

# Clinical features and treatment of spinal metastatic pheochromocytoma and paraganglioma: a single institutional experience with 18 patients

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## Research Article

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## Abstract

Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors, which can potentially metastasize to the spine. Clinical researches and treatment guideline on this entity are lacking. This study described the clinical features and treatment outcomes of metastatic PPGLs on the spine. We reviewed 18 patients with spinal PPGLs who were consecutively treated in our spinal center. The cohort included ten cases of pheochromocytomas and eight paragangliomas. The local pain and neurological deficits were the two most common symptoms. One third of the spinal PPGLs were diagnosed as functional tumors. The surgical strategies for the cohort included percutaneous vertebroplasty, neurological decompression and partial tumor resection with or without internal fixation, and total en-bloc resection. The postoperative courses were uneventful except one patient developed heart failure. The adjuvant therapies were implemented in six patients with  $^{131}\text{I}$ -MIBG, five with radiotherapy, two with chemotherapy and one with target therapy. The median survival period was 39 months. The patients' Karnofsky performance scores were positively correlated with the overall survival ( $p < 0.05$ ). Therefore, surgery is indicated for intractable local pain and neurological impairment in the patients with spinal PPGLs, while a holistic set of adjuvant therapies shall be incorporated for a better tumor control.

## Introduction

Pheochromocytoma and paragangliomas (PPGLs) are rare endocrine tumors arising from chromaffin cells, which are derived from the neural crest [1, 2]. According to the 2017 World Health Organization (WHO) classification system [3], Pheochromocytoma (PHEO) is an adrenal tumor, and paragangliomas (PGL) is an extra-adrenal tumor. Since the two tumor types cannot be differentiated on the basis of histologic findings, anatomical location is used to distinguish between them. PHEO develops from the adrenal medulla, while PGL arises in extra-adrenal sites, including the abdomen, thorax, head and neck. PPGLs has a low incidence, which is estimated at 2 to 8 cases per million per year, in which PHEOs are more common than PGLs [1, 4]. These neoplasms are mostly seen in the age of 4th to 6th decades, and do not show significant gender disparity. PPGLs have the capacity to synthesize, store, and secrete a variety of neurotransmitters, especially catecholamine, which predispose the patients to symptoms such as hypertension, palpitations, throbbing headaches, and diaphoresis [1, 5]. However, their clinical manifestations are extremely variable, depending on locoregional and distant involvement, tumor size, the secretion of catecholamines and function of altitude, and the malignancy potential [1, 2, 4, 6].

All PPGLs have the potential to metastasis, according to the last WHO classification in 2017 [3]. The prevalence of metastasis to non-chromaffin organs and structures is estimated 10% in PHEOs and 35–40% in PGLs, relatively [1, 4, 6, 7]. The common metastases include lymph nodes, liver, lung, urinary systems and bone [4, 6]. Spinal involvement is rare and was sporadically reported [8–17]. Currently, no mature guideline on the treatment of metastatic spinal PPGLs exists. Surgical resection is the treatment of choice for the spinal lesions, and a complete resection remains the goal of surgery, which, however, is hard to achieve due to the complex anatomic structures, adjacent to vital organs and heavy bleeding due to hypervascularity [4, 7, 16, 18]. In the present study, we retrospectively reviewed the patients who were consecutively treated in our spinal center and described their clinical features and surgical outcomes. Furthermore, we searched medical databases for reports, case series and researches on metastatic spinal PPGLs, in order to present a deep and precise appraisal of current therapeutic modalities.

## Materials And Methods

### Patients inclusion

The clinical data of 18 patients with metastatic spinal PPGLs, who were consecutively treated in our spinal center from May 2007 and August 2019, were reviewed. The inclusion criteria were as the following: 1) having a past history of PHEOs or PGLs, and the pathological specimens of spinal lesions were confirmed by the department of pathology in our center; 2) receiving surgical treatment in our center; 3) being regularly followed-up; and 4) the clinical data were fully accessible. This study was approved by our institutional ethics committee, and the written informed consent was obtained from all the patients.

### Data collection

In this study, we mainly focused on the review and analysis of clinical features, treatment information and follow-up data regarding spinal metastatic lesions. Specifically, the neurological status was rated according to ASIA scaling system. The life capacity of the patients was assessed with the Karnofsky performance scale (KPS) [19]. The Spinal Instability Neoplastic Score (SINS) system was used to assess spinal stability [20], and the Tomita and Tokuhashi scoring systems were used to assess the prognosis of patients and assist in the scheming of surgical plans [21, 22]. The advice from our institutional multidisciplinary team on the spinal tumors was also incorporated into the plans. The surgical strategies were categorized as the following: total resection (TR), partial resection (PR, including separation surgeries), and percutaneous vertebroplasty procedures (PVP). Besides, neurological decompression was undertaken in case of symptoms and signs of neurological compression. Surgical data, including blood loss, duration and perioperative complications, were reviewed and analyzed. The surgical outcomes were appraised mainly using overall survival (OS) after the indexed operation.

### Statistical analysis and data presentation

Data analysis was performed using IBM SPSS statistics for Windows Version 20 (IBM Corp., Armonk, NY, USA). Lilliefors test, which is an adaptation of the Kolmogorov-Smirnov test, was used to examine whether the data were normally distributed. Data presentation was provided in the forms of percentages, mean  $\pm$  standard deviation, or median (range). Two-tailed unpaired Student's *t* test and two-tailed Pearson's  $\chi^2$  test (or Fisher's exact test) were utilized to make a comparison between different groups. Spearman's rank correlation test was used for correlation analysis between the two parameters. Statistical significance was set at 0.05.

## Results

## Demographic data and medical history

This study had ten cases of PHEOs and eight cases of PGLs (Table 1). All patients received one year of follow-up at least. The cohort included 13 males and five females, and the median age was 45.1 years. 15 patients were initially referred to our institution for metastatic spinal PPGLs, and three had history of surgical interventions of spinal metastases in other hospitals. Half of the cases had history of local recurrence and/or metastasis to other organs. The period between the surgical resection of primary sites and the emergence of the spinal metastases ranged ten to 326 months, with a median of 32.5 months.

Table 1  
Clinical data and medical history of the included cohort

Case No.	Age (years)/sex	Primary site, year	Pathologies	Local control	Other metastasis*
1	32 y/M	Adrenal, 2006	Pheochromocytoma	Recurrence, 2007	No
2	42 y/M	Adrenal, 2008	Pheochromocytoma	Stable	No
3	47 y/F	Adrenal, 2013	Pheochromocytoma	Stable	No
4	50 y/M	Adrenal, 2015	Pheochromocytoma	Stable	No
5	55 y/F	Adrenal, 2010	Pheochromocytoma	Recurrence, 2015	Liver, 2018
6	30 y/M	Adrenal, 2011	Pheochromocytoma	Recurrence, 2016	No
7	57 y/M	Adrenal, 2014	Pheochromocytoma	Stable	No
8	46 y/M	Adrenal, 1992	Pheochromocytoma	Recurrence, 1994, 2008, 2013	No
9	20 y/M	Mediastinum, 2005	Paraganglioma	Stable	No
10	47 y/M	Bladder, 2001	Paraganglioma	Stable	Left ilium and rib, 2014
11	63 y/M	Bladder, 2013	Paraganglioma	Stable	Lung, 2015
12	56 y/M	Retroperitoneum, 2012	Paraganglioma	Stable	No
13	27 y/M	Retroperitoneum, 2013	Paraganglioma	Recurrence, 2016	Cervical lymph nodes and Left acetabulum, 2016
14	58 y/M	Retroperitoneum, 2014	Paraganglioma	Recurrence, 2012, 2015	No
15	51 y/M	Retroperitoneum, 2016	Paraganglioma	Recurrence, 2018	Lung and liver, 2018
16	47 y/F	Neck, superior mediastinum tumors, 2016	Paraganglioma	Stable	No
17	42 y/F	Adrenal, 2005	Pheochromocytoma	Stable	Liver, 2007
18	42 y/F	Adrenal, 2006	Pheochromocytoma	Stable	No

\*This item refers to the metastasis to other organs and structures except for the spine.

## Symptoms and imaging findings

Local pain was the most common symptom, as a percentage of 72.2% (13/18), and 66.7% (12/18) presented with different degrees of neurological deficits, including myelopathy and/or radiculopathy (Table 2). There were twelve cases (66.7%) of nonfunctional PPGLs and six cases (33.3%) of functional PPGLS that aroused different degrees of hypertension. According to the preoperative imaging work-ups, the imaging manifestations of the spinal metastases were consistent with osteolytic lesions (Fig. 1). They usually had no signs of calcification inside the mass. PET/CT and bone scan revealed abnormal high concentrations within the mass (Fig. 1). There were ten cases (55.6%) of solitary vertebral body metastasis and eight cases of multiple vertebral bodies with or without other visceral and lymph node metastases (Table 2 and Fig. 1). The whole mobile spine and sacrum were candidates for metastasis, with the thoracic spine involving in ten cases, lumbar in seven, cervical in four and sacrum in one case.

Table 2  
Clinical features, treatment and outcomes of the metastatic spinal PPGLs.

Case No.	Spinal metastases, time	Symptoms	Karnofsky Performance score	SINS score	Surgical strategies*	Blood loss (ml)	Postoperative complications	ASIA score (pre/postop)	Adjuvant therapies	Follow-Up (months)
1	Multiple, Mar 2012	Local pain	60	13	PVP for T4 and T5	20	None	D/E	MIBG therapy	Alive with disease, 96
2	Multiple, Mar 2014	Local pain and ND	80	6	Decompression with PR for S1	800	None	E/E	Radiotherapy	Alive with disease, 84
3	C2, Jul 2015	Local pain	80	14	TR	1600	None	D/E	None	Alive with disease, 53
4	T2, Jul 2016	Local pain, ND and secondary hypertension	40	14	Decompression with PR	1200	None	C/D	MIBG therapy	Death, 12
5	L4, Dec 2018	Local pain, ND and secondary hypertension	40	18	Decompression with PR	1200	None	B/D	MIBG therapy	Death, 14
6	T12, Dec 2018	Local pain	50	6	PR	700	pulmonary infection Massive thoracic hemorrhage	A/D	None	Death, 4
7	T5, Nov 2019	Local pain, ND and secondary hypertension	40	16	Decompression with PR	1000	None	A/A	Radiotherapy	Death, 5
8	C1, Dec 2018	Local pain and secondary hypertension	80	18	PR	1200	None	E/E	Radiotherapy	Alive with disease, 27
9	T6, Oct 2010	ND	90	15	Decompression with PR	800	None	D/E	None	Alive with disease, 125
10	T12, Feb 2014	Local pain and secondary hypertension	80	9	PR	2000	Heart failure	D/E	MIBG therapy	Death, 10
11	Multiple, Jan 2015	Local pain and ND	60	9	Decompression with PR	1600	None	E/E	Chemotherapy	Death, 39
12	L3, May 2015	ND	80	6	Decompression with PR	200	None	E/E	Radiotherapy	Alive with disease, 70
13	Multiple, Jun 2016	ND	50	13	Decompression with PR	1100	None	C/C	MIBG therapy,	Death, 38
14	Multiple, Feb 2017	Local pain and secondary hypertension	60	12	Decompression with PR	300	None	E/E	MIBG therapy	Alive with disease, 100
15	C7, Oct 2018	ND	70	15	Decompression with PR	900	None	E/E	Radiotherapy	Alive with disease, 29
16	L1, May 2019	Local Pain	70	13	PR	800	None	E/E	Anlotinib	Alive with disease, 22

\*Instrumented fixation was performed in all cases but case #1 and #2.

PPGL stands for pheochromocytoma and paraganglioma; SINS, spinal instability neoplastic score; ND, neurological deficits; PR, partial resection of the tumor; TR, total resection of the tumor; PVP, percutaneous vertebroplasty; MIBG, metaiodo-benzylguanidine.

Case No.	Spinal metastases, time	Symptoms	Karnofsky Performance score	SINS score	Surgical strategies*	Blood loss (ml)	Postoperative complications	ASIA score (pre/postop)	Adjuvant therapies	Follow-Up (months)
17	T4, May 2007	ND	60	15	Decompression with PR	2500	None	C/E	None	Death, 35
18	L1, Aug 2010	Local pain and ND	40	14	Decompression with PR	900	None	A/A	Chemotherapy	Death, 17

\*Instrumented fixation was performed in all cases but case #1 and #2.

PPGL stands for pheochromocytoma and paraganglioma; SINS, spinal instability neoplastic score; ND, neurological deficits; PR, partial resection of the tumor; TR, total resection of the tumor; PVP, percutaneous vertebroplasty; MIBG, metaiodo-benzylguanidine.

## Surgical strategies and adjuvant therapies

Surgical options for the cohort included PVP in one case (case #1), *en-bloc* tumor resection in one case (case #3, and Fig. 2), and partial tumor resection in the other 16 cases, among whom 13 cases received instrumented fixation and neurological decompression procedures in 12 cases. The mean bleeding volume for open surgeries in 17 cases was 1105.9 ml. Histological and immunostaining results of the removed specimens were consistent with PPGLs (Fig. 3). Preoperative embolization was performed in three patients to mitigate the bleeding during the operation. The postoperative course was uneventful in 17 patients, but one patient (case #10) developed heart failure (Table 2).

Adjuvant therapies were offered according to the advice from our institutional multidisciplinary treatment (MDT) team on spinal tumors. Five patients were treated with radiotherapy, two patients treated with chemotherapy, six patients treated with iodine(131)-metaiodobenzylguanidine (<sup>131</sup>I-MIBG), and one patients treated with targeted therapy. The other four patients did not receive adjuvant therapies (Table 2).

## Follow-up results

Up to the last follow-up, eight patients died due to tumors or tumor-related events from five to 39 months after the operation, and one patient (case #6) died of pulmonary infection and thoracic hemorrhage four months after the operation. The 1-year OS rates were 77.8% and the median survival period was 39.0 months (Fig. 4). We found that survival period was related with numbers of spinal metastases (solitary *versus* multiple,  $p < 0.05$ , two-tailed student *t* test) and that significantly correlated with KPS ( $\rho = 0.537$ ,  $p < 0.05$ , Spearman's correlation analysis).

## Discussion

PHEOs and PGLs have the same cellular origin. They are generally slow-growing but all have potentials of recurrence and metastasis, according to the last WHO classification (2017 version) on endocrine tumors, which eliminated benign versus malignant discrimination [1, 3]. In the clinical practice, the patients of PPGL are usually latent until huge massing effect and/or metastasis has occurred. Previous researches identified some factors associated with higher risk of metastasis, including the primary tumor site and size, age at diagnosis and some specific genotypes [1, 3–7, 23]. The bone is one of the most common metastatic sites (72%), and the spinal involvement is one of the most deadly situation [24, 25]. Metastatic spinal PPGLs can significantly impair patients' activity of daily living and quality of life, due to the emergence of devastating skeletal-related events, such as pathological fracture and severe local pain and paraplegia [24]. Literature regarding this entity is lacking, so few references are currently available about the clinical features and treatment outcomes of the spinal metastasis. In this report, we described and analyzed a cohort of 18 patients with metastatic spinal PPGLs, hoping to provide references for the future clinical practice in this field.

This study found that the spinal PPGL was mostly seen in mid-aged patients (Table 1), and that 94.4% (17/18) cases were younger than 60 years. The study noted gender variation with a predominance of males (2.6/1). The time between the prior surgery of primary site and the spinal metastasis varied in a wide range, from one to 27 years. The clinical symptoms of the cohort were not pathognomonic. Local pain and neurological dysfunction were related to bony erosion and pathological fractures. As the primary PPGLs, metastatic lesions can also be functional, which are capable to secrete catecholamines (Table 2). Typical catecholamine-arousing symptoms include headache, palpitation, fatigue, flushing, sweating and/or paroxysmal hypertension [1, 4, 24]. In our case series, there were six patients (33.3%, 6/18) having secondary hypertension, which were presumably related to the metastases. Malignant hypertension may cause a series of hemodynamic disorders and vascular events [1, 25]. As previously reported, we prepared these patients with  $\alpha$ -adrenergic receptor antagonists, in avoidance of perioperative hypertension crisis and lethal vascular events [1, 4, 6, 25].

In this study, all cases had different extents of pathological fractures, from cortical destruction to severe vertebral collapse. The thoracic spine was the most susceptible metastatic sites, as a percentage of 55.6%. The imaging manifestations of metastatic PPGLs were consistent with other osteolytic lesions. CT and MRI scans are the modalities of choice to identify the involved vertebral segments. On CT films, the lesions usually a homogeneously osteolytic mass within the vertebral body, with paraspinal soft tissue mass in some cases. Different from the inflections and metabolic bone diseases, the surrounding cancellous bone is normal and no existence of sclerotic girdle. On MRI scans, the lesion is a mass with hypointensive signal on T1-weighted images and hyperintense signal on T2-weighted images (Fig. 1). Sometimes, we could find the signs of vascular flow void on T2 sequences, due to the heavy vascularity in some cases [16, 18].

The treatment strategies of the case series were schemed by our institutional MDT team in a concerted way. As for spinal metastases, a holistic set of treatment modalities are emphasized, including surgery, radiotherapy, chemotherapy and/or other anti-tumor therapies [4, 7, 11, 16, 25]. Preoperative evaluation was carried out by our MDT team. Especially, the patients' physical condition (KPS), the spinal instability neoplastic score (SINS), Tokuhashi and Tomita staging systems were evaluated, to facilitate the scheming of surgical strategies. Surgical resection is the most effective way to reduce the tumor

burden, and it is recognized as the treatment of choice for spinal PPGLs, especially for those with intractable local pain and neurological impairment [4, 16, 25–28]. Preoperative hemodynamic reconditioning is essential to the safety of the operation. Preoperatively, adrenergic blockade is typically accomplished with either a nonselective or a selective  $\alpha$ -adrenergic receptor antagonist (e.g., phenoxybenzamine, and doxazosin), usually started at least one week before surgery [7, 15, 27]. The  $\beta$ adrenergic antagonist should be administered to control tachycardia after adrenergic blockade has been effective in normalizing blood pressure. Another precaution needs to be taken into account in the surgical planning of metastatic spinal PPGLs: the vascularity of the tumor. This spinal metastasis tends to be hypervascular, which can lead to significant blood loss intraoperatively. Our case series had an over 1100 ml of blood loss averagely. It has been suggested that preoperative embolization of the supplying arteries 24h-48 h before surgery can minimize blood loss [18].

Palliative surgeries, including separation surgeries, neurological decompression and vertebral augmentation procedures, are the mainstay of treatment choice, for the patients with multiple metastases, recurrent spinal lesions, acute neurological deterioration and intractable local pain. In our case series, 17 patients underwent palliative surgeries, and the main surgical goals were to restore the spinal stability with or without decompress the neurological elements. In recent years, separation surgery has gained wide acceptance for metastatic spinal tumors. In our series, the surgeries of 13 patients were performed under the principles of separation surgeries. Within the operation, two therapeutic goals were achieved, namely sufficient neurological decompression and sparing a safe distance for radiotherapy. Percutaneous vertebral augmentation procedure was proven to be an effective method to control the local pain for the patients with no symptoms of neurological impairment (case #1).

For the patients with solitary spinal metastasis, total resection shall be attempted. PPGLs have a high recurrent rate when partially resected. Richter et al. [13] reported that total *en-bloc* spondylectomy complemented with radiotherapy led to tumor-free survival at the 10-year follow-up in their patient. Yin et al. [16] shared a series of 18 patients with spinal PGLs and 15 of them received total tumor resection. The surgical outcomes were encouraging, with a relapse-free period over 40 months. However, given the intricate growth pattern and encasement of neural tissue by spinal metastases, intrusion to the spinal cord and paraspinal vital structures, and heavy bleeding during the surgery, total resection is not always feasible. Therefore, we should make a reasonable choice, based on the balance of the safety and efficacy of tumor resection for each surgical option. In recent years, the advances in the surgical tools and instruments, such as 3D printing prosthetic vertebra and ultrasonic bone scalpel, facilitate the challenging procedure of tumor resection [29, 30]. Even in the procedures of PR, maximal tumor mass resection should be attempted, to reduce the tumor load and spare more space in avoidance of relapse of neurological compression.

Locoregional recurrence or progression is a big concern for patients with spinal tumors. When removal of the entire tumor is not possible, radiation treatment is recommended [1, 16, 24]. The doses delivered to our cases ranged 35 Gy to 45Gy. The dose was referred to studies performed on giant cell tumors and chordomas. Overall, among the patients treated with radiotherapy in our study, four patients survived more than two years and one died five months after the indexed surgery. For the past several decades, systemic therapies for PPGLs have been mainly referred to  $^{131}\text{I}$ -MIBG. Current knowledge of systemic therapies relies on the results of a few mainly retrospective studies [25]. Up to 70% of metastatic PPGLs do not respond to the treatment [32]. Overall, six patients in our study were treated with  $^{131}\text{I}$ -MIBG, while three patients died ten to 14 months after the therapy, one died 38 months later and the other two patients enjoyed a long survival. The outcomes suggest that the use and efficacy of  $^{131}\text{I}$ -MIBG therapy in spinal PPGLs needs further exploration and verification.

The use of chemotherapy is controversial. The chemotherapeutic drugs are various for metastatic PPGLs, including almost all currently available agents. The single or combined use of chemotherapeutic drugs is practically experience based given the rarity of the diseases. CVD regimen (cyclophosphamide, vincristine and dacarbazine) is recommended as the best protocol. Ayala-Pamirez et al. [24] reported that 5-year OS rate of PPGLs patients who received CVD regimen was 51%. A meta-analysis found that only 37% of malignant PPGLs showed response to the regimen [33]. U-King-Im et al [32] reported successful therapeutic use of octreotide in a patient with carotid body PGL that metastasized to multiple vertebrae. Mertens et al. [11] demonstrated the successful regression and palliation of metastases of PGL with chemotherapy, particularly with the CVD regimen. However, the application and efficacy of chemotherapy after the surgeries were not well established and in need of support from high-quality, large-scale clinical trials. Radiotherapy is a valuable adjuvant therapy for spinal tumors after the operation, to provide a better locoregional control for the cases with residual tumor mass. In our cohort, five out of 13 patients who underwent separation surgeries received radiotherapy after the operation, among whom one patient died five after the therapy and the other four patients manifested a satisfying local control after more than 2 years of follow-up.

The present study has several limitations. Firstly, it is a retrospective study with a small sample size. Thus, the results of this study need further examination and references with caution.. Secondly, the primary tumors were operated many years ago in other hospitals, so access to information related to surgical margin status, the size of the primary tumor, and treatment after primary tumor resection was limited. Thirdly, it was difficult to obtain the continuity, regularity, periodicity and dose of radiotherapy and chemotherapy after the indexed surgeries for spinal PPGLs, because some of adjuvant therapies were not implemented in our hospital.

## Conclusions

This study described the clinical features, surgical strategies and outcomes of metastatic spinal PPGLs. The spinal metastases were generally latent and did not be recognized until local pain and the occurrence of neurological deficits. Functional spinal PPGL is a big concern during the surgical preparation and hemodynamic reconditioning with  $\alpha$ -adrenergic receptor antagonists recommended as the management of primary PPGLs, to avoid severe vascular events. PPGLs are very vascular tumors, so preoperative embolization of supplying vessels is recommended to mitigate the blood loss during the operation. The median survival period was 39 months and 1-year OS rate was 77.8%. Surgery is the treatment of choice for spinal PPGLs, and palliative surgery combined with  $^{131}\text{I}$ -MIBG and/or radiotherapy was proven a feasible and safe therapeutic strategy, with fair outcomes.

## Declarations

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### Author contributions

S. Du and P. Hu designed the study, reviewed the patients, collected and process the clinical data, and drafted the manuscript. S. Yang and H. Zhuang reviewed the patients and collected the data. F. Wei designed the study, selected the patients, processed the data and supervised the study. X. Liu and Z. Liu supervised the data collection and processing. All authors reviewed this manuscript.

### Ethics statement and approval

The study was approved by the institutional ethics committee of Peking University Third Hospital, and performed in accordance with the ethical standards of the Declaration of Helsinki (1964) and its subsequent amendments.

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### Competing interests

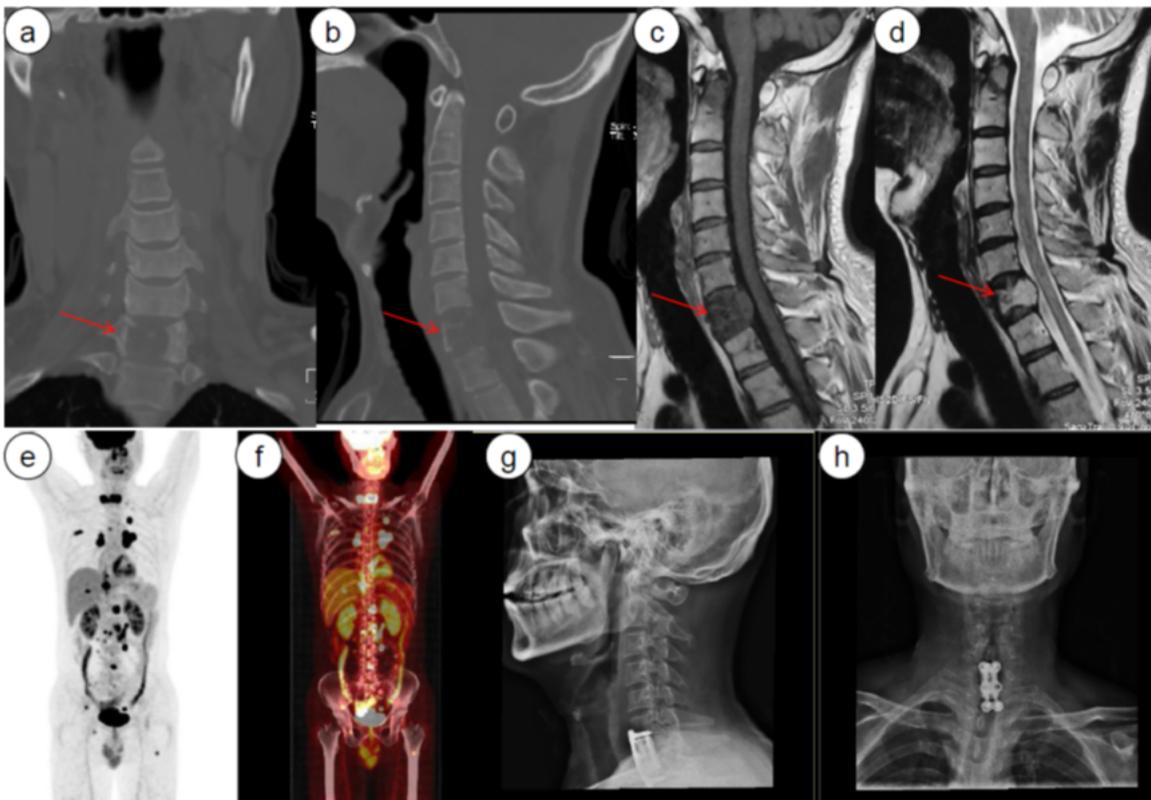
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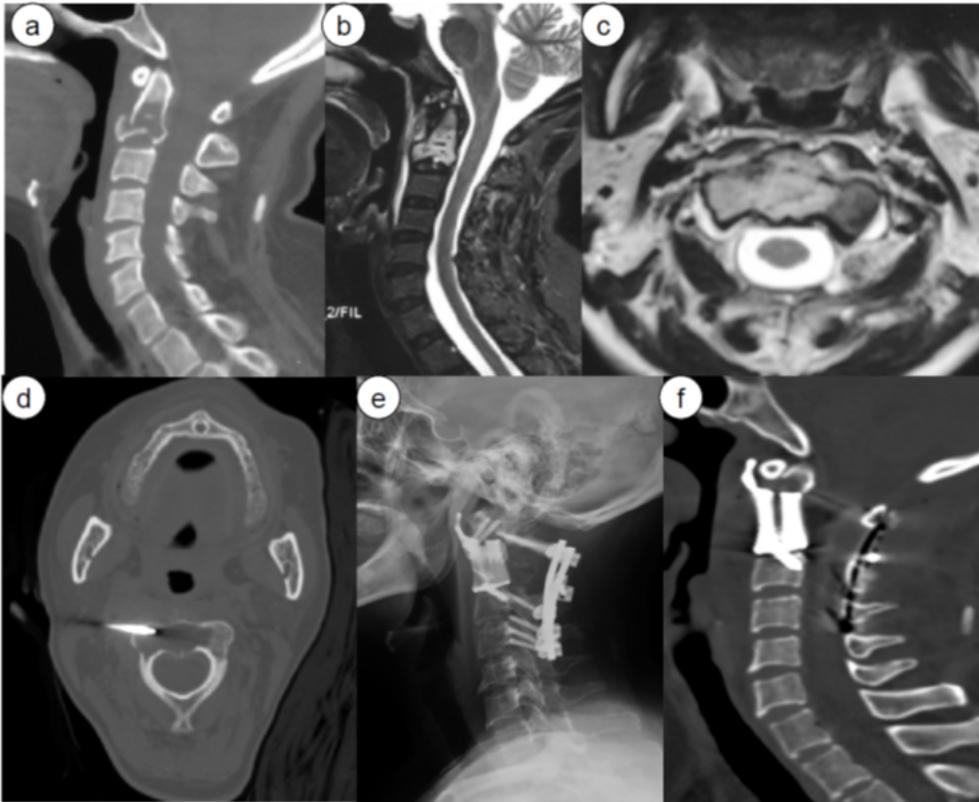
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## Figures

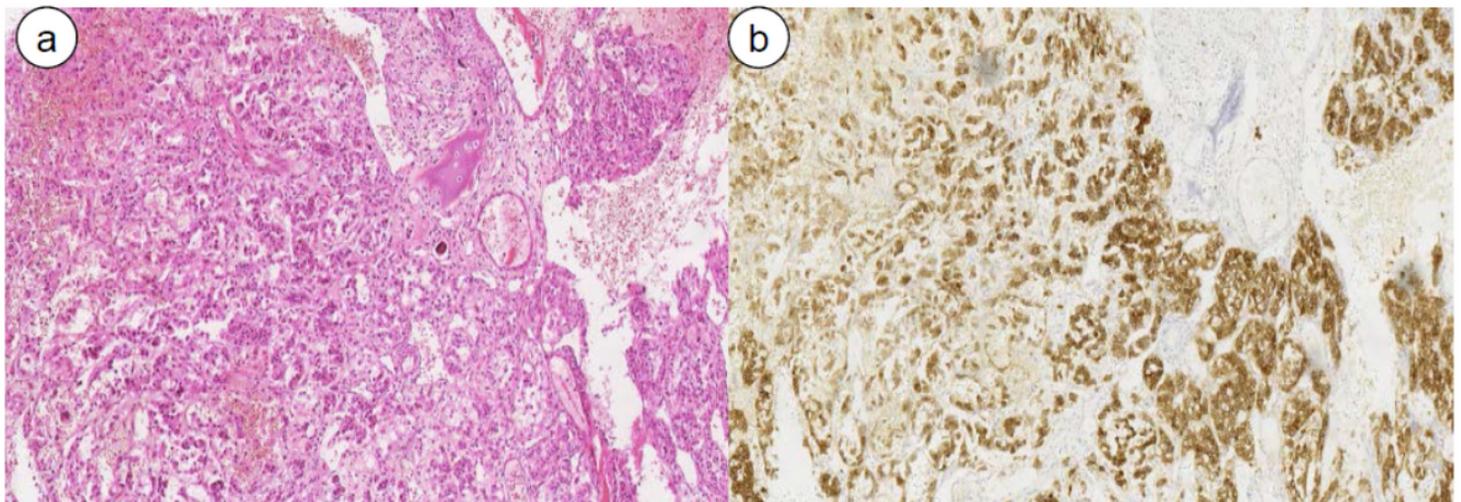


**Figure 1**

Imaging presentation of case #15. CT reconstruction films revealed an osteolytic lesion inside the C7 vertebral body (arrows in a and b). The lesion showed hypo-intensive signal on T1-weighted MRI sequences and hyper-intensive signal on T2-weighted sequences (arrows in c and d). PET/CT revealed elevated uptake of  $^{18}\text{F}$ -FDG in multiple foci, including systemic lymph nodes, lung, liver, pelvis and spine (e and f). The patient received C7 corpectomy and spinal reconstruction with 3D-printing prosthetic vertebral body (g and h).



**Figure 2**  
 Presentation of total tumor resection (case #3). Preoperative imaging work-up revealed an osteolytic lesion inside C2 vertebral body (a, b and c). The patient underwent CT-guided biopsy (d) and the result was consistent with paraganglioma. There was no signs of other metastasis by PET/CT, so a total tumor resection was obtained via one-staged posterior and anterior surgical approach. The reconstruction of anterior spinal column was made with a customized 3D-printing vertebral body (e and f).



**Figure 3**  
 Histological result of spinal lesion. Microphotography showing characteristic nests of tumor cells separated by vascular septa (Zellballen) with cells showing significant nuclear pleomorphism with prominent nucleoli (H&E, original magnification x20). Synaptophysin immunostaining shows strong, diffuse cytoplasmic staining in the tumor cells. (immunostaining, original magnification x20).

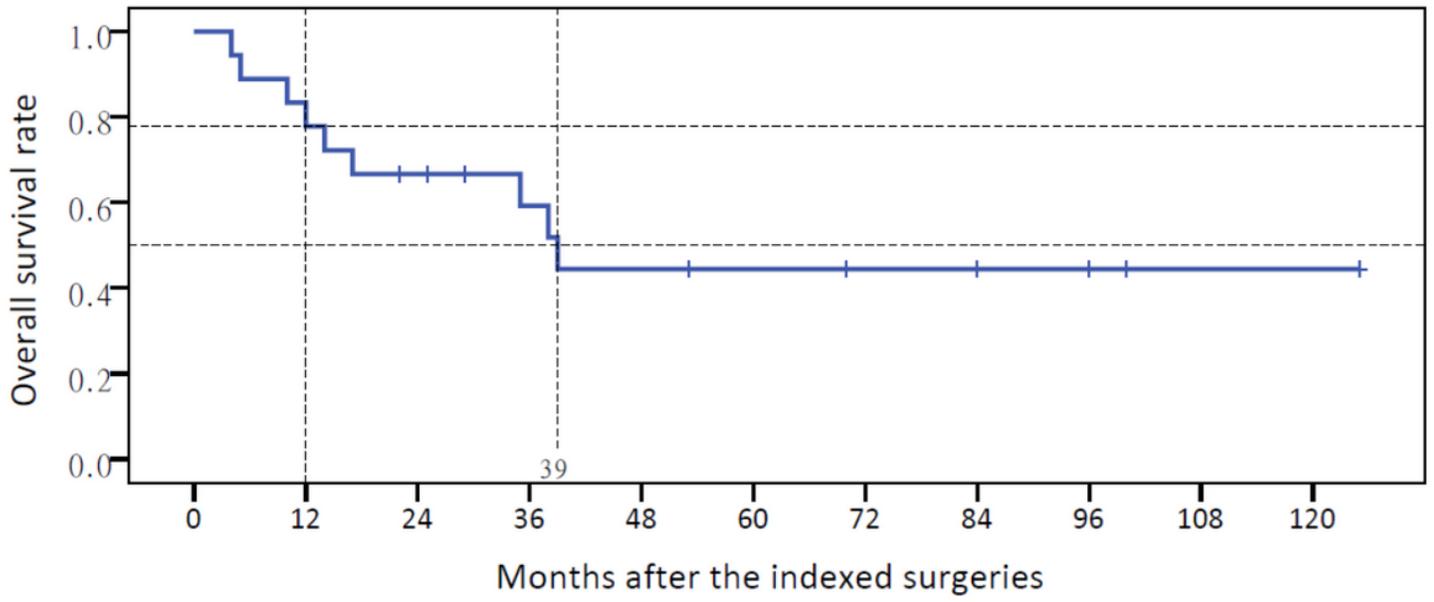


Figure 4

Kaplan-Meier survival curve of the cohort.