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# Survival outcomes of adolescent and adult patients with non-seminomatous testicular germ-cell tumors: A population-based study

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## Summary

### Background

In adolescents, approximately 90% of testicular germ cell tumors (T-GCTs) are non-seminomas (NS T-GCTs). Few studies have evaluated the impact of age, specifically in adolescence, on outcomes of NS T-GCTs.

### Objective

The purpose of this study was to review all patients diagnosed with NS T-GCTs in the Surveillance, Epidemiology, and End Results (SEER) database to evaluate the association between age (adolescents vs. adults) and survival outcomes.

### Method

The SEER database was queried for individuals ≥13 years old diagnosed with NS T-GCTs from 1995 to 2012. Patients were categorized into adolescent (13–19 years) and adult (≥20 years) cohorts. A Cox proportional hazards model was used for multivariate analysis (MVA).

### Results

A total of 13,963 patients (1496 adolescents, 12,467 adults) was included. Median follow-up was 71 months (range 1–215). Five-year overall survival (OS) for adolescent and adult patients was 94% and 92%, respectively ($p = 0.007$); 5-year cancer-specific survival (CSS) was 95% and 94%, respectively ($p = 0.139$). Under MVA, adolescent patients had improved OS (HR 0.61; 95% CI 0.50–0.75; $p < 0.001$) and CSS (HR 0.65; 95% CI 0.51–0.82; $p < 0.001$), when compared with adults (Table). In a logistic regression analysis adjusting for demographics, adolescent patients were more likely to present with regional or distant metastatic disease (OR 1.16; 95% CI 1.01–1.35; $p = 0.039$), undergo an orchiectomy (OR 2.44; 95% CI 1.50–4.00; $p < 0.001$) or tumor excision (OR 2.43; 95% CI 1.57–3.77; $p < 0.001$), and receive other adjuvant surgery (OR 5.87; 95% CI 2.25–15.30; $p < 0.001$).

### Conclusions

To our knowledge, this is the largest population-based comparative analysis in NS T-GCTs comparing outcomes between these two age groups. Adolescent patients with NS T-GCTs had slightly improved survival compared with adults, despite presenting with more advanced disease. While adolescent patients present at more advanced stage, they achieve excellent survival outcomes possibly at the cost of a greater therapeutic burden.

**Table** Multivariate analysis of predictors of cancer-specific survival (CSS).

| Variable | Multivariate | | |
|---|---|---|---|
| | HR | 95% CI | *p* |
| Age, years | | | |
| ≥20 | 1 | | |
| 13–19 | 0.65 | 0.51–0.82 | <0.001 |
| Histology | | | |
| Non-seminomatous germ-cell, NOS | 1 | | |
| Embryonal | 0.46 | 0.34–0.62 | <0.001 |
| Yolk sac | 0.91 | 0.62–1.35 | 0.646 |
| Choriocarcinoma | 1.43 | 1.04–1.96 | 0.027 |
| Teratoma | 0.94 | 0.63–1.39 | 0.753 |
| Mixed | 0.71 | 0.54–0.92 | 0.009 |
| Summary stage | | | |
| Localized | 1 | | |
| Regional/distant | 10.35 | 8.78–12.20 | <0.001 |
| Unknown | 2.37 | 1.19–4.72 | 0.014 |

HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified.

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## Introduction

Testicular germ cell tumors (T-GCTs) are the most common solid malignant tumors in adolescent and young adult men, accounting for 21% of all neoplasms in men aged 15–39 years [1]. In adolescents, approximately 90% of all T-GCTs are non-seminomas (NS T-GCTs). NS T-GCTs include the histologic subtypes of embryonal carcinoma, teratoma (mature, immature or with malignant differentiation), choriocarcinoma, yolk sac tumor, and mixed. These various NS-GCT histologic subtypes are known to behave differently and to have variable incidence based on patient age. For example, adolescents have a higher incidence of pure embryonal carcinoma and mixed non-seminoma and are similarly more likely to present with higher stage disease than their prepubertal counterparts [2,3].

In adolescent and young adult patients, cancer is the leading cause of non-accidental deaths in the USA [4]. Adolescent cancer patients present with unique challenges. While survival outcomes in this population have improved over the last several decades, their overall outcomes continue to lag behind either pediatric or adult patients with similar cancers [5]. Reasons for inferior survival outcomes are poorly understood. Several potential reasons include more aggressive tumor biology, socioeconomic factors such as the lack of social support, and potentially treatment-related factors. Adolescent patients can present a challenge for the oncology field at-large, especially as they are often caught at the interface between pediatric and adult oncology practices [6,7]. Additionally, adolescent and young adult patients face physical, emotional, and psychological challenges unique to their age group. Further, the lack of clinical trial availability and enrollment forces clinicians to extrapolate from either pediatric or adult studies to make informed clinical decisions, which may not necessarily apply to the unique biology of postpubertal adolescents and young adults [8].

Few studies, including population-based analyses, have assessed the impact of age on outcomes of NS T-GCTs, specifically in adolescence. The purpose of this study was to review all patients diagnosed with NS T-GCTs from 1995 to 2012 in the Surveillance, Epidemiology, and End Results (SEER) database to evaluate the association between age (adolescents vs. adults) and survival outcomes.

## Materials and methods

The NCI-sponsored SEER database including 18 registries was queried using SEER*Stat-v8.2.1 (seer.cancer.gov). A total of 34,684 patients who were diagnosed with testicular cancer between January 1, 1995 and December 31, 2012 were initially queried from the database. Patients initially selected had a histologic code consistent with NS T-GCTs using the International Classification of Disease for Oncology [third edition] histology codes: 9066, 9070, 9071, 9080–85, 9100–02. Complete survival data were required for inclusion. Adolescent and adult patients 13 years or older were included. A total of 13,963 patients met inclusion criteria.

### Patient demographics and treatment variables

Patient variables included age, gender, race, Hispanic descent, tumor histology, residence, percent of families below poverty by county, percent of unemployment by county, marital status, year of diagnosis, disease stage using SEER definitions (localized, regional, distant), and receipt of surgery and/or radiation. The age groups were defined as adolescent (13–19 years) and adult ($\geq$20 years). Residence included rural, urban, and metropolitan, as defined by the Rural–Urban Continuum Code for 2013. County attributes included percent of families below poverty and percent unemployed; county attributes were established from the Census 2007–2012 American Cancer Society data. Marital status included common-law marriages; single status included separated, divorced, widowed, and or unmarried or domestic partner. Metropolitan, rural, and urban designations were developed by the United States Department of Agriculture (USDA). Extent of disease coded by SEER was based on TNM staging and recorded as localized, regional, and distant. Localized includes invasive tumor with/without vascular invasion limited to body of testis, rete testis, and tunica albuginea. Regional includes extension to dartos muscle, epididymis, scrotum, or spermatic cord, and/or regional lymph node involvement. Distant stage includes distant lymph nodes and/or metastasis. Surgery was defined by testicular cancer site-specific SEER coding and included excision, orchiectomy, and surgery not otherwise specified (NOS) [9]. Radiation was coded as beam radiation. Receipt of systemic therapy was not included as SEER does not record this information. Primary endpoints of the study were cancer-specific survival (CSS) and overall survival (OS).

### Statistical analysis

Statistical analyses were performed using SPSS V22.0 (SPSS Inc., Chicago, IL, USA). Pearson chi-square tests were used to assess associations between categorical variables and comparison age groups (adolescent and adult). Proportionality was evaluated for covariates included in multivariate analysis and returned no significant results [10]. OS and CSS intervals were calculated from the date of diagnosis to the date of all-cause or testicular cancer-related death, respectively. OS and CSS were first examined using the Kaplan–Meier method. Univariate and multivariate Cox regression analyses were performed using OS and CSS as outcomes with a significance level of $p < 0.05$. Variables included in the MVA model were selected by backward selection with adjusted $p$-values $\leq$0.1. Multivariate logistic regression models were used to assess the associations among age groups, extent of disease at presentation, and receipt of surgery and/or radiotherapy.

### Ethical approval

Approval was not required for this study.

## Results

Table 1 illustrates the baseline patient and treatment characteristics of the 13,963 patients (1496 adolescents,