Incidence, mortality, and survival analyses for carcinosarcoma from 1975 to 2018: an epidemiological study

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Abstract

Introduction

Carcinosarcoma (CS) is a rare malignant tumor. Little is known about the epidemiological feature of the disease in literature. Our aim is to offer the largest and latest analysis of the incidence, mortality, and survival of CS.

Methods

Data of CS from the Surveillance, Epidemiology, and End Results (SEER) database (SEER-9 incidence database and SEER-9 incidence-based mortality database) were adopted. Incidence, mortality, and survival analyses were performed by SEER*Stat software. We used annual percentage change (APC) to evaluate the trends in incidence and mortality.

Results

Incidence rate increased from 0.36/100,000 to 0.83/100,000 with an APC of 3.4% from 1975 to 2018. Mortality rate followed a similar pattern of increase at an APC of 3.2% from 0.07/100,000 in 1975 to 0.54/100,000 in 2018. Most CS occurred in the female genital system and the 5-year survival rate of all patients was 34.9%.

Conclusion

CS is an aggressive tumor with increasing incidence and mortality trends. This tumor, especially CS in the female genital system, is no longer considered to be a rare tumor in the near future. This research will broaden our knowledge for CS as well as provide insight for clinicians.

Introduction

Malignant tumors have already turned into a major public health problem all over the world (Sung et al. 2021). Of them, carcinosarcoma (CS) is an unusual malignancy which was first reported by Virchow in 1863 (Virchow. 1863). In the World Health Organization (WHO) classification, CS is defined as a biphasic tumor composing of malignant epithelial and mesenchymal elements (Wick et al. 1993). Although various hypotheses have been presented, the pathogenesis of CS remains unclear (Wick et al. 1993). In the clinical setting, patients with CS have an unfavorable prognosis than patients with tumors at the same primary sites (Lin et al. 2019; Rauh-Hain et al. 2013). If without specific approaches supplied by clinical trials, the therapeutic regimens for CS generally refer to those tumors at the same anatomic sites (Pang et al. 2017).
CS is characterized by poor differentiation, rapid growth, extensive invasion and early metastasis. Therefore, it is widely recognized that CS is a highly aggressive tumor with poor prognosis (Lin et al. 2019; Rauh-Hain et al. 2013, Arrastia et al. 1997; Berton-Rigaud et al. 2014).

Owing to its rarity, the epidemiological feature of CS is not fully understood. Current knowledge about this tumor mainly derives from case reports and retrospective studies, which involved small samples and insufficient information. In addition, clinical trials or prospective analyses related to CS are limited in the domain of cancer research. Fortunately, the Surveillance, Epidemiology, and End Results (SEER) database provides plenty of resources for exploring rare tumors like CS. As a result, a large population-based study with the aim of improving our understanding of CS is underway.

Hence, the current study was designed to clarify the incidence and mortality trends among patients with CS, and further explore the trends by sex, race, age, pathological grade, SEER stage, and primary site using the SEER database from 1975 to 2018. Also, we investigated the survival rates according to the primary sites.

Methods

Data Source

SEER program (https://seer.cancer.gov) was launched by the National Cancer Institute (NCI) since 1973, which is an authoritative source for cancer statistics in the United States. The original nine population-based cancer registries (California (San Francisco and Oakland), Connecticut, Georgia (Atlanta), Hawaii, Iowa, Michigan (Detroit), New Mexico, Utah, and Washington (Seattle and Puget Sound region)) cover approximately 10% of the United States population (Qian et al. 2019). All data on incidence and survival were extracted from the SEER-9 incidence database, whereas they on mortality were obtained from the SEER-9 incidence-based mortality database.

Since SEER data are retrospective and anonymous, the Institutional Review Board (IRB) approval for this analysis was not required.

Study Population

A population of patients with CS were identified based on tumor histology using the International Classification of Diseases for Oncology, third edition (ICD-O-3) code 8980/3 provided in the SEER database. All eligible patients were diagnosed or died between 1975 and 2018. In addition, we also explored trends in incidence and mortality by pathological grade or SEER stage from 1975 to 2015. Given the small number of cases with available grade or stage, we cannot make relative analyses in 2016–2018.

Patient Characteristic
Demographic characteristics of interest included sex (male or female), race (White, Black, or others), and age at diagnosis (≤49 years, 50–69 years, or ≥70 years) as well as age at death (≤49 years, 50–69 years, or ≥70 years).

Tumor characteristics of interest included pathological grade, SEER stage, and primary site. Pathological grade was divided into two groups: low grade (grade I, well-differentiated; or grade II, moderately differentiated) and high grade (grade III, poorly differentiated; or grade IV, undifferentiated). SEER stage was recorded as early stage (localized, confined to primary site) and advanced stage (regional, spread to regional sites or lymph nodes; or distant, spread to distant sites or nodes). The primary site was defined as six categories: digestive system; respiratory system; breast; female genital system; urinary system and others.

Statistical Analysis

All calculations in the present study were performed with SEER*Stat version 8.3.9 software (https://seer.cancer.gov/seerstat/). Incidence-based mortality (IBM) rates are the proportion of the total number of deaths that are due to this cancer (Hur et al. 2013). Incidence and mortality rates were expressed per 100,000 persons, and the United States population for the year 2000 was regard as a standard population. We also calculated annual percentage changes (APCs) to quantify all trends according to the above characteristics. Differences between APCs and zero were compared by t-test, and two-sided p values < 0.05 were considered statistically significant. Relative survival rates are defined as the ratio of observed survivors in cancer patients to the expected survivors in non-cancer patients (Lewis et al. 2021). One- to five-year relative survival rates were generated. All rates mentioned above were age-adjusted and calculated as previously reported (Lewis et al. 2021; Mariotto et al. 2014).

Results

Overall incidence and mortality trends

The incidence and mortality trends of CS increased significantly during the study duration (1975-2018), and the results are illustrated in Figure 1. According to data from SEER-9 incidence database, the overall incidence of CS showed a rise, with an APC of 3.4% (95% CI:2.8-3.9, p < 0.05) (Figure 1A). CS incidence was 0.36 cases per 100,000 in 1975, whereas it was 0.83 cases per 100,000 in 2018. Meanwhile, based on data from SEER-9 incidence-based mortality database, the overall mortality of CS followed a similar pattern of increase at an APC of 3.2% (95% CI:2.8-3.6, p < 0.05) (Figure 1B). CS mortality exhibited a rising trend from 0.07 cases per 100,000 in 1975 to 0.54 cases per 100,000 in 2018.

Incidence and mortality trends by demographic characteristics

Our study further evaluated both incidence and mortality trends by sex, race, and age from 1975 to 2018 and results are as follows (Figure 2).
Firstly, both trends were steady in male patients (APC=-0.1%, 95% CI:-1.2%-1.0%, \( p > 0.05 \); APC=0.2%, 95% CI:-0.8%-1.3%, \( p > 0.05 \), respectively), but elevated rapidly in female patients (APC=4.0%, 95% CI:3.4%-4.6%, \( p < 0.05 \); APC=3.9%, 95% CI:3.3%-4.4%, \( p < 0.05 \), respectively). Besides, both rates were higher in women than in men (Figure 2A, 2B).

Seconded, both trends increased sharply in White (APC=3.1%, 95% CI:2.5%-3.6%, \( p < 0.05 \); APC=3.0%, 95% CI:2.6%-3.4%, \( p < 0.05 \), respectively) and Black (APC=4.1%, 95% CI:3.2%-5.1%, \( p < 0.05 \); APC=3.5%, 95% CI:2.6%-4.4%, \( p < 0.05 \), respectively) people. Among other races, weakly increasing trends were seen (statistic could not be calculated). In addition, both rates were higher in Black than in White or in other races (Figure 2C, 2D).

Thirdly, both trends elevated markedly in patients aged 50-69 (APC=3.4%, 95% CI:2.8%-4.0%, \( p < 0.05 \); APC=3.0%, 95% CI:2.4%-3.6%, \( p < 0.05 \), respectively) and \( \geq 70 \) (APC=3.4%, 95% CI:2.9%-3.9%, \( p < 0.05 \); APC=3.2%, 95% CI:2.8%-3.7%, \( p < 0.05 \), respectively) years. Furthermore, a steep increase with advanced age was found in both rates (Figure 2E, 2F).

**Incidence and mortality trends by tumor characteristics**

Subsequent analysis was performed to further identify the incidence and mortality trends by grade and stage from 1975 to 2015, and the findings are summarized in Figure 3. The duration between 2016 and 2018 was not included because the sample size with available grade and stage was small.

Firstly, no significant increase or decrease was noted in low grade (statistic could not be calculated), then, a obvious rise was detected in high grade (APC=7.1%, 95% CI:6.2%-8.0%, \( p < 0.05 \); APC=6.9%, 95% CI:5.9%-7.8%, \( p < 0.05 \), respectively). Moreover, both rates were higher in high grade than in low grade (Figure 3A, 3B).

Secondly, both trends were observed with statistical increase in early (APC=2.6%, 95% CI:1.8%-3.3%, \( p < 0.05 \); APC=2.3%, 95% CI:1.6%-3.1%, \( p < 0.05 \), respectively) and advanced (APC=4.7%, 95% CI:4.0%-5.3%, \( p < 0.05 \); APC=4.4%, 95% CI:3.8%-5.0%, \( p < 0.05 \), respectively) stages. Additionally, both rates were higher in advanced stage than in early stage (Figure 3C, 3D).

**Incidence, mortality, and survival analyses by primary site**

Between 1975 and 2018, a total of 5,281 patients with CS were enrolled from SEER-9 incidence database. As for tumor location, the most common site was female genital system (78.0%), followed by respiratory system (6.0%), digestive system (4.0%), urinary system (4.0%), and breast (3.0%) (Figure 4A). The primary site that contributed the most to the incidence rate was respiratory system in males and female genital system in females (Figure 4B).

In the current study, both incidence and mortality had rising trends in female genital system (APC=4.5%, 95% CI:3.7%-5.2%, \( p < 0.05 \); APC=4.2%, 95% CI:3.6%-4.9%, \( p < 0.05 \), respectively), while they showed stable
trends in other sites during 1975-2018. Furthermore, both rates were higher in female genital system than in other sites (Figure 4C, 4D).

Figure 4E shows that the relative survival of CS patients for the main primary sites. The breast tended to enjoy the longest survival, while digestive system had worst survival than other sites.

**Discussion**

In this study, we used the SEER database to report the epidemiology of CS for the first time, suggesting that the overall incidence and mortality rates of CS have increased from 1975 to 2018, and the 5-year survival of all patients is 34.9%. Our findings further verified that CS occurs more commonly in the female genital system, and the prognosis of it is associated with the primary sites.

For the study, we enrolled large-scale patients with CS, and discovered that the prevalence of it is very low with an overall incidence of 0.36–0.83 per 100,000 person-years. In addition, an increased incidence tendency was observed, partly because of a rapid improvement in detection practice and the rate of tamoxifen use (McCluggage et al. 1997; Palda et al. 1997). Mortality is a better indicator of prognosis than survival in tumors (Siegel et al. 2022). Unfortunately, marked rise in incidence as well as little improvement in treatment strategies have resulted in a 7.7-fold increase in the mortality of CS. In consistent with previous studies, CS, especially in the female genital system, is no longer considered to be a rare tumor in the near future (Matsuo et al. 2018).

The rates of incidence and mortality in CS have increased among female, White, Black, patients aged 50 years and older, patients with high grade or all stages over time. However, both rates increased the most in the group which with high grade, then advanced stage, Black and females. It is unclear whether these differences are related to lifestyle, environmental exposures or biological factors.

Many retrospective studies or case reports were launched around CS of different anatomic sites, including uterus, ovary, lung, bladder, breast, stomach and etc. (Lin et al. 2019; Rauh-Hain et al. 2013; McCluggage et al. 1997; Ersek et al. 2020; Argüelles et al. 2004; Marco et al. 2019). This tumor may appear in any anatomic site, however, to investigate the common primary site of CS, has not yet been systematically conducted and remains a blank field. In this paper, a comparison has been made to solve the problem, and showed that CS mainly happens in uterus, followed by ovary, lung and bronchus, urinary bladder and breast. Among all the patients, sites that reflected the greatest incidence of CS is the female genital system, followed by the respiratory system, the urinary system, the digestive system and breast. Our results are similar with the representation of Pang et al., and further pointed out other common locations (Pang et al. 2017).

Previously, former studies became aware of that the primary site of tumor is significantly linked with patient prognosis (Modlin et al. 2003; Wu et al. 2018). For instance, Modlin et al. showed that the survival rate is related with the primary site in carcinoid tumors (Modlin et al. 2003). Wu et al. carried out research in signet ring cell carcinoma and observed a definitive relation between prognosis and the primary site.
(Wu et al. 2018). We proposed that survival in CS might be impacted by the primary tumor location. As expected, a clear association was received. In the present study, we analyzed the relative survival of all patients, and found that compared with CS patients of female genital system, patients with breast CS are more likely to have a better survival, while patients with other CS have a relatively worse prognosis. One possible reason is that the prognosis of malignant tumor depend on not only the histology type, but also the molecular subtype (Bonazzi et al. 2022).

Anyway, several limitations need to be concerned in our research. First, the present study is retrospective and an inherent selection bias should be admitted. Second, invalid information recorded unknown is too large in the SEER database. For instance, TNM stage is unavailable in many patients, therefore, we were unable to verify both incidence and mortality trends by this critical factor. Finally, the SEER database merely covers partial American population, and other countries fail to be included for integral analysis, which may limit the generalizability of our current conclusions to other population.

Despite of the above shortages, our research also has following strengths. Mostly, to the best of our knowledge, the present study is the first analysis to specially describe the epidemiological feature of patients with CS, all of which may be helpful for clinical practice. More than that, as far as we know, our study based on the SEER database included the largest and latest CS patients in the literature.

**Conclusions**

To sum up, our study proved that CS is a rare tumor with increasing trends in incidence and mortality, and these trends especially evident in female population, Black people, senior groups and patients with poor differentiation or advanced stage. Furthermore, it has been demonstrated that CS most often appears in female genital system including uterus, ovary and etc.. Finally, our results suggested that the survival in patients may vary widely by the primary sites. As compared to CS in female genital system, breast CS has better prognosis, while other CS suffer shorter survival. This research will broaden our knowledge for CS as well as provide a theoretical basis to identify new approaches for prevention, surveillance, and treatment.

**Declarations**

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**Author Contributions** All authors contributed to the design, data collection and analysis, and drafted the manuscript. All authors have read and approved the final manuscript.

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**Conflicts of Interest** All authors declare that they have no conflicts of interest.
Ethical approval Since all SEER data are anonymous and publicly accessible, ethics board review and informed consent from the patient were not required.

Consent to participate Publicly available databases were analysed in this study. These data can be found in the SEER database (https://seer.cancer.gov/).

References


27.

Figures

Figure 1

Overall (A) incidence and (B) mortality trends of carcinosarcoma have increased from 1975 to 2018.

Abbreviations: APC, annual percentage change.
*Statistically significant.

Figure 2

Incidence and mortality trends by sex (A, B), race (C, D) and age (E, F) from 1975 to 2018.

Abbreviations: APC, annual percentage change, NR, not reached.

*Statistically significant.
Figure 3

Incidence and mortality trends by grade (A, B) and stage (C, D) from 1975 to 2018.

Abbreviations: APC, annual percentage change, NR, not reached.

*Statistically significant.
Figure 4

(A) Distribution, (B, C) incidence, (D) mortality, and (E) survival analyses by primary site or sex.

Abbreviations: APC, annual percentage change.

*Statistically significant.