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# Stage I Testicular Seminoma: A SEER Analysis of Contemporary Adjuvant Radiotherapy Trends

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## Abstract

**Purpose—**Patients with clinical stage I testicular seminoma have historically been treated with adjuvant radiotherapy in the United States. However, nearly 80% of patients on surveillance will not experience relapse and even with relapse, salvage rates approach 100%. It remains unclear how practice patterns have changed with recently accumulating evidence and changes in guidelines. In a population based setting we evaluated contemporary trends and factors that may affect the use of adjuvant radiotherapy.

**Materials and Methods—**A total of 8,151 men diagnosed with stage I testicular seminoma from 2000 to 2009 were identified in the national SEER (Surveillance, Epidemiology, and End Results) registry. A multivariate regression model was constructed to analyze the association of year, age, race, socioeconomic status, SEER region, pathological stage and tumor size with the administration of adjuvant radiotherapy.

**Results—**The use of adjuvant radiotherapy decreased significantly from 2000 to 2009. In 2000, 74.7% of patients received radiation, compared with only 37.7% of patients in 2009 ($p < 0.0001$). Later year of diagnosis was significantly associated with decreased odds of receiving adjuvant radiotherapy ($p < 0.0001$, 2000 to 2005 vs 2006 to 2009, OR 0.40, 95% CI 0.36–0.44). Men age 35 years or older ($p < 0.0002$, OR 1.20, 95% CI 1.09–1.32) and men in the highest socioeconomic index quartile ($p < 0.0001$, OR 1.34, 95% CI 1.16–1.54) were more likely to receive adjuvant radiotherapy.

**Conclusions—**The use of adjuvant radiotherapy for clinical stage I testicular seminoma has decreased significantly in the last decade. Older age and higher socioeconomic status are associated with higher rates of adjuvant radiotherapy.

### Keywords

seminoma; radiotherapy; chemotherapy; adjuvant; SEER program

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TESTICULAR cancer is relatively rare. However, it remains the primary cause of malignancy among men 15 to 35 years old.[1] NCCN guidelines recommend surveillance, radiotherapy or chemotherapy for patients with clinical stage 1A and 1B testicular seminoma, with surveillance being the preferred option as of 2009.[2] Regardless of the therapy chosen, disease specific survival for this disease remains greater than 99%.[3]

Historically, patients have overwhelmingly been treated with RT in the United States. In 1999 SEER data, 84% of localized testicular seminoma was treated with RT.[4] Yet nearly 80% of patients on surveillance will not experience relapse and even with relapse, salvage rates approach 100%.[5,6] Although RT could be considered a straightforward solution, concerns regarding long-term toxicity, specifically the risks of secondary nongerm cell malignancy in testicular cancer survivors, have prompted a reexamination of its use in the adjuvant setting.[7–12] Treatment specific risks of RT were further elucidated in 2007 when van den Belt-Dusebout et al reported that there was a 2.6-fold increase in the long-term development of secondary nongerm cell malignancy after subdiaphragmatic RT.[11]

Since 2009 surveillance has been the preferred option for the management of stage I seminoma according to NCCN guidelines. In 2011 the EAU guidelines were revised even further to recommend against RT for localized testicular seminoma.[2,7] We examine the evolution of care for localized testicular seminoma and factors that may influence therapeutic choices in the national population based SEER patient data.

## MATERIALS AND METHODS

### Data Source

The SEER program of the National Cancer Institute collects cancer incidence and survival data from population based cancer registries in the United States. Beginning in 2000 there were 18 registries participating in the SEER program, covering approximately 28% of the United States population. Relative to the United States population, the population residing in SEER catchment areas tends to be somewhat more urban and has a higher proportion of some minority groups and foreign born individuals, but is similar to the general population with regard to measures of poverty and education (http://seer.cancer.gov/registries/characteristics.html).[13] The SEER 18 database was used for our analysis.[14]

The SEER program registries routinely abstract detailed information on patient and tumor characteristics at diagnosis as well as the first course of therapy. Cases in the data file are also linked to census information on various county level socioeconomic characteristics (such as poverty, income and education) based on their residence at the time of diagnosis. At the time of this analysis socioeconomic indicators at smaller geographic levels were not available in the database.

### Study Cohort

We identified a total of 9,700 men diagnosed with localized or stage I testicular seminoma (ICD-O-3 codes 906.0–906.2) between January 1, 2000 and December 31, 2009. Because SEER registries used EOD coding for case medical record abstraction before 2003, cases diagnosed between 2000 and 2003 were selected based on having a SEER summary stage of

localized. Those diagnosed in 2004 or later were selected based on having an American Joint Committee on Cancer stage of I. We excluded men who did not undergo radical orchiectomy (723), had unknown tumor size (586), had unknown race (108) and for whom it was unknown whether RT was administered (132). The final study population consisted of 8,151 men. The primary end point of this analysis was receipt of RT. The SEER registry codes patients who did not receive RT as none or refused. Men who were offered RT but refused (70) were classified as not having received RT.

### Joinpoint Regression Analysis

We used Joinpoint Regression (Joinpoint Regression Program, Version 3.5.1, July 2011; Statistical Research and Applications Branch, National Cancer Institute) to analyze trends in the proportion of men receiving RT. This program models data as 1 or more continuous line segments that are joined at points ("joinpoints") to identify the time at which there was a statistically significant change in trend. Tests for statistical significance use a Monte Carlo Permutation method.[15]

### Logistic Regression Analysis

Univariate and multivariate logistic regression analyses were performed to model the association between receipt of RT and year of diagnosis, sociodemographic factors and tumor characteristics. Race/ethnicity, based on information recorded in patient medical records and enhanced with a name and birthplace based algorithm for Hispanic classification,[16] was classified as nonHispanic white, nonHispanic black, Hispanic or other nonHispanic. Age at diagnosis was categorized as younger than 35 years or 35 years or older, and tumor size was categorized as smaller than 4 cm or 4 cm or larger. We used information from SEER EOD extension codes for cases diagnosed in 2000 to 2003 and CS extension codes for cases diagnosed after 2003 to classify tumors as T1 (EOD codes 10, 40 or CS codes 100, 400, 320), T2 (EOD 15, 20, 30, 31, 45 or CS 150, 160, 200, 300, 310, 330, 450, 460) or T3/T4 (EOD 50, 60, 70, 75 or CS 500, 550, 600, 700, 750, 810, 800). The SEER registries were grouped into the geographic regions of California (Los Angeles, San Francisco-Oakland, San Jose-Monterey, Greater California), other West (Hawaii, New Mexico, Seattle [Puget Sound], Utah, Alaska Natives), Midwest (Detroit [metropolitan], Iowa), Northeast (Connecticut, New Jersey) and South (Atlanta [metropolitan], Rural Georgia, Greater Georgia, Kentucky, Louisiana). Because Joinpoint regression analysis identified 2006 as the year in which there was a statistically significant change in the trend for the proportion of men receiving RT, year of diagnosis was categorized as 2000 to 2005 vs 2006 to 2009.

Because county level measures of income, poverty and educational attainment tend to be correlated, we created a composite SES measure by summing the quartiles of 2000 Census county level measures of the percent of people living below the poverty level, the proportion of people age 25 years or older with less than a high school education and the cost of living adjusted median household income. This score was then divided into quartiles to create an SES index with 1 representing the lowest SES quartile.

Separate multivariate models were also built for each year group to look for possible effect modification. The OR estimates did not differ significantly between the models for 2000 to 2005 vs 2006 to 2009. Logistic regression modeling was performed using SAS® version 9.3.

## RESULTS

Between 2000 and 2009 a total of 8,151 men were diagnosed with localized testicular seminoma and had complete data annotation in the SEER database. Median age was 37 (IQR 30–44). The majority of tumors were pathological stage T1 (70.7%), with an additional 27.8% T2 and 1.6% T3/4. Tumor size was 4 cm or greater in 48.1% of cases. Race/ethnicity was 78.7% white. The California SEER region accounted for 44.2% of documented cases, with other Western (17.0%), South (15.3%), Northeast (13.7%) and Midwest (9.9%) accounting for the remainder.

Multivariate modeling with age, race, SEER region, SES quartile, tumor stage, tumor size and year of diagnosis confirmed a significant and independent association of diagnosis year with receipt of adjuvant RT (see table). Men diagnosed from 2006 to 2009 were less likely to receive adjuvant RT with an adjusted OR of 0.40 (50.8% vs 71.7%, $p < 0.0001$, 95% CI 0.36–0.44). Men 35 years old or older were more likely to receive RT ($p < 0.0002$, OR 1.20, 95% CI 1.09–1.32), as were men in the highest SES index quartile ($p < 0.0001$, OR 1.34, 95% CI 1.16–1.54). Use of RT also appeared to vary significantly by SEER region. Patients in the Western ($p < 0.0002$, OR 1.34, 95% CI 1.15–1.57), South ($p < 0.0019$, OR 1.25, 95% CI 1.09–1.44), Northeast ($p < 0.0002$, OR 1.34, 95% CI 1.15–1.56) or Midwest SEER regions ($p < 0.0002$, OR 1.41, 95% CI 1.18–1.68) were all more likely to receive RT compared to the California SEER region. No significant racial differences in adjuvant RT were noted. Tumor stage did not significantly affect rates of RT use. However, tumor size 4 cm or greater was associated with a significantly higher rate of RT ($p < 0.0005$, OR 1.18, 95% CI 1.08–1.30).

The majority of men, 74.7%, received adjuvant RT at the beginning of the study period in 2000. This steadily decreased throughout the study period with an inflection point and continuous accelerated decrease in use after 2006. In 2009, the most recent year of SEER data available, only 37.7% of men with localized testicular seminoma received adjuvant RT (see figure).

## DISCUSSION

The use of adjuvant RT for localized testicular seminoma has decreased steadily. Using a single institutional database and the National Cancer Data Base, Cooper et al reported a gradual decrease in the proportion of patients receiving RT and a corresponding increase in the proportion going on surveillance in the last 20 years up to 2007.[17] Hoffman et al previously reported a 75% rate of adjuvant RT recommendation in 2004, which represented a decrease from 85% in 1990.[18] Our study shows a significant and even more dramatic decrease in adjuvant RT use with only 37.7% of patients receiving adjuvant RT in 2009. A continuous and accelerated decrease was seen after 2006.

This dramatic change in clinical practice is observed as evidence accumulates on the potential long-term side effects of adjuvant RT. The increased risk of secondary malignancies has been well documented in testicular cancer survivors.[8,12,19] van den Belt-Dusebout et al first reported in 2007 that there was a 2.6-fold increase in secondary nongerm cell malignancies after adjuvant RT in a cohort of testicular cancer survivors over 17 years.[11] Another recent SEER analysis of patients undergoing adjuvant RT for testicular seminoma from 1973 to 2000 showed a 19% increase in secondary malignancies including thyroid cancer, pancreatic cancer, nonbladder urothelial malignancies, bladder cancer, all hematological malignancies and nonHodgkin's lymphoma.[20] In addition, adjuvant RT has been associated with an increased risk of cardiovascular disease,[20] nephrotoxicity,[21–23] diabetes[24] and infertility.[25]

At the same time, platinum based adjuvant chemotherapy and surveillance have emerged as alternatives for the management of localized testicular seminoma. Single dose carboplatin has few acute toxicities and the risk of recurrence was first shown to be comparable to adjuvant RT in a large randomized trial by Oliver et al in 2005.[26] A large pooled analysis by Warde et al in 2002 demonstrated that 82% of patients on surveillance for localized testicular seminoma would not have recurrence at 5 years.[5] Even with relapse, salvage rates approach 100%.[5,6] Surveillance allows many patients to avoid additional treatments and potential long-term side effects of those treatments. However, surveillance requires patients to undergo frequent followup CT that also carries some potential long-term risks. CT is an increasing source of radiation exposure[27] and the cumulative radiation exposure from repeated CT could have longer term attributable risks of secondary malignancy with longer followup intervals.[28] Unfortunately the national SEER registry does not include data on chemotherapy use and we are unable to discern whether patients in this contemporary population based cohort who did not receive RT are opting for single dose adjuvant chemotherapy or surveillance.

The accumulating evidence against adjuvant RT for localized testicular seminoma and the increase in treatment alternatives has been reflected in changing NCCN and EAU guidelines. Since 2009 surveillance has been the preferred option in the NCCN guidelines and the EAU guidelines have recommended against adjuvant RT since 2011.[2,7] Nevertheless, 37.7% of patients in our cohort diagnosed in 2009 received adjuvant RT. Patients 35 years old or older or in the highest SES index quartile (as represented by county of residence) were also more likely to receive adjuvant RT. This finding parallels previously noted findings of Hoffman et al, who found that patients older than 30 years and patients in the most educated counties were more likely to receive adjuvant RT.[18] Decreased use of adjuvant RT in younger patients may represent an attempt to avoid the potential risk of secondary malignancy[18] since younger patients have more time after exposure in which a secondary cancer can develop. Concerns regarding infertility could also be an additional factor in the decreased likelihood of younger patients receiving adjuvant RT.

We hypothesize that patients living in the highest SES counties may be more likely than those in lower SES counties to receive adjuvant RT because of increased access to specialized care. It may also be the case that men in the lowest SES index quartile have such decreased access to care that they are receiving neither adjuvant RT nor surveillance.

Because the SEER database does not document patient preferences, clinical decision making processes or long-term clinical followup, the underlying reasons why older patients and patients belonging to the highest SES index quartile were more likely to receive adjuvant RT remain speculative, but warrant further attention.

While we did observe regional variation in adjuvant RT administration rates, with patients in California less likely to receive adjuvant RT, underreporting of RT across SEER regions must be considered. Regional variation in the under-ascertainment of RT use for breast cancer has recently been reported, although the extent of interaction with SES variables remains to be defined.[29] Registry reporting variability may also affect the regional differences in RT use for localized testicular seminoma observed in this study.

Significant barriers remain to the adoption of evidence-based NCCN and EAU guidelines on localized testicular seminoma. More than a third of patients in the most recently available annual SEER data received adjuvant RT. Although risks associated with adjuvant RT are well documented, a recent survey of American radiation oncologists in 2010 revealed that 62% of respondents still recommended adjuvant RT over surveillance.[30] While localized testicular seminoma remains a model of curable malignancy, continuing to improve long-term morbidity will require increased provider awareness of current evidence and continued monitoring of sequelae in long-term survivors.

## CONCLUSIONS

The use of adjuvant RT for the management of localized testicular seminoma has significantly decreased from 2000 to 2009. Concerns regarding long-term toxicity and potential risks of secondary malignancies may have influenced clinical practice patterns. Older men and men with higher SES are still more likely to receive adjuvant RT for the management of localized testicular seminoma.

## Abbreviations and Acronyms

| | |
|---|---|
| **CS** | collaborative stage |
| **CT** | computerized tomography |
| **EAU** | European Association of Urology |
| **EOD** | Extent of Disease |
| **NCCN** | National Comprehensive Cancer Network |
| **RT** | radiotherapy |
| **SES** | socioeconomic status |

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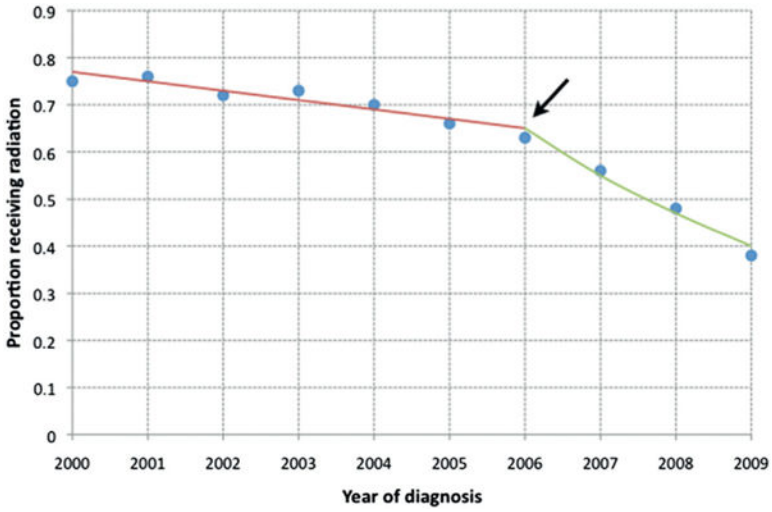


**Figure.**

Proportion of men receiving adjuvant RT for stage I seminoma 2000 to 2009 with Joinpoint regression lines showing rapid decrease (arrow) in use after 2006.

## Table

Multivariate adjusted model of patient demographics and tumor characteristics affecting receipt of RT

| | No. Pts | % Receiving RT | OR (95% CI) | p Value |
|---|---|---|---|---|
| Age (yrs): | | | | |
| Less than 35 | 3,321 | 60.0 | 1 | |
| 35 or Greater | 4,830 | 64.5 | 1.20 (1.09–1.32) | 0.0002 |
| Race: | | | | |
| White | 6,415 | 63.3 | 1 | |
| Hispanic | 1,202 | 60.1 | 1.10 (0.96–1.26) | 0.1860 |
| Black | 195 | 57.9 | 0.83 (0.61–1.12) | 0.2218 |
| Other | 339 | 61.7 | 1.02 (0.81–1.29) | 0.8770 |
| SEER region: | | | | |
| California | 3,602 | 59.1 | 1 | |
| Other Western | 1,382 | 65.7 | 1.34 (1.15–1.57) | 0.0002 |
| South | 1,247 | 63.0 | 1.25 (1.09–1.44) | 0.0019 |
| Northeast | 1,113 | 66.1 | 1.34 (1.15–1.56) | 0.0002 |
| Midwest | 807 | 67.7 | 1.41 (1.18–1.68) | 0.0002 |
| SES quartile: | | | | |
| Lowest | 2,230 | 57.6 | 1 | |
| 2 | 2,865 | 63.1 | 1.25 (1.11–1.40) | 0.0003 |
| 3 | 1,121 | 64.1 | 1.13 (0.95–1.35) | 0.1627 |
| Highest | 1,935 | 66.9 | 1.34 (1.16–1.54) | <0.0001 |
| Tumor stage: | | | | |
| T1 | 5,759 | 62.5 | 1 | |
| T2 | 2,264 | 63.2 | 1.03 (0.93–1.15) | 0.5761 |
| T3/4 | 128 | 60.2 | 1.08 (0.75–1.57) | 0.6723 |
| Tumor size (cm): | | | | |
| Less than 4 | 4,233 | 61.1 | 1 | |
| 4 or Greater | 3,918 | 64.3 | 1.18 (1.08–1.30) | 0.0005 |
| Yr of diagnosis: | | | | |
| 2000–2005 | 4,617 | 71.7 | 1 | |
| 2006–2009 | 3,534 | 50.8 | 0.40 (0.36–0.44) | <0.0001 |