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Systematic Review of Published Cases of Primary Epithelioid Sarcoma of the Spine

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Manuscript Preparation E
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Background: Epithelioid sarcoma is rare, represents less than 1% of all sarcomas, usually occurs in the extremities, and rarely presents as a primary sarcoma of the spine. Publications are usually single reports or case series. We aimed to undertake a systematic review of publications of cases of primary epithelioid sarcoma of the spine to evaluate clinical presentation, diagnosis, management, and patient outcomes.

Material/Methods: We searched studies on spinal epithelioid sarcoma in the PubMed database. Only studies with secondary epithelioid sarcoma or without effective data for analysis were excluded. Cases in which epithelioid sarcoma first invaded other sites and then affected the spine were also excluded.

Results: Twenty-three patients from 13 studies were included in the study, aged between 14 and 65 years, and the sex ratio of female to male was 1: 2.29. The survival time was 18.7±13.8 months. The survival time of males was longer than that of females (22.9±14.4 vs 9.0±4.6, *P*=0.027). The onset age was linearly correlated with the size of the lesion (size=-0.161*age+11.841).The lesions located in lumbar vertebra had the worst prognosis. Postoperative radiotherapy had a statistically significant effect on survival time (*P*=0.040).

Conclusions: This systematic review identified 23 published cases of primary epithelioid sarcoma of the spine. Pain was the main presenting symptom, and tumor size increased with patient age. Female sex and primary location in the lumbar spine were associated with poor survival. Although surgery was the first-line treatment, postoperative radiotherapy and chemotherapy may improve clinical outcomes.

Keywords: Sarcoma • Spine • Systematic Reviews as Topic

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Background

Epithelioid sarcoma was named in 1970 by Enzinger, who defined a sarcoma with a peak incidence in young adult males and predilection for extremities, involving subcutis or deeper tissue, and extending along tendon sheaths or aponeuroses [1]. Relevant studies suggest that epithelioid sarcoma accounts for only 1% of all bone and soft tissue tumors [2]. The incidence in Europe and the United States is less than 0.2 and 0.5 new cases per million inhabitants per year, respectively [3]. Most of the manifestations are painless slow growth of single hard nodules, can be adhered to tendon, deep fascia, nerves and bone, can be infiltrated along the neurovascular bundle, or can be compression growth [4]. The disease is poorly studied and often has a poor prognosis.

Most previous studies reported epithelioid sarcoma located in the extremities [1-4], while few reported epithelioid sarcoma located in the spine. The spine, as the axial bone of the human body, is the bridge supporting the upright human body, and its anatomical structure is complicated by surrounding blood vessels and nerves [5]. Spinal epithelioid sarcoma often leads to pathological vertebral fractures [6], and the growth of masses invading the spinal canal leads to spinal cord injury [7], making the treatment of spinal epithelioid sarcoma more challenging.

The incidence of spinal epithelioid sarcoma is extremely low and there is a lack of clinical understanding of this disease, so it is easy for patients to be misdiagnosed and mistreated [8]. Moreover, due to its characteristics of infiltration and growth, which are prone to recurrence and metastasis, the treatment becomes difficult [9]. At present, only a few cases have been reported, and no large sample analysis has been published. Therefore, in this study, we aimed to undertake a systematic review of publications of cases of primary epithelioid sarcoma of the spine to evaluate clinical presentation, diagnosis, management, and patient outcomes.

Material and Methods

Ethics Statement

Ethics review and approval were waived by the Ethics Committee of Henan Provincial People's Hospital for this study because all data in this manuscript were all obtained from published studies and the study was a systematic review.

Literature Research

A systematic review was performed in accordance with the PRISMA guidelines, and the literature search of the PubMed (www.ncbi.nlm.nih.gov/pubmed/) and Web of Science (www.webofscience.com/) databases was performed by 2 independent reviewers to identify studies with spinal epithelioid sarcoma; the publication dates included were between January 1, 2000, and December 31, 2021, and the publication language was limited to English. Search variables, including the search term "epithelioid sarcoma", were used in combination with controlling terms from MeSH, including "spine", "cervical", "thoracic", and "lumbar".

Eligibility Criteria

Only studies with spinal epithelioid sarcoma were considered for inclusion. Clinical studies, case reports, case series, and letters to the editor were also included in the study. Studies without spinal epithelioid sarcoma, with secondary epithelioid sarcoma, or without effective data for analysis were all excluded. Cases in which epithelioid sarcoma first invaded other sites and then affected the spine were also excluded.

Selection Process and Data Collection Process

Two reviewers independently screened the full articles to ensure that the recruited studies strictly complied with the eligibility criteria. The reviewers also scanned the reference lists of the included articles for additional studies that met the inclusion criteria. The reviewers independently participated in the extraction of effective data from the included reports. Disagreement about the included data was resolved by discussion, and a third reviewer's opinion was consulted to make the final decision if necessary (**Figure 1**).

Outcome Measures

The following information was extracted from the included studies: publication date, name of journal, nationality, sex, age, onset time, symptoms, size of the lesions, location of the lesions (cervical, thoracic, or lumbar spine), methods of surgery, follow-up, chemotherapy, and radiation therapy.

Statistical Analysis

Statistical analyses were performed using IBM SPSS statistics (version 22.0, IBM Corp., Armonk, NY, USA). Quantitative data are reported as the mean with standard deviation, and qualitative data are reported as counts and percentages. For data that fit a normal distribution, the *t* test was used to compare the differences between the independent groups. Otherwise, the Mann-Whitney U test was used. Kaplan-Meier analysis was used to estimate the cumulative survival rate, which was compared by the log-rank test. We compared the effects of surgery methods, complete resection or not, radiotherapy, and chemotherapy on survival time, and the survival curves were plotted using SPSS. All statistical tests were 2-sided, with $P<0.05$ considered statistically significant.

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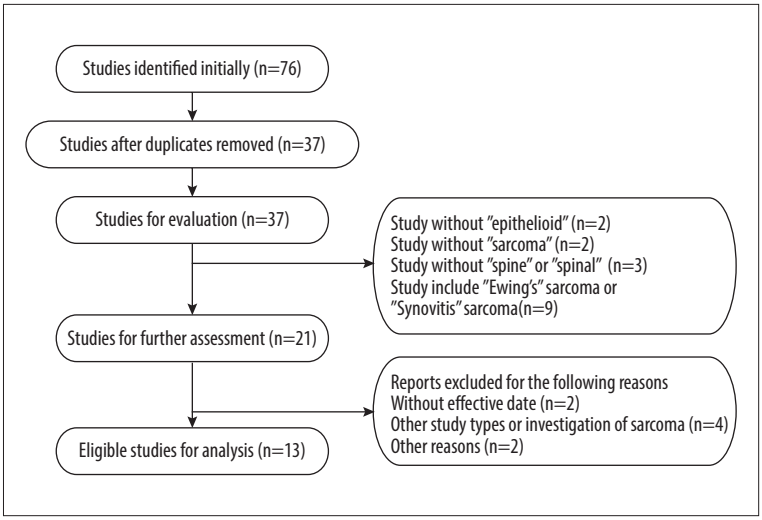

Figure 1. Literature screening process (Microsoft Office 2020).

Table 1. General information of the patients and the treatment methods.

Gender	Age (years)	Distal/proximal	Onset time (months)	Symptom	Size (cm)	Location
Male	30	Distal	3	Pain	7.5	Lumbar
Male	25	Proximal	1	Pain tweakness	4.5	Lumbar
Male	24	Proximal	4	Pain weakness	NA	Lumbar
Female	25	Proximal	6	Pain	5.8	Cervical
Male	19	Proximal	0.75	Pain weakness	NA	Cervical
Male	17	NA	13	Pain weakness	NA	Cervical
Male	14	NA	24	Pain paralysis	15.0	Thoracic
Male	14	NA	NA	Pain	9.0	Thoracic
Female	45	NA	NA	Pain	NA	Thoracic
Male	21	NA	4	Pain	NA	Cervical
Male	35	Proximal	12	Pain	NA	Lumbar
Female	49	NA	10	Pain	NA	Lumbar
Male	49	NA	9	Pain weakness	NA	Thoracic
Male	58	NA	11	Pain	NA	Thoracic
Male	21	NA	NA	Pain	NA	Thoracic
Male	29	NA	2	Pain	NA	Thoracic
Female	65	NA	3	Pain	NA	Thoracic
Male	42	NA	3	Pain	7.6	Cervical
Female	29	NA	NA	Pain	7.0	Lumbar
Female	44	NA	3	Pain	3.9	Lumbar
Male	50	NA	3	Pain paralysis	5.0	Lumbar
Male	28	NA	5	Pain	4.5	Thoracic
Female	41	NA	NA	NA	5.5	Lumbar

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Table 1 continued. General information of the patients and the treatment methods.

Gender	Surgery method	Gross total resection	Follow-up (months)	Survival state	Chemotherapy	Radiotherapy
Male	EN	Y	8	Dead	Y	N
Male	PR	NA	NA	NA	NA	NA
Male	PA	N	4	Dead	Y	Y
Female	PR	Y	0	Dead	NA	NA
Male	PR	Y	25	Dead	Y	Y
Male	EN	NA	36	Alive	Y	Y
Male	EN	Y	26	Alive	NA	NA
Male	PR	Y	36	Alive	Y	Y
Female	PR	NA	12	Alive	NA	Y
Male	PR	NA	NA	NA	NA	NA
Male	PA	N	3	Dead	Y	Y
Female	PR	N	35	Alive	NA	N
Male	PA	N	26	Alive	NA	Y
Male	PA	N	33	Alive	NA	Y
Male	PR	Y	6	Alive	NA	N
Male	PR	N	36	Alive	NA	Y
Female	PA	N	24	Alive	NA	Y
Male	EN	Y	35	Dead	Y	Y
Female	PA	N	9	Dead	N	N
Female	EN	Y	22	Dead	Y	N
Male	PA	N	4	Dead	Y	NA
Male	PA	N	55	Dead	Y	Y
Female	PA	N	NA	NA	N	Y

NA – no value; Y – yes; N – no; EN – en bloc; PR – piecemeal resection; PA – partial resection.

Results

Study Inclusion

A total of 13 studies were included in this study [10-22], including 5 studies from the United States and 1 study each from Japan, Portugal, South Korea, Italy, Thailand, Germany, Switzerland, and Canada. The studies were published from 2006 to 2021. All included studies were case reports or serial case reports.

General Information of the Patients

A total of 23 patients were included, with an average age range of 33.7±14.1 years, and an age distribution of 14.2 to 65.7 years. There were 7 female and 16 male patients, with a sex ratio of females to males of 1: 2.29. The onset time was 6.5±5.8 months, and the distribution ranged from 0.8 to 24.0 months. The main symptoms were pain (23/23,100%), weakness (5/23, 21.7%), and paralysis (2/23, 8.6%).

There were 5 cases with lesions in the cervical spine (21.7%), 9 cases in the thoracic spine (39.1%), and 9 cases in the lumbar spine (39.1%). All the cases for which information could be obtained were primary lesions (15/15), and in the distribution of pathological type, 1 was distal and the other 6 were proximal. The average diameter of the lesions was 6.8±3.1 cm, and the size distribution ranged from 3.9 to 15.0 cm (**Tables 1, 2**).

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Table 2. Clinical characteristics of the spinal epithelioid sarcoma.

Variables	
Sex (male/female)	16/7
Age (year)	33.7±14.1
Distal/proximal	1/5
Onset time (months)	6.5±5.8
Symptom	
Pain	23 (100%)
Weakness	5 (21.7%)
Paralysis	2 (8.6%)
Size (cm)	6.8±3.1
Location	
Cervical	5 (21.7%)
Thoracic	9 (39.1%)
Lumbar	9 (39.1%)
Surgery method	
En bloc	5 (21.7%)
Piecemeal resection	9 (39.1%)
Partial resection	9 (39.1%)
Survival time(months)	18.7±13.8

Treatment Method

All the patients underwent surgical treatment, including en bloc resection in 5 cases (21.7%), piecemeal resection in 9 cases (39.1%), and partial resection in 9 cases (39.1%). Among them, 8 cases reached gross total resection, and the other 9 cases did not. A total of 10 patients received chemotherapy, and the situation of the remaining cases was unknown. The most commonly used chemotherapy regimen was ifosfamide + doxorubicin. A total of 14 patients received radiotherapy. The survival time of the patients after treatment was 18.7±13.8 months, and the survival time distribution was 0 to 55 months. One patient died immediately after surgery due to complications.

Correlations Between Clinical Features

Using univariate correlation analysis, it was found that age was linearly correlated with the size of the lesion (R^2=0.372, *P*=0.046), and the regression equation could be expressed as size=-0.161*age+11.841 (**Figure 2**). In other words, the younger the patient was, the larger the lesion diameter. By comparing the survival time of the different sexes, we found that the survival time of male patients was longer than that of female patients (22.9±14.4 vs 9.0±4.6 months, *P*=0.027). We found that the survival time of lesions in thoracic vertebra was 27.9±14.6 months, in lumbar vertebra was 10.4±6.6 months, and in cervical vertebra was 17.0±13.8 months, with statistically significant differences among the 3 groups (*P*=0.017). Patients with lesions in the lumbar spine had the shortest survival time.

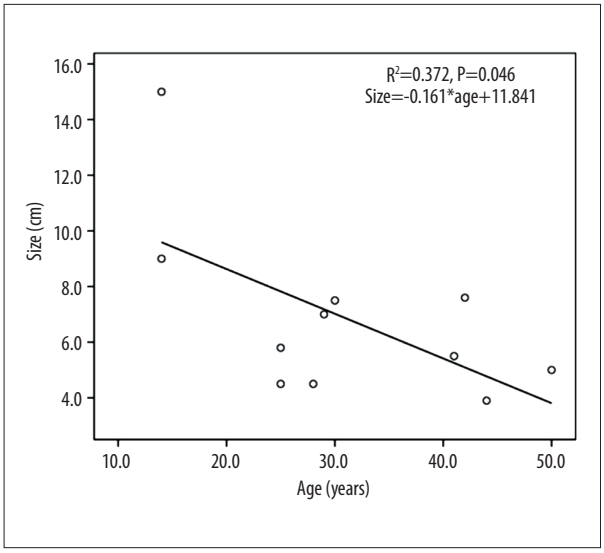

Figure 2. Correlation between age of onset and size of tumor lesion (IBM SPSS statistics, version 22.0, IBM Corp.).

Correlation Between Treatment and Survival Time

Kaplan-Meier survival analysis was used to study the correlation between treatment and survival time, and we found no differences in the survival time among the 3 surgical methods (*P*=0.366; **Figure 3C**). There was no significant difference in survival time of patients with or without complete resection of the tumor boundary (*P*=0.924; **Figure 3D**). The effect of postoperative chemotherapy on survival time was not statistically significant (*P*=0.033; **Figure 3B**). Postoperative radiotherapy had a statistically significant effect on survival time (*P*=0.040; **Figure 3A**).

Discussion

In this study, we make a systematic review of publications of cases of primary epithelioid sarcoma of the spine. A total of 23 cases in 13 studies from 9 countries were included in this study, and clinical presentation, diagnosis, management, and patient outcomes were evaluated. To the best of our knowledge, this is the largest sample size in a study of spinal epithelioid sarcoma and the first systematic review of spinal epithelioid sarcoma.

In this study, there were 7 female and 16 male patients, with a ratio of females to males of 1: 2.29, which was similar to what was previously reported; the average patient age was 33.7 years, which was consistent with the feature that epithelioid

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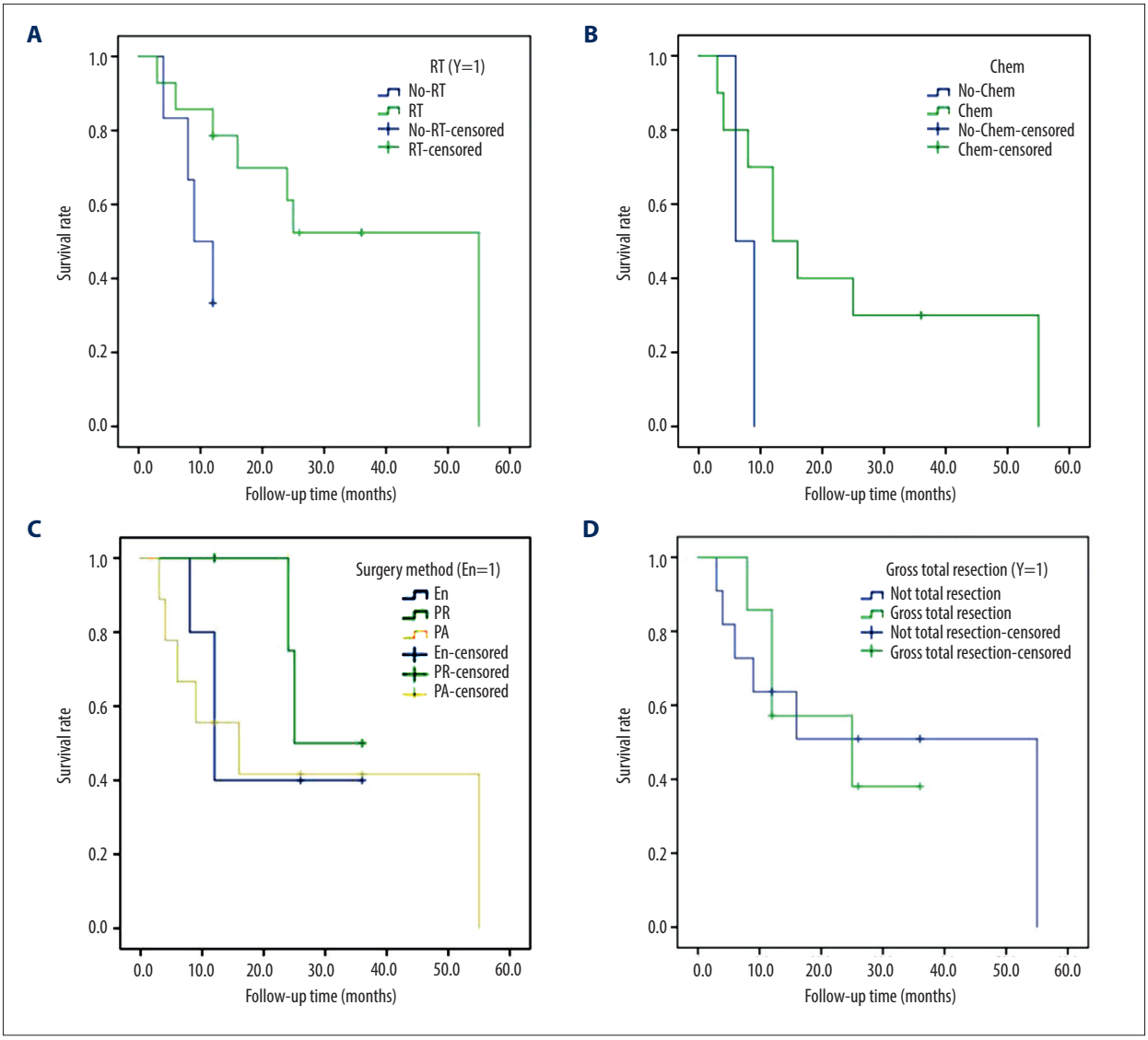

Figure 3. Kaplan-Meier curves of potential prognostic factors for epithelioid sarcoma. The log-rank test was used to detect the potential prognostic factors. (**A**) Radiotherapy (RT), *P*=0.040. (**B**) Chemotherapy (Chem), *P*=0.033. (**C**) Surgery method (En – en bloc; PR – piecemeal resection; PA – partial resection), *P*=0.366. (**D**) Gross total resection, *P*=0.924 (IBM SPSS statistics, version 22.0, IBM Corp.).

sarcoma tends to occur in young adults [23-25]. Spillane [25] reviewed the Royal Marsden National Health Service Trust and concluded that the average onset age was 29 years and the male to female ratio was 2.7: 1. The average onset time of patients is 6 months, and patients often have only the symptom of pain, which often leads to missed diagnosis and misdiagnosis. In 1 case in this study, a patient was misdiagnosed as having lumbar disc herniation and mistreated. In addition, the average diameter of lesions was more than 6 cm; this also demonstrates the insidious and rapidly growing nature of epithelioid sarcoma. The absence of characteristic clinical manifestations of epithelioid sarcoma requires the attention of physicians. Therefore, unexplained pain and a mass in the spinal area should be checked regularly. MRI of the affected spinal region is recommended if the patient fails to progress within 6 weeks of conservative care.

According to the classification of epithelioid sarcoma, only 1 of the cases was distal, and the rest were proximal. Classic distal-type epithelioid sarcoma shows characteristic histological features of a nodular growth pattern of plump epithelioid cells with a relatively abundant eosinophilic cytoplasm [26]. The proximal-type epithelioid sarcoma is characterized by multinodular distributions and sheets of large polygonal cells with pleomorphic vesicular nuclei and prominent nucleoli [27]. Based on a previous study, the distal type often occurs on extremities

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while proximal type occurs on the head, neck, and trunk [28]. The cases included in this study were all spinal epithelioid sarcoma; this is also in line with the distribution of the proximal type. What is more interesting is that the location of the sarcoma also affects survival time, and the lesions in the lumbar spine have the shortest survival time.

Epithelioid sarcomas are prone to recurrence, metastasis, and patient death, and complete boundary resection is still considered to be the most effective treatment [29]. In our study, there was no significant difference in the impact of surgical methods on survival time. However, the complex anatomy surrounding the spine makes complete resection extremely difficult. In this study, en bloc was performed in 21.7% of patients, piecemeal resection was performed in 39.1% of patients, and partial resection was performed in the remaining patients. Sambri [30] found that only 10 of 35 patients had the possibility of boundary resection, which also illustrated the difficulty of gross total resection. The tumor diameter of all cases included in the present study was greater than 6 cm, and the large tumor volume predicted a poor prognosis. Zhang [31] and Jawad [24] found that tumor size >5 cm meant poor survival outcome. The cases included in the present study were basically the proximal type, which has a higher recurrence rate than the distal type [32].

The survival time of male patients was longer than that of female patients; this finding differs from previous studies, which may be characteristic of spinal epithelioid sarcoma. Xiong et al [33] reached the opposite conclusion in their study, finding that female sex and Black race were risk factors for poor prognosis. Therefore, the effect of sex on epithelioid sarcoma remains to be studied in a large case-control study. We also found that age was negatively correlated with tumor size, and the regression equation could be expressed as size=-0.161*age+11.841(R^2=0.372, *P*=0.046), which means the younger the age of onset, the larger the tumor size, which further confirms the high mortality rate of the sarcoma. Grunwald et al [34] found that a 10% increase in tumor volume indicated a poorer survival time. Frezza et al [35] found that the 5-year survival rate of patients with tumors smaller than 5 cm was 78%, while that of patients with tumors larger than 5 cm was only 53%.

Epithelioid sarcoma is distributed in all positions of the spine, and cases with thoracic and lumbar lesions were higher (39.1%). At the same time, our study found that the location of lesion distribution also affected the survival time; the survival time of lesions in thoracic vertebra was 27.9±14.6 months, in lumbar vertebra was 10.4±6.6 months, and in cervical vertebra was 17.0±13.8 months, with statistically significant differences among the 3 groups (*P*=0.017), which means the lesions in the lumbar spine have the shortest survival time. More lesions were located in the lumbar spine, which indicates the worst prognosis, which deserves the attention of clinicians.

Another important founding was that only postoperative radiotherapy (*P*=0.040) and chemotherapy (*P*=0.033) was shown to have an impact on the survival time of patients, after Kaplan-Meier survival analysis, while surgical method did not have an impact on the survival time of patients. This may be the unique feature of spinal epithelioid sarcoma. Previous studies concluded that complete resection of tumor margins and postoperative radiotherapy for epithelioid sarcoma were independent factors in prolonging postoperative tumor-free survival [36,37]. Touati et al [38] conducted a retrospective analysis of the clinical efficacy of chemotherapeutic drugs on epithelioid sarcoma, and all patients but 1 progressed on treatment. To analyze the response rate and progression-free survival of epithelioid sarcoma to chemotherapy, Jones et al [39] found that the median progression-free survival time was 29 weeks (95% confidence interval: 23-35) after chemotherapy. Their study validated the effectiveness of chemotherapy.

There were limitations in this study. First, the low incidence rate of spinal epithelioid sarcoma resulted in a limited number of references, and only 13 articles were included in this study. Second, the insufficient sample size may lead to the bias of the results of this study. Many included case reports are only the summary of the author's personal experience, and the research on epithelioid sarcoma needs to be further understood. Third, due to the limitation of the cases and the lack of description of chemotherapy regiments in some studies, the clinical efficacy of specific chemotherapy regiments was not analyzed in detail in this study.

Conclusions

To the best of our knowledge, this is the largest sample size in a study of spinal epithelioid sarcoma and this is the first systematic review of this disorder. Because primary epithelioid sarcoma of the spine is very rare and only case reports and small case series exist, this systematic review has identified 23 cases and has shown that pain was the main presenting symptom and tumor size increased with patient age. Female sex and primary location in the lumbar spine were associated with poor survival. Although surgery is the first-line treatment, postoperative radiotherapy and chemotherapy may improve clinical outcomes.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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