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Clinical characteristics and survival analysis of patients with limb epithelioid sarcoma

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Abstract

Limb epithelioid sarcoma (LES) is a rare and aggressive soft tissue sarcoma, which is scarcely reported. Therefore, the current study was performed to analyze the clinicopathologic features and risk factors of survival among patients with LES.

By using the Surveillance, Epidemiology, and End Results database, data were obtained regarding patients who were diagnosed with LES for the period between 2010 and 2016. We first analyzed overall survival (OS) and cancer-specific survival (CSS) by applying univariate Cox regression analysis. Then we performed multivariate analysis to confirm independent predictors of survival.

In total, we identified 475 patients with LES for survival analysis, of which 291 were males (61.3%) and 184 females (38.7%). The mean and median age at diagnosis were 38 and 36 years, respectively. The 5-year OS and CSS rates among Patients with LES were 65.4% and 69.5%, respectively. Gender, age, tumor stage, tumor size, and treatment type were significant predictors of OS on both univariate and multivariate analyses ($P < .05$). As for CSS, multivariable analysis revealed that age <60 years, localized stage, and tumor size <5 cm were significantly associated with increased survival ($P < .05$).

Predictors of improved survival for LES patients include gender, age, tumor stage, tumor size, and treatment type. Surgery only was recommended for treating LES patients. Future studies are warranted to determine effective treatment types for LES patients.

Abbreviations: CI = confidence interval, CSS = cancer-specific survival, ES = epithelioid sarcoma, HR = hazard ratio, LES = Limb epithelioid sarcoma, OS = overall survival, SEER = Surveillance, Epidemiology, and End Results.

Keywords: clinical characteristics, epithelioid sarcoma, limb, survival, risk factor

1. Introduction

Epithelioid sarcoma (ES) is a rare, aggressive soft tissue malignancy with a multifocal disease at presentation.[1,2] ES is predominantly epithelial and accounts for <1% of all soft tissue sarcomas.[3] ES arises predominantly on the extremities of young male adults.[4] ES has a poor outcome due to its higher tendency toward local recurrence and metastatic spreading.[5] Despite intensive treatments, recurrence and metastasis were observed in up to 77% and 45% of patients, respectively.[6,7] Mainstream treatments of ES include surgical resection, radiotherapy, and chemotherapy. Although surgery is the mainstay of treatment for local disease, treatment methods for patients with metastatic disease remain unknown.[5]

Previous studies on ES were mostly small-sample clinical studies, and there was a lack of large-sample studies to analyze the prognosis. Frezza et al[5] could not perform a multivariate analysis of ES due to the limited sample size (n = 52). To provide an insight into the limb ES (LES), we applied the Surveillance, Epidemiology, and End Results (SEER) database to explore the clinicopathologic features and survival predictors. Furthermore, this large population study was able to perform multivariate analysis of LES, which will assist the clinicians in decision making.

2. Materials and Methods

2.1. Patient population

Clinical data from the SEER database on LES patients were obtained by using the case-listing session on the SEER*Stat version 8.3.9 software. We selected ES cases by using the International Classification of Diseases for Oncology, 3rd edition codes "8804, Epithelioid sarcoma." Meanwhile, we set the primary tumor site to limb site. The inclusion criteria were as follows: LES patients from 2010 to 2016 in the US and patients with pathological diagnosis. The exclusion criteria were as follows: patients with death certificate, unknown survival time, and not primary sequence only. This database is free to the public without patient identification information.

HL, QX, and XC contributed equally to this article.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Thus, the Ethics Committee approval was not applicable to this study.

Information collected from the SEER database includes race, gender, year of diagnosis, age at diagnosis, tumor site, tumor stage, tumor size, surgery radiotherapy, chemotherapy, marital status, vital status, survival time, and cause of death. Surgery or radiotherapy in the current study refers to treatment for primary tumor sites. Overall survival (OS) and cancer-specific survival (CSS) were defined as the time from diagnosis till death due to any cause and due to primary cancer, respectively.

2.2. Statistical analysis

All statistical and descriptive analyses were performed by using the SPSS Version 21.0 software. Univariate Cox regression analysis was performed by analyzing race, gender, age at diagnosis, primary tumor site, pathological type, tumor size, treatment type, visceral metastasis, and marital status. Significant risk factors from univariate analysis were incorporated for multivariate Cox regression analysis. Meanwhile, hazard ratio (HR) and its 95% confidence interval (95% CI) were presented in univariate and multivariate analyses. Kaplan–Meier method was applied to intuitively show the survival difference of key survival predictors. Statistical significance was considered if bilateral P value was <.05.

3. Results

3.1. Baseline characteristics

Clinical characteristics are summarized in Table 1. In total, 475 cases who met the eligibility criteria were included in this study, of which 291 were males (61.3%) and 184 females (38.7%). About three-fourths (79.4%) of patients were White race. We divided the year of diagnosis into 3 groups: <2000 (24.8%), 2000–2010 (52.8%), and >2010 (22.3%). We divided the age into 2 groups: <60 years (82.7%) and ≥60 years (17.3%). In terms of primary tumor site, 280 (58.9%) tumors were located in the upper limb and 195 (41.1%) tumors were in the lower limb. Patients with localized stage accounted for 56.2%, regional stage 24.0%, and distant stage 13.1%. There were 198 (41.7%), 134 (28.2%), and 143 (30.1%) patients who had tumor size of <5 cm, of ≥5 cm, and of unknown size, respectively. Overall, most of the patients (89.5%) received surgery, 32.0% of patients received radiotherapy, and 23.6% of patients had chemotherapy. There were 50 (10.5%), 231 (48.6%), and 194 (40.8%) patients who had no surgery, surgery only, and surgery + radio/chemotherapy, respectively. There were 192 patients (40.4%) with married status, 256 patients (53.9%) with other marital status, and 27 patients (5.7%) with unknown marital status. The 5-year OS and CSS rates of patients with LES were 65.4% and 69.5%, respectively.

Table 1

Baseline characteristics of 475 patients with limb epithelioid sarcoma.

Variable	Value
Race	
White	377 (79.4%)
Black	62 (13.1%)
Others	36 (7.6%)
Gender	
Female	184 (38.7%)
Male	291 (61.3%)
Year of diagnosis	
<2000	118 (24.8%)
2000–2010	251 (52.8%)
>2010	106 (22.3%)
Age (yr)	
<60	393 (82.7%)
≥60	82 (17.3%)
Tumor site	
Upper limb	280 (58.9%)
Lower limb	195 (41.1%)
Tumor stage	
Localized	267 (56.2%)
Regional	114 (24.0%)
Distant	62 (13.1%)
Unknown	32 (6.7%)
Tumor size (cm)	
<5	198 (41.7%)
≥5	134 (28.2%)
Unknown	143 (30.1%)
Surgery	
Yes	425 (89.5%)
No	50 (10.5%)
Radiotherapy	
Yes	152 (32.0%)
No	323 (68.0%)
Chemotherapy	
Yes	112 (23.6%)
No	363 (76.4%)
Treatment type	
No surgery	50 (10.5%)
Surgery only	231 (48.6%)
Surgery + radio/chemotherapy	194 (40.8%)
Marital status	
Married	192 (40.4%)
Others	256 (53.9%)
Unknown	27 (5.7%)
Dead	
Yes	209 (44.0%)
No	266 (56.0%)
5-yr OS rate	65.40%
5-yr CSS rate	69.50%

CSS = cancer-specific survival, OS = overall survival.

3.2. Univariate Cox regression analysis

Univariate analysis results of LES patients are summarized in Table 2. No significance on OS or CSS was observed in terms of race, year of diagnosis, and marital status. Male patients were significantly associated with worse OS (HR = 1.409, 95% CI = 1.057–1.878; P = .02) and CSS (HR = 1.495, 95% CI = 1.050–2.129; P = .02). Age ≥60 years (OS: HR = 2.971, 95% CI = 2.189–4.033, P < .001; CSS: HR = 2.597, 95% CI = 1.705–3.957, P < .001) was independently associated with worse survival. Patients with tumors located in the lower limb had a significant worse prognosis than those with tumors located in the upper limb (OS: HR = 1.645, 95% CI = 1.252–2.162, P < .001; CSS: HR = 1.628, 95% CI = 1.173–2.258, P < .001). Distant or regional involvement significantly decreased OS and CSS (P < .001). Patients with tumor size ≥5 were significantly correlated with worse OS (HR = 3.936, 95% CI = 2.760–5.613; P < .001) and CSS (HR = 4.702, 95% CI = 3.060–7.226; P < .001). Patients receiving surgery only and surgery + radio/chemotherapy had significantly better OS and CSS (P < .001).

3.3. Multivariate Cox regression analysis

The multivariate Cox regression models identified 5 significant predictors of OS, including gender, age, tumor stage, tumor size, and treatment type (Table 3). On multivariable analysis of OS, male (HR = 1.362, 95% CI = 1.011–1.836; P = .042), age ≥60 years (HR = 2.393, 95% CI = 1.711–3.345; P < .001), regional (HR = 1.675, 95% CI = 1.181–2.374; P = .002) and distant stage (HR = 4.034, 95% CI = 2.686–6.058; P < .001), and tumor size ≥5 cm (HR = 2.070, 95%

Table 2

Univariate Cox analysis of variables in patients with limb epithelioid sarcoma.

	OS		CSS	
Variable	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Race				
White	1		1	
Black	1.322 (0.908–1.925)	.146	1.486 (0.959–2.300)	.076
Others	1.376 (0.854–2.215)	.189	1.618 (0.956–2.741)	.073
Gender				
Female	1		1	
Male	1.409 (1.057–1.878)	.02	1.495 (1.050–2.129)	.02
Year of diagnosis				
<2000	1		1	
2000–2010	1.292 (0.932–1.791)	.124	1.015 (0.693–1.487)	.94
>2010	1.174 (0.713–1.935)	.529	1.041 (0.596–1.817)	.887
Age (yr)				
<60	1		1	
≥60	2.971 (2.189–4.033)	<.001	2.597 (1.705–3.957)	<.001
Tumor site				
Upper limb	1		1	
Lower limb	1.645 (1.252–2.162)	<.001	1.628 (1.173–2.258)	.004
Tumor stage				
Localized	1		1	
Regional	2.126 (1.518–2.976)	<.001	2.685 (1.786–4.036)	<.001
Distant	6.596 (4.621–9.414)	<.001	8.958 (5.893–13.618)	<.001
Tumor size (cm)				
<5	1		1	
≥5	3.936 (2.760–5.613)	<.001	4.702 (3.060–7.226)	<.001
Treatment type				
No surgery	1		1	
Surgery only	0.229 (0.154–0.341)	<.001	0.179 (0.111–0.291)	<.001
Surgery + radio/chemotherapy	0.385 (0.263–0.562)	<.001	0.393 (0.255–0.607)	<.001

CI = confidence interval, CSS = cancer-specific survival, HR = hazard ratio, OS = overall survival.

Table 3

Multivariate Cox analysis of variables in patients with limb epithelioidsarcoma.

	OS		CSS	
Variable	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Gender				
Female	1		1	
Male	1.362 (1.011–1.836)	.042	1.376 (0.955–1.982)	.086
Age (yr)				
<60	1		1	
≥60	2.393 (1.711–3.345)	<.001	1.772 (1.125–2.793)	.014
Tumor site				
Upper limb	1		1	
Lower limb	1.224 (0.913–1.640)	.176	1.249 (0.884–1.765)	.207
Tumor stage				
Localized	1		1	
Regional	1.675 (1.181–2.374)	.004	1.945 (1.271–2.977)	.002
Distant	4.034 (2.686–6.058)	<.001	4.961 (3.059–8.044)	<.001
Tumor size (cm)				
<5	1		1	
≥5	2.070 (1.401–3.058)	<0.001	2.447 (1.528–3.919)	<0.001
Treatment type				
No surgery	1		1	
Surgery only	0.621 (0.393–0.980)	0.041	0.587 (0.337–1.022)	0.060
Surgery + radio/chemotherapy	0.768 (0.499–1.182)	0.230	0.858 (0.528–1.396)	0.538

CI = confidence interval, CSS = cancer-specific survival, HR = hazard ratio, OS = overall survival.

CI = 1.401–3.058; $P < .001$) were significantly associated with decreased survival. Surgery only was significantly associated with increased OS ($P = .041$) not CSS ($P = .060$). By multivariate analysis of CSS, age ≥60 years (HR = 1.772, 95% CI = 1.125–2.793; $P = .014$), regional (HR = 1.945, 95% CI = 1.271–2.977; $P = .002$) and distant stage (HR = 4.961, 95% CI = 3.059–8.044; $P < .001$), and tumor size ≥5 cm (HR = 2.447, 95% CI = 1.528–3.919; $P < .001$) were associated with decreased survival (Table 3). Kaplan–Meier survival analysis stratified by gender, age, tumor stage, tumor size, and treatment type revealed significant discrimination ($P < .05$) in Figures 1 to 5, respectively.

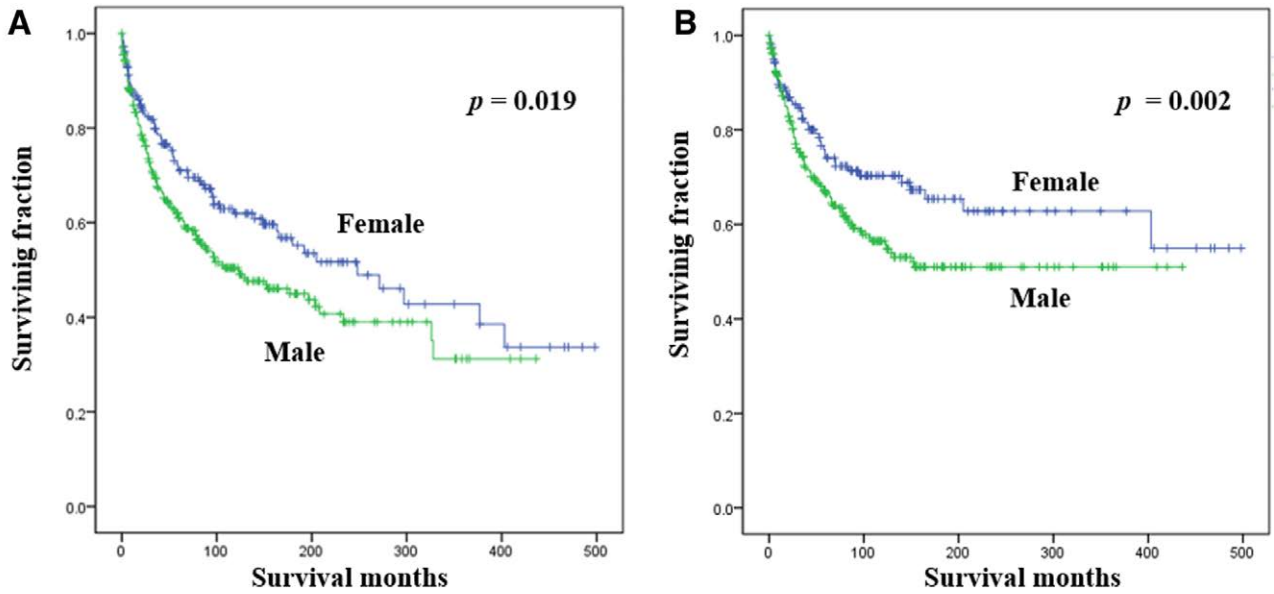

Figure 1. Kaplan–Meier method estimated OS and CSS in patients with limb epithelioid sarcoma stratified by gender. (A) OS stratified by gender; (B) CSS stratified by gender. CSS = cancer-specific survival, OS = overall survival.

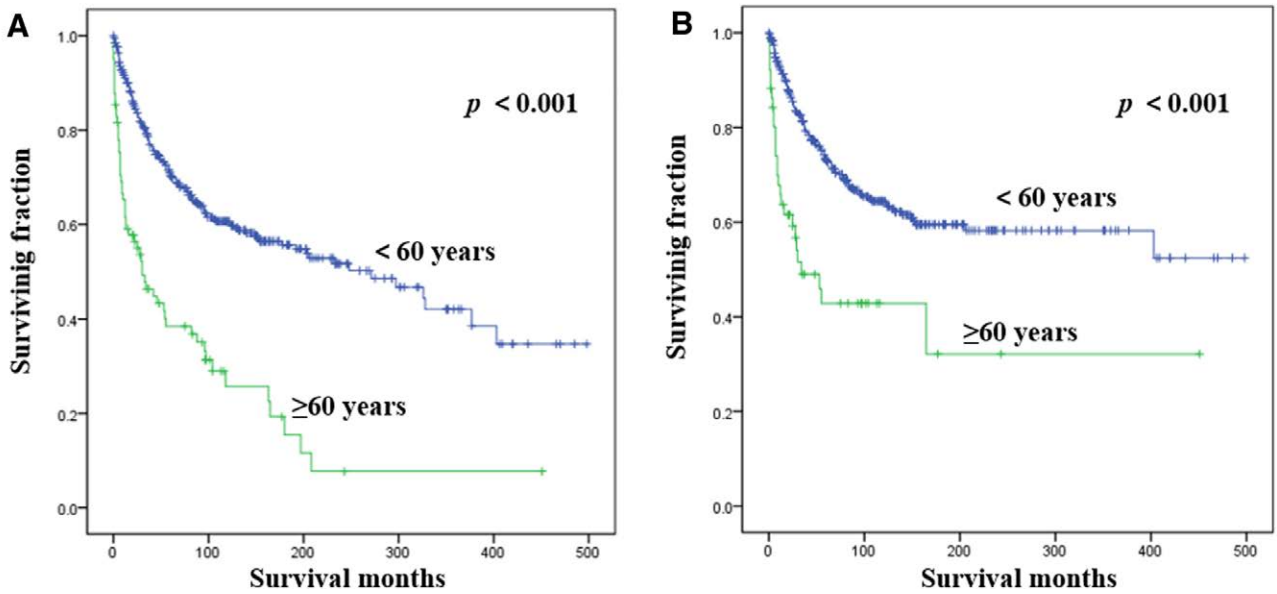

Figure 2. Kaplan–Meier method estimated OS and CSS in patients with limb epithelioid sarcoma stratified by age. (A) OS stratified by age; (B) CSS stratified by age. CSS = cancer-specific survival, OS = overall survival.

4. Discussion

ES is described as a "great masquerader" and "a wolf in sheep's clothing" due to its various clinical manifestations, diagnostic difficulty, aggressive characteristics, and uncertain treatment.[8,9] To date, this is the largest population-based study to describe the clinical features and analyze the survival of patients with LES. The 5-year OS and CSS rates for 475 LES patients were 65.4% and 69.5%, respectively. Moreover, our study showed that gender, age, tumor stage, tumor size, and treatment type were significant independent predictors of survival, which may be helpful for both clinicians and patients in clinical decisions.

In terms of race, no significant difference was observed among LES, which was not consistent with other soft tissue sarcomas.[10–12] Xiong et al[10] reported that Black race was independently associated with worse survival in synovial sarcoma. Additionally, Lazarides et al[11] identified race as an independent predictor of survival in patients with extremity soft tissue sarcoma. Male predominance was found for LES (male vs female, 1.6:1). It is important to note that gender is an independent risk factor for OS rather than CSS among LES patients. Further researches are needed to confirm this finding. Many previous studies on sarcomas also showed that gender was a significant prognostic factor and female patients usually had significantly improved survival.[10,13–15] In our series, univariate analysis showed no significant correlation between year of diagnosis and prognosis, which means there has not been much progress in treating ES in recent years. Based on the results of univariate and multivariate analyses, age <60 years significantly predicted an improved survival among patients with LES, which was in

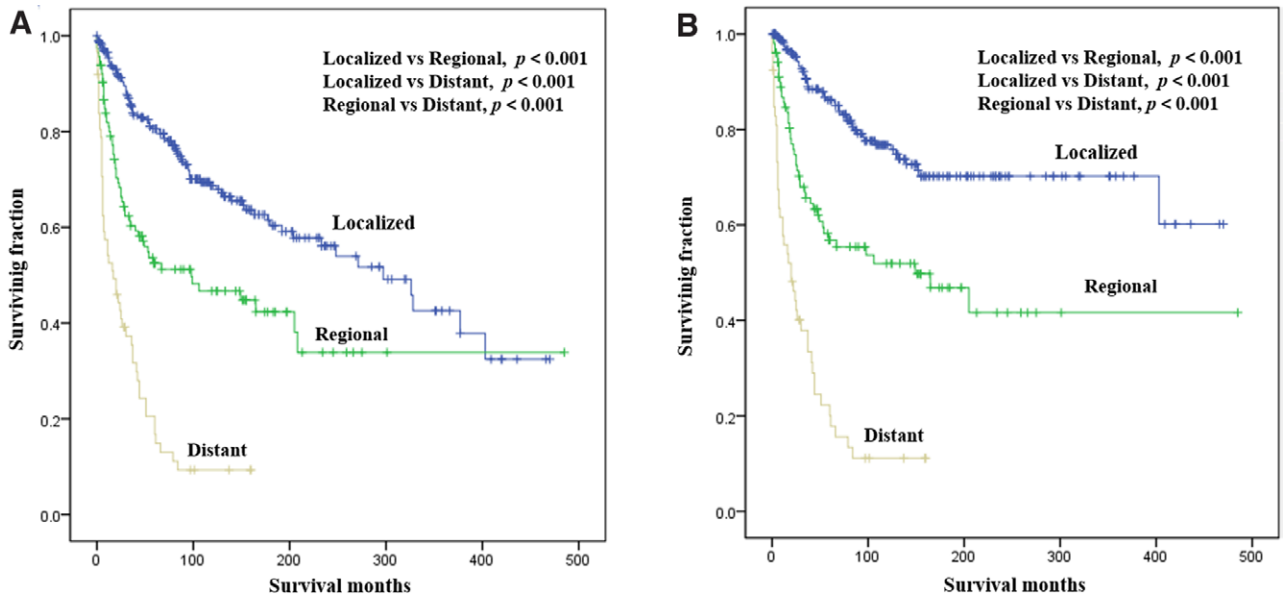

Figure 3. Kaplan–Meier method estimated OS and CSS in patients with limb epithelioid sarcoma stratified by tumor stage. (A) OS stratified by tumor stage; (B) CSS stratified by tumor stage. CSS = cancer-specific survival, OS = overall survival.

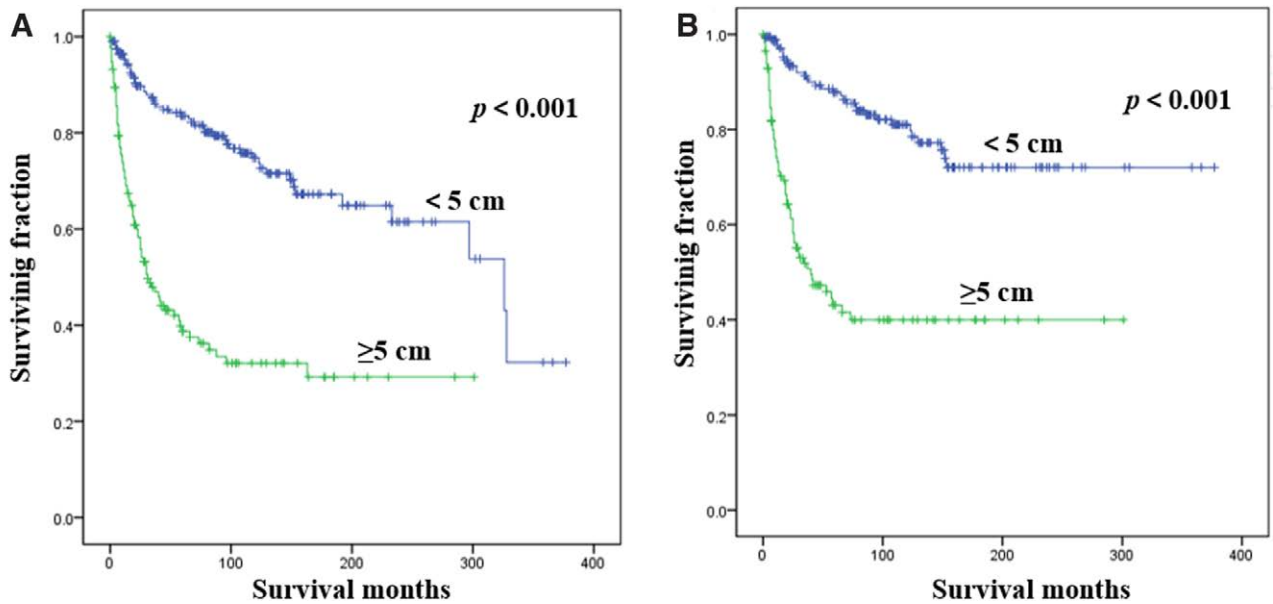

Figure 4. Kaplan–Meier method estimated OS and CSS in patients with limb epithelioid sarcoma stratified by tumor size. (A) OS stratified by tumor size; (B) CSS stratified by tumor size. CSS = cancer-specific survival, OS = overall survival.

agreement with previous studies on soft tissue sarcomas.[16] Although univariate analysis revealed that tumor site was significantly associated with survival among LES, multivariate analysis showed that tumor site had no effect on survival. In our patients, tumor stage significantly and independently predicted survival of LES. Patients with distant or regional diseases experienced significantly worse prognosis than those with localized disease. Treatment management of patients with distant and regional diseases should be strengthened in the future. Our study demonstrated that tumor size was an important prognostic factor, which was in line with the results of other soft tissue sarcomas.[15,17,18] Our study revealed that marital status was not associated with survival of LES patients. However, Zhang et al[19] demonstrated that marital status was an independent prognostic factor for patients with soft tissue sarcomas.

Surgical excision is the mainstream treatment of ES. Chemotherapy and radiotherapy have limited effectiveness and are occasionally used as adjuvant therapy.[20] Sparber-Sauer et al[21] reported that complete tumor resection was correlated with long-term survival in patients with ES. Univariate analysis and multivariate analysis revealed that surgery only was significantly correlated with OS. However, no significant association between surgery + radio/chemotherapy and survival was observed among patients with LES. Future studies are warranted to further determine the current treatment methods for LES patients.

SEER database makes it possible to explore the clinical features and prognosis of rare LES. However, there are some shortcomings in the present study. First, the present study has a retrospective nature. Second, information regarding the surgical method, radiotherapy, and chemotherapy procedure was not available in the

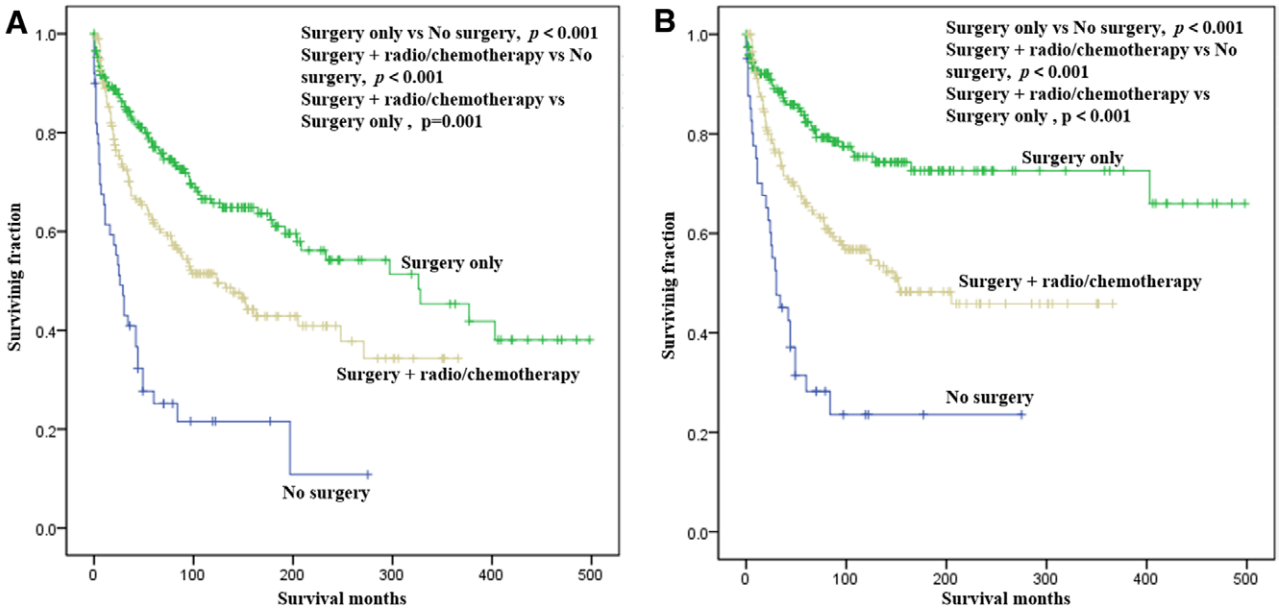

Figure 5. Kaplan–Meier method estimated OS and CSS in patients with limb epithelioid sarcoma stratified by treatment type. (A) OS stratified by treatment type; (B) CSS stratified by treatment type. CSS = cancer-specific survival, OS = overall survival.

database. Third, although LES is well known for its high recurrence rate, the SEER database does not provide any information regarding local recurrence or distant metastasis during follow-up. Previous studies indicated that local recurrence has little influence on survival among extremity soft tissue sarcoma.[22] Local recurrence should be viewed as a marker of tumor aggressiveness rather than the cause of poor survival.[23] However, further randomized trials are warranted to provide conclusive evidence.

5. Conclusion

This study offers insight into the clinical characteristics and survival prediction of LES. Surgery only may be beneficial for prolonging the OS of patients with LES. Further studies are urgently needed to clarify these findings and improve the survival of this special population.

Author contributions

Conceptualization and Data curation: Fangming He and Zhan Wang
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Writing–review & editing: Fangming He and Zhan Wang

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