic factors of the disease.

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KEYWORDS
Salivary gland malignant tumor; skull base metastasis; radiotherapy; chemotherapy; clinical study

Introduction

The salivary glands are divided into major salivary glands and minor salivary glands. Majority of salivary neoplasms originate from the epithelial cells. Salivary gland malignant tumor (SGMT) has an estimated incidence of 0.5–2.5 per 100,000 individuals.[1] SGMT constitute approximately 1–7% of all head and neck malignancies.[2] It has been characterized by slow growth, long course of disease and frequent distant metastasis.[3] Its 5-year specific survival rate is about 60–80% and 10-year survival rate is about 50%.[4]

The diversified pathological types of SGMT led to differences in its biological behavior and prognosis.[5] The pathological features of SGMT remain complex. According to the WHO classification in 2005, there are up to 24 SGMT pathological types. The pathological types of SGMT are varied, and the most common types include mucoepidermoid carcinoma, adenoid cystic carcinoma, adenocarcinoma, and acinar cell carcinoma.[6] The degree of tumor metastasis is related to the pathological type of the tumor. For example, salivary adenoid cystic carcinoma has strong invasion and high metastatic and recurrence rates, and its late distant metastasis rate was about 22–49%. The main routes of metastasis include direct invasion, perineural spread, hematogenous spread and lymph node metastasis.[7,8] The most common sites of metastasis include lung (80%), bone (15%), liver and other sites (5%), and metastases to the brain are very rare.[9,10] Brain metastases develop as late sequelae in patients with salivary gland malignancy, SGMT metastasis to the middle and posterior cranial fossa are even more rarely observed and discussed, patients may present with single or multiple cranial nerve palsies, and metastases may have very similar radiological appearances, so they are often misdiagnosed as meningiomas or schwannomas, it can present a challenge to neurosurgeons, neuro-radiologists and head-and-neck surgeons. Herein, we reported five cases of SGMT with skull base metastasis to discuss the clinical characteristics and treatment of the disease.

Methods and materials

General information

Five SGMT patients with skull base metastasis who were treated in our center between March 2014 and January 2018 were enrolled. Our research was approved by our local institutional review board. There were 3 males and 2 females, with age range from 46 to 70. Three patients had a previous history of SGMT resection. The clinical symptoms included headache, facial paralysis, and ear hearing loss (Table 1).

Imaging information

CT was performed with a 64-section scanner (Siemens Healthineers, Germany). MRI was performed with a 3.0-T system

CONTACT You-Xin Zhou zhouyouxin@suda.edu.cn Department of Neurosurgery and Brian and Nerve Research Laboratory, The First Affiliated Hospital of Soochow University, 899 Pinghai Street, Suzhou, Jiangsu, 215006, China
Lin Yao and Ming Feng are co-first authors

Table 1. Clinical features of patients.

Patient	Sex	Age (year)	Symptom	Treament methods	Pathological types	Follow-up time (month)	Outcome
1	Male	46	Facial paralysis and right ear hearing loss	Surgery and Radiotherapy and Chemotherapy	Adenocarcinoma	12	No recurrence
2	Male	48	Facial paralysis and headache	Surgery and Radiotherapy and Chemotherapy	Squamous cell carcinoma	6	No recurrence
3	Female	67	Headache	Radiotherapy and Chemotherapy	Adenocarcinoma	12	No enlarged
4	Male	62	Headache	Surgery and Radiotherapy and Chemotherapy	Salivary duct carcinoma	24	Death
5	Female	70	Headache	Radiotherapy and Chemotherapy	Acinar cell carcinoma	24	No enlarged

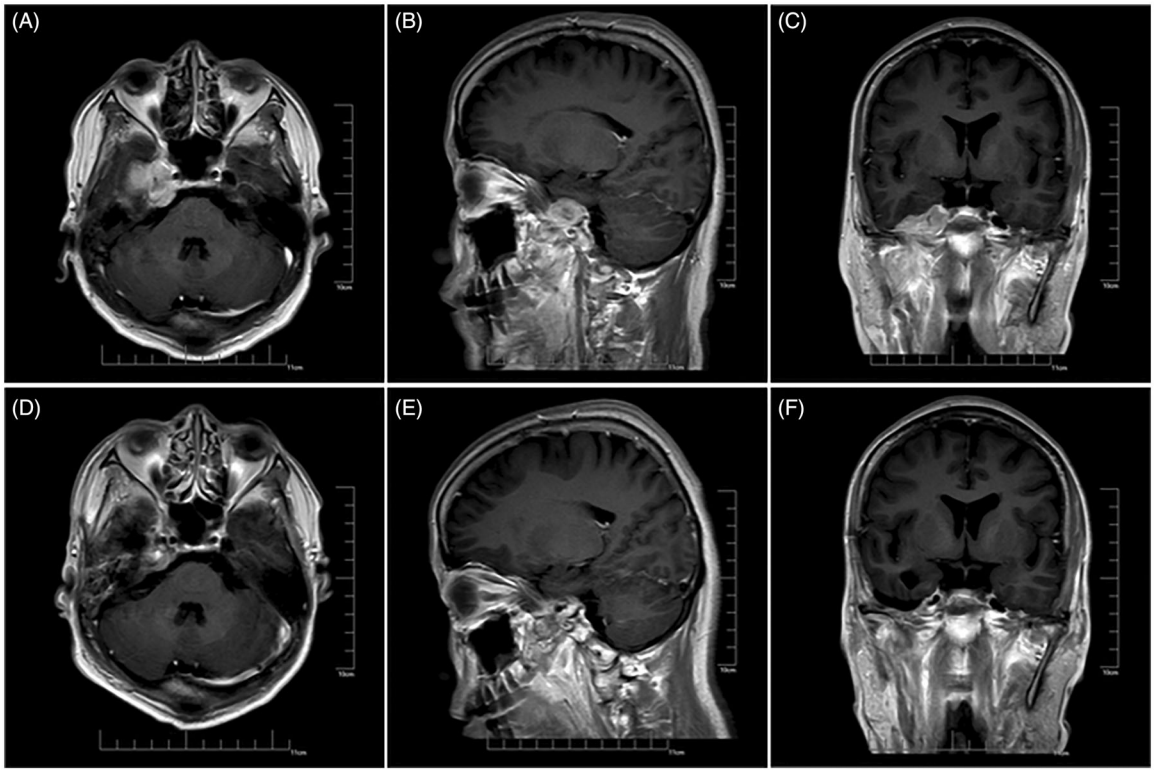

Figure 1. Patient 1: A 46-year-old male was referred to our hospital with numbness and pain on the right side of the face in June 2017. Preoperative MRI (A–C) showed a tumor of about 2.8 × 2.9 cm size in the right temporal base. Postoperative MRI (D–F) showed no recurrence of tumor after 24 months follow-up, i.e. in June 2019.

for the head (Siemens Healthineers, Germany). Preoperative CT and MRI were performed in all the five cases. The maximum diameter of intracranial tumor was 3.0cm ∼ 8.0cm. The tumor was located in the posterior fossa in one patient, in the middle cranial fossa in one patient, in the middle and posterior fossa in one patient. The results of CT showed that the skull bases were destroyed by tumor in all the one patients. The MRI showed that the tumor emitted equal or high signals on T1-weighted images and T2-weighted images, and were significantly enhanced (Table 2, Figures 1–2).

Treatment methods

Craniotomy was performed in three patients, two patients were misdiagnosed as meningioma or schwannoma, and postoperative PET-CT showed increased radioactivity in the salivary gland; and one patient underwent craniotomy because of high intracranial pressure. The tumors were resected in the middle cranial fossa through subtemporal approach, and the suboccipital sinus was combined with subtemporal approach for the tumors located in the middle and posterior fossa. Two elderly patients refused surgical treatment, and fine needle aspiration cytology was used to identify the pathological type. All the five patients underwent radiotherapy and were treated with paclitaxel and nedaplatin after radiotherapy (Figures 3–9).

Follow-up

The methods of out-patient clinic follow-up and telephone follow-up were used to examine for the improvement of clinical symptoms in patients and for tumor recurrence. In this group, all patients were followed up from 6 to 24 months, and postoperative follow-up time ended in May 2019. MRI was performed during the follow-up periods at 3, 6, and 12 months postoperatively and then annually thereafter.

Table 2. The MRI imaging data of five patients.

Patient	Sex	Age (year)	Tumor position	Size in cm (largest diameter)	T1-weighted image	T2-weighted image
1	Male	46	Middle cranial fossa	3.0	High signal	High signal
2	Male	48	Middle and posterior fossa base	7.5	Equal signal	Equal signal
3	Female	67	Middle cranial fossa	6.2	High signal	High signal
4	Male	62	Middle cranial fossa	4.0	Equal signal	High signal
5	Female	68	Middle cranial fossa	8.0	Equal signal	High signal

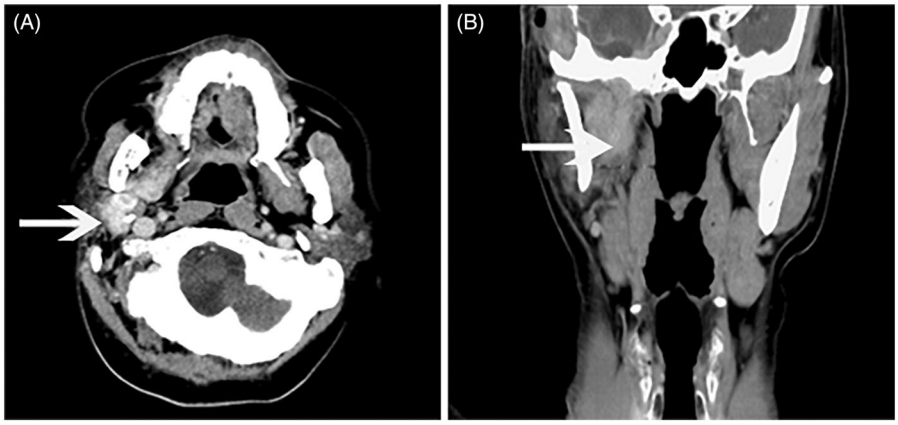

Figure 2. Patient 1 with brain metastasis. The postoperative enhanced CT (A, B) scan showed a tumor of about 2.0 × 1.9 × 1.8cm size located on the deep parotid gland, and was significantly increased, (White arrow).

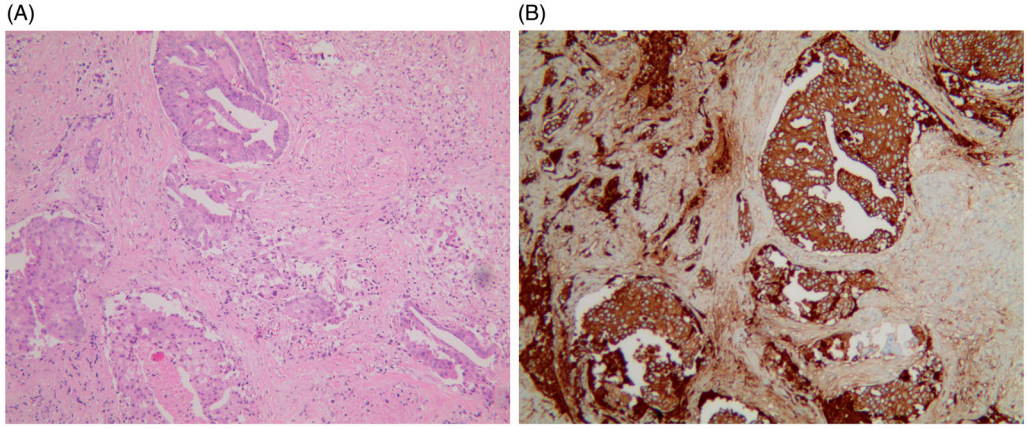

Figure 3. Patient 1 with brain metastasis. Histopathological examination of the surgical samples (hematoxylin and eosin staining) showing (A) low differentiated adenocarcinoma (original magnification× 100), and adenoid structure, where the nuclear mitosis are obvious and CK7 positive (B).

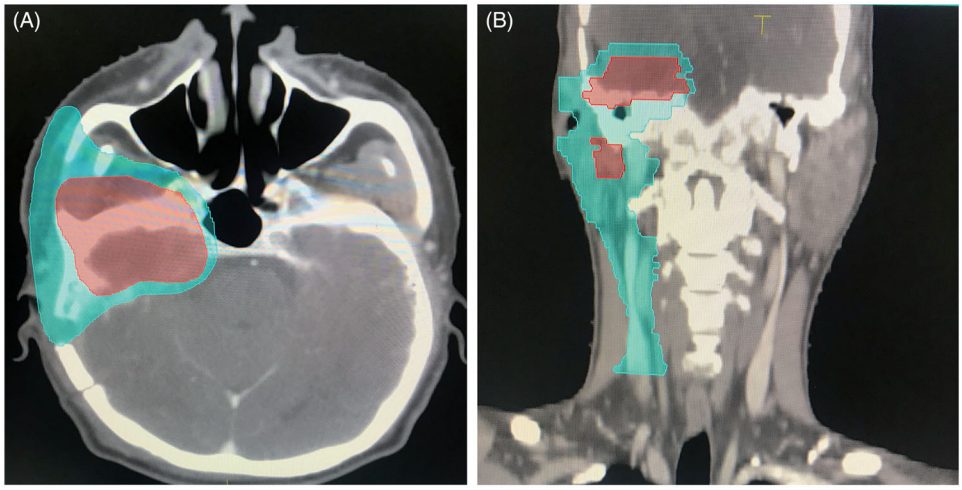

Figure 4. Patient 1 was treated with radiotherapy. GTVnx are delineated in red, and planned radiotherapy dose was 68 Gy, administered as 32 fractions of 2.0625 Gy. CTV1 are delineated in blue, and planned radiotherapy dose was 60 Gy, administered as 32 fractions of 1.875 Gy.

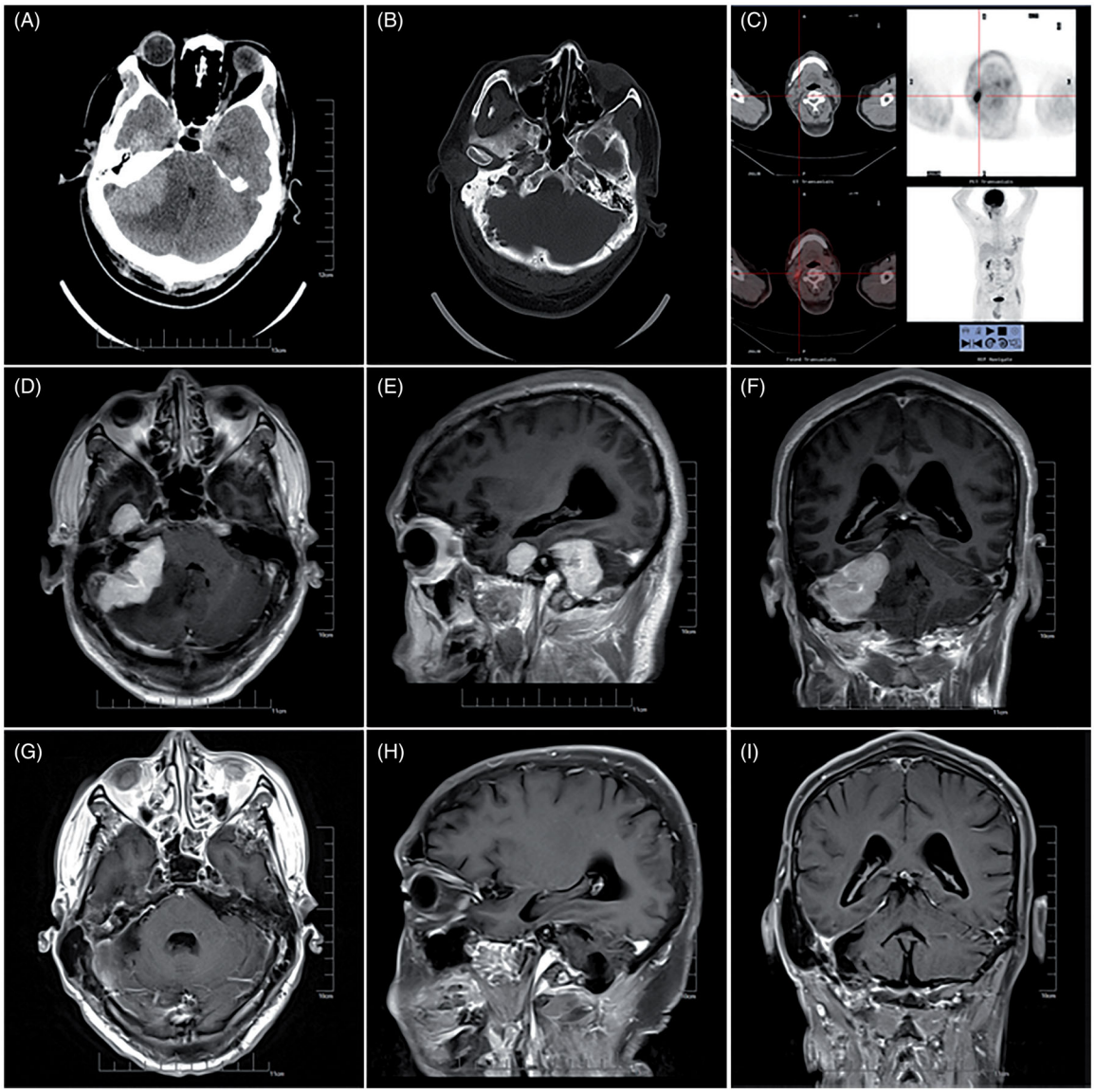

Figure 5. Patient 2: A 48-year-old male was referred to our hospital with headache in January 2018. Preoperative CT (A, B) showed a tumor of about 5.0 × 2.7 cm size in the middle and posterior cranial bone was destroyed. Postoperative PET-CT (C) showed increased radioactivity in the right parotid gland. Preoperative MRI (D–F) showed a tumor of about 2.0 × 6.0 × 3.0 cm size in the middle and posterior cranial, which was significantly enhanced in January 2018. Postoperative MRI (G–I) showed no recurrence of tumor after 18 months follow-up, i.e. in July 2019.

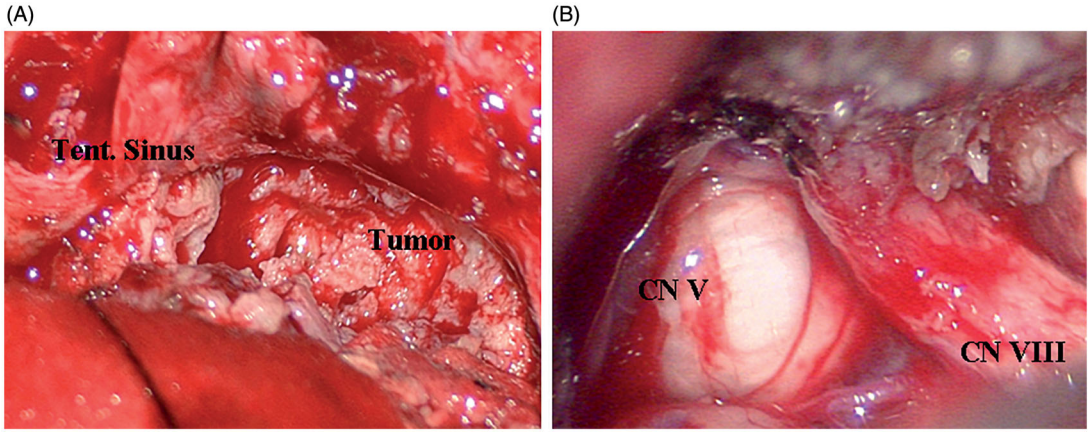

Figure 6. Patient 2 with brain metastasis. We performed suboccipital sinus combined with subtemporal approach for craniotomy. Intraoperative image A showed that gray white tumor tissue was found attached to the skull base meninges. Image B showed that the CNV and the CNVIII were protected.

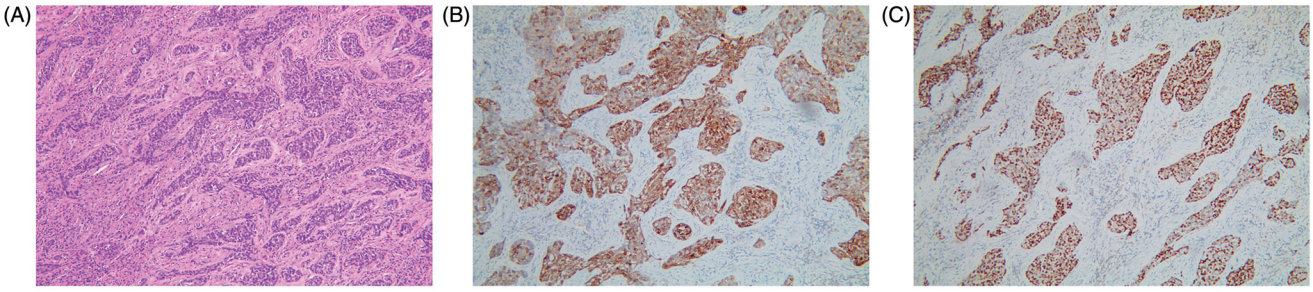

Figure 7. Patient 2 with brain metastasis. Histopathological examination of the surgical samples (hematoxylin and eosin stain) showing (A) low differentiated squamous cell carcinoma (original magnification× 100), where tumor cells have high density, and are arranged into nests, as the size of the nucleus was different and the nuclear mitosis was obvious. CK5-6 positive (B) and P63 positive (C).

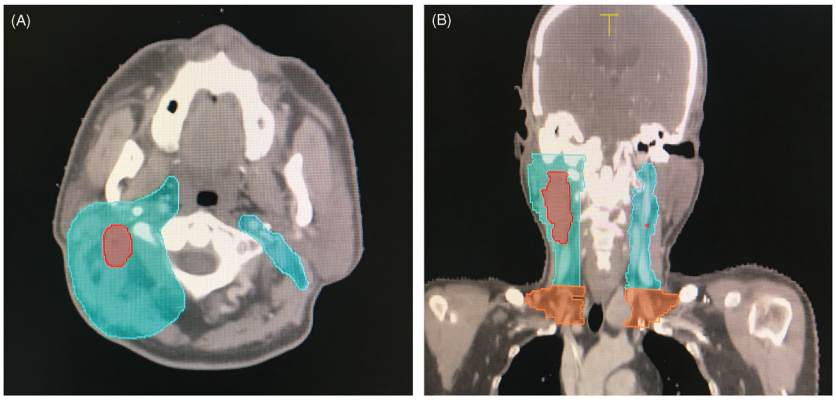

Figure 8. Patient 2 was treated with radiotherapy. GTV are delineated in red, and planned radiotherapy dose was 68 Gy, administered as 32 fractions of 2.125 Gy. CTV1 are delineated in blue, planned radiotherapy dose was 60 Gy, administered as 32 fractions of 1.875 Gy. CTV2 are delineated in yellow, and planned radiotherapy dose was 60 Gy, administered as 32 fractions of 1.6875 Gy.

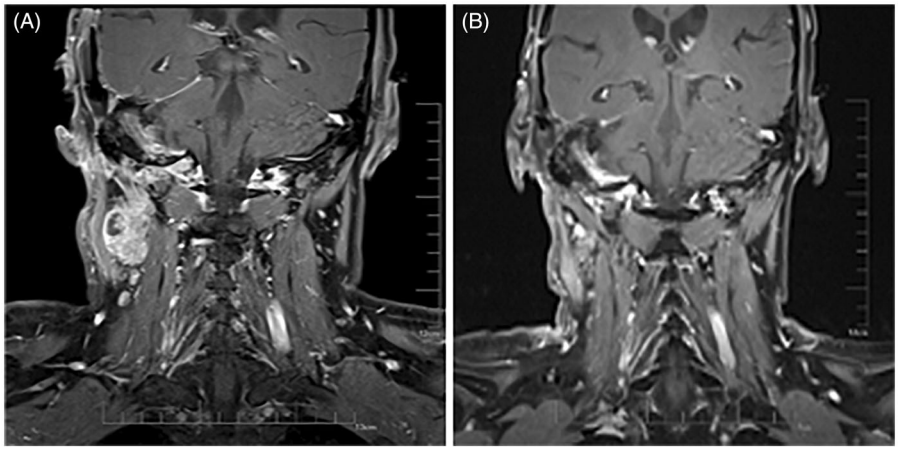

Figure 9. Patient 2 with brain metastasis. Preoperative MRI (A) showed the regional lymph nodes in the right neck were enlarged. MRI (B) showed after 3 months of radiotherapy, and the lymph nodes in the right neck were significantly smaller.

Results

Two patients were confirmed with adenocarcinoma, one patient was pathologically confirmed as squamous cell carcinoma, one patient with ductal carcinoma, and one patient with acinar cell carcinoma. After postoperative follow-up, 1 male patient died 2 years after surgery because of high intracranial pressure. The remaining two patients underwent surgery combined with radiotherapy and chemotherapy and had no tumor recurrence. The tumor size was not enlarged in two elderly patients who received only radiotherapy and chemotherapy (Figure 10).

Discussion

SGMT has a protracted disease course. The salient features of SGMT include facial nerve invasion, and increased potential of regional lymph nodal involvement and distant metastases.[11] SGMT with skull base metastasis is considered to be relatively rare, Wilson [12] reported a case of a 72-year-old man with parotid mucoepidermoid carcinoma metastatic to the cerebellopontine angle (CPA), the patient was misdiagnosed as schwannoma before surgery and only received radiation therapy, MRI following a 4-month interval demonstrated further

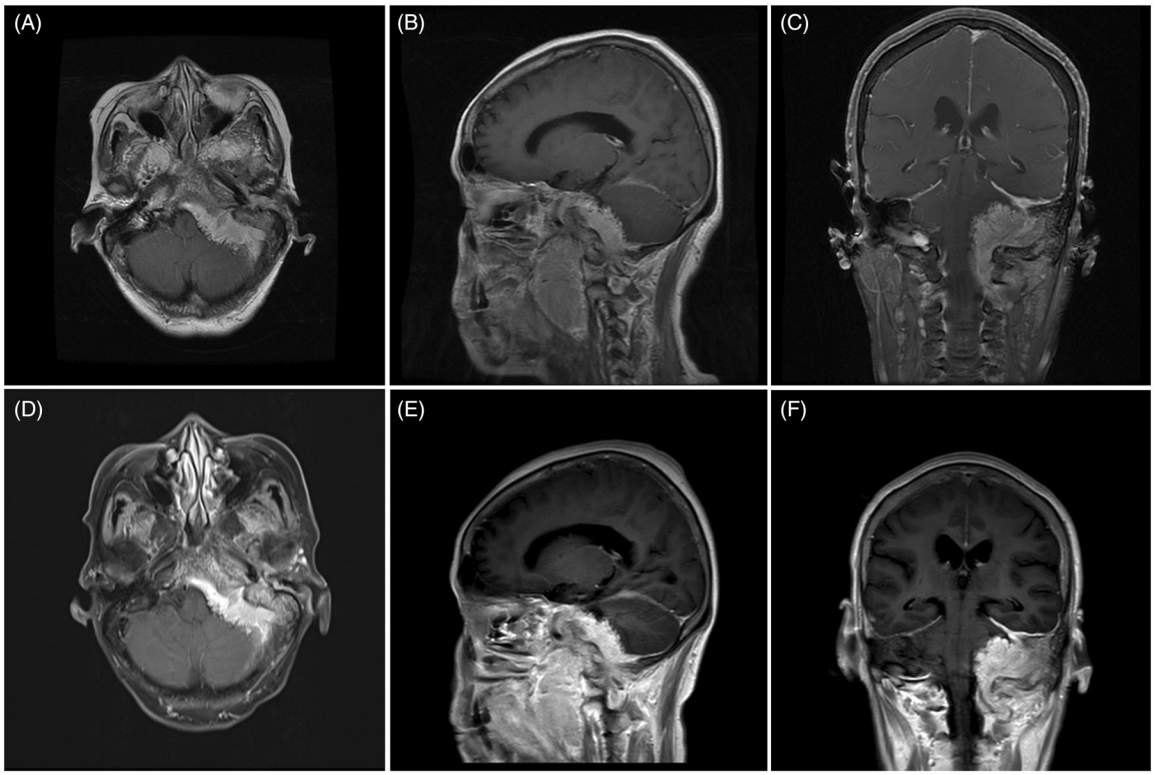

Figure 10. Patient 3: A 69-year-old female was referred to our hospital with headache in June 2016. The head MRI (A–C) showed a tumor size of about 7.7 × 3.3 × 3.0 cm in the posterior cranial in March 2017. The head MRI (D–F) showed that the tumor size was not enlarged in June 2019 (after radiotherapy and chemotherapy).

enlargement of the CPA lesion to 45 × 25 mm and then underwent removal of only the CPA component, and eventually died 9 months after surgical intervention. The CT scans provide information related to bone infiltration, schwannomas and meningiomas have relatively less bone infiltration compared with metastases. In our study, the results of CT showed that the skull bases were destroyed by tumor in all the five patients. MRI can show clear boundaries of tumor, the size and shape of the tumor, as well as brain tissue structures around the tumor.[13] It should always be considered in the differential diagnosis for a patient presenting with an enhancing lesion in the skull base, particularly if the patient has a history of SGMT or with facial paralysis and ear hearing loss. In case of an uncertain diagnosis, PET/CT imaging can be performed.[14] The final diagnosis depends on the pathological diagnosis after the operation. Two elderly patients in our group underwent fine needle aspiration biopsy (FNAB) to identify the pathological type. The preoperative fine needle aspiration biopsy (FNAB) has high diagnostic sensitivity and specificity, which can in turn guide the operation better. However, FNAB is less sensitive in diagnosing the malignant tumors, and there is a chance of obtaining false negative results.[15,16]

Management of brain metastases from SGMT was the same as the general management of brain metastases from other tumor types. Symptomatic lesions are resected if the tumor location remains favorable. Hughes [17] reported a case of a 72-year-old woman with adenoid cystic carcinoma metastatic to the pituitary, the tumor was resected through a transsphenoidal approach, and had obtained the better therapeutic effect. In our study, for these three patients with middle and posterior cranial fossa metastases, surgical approach and intraoperative nerve protection are the key to surgery, and proper operative approach can protect the normal cerebral vessels and avoid unnecessary brain traction, achieving the most effective resection of the lesion. In these three patients, we used suboccipital sinus combined with subtemporal approach and subtemporal approach for craniotomy. We found that the tumors were closely related to cranial nerves and important blood vessels during operation, and damage of these important tissue structures may cause serious consequences. Radiotherapy plays an important role in the management of SGMT with intracranial metastases.[18] The clinical study showed that postoperative radiotherapy obviously improves the survival rate and prolongs the survival time of the patients.[19] Postoperative radiotherapy is considered to be suitable for patients with lymph node metastases, locally advanced disease, bone or nerve involvement, and recurrent disease.[20] There are not many reports on the treatment of salivary adenocarcinoma with concurrent chemoradiotherapy, and few of the existing reports have achieved encouraging results.[21] In our study, All the five patients had high-grade and unresectable primary tumor, and were treated with paclitaxel (75mg/m^2, d1) and nedaplatin (100mg/m^2, d2) every 28 days, five cylces were required for chemotherapy. Chemotherapeutic drugs have strong cytotoxic effect, and the tumor molecular targeting therapy has a prominent specific antitumor effect, significantly reducing the drug toxicity. Epidermal growth factor receptor (EGFR), HER2, and c-kit are important hormonal receptors and molecular markers.[22] C-Kit protein is a transmembrane tyrosine kinase receptor that is associated with the regulation of cell migration, differentiation, and proliferation.[23] The use of tyrosine kinase inhibitors in the treatment of salivary gland malignancies is still under research.

Diagnostic errors are experienced much more frequently in rare diseases, as these are misinterpreted as more common diseases. Because the symptoms and imaging findings of patients with diseases are not typical, it is indeed very difficult to make a correct diagnosis early. For the diagnosis of SGMT with brain

metastases, the patient's detailed medical history, careful physical examination and important imaging data are essential. Although limited evidence is available regarding optimal management of SGMT with skull base metastases, best practice should be a collaborative multi-disciplinary approach. Surgical resection can be offered in those with potential benefit, and adjuvant therapy should be considered by the appropriate oncology services. It should be pointed out that because SGMT with skull base metastasis is relatively rare, and there is no standard treatment plan at present, especially standard radiotherapy and chemotherapy regimens. In this group of cases, the patients achieved a longer survival period except for one patient died of cranial hypertension. We hope to provide some help to neurosurgeons in their future work by presenting our experiences.

This study has several limitations. As the follow-up time was short, the patient's long-term effect needs further follow-up observation. And the tumor microenvironment and metastasis mechanism have not been studied and need to be studied in the future.

Conclusion

SGMT with skull base invasion is very rare, and because of the lack of specific clinical and imaging findings, it can be easily misdiagnosed. For skull base metastatic tumors, we need to further investigate the metastasis. For patients with neurological deficits, the optimal therapy includes surgery plus postoperative radiotherapy, and chemotherapy should be formulated according to the pathological results of tumors and positive treatment may improve the prognosis and prolong the survival time.

Ethical approval

This study was approved by the China Ethics Committee of Registering Clinical Trials.

Informed consent

Informed consent was obtained from all patients.

Disclosure statement

The authors have no conflicts of interest.

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