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# Cardiovascular Mortality in Testicular Nonseminomatous Germ Cell Tumors: Does Statistical Significance Imply Clinical Significance?

**Jorge D. Ramos** and **Evan Y. Yu**

University of Washington School of Medicine, Seattle, WA

Testicular germ-cell tumors (GCTs) represent one of the few solid tumors in which the majority of patients with metastatic disease are cured. In 2015, it is estimated that there will be 8,430 new occurrences and only 380 deaths as a result of testicular cancer.[1] Treatment for testicular GCTs involves radical orchiectomy in almost all patients, regardless of the extent of disease. Subsequent treatment options, which depend on disease stage, include active surveillance, retroperitoneal lymph node dissection (RPLND), and cytotoxic chemotherapy. Radiation therapy is also an option in patients diagnosed with pure seminoma.[2,3] With the implementation and refinement of cisplatin-based combination chemotherapy in the late 1970s and 1980s, approximately 80% of all patients with metastatic GCTs now are cured.[4] Therefore, understanding the acute and long-term effects associated with treatment for a largely curable disease is important to optimize the care of this patient population.

In the article accompanying this editorial, using the SEER database, Fung et al[5] compared the cardiovascular disease (CVD) mortality risk in 15,006 patients with nonseminomatous germ-cell tumors (NSGCTs) who either received chemotherapy as part of their initial treatment plan (n = 6,909) or underwent surgery alone (n = 8,097) with the CVD mortality risk in the general population.[5] Compared with the general population, there was an increased risk in CVD mortality in patients who were treated with chemotherapy; however, there was no difference in CVD mortality in the surgery-alone group. In total, 54 cardiovascular deaths occurred in the chemotherapy group, and 50 occurred in the surgery-only group. Of unterest, the statistically significant increase in CVD mortality in the chemotherapy group compared with the general population was limited to the first year after the diagnosis of testicular NSGCT. In the first year after diagnosis, 11 patients who received

Corresponding author: Evan Y. Yu, MD, Seattle Cancer Care Alliance, 825 Eastlake Ave E, MSG4-830, Box 358081, Seattle, WA 98109-1024; evanyu@u.washington.edu.

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chemotherapy for the treatment of testicular NSGCT, versus two patients in the surgery-only group, had a cardiovascular cause of death.

Several population-based, observational studies have shown an increased long-term risk of developing CVD in testicular GCT survivors.[6-8] The most likely explanation for the increased incidence of CVD seen in this patient population is the early development of atherosclerotic disease, possibly secondary to metabolic syndrome. Willemse et al[9] demonstrated a 1.9-fold increased risk of developing metabolic syndrome in testicular GCT survivors and a 2.3-fold higher risk in the subgroup that received chemotherapy compared with healthy men as controls. The mechanism for the development of metabolic syndrome in long-term survivors is not completely understood but may be associated with hypogonadism that results from cytotoxic chemotherapy.[9-11] Conversely, Fung et al[5] hypothesize that their novel finding of early CVD mortality may at least partially occur through the direct toxic effect of cisplatin on the vascular system and the resultant endothelial dysfunction.

SEER is a large, population-based cancer database that provides extensive information on demographics, tumor characteristics, and initial treatment modalities. The SEER registries also collect and report data on vital status and cause of death, which allow for the study of cancer incidence, survival, and trends in care over time.[12] However, it is important to be aware of some pitfalls when analyses are conducted with the SEER database. First, analyses from SEER are limited by the potential inherent confounders and bias associated with any retrospective analysis. In addition, the heterogeneity and lack of granularity in the SEER-coded causes of death may make the true etiology less clear. In the study by Fung et al,[5] the SEER-coded diseases of heart account for six of the 11 deaths in the chemotherapy group in the first year after testicular NSGCT diagnosis, which suggests an arterial thrombotic event as the cause of death. However, this SEER category also includes the International Classification of Diseases, 9th and –10th Revisions, codes for acute pulmonary embolism, a venous thromboembolic event (VTE).[5]

There is abundant retrospective evidence that cisplatin increases the risk of VTE in a multitude of malignancies.[13,14] In testicular GCTs, the estimated thromboembolic (arterial and venous) rate has ranged from 8.4% to 18% in patients who received cisplatin-based chemotherapy.[15,16] Greater than 80% of the events were VTE in these studies. It is also established that VTE leads to increased mortality in patients with cancer.[17,18] Because there is a known predominance of VTE association with cisplatin, the inclusion of pulmonary embolism in the analysis may have contributed significantly to the CVD mortality seen in the chemotherapy group in the study by Fung et al.[5]

In addition to the aforementioned six deaths as a result of diseases of heart, the remaining five deaths in the first year resulted from cerebrovascular diseases. This SEER-coded category also is heterogeneous, because it is not possible to discern whether the deaths as a result of cerebrovascular diseases represent ischemic or hemorrhagic strokes. The two most commonly used chemotherapy regimens in the advanced disease setting in NSGCT are bleomycin, etoposide, and cisplatin, and etoposide, ifosfamide, and cisplatin. The rates of grade 3 or greater thrombocytopenia (ie, platelet count ≤ 50,000) with bleomycin, etoposide, and cisplatin, and etoposide, ifosfamide, and cispla-tin are approximately 14% and 28%,

respectively.[19,20] Therefore, this patient population is at a small but potentially increased risk for hemorrhagic stroke, which raises the possibility that some of these events may not have been arterial ischemic events. Thus, because there were so few events, any misclassification could have affected the results and conclusions of the study and detracted from the novelty of the findings.

Differences in the baseline patient characteristics of the analyzed populations may also affect the study conclusions. In the study by Fung et al,[5] 71% of the chemotherapy group had regional or metastatic disease, versus 14.9% in the surgery group. Recently, Srikanthan et al[21] demonstrated that retroperitoneal lymph nodes greater than 5 cm increased VTE risk, presumably through vascular compromise of the deep venous system of the lower extremities.[21] Moreover, it is likely that more patients in the chemotherapy group than in the surgery-alone group underwent RPLND. Given that RPLND is a longer, more invasive surgery, it is likely that the cardiovascular complication and VTE rates would be higher than with radical orchiectomy alone. Thus, the chemotherapy group is inherently at higher risk of thrombotic events that could be unrelated to chemotherapy because of the greater burden of disease and higher complication rates associated with RPLND. Unfortunately, as the authors point out,[5] it is not possible to discern retroperitoneal lymph node size or the proportion of patients who underwent RPLND from the SEER database.

Finally, it is crucial to place the results of this study in clinical context. Statistical significance is defined as a difference between two groups that is likely to be real and not caused by chance. Nonetheless, it does not imply clinical significance. In the first year from the time of diagnosis, there were 11 events in the 6,909 patients treated with chemotherapy, which provides a 1-year incidence rate of CVD mortality of 0.16%. Thus, 628 patients would need to be treated with chemotherapy to have one death as a result of CVD. On the basis of the relative infrequency of CVD mortality in this clinical setting, it is likely that a practicing oncologist may never see a patient with this unfortunate outcome. Conversely, we have to consider what the alternative outcome would be if treatment with chemotherapy was not pursued. Given that the preponderance of patients treated with chemotherapy had regional or metastatic disease, the majority would die as a result of the disease. Therefore, the benefit of chemotherapy in this patient population far exceeds the associated CVD mortality risk.

Fung et al[5] have provided provocative, new data that suggests increased cardiovascular mortality in patients with NSGCT treated with chemotherapy.[5] Patients who are considering treatment with chemotherapy for advanced NSGCT could be made aware of the possibility of a small, acute, increased cardiovascular mortality risk, but caution is advised about making definitive statements on the basis of the current study alone. The low event rate and the multiple potential confounders in this study, especially the granular details surrounding the events, make it difficult to make conclusive statements about risk of cardiovascular death. More investigation would be necessary to support these findings. Additional studies to identify a subset of patients at particularly high risk of CVD mortality may be worthwhile. High-risk patients could benefit from primary prevention strategies, but we must be cognizant that primary preventive interventions also carry risk. Therefore, it is crucial to

identify a sufficiently high-risk population to maximize the benefit of intervention and not introduce unnecessary harm in the care of patients with testicular GCT.

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