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Case report

# Multi-disciplinary surgery for simultaneous resection of multiple tumors in a patient with newly diagnosed metastatic pheochromocytoma/paraganglioma

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## HIGHLIGHTS

- This report describes a rare case of metastatic pheochromocytoma/paraganglioma (MPP) where the patient was initially diagnosed with two lesions.
- Multi-disciplinary surgery was performed to simultaneously resect both lesions.
- The cutting edge of the head tumor was positive.
- Patients who received targeted sunitinib therapy showed normal endocrine levels and no signs of recurrence during follow-up.

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## ABSTRACT

Metastatic pheochromocytoma/paraganglioma (MPP) is a rare endocrine tumor that originates from extra-adrenal chromaffin cells such as the paraganglia cells of sympathetic and parasympathetic nerves. It usually causes multiple solid tumors and exhibits strong aggressiveness with poor prognosis, with a reported 5-year survival rate of less than 50%. Cases of brain and retroperitoneal metastases at the initial diagnosis have not yet been reported. We report a 41-year-old male patient initially diagnosed with MPP in the brain and retroperitoneum who underwent multi-disciplinary collaborative surgery and simultaneous removal of two tumors at our center. Postoperative pathology revealed infiltrative growth of a skull base tumor. The patient chose to receive the tyrosine kinase inhibitor sunitinib as a targeted treatment. A 3-month follow-up after surgery showed that the patient recovered well without signs of metastasis or recurrence. We present multi-disciplinary surgery under similar circumstances for enhanced treatment and postoperative management. The patient demonstrates a favorable prognosis during postoperative follow-up, indicating that simultaneous multidisciplinary surgery may offer greater benefits for MPP patients.

## Introduction

Pheochromocytomas (PHEO) and paragangliomas (PGL) are rare endocrine tumors that stem from adrenal or extra-adrenal chromaffin cells, such as paraganglia cells of the sympathetic and parasympathetic nerves. These tumors are defined as metastatic pheochromocytoma/paraganglioma (MPP) when they appear or metastasize to non-chromophilic tissues.[1] MPP usually causes multiple solid tumors and exhibits strong aggressiveness, poor prognosis, and a reported 5-year survival rate of less than 50%.[2]

Surgical resection of the primary and secondary tumors remains the most important treatment for MPP.[3] Considering MPP with two or more solid tumors at the initial diagnosis, the removal of multiple tumors in phase I not only reduces the risk of surgery but also provides better conditions for follow-up treatments (such as nuclear medicine treatment and chemotherapy).[4] However, such tumors often invade multiple systems and disciplines, making surgery more challenging. Therefore, it is often difficult to resect all tumors during a single operation. Additionally, the unique circulatory-endocrine effect of PGL increases the risk of one-stage combined surgery.

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In the present study, we report a case of an MPP in China, where the patient underwent resection of the skull base and retroperitoneal tumors in a single multi-disciplinary surgery. The multidisciplinary treatment (MDT) team developed a postoperative treatment plan for the patient. We also discuss treatment strategies for new MPP patients with multiple tumors.

## Case presentation

### *Medical history*

In September 2022, a 43-year-old man visited the Beijing Hospital of China for treatment. The patient complained that his right eyeball was found to be slightly protruding 18 months earlier and had gradually progressed. Imaging examinations at other hospitals revealed a solid mass at the right skull base and retroperitoneum. The tumor at the skull base was approximately 4.5 cm by 2.3 cm by 3.0 cm in size, while the one in the retroperitoneum measured approximately 6.1 cm by 4.0 cm by 4.7 cm. His whole-body $^{18}$F fluoro-D-glucose positron emission tomography ($^{18}$F-FDG-PET) combined with low-dose computed tomography showed that the mass at the right skull base had invaded the anterior cranial fossa and extraocular muscles. In contrast, the retroperitoneal mass was adjacent to the abdominal aorta and the boundaries were unclear. Except for these two masses, no signs of involvement were observed in other organs or systems [Figure 1A]. However, the patient did not undergo surgery because the hospital stated that his tumor required at least two surgeries before it could be removed.

Thereafter, when the patient visited another hospital, he underwent 99mtechnetium-hydrazinonicotinyl-99mtechnetium-hydrazinonicotinyl-tyr3-octreotide (99mTc-HTOC-traced) imaging and I131-metaiodoenzylguanidine (MIBG) imaging because his doctor discovered his history of persistent hypertension for two and a half years. The results showed that tumors at the skull base and retroperitoneum ingested high levels of octreotide and MIBG [Figure 1B]. Therefore, PGLs were strongly suspected. Although the patient had commenced taking the non-selective alpha (α)-receptor blocker phenoxybenzamine for preoperative preparation, in the follow-up communication, he was told that only the retroperitoneal tumor can be removed in this surgery, and the treatment of tumors at the base of the skull requires further consultation with neurosurgery or ophthalmology.

In addition, the patient's medical history suggested that he had a sustained increase in blood pressure for two and a half years, with a maximum of 170/110 mmHg. However, he did not exhibit the typical symptoms of PHEO, such as tachycardia, sweating, headaches, or tremors. He started taking phenoxybenzamine for more than 1 week with approximately 20 pills per day and had a history of smoking for 27 years.

### *Imaging examination*

After the patient was admitted to the hospital, abdominal CT angiography (CTA) and craniocerebral perfusion CT were performed. These imaging examinations revealed that the occupation of the patient's skull base had broken through the skull and entered the anterior cranial fossa, suspected of infiltrating the skull and invading the extraocular muscles [Figure 1C]. The tumor in the retroperitoneum was close to the abdominal aorta and duodenum, and its blood supply relationship was unclear [Figure 1D]. This implies that the surgery required the cooperation of at least three departments: urology, ophthalmology, and neurosurgery. Gastrointestinal surgery may be required in severe cases.

### *Laboratory test*

Laboratory examinations showed that the patient's tumor had a catecholamine endocrine function [Supplementary Table 1].

### *Treatment*

After the above examination, nearly 10 departments, including ophthalmology, neurosurgery, intensive care unit (ICU), nuclear medicine, and oncology, were invited to discuss the patient's condition. The discussion opinions were as follows: (1) Surgery is currently the primary treatment option. According to the preoperative imaging examination, although there are certain surgical difficulties and risks, it is feasible to resect two masses at one stage. The retroperitoneal tumor should be removed first, and the decision to resect the skull base masses simultaneously should be determined if the first part of the operation is successful; and (2) According to the pathological results, targeted drug therapy or radionuclide adjuvant therapy can be considered after surgery.

### *Operation*

The patient successfully underwent a combined surgery and was transferred to the ICU ward after the surgery. The surgical preparation and specific process are detailed in the Supplementary file.

The patient returned to the urology ward, and the craniocerebral drainage tube was removed on the first postoperative day. The abdominal drainage tube was removed on postoperative day three. Afterward, the patient was able to get out of bed and perform daily activities unaided. A week after the operation, the patient's eye movements were normal, and lacrimal gland function was not affected. Stable postoperative changes were observed in the retroperitoneal and skull base surgical areas one week after surgery [Supplementary Figure 1B–E]. The patient was discharged after evaluation.

### *Adjuvant treatment and follow-up*

Owing to the socioeconomic circumstance of the patient, sunitinib (a type of tyrosine kinase inhibitor [TKI]) was administered as an adjuvant targeted therapy, and the patient agreed to regular follow-ups every three months. Owing to the positive surgical margin of the patient's head tumor, blood catecholamine levels were tested during the first follow-up. The dopamine and norepinephrine levels decreased to 48.43 pg/mL and norepinephrine decreased to 156.27 pg/mL. Catecholamine metabolites also decreased significantly (VMA 7.3 mg/24 h).

At the second follow-up (6 months after surgery), the patient's octreotide imaging showed that the uptake of the abdominal mass tumor had disappeared, with slight uptake in the right frontal area, considering the possibility of non-specific inflammation [Figure 1E]. Because the patient's blood pressure and hormone levels were normal, the doctor suggested that he discontinue taking phenoxybenzamine.

### *Pathology*

The postoperative pathological results showed that the tumors at the skull base and retroperitoneum had the same origin and were PGLs. Nuclear atypia was observed, mitosis was approximately 1–3/10 per High-power field, and envelope infiltration was also present. Furthermore, the tumor at the skull base infiltrated the surrounding bone tissue.

## Discussion

MPP accounts for 10–17% of all PHEO/PGL cases. Compared to PHEO, PGL is more prone to metastasis. Approximately 5–20% of PHEO and 15–35% of sympathetic PGL metastasize.[5] Although MPP occurs in various organs and systems, functional MPPs are most commonly found in the retroperitoneum.[6] Moreover, because the head and neck are

sympathetic ganglia, most PGLs in the head and neck are non-functional and do not secrete catecholamines. However, according to the results of octreotide and MIBG imaging, both lesions have secretory abilities.

To our knowledge, this is a rare case of a patient with functional dual foci in the head, neck, and retroperitoneum. Pathological analysis revealed that the two tumors had the same origin and similar pathological features, suggesting that one was metastatic. Given the patient's young age and the fact that he had only been experiencing symptoms (raised blood pressure) for 2 years, it is unclear whether this case is simply an unusual occurrence or if our current understanding of the tumor is incomplete. Further research is required to address this issue.

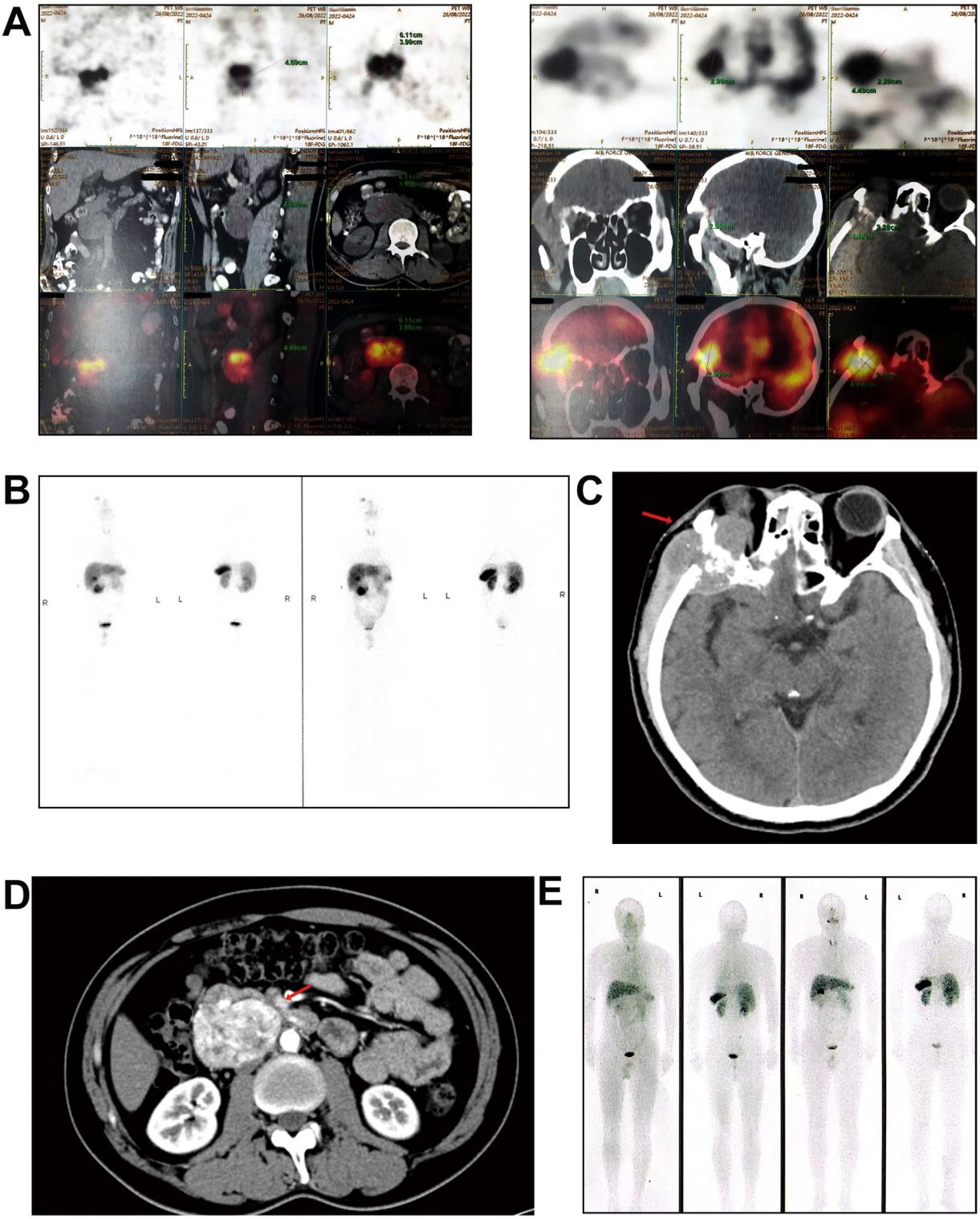


**Figure 1.** Summary of preoperative imaging examinations for patients (A) $^{18}$F fluoro-D-glucose positron emission tomography combined with low-dose computed tomography examination presents increased metabolism in the retroperitoneum and skull base; (B) Octreotide is highly ingested by the tumors at the skull base and retroperitoneum; (C) Six months after surgery, the uptake of the abdominal mass tumor disappears, with a slight uptake in the right frontal area; (D) Retroperitoneum mass was adjacent to the abdominal aorta, and the boundaries are unclear; (E) Mass at the right skull base invades the anterior cranial fossa and extraocular muscles.

Although it is currently believed that the survival benefits of surgery for MPP patients are obscure, surgery remains the first choice of treatment for them.[7] Surgical treatment not only reduces the catecholamine load in patients but also leads to long-term cardiovascular benefits.[8] In 2013, He et al.[4] reported a 42-year-old female patient with a retroperitoneal PGL and metastasis to the abdominal spine. The patient was successfully treated by completely removing the tumor and its metastasis. The patient was followed up for 4 years and maintained a disease-free state.[4] Surgery can significantly improve the prognosis of patients with malignant tumors or intracranial metastasis.[9] The patient was only 41 years old. Although the patient presented with a high level of circulating catecholamines, there were no other symptoms except hypertension. Surgery was the only possible treatment option for the patient.

Simultaneous surgery has significant potential benefits for patients. First, the repetitive aspects of the two surgeries (preoperative preparation and anesthesia management) will be eliminated. Similarly, simultaneous multi-disciplinary surgeries can provide surgical support from a more comprehensive perspective compared to two separate surgeries. For example, when head and neck surgeons handle skull base tumors, urologists provide surgical support in the waiting area and are ready to join the surgery at any time, thereby reducing potential risks. Second, patients only require one surgical recovery period, eliminating the waiting period between the two surgeries, and thereby avoiding the possibility of tumor progression during the waiting period. Finally, simultaneous surgery significantly reduces the consumption of medical resources and decreases the economic pressure on patients.

However, the corresponding challenges must be acknowledged. First, the extension of the surgical time and potential blood pressure fluctuations caused by the removal of the two tumors placed great pressure on intraoperative circulation management. Therefore, in addition to routine preoperative preparation, we administered a non-selective α-receptor blocker, phentolamine, and adopted a shallow anesthesia strategy (bispectral index [BIS], maintained at 50–60). In terms of surgery, in addition to preoperative blood supply embolization and a large amount of blood preparation, anatomical dissection, to a great extent, is based on the principle of preserving the integrity of the tumor itself. This is performed using bipolar electrocoagulation dissection, avoiding compression and cutting of the tumor body to minimize stimulation of the tumor. In addition, concurrent surgery presents a challenge, which involves postoperative joint management of patients. After MDT discussions, we establish a postoperative management team centered around the ICU to treat and manage patients until discharge.

Unfortunately, the tumor in his head was found to be infiltrating during surgery. Although the tumor was removed, and the residual base was burned during the operation, the patient's postoperative pathology showed that the cutting margin was still positive. However, we believe that this surgery is beneficial. In 2019, Dong et al.[10] reported the case of a 39-year-old woman with liver metastasis six years after retroperitoneal PGL resection. Although the metastatic tumor failed to respond to follow-up treatment, it remained stable and did not progress during a follow-up period of the following seven years.

However, the patient who was from another province did not undergo genetic testing owing to considerations of treatment convenience and economic constraints, which are essential in making treatment decisions.

Therefore, our MDT team provided several postoperative adjuvant treatment options to the patient. First, peptide radioreceptor therapy (PRRT) with 177Lu-dotatate or somatostatin assays (SSAs) was recommended. Nuclear medicine imaging of the patient before surgery indicated that the tumor had significantly absorbed the aforementioned substances. Current research suggests that nuclide therapy has a response rate of up to 50% for tumors $<2$ cm,[11] making it an ideal choice for tumors that cannot be completely removed. However, nuclear therapy requires long-term and regular treatment, which may be difficult for patients because of their economic conditions.

Second, sunitinib, a type of TKI, has been reported to significantly improve the prognosis of patients with MPP when administered as sunitinib (37.5 mg) once daily. It is also recommended by the National Comprehensive Cancer Network (NCCN) 2022 guidelines.[12] Ultimately, the patient chose the latter. Our MDT team recommends that patients continue to take a non-selective α-blocker while using sunitinib and decide whether to continue based on follow-up monitoring of tumor secretion function.

Another issue that must be addressed is the need for concurrent surgery. Due to excessive catecholamines in the MPP, severe blood pressure fluctuations often occur during surgery, and catecholamine crises may also occur owing to catecholamine depletion. Therefore, preoperative preparation is critical.[13] As an ordinary farmer, it was difficult for the patient to seek medical treatment outside the province. Having two surgeries would double the treatment cycle, and combined with economic conditions, could seriously affect patient compliance with the treatment. Therefore, without violating basic medical principles, simultaneous resection of two lesions is not only for compassionate and ethical considerations but also beneficial to the treatment and follow-up of patients.

Here, we present the patient with MPP who was initially diagnosed with two lesions. A multi-disciplinary surgical team performed the simultaneous resection of both lesions, followed by optional adjuvant therapy and regular follow-up. This approach was chosen because of the patient's unique circumstances, including difficulties in seeking medical treatment outside of their province and economic constraints. This case highlights the potential benefits of simultaneous surgeries for patients with similar conditions.

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## Authors contribution

Conceptualization: Jibo Jing, Lingfeng Meng. Methodology: Jibo Jing, Lingfeng Meng, and Xinhao Wang. Validation: Lingfeng Meng, Yaoguang Zhang, and Xinhao Wang. Resources: Jibo Jing, Runhua Tang, Haoran Wang, Jiaxing Ning, and Xinhao Wang. Data Curation: Runhua Tang, Haoran Wang, Jiaxing Ning, and Xinhao Wang. Writing – Original Draft Preparation: Jibo Jing. Visualization: Jibo Jing, Runhua Tang. Supervision: Yaoguang Zhang, Jibo Jing. Project Administration: Yaoguang Zhang. Funding Acquisition: Lingfen Meng, Yaoguang Zhang.

## Ethics statement

This study was conducted in accordance with the ethical principles outlined in the *Declaration of Helsinki*, and was approved by the involved center. The patients provided informed consent for the publication of their cases and all identifying information was removed to protect their privacy.

## Data availability statement

Data used in this case report are available upon request from the corresponding author. However, owing to the sensitive nature of patient medical information, some data may be restricted to protect patient privacy.

## Conflict of interest

None.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpt.2023.05.003.

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