Long-term Survival and Competing Causes of Death in Men with Stage I Seminoma

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Background

- Testicular cancer is the most common malignancy in young men and the incidence of the disease is on the rise, mostly due to increases in cases of seminoma.
- Seminoma represents 45% of all germ cell tumors and half of all patients presenting with newly diagnosed testicular cancer present with stage I disease.
- Almost all men diagnosed with seminoma will be cured and since most men are young at the time of diagnosis, they have a long life expectancy. Long-term side effects of adjuvant treatment thus must be carefully weighed against the risk of disease relapse.
- Management of patients with Stage I seminoma following orchiectomy includes surveillance, radiation therapy, or chemotherapy.
- In selection of appropriate treatment, therapy-related morbidity, economic costs, and quality of life issues should be considered.
  - Surveillance carries high stress, costs, and risk of late relapse (up to 10+ years). It also requires diligence on both the part of the physician and patient.
  - Radiation therapy (RT) was the first successful, and remains the most widely utilized postorchiectomy treatment of seminoma.
  - Both chemotherapy and radiation are associated with excellent short-term outcomes in men with seminoma, but the long-term health effects must be considered when either modality is employed.
  - To better understand the impact of RT on mortality, the authors analyzed long-term survival and patterns of excess mortality in men with stage I seminoma.

Materials and Methods

- In total, 9,045 men diagnosed at ages 15-70 with stage I seminoma from 1973 to 2001 were identified in the Surveillance Epidemiology and End Results (SEER) database.
- Time to testicular-cancer mortality (TCM), death from second malignancy (SM), cardiovascular mortality (CVM), suicide (SUIC), and all-cause mortality (ACM) were calculated from diagnosis age.
- Survival estimates were calculated using the Kaplan-Meier method.
- Gender- and age-adjusted standardized mortality ratios (SMR) were calculated using U.S. population data.
- Cox and Fine and Gray multivariable analysis were used to evaluate the independent effect of RT on mortality outcomes.

Results

- The median age of patients in this study was 36 years and 7,025 men (78%) received RT.
- After a median follow-up of 11.7 years, 869 men (9.6%) died overall.
  - Sixty-five died from TCM, 279 from SM, 169 from CVM and 37 from SUIC.
Ten-year rates of ACM and TCM were 4.24% and 0.52% among men who received RT and 7.14% and 1.22% among men who did not.

Compared to the gender- and age-adjusted general population, men with seminoma had an increased risk of ACM (SMR 1.12; 95% confidence interval [CI] 1.12-1.28), SM (SMR 1.78; 95% CI 1.58-2.00) and SUIC (SMR 1.40; 95% CI 1.02-1.94) and a decreased risk of CVM (SMR 0.73; 95% CI 0.62-0.84).

Rates of ACM, SM, and SUIC (SMR, all p <0.05) were increased whether RT was used or not.

After adjustment for year of diagnosis, age at diagnosis and race, men who received RT were less likely to die (adjusted hazard ratio [AHR] 0.76; 95% CI 0.65-0.89; p <0.001) and had a lower risk of TCM (AHR 0.39; 95% CI 0.24-0.65; p <0.001).

There was no difference in CVM between men who did and did not receive RT (AHR 0.89; 95% CI 0.60-1.15; p = 0.230) and a numerical but non-statistically significant increase in SM in men who received RT as compared to others (AHR 1.25; 95% CI 0.90-1.72; p = 0.180).

At 15 years, 2.57% of the men who received RT and 1.82% of the men who did not receive RT had died of SM.

**Author's Conclusions**

- Compared to the general population, men with a history of Stage I seminoma had increased risks of all-cause mortality, death from second malignancies, and suicide.
- The decreased risk of cardiovascular mortality observed in patients receiving radiation may reflect competing risks from testicular cancer, second malignancies, and suicide.
- The data suggest that 15 years after diagnosis, men who did receive RT may be more likely to die from a second malignancy than men who did not, although the effect was not statistically significant.
- Although not receiving RT was associated with higher testicular-cancer mortality, the results may reflect decreased access to care or follow-up, as active surveillance protocols were not common during the study era.

**Clinical Implications**

- The authors’ conclusions that the mortality of stage I patients, most of whom were treated with postorchiectomy RT, exceeds mortality in age matched controls agrees with published data, although is discordant with some published data previously reporting increased mortality from cardiac disease in patients receiving adjuvant radiation, the opposite of which was observed in this study.
- In this study, the authors observe that the administration of adjuvant RT following orchietomy resulted in a lower risk of TCM and ACM.
- Although not statistically significant between patients receiving radiation and those who did not, the authors observed an overall increased mortality from second cancers in the examined population as compared to age-matched controls. Although the authors do not speculate on the reasons for this observation, it is probable that there are underlying genetic abnormalities which not only resulted in the increased risk of testicular cancers but also to increased rates of secondary neoplasms.
- These results, along with previously published data on this population of men, point to the importance of optimizing initial therapy in this group of patients. Strategies for accomplishing this task include reduction of RT fields, potential use of carboplatin instead of radiation therapy in select patients, and increased use of surveillance in selected populations with low risk features.
- While the SEER database is an extremely valuable tool for clinical cancer research, several limitations should be taken into account when interpreting results from a SEER observational study, especially when there is an attempt to generate hypotheses regarding adjuvant therapy. Specifically, there are limitations with respect to causes of death and further limitations revolve around underreported and incomplete data regarding adjuvant therapy (no information on radiation dose, field design or administration of chemotherapy), unrecorded variables, variations in data reporting, migration of patients in and out of SEER registry areas, and selection bias.