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Original Article

Epidemiology of and prognostic factors for patients with sarcomatoid carcinoma: a large population-based study

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Abstract: Sarcomatoid carcinoma (SC) is regarded as a rare malignant neoplasm associated with poor outcomes. This study aimed to explore the epidemiological characteristics and prognostic factors of SC, and establish a clinical predictive model. The Surveillance, Epidemiology, and End Results database was used for data inquiry of patients with SC. Relevant population materials were used for age-adjusted incidence, limited-duration prevalence and prognostic analyses, and also for nomogram construction and validation. A total of 17,917 cases of SC were identified. Among them, 12,276 (68.52%) were women and 14,265 (79.62%) were white. Most cases occurred in the female genital system, accounting for 41.10% of all SCs. The median age at diagnosis was 68 years. The incidence and prevalence of SC increased substantially over time. The age-adjusted incidence increased from 0.31/100,000 in 1973 to 1.26/100,000 by 2014, a 4.06-fold change. Among site groups, the incidence of SC in the female genital and the respiratory system increased most significantly ($P < 0.001$). As for stage and grade, the incidence increased the most in distant and high-grade SC, respectively ($P < 0.001$). Moreover, the survival duration varied significantly by site, histology, stage and grade ($P < 0.001$). The multivariable analyses showed that the year of diagnosis, age, sex, race, grade, stage, and site were all significant prognostic factors ($P < 0.001$). Among these, stage and primary tumor site were the most valuable indicators of outcomes. Furthermore, a nomogram comprising age, histology, grade, stage and site were established to predict the 3-/5-year survival probability. The concordance indexes of the nomogram were 0.745 (95% confidence interval [CI]: 0.737-0.753) and 0.743 (95% CI: 0.728-0.756) for the internal and external validations, respectively. The calibration plot demonstrated satisfactory consistency between the actual and predicted outcomes in both the internal and external validations. In conclusion, increasing incidence and prevalence of SC was observed in our study, suggesting that SC is more prevalent than previously reported. Clinicians should be familiar with the characteristics of these tumors. Furthermore, the established nomogram could accurately predict the 3-/5-year survival rate of patients with SC, which may be of value for patient counselling and risk stratification.

Keywords: Epidemiology, incidence, nomogram, prognosis, SEER, sarcomatoid carcinoma

Introduction

Sarcomatoid carcinoma (SC) is an unusual type of neoplasm identified in a variety of organs, including breast, esophagus, lung, kidney and prostate [1-6]. It contains both carcinomatous and sarcomatous components, each of which exhibits typical histological, immunohistochemical, and ultrastructural patterns, indicative of their diverse differentiation [7, 8]. Since its first description by Virchow in 1864, different terms, such as sarcomatoid carcinoma, carcinosarcoma, pseudosarcoma, pleomorphic carcinoma and spindle cell carcinoma, have been used to represent SC due to its unclear etiology [9-15]. Due to its frequent metastasis and chemoresistance, SC tends to present at an advanced stage at diagnosis and is associated with poor outcomes [16].

At present, almost all studies on SC have been case reports or clinical series. There is a lack of the population-based study, let alone a systematically comparative study on the incidence, prevalence and survival of SC through all anatomical sites. The National Cancer Institute's

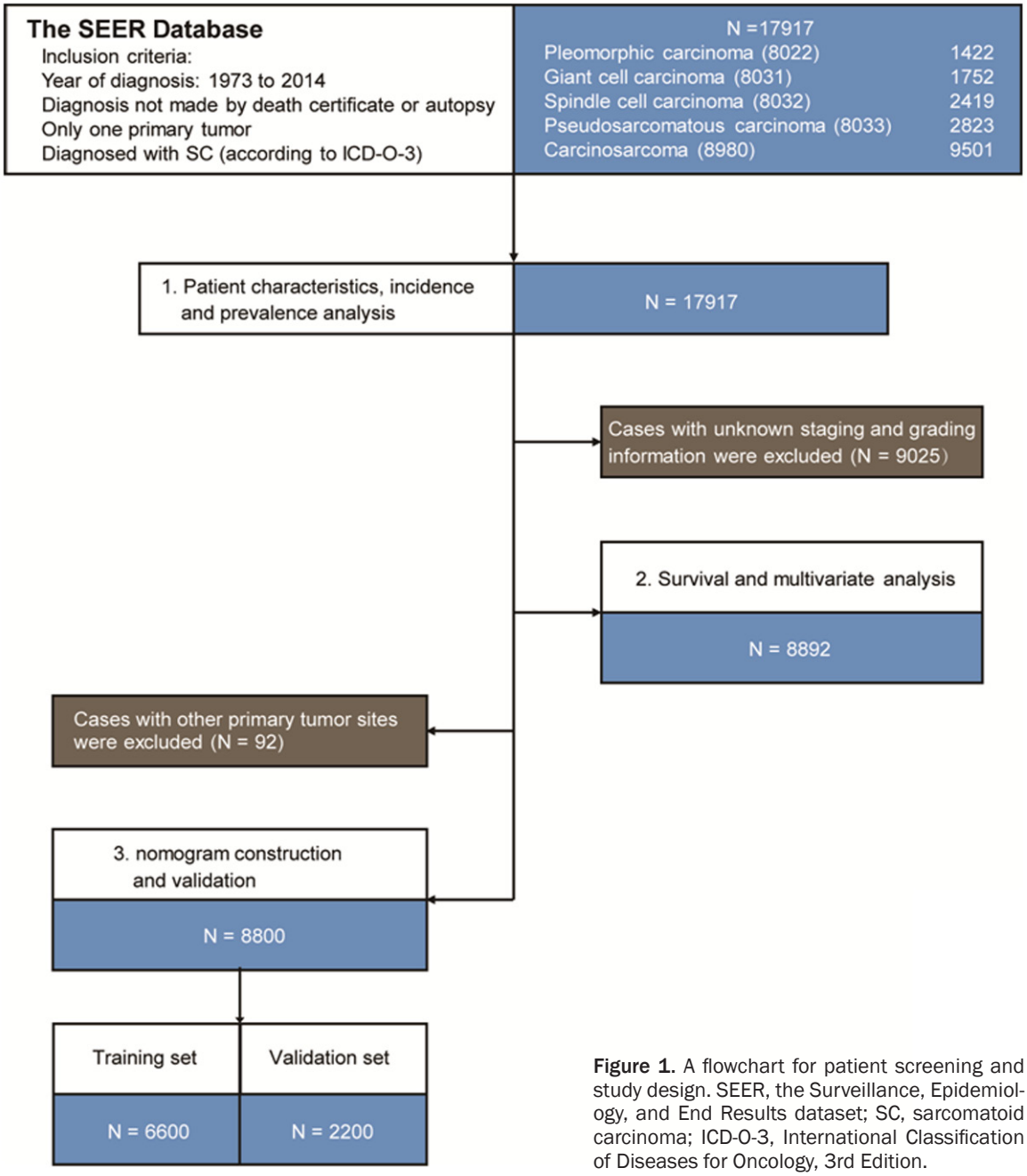


Figure 1. A flowchart for patient screening and study design. SEER, the Surveillance, Epidemiology, and End Results dataset; SC, sarcomatoid carcinoma; ICD-O-3, International Classification of Diseases for Oncology, 3rd Edition.

Surveillance, Epidemiology, and End Results (SEER) Program is a comprehensive population-based database updated annually [17, 18]. Therefore, this population-based study was conducted through collating and analyzing data from the SEER database to determine the epidemiological, clinical, and prognostic features of SC systematically.

Besides, there is currently no study to generate a nomogram to predict the prognosis for patients with SC. Hence, this study also aimed to develop a unique nomogram based on a large population-based cohort from the SEER database to assist clinicians with the prediction of 3-/5-year overall survival (OS) rates in patients with SC.

Materials and methods

Data source

The SEER database submitted in November 2018 was used in this study [18]. The study design is presented in **Figure 1**. The histologic codes from the *International Classification of*

Diseases for Oncology, 3rd Edition (ICD-O-3), were used to identify patients with SC. The correspondences between the codes and clinical/histological diagnoses for all anatomical sites were as follows: pleomorphic carcinoma (8022); giant cell carcinoma (8031); spindle cell carcinoma (8032); pseudosarcomatous carcinoma (8033); and carcinosarcoma (8980).

SC stage and classification

The SEER staging system was used for analysis in the present study due to the lack of a unified staging system for SC. Tumors were classified as localized, regional, or distant. A localized SC was defined as an invasive neoplasm confined entirely to the organ of origin. A regional SC was defined as a neoplasm extended beyond the limits of the organ of origin but with no distant metastasis. Finally, a distant SC was defined as a neoplasm invading the areas of the body distant or remote from the primary tumor. The SEER grading system was used to classify cases as grade (G) I, well differentiated; GII, moderately differentiated; GIII, poorly differentiated; and GIV, undifferentiated or anaplastic.

Nomogram construction and validation

All eligible patients (8800) were randomly divided into 3:1 training (6600) and validating (2200) groups. Multivariable Cox proportional hazards models were used for evaluating prognostic factors. Afterward, a nomogram model was constructed based on the training cohort to predict 3-/5-year OS by including significant prognostic factors, according to the Cox regression model. The nomogram was validated based mainly on the internal (training cohort) and external (validation cohort) discrimination and calibration measurements. The concordance index (C-index) was used to evaluate the discriminative capacity of the nomogram, which mainly measured the differences between predicted and actual outcomes. A higher C-index suggested a superior discriminative capacity for survival outcomes. Calibration, which compared the predicted survival with the actual survival, was evaluated with a calibration curve. A calibration plot along the 45-degree line indicated a perfect model, with remarkable consistency between the predicted and actual outcomes.

Statistical analysis

In this study, descriptive statistics were used to analyze the demographic and tumor characteristics of patients. The Pearson Chi-square test was used to compare categorical variables among different groups. Continuous variables were compared using one-way analysis of variance. The survival analysis was completed with the log-rank test. To identify the risk factors for survival, the Cox proportional hazards model was used for multivariate analysis and to calculate the corresponding 95% confidence interval (CI). The incidence with 95% CI and limited-duration prevalence rates (10-year and 20-year) was calculated using the SEER*Stat software (version 8.3.6; Surveillance Research Program, National Cancer Institute). All other statistical calculations were performed using SPSS (version 23, IBM, NY, USA). Significance was set as $P < 0.05$ in a two-tailed test.

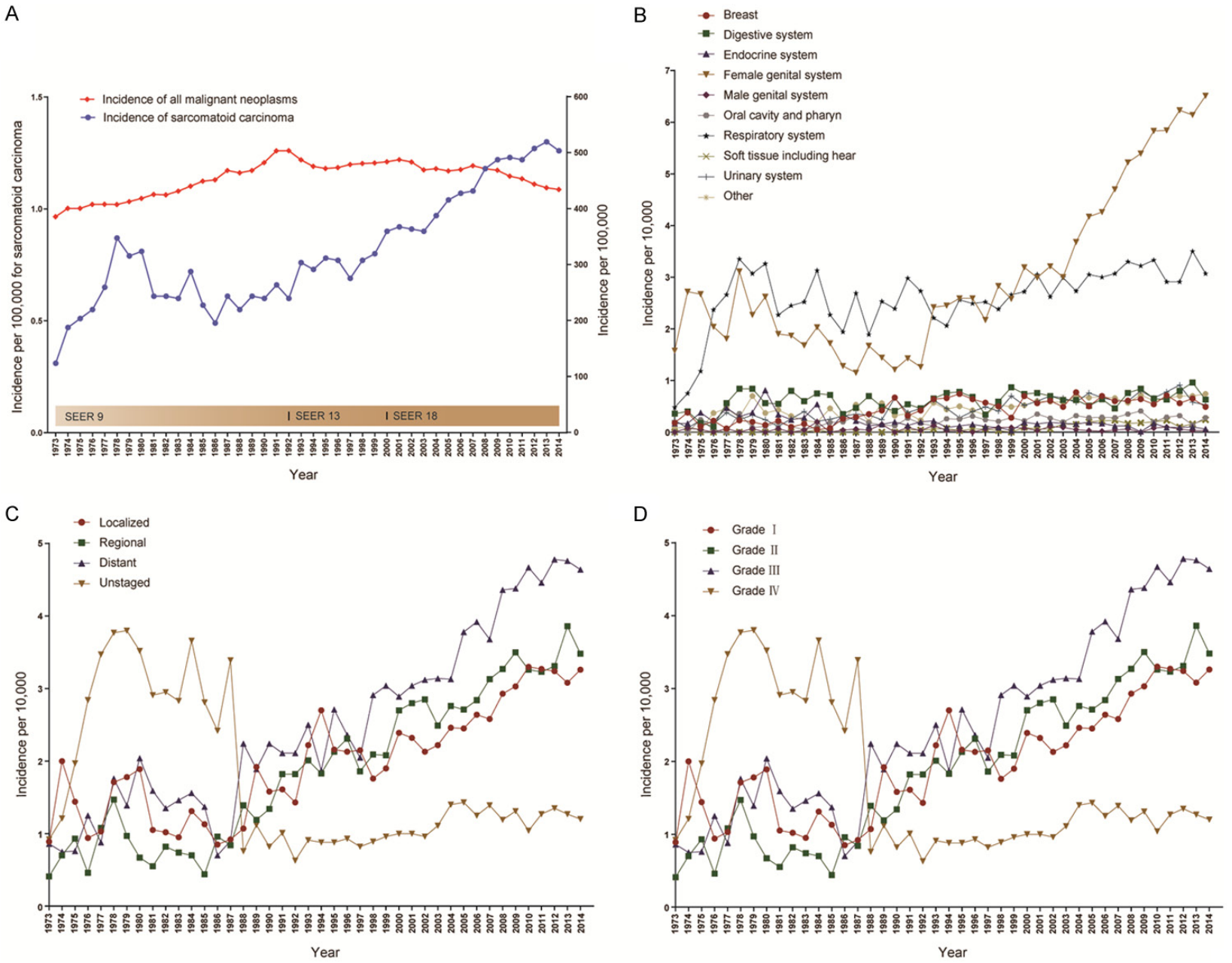
Results

Annual incidence

The age-adjusted incidence of SC based on the 2000 US standard population was calculated using information from the SEER database. Since the SEER 9 (1973-1991), 13 (1992-1999), and 18 (2000-2014) registries were associated with different population datasets, we calculated the age-adjusted incidence for three time periods. The age-adjusted incidence of SC increased significantly over time, specifically from 0.31/100,000 in 1973 to 1.26/100,000 in 2014, as shown in **Figure 2A** (compared with the age-adjusted incidence of all malignancies) and Supplementary Table 1.

In addition, we specifically analyzed the incidence trend of different primary tumor sites and noted a significant increase of SC in the female genital system and respiratory system, with an age-adjusted incidence from 1.58/10,000 in 1973 to 6.51/10,000 in 2014 and 0.48/10,000 in 1973 to 3.07/10,000 in 2014, respectively (**Figure 2B**).

Then, the incidence of different stage groups was analyzed, revealing that the incidence of distant SC increased most significantly, from 0.86/10,000 in 1973 to 4.64/10,000 in 2014 ($P < 0.001$, **Figure 2C**). Among grade groups,


A
Incidence of all malignant neoplasms
Incidence of sarcomatoid carcinoma
Incidence per 100,000 for sarcomatoid carcinoma
Incidence per 100,000
SEER 9
SEER 13
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Year
B
Breast
Digestive system
Endocrine system
Female genital system
Male genital system
Oral cavity and pharyn
Respiratory system
Soft tissue including hear
Urinary system
Other
Incidence per 10,000
Year
C
Localized
Regional
Distant
Unstaged
Incidence per 10,000
Year
D
Grade Ⅰ
Grade Ⅱ
Grade Ⅲ
Grade Ⅳ
Incidence per 10,000
Year

Figure 2. The age-adjusted incidence of sarcomatoid carcinoma (SC) over time by primary tumor site, stage and grade. (A) The age-adjusted incidence of all SCs and malignant neoplasms. (B) The age-adjusted incidence of SC by primary tumor site, (C) stage, and (D) grade at diagnosis (1973-2014).

the incidence increased the most in GIII SC, from 0.54/10,000 in 1973 to 2.61/10,000 in 2014 ($P < 0.001$, **Figure 2D**).

Prevalence

To further investigate the burden of SC, we analyzed the 10-/20-year limited-duration prevalence of SC. The results suggested that the 20-year limited-duration prevalence of SC increased significantly, from 0.00035% in 1995 to 0.00393% in 2014 ($P < 0.001$) (**Figure 3A**). Supplementary Table 2 shows the details of the 10-/20-year limited-duration prevalence and absolute counts of SC. Among site groups, the prevalence was the highest in the female genital system, followed by the respiratory system and breast. Regarding tumor grade, the prevalence of GIII SC increased most significantly and the prevalence was the highest in localized disease among stage groups (**Figure 3**).

Patient characteristics

The collected datasets contained a total of 17,917 patients with SC, including 2,183, 1,913, and 13,821 in SEER 9, 13, and 18 registries, respectively. Among them, 12,276 (68.52%) were women and 5,641 (31.48%) were men. Further, 79.62% were white, 14.13% were black, 5.58% were Asian/Pacific Islander, and 0.47% were American Indian/Alaskan native. For the whole cohort, the median age at diagnosis was 68 years (mean, 68; standard deviation, 13). Regarding the primary tumor site, most cases had primary tumor sites in the female genital system and respiratory system, accounting for 41.10% and 29.09%, respectively (Supplementary Table 3). In the female genital tract, approximately 79.63% arose from the uterus and 17.48% from the ovary. In the respiratory system, most cases were of the lung and bronchus (93.51%). The details related to the site distribution of SC are shown in Supplementary Table 4.

Age at diagnosis

The study then analyzed differences in the age at diagnosis of SC based on sex, race and primary tumor site. No difference was observed in age at diagnosis between men and women ($P = 0.543$). Among race groups, white patients had the maximum median and mean ages at diagnosis ($P < 0.001$). Besides, the ages at diagnosis of patients with SC in different primary tumor sites also differed significantly ($P < 0.001$). The details are shown in **Table 1**.

Tumor stage

Next, we explored the factors associated with the disease stage. A strong correlation was found between the primary tumor site and disease stage in 15,355 SC cases with explicitly stated stage information (**Table 1**; $P < 0.001$). In addition, the analysis of 9671 patients with grade information confirmed that tumor grade was also strongly associated with the disease stage ($P < 0.001$). Further, 12.93% of GI and 13.05% of GII tumors had synchronous distant metastasis at diagnosis, while for high-grade tumors (GIII and GIV), patients with synchronous distant metastasis accounted for 36.49% and 40.26%, respectively.

In addition, other factors related to the disease stage included sex and race (**Table 1**). The present study found that male patients were more likely to have synchronous distant metastasis at diagnosis compared with female patients (45.36% vs 37.48%; $P < 0.001$). For different races, about 53.33% of American Indian/Alaskan Native patients had metastasis at presentation, which was most likely to present with advanced disease among race groups ($P = 0.008$).

Survival

The median OS for all patients was 24 months. SC in the breast (> 360 months) and soft tissue (> 360 months) had the best median OS among site groups, while SC in the endocrine system (5 months) and digestive system (6 months) had the worst median OS. Among different histology groups, carcinosarcoma (36 months) had the best median OS, while giant cell carcinoma (6 months) had the worst median OS. Localized SC (> 360 months) performed the best compared with regional (30 months) and

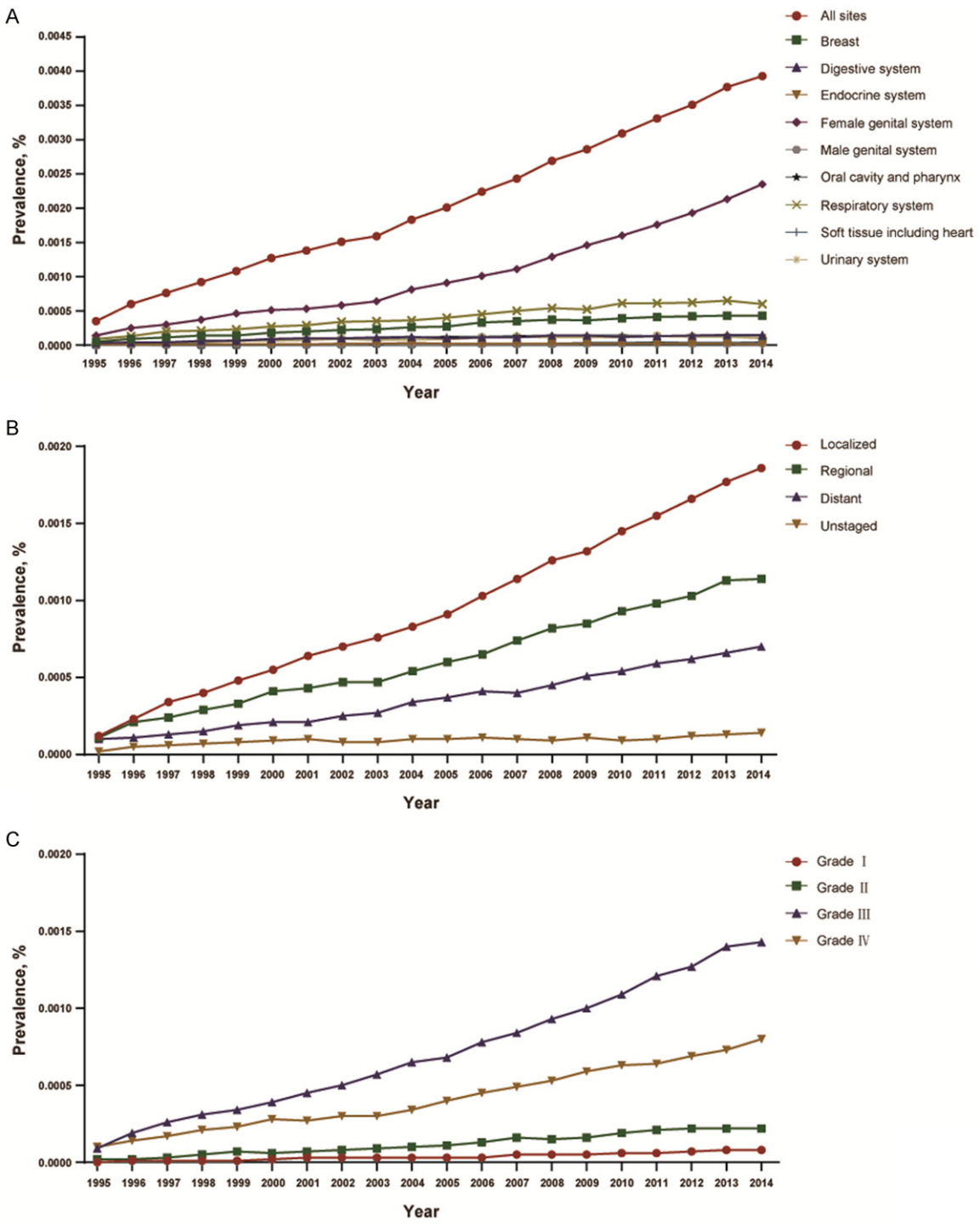


Figure 3. Limited-duration prevalence of sarcomatoid carcinoma (SC). (A) 20-Year limited-duration prevalence of all SCs and according to the primary tumor site. (B) 20-Year limited-duration prevalence of SC by stage, and (C) grade.

distant SC (7 months) ($P < 0.001$). For tumor grade, the study found that patients with GI and GII SC had similar survival curves, and did not achieve their median OS. The median survival duration in patients with GIII and GIV tumors was 124 and 64 months, respectively (Supplementary Figure 1). All these comparisons were statistically significant ($P < 0.001$).

Table 1. Age and disease stage at diagnosis of sarcomatoid carcinoma (SC) by sex, race, and primary tumor site

Characteristic	Age at Diagnosis (years)			Disease Stage (%)		
	Median	Mean	Standard Deviation	Localized	Regional	Distant
Sex						
Male	69	68	13	20.33	34.30	45.36
Female	68	68	13	32.94	29.58	37.48
Race						
White	69	68	12	29.93	30.58	39.50
Black	65	65	12	27.49	33.26	39.25
Asian/P Islander	64	64	13	27.62	29.54	42.84
AI/AN	63	63	13	17.33	29.33	53.33
Tumor site						
Breast	63	63	15	63.84	26.56	9.60
Digestive system	69	68	13	24.09	29.66	46.26
Endocrine system	70	68	14	11.42	40.94	47.64
Female genital system	68	68	12	33.14	28.09	38.77
Male genital system	75	73	12	22.86	14.29	62.86
Oral cavity and pharynx	66	64	16	39.23	44.98	15.79
Respiratory system	68	68	12	17.93	31.01	51.07
Soft tissue including heart	69	67	16	38.34	27.46	34.20
Urinary system	73	71	14	21.82	50.05	28.13
Other	71	70	14	35.91	25.97	38.12

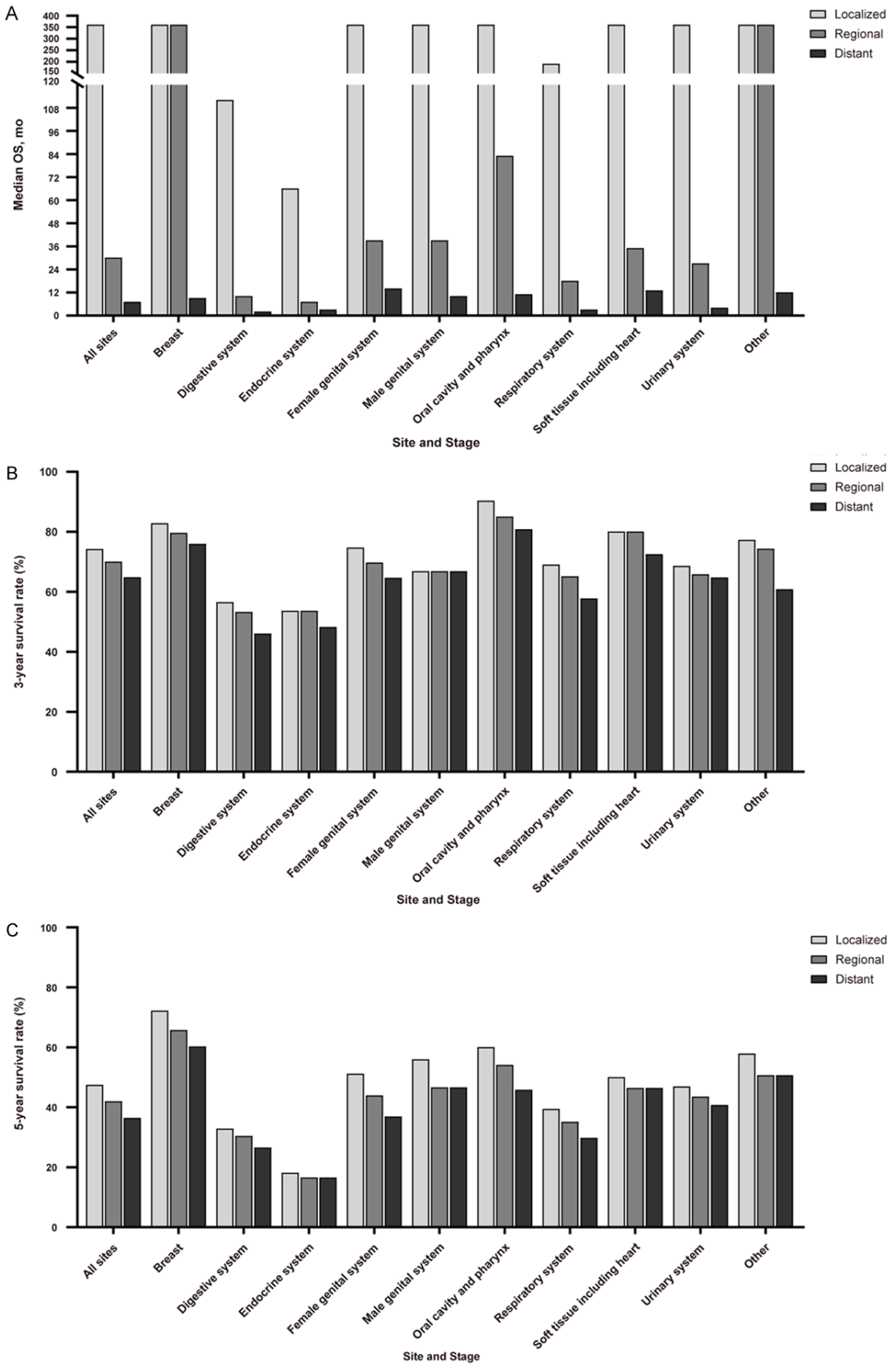
Abbreviations: P Islander, Pacific Islander; AI/AN, American Indian/Alaskan native.

The survival patterns were then assessed based on the primary tumor site and stage (**Figure 4A** and Supplementary Table 5). In localized SC, the median OS of most sites had not been reached, except for those in the digestive system (112 months), endocrine system (66 months) and respiratory system (191 months). Regarding regional SC, the median OS ranged from 7 months for SC in the endocrine system to more than 360 months in the breast. For distant SC, cases in the female genital system had the best median OS (14 months); the median OS of SC in the digestive system (2 months), endocrine system (3 months) and respiratory system (3 months) was the worst. All these differences in OS were significant ($P < 0.001$).

Finally, we evaluated the 3-/5-year survival rates according to the primary tumor site and stage (**Figure 4B**, **4C**). The 3-year survival rates for patients with local disease ranged from 53.6% for those with SC in the endocrine system to 90.3% for those in the oral cavity and pharynx. Even for regional/distant disease, the 3-year survival rates of each tumor site varied greatly, ranging from 53.2%/46% for regional/distant SC in the digestive system to 85%/80.8% for regional/distant SC in the oral cavity and pharynx. Similarly, for localized, regional and distant disease, the 5-year survival rates of SC in different primary tumor sites also varied greatly. The details are shown in Supplementary Table 5.

Multivariable analysis of OS

Next, multivariate analysis was performed using the Cox proportional hazards model to further explore the risk factors for patients with SC. Potentially prognostic factors were included in this model, including age, sex, race, histology, grade, disease stage, primary tumor site and period of diagnosis (1973-1986, 1987-2000 and 2001-2014). All included parameters were found to have a correlation with survival. Patients with GIII and GIV SC (GIII: HR, 1.53; 95% CI, 1.13-2.07; GIV: HR, 1.55; 95% CI, 1.14-2.10) had worse OS compared with those with GI SC. Regarding the disease stage, the OS of regional SC (HR, 2.16; 95% CI, 2.01-2.32) and distant SC (HR, 5.14; 95% CI, 4.81-5.49) was significantly worse compared with that of local-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Localized
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All sites
Breast
Digestive system
Endocrine system
Female genital system
Male genital system
Oral cavity and pharynx
Respiratory system
Soft tissue including heart
Urinary system
Other
Site and Stage
B
3-year survival rate (%)
100
80
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0
Localized
Regional
Distant
All sites
Breast
Digestive system
Endocrine system
Female genital system
Male genital system
Oral cavity and pharynx
Respiratory system
Soft tissue including heart
Urinary system
Other
Site and Stage
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5-year survival rate (%)
100
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Localized
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Digestive system
Endocrine system
Female genital system
Male genital system
Oral cavity and pharynx
Respiratory system
Soft tissue including heart
Urinary system
Other
Site and Stage

Figure 4. (A) Median overall survival (OS), (B) 3-year survival rate, and (C) 5-year survival rate of sarcomatoid carcinoma (SC) across the primary tumor site according to disease stage. The maximum follow-up time was 360 months.

ized SC. The primary tumor site was also an important factor affecting the prognosis of patients with SC. This disease had the worst OS in the endocrine system (HR, 2.86; 95% CI, 2.36-3.46) compared with the breast (**Figure 5**).

Nomogram

A total of 8800 patients from all included cohorts were brought into the study according to the model-building requirements (**Figure 1**). Among all eligible patients, 6600 and 2200 subjects were assigned to the training and validation cohorts, respectively. Supplementary Table 6 lists the baseline clinicopathological characteristics; no statistically significant differences were found between the two groups. Afterward, a nomogram model was constructed based on the training cohort by including the significant prognostic factors, according to the Cox regression model (**Figure 6A**). The nomogram was internally and externally validated. The C-indexes for OS prediction in the nomogram were 0.745 (95% CI: 0.737-0.753) and 0.743 (95% CI: 0.728-0.756) for the training (internal validation) and validation (external validation) cohorts, respectively. The predictors included age, histology, grade, stage and primary tumor site. Although sex and race were statistically significant predictors of prognosis in Cox regression analysis, they were also excluded to maintain the simplicity and applicability of the predictive model due to their little impact on survival. In the nomogram, the primary tumor site had the greatest prognostic significance among all predictive indicators, which got a maximum of 100 points. In addition, stage (73 points), age (55 points), grade (29 points) and histology (14 points) were also individually important predictors of OS. Supplementary Table 7 shows the specific scores for each variable. Each number/category of these variables corresponded to a score on the "Points" scale. After summing up the total score and locating it on the "Total Points" scale, a line drawn straight down to the "3-/5-Year Survival Probability" scale showed the probability at each time point. Finally, the internal (**Figure 6B**) and external (**Figure 6C**) calibration plots of the nomogram showed great consistency between the nomogram-based predictions and actual outcomes.

Discussion

In this population-based study, we analyzed the epidemiology and prognostic factors of SC using a large amount of data integrated into the SEER program. The study demonstrated a 4.06-fold increase in the annual age-adjusted incidence of SC from 1973 (0.31/100,000) to 2014 (1.26/100,000), indicating a significant increase over time. In addition, a systematically comparative analysis of SC cases from 1973 to 2014 provided extensive details about the trends of SC incidence in different anatomical sites, which was very different from that in previous studies focusing only on a single anatomical site in a limited period. Our results showed that the increase in incidence was the greatest in the female genital system (4.12-fold) and respiratory system (6.39-fold). It was speculated that the aforementioned increasing trends might be closely related to the increased application of endoscopic and imaging procedures in patients with SC. Notably, the present study using the SEER 18 registry program (2000-2014) found that the highest incidence of SC was 6.51 per 10,000 in the female genital system. Indeed, the study by Gunjal Garg et al. [19] demonstrated that the age-adjusted incidence of uterine and ovarian SC was 6/10,000 and 1.9/10,000, respectively, which was consistent with present results. Moreover, although the rise in incidence occurred across all tumor stages of patients with SC, the distant disease increased most significantly. Interestingly, with the improvement in the guideline on the staging system of SC, the incidence of unstaged cases has significantly decreased. Regarding tumor grade, previous studies showed that most cases of SC were high grade (GIII and GIV) [20, 21]. In this study, we found that the incidence of high-grade tumors increased most significantly. The increase was likely caused in part by the improvements in the classification of these tumors.

Currently, published case reports and clinical series have indicated dismal outcomes for SC [22-28]. However, still no survival studies based

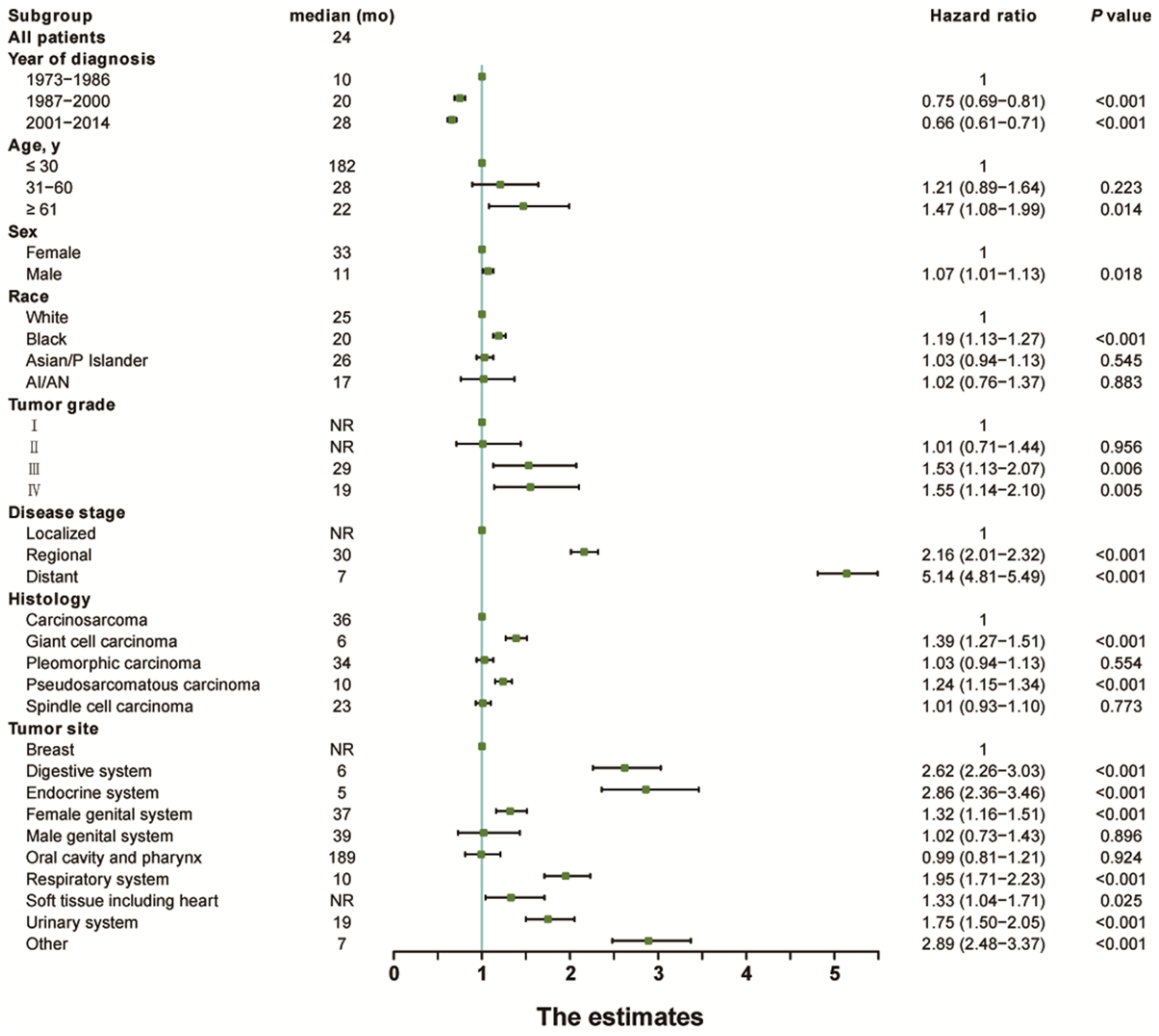

Figure 5. Forest plot of Cox regression analysis for sarcomatoid carcinoma (SC). Horizontal axis: hazard ratio with the reference line, hazard ratios (square) and 95% CI (whiskers).

on the primary tumor site and stage have been reported. Previous studies reported a short median OS ranging from 8 to 19 months [28-30] for patients with pulmonary SC, from 16 to 40 months for uterine SC [31, 32], and from 8 to 32 months for ovarian SC [33-36]. However, in the present study, the population-based analysis showed that SC in the endocrine system (5 months) and digestive system (6 months) had the worst median OS among all site groups. In addition, the prognosis of patients with SC in different stage groups varied greatly. In the present study, patients with localized SC did remarkably well and did not yet achieve their median OS. However, the prognosis of regional and distant SC was extremely poor and the median OS was 30 and 7 months, respectively. Favorable outcomes in the local disease group highlighted the importance of early disease detection and treatment. Although the prognosis of patients with SC was poor, their OS improved over time, reflecting the improvement in anticancer therapies, including the emerging targeted therapy and immunotherapy [37, 38].

For further exploration of the risk factors for patients with SC, we performed multivariate survival analysis using the Cox proportional hazards model. Among the included parameters, the primary tumor site and disease stage were the most useful prognostic predictors in patients with SC. Therefore, combining the primary tumor site and disease stage as prognostic markers, we were better able to separate prognosis into categories. Based on the aforementioned analysis, the stratified analysis of

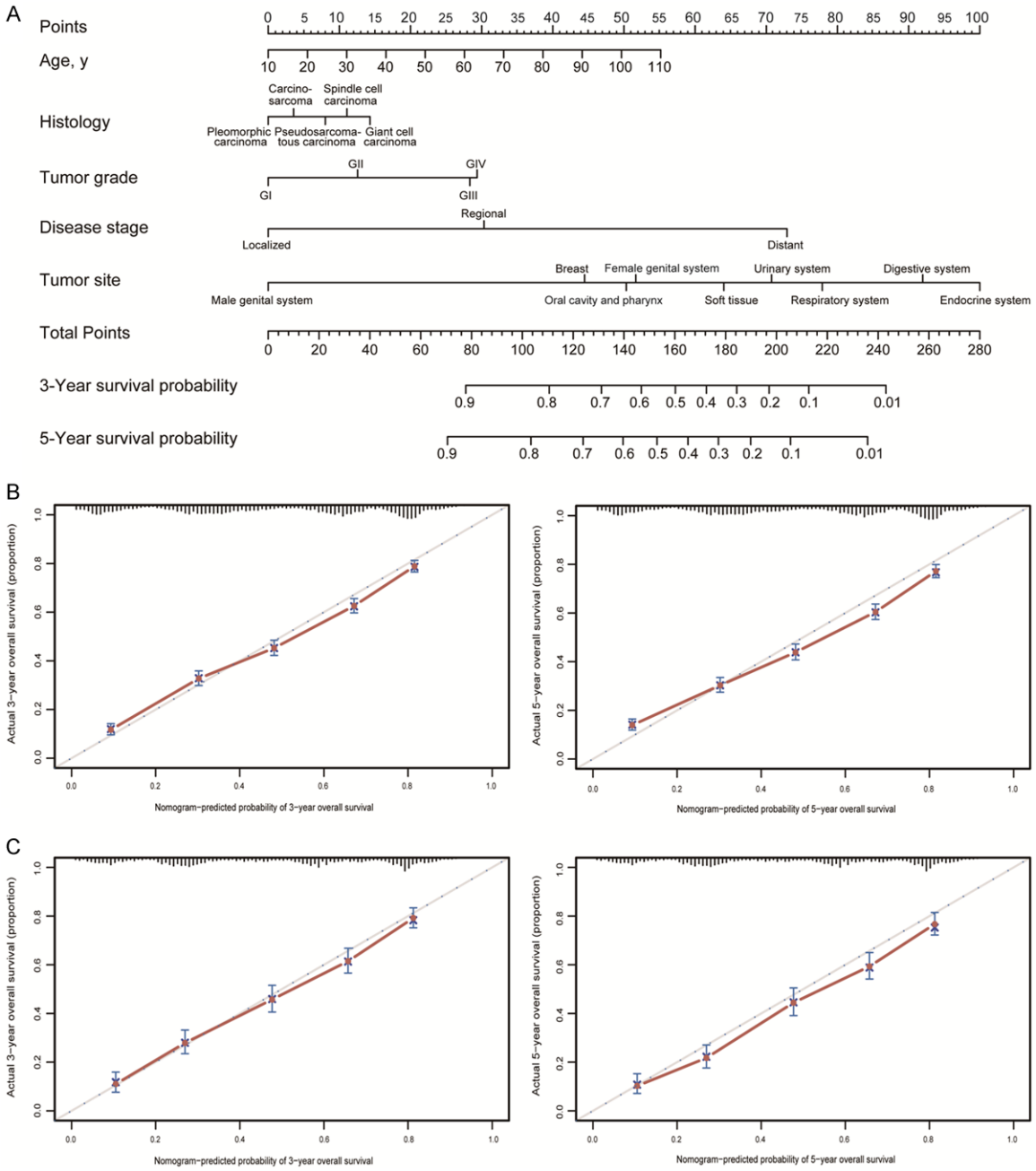

Figure 6. Nomogram to predict the 3-/5-year survival probabilities of patients with sarcomatoid carcinoma (SC) and the calibration of the nomogram using the training and validation sets. (A) Points are assigned for age, histology, tumor grade, disease stage and primary tumor site by drawing a line upward from the corresponding values to the "Points" line. The sum of these five points is located on the "Total Points" line, and a line projected down to the bottom scales determines the probabilities of 3-/5-year overall survival (OS). Calibration plots of the nomogram for 3-/5-year OS prediction in the training set (B) and 3-/5-year OS prediction in the validation set (C). The gray line represents the ideal nomogram, and the red line represents the observed nomogram. The predicted probability of OS by the nomogram is projected onto the *x*-axis, and the actual OS is projected onto the *y*-axis.

patients diagnosed from 1973 to 2014 was performed according to the primary tumor site and disease stage. The results are listed in Supplementary Table 5, which can be a practical guide for clinicians.

In recent years, nomograms based on the SEER database have been developed and shown to be more accurate compared with the conventional staging systems for predicting prognosis in some cancers, and demonstrated favorable

discrimination and calibrations, which were internally and externally validated within the database [39-41]. In the present study, a nomogram, including age, histology, grade, stage, and primary tumor site, was established to predict individual survival probability. In the internal and external validation sets, the calibration plots confirmed that the probabilities of 3-/5-year OS predicted using the nomogram were consistent with the actual survival rates, with the C-indexes of 0.745 (95% CI: 0.737-0.753) and 0.743 (95% CI: 0.728-0.756), respectively. Thus, the nomogram overcame the complexity of assessing the impact of multiple prognostic factors simultaneously and could provide patients with SC with simple and accurate prognostic predictions. It could support clinical decision-making and assist clinicians in communicating with patients and their families. To our knowledge, this was the first prognostic prediction model specifically developed for patients with SC.

In spite of the advantages using the SEER database to integrate a large number of cases to analyze the epidemiology and prognostic factors for SC, there also exits some limitations such as the information missing on the functional status and therapy strategies in patients with SC, both of which might be involved in the survival analysis of these patients. In addition, patients with SC would likely not report to the SEER registries unless considered to be malignant. Therefore, the true incidence and prevalence of SC might be actually underestimated. Indeed, any retrospective population-based study could not avoid these shortcomings. However, to our knowledge, this study was the most comprehensive exploration of SC with the largest sample size by far, and its size and long-term follow-up data have largely made up for the shortcomings.

Conclusions

The incidence and prevalence of SC were continuing to rise, and our results showed that in specific sites such as the female genital system and respiratory system, both of them were increasing at a higher rate. Differences were seen in survival rates according to the primary tumor site, grade and stage. However, it was certain that the outcomes generally improved with diagnosis and treatment progression. Furthermore, a unique nomogram, in which the primary tumor site was the most useful prognostic indicator, was established and validated internally and externally in the present study and could provide doctors and patients with accurate and useful information and guide the clinical decision-making for patients with SC.

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The authors have consented to publication after having read the final manuscript. No IRB approval was required because the SEER Database uses pseudonyms rather than real patient demographic data.

Disclosure of conflict of interest

None.

Abbreviations

SC, sarcomatoid carcinoma; SEER, surveillance, epidemiology and end results; ICD-O-3, international classification of diseases for oncology, 3rd Edition; PH, proportional hazard; C-index, concordance index; CI, confidence interval; OS, overall survival.

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Supplementary Table 1. Incidence of sarcomatoid carcinoma (SC) over time

Registry	Year	Rate	Number of SC cases	Number at risk
SEER 9	1973	0.31	42	16,383,240
	1974	0.47	72	18,804,226
	1975	0.51	89	20,491,638
	1976	0.55	94	20,645,967
	1977	0.65	110	20,824,399
	1978	0.87	157	21,035,770
	1979	0.79	146	21,272,552
	1980	0.81	144	21,526,796
	1981	0.61	110	21,689,241
	1982	0.61	114	21,822,466
	1983	0.6	119	21,998,396
	1984	0.72	140	22,197,735
	1985	0.57	116	22,423,982
	1986	0.49	99	22,644,373
	1987	0.61	125	22,872,669
	1988	0.55	114	23,111,066
	1989	0.61	126	23,349,445
	1990	0.6	127	23,657,474
	1991	0.66	139	23,998,620
SEER 13	1992	0.6	185	35,796,360
	1993	0.76	239	36,209,880
	1994	0.73	228	36,515,300
	1995	0.78	251	36,853,744
	1996	0.77	251	37,247,652
	1997	0.69	227	37,697,798
	1998	0.77	257	38,144,594
	1999	0.8	275	38,555,266
SEER 18	2000	0.9	650	78,996,813
	2001	0.92	667	79,867,817
	2002	0.91	675	80,629,975
	2003	0.9	681	81,347,854
	2004	0.97	755	82,055,585
	2005	1.04	796	80,414,399
	2006	1.07	853	83,099,557
	2007	1.08	886	83,810,676
	2008	1.18	982	84,618,783
	2009	1.22	1046	85,402,713
	2010	1.23	1096	86,160,301
	2011	1.22	1092	86,838,944
	2012	1.27	1175	87,492,533
	2013	1.3	1230	88,094,149
	2014	1.26	1237	88,731,591

Supplementary Table 2. 10-year and 20-year prevalence of sarcomatoid carcinoma (SC)

Year	20-year duration Prevalence	20-year Count	10-year duration Prevalence	10-year Count
1995	0.00035%	131		
1996	0.0006%	223		
1997	0.00076%	288		
1998	0.00092%	354		
1999	0.00108%	417		
2000	0.00127%	496		
2001	0.00138%	545		
2002	0.00151%	597		
2003	0.00159%	632		
2004	0.00183%	731		
2005	0.00201%	806	0.00052%	208
2006	0.00224%	905	0.00090%	363
2007	0.00243%	992	0.00120%	491
2008	0.00269%	1,107	0.00156%	642
2009	0.00286%	1,186	0.00157%	742
2010	0.00309%	1,290	0.00158%	870
2011	0.00331%	1,395	0.00159%	998
2012	0.00351%	1,491	0.00160%	1,121
2013	0.00377%	1,616	0.00161%	1,269
2014	0.00393%	1,696	0.00162%	1,370

Supplementary Table 3. Baseline clinicopathological characteristics of sarcomatoid carcinoma (SC)

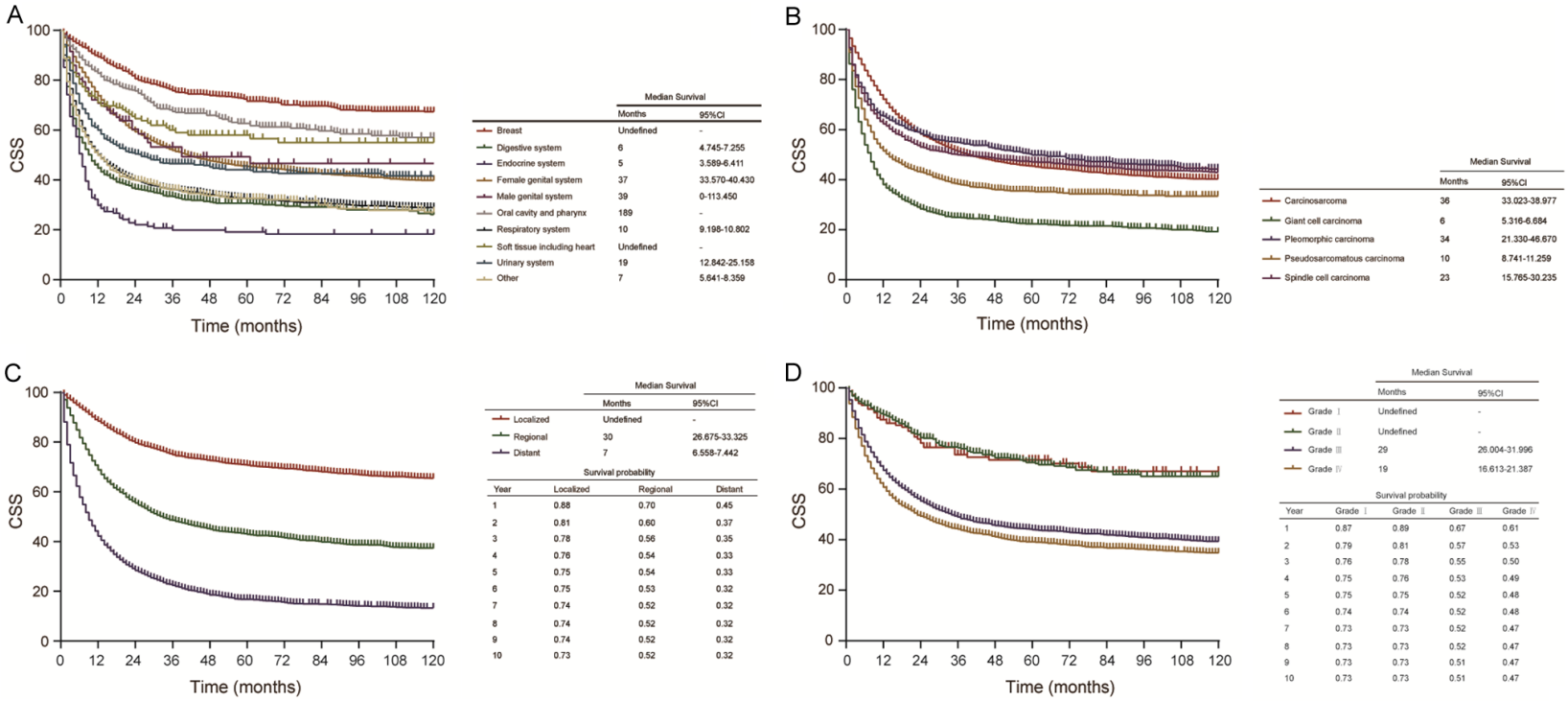
Variable	N	%
Year of diagnosis		
1973-1986	1552	8.66
1987-2000	3194	17.83
2001-2014	13171	73.51
Age, y		
≤ 30	97	0.54
31-60	4869	27.18
≥ 61	12951	72.28
Sex		
Male	5641	31.48
Female	12276	68.52
Race		
AI/AN	85	0.47
Asian/P Islander	1000	5.58
Black	2531	14.13
White	14265	79.62
Unknown	36	0.20
Marital status		
Single	2383	13.30
Married	9102	50.80
Sep/Div/Wid	5652	31.55
Unknown	780	4.35

Grade		
I	153	0.85
II	426	2.38
III	5571	31.09
IV	3521	19.65
Unknown	8246	46.02
Disease stage		
Localized	4516	25.20
Regional	4745	26.48
Distant	6094	34.01
Unknown	2562	14.30
Histology		
Pleomorphic carcinoma	1422	7.94
Giant cell carcinoma	1752	9.78
Spindle cell carcinoma	2419	13.50
Pseudosarcomatous carcinoma	2823	15.76
Carcinosarcoma	9501	53.03
Primary tumor site		
Breast	1003	5.60
Digestive system	1076	6.01
Endocrine system	288	1.61
Female genital system	7364	41.10
Male genital system	99	0.55
Oral cavity and pharynx	464	2.59
Respiratory system	5212	29.09
Soft tissue including heart	223	1.24
Urinary system	1040	5.80
Other	1148	6.41

Supplementary Table 4. Site distribution of sarcomatoid carcinoma (SC)

Tumor Site	N	%
Breast	1003	
Digestive system	1076	
Anus, Anal Canal and Anorectum	6	0.56
Appendix	2	0.19
Colon	55	5.11
Cecum	9	0.84
Esophagus	135	12.55
Gallbladder	112	10.41
Liver	119	11.06
Pancreas	371	34.48
Rectum	20	1.86
Small Intestine	62	5.76
Stomach	133	12.36
Other Digestive Organs	52	4.83
Endocrine system	288	
Thyroid	248	86.11
Other Endocrine including Thymus	40	13.89

Female genital system	7364	
Ovary	1287	17.48
Uterus	5864	79.63
Vagina	50	0.68
Vulva	13	0.18
Other Female Genital Organs	150	2.04
Male genital system	99	
Penis	5	5.05
Prostate	83	83.84
Testis	7	7.07
Other Male Genital Organs	4	4.04
Oral cavity and pharynx	464	
Floor of Mouth	13	2.80
Gum and Other Mouth	69	14.87
Hypopharynx	28	6.03
Lip	20	4.31
Nasopharynx	42	9.05
Oropharynx	16	3.45
Salivary Gland	192	41.38
Tongue	52	11.21
Tonsil	18	3.88
Other Oral Cavity and Pharynx	14	3.02
Respiratory system	5212	
Larynx	230	4.41
Lung and Bronchus	4874	93.51
Nose, Nasal Cavity and Middle Ear	91	1.75
Other Respiratory Organs	17	0.33
Soft tissue including heart	223	
Urinary system	1040	
Kidney and Renal Pelvis	263	25.29
Ureter	12	1.15
Urinary Bladder	751	72.21
Other Urinary Organs	14	1.35
Other	1148	



Supplementary Figure 1. Survival analysis by (A) primary tumor site, (B) histology, (C) stage, and (D) grade. Cases of sarcomatoid carcinoma (SC) identified at autopsy or only based on death certificates were excluded. Median survival was presented in months with 95% confidence interval (CI).

Supplementary Table 5. Survival analysis of patients with sarcomatoid carcinoma (SC): Actuarial survival of SC patients diagnosed from 1973 to 2014 by disease stage and primary tumor site

Tumor Site	Localized				Regional				Distant			
	Median Survival (months)	Survival Rate (%)			Median Survival (months)	Survival Rate (%)			Median Survival (months)	Survival Rate (%)		
		3-Year	5-Year	10-Year		3-Year	5-Year	10-Year		3-Year	5-Year	10-Year
All sites	NR	74.2	47.4	19.9	30	70	41.9	15	7	64.8	36.4	11.8
Breast	NR	82.8	72.2	33	NR	79.6	65.7	26.7	9	75.9	60.2	17.1
Digestive system	112	56.5	32.8	6.2	10	53.2	30.4	4.4	2	46	26.5	3.7
Endocrine system	66	53.6	18.1	2.2	7	53.6	16.5	2.2	3	48.2	16.5	2.2
Female genital system	NR	74.7	51.1	28.1	39	69.7	43.9	20.9	14	64.6	36.9	15.9
Male genital system	NR	66.8	55.9	36.2	39	66.8	46.6	28.9	10	66.8	46.6	28.9
Oral cavity and pharynx	NR	90.3	60	23.6	83	85	54.1	23.6	11	80.8	45.8	23.6
Respiratory system	191	69	39.4	11.4	18	65.1	35.1	8.6	3	57.7	29.7	7.7
Soft tissue including heart	NR	80	50	23.3	35	80	46.4	18.7	13	72.5	46.4	18.7
Urinary system	NR	68.6	46.9	10	27	65.8	43.5	10	4	64.7	40.7	8.3
Other	NR	77.2	57.8	28.3	NR	74.3	50.6	18.9	12	60.8	50.6	18.9

Supplementary Table 6. Baseline clinicopathological characteristics of patients in the training and validation cohorts

Variables	All patients (n = 8800) N (%)	Training set (n = 6600) N (%)	Validation set (n = 2200) N (%)	*P* value
Year of diagnosis				0.824
1973-1986	232 (2.64)	178 (2.70)	54 (2.45)	
1987-2000	1503 (17.08)	1125 (17.05)	378 (17.18)	
2001-2014	7065 (80.28)	5297 (80.26)	1768 (80.36)	
Age, y				0.347
≤ 30	48 (0.55)	37 (0.56)	11 (0.50)	
31-60	2425 (27.56)	1793 (27.17)	632 (28.73)	
≥ 61	6327 (71.90)	4770 (72.27)	1557 (70.77)	
Sex				0.317
Male	2354 (26.75)	1747 (26.47)	607 (27.59)	
Female	6446 (73.25)	4853 (73.53)	1593 (72.41)	
Race				0.141
AI/AN	41 (0.47)	31 (0.47)	10 (0.45)	
Asian/P Islander	555 (6.31)	407 (6.17)	148 (6.73)	
Black	1244 (14.14)	914 (13.85)	330 (15.00)	
White	6945 (78.92)	5240 (79.39)	1705 (77,50)	
Unknown	15 (0.17)	8 (0.12)	7 (0.32)	
Marital status				0.418
Single	1177 (13.38)	889 (13.47)	288 (13.09)	
Married	4515 (51.31)	3397 (51.47)	1118 (50.82)	
Sep/Div/Wid	2785 (31.65)	2084 (31.58)	701 (31.86)	
Unknown	323 (3.67)	230 (3.48)	93 (4.23)	
Grade				0.938
I	146 (1.66)	111 (1.68)	35 (1.59)	
II	404 (4.59)	306 (4.64)	98 (4.45)	
III	5147 (58.49)	3866 (58.58)	1281 (58.23)	
IV	3103 (35.26)	2317 (35.11)	786 (35.73)	
Disease stage				0.636
Localized	2599 (29.53)	1932 (29.27)	667 (30.32)	
Regional	3007 (34.17)	2267 (34.35)	740 (33.64)	
Distant	3194 (36.30)	2401 (36.38)	793 (36.05)	
Histology				0.408
Pleomorphic carcinoma	737 (8.38)	534 (8.09)	203 (9.23)	
Giant cell carcinoma	761 (8.65)	577 (8.74)	184 (8.36)	
Spindle cell carcinoma	923 (10.49)	684 (10.36)	239 (10.86)	
Pseudosarcomatous carcinoma	1313 (14.92)	980 (14.85)	333 (15.14)	
Carcinosarcoma	5066 (57.57)	3825 (57.95)	1241 (56.41)	
Primary tumor site				0.214
Breast	701 (7.97)	531 (8.05)	170 (7.73)	
Digestive system	507 (5.76)	382 (5.79)	125 (5.68)	
Endocrine system	208 (2.36)	165 (2.50)	43 (1.95)	
Female genital system	4137 (47.01)	3120 (47.27)	1017 (46.23)	
Male genital system	19 (0.22)	12 (0.18)	7 (0.32)	
Oral cavity and pharynx	206 (2.34)	139 (2.11)	67 (3.05)	
Respiratory system	2350 (26.70)	1751 (26.53)	599 (27.23)	
Soft tissue including heart	92 (1.05)	68 (1.03)	24 (1.09)	
Urinary system	580 (6.59)	432 (6.55)	148 (6.73)	

Supplementary Table 7. Detailed score assignment for specific number/category of the parameters included in the nomogram

Prognostic factors		
Variable	Category	Score
Age, y	10	0
	20	6
	30	11
	40	17
	50	22
	60	28
	70	33
	80	39
	90	44
	100	50
	110	55
Histology	Pleomorphic carcinoma	0
	Carcinosarcoma	4
	Pseudosarcomatous carcinoma	8
	Spindle cell carcinoma	11
	Giant cell carcinoma	14
Tumor grade	GI	0
	GII	13
	GIII	28
	GIV	29
Disease stage	Localized	0
	Regional	30
	Distant	73
Tumor site	Male genital system	0
	Breast	45
	Oral cavity and pharynx	50
	Female genital system	52
	Soft tissue including heart	64
	Urinary system	71
	Respiratory system	78
	Digestive system	92
	Endocrine system	100
3-year survival		
Total score	3-year survival probability	
	0.01	243
	0.1	213
	0.2	197
	0.3	184
	0.4	172
	0.5	160
	0.6	147
	0.7	131
	0.8	111
	0.9	78

5-year survival		
Total score	5-year survival probability	
	0.01	236
	0.1	206
	0.2	190
	0.3	177
	0.4	165
	0.5	153
	0.6	140
	0.7	124
	0.8	103
	0.9	70