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ORIGINAL RESEARCH

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

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Abstract

Carcinosarcoma (CS) is a rare malignant tumor, with little known about its epidemiological features in literature. This study aimed to report the largest and latest analysis on the incidence, mortality and survival of CS. Data of CS from the Surveillance, Epidemiology and End Results (SEER) database (SEER-9 incidence database and SEER-9 incidence-based mortality database) were retrieved and assessed. Incidence, mortality and survival analyses were performed using the SEER*Stat software. We used annual percentage change (APC) to evaluate the trends in incidence and mortality. The results showed that the incidence rate of CS increased from 0.36/100,000 to 0.83/100,000, with an APC of 3.4%, from 1975 to 2018. Its mortality rate followed a similar pattern, with an APC increase of 3.2% from 0.07/100,000 in 1975 to 0.54/100,000 in 2018. Most CS cases were reported to be from the female genital system. The 5-year survival rate of all patients was 34.9%. CS is an aggressive tumor with increasing incidence and mortality trends. This tumor, especially CS in the female genital system, should no longer be considered a rare tumor. This research broads our knowledge of CS and provides important insights for clinicians.

Keywords

Carcinosarcoma; Epidemiology; Incidence; Mortality; Survival

1. Introduction

Malignant tumors are a major public health problem worldwide [1]. Carcinosarcoma (CS) is an unusual malignancy that was first reported by Virchow in 1863 [2]. The World Health Organization (WHO) classification defines CS as a biphasic tumor composed of malignant epithelial and mesenchymal elements [3]. In clinical settings, patients with CS have an unfavorable prognosis than patients with other tumors at the same primary sites [4, 5]. Due to limited research and a lack of clinical trials on CS, its treatments are generally based on tumors at the same anatomic sites [6].

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 [4, 5, 7, 8].

Owing to its rarity, the epidemiological features of CS are not fully understood. Current knowledge about this tumor mainly derives from case reports and retrospective studies involving small samples and insufficient information. In addition, clinical trials or prospective analyses related to CS are limited in the domain of cancer research. Encouragingly, the Surveillance, Epidemiology and End Results (SEER) database provides resources for exploring rare tumors like CS. As a result, we used the SEER data to perform a large population-based study to improve our understanding of CS.

This current study was designed to clarify the incidence and mortality trends of 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. We also investigated the survival rates according to the primary sites.

2. Methods

2.1 Data Source

The SEER program (https://seer.cancer.gov) was launched by the National Cancer Institute (NCI) in 1973, 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 [9]. All data on incidence and survival were extracted from the SEER-9 incidence database, and mortality data 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.

2.2 Study Population

A population of patients with CS was 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. 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 data, we could not perform relative analyses in 2016–2018.

2.3 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 the 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 grouped into the following six categories: digestive system, respiratory system, breast, female genital system, urinary system and others.

2.4 Statistical Analysis

All calculations in this present study were performed with SEER*Stat 8.3.9 software (Surveillance Research Program, National Cancer Institute, USA, https://seer.cancer.gov/seerstat/). Incidence-based mortality (IBM) rates were defined as the proportion of the total number of deaths due to this cancer [10]. Incidence and mortality rates are expressed per 100,000 persons, and the United States population for the year 2000 was regarded as the standard population. We also calculated the annual percentage changes (APCs) to quantify all trends according to the above characteristics. Differences between APCs and zero were compared using *t*-test, and two-sided *p* values < 0.05 were considered statistically significant. APCs for part of the subgroup could not be calculated due to the low number of cases. Relative survival rates are defined as the ratio of observed survivors in cancer patients to the expected survivors in non-cancer patients. One- to five-year relative survival rates were generated. All rates mentioned above were age-adjusted and calculated as previously reported [11, 12].

3. Results

3.1 Overall incidence and mortality trends

The incidence and mortality trends of CS increased significantly during the study duration (1975–2018) (Fig. 1). According to data from the SEER-9 incidence database, the overall incidence of CS showed a rising trend, with an APC of 3.4% (95% CI: 2.8–3.9, $p < 0.05$) (Fig. 1A). CS incidence was 0.36 cases per 100,000 in 1975 and increased to 0.83 cases per 100,000 in 2018. Meanwhile, based on the 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, $p < 0.05$) (Fig. 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.

3.2 Incidence and mortality trends by demographic characteristics

We further evaluated both incidence and mortality trends by sex, race, and age from 1975 to 2018 (Fig. 2). First, the results showed that both incidence and mortality 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 incidence and mortality rates were higher in women than in men (Fig. 2A,B).

Second, both incidence and mortality 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. Weak increasing trends were observed for other races, and the corresponding APCs could not be calculated due to the low number of cases. In addition, both incidence and mortality rates were higher in Black than in White or other races (Fig. 2C,D).

Third, both incidence and mortality trends elevated significantly in patients aged 50–69 years (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 ≥70 years (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). Furthermore, a steep increase with advanced age was found in both incidence and mortality rates (Fig. 2E,F).

3.3 Incidence and mortality trends by tumor characteristics

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

The results showed no significant increase or decrease in low-grade cases (APCs could not be calculated due to the low number of cases), but an obvious increase was observed in high-grade cases (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 incidence and mortality rates were higher in patients with high- and low-grade (Fig. 3A,B). The results also showed that both incidence and mortality trends increased in the 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.

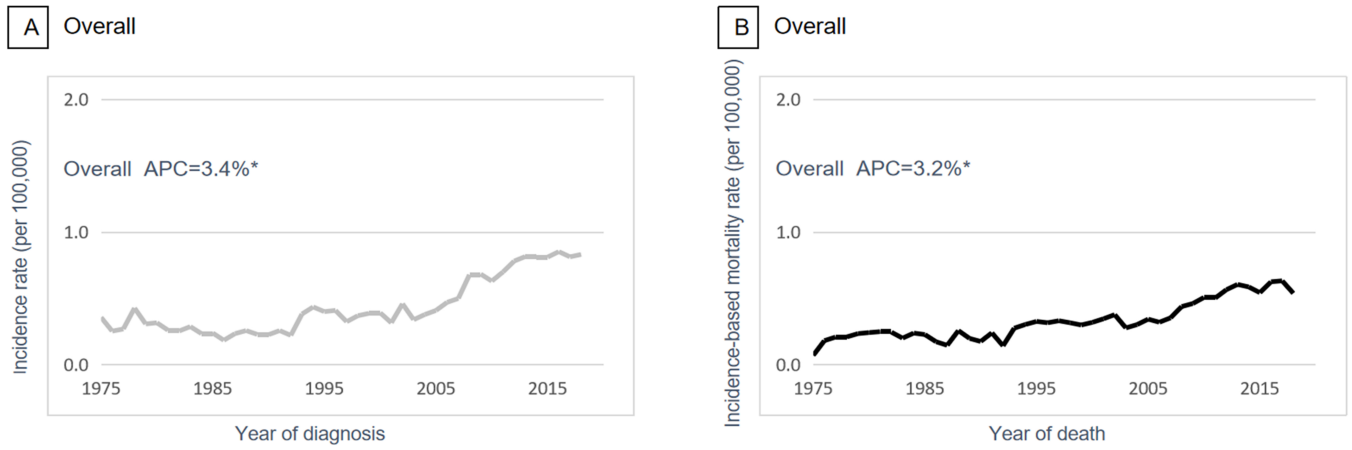

FIGURE 1. Overall incidence and mortality trends of carcinosarcoma have increased from 1975 to 2018. (A) Incidence. (B) Mortality. Abbreviations: APC, annual percentage change. *Statistically significant.

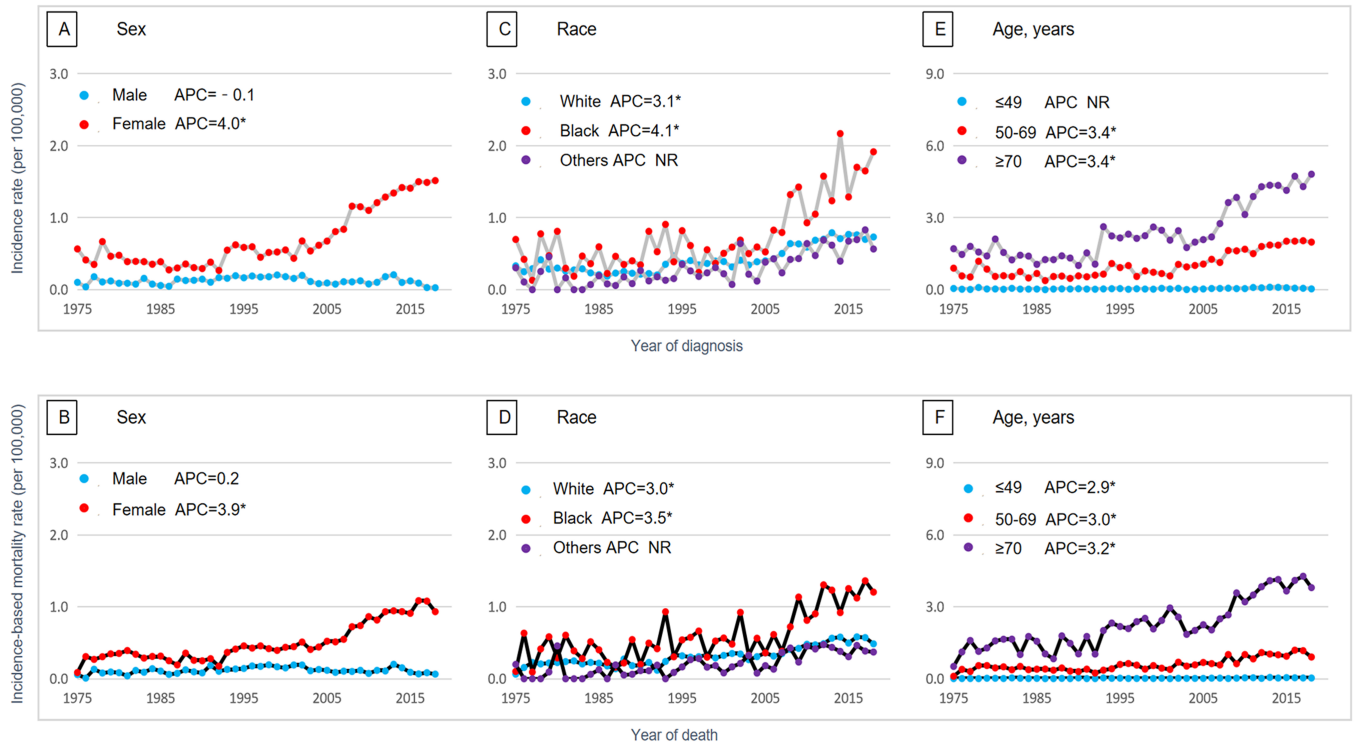

FIGURE 2. Incidence and mortality trends by demographic characteristics from 1975 to 2018. (A) Incidence trend by sex. (B) Mortality trend by sex. (C) Incidence trend by race. (D) Mortality trend by race. (E) Incidence trend by age. (F) Mortality trend by age. Abbreviations: APC, annual percentage change, NR, not reached. *Statistically significant.

Additionally, both incidence and mortality rates were higher in the advanced stage than in the early stage (Fig. 3C,D).

3.4 Incidence, mortality and survival analyses by primary site

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

Further analysis showed that both incidence and mortality showed rising trends in the 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 tumor sites from 1975 to 2018. Additionally, both incidence and mortality rates were higher in the female genital system than in other sites (Fig. 4C,D).

Fig. 4E shows the relative survival of CS patients for the main primary sites, from which it could be observed that patients with breast CS tended to have the longest survival, while those from the digestive system had the worst survival compared with other CS sites.

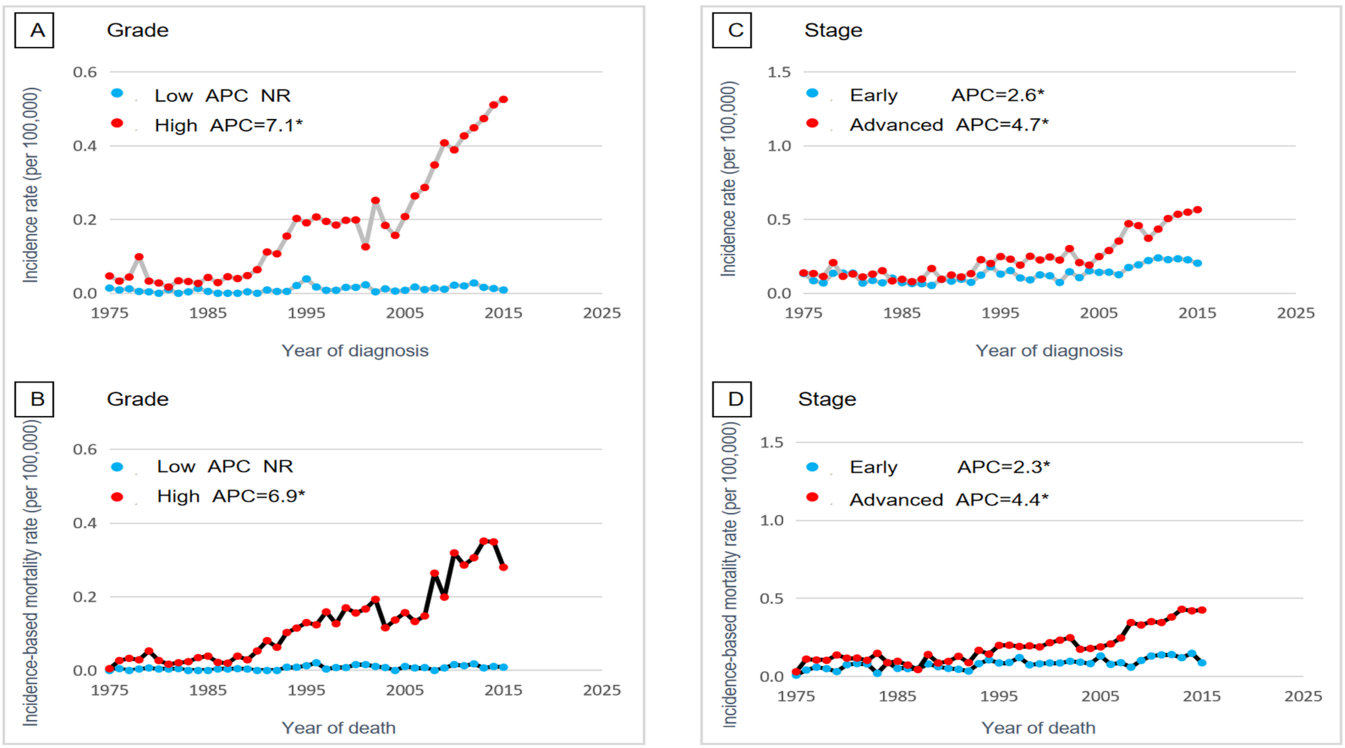

FIGURE 3. Incidence and mortality trends by tumor characteristics from 1975 to 2018. (A) Incidence trend by grade, (B) Mortality trend by grade. (C) Incidence trend by stage. (D) Mortality trend by stage. Abbreviations: APC, annual percentage change, NR, not reached. *Statistically significant.

FIGURE 4. Distribution, incidence, mortality and survival analyses of carcinosarcoma by primary site or sex. (A) Distribution analysis by primary site. (B) Incidence analysis by sex. (C) Incidence analysis by primary site. (D) Mortality analysis by primary site. (E) Survival analysis by primary site. Abbreviations: APC, annual percentage change. *Statistically significant.

4. Discussion

In this study, for the first time, the SEER database was used to report the epidemiology of CS. The results showed that the overall incidence and mortality rates of CS had increased from 1975 to 2018, and the 5-year survival of the whole cohort was 34.9%. Our findings further verified that CS occurred more commonly in the female genital system, and the prognosis of CS was associated with their primary site.

For this study, we enrolled large-scale patients with CS and discovered that its prevalence was 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 its detection in clinical practice and the rate of tamoxifen exposure [13, 14]. Mortality is a better indicator of prognosis than survival in tumors [15]. However, the marked increase in the incidence of CS but little improvement in its treatment strategies have resulted in a 7.7-fold increase in CS mortality. Consistent with previous studies, our data suggest that CS, especially those from the female genital system, should no longer be considered a rare tumor [16].

The incidence and mortality rates of CS have increased among females, Whites, Blacks, patients aged $\geq$50 years and those with high-grade or all stages over time. However, both incidence and mortality rates increased the most in patients with high-grade CS, then advanced stage, followed by Blacks and females. It is unclear whether these differences could be related to lifestyle, environmental exposures or biological factors.

Matsuo *et al.* [16] demonstrated that the proportion of uterine CS has increased within endometrial cancer [16]. They further suggested that this trend could be due to the increase in the proportion of Black or older women [16]. Besides, an increasing proportion of the obese population could be another reason for this trend [16]. Obese patients have a high risk of breast cancer, for which tamoxifen is commonly used [16]. Exposure to tamoxifen has been related to the genesis of uterine CS [13, 14]. In this study, uterine CS accounted for at least 60% of the total cases in the incidence analysis. We also found that Blacks and females had a higher incidence than other races and males. Additionally, an increased incidence tendency was observed in the female genital system.

Many retrospective studies or case reports were launched around CS of different anatomic sites, including the uterus, ovary, lung, bladder, breast, stomach, *etc.* [4, 5, 13, 17–19]. Although CS was reported to appear in any anatomic site, we could not systematically assess all the common primary sites of CS due to limited data. Thus, based on existing data, we observed that CS mainly occurred in the uterus, followed by the ovaries, lungs and bronchus, urinary bladder and breast. Among all patients, CS sites with the greatest incidence were the female genital system, followed by the respiratory system, urinary system, digestive system and breast. Our results concurred with those of Pang *et al.* [6] and we further pointed out other common locations.

Previously, it was reported that the primary site of a tumor is significantly linked with a patient's prognosis [20, 21]. For instance, Modlin *et al.* [20] showed that the survival rate of patients with carcinoid tumors was related to their primary site. Wu *et al.* [21] performed an investigation on signet ring cell carcinoma and observed a definitive relation between prognosis and the primary site. Thus, we investigated whether the survival of CS patients could be impacted by primary tumor location. As expected, a clear association was observed. In this present study, we analyzed the relative survival of all patients and found that compared with CS patients of the female genital system, patients with breast CS were more likely to have a better survival, while patients with other CS had a relatively worse prognosis. One possible reason could be that the prognosis of CS may not only depend on the histology type but also on the molecular subtype, progression rate and treatment options [22].

There were several limitations in this research. First, inherent selection bias could have been present as this was a retrospective study. Second, many important information was unavailable and recorded as unknown in the SEER database. For instance, TNM stage data was unavailable for many patients; therefore, we could not verify the incidence and mortality trends by this critical factor. Additionally, the SEER database does not cover the whole American population and other countries, limiting our current results' generalizability to other populations.

Despite the described limitations, this study had the following strengths. To the best of our knowledge, this is the first analysis to describe the epidemiological feature of patients with CS, providing helpful data for clinical practice. Also, as far as we know, our study based on the SEER database included the largest and latest data on CS patients in the literature.

5. Conclusions

In summary, our study showed increasing trends in the incidence and mortality of CS, especially in the female population, Black people, older age groups and patients with poor differentiation or advanced stage. Furthermore, it was observed that CS most often appeared in the female genital system, including the uterus, ovary, *etc.* Lastly, our results suggested that the survival of CS patients may vary widely depending on the primary tumor site. Compared with CS in the female genital system, breast CS was associated with better prognosis, while patients with other CS had shorter survival. This research broadens our knowledge on CS and provides a theoretical basis to improve approaches for its prevention, surveillance and treatment.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

LL—Data curation, Formal analysis, Writing-Original Draft, Writing-Review & Editing; YZ—Data curation, Formal analysis, Writing-Original Draft; CZ—Data curation, Writing-Original Draft; YT—Conceptualization, Methodology, Super-

vision, Writing-Review & Editing.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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The data supporting this study's findings are available at https://seer.cancer.gov/.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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