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Comparative analysis of testicular and nontesticular choriocarcinoma: a population-based study

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Background: Germ cell tumors (GCTs) are common solid tumors in young men, originating in the testicles or outside the gonads. Choriocarcinoma, a rare and aggressive subtype, primarily affects females but can also occur in males. Treatment options depend on the stage and location of the tumor, with early recognition being crucial for better outcomes. Comparative studies between testicular and nontesticular choriocarcinoma are crucial for understanding distinct features and prognoses.

Methods: The study utilized SEER*Stat software to extract data and applied statistical methods such as χ^2 analysis and Kaplan–Meier method. Inclusion criteria focused on patients diagnosed with choriocarcinoma between 2000 and 2018, while exclusion criteria eliminated cases without histological confirmation or with other tumors.

Results: Among 363 patients, 270 (74.4%) had testicular CC, and 93 (25.6%) had nontesticular CC. Notably, testicular CC was more common in white patients, which could indicate demographic or environmental factors at play. Patients with testicular CC were more likely to undergo surgery, suggesting a significant treatment trend. It is worth exploring whether patient preferences or observed postsurgery improvements contribute to this pattern. Testicular CC had a higher 5-year OS rate of 54% versus 29%, and a higher 5-year CSS rate of 56.3% versus 31.9%, respectively.

Conclusion: This study reveals distinct characteristics and treatment responses in testicular and nontesticular choriocarcinoma, emphasizing the need for personalized management based on subtype. Our findings highlight racial disparities in incidence and the efficacy of surgical intervention for both types, while chemotherapy benefits extragonadal cases and radiotherapy's role requires further evaluation.

Keywords: choriocarcinoma, germ cell tumor, prognosis, survival rates, testicular choriocarcinoma

Introduction

Germ cell tumors (GCTs) are one of the most common solid tumors in young men aged between 20 and 34[1,2]. These tumors can originate in the testicles (gonads) or develop in areas outside of the gonads (extragonadal), such as the mediastinum or retroperitoneum. The primary distinction between gonadal and extragonadal tumors lies in their clinical presentation and behavior, with extragonadal tumors occurring in regions where germ cells migrate during development and exhibiting different characteristics from those found in the testicles[3]. Choriocarcinoma is a rare and highly aggressive subtype of GCT worldwide. It primarily affects in females, constituting less than 0.1% of all primary ovarian tumors in its pure form. However, it can also occur in males at a similar rate as in females, accounting for less than 0.1% of pure testicular tumors[4].

The clinical significance of CC stems from the presence of early widespread metastasis and high serum human chorionic gonadotropin levels[5]. Testicular CC, also called intragonadal, is the most common primary site. When the primary tumor is extragonadal, it develops in the midline locations of the body, such as the anterior mediastinum, retroperitoneum, pineal gland, lung, brain, and digestive tract[1,2]. The age group of peak occurrences is 20–29 years. It spreads widely via the hematogenous route, resulting in poor prognosis, and no standard therapy exists[6].

According to the International Germ Cell Cancer Collaborative Group, nonseminomatous, which is a cancer that begins in cells that form sperms, primary mediastinal GCT have a worse

HIGHLIGHTS

- Testicular CC patients were more likely to undergo surgery, while nontesticular CC had poorer survival rates.
- Our study found that whites were more likely to have testicular CC, while blacks were more likely to have extragonadal CC.
- Surgery improved survival for both testicular and nontesticular CC subtypes.
- Chemotherapy benefited only nontesticular CC cases, but radiotherapy did not significantly impact patient outcomes.

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prognosis than other extragonadal types[7]. Treatment depends on the stage of the disease, and early recognition is essential to improve the chances of recovery. The main treatment for early stages is radical inguinal orchiectomy, while other options include lymph node dissection (RPLND) and chemotherapy, which have shown an 80% 5-year overall survival rate, even in late stages[6,8]. Treatment options for extragonadal GCTs include chemotherapy, surgery, and radiation, as determined by the location, size, and histology of the tumor[9,10].

The rarity of CC poses challenges in understanding its clinical behavior and optimal management. Consequently, comparative studies between testicular and nontesticular CC are essential to highlight the clinical significance of understanding the differences in prognosis and treatment response. We collected the largest sample to date from the SEER database and applied strict inclusion criteria to compare their features, prognoses, and outcomes. This research aims to contribute to a better understanding of CC and GCTs, ultimately improving patient care and outcomes.

Methodology and materials

Data extraction

We selected and extracted the data from the 'Incidence-SEER 18 Regs Custom Data (with additional treatment fields), Nov 2020 Sub (2000–2018 varying)' database using SEER*Stat software (version 8.4.2) for their reliability in providing accurate and comprehensive cancer-related data. The statistical methods used, such as the χ^2 analysis and the Kaplan–Meier method, were chosen for their ability to assess clinical and pathological characteristics accurately and analyze survival rates effectively. This study is in line with strengthening the reporting of cohort, cross-sectional, and case–control studies in surgery STROCSS reporting guidelines[11].

Inclusion and exclusion criteria

We established inclusion and exclusion criteria to ensure the accuracy and proper representation of patients with choriocarcinoma. Patients diagnosed with CC between 2000 and 2018 based on the third edition of the International Classification of Diseases for Oncology (ICD-O-3) were included in this study. The histology code for the disorder was as follows: 9100/3 (choriocarcinoma). Patients whose diagnoses were not confirmed by histological analysis or who had other tumors were excluded to minimize bias in the results. Finally, 426 eligible patients diagnosed with CC remained. The detailed screening process is shown in the flow diagram in Figure 1.

These criteria were essential for maintaining the internal validity of the study by ensuring that the included patients were truly representative of the target population of interest. However, it is important to acknowledge that these strict criteria may limit the generalizability of the findings to a broader population. Future research could explore the impact of different inclusion and exclusion criteria on the generalizability and potential biases in similar studies.

Variables

Clinical and demographic data for each patient were organized according to age, race, marital status, tumor size, stage, surgery, chemotherapy, and radiation therapy because these variables provide a comprehensive view of disease characteristics and their impact on survival. Age was reported in two groups (<30 years and ≥ 30 years). The race was classified into (white, black, or other). Tumor-related characteristics have also been reported. The tumor size was divided into <4 cm and ≥ 4 cm. SEER stage was classified as (localized, regional, or distant). Treatment modalities (surgery, chemotherapy, and radiation therapy) were categorized as yes, or no. OS and CSS were the primary study endpoints and were analyzed at 1-year, 3-year, and 5-year.

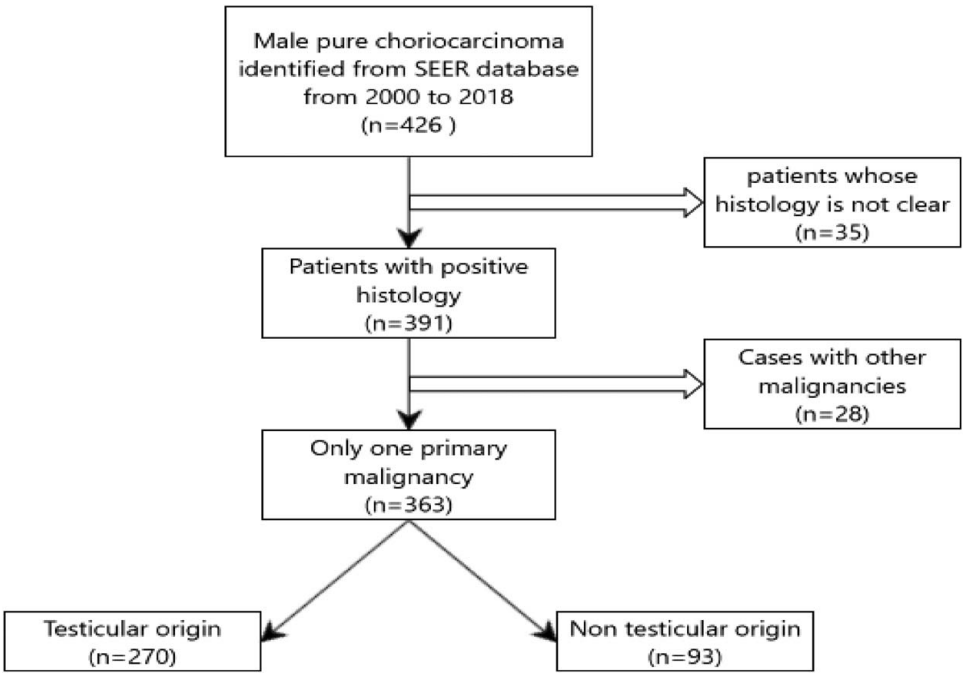

Figure 1. Flow diagram for patients' selection.

Statistical analysis

The Extracted SEER data were analyzed by R language (v4.0.0) software, and the elementary packages were 'readxl', 'tidyverse', 'Hmisc', 'data. table', Table 1, 'MatchIt', 'survminer', 'survival' and 'broom'. We used χ^2 analysis to evaluate distinct clinicopathological characteristics between patients with testicular and nontesticular choriocarcinoma. We estimated survival rates [overall survival (OS) and cancer-specific survival (CSS)] using the Kaplan–Meier method and we interpret the results as a HR with 95% CIs. The log-rank test was employed to compare survival curves. Multivariable Cox Proportional Hazards Models were used to identify independent predictors of OS and CSS.

Based on multivariable Cox regression results, we formulated a nomogram to predict 5-year survival. A nomogram allows the estimation of mortality risks based on specific variables and assists in making informed treatment decisions. We evaluated its performance using receiver operating characteristic (ROC) curves and calibration plots. A two-tailed *P*-value less than 0.05 was considered statistically significant.

Table 1

Clinicopathological characteristics for testicular and nontesticular CC patients

Characteristics	Nontesticular CC (*N* = 93)	Testicular CC (*N* = 270)	Overall (*N* = 363)	*P*
Age				
< 30	48 (51.6%)	144 (53.3%)	192 (52.9%)	0.96
≥ 30	45 (48.4%)	126 (46.7%)	171 (47.1%)	
Race				
Black	12 (12.9%)	11 (4.1%)	23 (6.3%)	0.002
Other	15 (16.1%)	20 (7.4%)	35 (9.6%)	
White	66 (71.0%)	239 (88.5%)	305 (84.0%)	
Marital status				
Married	27 (29.0%)	76 (28.1%)	103 (28.4%)	0.997
Not married	63 (67.7%)	183 (67.8%)	246 (67.8%)	
Unknown	3 (3.2%)	11 (4.1%)	14 (3.9%)	
Laterality				
Bilateral	1 (1.1%)	4 (1.5%)	5 (1.4%)	< 0.001
Left or right	11 (11.8%)	266 (98.5%)	277 (76.3%)	
Not a paired site	81 (87.1%)	0 (0%)	81 (22.3%)	
Tumor size				
< 4 cm	18 (19.4%)	137 (50.7%)	155 (42.7%)	< 0.001
≥ 4 cm	75 (80.6%)	133 (49.3%)	208 (57.3%)	
Stage				
Distant	62 (66.7%)	235 (87.0%)	297 (81.8%)	< 0.001
Localized	18 (19.4%)	24 (8.9%)	42 (11.6%)	
Regional	13 (14.0%)	11 (4.1%)	24 (6.6%)	
Metastasis				
No	37 (39.8%)	75 (27.8%)	112 (30.9%)	0.097
Yes	56 (60.2%)	195 (72.2%)	251 (69.1%)	
Surgery				
No	61 (65.6%)	92 (34.1%)	153 (42.1%)	< 0.001
Yes	32 (34.4%)	178 (65.9%)	210 (57.9%)	
Chemotherapy				
No	19 (20.4%)	33 (12.2%)	52 (14.3%)	0.15
Yes	74 (79.6%)	237 (87.8%)	311 (85.7%)	
Radiation				
No	66 (71.0%)	231 (85.6%)	297 (81.8%)	0.007
Yes	27 (29.0%)	39 (14.4%)	66 (18.2%)	

CC, choriocarcinoma.

Ethical approval

Ethics approval was not required for this study.

Results

Clinicopathological characteristics of testicular and nontesticular CC patients

A total of 363 patients with CC were identified in the SEER database and divided into 270 patients with testicular CC and 93 patients with nontesticular CC. Detailed clinicopathological characteristics are summarized in Table 1. When comparing testicular with nontesticular CC patients, we found that testicular CC patients had a higher proportion of being white compared to nontesticular CC patients (88.5% vs. 71.0%, $P = 0.002$). Testicular subtype tumors were significantly smaller (< 4 cm: 50.7% vs. 19.4%; ≥ 4 cm:49.3% vs. 80.6%; $P < 0.001$) and had a more advanced SEER stage (distant: 87.0% vs. 66.7%; localized:8.9% vs. 19.4%; regional:4.1% vs. 14.0%; $P < 0.001$) than nontesticular CC. Regarding treatment options, patients with testicular CC were more likely to undergo surgery (65.9% vs. 34.4%, $P < 0.001$) and less likely to receive radiation (14.4% vs. 29.0%, $P = 0.007$). However, age, marital status, metastasis, and chemotherapy were not significantly different between the two choriocarcinoma subtypes ($P = 0.96$, 0.997, 0.097, and 0.15, respectively).

Survival analysis of testicular and nontesticular CC patients

Nontesticular CC was associated with worse CSS and OS rates than testicular CC, as shown in Figure 2. Testicular CC had a higher 5-year OS rate of 54% versus 29%, and a higher 5-year CSS rate of 56.3% versus 31.9%, respectively. The 3-year survival rates for OS and CSS were 55.1% and 56.8%, respectively, in testicular CC, compared with 36.2% and 37.7%, respectively, in nontesticular CC. Also, 1-year survival rates for OS and CSS were 67.3 and 69.5% in testicular CC vs. 47.1 and 49.1% in nontesticular CC, respectively.

Prognostic factors for OS and CSS in nontesticular and testicular CC patients

To identify potential independent predictors of CC, we used a univariate Cox regression model to identify significant factors and used them in a multivariate Cox regression. Regarding nontesticular CC, older age was associated with poor OS, whereas surgery and chemotherapy were associated with better OS Figure 3. In testicular CC, the presence of metastasis was associated with poor survival, whereas surgery was associated with better OS and CSS Figure 4.

Performance and validation of the nomogram for predicting 5-survival in testicular and nontesticular CC

A nomogram that integrated all significant factors for testicular and nontesticular CC in the multivariate Cox regression models was developed and presented in Figures 5A, 6A. The calibration curves for both nomograms showed good agreement between predicted and observed probabilities for 5-year survival, with a mean error of 0.025 for the testicular CC nomogram and 0.037 for the nontesticular CC nomogram Figure 5B, Figure 6B. The AUC of the testicular CC nomogram was 0.716 (95% CI:

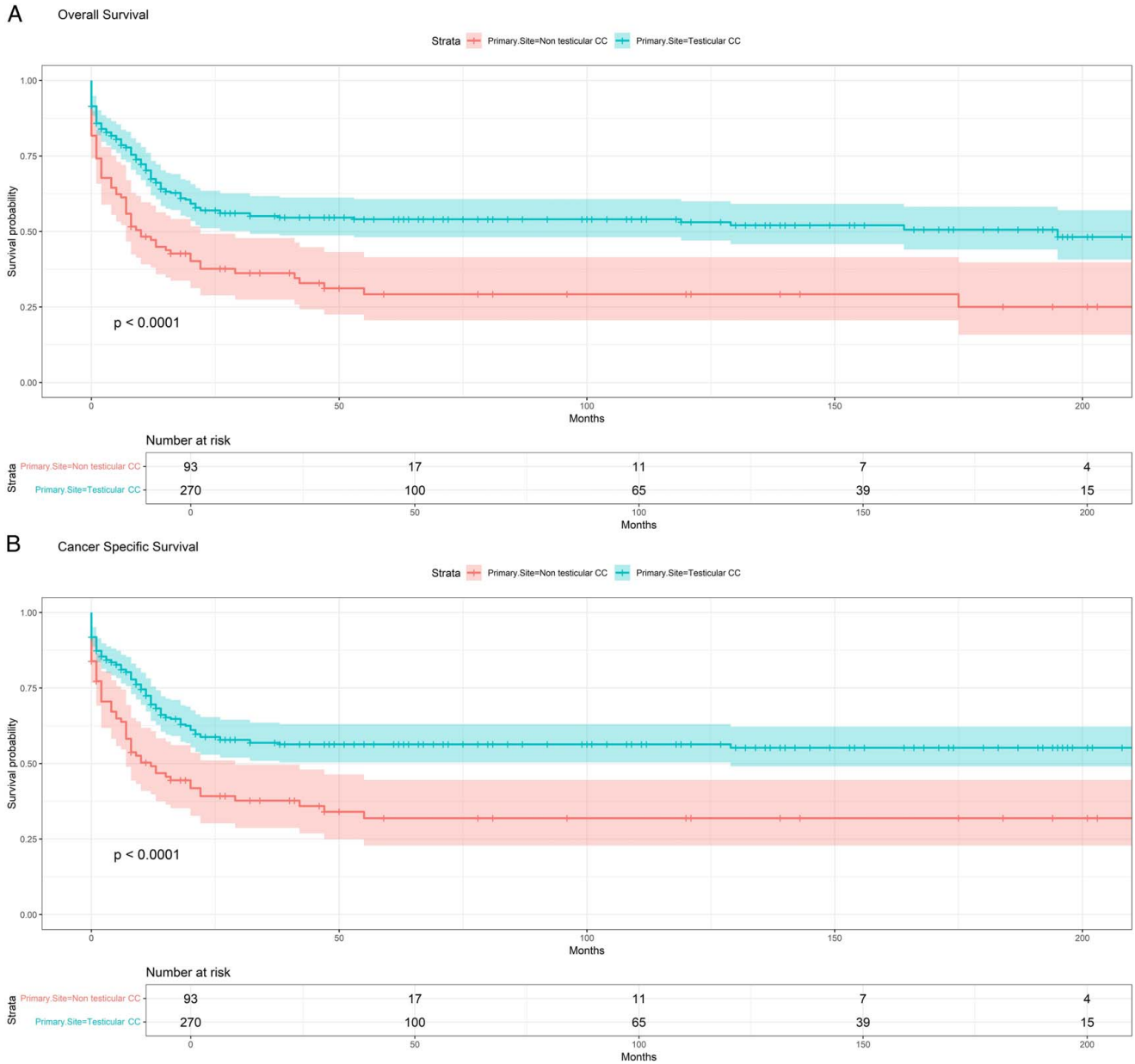

Figure 2. Kaplan–Meier curves showing a comparison of (A) overall survival and (B) cancer-specific survival in testicular and nontesticular choriocarcinoma.

0.65–0.78), whereas that of the nontesticular CC nomogram was 0.715 (95% CI: 0.61–0.82) Figure 5C, Figure 6C.

Discussion

CC is a rare form of cancer that occurs in both men and women. In women, the most common type is gestational CC, which originates from trophoblast cells of the placenta. In men, it is a rare subtype of nonseminomatous germ cell tumor and is a much more aggressive form of this disease with a poor prognosis[12,13]. Approximately 5% of individuals with gonadal cell tumors have a tumor that develops at an extragonadal location along the midline of the body, including extragonadal CC[14].

Stang *et al.*[15] demonstrated that the different time trends of gonadal and extragonadal GCTs may indicate a difference in etiology and explain the clinicopathological differences between the two. However, the origin of extragonadal GCTs remains controversial. The classical hypothesis states that they are derived from emigrating primitive germ cells, which explains their anatomical distribution in the midline locations of the tumor[16]. More recently, McKenney *et al.*[17] suggested GCTs could be a metastasis from an original dormant, or undiagnosed primary germ cell tumor in the testes. The latter hypothesis better explains the more aggressive nature of extragonadal CC as opposed to gonadal CC, which aligns with our results.

In our study, the median ages of both testicular and nontesticular CC patients were similar (30 and 32 years, respectively). Previous reports have shown very similar median ages ranging from 29 to 34 of both subtypes[18,19]. Although there is limited data on the median age of CC incidence, our results seem

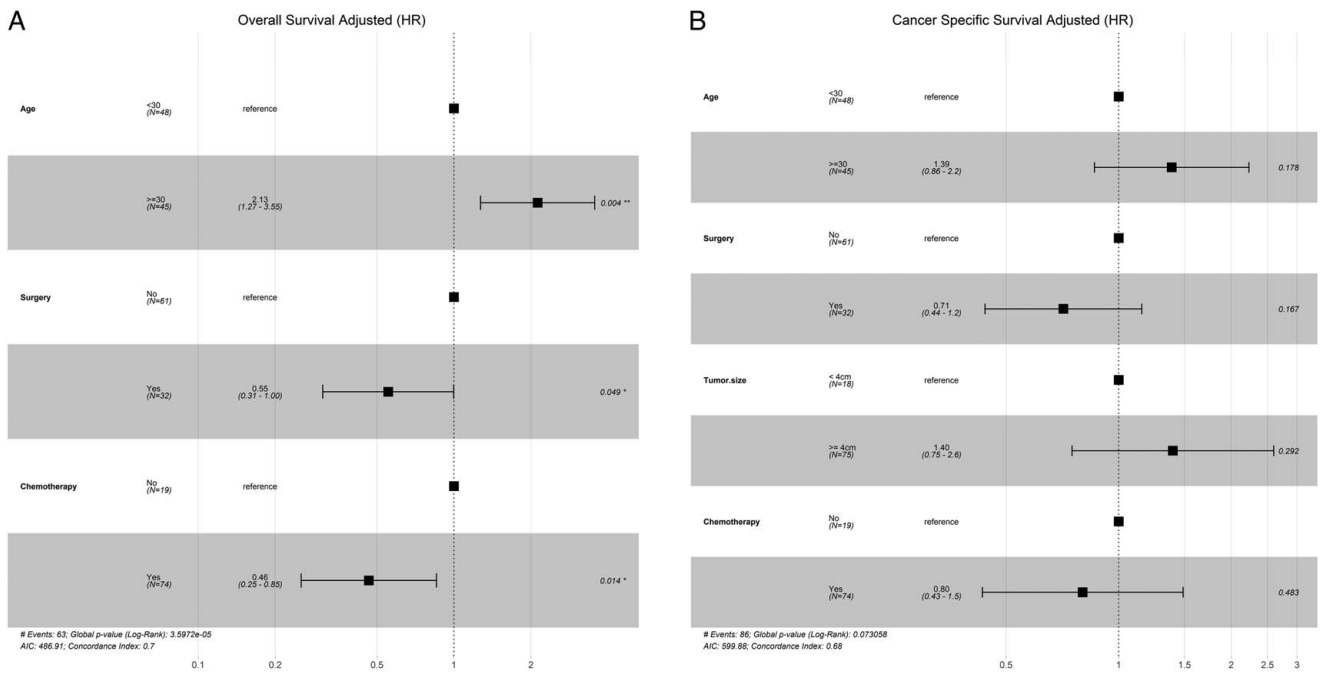

Figure 3. Multivariate Cox proportional hazards regression model results of (A) OS and (B) CSS for Nontesticular choriocarcinoma patients.

consistent with the available literature. We found that the most common location of the extragonadal tumors was the mediastinum (41.9%), followed by the retroperitoneum (10.7%). This is also in line with the findings of a larger study of 21,170 men with GCTs, where the mediastinum was the most common site for extragonadal tumors, followed by the retroperitoneum and brain[15]. While extragonadal tumors can occur in any midline location, there have been rare cases of extragonadal tumors found in unexpected locations, such as the prostate[20]. Our findings align with the established differences between gonadal and extragonadal germ cell tumors in relation to race. A study by Stang *et al*. in 2013 found that gonadal GCTs were more prevalent among white males (56.3/1 000 000) compared to black males (10.0/1 000 000), while extragonadal GCTs rates among

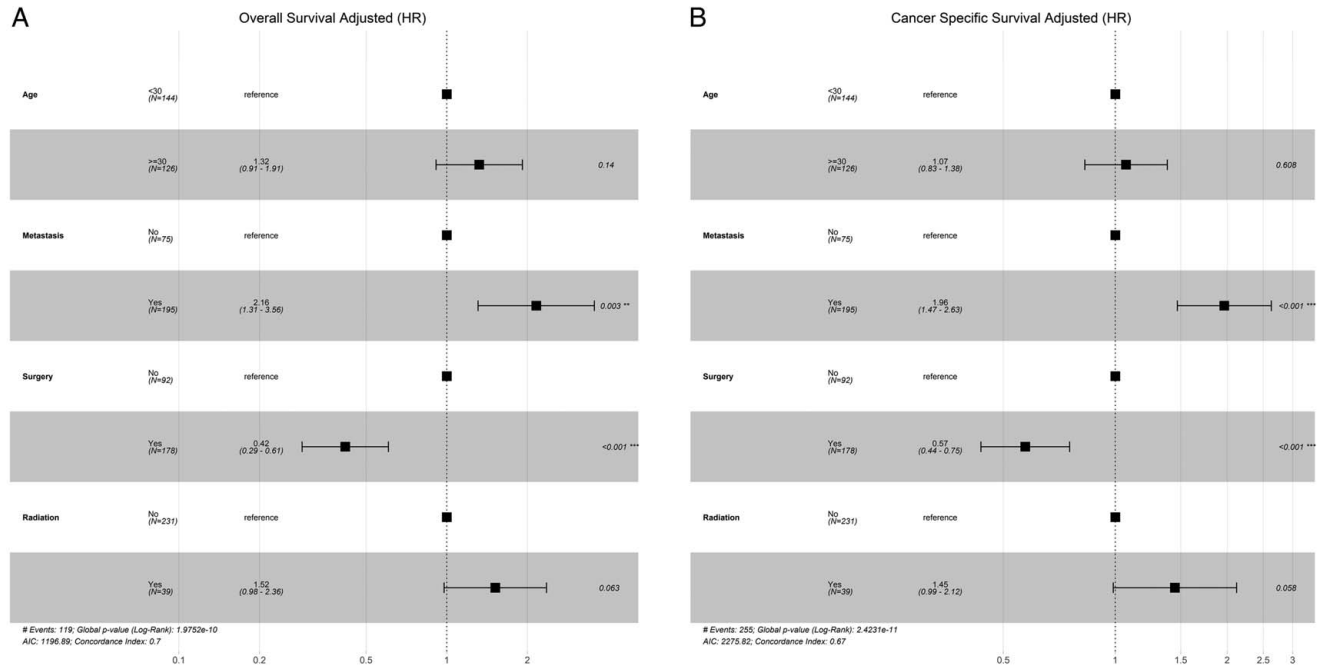

Figure 4. Multivariate Cox proportional hazards regression model results of (A) OS and (B) CSS for testicular choriocarcinoma patients.

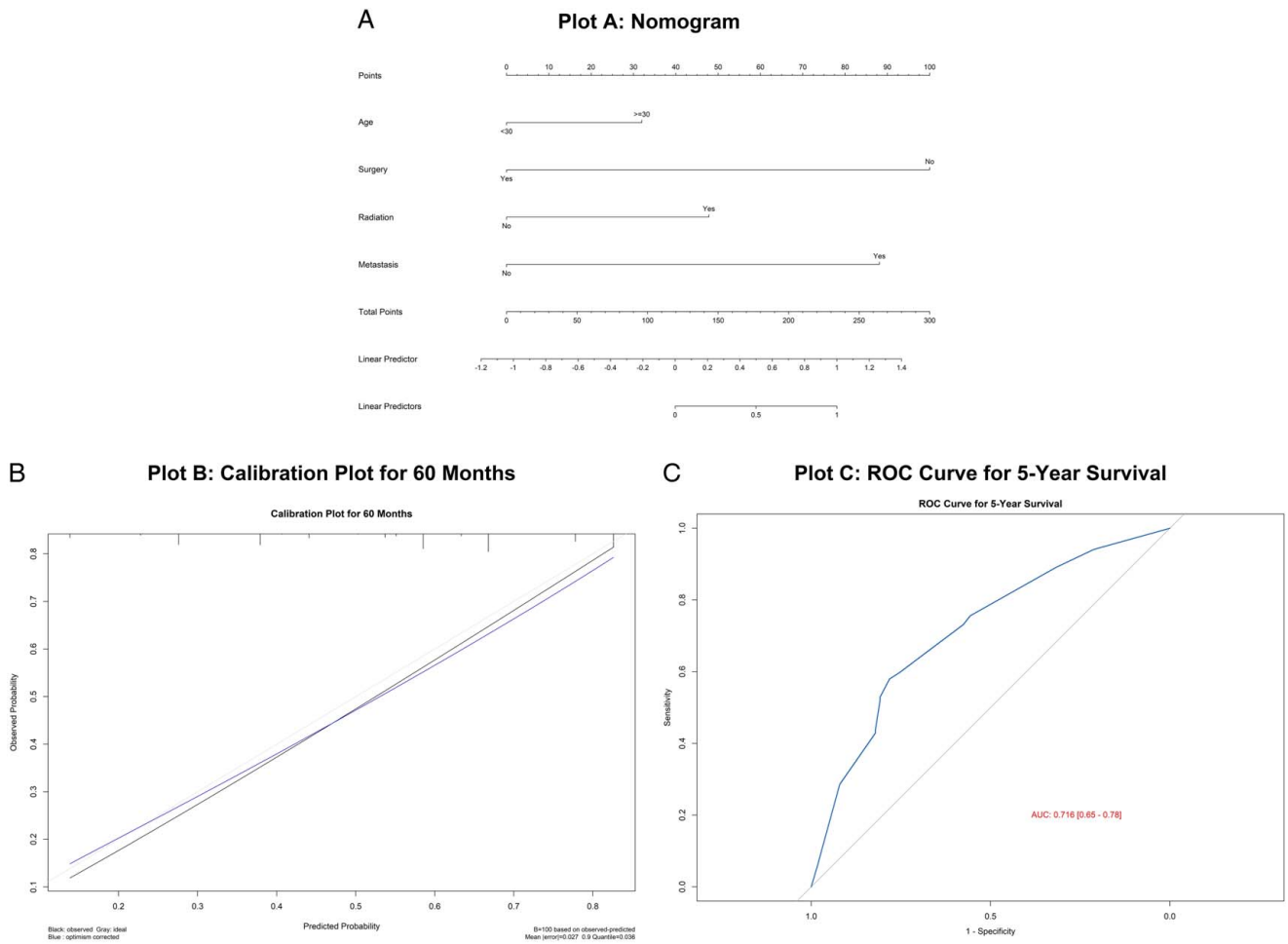

Figure 5. (A) Nomogram to predicate 5-year survival in testicular choriocarcinoma patients. (B) The calibration curves of the nomogram. (C) The area under the time-dependent receiver operating characteristic (ROC) curve (AUC) is based on the nomogram.

both races were similar (ranging from 1.9 to 3.4/1 000 000)[15]. Similarly, another study showed that non-Hispanic whites had a significantly higher incidence of testicular cancer than other racial groups, including blacks[21]. In our study, we found that among CC patients, whites were more likely to have testicular CC, whereas blacks were more likely to have extragonadal CC.

In our analysis of testicular CC patients compared with non-testicular CC patients, we found that the former group was more likely to have bilateral tumors and smaller tumors in general. However, it is worth noting that among both groups, only five patients had bilateral tumors. Our survival outcomes revealed a significant difference between nontesticular CC and testicular CC, with 5-year CSS rates of 32% for nontesticular CC and 57% for testicular CC. CC has the poorest prognosis among non-seminomatous GCTs, with 5-year survival of about 80%[22]. The survival rate in our study was lower. However, our finding of a lower survival rate in nontesticular CC compared to testicular CC aligns with the existing literature on germ cell tumors. As previously noted, Stang *et al.*[15] found that the 5-year relative survival rates of extragonadal GCTs were lower than those of gonadal GCTs. According to a review article by Zeki *et al.*, the 5-year survival rates for synchronous and metachronous testicular tumors are 88 and 95%, respectively. This indicates that patients with bilateral testicular tumors have relatively good prognoses, with high survival rates according to the study[23].

Bokomeyer *et al.*[24] discovered that a primary mediastinal location and elevated beta-human chorionic gonadotropin (hCG) levels were negative prognostic factors for survival in extragonadal germ cell tumors in the mediastinum and retroperitoneum. Ronchi *et al.*[25] found that the most elevated serum markers in extragonadal GCTs included alpha-fetoprotein, beta-hCG, and lactate dehydrogenase. Alvarado-Cabrero *et al.*[19] found that immunohistochemical staining using p63 and HPL can be helpful in diagnosing CC, with all six cases of pure or mixed CC showing positive results. The aggressive nature of choriocarcinoma, characterized by its ability to invade host blood vessels, contributes to its poor prognosis. In their study, Li and colleagues[6] reported that remote metastasis accounted for 41.0% of all choriocarcinoma patients. High metastatic rate is a prominent feature of choriocarcinoma. So, it is crucial to keep an open mind when diagnosing CC, as its aggressive nature can result in symptoms caused by metastasis, such as repeated episodes of melena[26].

Our study found that surgery was a positive predictor of cancer survivability for both gonadal and extragonadal CC, whereas chemotherapy was only effective for extragonadal CC. Li *et al.*

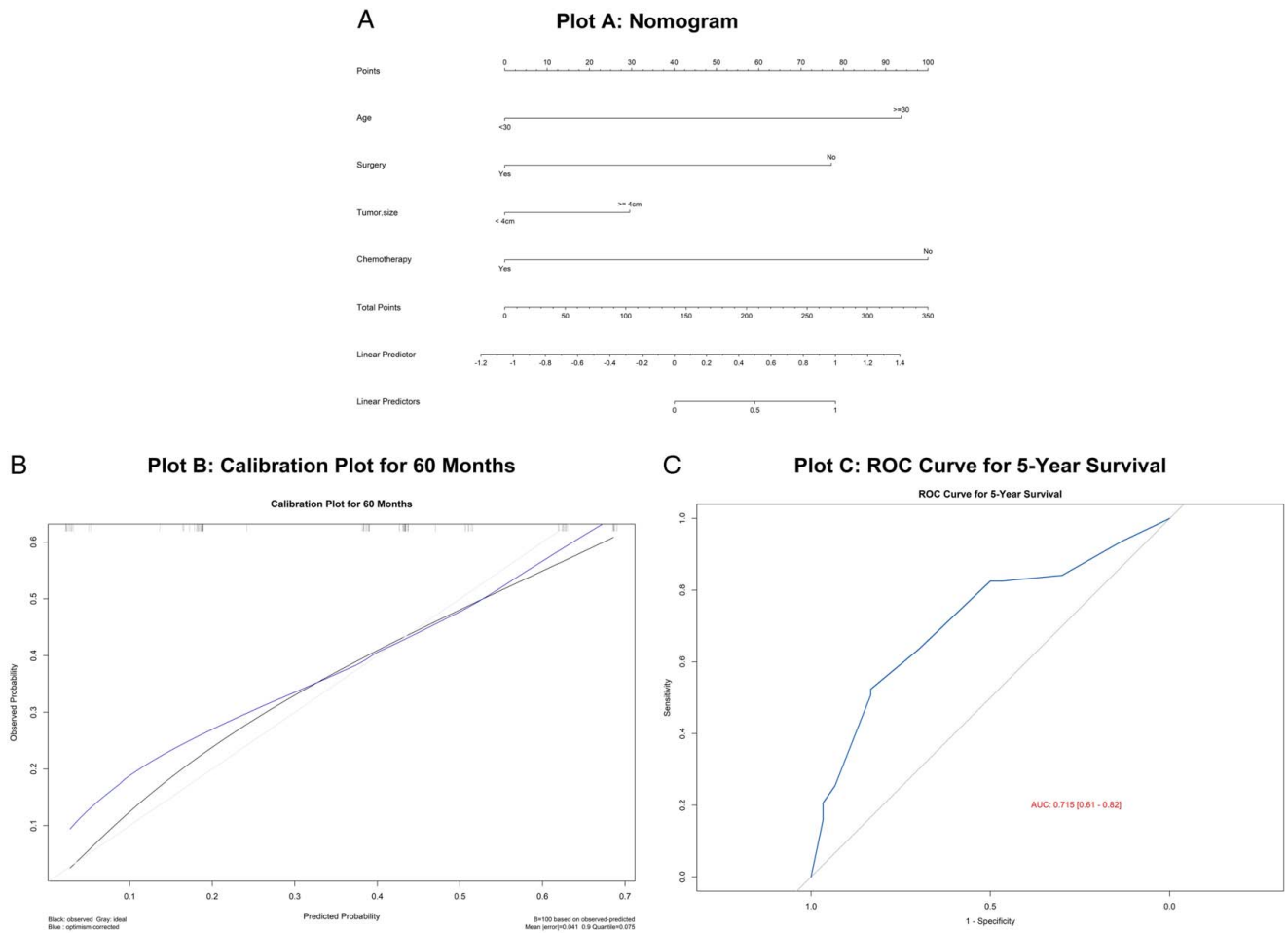

Figure 6. (A) Nomogram to predicate 5-year survival in nontesticular choriocarcinoma patients. (B) The calibration curves of the predicting nomogram. (C) The area under the time-dependent receiver operating characteristic (ROC) curve (AUC) is based on the nomogram.

also found that surgery was a positive prognostic factor for both OS and CSS; however, they found that chemotherapy was a negative prognostic factor. Nevertheless, they still consider chemotherapy beneficial for a patient's survival time[6]. Kier *et al*.[27] studied the survival rates and treatment results after the use of bleomycin, etoposide, and cisplatin (BEP) in germ cell cancer and found improved survival in disseminated germ cell cancer throughout the study period. Oliver *et al*. and Tandstad *et al*. demonstrated the importance of chemotherapy in nonseminomatous patients[28,29]. Tandstad *et al*.[28] found that 41.7% of vascular invasion clinical stage I nonseminoma patients relapsed in the surveillance group, whereas only 3.2% of vascular invasion patients relapsed in the BEP chemotherapy group.

For extragonadal CC specifically, a study by Shinoda *et al*.[30] analyzed the survival of 66 extragonadal CC, specifically primary intracranial CC, and found that subtotal surgical removal or more, radiotherapy, and chemotherapy were significant prognostic factors.

Interestingly, they also suggested that biopsy for histological diagnosis may no longer be needed in cases with extremely elevated HCG levels, further emphasizing the importance of beta-hCG in the diagnosis and treatment of CC[30]. We found that chemotherapy played a significant role in the treatment of extragonadal CC. Casey *et al*.[31] found that patients with brain metastases from nonseminomatous germ cell tumors (NSGCT) experienced a longer overall survival OS of up to 4 years following radiation therapy.

However, the efficacy of radiotherapy for nonseminomas remains unclear. Our study found that radiation therapy for CC was not associated with any significant prognostic effect. Therefore, the idea of whether to administer radiotherapy to future patients should be considered, since radiotherapy treatment is associated with many side effects and may cause more harm than good. For example, radiotherapy can cause central nervous system toxicity in patients with brain metastases from GCTs[32,33]. Further research is necessary to compare the effectiveness of radiotherapy with other treatment methods for GCTs.

There is increasing interest in the use of immunotherapy for the treatment of cancer, including CC. Recent studies have explored the potential of blocking PD-1 for the treatment of gestational trophoblastic disease in women[34]. In one study, a woman with chemorefractory CC showed a remarkable response after receiving two doses of pembrolizumab, an anti-PD-1[35]. Another study reported that pembrolizumab was effective in treating drug-resistant CC in women[36]. The first clinical trial evaluating immune checkpoint inhibitors was conducted in men with CC,

but single-agent pembrolizumab did not show clinical benefits in patients with refractory GCT[37].

Another study treated seven patients with Nivolumab or Pembrolizumab, with long-term tumor response achieved in two of the three surviving patients. Both patients who responded positively to the treatment tested positive for PD-L1 staining[38]. Both studies reported no significant treatment-related toxicity[37,38]. Despite the promising results of these studies, there is still a scarcity of data regarding the efficacy of immune checkpoint inhibitors in CC. Further research is required to fully understand the role of immunotherapy in cancer treatment.

Our broad demographic and clinical analyses provide valuable insights into this rare cancer. The application of rigorous statistical methods such as multivariate analyses and nomograms for survival prediction demonstrates a high level of methodological robustness. The comparison of testicular and nontesticular CC is particularly valuable because of the scarcity of literature on these subtypes. The identification of prognostic factors, survival rates, and treatment effectiveness, such as surgery and chemotherapy, directly impacts clinical management and could guide future treatment protocols.

Conclusion

CC is a rare cancer occurring in both sexes. This study provides valuable insights into the distinct characteristics and treatment outcomes of testicular and nontesticular CC. Our findings highlight the importance of considering racial differences in CC incidence, with testicular CC being more prevalent among Whites and nontesticular CC among Blacks. This underscores the need for further investigation into the underlying factors contributing to these disparities, potentially leading to targeted prevention and early detection strategies for at-risk populations. Surgical intervention proved beneficial for both types of CC, whereas chemotherapy showed significant benefits only in cases of extragonadal CC. Radiotherapy did not demonstrate a significant impact on patient outcomes, suggesting the need for further studies to evaluate its effectiveness and balance its potential benefits against its risks. We also developed prognostic nomograms for predicting 5-year survival in testicular and nontesticular CC, which can assist clinicians in personalizing prognosis assessments and treatment plans. In terms of clinical practice, these results suggest the importance of considering racial disparities in CC incidence when developing treatment plans. Clinicians should consider the differences in response to various treatments based on the type of CC. Future research should focus on optimizing therapeutic strategies and exploring new avenues for improving outcomes in CC patients, with a particular emphasis on personalized medicine and targeted interventions.

Ethical approval

Ethics approval was not required for this study. Authorization and data were obtained through the SEER website and database, respectively.

Consent

Informed consent was not required for this study. Authorization and data were obtained through the SEER website and database, respectively.

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None.

Author contribution

S.A.: conceptualization, formal analysis, methodology, software, visualization, and writing – original draft; M.S.S., T.A.A., H.H., and R.M.O.: writing – original draft; M.T.Q.: methodology; O.A.: formal analysis and software; R.S.A.: supervision, writing – review, and editing.

Conflicts of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Research registration unique identifying number (UIN)

1. Name of the registry: not applicable.
2. Unique Identifying number or registration ID: not applicable.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): not applicable.

Guarantor

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Data availability statement

The data in this article is not sensitive in nature and is accessible in the public domain. The data is therefore available and not of a confidential nature.

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Presentation

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