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Clinical presentation and long-term outcome of primary spinal intradural malignant peripheral nerve sheath tumors

Jun Chen, Yifeng Zheng, Zirong Chen, Fanfan Fan, Yu Wang*

Department of Neurosurgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, China

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ABSTRACT

Objective: Primary spinal intradural malignant peripheral nerve sheath tumors (MPNSTs) are exceedingly rare, and there is limited published information regarding these lesions. The purpose of this study was to analyze the clinical course, treatment, and outcome of primary spinal intradural MPNSTs.

Patients and Methods: A retrospective study was performed on 8 patients with primary spinal intradural MPNSTs who were surgically treated and pathologically confirmed in our institution between 2007 and 2018.

Results: There were 3 females and 5 males, with a median age of 46.5 years (range, 21–68 years). Limb weakness was the most common clinical symptom (5/8, 62.5%). The radiological diagnosis was meningioma or schwannoma in most patients (7/8, 87.5%). Malignancies were graded high in 5 cases (62.5%) and low in 3 cases (37.5%). Gross total resection (GTR) was performed in 5 cases, while subtotal resection (STR) was achieved in 3 cases. The mean follow-up period was 48.9 months (range, 10–160 months). During follow-up, local recurrence occurred in 6/8 cases (75.0%) and distant metastasis occurred in 2/8 cases (25.0%). The median survival time (MST) of these 8 patients was 21.0 months. The overall 1-year, 2-year, and 5-year survival rates were 87.5% (7/8), 50.0% (4/8), and 25.0% (2/8), respectively.

Conclusions: Primary spinal intradural MPNST is a challenging clinical entity given its high local relapse rate. Primary spinal intradural MPNSTs radiologically present themselves heterogeneous and thus difficult to distinguish from schwannomas or meningiomas. Surgical resection, especially GTR, is the preferential treatment for primary spinal intradural MPNSTs.

1. Introduction

Malignant peripheral nerve sheath tumors (MPNSTs) are exceedingly rare lesions, accounting for only 5% of all soft-tissue sarcomas, and having an overall incidence rate of 0.001% [1,2]. MPNSTs usually arise from neural crest cells and Schwann cells. Approximately 20–30% of MPNSTs occur in patients with neurofibromatosis type 1 (NF-1) [3]. The majority of these tumors are located in the trunk, extremities, head, and neck [4]. Primary spinal intradural MPNSTs in patients without neurofibromatosis, however, have been rarely reported. Approximately 24 cases of primary spinal intradural MPNSTs have been reported in English-language publications, with a few studies reporting more than 4 cases [5]. Due to the limited number of reports, the clinical and imaging characteristics of these tumors remain unclear. Therefore, almost all primary spinal intradural MPNSTs are misdiagnosed as meningioma or schwannoma prior to initial surgery. In addition, a timely and accurate preoperative diagnosis of primary spinal intradural MPNST is especially important due to the highly malignant and invasive nature of the disease. Therefore, we believe that a comprehensive investigation of the diagnosis, treatment, and outcome of patients with spinal MPNSTs is warranted.

In the present report, we conducted a retrospective study to characterize the clinical and imaging features of patients with this rare disease in order to improve preoperative diagnosis of primary spinal intradural MPNSTs. We also summarized our experience with 8 consecutive patients, thereby providing a large case series focused on surgical treatment strategies and long-term outcomes of primary spinal intradural MPNSTs.

2. Materials and methods

This study included 8 patients who were diagnosed with primary spinal intradural MPNSTs in Tongji Hospital (Tongji Medical College, Huazhong University of Science and Technology) from May 2007 to August 2018. Patients with tumor dissemination from the intracranial origin were excluded. The 8 cases of primary spinal intradural MPNSTs

* Corresponding author.
E-mail address: 330722474@qq.com (Y. Wang).

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Table 1
Clinical characteristics, treatment modality, and follow-up data of eight patients with primary spinal intradural MPNSTs.

Case	Sex/age (years)	Clinical symptoms	History (months)	Level	Size (cm)	Malignancy grade	Extent of resection	Adjuvant therapy	Frequency of recurrence	Metastasis	Follow-up (months)
1	M/21	LE pain, low back pain	12	T11-T12	3.0	High	GTR	CHE	2	–	Died at 56
2	F/29	rt LE numbness and weakness	6	L3-S1	4.0	High	GTR	RAD	–	Lung	Died at 21
3	M/52	Low back pain	8	L3-L4	7.2	Low	GTR	RAD	1	–	Died at 82
4	M/47	lt LE pain and weakness	1	T12-L1	4.6	High	STR	CHE, RAD	1	–	Died at 19
5	F/39	lt UE and LE numbness and weakness	3	C1-C3	6.5	Low	STR	RAD	2	–	Died at 160
6	M/68	LE weakness	3	T6-T8	4.7	High	GTR	–	1	–	Died at 15
7	F/53	UE pain	6	C5-C6	3.2	High	STR	RAD	1	Lung	Died at 10
8	M/46	LE weakness	1	T11	2.0	Low	GTR	–	–	–	Alive at 28

Abbreviations: M, Male; F, Female; lt, left; rt, right; LE, lower extremity; UE, upper extremity; GTR, gross total resection; STR, subtotal resection; CHE, chemotherapy; RAD, radiotherapy.

occurred in 3 females and 5 males. The clinical presentation, disease history, tumor pathology, extent of resection, adjuvant therapy, postoperative tumor recurrence, and survival of the 8 patients are presented in Table 1. The pathological diagnosis of MPNST was confirmed by 2 experienced independent pathologists. Pathological grading of the MPNSTs was performed according to the World Health Organization (WHO) grading system [6].

Under general anesthesia and neurophysiological monitoring conditions, all patients were operated on using a dorsal standard midline approach. During the operation, the originating nerve could be found in all cases. The tumors appeared as solid soft lesions, grayish or reddish in color, with abundant blood supply. The extent of tumor resection was classified as either gross total resection (GTR) or subtotal resection (STR), based on the postoperative magnetic resonance imaging (MRI) and surgical record. GTR was defined as the entire lesion being resected and no evidence of residual tumor on postoperative MRI. STR was defined as 80%–99% of the lesion being resected [7].

Clinical and spinal MRI follow-up data for all patients with MPNSTs were primarily obtained through outpatient review, supplemented by a telephone interview. To reveal distant metastases, some patients underwent positron emission tomography/computed tomography (PET/CT) examination. The mean follow-up period was 48.9 months (range, 10–160 months). Follow-up ended on March 25, 2019. Due to the limited number of patients, statistical analysis was not used in this study.

3. Results

3.1. Demographic and clinical features

A total of 8 patients met the inclusion criteria. The clinical characteristics of all patients are listed in Table 1. There were 3 females and 5 males (sex ratio 0.6) with a median age of 46.5 years (range, 21–68 years). The most common preoperative clinical symptom was limb weakness (5/8, 62.5%), followed by pain (4/8, 50.0%) and limb numbness (2/8, 25.0%). The disease duration ranged from 1 month to 12 months (median disease duration, 4.5 months).

3.2. Imaging findings

All patients underwent whole spine MRI examination before the initial surgery. The prevalence of various imaging characteristics is presented in Table 2. The maximum diameters of the tumors ranged from 2.0 to 7.2 cm (median maximal diameter, 4.3 cm). The tumors were oval in 4/8 cases (50.0%), irregular in 3/8 cases (37.5%), and dumbbell-shaped (Fig. 1) in 1/8 cases (12.5%). The tumor border was well-defined in 5 cases and had a relatively unclear boundary with the surrounding tissue in 3 cases. Tumor lesions involved the cervical level in 2/8 cases (25.0%), thoracic level in 4/8 cases (50.0%), lumbar level in 3/8 cases (37.5%), and sacral level in 1/8 cases (12.5%). Of the 8 spinal tumors, 1 case showed involvement of both the lumbar and sacral spine and 1 case showed involvement of both the thoracic and lumbar spine (Fig. 2). Based on the MRI scans, the tumors were isointense (4/8, 50.0%) or hyperintense (4/8, 50.0%) in the T1-weighted images (Figs. 1 and 2), and isointense (3/8, 37.5%) (Fig. 2) or hyperintense (5/8, 62.5%) in the T2-weighted images (Fig. 1). Five (62.5%) of the tumors showed heterogeneous enhancement and 3 (37.5%) showed homogeneous enhancement on the MRI scans (Fig. 2). Based on the clinical features and preoperative imaging findings, all of the patients with primary spinal intradural MPNSTs in the present study were preoperatively misdiagnosed as having other lesions, including schwannoma (4/8, 50%), meningioma (3/8, 37.5%) and neurofibroma (1/8, 12.5%).

Table 2
Radiological characteristics of eight patients with primary spinal intradural MPNSTs.

Characteristic	No. of cases
Size (cm)	
≤ 4	4
> 4	4
Shape	
irregular	3
oval	4
dumbbell	1
Border of tumor	
well defined	5
poorly defined	3
T1 and T2 signals	
isointense T1 and hyperintense T2	4
hyperintense T1 and isointense T2	3
hyperintense T1 and hyperintense T2	1
Enhancement	
homogeneous	3
heterogeneous	5
Bone destruction	
yes	1
no	7

3.3. Pathologic findings

Histological examination of hematoxylin-eosin-stained slides revealed that the neoplastic cells were mainly comprised of tapered spindle cells with irregular buckled nuclei and marked nuclear atypia (Fig. 1). Immunohistochemical studies revealed that S-100 was positive in 6/8 cases (75.0%) (Fig. 1), desmin in 4/8 cases (50.0%) cases, vimentin in 5/8 cases (62.5%) (Fig. 1), GFAP in 3/8 cases (37.5%), CD34 in 6/8 cases (75.0%), SMA in 4/8 cases (50.0%), EMA in 2/8 cases (25.0%), and cytokeratin in 1/8 cases (12.5%). Based on the WHO classification, 5 lesions were diagnosed as high-grade and the remaining 3 were diagnosed as low-grade. The mean Ki-67 labeling index was 40.0%, with a range of 20–60%, for high-grade MPNSTs, and 6.8%, with a range of 5–10%, for low-grade MPNSTs.

3.4. Surgical findings, treatment, and long-term outcomes

During surgery, the originating nerve could be found in all cases. Of the 8 spinal intradural MPNSTs, 2 originated from the cervical nerve, 4 from the thoracic nerve, and 2 from the cauda equina. Surgical treatment and outcomes are presented in Table 1. GTR was performed in 5 cases, and STR was achieved in 3 cases. Postoperative radiotherapy was administered to 5 patients, with a median dose of 50 Gy (range, 45–55 Gy), and chemotherapy was administered to 2 patients. At the last follow-up, 6/8 cases (75.0%) had local recurrence, 2 of which underwent a second or third operation. The distant metastatic site was the lung in 2/8 cases (25.0%). The cause of death was tumor recurrence and/or distant metastasis. Case 5 with a primary spinal intradural MPNST experienced tumor recurrence twice, 120 months after the first operation and 25 months after the second operation, at which point the tumor invaded the vertebral body. The patient had died of the disease by the end of our study. After the initial surgery, neurological function was improved or maintained in 7/8 cases (87.5%) and aggravated in 1/8 cases (12.5%). The median survival time (MST) of these 8 patients was 21.0 months. The overall 1-year, 2-year, and 5-year survival rates

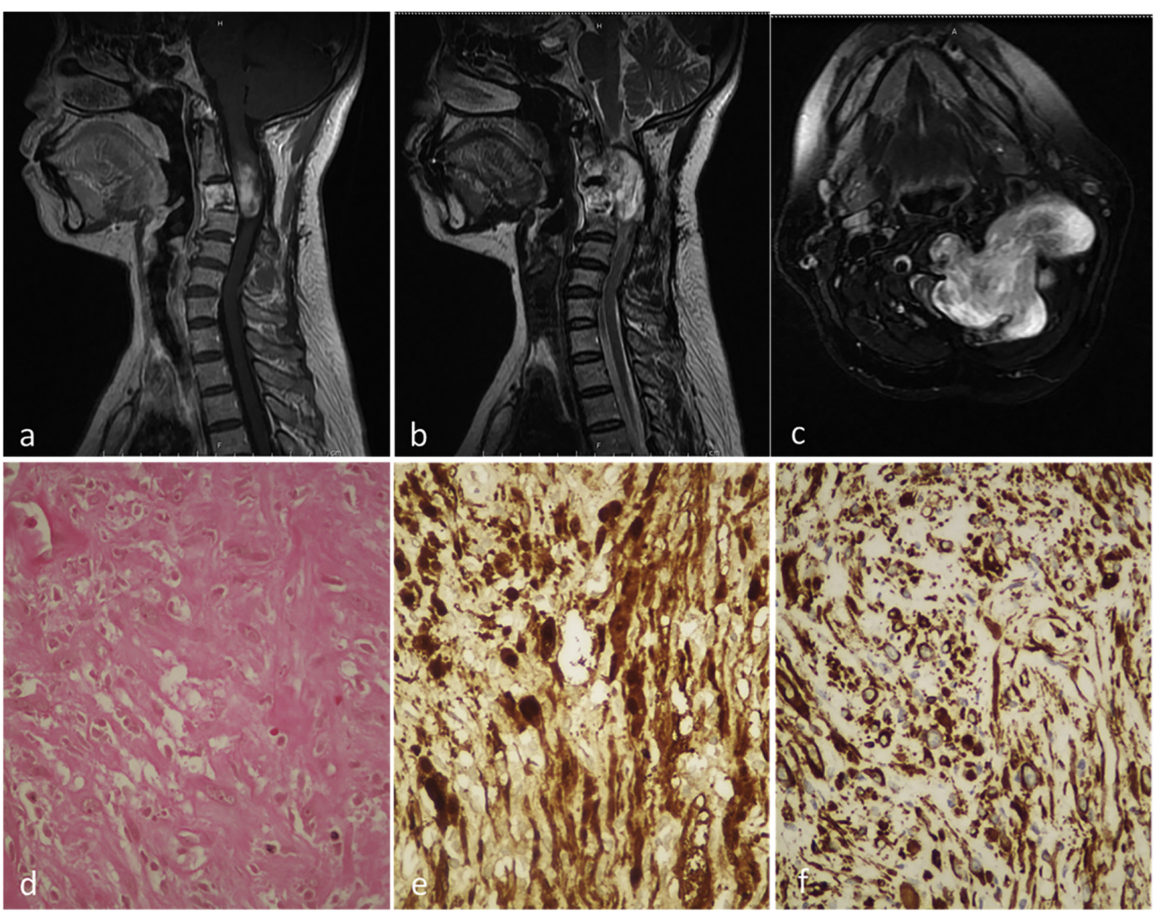

Fig. 1. Case 5. Images obtained 145 months after the first surgery (a, b) showed second tumor recurrence at the C1–3 level. An axial image (c) revealed a dumbbell-shaped intradural lesion in the cervical spinal canal. Proliferation of neoplastic cells with pleomorphic and hyperchromatic round to spindle-shaped cell nuclei (hematoxylin–eosin × 40) (d). Immunohistochemical staining showed positivity for S-100 (× 40) (e) and VIM (× 40) (f).

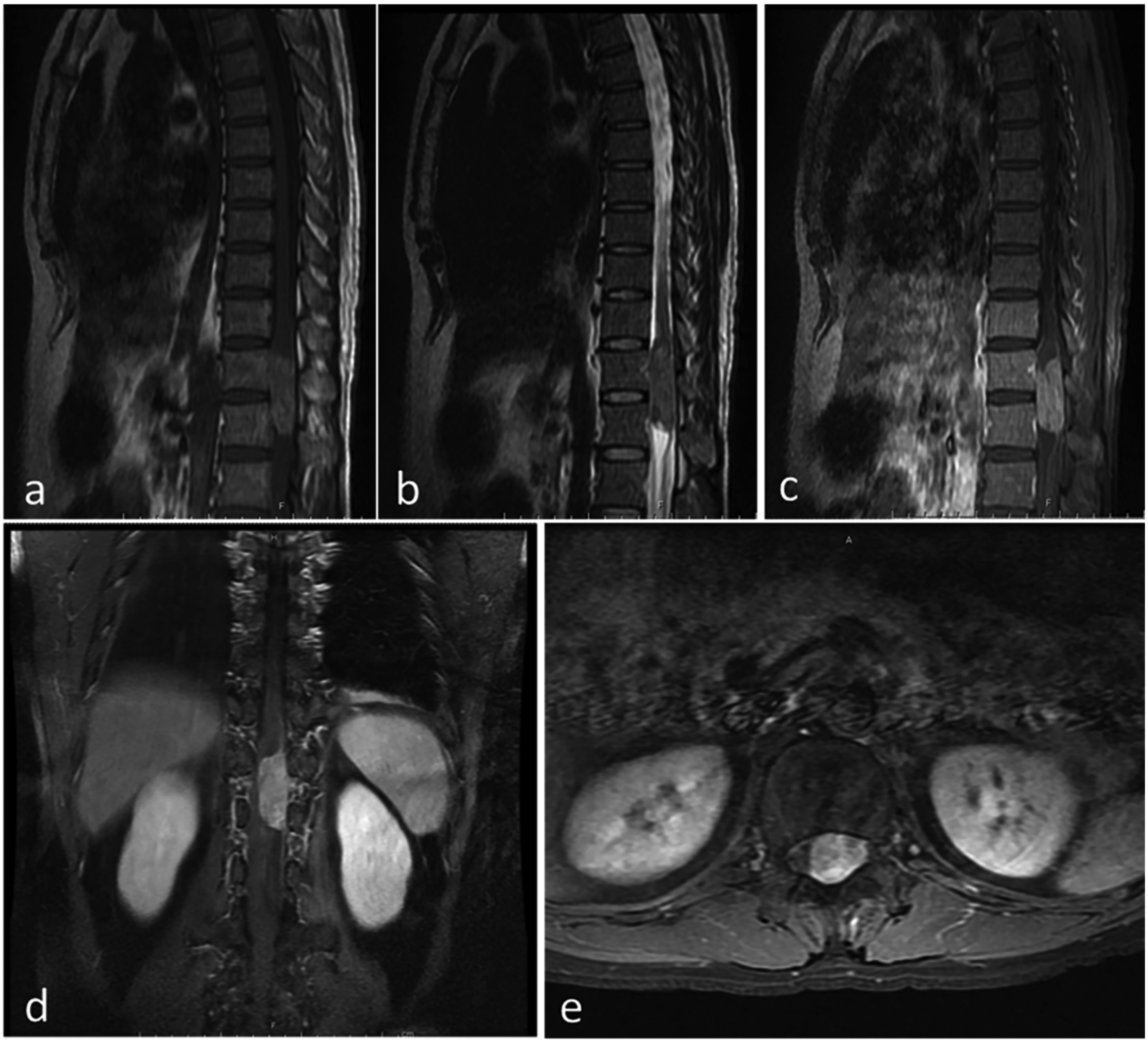

Fig. 2. Case 4. Preoperative magnetic resonance imaging (MRI) of the thoracic and lumbar spine revealed a lesion at the T12-L1 level. T1-weighted sagittal (a) view shows a hyperintense signal of the lesion. T2-weighted sagittal (b) view shows an isointense signal of the lesion. Enhanced MRI sagittal (c), coronary (d), and axial (e) views show a significantly enhanced intradural mass.

were 87.5% (7/8), 50.0% (4/8), and 25.0% (2/8), respectively.

3.5. Complications

Cerebrospinal fluid fistula occurred in 2 cases and was cured within 5 days by lumbar cistern drainage. Urinary tract infection and postoperative pneumonia occurred in 1 and 2 cases, respectively, and were both cured by antibiotics in approximately 1 week. No wound infection, thrombosis, or secondary spinal malformation was found after surgery or during the long-term follow-up.

4. Discussion

Spinal intradural MPNSTs are commonly divided into 2 types based on their sources: primary or metastatic [8–11]. Primary spinal intradural MPNSTs are exceedingly rare in patients without neurofibromatosis, and most have been presented as case reports. Due to the limited number of reports, the clinical and imaging characteristics remain unclear. In the present investigation, we conducted a retrospective study in order to thoroughly analyze the clinical and imaging features, as well as the diagnosis, treatment, and long-term outcomes, of primary spinal intradural MPNSTs.

It has previously been reported that primary spinal intradural MPNSTs occurred primarily in adults. To date, there have been only 6 pediatric patients (6/24, 25%) reported in English-language publications [5,12–15]. In the present study, the median age at diagnosis was 46.5 years, with a range of 21–68 years, which is greater than that in previous reports [14]. The clinical presentation of primary spinal intradural MPNSTs varies in terms of tumor size, tumor location, and tumor invasion. In our study, the most common preoperative clinical symptom was limb weakness (5/8, 62.5%), followed by pain (4/8, 50.0%), and limb numbness (2/8, 25.0%), findings that are largely consistent with those of previous reports [5]. All of these symptoms, however, are nonspecific. The disease duration ranged from 1 month to 12 months, with a median of 4.5 months, which was longer than that found in previous reports [5,14].

Due to the rarity of this disease and the small amount of published information concerning it, the radiological features of primary spinal intradural MPNSTs remain largely unknown. As observed in the present study, primary spinal intradural MPNSTs usually present as oval or irregular masses with well-defined or ill-defined margins on MRI. To our knowledge, case 5 is the first report of a dumbbell-shaped intradural and primary spinal intradural MPNST. Previous studies have reported that primary spinal intradural MPNSTs generally exhibit an isointense signal in T1-weighted imaging and a hyperintense signal in T2-weighted imaging [5,16]. However, our study revealed that 50.0% of the tumors exhibited a hyperintense signal in the T1-weighted imaging and 62.5% exhibited a hyperintense signal in the T2-weighted images. Xu et al. [14] reviewed the literature and found that varying enhancement had been noted by previous researchers. Significant heterogeneous enhancement was present in most of our cases. A previous study had shown that 31.58% of the tumors were located at the thoracic spine level and 26.32% at the cervical spine level [16]. Xu et al. [14] also reported that the cervical spine was the most frequently affected area. In our series, 4/8 (50.0%) of the tumors were located at the thoracic level and 3/8 (37.5%) at the lumbar level, which is contrary to previous findings. The radiographic findings of primary spinal intradural MPNSTs usually have limited value in accurate preoperative diagnosis. Radiological diagnoses tend to be either meningioma or neurofibroma, especially benign and conventional schwannomas [17].

Pathologic diagnosis of spinal MPNSTs is made by identifying typical characteristics such as high cellularity with spindle-shaped cells, nuclear atypia, necrosis, and endothelial proliferation [18]. In our study, all of the tumors contained some isolated regions with high cellularity and spindle-shaped cells. The Ki-67 labeling index, as a marker of cell proliferation, has been used to determine the prognosis of some malignant tumors [19,20]. In the present study, the mean Ki-67 labeling index was 40.0%, with a range of 20–60%, for high-grade MPNSTs, and 6.8%, with a range of 5–10%, for low-grade MPNSTs. Due to the small number of cases, no statistical analysis was performed to confirm whether Ki-67 was a potential indicator of the poor prognosis of MPNSTs.

Due to the paucity of primary spinal intradural MPNST cases, there is no consensus regarding the optimal treatment protocol. However, surgical resection of the lesions remains the cornerstone of therapy. Previous research has shown that GTR of the lesions can improve the prognosis [1,21]. Although local recurrence and metastases may occur even with GTR, radical excision of a mass is still recommended to reduce complications, elucidate the histopathological features of the tumor, achieve sufficient volume reduction for further adjuvant therapies, and effectively prolong survival. GTR was performed in 5/8 (62.5%) of the cases in our series without causing further neurological damage. Several studies have recommended that the ideal surgical treatment of malignant tumors, including MPNSTs, consists of en bloc resection of the lesion in order to improve prognosis [15,22]. However, radical excision of spinal intradural MPNSTs with a wide margin may be very difficult due to residual tumor cells on such vital structures as the spinal cord, dura, major blood vessels, or other critical nerves. In the present study, 3 patients underwent STR of the tumors, and local recurrence was found in all of them during follow up. This result indicates that insufficient resection of the lesion and release of highly malignant cells may lead to a high rate of tumor recurrence. In addition, of the 5 patients who underwent GTR, 3 of them still relapsed and 1 progressed to metastasis. The reason for these outcomes may have to do with the fact that piecemeal total resection is associated with possible tumor cell contamination in the surgical field.

With regard to auxiliary therapy for MPNSTs, some studies have proven that adjuvant radiotherapy may contribute to local control of these tumors [4,23,24]. Acharya et al. [25] also suggested that postoperative radiotherapy might help suppress or eradicate residual tumor growth. Other studies revealed, however, that adjuvant radiotherapy is ineffective in controlling recurrence and does not appear to affect overall survival [4,26]. Thus, the effect of adjuvant radiotherapy in the treatment of MPNSTs requires further exploration. In our cohort, 5 patients received postoperative radiotherapy, with a median dose of 50 Gy. Tumor-bed radiotherapy is recommended for high-grade MPNSTs regardless of the extent of resection and for low-grade MPNSTs if removal is insufficient. The benefit of adjuvant chemotherapy for MPNSTs remains unclear. However, it is worth noting that a 45% response rate has been observed in pediatric patients with MPNSTs who underwent chemotherapy [27]. Indeed, in our present study, only 2 patients underwent postoperative chemotherapy.

Primary spinal intradural MPNSTs are aggressive malignant tumors, and the clinical outcome is poor. In the present study, the rate of tumor recurrence was 75.0% and the 5-year overall survival rate was only 25.0%. Even after a radical resection followed by adjuvant therapy, the rates of local recurrence and metastases were high. The most common sites for metastatic spread after the resection of spinal intradural MPNSTs are the lungs and the liver [13]. In our series, tumor metastasis to lungs was discovered in 2 cases, both of which were diagnosed as high-grade MPNSTs. Due to the limited number of reports in English-language publications, the prognostic factors for MPNSTs remain unclear. Previous studies have reported that the nuclear expression of p53, S-100, and neurofibromatosis type I were prognostic factors for MPNSTs [28–30]. In our series, incomplete removal, high histological grade, local recurrence, and metastasis seemed to predict a worse outcome.

5. Conclusions

Given its high local relapse rate, primary spinal intradural MPNST is a challenging clinical entity. Primary spinal intradural MPNSTs radiologically present themselves heterogeneous and thus difficult to distinguish from schwannomas or meningiomas. There is no consensus regarding the optimal treatment protocol due to the rarity of this disease. Surgical resection, especially GTR, is the preferred treatment for primary spinal intradural MPNSTs. The benefit of adjuvant therapy for primary spinal intradural MPNSTs remains controversial. Further studies with larger cohorts are needed to explore both the effects of adjuvant therapy as well as the prognostic factors for primary spinal intradural MPNSTs.

Declaration of Competing Interest

The authors declare no conflict of interest.

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