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ORIGINAL ARTICLE

Survival analysis of patients with spinal chordomas

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Abstract

This study was aimed to analyze the survival of patients with spinal chordomas. Patients' data in the Surveillance, Epidemiology, and End Results (SEER) database were retrieved and analyzed statistically. There were 765 patients with spinal chordomas between 1974 and 2013. The overall survival did not improve significantly over decades for patients receiving surgery and radiotherapy (SR) ($P = 0.221$). There were significant differences in overall survival among subgroups of patients receiving surgery (S), radiotherapy (R), and neither S nor R (NSR) ($P = 0.031$, 0.037, and 0.031, respectively). Cancer-specific survival did not change significantly among subgroups of patients receiving R ($P = 0.411$), while it increased steadily among subgroups of patients receiving S, SR, and NSR ($P < 0.001$, 0.001, and 0.049, respectively). In the multivariate Cox regression model, younger onset age (hazard ratio [HR] 1.052, $P < 0.001$), surgery (HR 0.291, $P = 0.001$), and tumor location of the sacrum (HR 0.401, $P = 0.002$) were associated with a better overall survival. Similarly, younger onset age (HR 1.036, $P = 0.029$), surgery (HR 0.221, $P = 0.009$), and tumor location of the sacrum (HR 0.287, $P = 0.002$) were also associated with a higher cancer-specific survival. The changes in overall and cancer-specific survival over time differ among different treatment groups. Younger onset age, surgical strategy, and tumor location of the sacrum may be correlated with a higher overall and cancer-specific survival.

Keywords Spinal chordomas · Clinical factors · Incidence · Survival · SEER

Introduction

Chordomas are rare malignant tumors that originate from notochordal remnants during the spine development period. They are typically low grade but locally invasive malignancies [1]. The tumors prefer occurring in patients with mean age of 60 years old [2]. The overall incidence is about one per million individuals and they account for approximately 1 to 4% of all bone malignancies [3, 4].

Chordomas are often divided into three types according to the tumor location: skull base, mobile spine, and sacral chordomas, with incidence rates of 30, 20, and 50% respectively [1]. Cases originating from other sites have also been described, but they are very rare [5]. According to their histopathological classification, chordomas can also be divided into three types: classic, chondroid, and dedifferentiated chordomas. However, the latter two types are rarely studied because they are much more infrequent than classic cases.

Patients are often clinically asymptomatic until later stages [6] when the tumors invade into adjacent tissues and cause the local destruction of bone or dysfunction of nerves. The destructive and latent characteristics make it a terrible disease. In addition, approximately 30–40% of patients develop metastases, usually after evidence of local recurrence. Metastases can occur in the lung, liver, bone, and other sites. However, the lethal effect of this disease is primarily due to its local aggressiveness instead of its potential to metastasize [1]. The overall survival rates are 65 and 35% at years 5 and 10, respectively [7–9].

Chordomas are the most frequent primary tumors of the mobile spine [10]. Due to their close relationship with the backbone and their invasion to the spinal cord and nerve roots, an increasing number of (radio)surgical strategies have been investigated [10–13]. However, most studies

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mainly focused on skull base and sacral chordomas [14–20]. Some publications reported both mobile spine and sacral chordomas, but they included very few cases [10, 12, 21]. Besides, treatment strategies have changed over time, especially radiotherapy strategies [22–27]. Although new treatment strategies have been described with longer survival time and better local control when compared with control group horizontally [28], there is no previous study demonstrating the longitudinal changes in survival in different treatment groups over the last few decades. Thus, whether the survival of patients with spinal chordomas has improved significantly over time is not well understood. In addition, to the best of our knowledge, there is no recent large-scale study investigating the incidence patterns and the influence of clinical factors on overall and cancer-specific survival of patients with spinal chordomas (including mobile spine and sacral chordomas). Silvia et al. reported the largest study with 138 consecutive patients [12]. Although 345 cases of sacral chordomas were investigated last year, a study of mobile spine chordomas and cancer-specific survival has not been conducted, and changes in survival were also not well described [20].

In this study, 765 cases diagnosed between 1974 and 2013 were evaluated using the Surveillance, Epidemiology, and End Results (SEER) program database to reveal the changes in incidence and survival of spinal chordomas. In order to avoid the bias produced by evolution of treatment strategies, 379 patients diagnosed between 2004 and 2013 were further investigated exclusively to determine the influence of clinical factors on the overall and cancer-related survival.

Methods

The SEER database and related codes

The study cohort was obtained from the SEER program's 2015 Research Data release. We used code number "011" under the North American Association of Central Cancer Registries item "CS Schema v0204+" and found all bone malignancies. All patients with bone malignancies were filtered by the International Classification of Diseases for Oncology (ICD-O-3 edition) histology codes consistent with chordomas (9370, 9371, 9372). Mobile spine and sacrum were coded as C412 and C414. All patients diagnosed with spinal chordomas between 1974 and 2013 were included to reveal the changes in incidence and survival. Patients with unknown treatment strategies (code numbers 8 and 9) were excluded when investigating the influence of clinical factors on survival. Survival time was calculated from the date of diagnosis to the date of death or last follow-up.

Statistical analysis

All patients were divided into four groups according to the treatment strategies: radiotherapy alone (R), surgery alone (S), and surgery combined with radiotherapy (SR), neither surgery nor radiotherapy (NSR). To study the changes in survival over time, each of the groups was further divided into four subgroups according to the year of diagnosis: 1974–1983, 1984–1993, 1994–2003, and 2004–2013.

Changes in survival over time were analyzed via Kaplan-Meier survival analysis. The Cox proportional hazard model was utilized for univariate and multivariate analysis to identify factors associated with survival. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. The significance level for all tests was two sided at 5%. Original data were extracted using Perl language. All data were analyzed using SPSS Statistics software (V.24; IBM Corporation, USA).

Results

Demographics

There were 765 patients with spinal chordomas between 1974 and 2013 (Table 1). Mobile spine and sacral chordomas accounted for 44.3% ($n = 339$) and 55.7% ($n = 426$) of total cases, respectively. The median follow-up time was 52 months. The 5- and 10-year overall survival rates for all patients were 65.6 and 38.1%, respectively. The 5- and 10-year cancer-specific survival rates were 71.5 and 47.8%, respectively.

Table 1 Patient and tumor characteristics

Characteristics		Number (%)
Patients, *n*		765
Mean age (years) (± SD)		60.3 ± 17.1
Mean tumor size (mm) (± SD)		82.5 ± 74.2
Gender		
Men		475 (62.1)
Women		290 (37.9)
Marriage status	Married	459 (60.0)
	Never married	127 (16.6)
	Widowed	79 (10.3)
	Divorced	44 (5.8)
	Others	56 (7.3)
Race	White	676 (88.4)
	Asian/Pacific Islander	55 (7.2)
	Black	19 (2.5)
	Others	15 (2.0)
Tumor location	Mobile spine	339 (44.3)
	Sacrum	426 (55.7)
Pathology	Classic	747 (97.6)
	Chondroid	12 (1.6)
	Dedifferentiated	6 (0.8)

Data presented as number of patients (%) unless otherwise indicated

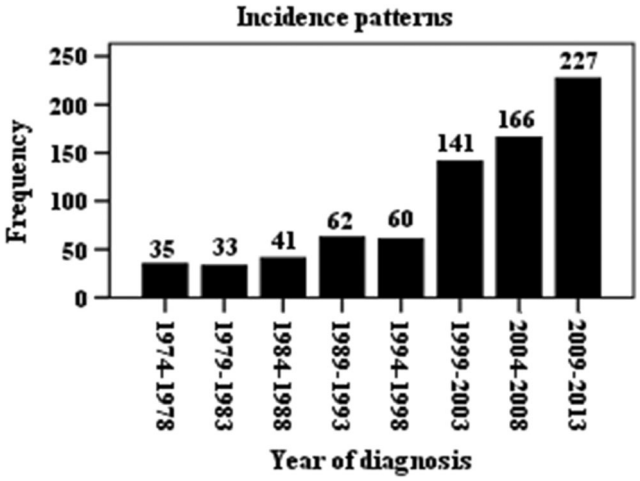

Fig. 1 The incidence of spinal chordomas increased obviously during last few decades

Incidence and changes in survival

The frequency of spinal chordomas increased obviously over the last 40 years (Fig. 1). The incidence rate of such disease was 0.3 per 100,000 and was age-adjusted to the 2000 US Standard Population.

There were no significant differences in overall survival among subgroups of patients receiving SR ($P = 0.221$) (Fig. 2c), while there were significant differences among subgroups of patients receiving S, R, and NSR ($P = 0.031$, 0.037, and 0.031, respectively) (Fig. 2b, Fig. 2a, and Fig. 2d). For patients receiving S and NRS, overall survival increased steadily over time, with those diagnosed between 2004 and 2013 presenting the longest overall survival. However, for patients receiving R, those diagnosed between 1984 and 1993 presented the longest overall survival.

Cancer-specific survival did not change significantly among subgroups of patients receiving R ($P = 0.411$) (Fig. 3a), while it changed significantly among subgroups of patients receiving S, SR, and NSR ($P < 0.001$, 0.001, and 0.049, respectively) (Fig. 3b, Fig. 3c, and Fig. 3d). For patients receiving S, SR, and NSR, cancer-specific survival increased steadily over time, with those diagnosed between 2004 and 2013 presenting the longest cancer-specific survival.

Influence of clinical factors on survival

As described above, to avoid bias produced by the evolution of treatment strategies, only 379 patients diagnosed between 2004 and 2013 were further investigated to reveal the influence of clinical factors on survival. 27.4% ($n = 104$) of them were dead at last follow-up and 13.7% ($n = 52$) died due to other reasons instead of chordomas. 82.1% SR were radiotherapy after surgery. 94.8% of radiotherapy was beam radiation; the others included radioactive implants, radioisotopes, and their combination. 6.6% ($n = 25$) patients were treated with chemotherapy, 80% ($n = 20$) of which were chemotherapy with radiation or surgery, while 20% ($n = 5$) were chemotherapy alone. 93.4% ($n = 354$) patients did not receive

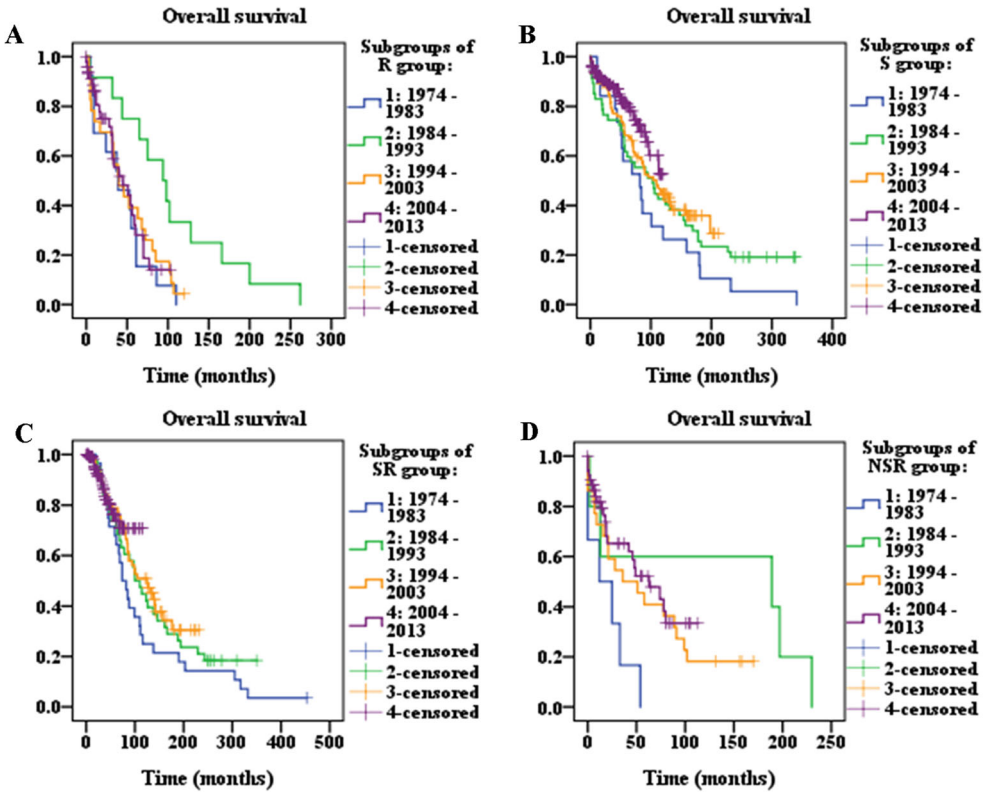

Fig. 2 **a** The difference in overall survival among subgroups of patients receiving R was statistically significant ($P = 0.037$), with patients in 1984–1993 presenting the best overall survival. **b** The difference in overall survival among subgroups of patients receiving S was statistically significant ($P = 0.031$), with survival rate increasing steadily over time. **c** There is no significant difference in overall survival among subgroups of patients receiving SR ($P = 0.221$). **d** The difference in overall survival among subgroups of patients receiving NSR was statistically significant ($P = 0.031$), with survival rate increasing steadily over time

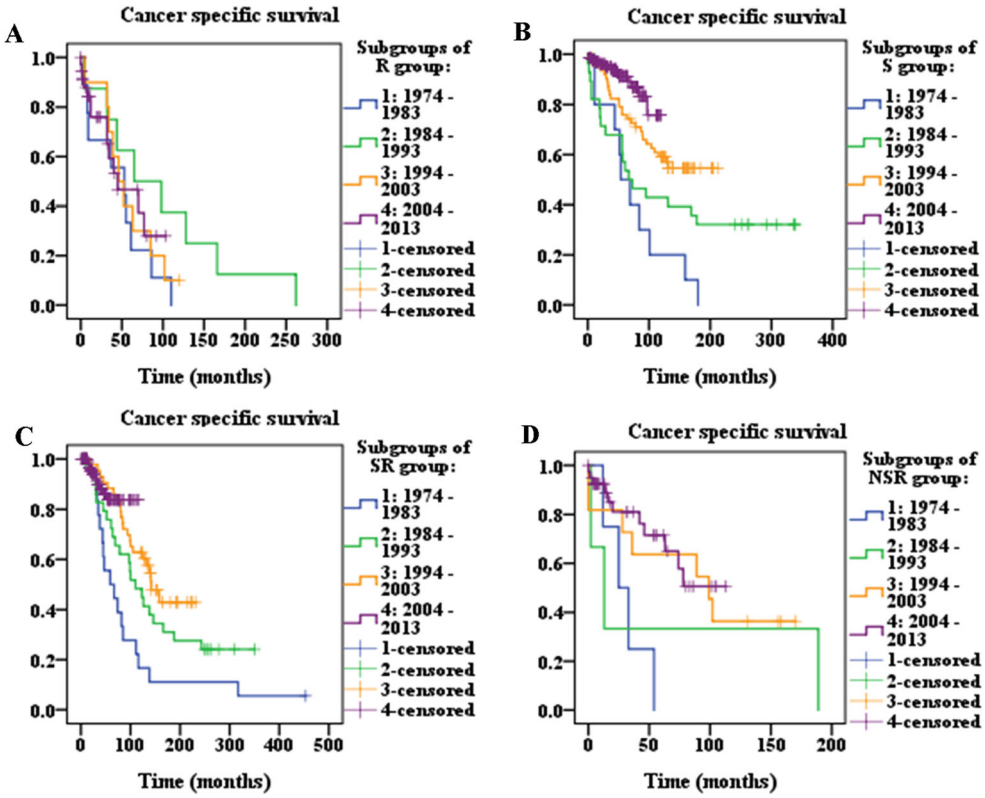

Fig. 3 **a** There is no significant difference in cancer-specific survival among subgroups of patients receiving R ($P = 0.411$). **b** The difference in cancer-specific survival among subgroups of patients receiving S was statistically significant ($P < 0.001$), with survival rate increasing steadily over time. **c** The difference in cancer-specific survival among subgroups of patients receiving SR was statistically significant ($P = 0.001$), with survival rate increasing steadily over time. **d** The difference in cancer-specific survival among subgroups of patients receiving NSR was statistically significant ($P = 0.049$), with survival rate increasing steadily over time

chemotherapy or whether they received chemotherapy or not was unknown (incomplete data).

In univariate analysis, factors predicting longer overall survival were younger onset age (HR 1.052, $P < 0.001$), tumor location of the sacrum (HR 0.668, $P = 0.042$), surgery (HR 0.288, $P < 0.001$), and surgery and radiotherapy (HR 0.524, $P = 0.010$), as well as classic chordomas (HR 0.215, $P = 0.009$). In the multivariate model, only younger onset age (HR 1.052, $P < 0.001$), tumor location of the sacrum (HR 0.401, $P = 0.002$, Fig. 4a), and surgery (HR 0.291, $P = 0.001$) were significantly associated with improved overall survival (Table 2).

Similarly, factors predicting better cancer-specific survival by univariate analysis included younger onset age (HR 1.053, $P < 0.001$), tumor location of the sacrum (HR 0.547, $P = 0.034$), surgery (HR 0.208, $P < 0.001$), and classic chordomas (HR 0.086, $P = 0.001$). While in a multivariate model, younger onset age (HR 1.036, $P = 0.029$), tumor location of the sacrum (HR 0.287, $P = 0.002$), and surgery (HR 0.221, $P = 0.009$) were significantly associated with improved cancer-specific survival (Table 3).

Discussion

Chordomas are very rare malignancies, which makes them very difficult to study. The SEER database has accumulated enough cases for large-scale research. We acknowledge that

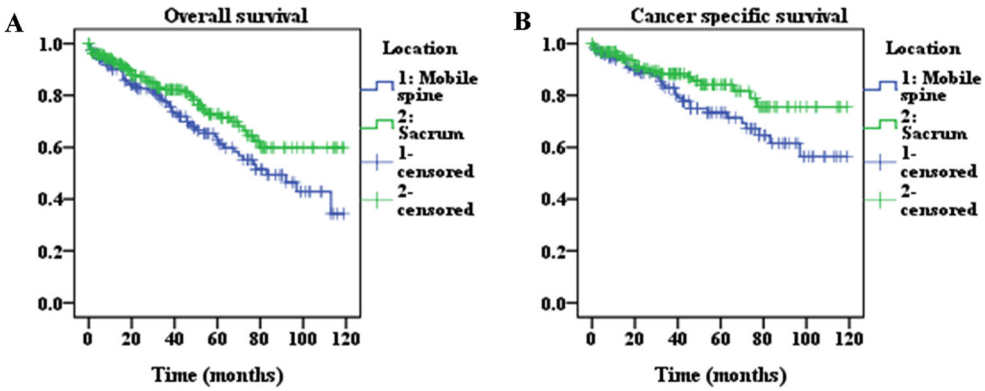

Fig. 4 **a** Patients with tumors on the sacrum presented significantly higher overall survival than those with tumors on mobile spine ($P = 0.002$). **b** Patients with tumors on the sacrum presented significantly higher cancer-specific survival than those with tumors on mobile spine ($P = 0.006$)

Table 2 Overall survival for patients with spinal chordomas: Cox proportional hazards analysis

	Univariate			Multivariate (final model)		
Variable	HR	95% CI	*P* value	HR	95% CI	*P* value
Onset age	1.052	1.036–1.068	< 0.001	1.052	1.027–1.078	< 0.001
Tumor size	1.001	0.999–1.002	0.525	–		
Married (vs others)	0.790	0.536–1.164	0.234	–		
Male (vs female)	1.138	0.762–1.699	0.528	–		
White race (vs others)	1.627	0.789–3.353	0.187	–		
Sacrum (vs mobile spine)	0.668	0.453–0.985	0.042	0.401	0.225–0.714	0.002
Surgery (vs no surgery)	0.288	0.195–0.424	< 0.001	0.291	0.139–0.610	0.001
Radiotherapy (vs no radiotherapy)	0.861	0.583–1.271	0.451	–		
Surgery and radiotherapy (vs others)	0.524	0.322–0.855	0.010	–		
Classic chordomas (vs dedifferentiated)	0.215	0.067–0.685	0.009	–		
Chondroid chordomas (vs dedifferentiated)	0.507	0.113–2.279	0.376	–		

No surgery means all other treatment options but surgery (R + SR). It is the same for the other treatment groups

limited information exists regarding local recurrence, complications, chemotherapy, dose of radiotherapy, and margin status in the final pathological examination. To the best of our knowledge, however, this is the largest study on mobile spine and sacral chordomas up to now. In addition, this is the first research regarding the changes in incidence and survival of patients with spinal chordomas over the last decades.

In the updated SEER database, overall specificity and sensitivity are 100 and 80% for SEER radiotherapy data [29]. Since cases with unknown radiotherapy were excluded (n = 14) from our research when investigating the influence of clinical factors on survival, the sensitivity of the radiotherapy data should be higher than 80%. Although this is a retrospective study with inevitable limitations, the data are highly homogeneous since patients with skull base chordomas were excluded and patients were from almost everywhere in the USA, making the results highly generalizable. In addition, the follow-up time was reasonably long. The length of follow-up is important because tumor recurrence is often diagnosed more than 5 years after initial treatment [30].

Consistent with previous studies, our study showed that spinal chordomas occurred in all age groups, with a median age in the sixth decade [30]. We found that the incidence of spinal chordomas increased obviously over the last 40 years, especially during the last 10 years. In addition, our study showed the overall and cancer-specific survival improved steadily over time for patients receiving S. However, there was no significant difference in overall survival among subgroups of patients receiving SR. Surprisingly, patients receiving R diagnosed between 1984 and 1993 had the longest

Table 3 Cancer-specific survival for patients with spine chordomas: Cox proportional hazards analysis

	Univariate			Multivariate (final model)		
Variable	HR	95% CI	*P* value	HR	95% CI	*P* value
Onset age	1.053	1.031–1.075	< 0.001	1.036	1.004–1.070	0.029
Tumor size	1.001	0.999–1.003	0.420	–		
Married (vs others)	0.784	0.452–1.360	0.387	–		
Male (vs female)	1.070	0.609–1.880	0.813	–		
White race (vs others)	1.800	0.647–5.006	0.260	–		
Sacrum (vs mobile spine)	0.547	0.313–0.955	0.034	0.287	0.129–0.639	0.002
Surgery (vs no surgery)	0.208	0.120–0.362	< 0.001	0.221	0.071–0.689	0.009
Radiotherapy (vs no radiotherapy)	0.655	0.377–1.138	0.133	–		
Surgery and radiotherapy (vs others)	0.541	0.278–1.056	0.072	–		
Classic chordomas (vs dedifferentiated)	0.086	0.020–0.374	0.001	–		
Chondroid chordomas (vs dedifferentiated)	0.219	0.030–1.607	0.219	–		

No surgery means all other treatment options but surgery. It is the same for the other treatment groups

overall survival among subgroups of patients receiving the same treatment. In addition, survival of patients receiving NSR also improved during the most recent decades.

The current standard treatment of chordomas is an *en bloc* tumorectomy with negative margins [30]. The surgical techniques for margin free, including *en bloc* tumor resection, are effective in terms of local control and long-term prognosis of thoracic and lumbar spine chordomas [21, 31, 32]. In our study, we confirm that surgery was independently associated with improved survival outcomes.

Survival and local recurrence mainly depend on a complete resection with negative surgical margins. If negative margins are not achieved, recurrence rates will increase to 70% [33]. Unfortunately, a complete resection is almost impossible because chordomas are characterized by disseminated tumor islands, which are often far from the primary tumor mass. These islands are difficult to identify radiologically and intraoperatively [34]. In addition, gross total resection can result in many complications and patients have a high risk of local treatment failure [35]. Thus, local recurrences are frequent, even many years after primary resection [10, 36, 37]. In this situation, radiotherapy has been used as an adjuvant treatment [35].

Current National Comprehensive Cancer Network guidelines recommend surgical resection with or without adjuvant radiotherapy or definitive radiotherapy for unresectable cases [38]. Indeed, high doses of radiotherapy are often employed as an alternative for patients with inoperable chordomas [35, 39], and about 50% patients are recommended to receive postoperative radiotherapy [40]. However, the utilization of radiotherapy decreased over the last 40 years but the reason is still unknown [20]. Some different types of radiotherapy have been described in recent years, including conventional photon beam radiation, intensity-modulated radiation, stereotactic radiation, brachytherapy, and proton beam radiation [41]. Some other published series showed better local control and survival with particle therapy compared with conventional radiotherapy techniques [24, 42, 43]. Combining surgery and radiotherapy resulted in a significant improvement in local control and in a decreased surgical morbidity compared with surgery alone in skull base and cervical spine chordomas [39, 44–46]. Despite all this improvement in radiotherapy, the present study revealed that it was not independently associated with higher survival and this was consistent with the results of several other studies [12, 20, 41, 47, 48].

Chordomas have historically been described as radioresistant [30], requiring at least 60 Gy with a standard, fractionated external beam radiation to achieve durable local control [26, 49]. However, the doses of radiotherapy were not recorded in the SEER database. Besides, the majority of cases of radiotherapy in the SEER database were adjuvant radiotherapy, and the timing of treatment was unclear. The benefits may be offset if the adjuvant radiotherapy is not delivered in a timely fashion [50].

Whether tumor size is associated with survival is controversial. Smaller tumor size has been shown to be associated with improved survival [9, 12, 51], while Jones et al. also demonstrated that there was no statistically significant difference in survival among groups based on mean tumor size for patients with skull base chordomas [48]. By using univariate and multivariate Cox proportional hazards analysis, our study showed that tumor size was not an independently prognostic factor for overall survival or cancer-specific survival for patients with spinal chordomas.

In addition, there was no significant difference on overall survival between patients with tumors on mobile spine and sacrum as reported [12]. However, our study proved that patients with tumors on the sacrum presented significantly better overall and cancer-specific survival than those with tumors on mobile spine. The reason to such a controversial outcome might be that the cohort and the potential prognostic factors in their study were different from ours. Only patients who experienced surgery were included in their study.

Clinically, the prognosis of dedifferentiated chordomas was worse than that of the other two histologic subtypes, and histological subtype was a prognostic factor to survival in univariate Cox regression model in our study. However, it was not an independently prognostic factor to survival in the multivariate Cox regression model. Small sample size of dedifferentiated cases might be the potential reason, since the incidence of such cases is particularly rare.

Conclusions

In conclusion, the incidence of spinal chordomas increased over the last 40 years. The changes in overall and cancer-specific survival over time differ among different treatment groups. We confirmed that younger onset age, tumor location on the sacrum, and surgical strategy may be correlated with a longer overall and cancer-specific survival. Large-scale and multi-center studies with more detailed treatment information are required to further determine the optimal treatment strategies for this disease.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the

institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent We signed the Data-Use Agreement for the SEER 1973–2013 Research Data File and had permission to use the database for research.

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