

Treatment and outcome of metastatic paraganglioma of the spine

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Abstract

Background Spinal metastatic paraganglioma (MPG) is rare and only reported in individual case reports. The low incidence makes it difficult to define appropriate therapy and prognosis. Our study illustrated the largest series to discuss the possible treatment and outcomes of patients with spinal MPG.

Methods A retrospective study of 15 patients with spinal MPG who were surgically treated between 2005 and 2014 was performed. Three surgical modalities were applied, and radiotherapy and chemotherapy were utilized as adjuvant therapy.

Results The mean patients age was 40.9 (range 23–58) years. The period between primary surgery and spinal metastasis averaged 8.2 (0.5–15) years. Lesions were mainly located in cervical spine (2), thoracic spine (8), lumbar spine (3), and sacrum (2). The mean follow-up period was 35.0 months. Lesion progression was detected in nine patients, whereas five patients (33.3%) passed away. For solitary spine, multiple bone and both bone and nonosseous metastasis cases, the mean progression-free

survival was 41 (range 9–56), 22.5 (range 12–38) and 8.3 (range 3–18) months, respectively.

Conclusions The cases presented in the current study highlight the crucial role of surgery. Total en bloc for solitary spinal MPG could result in a satisfying prognosis and piecemeal total resection with postoperative radiotherapy could be an alternative therapy. Radiotherapy and chemotherapy were advocated, especially for the multiple metastasis.

Keywords Metastatic paraganglioma · Spine · Retrospective study · Total en bloc spondylectomy · Adjuvant therapy

Introduction

According to the World Health Organization, paraganglioma (PG) is defined as a tumor arising from the paraganglia outside the adrenal medulla [1]. PG, a relatively rare tumor and mainly occurring in the head, neck, thorax, abdomen, and pelvis, accounts for about 0.3% of all neoplasms with an annual incidence of 1/100,000 [2, 3]. It is a slow-growing tumor that often presents as a painless mass in the fifth or sixth decade of life [4], and often recurs after incomplete surgical resection. Although regarded as benign in nature, PG possesses metastatic possibility which is a marker of malignant transformation [5, 6] as there are no molecular or cellular markers existing for determining whether PG is malignant [7–9]. Metastatic PGs (MPG) are among the solid tumors that most frequently spread to the skeleton, with spine being the most frequently affected site [10].

Spinal MPG was uncommon and sporadically reported in the English literature [2–6, 11–17] with no case series

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study. Spinal lesions could cause bone destruction or compression of the spinal cord, clinically manifesting as pain or neurological deficits. Surgical treatment including subtotal (curettage) or total resection with/without adjuvant radiation was recommended by some authors [1, 2, 15] which could provide limited information to the treatment of spinal cases. The probably epidemiological and treatment features of spinal MPG are not clear as well. Here, we present our experience of 15 consecutive spinal MPG patients with middle to long-term follow-up, trying to illustrate the clinical features and different treatments and outcomes of spinal MPG.

Materials and methods

A retrospective review of 15 patients with spinal MPG who were surgically treated in our institution between 2005 and 2014 was performed. Surgery was performed in all patients using different surgical modalities according to the Tokuhashi [17] and Tomita [18] scoring system. We focused on the tumor progression status and overall survival (OS) after the initial surgery in our center, and progression-free survival (PFS) was defined as the interval between the date of surgery and the date of tumor progression or other new metastasis. This study was approved by the Ethics Committee of the hospital, and informed consent was obtained from the surviving patients or family members of those who had passed away.

The clinical information and surgical data of 15 patients are shown in Table 1. All patients had undergone primary surgery with the pathological diagnosis of extra-adrenal PG before admission into our center before. The diagnosis of spinal MPG was confirmed by three criteria: (1) identified on a plain standard X-ray, computed tomography (CT), magnetic resonance imaging (MRI), bone scan, or fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scan; (2) had the primary PG treatment history; (3) identified in a pathological specimen from a biopsy or open surgery. The preoperative neurologic status was classified according to the Frankel score [20]. The life quality of all patients was assessed with the Karnofsky score system [21]. Surgery through individualized approaches was conducted by the surgery team led by professor Xiao. The screw-rod system was used to reconstruct stability of the spine [22], and an anterior titanium mesh and plate was applied to patients with cervical lesions.

Regular radiographic assessment (X-ray, CT or MRI) was performed at 3, 6, and 12 months after surgery, every 6 months for the next 2 years, and then annually for life. For patients showing tumors progression, PET-CT was recommended. Follow-up data were obtained from office

visits and telephone interviews. In the follow-up visits at 3 months after surgery, neural function and lift quality were re-evaluated based on the Frankel score system and Karnofsky score system. The follow-up period was defined as the interval from the date of surgery to death, or until September 2016 for patients alive.

Results

Patient features

Our series comprised 13 men and 2 women, with an average age of 40.9 (ranging 23–58) years. Lesions were mainly located in cervical spine in two cases, thoracic spine in eight cases, lumbar spine in three cases, and sacrum in two cases. In addition, solitary spine, multiple bone and both bone and nonosseous metastasis occurred in 7, 4 and 4 patients, respectively. Localized pain was the most consistent complaint, with a mean duration of 8.8 months as the preoperative symptom. Additional symptoms included catecholamine-related symptoms with remarkable hypertension (180/110 mm Hg) in one patient (Case 5), and varying degrees of cord compression at diagnosis in 10 patients.

The mean follow-up period was 35.0 (range 6–118) months. Lesion progression was detected in 9 patients (60%) with a mean PFS of 19.6 (range 3–56) months after the initial surgery in our center, whereas 5 patients (33.3%) passed away with the mean period of 38.2 (range 6–118) months. For solitary spine, multiple bone and both bone and nonosseous metastatic cases, the mean PFS time was 41 (range 9–56), 22.5 (range 12–38) and 8.3 (range 3–18) months, respectively (Fig. 1a).

Treatment history

Before admission into our center, all patients had undergone total resection of primary tumors locating at the retroperitoneum ($n = 10$, 66.7%), para-aortic region ($n = 2$, 13.3%), and upper mediastinum ($n = 3$, 20.0%). The mean maximum diameter of the lesions in CT images was 6.3 (range 3.5–8.5) cm with 2 lesions less than 5 cm. The period between previous surgery and spinal metastasis averaged 8.2 (0.5–15) years (Table 1).

Radiologic study

Osteolytic change of spinal lesion was common in X-ray radiography and CT scans. MRI is considered to be the superior imaging modality for extra-adrenal PG [16], but it cannot specifically distinguish spinal MPG from other spinal malignant tumors. In our series, giant cell tumors

Table 1 Patients' demographic details of MPG of the spine

No.	Age (years)/gender	Primary surgery time (years)/location	Primary PG Tumor size (cm)	DS (m)	LC	F-S pre	Kamofsky score pre	Tokuhashi score	Tomita score
1	34/M	10/retroperitoneum	6.5	3/Pain and paraparesis	T2, femur	D	50	9	3
2	47/M	10/upper mediastinum	6.4	3/Pain	T10, ribs	E	70	10	3
3	47/M	10/upper mediastinum	8.5	3/pain	T3	E	80	11	3
4	58/F	11/retroperitoneum	3.5	36/low back pain, sphincter disturbance	S1	D	60	10	3
5	23/M	0.5/retroperitoneum	7.6	4/pain HBP and headache	T2	E	80	10	3
6	24/M	6/para-aortic	7	12/low back pain and paraparesis	T2, L3, S1, lung	D	70	7	5
7	29/M	9/retroperitoneum	6.5	1/Pain, weakness, and numbness in right arm	C2, L2–4, tibia, lung	D	60	6	5
8	58/F	15/retroperitoneum	6	12/low back pain and paraparesis	L4, liver	D	60	9	4
9	37/M	3/para-aortic	5.5	2/pain and paraparesis	T1	D	60	11	3
10	25/M	0.5/retroperitoneum	4.5	2/pain, paraplegia for 1 week	T7, lung	B	30	7	4
11	37/M	3/right mediastinum	6.6	24/pain and paraparesis	T7-8	D	70	10	2
12	64/M	5/retroperitoneum	8	3/neck pain and dysarthria	C3-4	D	80	10	2
13	40/M	18/retroperitoneum	6	12/pain, paraparesis for 2 ms	T3	D	70	10	2
14	56/M	12/retroperitoneum	5.5	12/low back pain	L2, L4, S1	E	80	9	3
15	35/M	10/retroperitoneum	6.9	2/low back pain	S1	E	80	11	2
x	40.9	8.2	6.3	8.8					
No.	Age (years)/gender	Surgical approach	Treatment	F-S post (3 ms)	Kamofsky score post	Complications	FU (m)	LP (m)	Last status (m)
1	34/M	P	Total + RT	E	80		27	Yes (27)	AWD
2	47/M	P	Total + RT	E	90		48	Yes (38)	AWD
3	47/M	P	En bloc	E	90	Pleural tear	42	No	NED
4	58/F	P	En bloc + RT	E	80	Constipation	54	No	NED
5	23/M	P	Total + RT	E	90	Wound infection	12	No	NED
6	24/M	P	Subtotal + CT	E	80	Fever	6	Yes (3)	DEAD (6)
7	29/M	P + A	Subtotal + CT	E	85		35	Yes (18)	DEAD
8	58/F	P	Subtotal + CT	E	90		9	Yes (6)	AWD
9	37/M	P + A	Total + RT	E	90		118	Yes (56)	DEAD(118)
10	25/M	P	Total + RT + CT	C	70	CSF leakage	8	Yes (6)	DEAD
11	37/M	P	Total + RT	E	90	CSF leakage	21	Yes (9)	AWD
12	64/M	P	Total + RT	E	100		30	No	NED

Table 1 continued

No.	Age (years)/gender	Surgical approach	Treatment	F-S post (3 ms)	Kamofsky score post	Complications	FU (m)	LP (m)	Last status (m)
13	40/M	P	En bloc	E	100	Pulmonary edema	46	No	NED
14	56/M	P	Subtotal + CT	E	90		24	Yes (13)	DEAD
15	35/M	P	Total + RT	E	90		50	No	NED
x	40.9						35		

MPG malignant paragangliomas, x mean, M male, F female, DS duration of preoperative symptom, LC location, C cervical, T thoracic, L lumbar, S sacral, HBP high blood pressure, F-S Frankel score, pre preoperation, P posterior, A anterior, subtotal subtotal resection, total total piecemeal resection, En bloc en bloc spondylectomy, RT radiotherapy, CT chemotherapy CSF cerebral spinal fluid, FU follow-up, LP lesion progression, NED no evidence of disease, AWD alive with disease

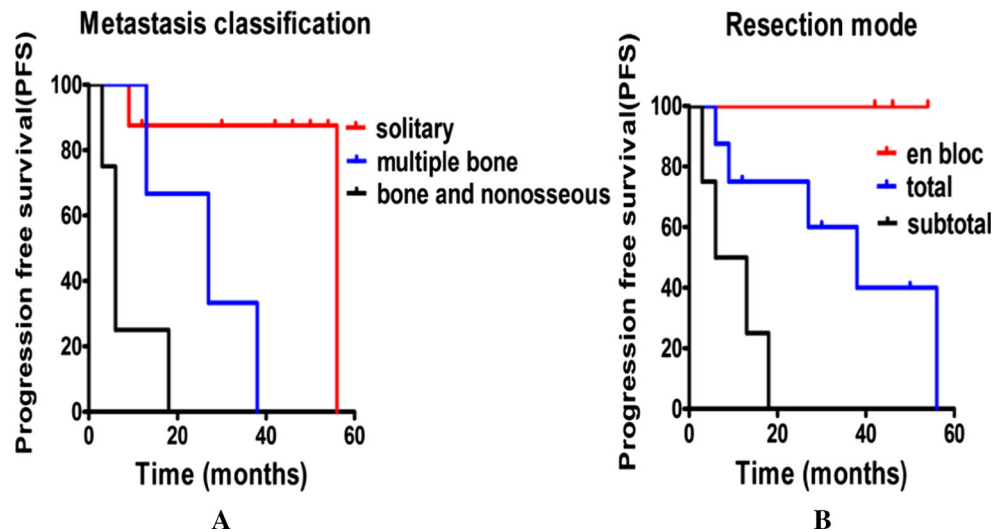
Case 7 and 15), osteosarcoma (Case 6), and neurogenic tumor (Case 10) were misdiagnosed on preoperative MR images. Hypointense or iso-intense signals on T1 and hyperintense signals on T2 were common findings (Fig. 2). Functional imaging studies such as FDG-PET/CT were performed in 8 patients with multiple lesions, showing an unusual concentration of 18F-FDG in the lesions. 3 patients underwent bone scans, which was also useful for detecting multiple lesions of the bone.

Treatment and outcome

Preoperative fine-needle biopsy and intraoperative fast pathologic examination were performed in six and nine patients, respectively, but the results were not all consistent with the final diagnosis of MPG. Only eight intraoperative fast pathologic examination was consistent with the diagnosis of MPG, and the results in the other seven patients suggested the diagnosis of malignancy or metastasis. Noncompetitive alpha-blockade antagonists were given 2 weeks before surgery in patient (Case 5) who showed catecholamine-related symptoms to control hypertensive crisis during surgery. Selective arterial embolization was used through digital subtraction arteriography (DSA) 24–48 h before surgery in eight patients whose lesions occurred below T4 in our center.

For solitary metastatic lesion, we preferred total resection including piecemeal total resection and total en bloc spondylectomy (TES). TES was performed in three patients in our series including one patient with contaminated margins that supplemented with posterior adjuvant radiotherapy. Eight patients received piecemeal total resection to remove the bone lesions to the maximum extent assisted with local radiotherapy and for the lung metastasis (Case 10) that could not be surgically removed, chemotherapy was added. Decompression and reconstruction surgery was applied to four patients with multiple metastasis combined with cyclophosphamide–dacarbazine based regimens chemotherapy according to the Tokuhashi and Tomita scoring system. The mean PFS time for TES, piecemeal total, and subtotal resection cases was 47.3 (range 42–54), 28.5 (range 6–56) and 10 (range 3–18) months, respectively (Fig. 1b). Intraoperative blood loss ranged from 600 to 3300 (mean 1978) ml. All surgical procedures were performed uneventfully without severe blood pressure fluctuations. The local pain symptom resolved or disappeared in all patients after surgical treatment. The neurological status at 3-month follow-up showed that the Frankel score improved by 1–2 grades. Catecholamine-related symptoms in Case 5 including the unusual hypertension and headache disappeared immediately after operation, and showed no relapse during the follow-up period.

Fig. 1 Graphs of survival curve showing the progression-free survival in different metastatic classification (a) and resection mode (b)



The treatment modalities and outcomes for nine lesion progressive patients are listed in Table 2. Two patients selected the revision surgery at least once in our center (Case 9 and 11). Case 2 who had the T3 vertebrae metastasis again accepted the revision surgery combined with the adjuvant radiotherapy. Conservative treatments, including cyclophosphamide–dacarbazine based chemotherapy, local radiotherapy and analgesics (such as Morphine), were applied to the other six patients to alleviate the symptoms and prolong the lives.

Pathology

Histologic diagnosis was obtained in all our cases. In patients receiving TES, all cutting margins (gross normal surrounding tissue) were submitted for pathologic examination at the same time and 1 of 3 showed contamination margins. Histo-morphologic features of the MPG were similar to the primary PG. Immunohistochemical study showed that the lesions were mostly positive in Vimentin, CD56, chromogranin A, NSE, S-100, synaptophysin and Ki-67 and negative in cytokeratin, epithelial membrane antigen and CK-pan. The value of Ki-67 was commonly positive with a range of 3–30% and it increased in three patients who had revision surgery for the progressive spinal lesions.

Discussion

PGs are slow-growing tumors with the risk of malignant transformation [25] which require long-term clinical and radiographic follow-up (MRI and CT scan). Unlike other malignant cancers with lung or liver being the first metastatic organ, the most common site for MPG was skeleton

[10], especially spine, and in our cases nine patients showed the spinal metastasis only (including two multiple metastasis) and six patients presented with multiple metastasis. The reasons that PG cells were inclining to spread to the skeleton were still unclear, but the homing mechanism has been proposed because of strong CXCR4 and CCR9 expression [10, 23].

Although spine is the most frequently metastatic site, due to the low incidence of the primary PGs and only 10–17% of them evolving to metastasis, reports about MPG involving the spine are quite rare and the epidemiological features, treatment protocols and prognosis are ambiguous. Montserrat Ayala-Ramirez et al. [10] had reported that the median OS was 12 years for patients with only bone metastasis, whereas 5 years for patients with both bone and nonosseous metastases which indicated the better prognosis for bone metastatic patients. Because of the complex anatomical constraints and sometimes lesion-related spinal cord injured symptoms (paraplegia or paraparesis), the treatment for spinal lesions was tougher than extra-axis bone lesions. In this study, we analyzed the clinical data of 15 cases of spinal MPG and reported our treatment experience which could provide more information about this disease. To the best of our knowledge, this is the largest cohort of patients with spinal MPG so far.

Primary PGs usually arise in the fifth or sixth decade of life [4], but our cohort had a broad age demographic structure with a mean age of 40.9 (range 23–58) years. In our series, 11 (73.3%) of the 15 patients were below 50 years which seems to indicate that spinal MPG is more likely to occur in young patients with PG treatment history. This is an interesting phenomenon worthy of further research. We also found male gender predominance (13:2), which is similar to primary PG [17]. Retroperitoneal PG showed easier later metastasis than other primary PG,

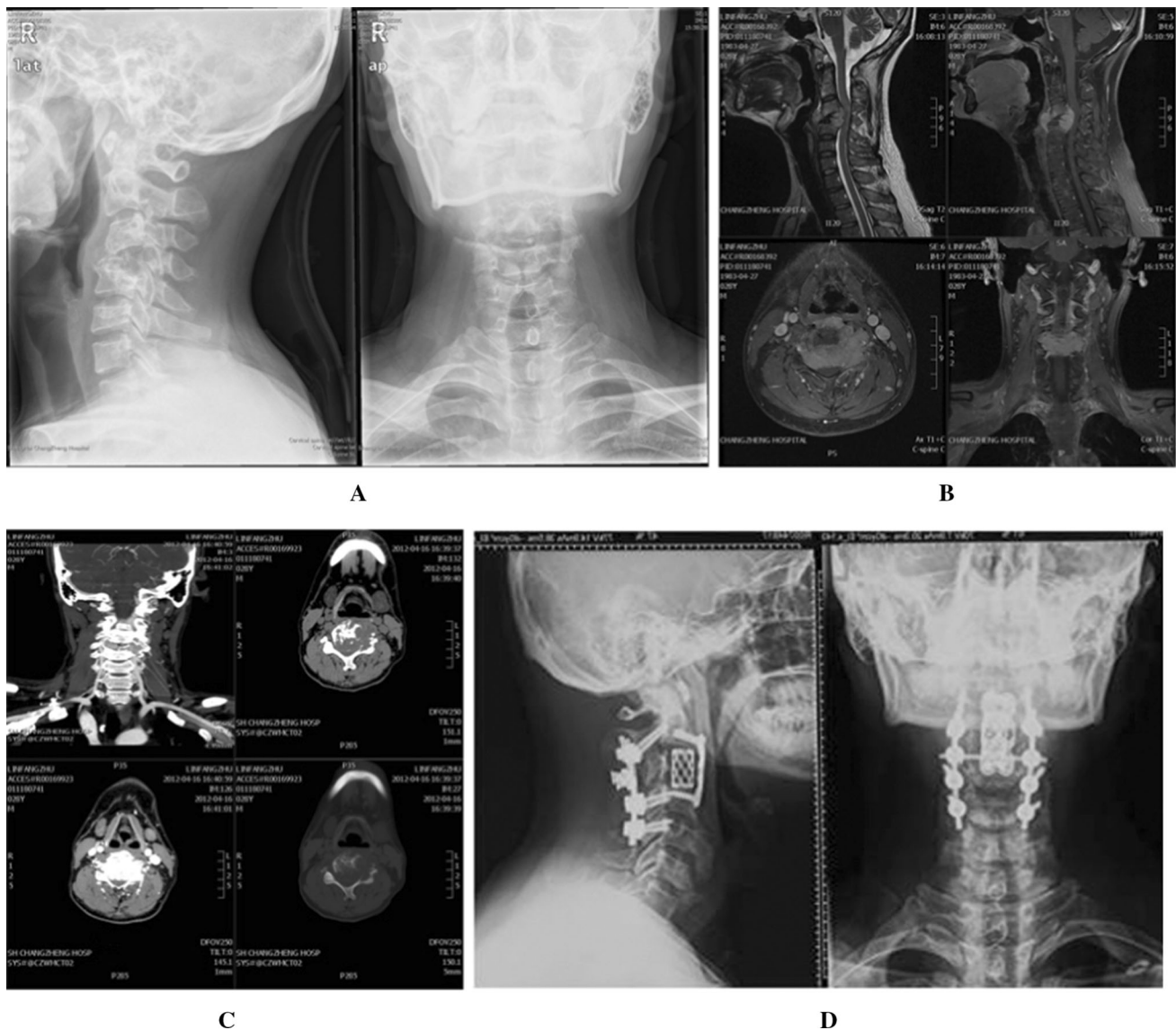


Fig. 2 Radiologic images (Case 12). **a** Preoperative X-ray: an osteolytic lesion in C4; **b** MRI images: hyperintense in T2 and enhancement after gadolinium injection in C3-4; **c** CT images: lytic

changes and compression fracture; **d** Postoperative X-ray: reconstruction by anterior titanium mesh and plate and posterior screw-rod system from C2 to C6

accounting for 66.7% of all our cases. Metastasis could be presented at the time of diagnosis of the PG or years later [7, 14] and the mean duration from surgical resection of the primary tumor to spinal metastasis was 8.2 (0.5–15) years. As a result, long-term follow-up was recommended for patients who had the PG treatment history, especially retroperitoneal ones. With respect to location, spinal MPG was most likely to infringe up on the thoracic spine in our series (53.3%), which is in line with previous studies in the literature [24].

Spine MPG usually induces intractable local pain and put patients at risk of spinal cord compression [13, 17, 25]. In our cases, local pain is the most common symptom and ten patients (66.7%) presented with varying degrees of cord

compression at diagnosis. Less frequently, spinal MPG could present with catecholamine-related symptoms, such as elevated blood pressure, diaphoresis, and headache [15] and only one patient (Case 5) showed these symptoms which indicated the low incidence of the catecholamine release for spinal MPG. The radiographic appearance (X-ray, CT, MRI) of spinal MPG is nonspecific and somewhat similar to that of other lytic bone lesions; however, certain findings can be integral in establishing the diagnosis in the setting of primary PG surgery history. Compression fracture was common in our cases (66.7%). 18F-FDG-PET/CT has been used for diagnosis of various neoplasms including MPG [26]; it is also the most effective method to evaluate the metastasis of PGs [10].

Table 2 Treatment and outcomes for progressive lesions

Case no.	Recurrent Location	recurrent time (m)	Previous resection mode	Treatment strategies	FU (m)	Last status (m)	Reasons of death
1	T2	27	Total	RT	27	AWD	
2	T3	38	Total	Surgery and RT	48	AWD	
6	L3	3	Subtotal	RT and CT	6	DEAD (6)	Severe pneumonia
7	C2-3	18	Subtotal	RT, CT and analgesics	35	DEAD	Multiple metastasis
8	L4	6	Subtotal	RT and CT	9	AWD	
9	T1	56	Total	56 months recurred (T1)-revision surgery 72 months recurred (T1–2)-revision surgery and AT 116 months recurred-conservative treatment	118	DEAD (118)	Spinal cord compression and paralysis
10	T7	6	Total	RT	8	DEAD	Pulmonary embolization
11	T7-8	9	Total	Revision surgery and RT	21	AWD	
14	L2	13	Subtotal	RT and CT	24	DEAD	Multiple metastasis

C cervical, T thoracic, L lumbar, S sacral, *subtotal* subtotal resection, *total* total piecemeal resection, RT radiotherapy, CT chemotherapy, FU follow-up, AWD alive with disease

There is no doubt that a preoperative biopsy can facilitate surgery protocol formulation, especially for the solitary lesion. Thus, it is regrettable that patients forego it based on fear of possible nerve damage. Surgical treatment is the foundational treatment for spinal MPG. Adequate catecholamine blockage and an excellent anesthesia are necessary to conduct an uneventful surgery, especially for MPG secreting catecholamines [14]. The strategy must be carried on the adequate study of the tumors according to the Tokuhashi and Tomita scoring system. Alexander Richter et al. [6] had reported TES and reconstruction of a solitary spinal MPG in L1 vertebral body with a follow-up time for 10 years which indicated the significance of TES. As a result, with surgical and internal fixation techniques rapidly improving, total resection, even TES when possible, is necessary to treat spinal MPG, especially solitary lesion, to achieve satisfying results. In some cases, an ideal en bloc resection could not be achieved unless the spinal cord and nerve root are killed or multiple metastasis that could not be removed totally, piecemeal total resection or curettage was conducted combined with adjuvant radiotherapy and/or chemotherapy. The mean PFS time for piecemeal total resection combined with radiotherapy was lower than TES and, however, higher than subtotal resection which may indicate that it is an alternative choice when multiple bone metastasis occurred which could not be removed by TES. For bone and nonosseous metastatic patients, although the neurologic status improved and intractable pain resolved after decompression surgery, the prognosis was not satisfied with the mean follow-up time of 18.5 (range 6–35) months. Therefore, although the

lesions were metastasis, TES for solitary spinal MPG could result in satisfied prognosis and piecemeal total resection with postoperative radiotherapy can be an acceptable alternative therapy when en bloc resection is not feasible.

Immunohistochemically, there were no reliable markers to predict the malignant potential of PG [12]. Lui et al. [27] found that the Ki-67 index (>3%) was a useful marker for predicting malignancy. All our cases showed the index of Ki-67 higher than 3%, and as high as 30%. Also, for the progressive spinal MPG, 3 cases receiving revision surgery showed the increase of Ki-67 index which may indicate the positive association between the Ki-67 and the possibility of metastasis. In our cohort, 13 primary PG specimens were bigger than 5 cm in maximum diameter which accorded with reports that bigger than 5 cm was more likely to transfer to malignancy and metastasis [7, 10].

Radiotherapy and chemotherapy using as adjuvant treatment for spinal MPG were usually advocated [2, 12, 29, 30]. Radiotherapy with a total of 30–50 Gy had been reported to be helpful for the treatment of spinal MPG [2, 6, 12, 15, 30]. Mertens et al. [28] had reported initial chemotherapy including cyclophosphamide, vincristine and dacarbazine could alleviate symptoms at metastatic sites. Patel et al. [29] proposed the clinically beneficial in MPG patients by cyclophosphamide–dacarbazine based regimens in spite of no obvious benefits in OS. As a result, although litter information could be concluded from our study, for the spinal MPG, especially multiple metastatic ones, radiotherapy and chemotherapy were helpfully supplementary therapy.

The limitation of the present study is its retrospective nature, being performed about ten years. Surgical

techniques and various kinds of radiotherapy and chemotherapy have been considerably more developed during the follow-up period which may aid in safely accomplishing tumor removal and improve the prognosis. Additionally, the number of our study was too small to conduct the statistic analysis. Although 15 cases appear to be a small number for the study of metastatic lesions, the present cases constitute the first reported clinical series concentrating on surgery-based treatment and prognosis of spinal MPG which may aid the improvement of treatment of this rare disease.

Conclusion

MPG in the spine is rare, and pain in the involvement site is the most common complaint. The cases presented in the current study highlight the crucial role of surgery. TES for solitary spinal MPG could result in a satisfying prognosis and piecemeal total resection with postoperative radiotherapy should be an alternative therapy when en bloc resection is not feasible. Radiotherapy and chemotherapy were advocated, especially for the multiple metastasis. Long-term follow-up trials are mandatory for patients who have primary PG surgical treatment history especially for the retroperitoneal ones. For spinal MPG patients who present with catecholamine-related symptoms, surgery is also useful to alleviate the symptoms to a great extent.

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Compliance with ethical standards

Conflict of interest No conflict of interest exists in the submission of this manuscript for all authors, and manuscript is approved by all authors for publication.

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