Clinical features and prognosis analysis of metastatic spinal pheochromocytoma: A single center retrospective study

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A B S T R A C T

Purpose: Metastatic spinal pheochromocytoma (MSP) is very rare in clinical practice, with only a few case reports in the literature. Its low incidence makes it profoundly difficult for clinicians to determine appropriate treatment strategies and predict the prognosis. In this study, we analyzed the clinical characteristics, surgical procedure and prognosis of patients with MSP in one of the largest clinical investigations of this entity to date.
Methods: In this study, we conducted a retrospective analysis of the clinical data of 10 patients with MSP who were treated in our department from 2012 to 2020. We performed a total of 14 operations using two types of surgery: open surgery and percutaneous vertebroplasty.
Results: Among them, nine patients underwent 14 spinal operations with satisfactory effect and without any perioperative complications. The mean time from the initial operation to detection of spinal metastasis was 85.3 (12–132) months. The average follow-up time was 27.3 months. Disease progression was detected in nine patients, and eight patients (80%) died during the follow-up period. Univariate analysis showed that extraosseous visceral metastasis ($P = 0.022$), Tomita score ($P = 0.027$), and number of spinal metastases ($P = 0.024$) were associated with overall survival (OS). In addition, extraosseous visceral metastasis ($P = 0.030$), Tomita score ($P = 0.013$), and number of spinal metastases ($P = 0.026$) were associated with progression-free survival (PFS).
Conclusions: Surgical treatment is an effective option in treating MSP and plays an important role in improving patients' quality of life, due to its efficacy in relieving pain, reconstruction of stability, and restoration of function. Extraosseous metastasis, Tomita score, and number of spinal metastases are all potential prognostic factors for OS and PFS.

1. Introduction

According to the definition of the World Health Organization, pheochromocytoma is defined as a neuroendocrine tumor with metabolic activity originating from the chromaffin cells of the adrenal medulla [1–3]. Pheochromocytoma occurs in the adrenal gland, accounting for 0.3% of all tumors [2,4]. Although it is considered to be benign in nature and is a slow-growing tumor, it has the potential for local or distant metastasis, which is a marker of malignant tumor transformation. The incidence of pheochromocytoma is 0.2–0.9/100,000 per year, with malignant forms accounting for approximately 10% [2,5].

Characterization of the biological behavior of this rare entity has always been the focus as well as the challenge in clinical and pathological diagnosis. The 5-year survival rate of benign pheochromocytoma is reported to be between 84% and 96%, while that of malignant pheochromocytoma is only 40% [2,6–10]. In malignant pheochromocytoma patients, tumor recurrence and metastasis are more common, with lymph nodes, liver, and lung as the most common sites of metastasis [11,12]. Although malignant pheochromocytoma is relatively rare, adrenal pheochromocytoma with spinal metastasis is even more unusual in clinical practice. To date, only around 30 cases of MSP have been reported worldwide [2,10,13–15].

Metastatic spinal lesions can cause bone destruction, vertebral fracture, and spinal cord or nerve root compression, leading to clinical manifestations of lumbar pain or neurological deficits. Surgical treatment (including vertebroplasty or open surgery) combined with adjuvant treatment may improve the prognosis of patients with spinal metastasis [2,16,17]. The epidemiological and therapeutic characteristics of MSP have not been fully elucidated. Here, we describe the

Table 1
Clinical review of 10 patients with metastatic pheochromocytomas of spine in our single centre.

Patients	Operations	Year	Age (y), sex	Symptoms and signs	Spinal metastases location	Incomplete paralysis or paralysis	Resection of primary lesion	Preoperative treatments	Surgery	Adjuvant treatment	Postop complications
1	1	2012	31,F	Hypertension, paroxysmal headaches, low back pain	L3	No	Yes	Phenoxybenzamine (10 mg every 8 h)	Dorsal instrumentation	None	None
2	2	2015	58,M	Hypertension, progressive low back pain	Sacrum	No	Yes	Phenoxybenzamine (5 mg every 12 h)	Dorsal instrumentation and cement augmentation	None	None
	3	2015		Radiating pain and numbness of his lower limbs	Sacrum	No	Yes	Phenoxybenzamine (5 mg every 12 h)	Circumferential decompression procedure of the sacral metastasis to alleviate the symptoms caused by the spinal cord compression	None	None
3	4	2016	26,F	Paroxysmal hypertension, acute incomplete paralysis	T8, T11, T12	Acute incomplete paralysis	No	Phenoxybenzamine (10 mg every 8 h)	Dorsal instrumentation	Radiotherapy, chemotherapy, MIBG therapy	None
4	5	2016	32,M	Progressive paraplegia and numbness of the bilateral lower limbs	T4	Yes, worsened muscle strength of the bilateral lower limbs, grade 3/5	Yes	/	Posterior decompression, tumor resection as well as T3-T8 internal fixation	None	None
5	6	2016	59,M	Progressive back pain, numbness and decreased muscle strength of bilateral lower limbs	T9, T10	No	Yes	Phenoxybenzamine (10 mg every 12 h)	Posterior decompression, tumor resection as well as internal fixation	Radiotherapy, MIBG therapy	None
6	7	2018	63,M	Hypertension, progressive low back pain	T2, T4, T7, L1, L3, sacrum	No	Yes	Phenoxybenzamine (10 mg every 8 h)	Percutaneous vertebroplasty procedure to the spinal metastases in T7 and sacrum	MIBG therapy	None
	8	2019		Hypertension, back pain	T2, T4, T7, L1, L3, sacrum	No	Yes	Phenoxybenzamine (20 mg every 8 h)	Percutaneous vertebroplasty procedure to the spinal metastases (T2, T4)	MIBG therapy	None
7	9	2013	27,M	Back pain	L1、L4	No	Yes	Phenoxybenzamine (10 mg every 8 h)	Percutaneous vertebroplasty of L1 and L4	/	None
	10	2018		Decreased muscle strength of both lower limbs	T11、T12、L1	Yes, incomplete paralysis	Yes	Phenoxybenzamine (10 mg every 8 h)	Posterior decompression, tumor resection and internal fixation	/	None
8	11	2019	22,F	Headache, back pain	T5	No	Yes	Phenoxybenzamine (15 mg every 8 h)	Percutaneous vertebroplasty of T5	/	None
9	12	2019	60,M	Numbness of both legs	T11、L1、L3	No	Yes	Phenoxybenzamine (10 mg every 8 h)	Percutaneous vertebroplasty of T11, L1, L3	Radiotherapy	None
	13	2019		Numbness of both legs	L5	No	Yes	Phenoxybenzamine (10 mg every 8 h)	Posterior decompression, tumor resection and internal fixation	Radiotherapy	None
10	14	2019	38,M	Sacrococcygeal pain	Sacrum	No	No	/	Biopsy	MIBG therapy	None

clinical characteristics, different treatment options and prognosis of 10 patients with MSP followed up at a single center.

2. Patients and methods

The clinical data of 10 patients with MSP treated at our institution between 2012 and 2020 were analyzed retrospectively. According to the Tomita and revised Tokuhashi scoring systems [18,19], 9 patients were treated with different surgical methods, and one patient rejected surgical treatment after full consideration. We focused mainly on the state of spinal tumor progression and overall survival (OS) of patients after the initial spinal surgery. OS was defined as the interval between the date of spinal surgery and death due to illness (excluding accidents and other diseases) or to the last follow-up by outpatient visits and telephone interviews. Progression-free survival (PFS) was defined as the interval between the date of primary spine surgery and tumor progression or other new metastasis. This study was approved by our hospital's ethics committee and written informed consent was obtained from all the patients.

The clinical data and details of surgical procedures of 10 patients are shown in Table 1. All 10 patients received surgical resection or biopsy of the primary adrenal tumor before admission, and were diagnosed as pheochromocytoma by pathological examination. The final diagnosis of MSP was confirmed according to the following criteria: (1) the imaging findings from standard X-ray, computed tomography (CT), magnetic resonance imaging (MRI), bone scan or FDG positron emission tomography (PET/CT) examinations were consistent with MSP; (2) a clear medical history of pheochromocytoma; (3) the final diagnosis was made via pathological samples obtained during spinal surgery.

Preoperative neural function was classified according to the Frankel score and the ASIA injury grade [20,21]. The quality of life of all patients was evaluated using the Karnofsky, ECOG and VAS scoring systems [22,23]. The operations were all carried out by the surgical team led by Professor Liu. The SINS scoring system was used to assess spinal stability [24], and the revised Tokuhashi and Tomita scoring systems were modified to initially assess the prognosis of patients and assist in the development of surgical protocols.

After comprehensive evaluation, surgical treatment was recommended for all patients; nine patients finally underwent spinal surgery, and a total of 14 operations were performed. The indications for surgery included: (1) initial definite spinal metastasis with intolerable pain or neurological deficit; (2) satisfactory disease control could not be achieved by conservative treatment; (3) no definite contraindications for surgery after comprehensive evaluation by subspecialties; (4) sufficient preoperative preparation according to the guidance of the multi-disciplinary team; (5) all patients had been confirmed to be able to tolerate undergoing surgery according to their general condition; and (6) patients and their families were willing to undergo surgical treatment. According to the location, involvement and general situation of spinal tumors, surgical strategies were individualized for each patient. After the operation, suggestions for adjuvant treatment were offered according to the individual situation of each patients.

Physical examination and radiological assessment of the spine (radiograph, computed tomography or magnetic resonance imaging) were performed at scheduled intervals of 3 and 6 months postoperatively, and every 6 months for the next 2 years, followed by yearly assessment thereafter. Bone scan or PET/CT, as well as chest CT scan and abdomen ultrasound, were performed to assess relapse in situ or systemic metastasis. For patients showing tumor progression, PET-CT is highly recommended for postoperative assessment. Follow-up data were obtained from outpatient visits and telephone interviews. During the follow-up of the postoperative situation, neurological function and quality-of-life improvements were re-evaluated according to the VAS, Frankel and Karnofsky scoring systems. The follow-up period was defined as the interval from the date of spinal surgery to the date of death, or to the last follow-up visit.

2.1. Statistical analysis

The Kaplan–Meier method and log-rank tests were adopted in univariate analysis to determine factors that may affect local progression and OS. Patient factors included age, sex, visceral metastasis, primary tumor treatment, number of spinal metastases, duration of symptoms, condition of defecation, complications, ECOG score, SINS, KPS score, ASIA grade, VAS score, revised Tokuhashi score, Tomita score, and Frankel score before operation. The treatment factors were surgical methods, intraoperative blood loss, and adjuvant therapies. Tumor factors were location, bone change, spinal cord compression, paravertebral expansion and tumor markers. All statistical analysis was performed with IBM SPSS 23.0 statistical software (IBM Corp., Armonk, NY, USA). $P \leq 0.05$ was considered to indicate statistical significance.

3. Results

3.1. Patient characteristics

Our study included seven male patients and three female patients, with an average age of 41.6 (22–64) years; a total of 14 operations were performed. In terms of the predominant locations, there were seven cases of thoracic spine lesion, four cases of lumbar spine lesions and three cases of sacral lesions. There were four cases of single vertebral body metastasis and six cases of multiple vertebral body metastasis. In addition, five patients had spinal and other visceral metastasis. Local pain was the most common complaint of patients. The average duration of preoperative symptoms was 4.3 (0–11) months. Other symptoms included symptoms related to catecholamine, with four patient suffering from hypertension (more than 140/90 mmHg) and seven patients diagnosed with varying degrees of spinal cord compression. The mean follow-up period was 27.3 (6–108) months. The average PFS was 20.1 (4–108) months, while seven (70%) patients died with an average disease course of 4.3 (0–11) months.

3.2. Treatment history

Before admission to our institution, the primary adrenal pheochromocytomas were completely resected in eight patients, and the other two patients underwent ultrasound-guided biopsy of the adrenal lesions (one was a Chinese female graduate student in Edinburgh, suffered from a sudden onset of incomplete paralysis of both lower limbs; the other refused to undergo further resection of adrenal pheochromocytoma after undergoing biopsy). The mean time from prior surgery to spinal metastasis was 85.3 (12–132) months.

3.3. Laboratory examinations

With respect to tumor markers, eight (80%) patients tested positive for neuron-specific enolase (NSE) positive (median 22.3; range 12.9–32.5; reference 0–16.3 ng/ml), and no other significantly abnormal tumor markers were detected (Table 2). Urinary adrenaline (24-h), urinary noradrenaline (24-h), dopamine (24-h), urinary free cortisol, urine volume, and other endocrine indexes were tested to identify endocrine activity of tumor. Endocrine laboratory tests revealed an average urinary adrenaline level of 4.9 µg/24 h (1.74–6.42 µg/24 h), an average noradrenaline level of 303.1 µg/24 h (16.69–40.65 µg/24 h), and an average urinary dopamine level of 443.9 µg/24 h (120.93–330.59 µg/24 h). There were three, six, and four patients who exceeded the upper limit of urinary adrenaline, urinary noradrenaline, and urinary dopamine before the spinal surgery, respectively.

Table 2
The levels of NSE in 10 patients with metastatic pheochromocytomas of spine in our single centre.

Patients	Year	Age (y), sex	NSE (ng/ml)
1	2012	31,F	27.8
2	2015	58,M	25.3
3	2016	26,F	32.5
4	2016	32,M	12.9
5	2016	59,M	18.8
6	2018	63,M	15.9
7	2018	27,M	22.5
8	2019	22,F	16.9
9	2019	60,M	21.8
10	2019	38,M	28.3

3.4. Radiographical studies

Radiological assessment of the spine (radiograph, computed tomography or magnetic resonance imaging) was performed in all patients, and the spinal metastases were commonly osteolytic. Functional radiological studies (bone scan, ^{131}I-mIBG, ^{18}F-FDG-PET/CT) performed in 10 patients with spinal metastatic lesions revealed abnormal concentrations of ^{18}F-FDG within the lesions. Bone scanning was performed in seven patients, which was also helpful for detecting the number and nature of bone lesions.

3.5. Treatment, histopathological features, and follow-up

To prepare for surgery, patients were recommended to receive α receptor blockers (phenoxybenzamine) 2–4 weeks before the operations to prevent catecholamine-related symptoms and control hypertension crisis during the perioperative period.

For isolated spinal metastasis, we prefer complete resection of spinal metastases, including total tumor resection and en-bloc resection. In this study, seven patients underwent open resection to remove the metastatic lesions and reconstruct the stability of the spine as much as possible (Fig. 1). Seven bone cement augmentation procedures were performed as a minimally invasive approach to increasing spine stability (Fig. 2). According to the Tomita and the revised Tokuhashi scoring systems, four patients with multiple metastases were treated by decompression and reconstruction combined with chemotherapy. The mean OS times of patients undergoing open surgery and bone cement augmentation were 24.1 (7–68) months and 26.9 (6–108) months, respectively. The mean blood loss was 1400 ml (400–3000 ml) during open surgery and 37.5 ml (0–100 ml) during minimally invasive surgery. All the operations were conducted without complications, although patients had severe blood pressure fluctuations during the operation, which were gradually relieved to acceptable levels after suspension of the operation and anesthesia management, without perioperative cardiovascular or cerebrovascular complications. For all patients, the local pain symptoms were improved after the operation.

Histologic diagnosis was obtained in all cases. All pathological results were consistent with the final diagnosis of MSP, with a negative specimen margin. The histomorphology of MPG is similar to that of primary pheochromocytoma. The histopathological features were characterized by the tumor cell nests which were observed to be separated by the vascular septum under the microscope, and significant nuclear pleomorphism with prominent nucleoli in the tumor cells accompanied by broken bone tissue. Immunohistochemistry showed that chromaffin A, synaptophysin, vimentin, CD56, NSE, and S-100 were commonly positive, while cytokeratin, epithelial membrane antigens and other markers were negative (Table 3). The Ki-67 value was generally positive, ranging from 3% to 50%, and sometimes varied in different segments or stages of spinal lesions in the same patient, confirming that the tumor grade may increase during the process of spinal metastasis (Table 3).

During the 3-month follow-up period, the Frankel score in three patients with neurological deficits improved by 1–2 grades. Symptoms associated with catecholamine, including abnormal hypertension and headache, were partially relieved postoperatively. Table 1 shows the treatment strategy and follow-up results of 10 patients with MSP. In this single center study, one patient underwent a revision surgery. After admission, another patient received conservative treatments including chemotherapy, local radiation therapy and analgesics (such as morphine) to reduce symptoms and improve their quality of life. After spinal surgery, three patients received radiotherapy for spinal lesions at a total dose of 30–50 Gy. Four patients were received MIBG therapy.

3.6. Univariate analysis of clinical factors

The results of the univariate prognostic analysis of OS and PFS in all patients are shown in Fig. 3. Patients without an extraosseous visceral metastasis tended to have better OS ($P = 0.022$) and PFS ($P = 0.030$). In addition, a low Tomita score was found to be an indicator of better OS ($P = 0.027$) and PFS ($P = 0.013$). The number of spinal metastases also showed prognostic value for OS ($P = 0.024$) and PFS ($P = 0.026$) in MSP patients. For local control and better prognosis, application of bone cement showed similar predictive value to that of open surgery. Prognostic factors affecting OS and PFS are presented in Figs. 4 and 5.

4. Discussion

The diagnosis and treatment of patients with MSP represents one of the most complex and difficult problems facing clinicians, and the delays may have fatal consequences [2,3,10]. Low back pain is a common symptom of MSP, which lacks specificity, is often occult, leading to missed diagnosis and misdiagnosis [2,10]. Due to the extremely low incidence of MSP, there is a lack of worldwide and large-scale clinical experience in the diagnosis and treatment of this rare entity. The clinical features of about 30 case reports of MSP diagnosis available in the PubMed database indicate that MSP is more common in the thoracic region (approximately 50%), and occurs mainly in middle-aged people (40–50 years) [13–15,25]. In our center, the average age of patients was 41.6 (22–64) years, and eight of 10 patients (80%) were aged under 50 years. Metastasis may occur at the time of diagnosis of pheochromocytoma or several years later [25]. The average duration from primary tumor resection to spinal metastasis is 85.3 (12–132) months. Therefore, long-term follow-up is recommended for patients with MSP. In terms of location, MSP occurred most frequently in the thoracic spine in our series (70%), which is consistent with previous reports [25,26].

Typical clinical manifestations of pheochromocytoma include headache, palpitations, abnormal sensation, fatigue, flushing, sweating or paroxysmal hypertension [2,3,10,25,26]. For some pheochromocytomas, there are clear symptoms related to catecholamine release from tumor cells. Because the primary focus and spinal metastasis can produce, store and secrete catecholamine, any kind of stimulation can lead to catecholamine release from the primary or metastatic sites [25,26]. This phenomenon causes hemodynamic disorder, which is a great challenge to the clinical diagnosis and treatment of such patients, and directly related to the choice of treatment strategy [2,10,25]. Similar to other types of spinal metastases, the location of the spinal cord injury in MSP cases determines the type of neurological deficit, while lesions in the thoracolumbar regions are often manifested as low back pain, lower extremity sensory abnormality, weakness, and dysuria [25]. In the cases we analyzed, local pain was the most common symptom. At the time of diagnosis, seven patients (70%) had different degrees of spinal cord compression. Five patients had symptoms related to catecholamine, such as hypertension, sweating and headache, indicating the release of catecholamine from the primary or metastatic tumor.

In terms of laboratory examinations, diagnostic tests include urinary adrenaline (24-h), urinary noradrenaline (24-h), urinary catecholamine (24-h), dopamine (24-h), urinary free cortisol, and urine volume
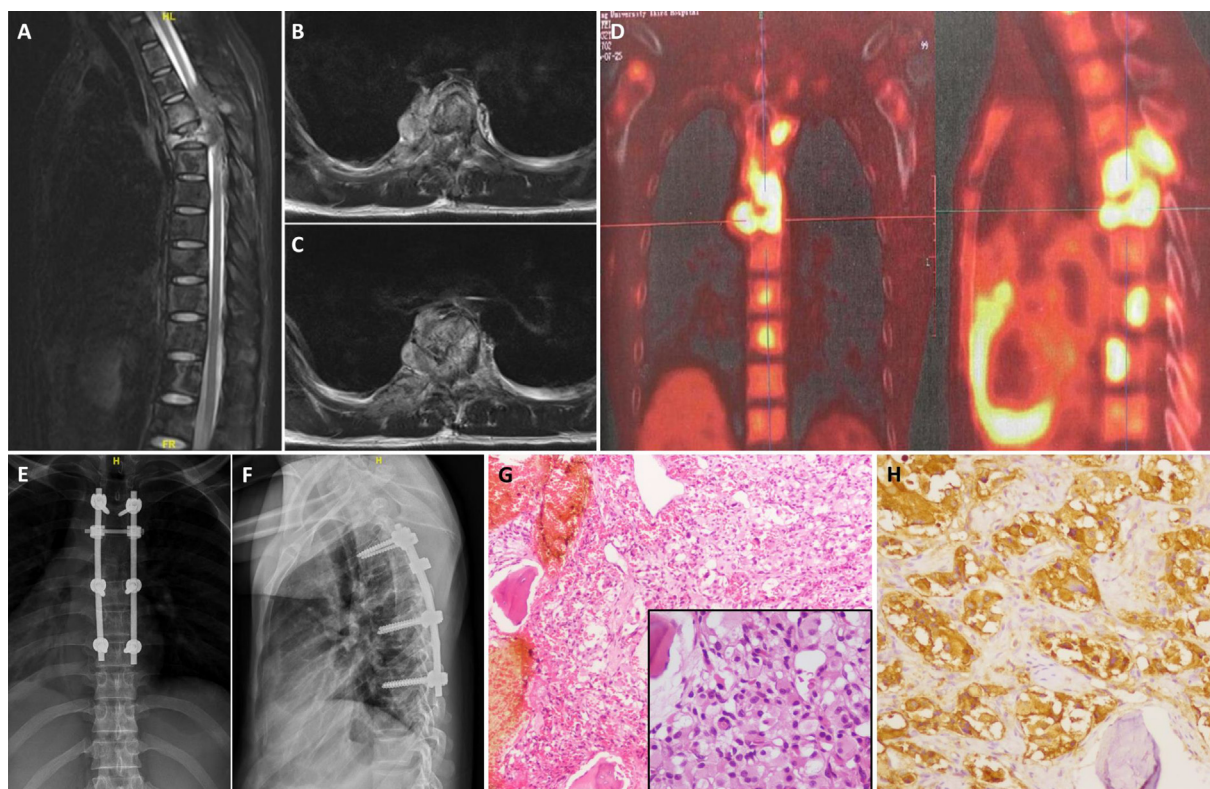
Fig. 1. Radiographic and pathological images of a representative 32-year-old male patient (Case #4). (A–C) Preoperative sagittal and transverse T2-weighted MRI scan revealing vertebral metastases, pathological vertebral fractures, and thoracic spinal cord compression. (D) Positron emission tomography-computed tomography revealing metastases of the spine. (E, F) X-ray images of the thoracic spine obtained postoperatively. (G, H) 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 100×). Chromogranin A immunostaining is strongly positive in the chromaffin cells.

[2,25,27]. These indicators have high sensitivity and specificity. In addition, genetic analysis can further assist in the diagnosis of pheochromocytoma. Detailed evaluation of the locations of primary and spinal metastasis requires imaging examinations including CT, MRI, bone scan, ^{131}I-MIBG, and PET-CT [28,29]. The osteolytic changes of spinal lesions are more easily identified in X-ray and CT scans than in MRI. MRI is considered to be a superior method for identifying spinal metastasis, although it is difficult to distinguish MSP from other spinal malignancies. MRI features include hypointense or isointense signals on T1-weighted images and hyperintense signals on T2-weighted images. Due to the similarity of the imaging features of the primary pheochromocytoma with other abdominal neoplasms in ultrasound, CT, MRI, bone scan, PET-CT and other imaging examinations, the clinical manifestations are complex and variable, which often leads to misdiagnosis. In this case, the history of primary pheochromocytoma surgery is very important to establish the preoperative diagnosis.

In the clinic, the diagnosis of malignant pheochromocytoma is closely related to its pattern of metastasis [2,25,29]. The "gold standard" for the diagnosis of primary and metastatic pheochromocytoma depends on pathological examination [2,25]. The histopathological features are characterized by the tumor cell nests which are separated by the vascular septum under the microscope, and significant nuclear pleomorphism with prominent nucleoli in the tumor cells. Normally, chromogranin A (CgA) and synaptophysin (Syn) are positively detected in immunohistochemical analysis of metastatic pheochromocytoma, which can be used to make a definite diagnosis [25,29]. Although the Ki-67 index is recognized as a useful marker for predicting malignant tumors, we should also carefully consider the existence of false-negative and false-positive results [30,31]. All of the cases in this study had a Ki-67 index higher than 3%, with the highest reaching 50%. In our cohort, we found that some different metastatic sites exhibited varying degrees

of malignancy according to the Ki-67 index. For progressive MSP, one patient undergoing revision surgery showed an increase in Ki-67 index obtained from the second spinal operation compared with that from the initial spinal operation.

In recent years, surgery has been reported to be the best treatment for MSP; however, there is no worldwide consensus regarding the treatment procedure [2,10,25,32]. In spinal surgery, especially for patients with MSP-related catecholamine release, effective catecholamine blockade and good anesthesia are essential. Preoperative evaluation must be carried out in orthopedics, endocrinology, radiology, anesthesiology and critical medicine. The best treatment option for MSP, which leads to acute paralysis and intractable back pain, is posterior decompression, tumor resection and internal fixation [25,26,32]. Surgical treatment can alleviate the damage to neurological function by reducing the spinal cord compression, and provide histopathological specimens for definite diagnosis. Similar to other types of primary spinal metastases, treatments include posterior laminectomy and internal fixation, subtotal corpectomy, corpectomy, and total spondylectomy [2,25,32].

Rittirsch et al. reported pioneering treatment of one MSP patient with bone cement technology combined with posterior decompression and internal fixation [33]. Cai et al. achieved satisfactory clinical effects using bone cement augmentation to treat patients with bone metastasis of pheochromocytoma, with no tumor recurrence or complications reported in the follow-up of two patients after 6 months [34]. The application of minimally invasive bone cement technology in MSP patients has the following advantages: (1) bone cement surgery can be completed under local anesthesia to minimize the risk of surgery; (2) the surgical trauma is small, and the treatment effect is significant; (3) the scope of bone cement technology application in MSP treatment can be further expanded, not only for the reinforcement of spinal
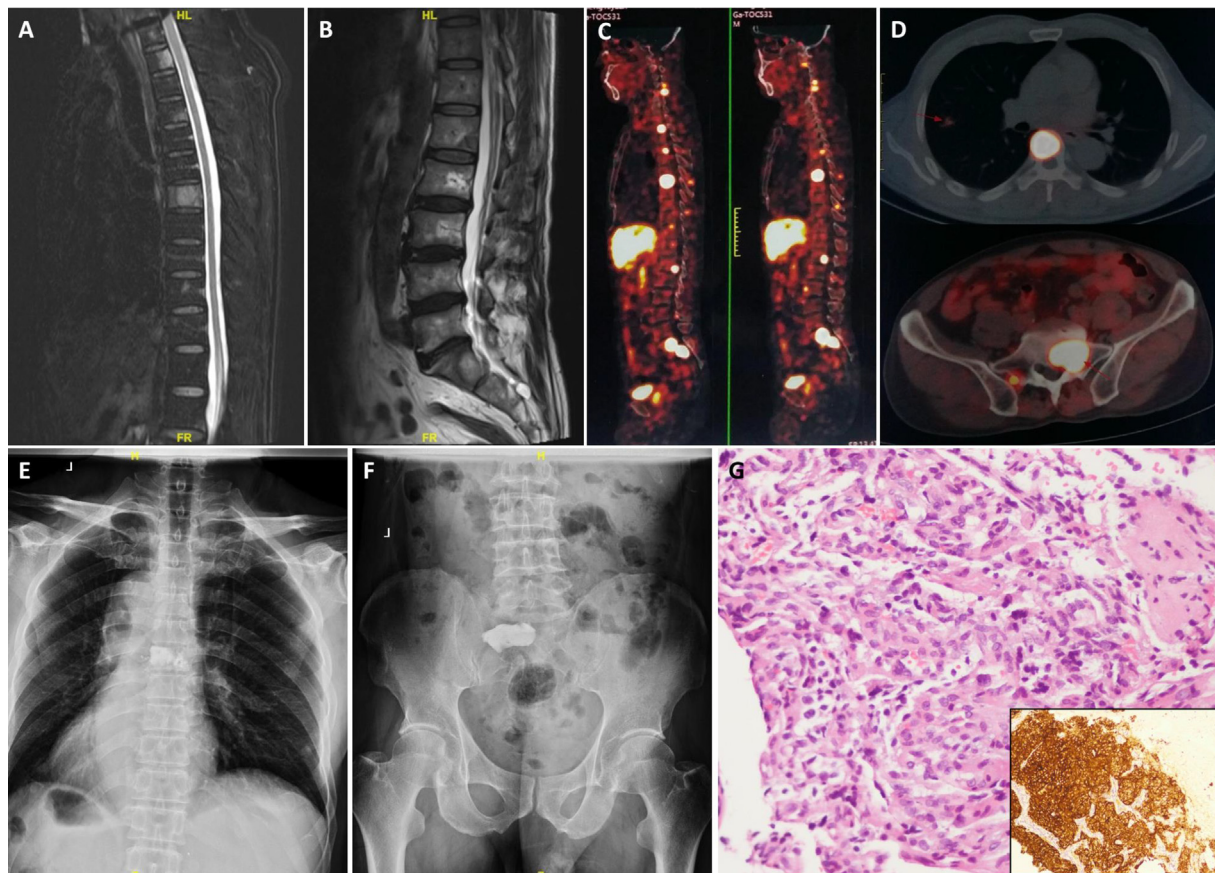
Fig. 2. Radiographic and pathological images of a representative 64-year-old male patient (Case #6). (A, B) Preoperative sagittal T2-weighted MRI scan revealing vertebral metastases. (C, D) Positron emission tomography-computed tomography revealing multiple metastases of the spine. (E, F) Postoperative X-rays of the thoracic spine. (G) Microphotography showing significant nuclear pleomorphism with prominent nucleoli (H & E, original magnification 200×).

metastasis, but also for other types of treatment for damaged bone; (4) for patients considering the diagnosis of MSP, tissue biopsy can be carried out at the time of treatment to obtain a clear pathological diagnosis; and (5) bone cement material has bacteriostasis and tumor inhibition potential, and novel bone cement materials have been developed that can be loaded with drugs for targeted treatment, which is expected to further improve the effect of local disease control [25,26,32]. Therefore, the minimally invasive bone cement technology provides a new approach and choice for the early diagnosis and treatment of MSP patients.

The following points should be considered in the selection of surgical treatment of MSP: the effective control of preoperative hemodynamic instability and arrhythmia, the scope of resection of the spinal metastasis focus, the treatment of intraoperative blood loss and hemodynamic instability, and the selection of a postoperative adjuvant treatment plan [2,10,25,26,32]. As part of the preoperative preparation and on the basis of full and comprehensive evaluation of the general condition of patients and spinal metastasis, adrenergic receptor blockers should be used to control blood pressure and heart rate, expand blood volume, improve heart function, and prepare for expansion. The goal of blood pressure control is below 140/90 mmHg to ensure hemodynamic stability and reduce the risk of perioperative complications [25]. Due to the abundant blood supply of spinal metastases in MSP patients, intraoperative bleeding may be significant. Conventional

Table 3
Pathological characteristics of 10 patients with metastatic pheochromocytomas of spine in our single centre.

| Patients	Operations	Year	Age (y), sex	CgA	Syn	S-100	Ki-67 (%)
1	1	2012	31,F	Positive	Positive	Positive	6
2	2	2015	58,M	Positive	Positive	Positive	5
	3	2015		Positive	Positive	Positive	5
3	4	2016	26,F	Positive	Positive	Positive	3
4	5	2016	32,M	Positive	Positive	Positive	3
5	6	2016	59,M	Positive	Positive	Positive (sporadic)	3
6	7	2018	63,M	Positive	Positive	Positive (sporadic)	6
	8	2018		Positive	Positive	Positive (sporadic)	6
7	9	2011	27,M	Positive	Positive	Positive	5
	10	2018		Positive	Positive	Positive	5
8	11	2019	22,F	Positive	Positive	Positive	3
9	12	2019	60,M	Positive	Positive	Positive (sporadic)	15
	13	2019		Positive	Positive	Positive (sporadic)	50
10	14	2019	38,M	Positive	Positive	Positive	11
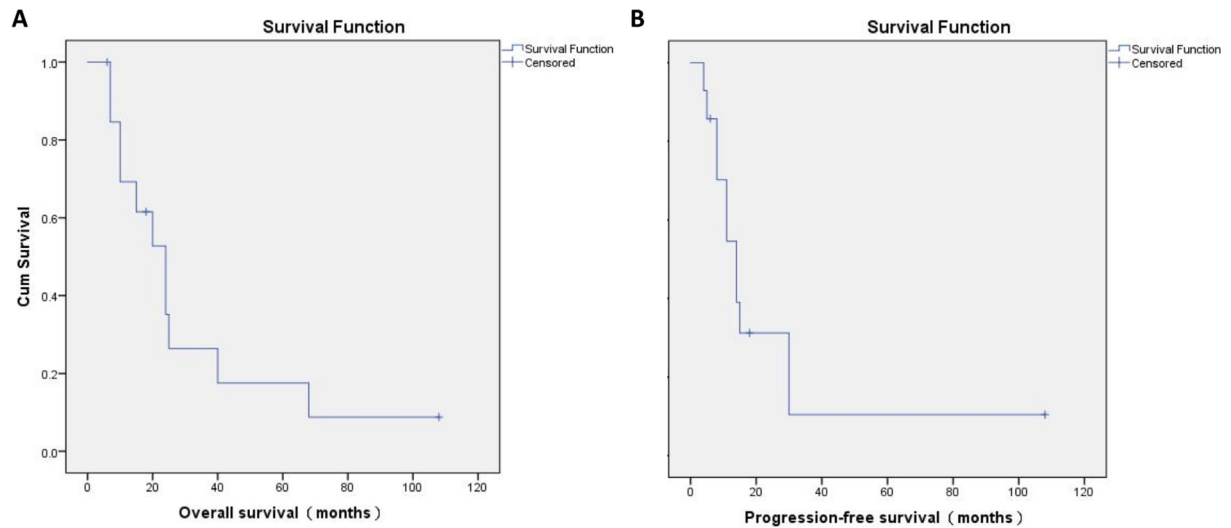
Fig. 3. Overall survival and progression-free survival of all patients enrolled in our study.
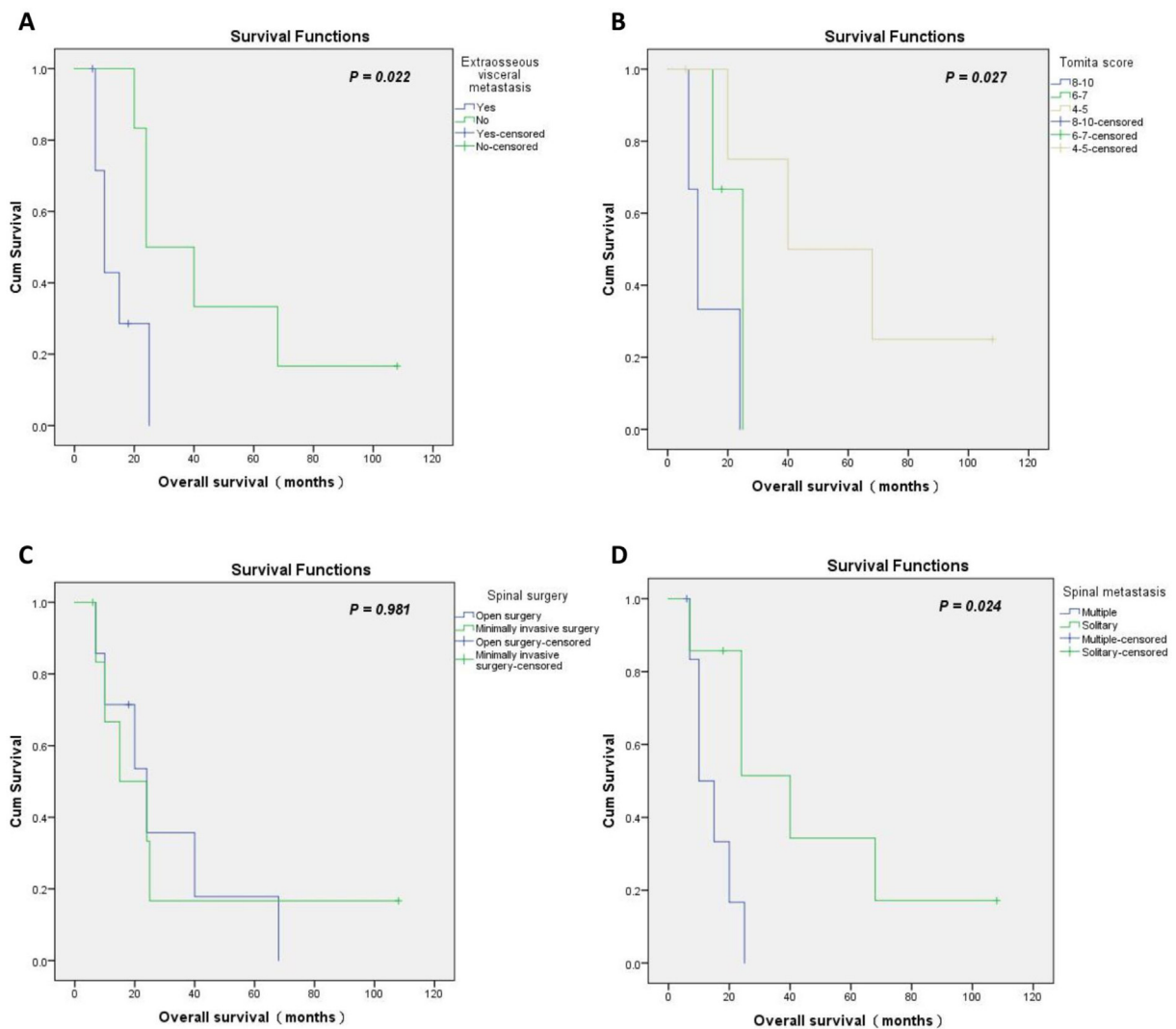

Fig. 4. Univariate analysis of prognostic factors significantly affecting overall survival.
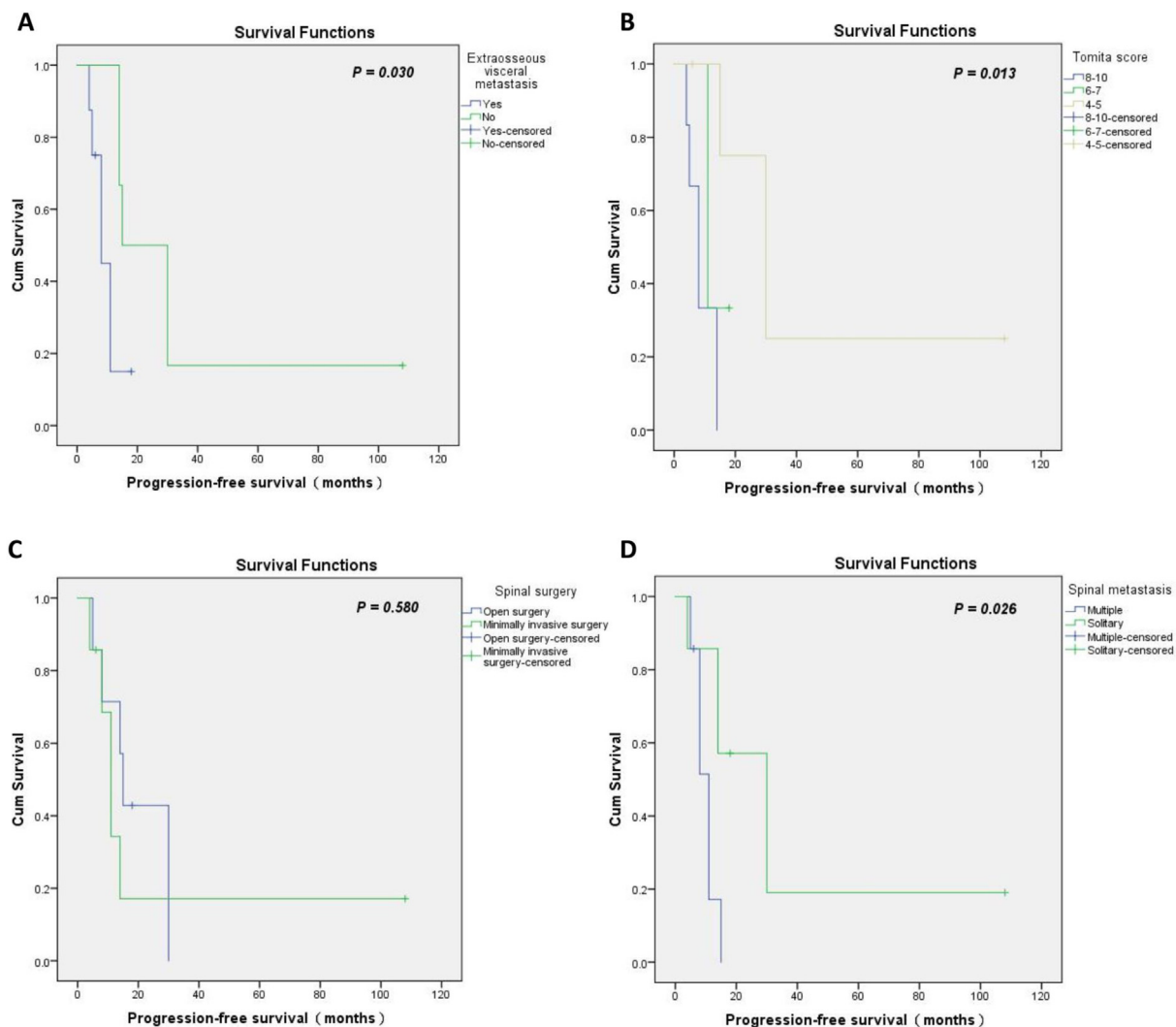
Fig. 5. Univariate analysis of prognostic factors significantly affecting progression-free survival.

preoperative use of α-adrenergic receptor blockers and tumor-supporting vascular embolization technology can effectively reduce the amount of intraoperative blood loss. Fluctuations in blood pressure and heart rate may be due to anesthesia and the operative procedure. We found that mechanical stimulation of pheochromocytoma during surgery increased blood pressure to more than 200/100 mmHg over a short period of time. To avoid hemodynamic complications, we found that unnecessary mechanical stimulation should be avoided during the operation to minimize the release of catecholamine from tumor cells. The vascularization and high infiltration of pheochromocytoma make it difficult to achieve complete resection of spinal metastases. To date, most MSP cases have been treated with palliative surgery with the main aim of decompression and tumor removal; therefore, there is still a risk of tumor recurrence and metastasis [2,32]. Patients with MSP are prone to hemodynamic disorders during the perioperative period; therefore, it is recommended that patients should transition to the intensive care unit and hemodynamic indexes should be closely monitored [25].

At present, there is a lack of an effective clinical prognosis evaluation system for MSP [2,10,32]. The revised Tokuhashi and Tomita scoring systems, which are widely used in the clinic, have only a certain reference value and there is worldwide controversy regarding the indication of MSP operation and the choice of treatment plan [2,10,18,19,25,26,35]. Comprehensive preoperative evaluation of MSP patients is the key to the success of the treatment. Surgery is an efficient option in treating MSP and plays an important role in improving the

patients' quality of life due to its efficacy in pain alleviation, function restoration, and reconstruction of spinal stability [2,10,25,32,36]. In the univariate analysis of clinical factors, there was no significant difference in predicting the prognosis of patients treated by open surgery group and bone cement augmentation. Based on the experience of our single center, we found that extraosseous visceral metastasis, Tomita score, and number of spinal metastases are all potential prognostic factors for OS and PFS of MSP patients. Compared with the Tomita scoring system, the revised Tokuhashi scoring system did not show good predictive value for OS and PFS.

Some limitations of this study should be noted. This is a retrospective study spanning seven years. During the follow-up period, surgical techniques and various adjuvant therapies have been greatly developed and changed. These advances may be beneficial for complete tumor resection and improve prognosis, but also may influence the results of research analysis. Secondly, we have fully considered the accuracy and scientific validity of the conclusions, so no further comparative studies between the initial biopsy lesions (adrenal glands) and the metastatic spinal lesions have been conducted. In addition, the small number of patients included may limit the accurate and detailed statistical analysis. Although this case series constitutes the first clinical series reported that focuses on the surgical treatment and prognosis of MSP, this analysis will help to improve the clinical treatment of this rare disorder, reduce the incidence of perioperative complications, and maximize the survival and prognosis of patients with MSP.

5. Conclusions

In this retrospective study, we analyzed the clinical characteristics of 10 patients with MSP, and described our research results and treatment experiences to provide a reference for the diagnosis and treatment as well as details of practical experience of this disease. To the best of our knowledge, this is the largest cohort of MSP patients in the world. MSP is exceedingly rare in clinical practice, and the cases presented in the current study highlight the key role and potential advantages of surgical treatment. To sum up, for pheochromocytoma patients with spinal metastasis, the clinical symptoms are generally the result of tumor load, and clinical manifestations and auxiliary examinations often lack specificity. Histopathological diagnosis is still the "gold standard" for the diagnosis of malignant pheochromocytoma spinal metastasis.

At present, a prognosis evaluation system for MSP has not yet been established. Individualized treatment plans should be developed based on the actual situation of each patient. Through a multi-disciplinary collaborative diagnosis and treatment mode, reasonable evaluation, preoperative planning and perioperative management, patients with spinal metastatic pheochromocytoma can be treated more effectively and in a timely manner, which is expected to improve the quality of life and survival of MSP patients.

Authors' contributions

SZL wrote the paper. SZL, XZ, ZH, and SYY collected the data. SZL, XZ, and ZH analyzed the collected data for patients. XZ and YL performed the operations. YL and YPW revised the manuscript for important intellectual content and technical details. All authors have read and approved the final manuscript. We confirm that all of us have met the criteria for authorship as established by the ICMJE.

Availability of data and materials

The anonymized data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Peking Union Medical College Hospital. Informed consent for the surgical procedures was obtained from each patient.

Consent for publication

Consent for publication was obtained from each patient.

Competing interests

The authors declare that they have no competing interests.

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