



# Stage IIA and IIB testicular seminoma treated post-orchietomy with radiation therapy versus other approaches: a population-based analysis of 241 patients

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## ABSTRACT

**Objectives:** To evaluate post-orchietomy utilization of radiation therapy (RT) versus other management approaches in stage IIA and IIB testicular seminoma patients.

**Materials and Methods:** Two hundred and forty-one patients with stage IIA and IIB testicular seminoma were identified between 1988 and 2003 using the Surveillance, Epidemiology, and End Results (SEER) database.

**Results:** Median follow-up was 10 years. Patients with stage IIA disease underwent RT more frequently than those with stage IIB disease (72% vs. 46%, respectively;  $P < 0.001$ ). There was no significant change in RT utilization for stage IIA or IIB disease between 1988 and 2003 ( $P = 0.89$ ).

**Conclusions:** Between 1988 and 2003, stage IIA patients underwent RT more often than stage IIB patients in the United States. There was no significant change in RT utilization for stage IIA or IIB disease during this time period. Based on reports describing excellent progression-free survival with cisplatin-based chemotherapy, this approach has increased in popularity since 2003 and may eventually become the most popular treatment approach for both stage IIA and IIB testicular seminoma.

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## INTRODUCTION

Testicular cancer is the most commonly-diagnosed malignancy in men between the ages of 20 and 45 years. The American Cancer Society estimates that there were 7,920 new cases and 370 deaths due to testicular cancer in the United States (U.S.) in 2013 (1). Eighty percent of testicular seminoma patients present with stage I disease and 11% present with stage II disease (2).

Standard of care post-orchietomy for stage IIA and IIB testicular seminoma is radiation therapy (RT) or cisplatin-based combination chemotherapy (3, 4).

Prior studies of RT for stage IIA and IIB testicular seminoma have involved fewer than 130 patients (5-8). The purpose of this study is to analyze utilization of RT vs. other management approaches for stage IIA or IIB testicular seminoma in a relatively large number of patients

based upon an analysis of the Surveillance, Epidemiology and End Results (SEER) database.

## MATERIALS AND METHODS

The SEER program created by the National Cancer Institute (NCI) includes population-based cancer registries from 20 selected geographic areas in the U.S., covering approximately 28% of the national population. Data is submitted to the NCI registry on an annual basis without “identifiable” private information, and the NCI makes the data available to the public for research purposes. As a result, this study was exempt from Institutional Review Board review. Patient data was obtained via a query of the SEER dataset (November 2012 edition). The population for this study consisted of patients diagnosed with stage IIA and stage IIB pure testicular seminoma. Patients treated between 1988 and 2003 were identified using the following extent of disease codes for the primary tumor: T1: 10, 20, 30, and 40; T2: 15 and 45; T3: 50; and T4 60 and 70. For regional lymph nodes, extent of disease code one was used for N1 disease and code two was used for N2 disease. In the SEER database, patients are listed simply as having received RT or not having received RT. The database does not state the management approach that was used post-orchietomy in patients who did not undergo RT. Also, it does not state whether a particular treatment approach (RT vs. other) was based upon physician recommendation or patient preference. In addition, RT and chemotherapy details, including dosages, are not included in the SEER database. Moreover, initial volume of nodal disease, relapse-free survival including sites of relapse, and non-lethal toxicities are not included. Patients in whom the stage grouping was unknown were excluded. Stage IIC disease was excluded because cisplatin-based combination chemotherapy for good-risk patients as defined by the International Germ Cell Cancer Collaborative Group (IGCCCG) constitutes the standard of care (9), precluding a statistical analysis of RT vs. other management approaches. There is no consensus on the definition of educational level. A low educational level was defined in this study

as a high school graduation rate of <75%, a moderate educational level was defined as a high school graduation rate of 75-85%, and a high educational level was defined as a high school graduation rate of >85%.

Statistical analysis was performed using SAS 9.2 and JMP 7 (SAS Institute Inc., Cary, NC). Survival analysis was carried out using Kaplan-Meier estimates. The log-rank test was used to test for differences in survival. A non-parametric test of medians was used to assess continuous variables. A P-value less than 0.05 was considered to be statistically significant. The Cox proportional hazard model was used for univariate and multivariate analyses to assess the effect of patient characteristics on outcomes.

## RESULTS

### Patient Characteristics

One hundred and forty-five of 241 (60%) patients had stage IIA testicular seminoma and 96/241 (40%) patients had stage IIB testicular seminoma in the SEER database between the years of 1988 and 2003. Patient characteristics are presented in Table-1.

### Stages IIA and IIB Combined

Median follow-up was 10 years. Twenty-two of 241 (9%) patients died. For stages IIA and IIB combined, the 5-, 10-, and 15-year overall survival (OS) rates were 95%, 91%, and 89%, respectively. The 5-, 10-, and 15-year cause-specific survival (CSS) rates were 98%, 97%, and 97% respectively.

### Stage IIA vs. IIB

Race, age, educational level, and marital status did not correlate with patient selection for RT. Patients with T1 disease underwent RT more frequently than those with T3 disease (64% vs. 16%, respectively;  $P < 0.001$ ). Also, patients with stage IIA disease underwent RT more frequently than those with stage IIB disease (72% vs. 46%, respectively;  $P < 0.001$ ). There was no significant change in RT utilization for stage IIA or IIB disease between 1988 and 2003 ( $P = 0.89$ ). Causes of death in stage IIA and IIB patients are presented in Table-2.

**Table 1 - Characteristics of Stage IIA and IIB Testicular Seminoma Patients.**

Characteristic	All Patients (n = 241)		Radiotherapy (n = 136)		No Radiotherapy (n = 105)		P
	n	%	n	%	n	%	
<b>Age (years)</b>							
18-39	139	58%	76	55%	63	45%	0.52
40-76	102	42%	60	59%	42	41%	
<b>Marital Status</b>							
Single	97	40%	52	54%	45	46%	0.59
Married	125	52%	75	60%	50	40%	
Divorced	16	7%	8	50%	8	50%	
Unknown	3	1%	1	33%	2	67%	
<b>Race</b>							
White	219	91%	127	58%	92	42%	0.12
Non-White	22	9%	9	41%	13	59%	
<b>Year of Diagnosis</b>							
1988-1991	14	6%	7	50%	7	50%	0.89
1992-1995	43	18%	23	53%	20	47%	
1996-1999	52	22%	31	60%	21	40%	
2000-2003	132	54%	75	56%	57	44%	
<b>Educational Level</b>							
Low	65	27%	37	57%	28	43%	0.47
Intermediate	102	42%	56	55%	46	45%	
High	74	31%	43	58%	31	42%	
<b>Primary Tumor (T)</b>							
T1	150	62%	96	64%	54	36%	<0.001
T2	39	16%	23	59%	16	41%	
T3	18	7%	3	16%	15	84%	
T4	5	2%	3	60%	2	40%	
TX	29	12%	11	38%	18	62%	
<b>Regional Lymph Nodes</b>							
N1 *	96	40%	69	72%	27	28%	<0.001
N2†	145	60%	67	46%	78	54%	

\*Stage IIA

†Stage IIB

**Table 2 – A) Causes of Death in Stage IIA Testicular Seminoma Patients, B) Causes of Death in Stage IIB Testicular Seminoma Patients.****A**

Cause of Death (n=9)	Radiotherapy (n=69)	No Radiotherapy (n=27)
Testicular Cancer	2	2
Lung Disease	1	1
Acute Myeloid Leukemia	0	1
Accident	0	1
Unknown	0	1

**B**

Cause of Death (n=13)	Radiotherapy (n=67)	No Radiotherapy (n=78)
Unknown	1	3
Testicular Cancer	1	2
Heart Disease	2	1
Lung Disease	1	0
Infection	0	1
Colon Cancer	0	1

Patients with stage IIA disease who received RT had a 5-, 10-, and 15-year OS rate of 96% compared with 88%, 77%, and 77%, respectively, for those who underwent other management approaches ( $P = 0.008$ ; Figure-1). The 5-, 10-, and 15-year CSS rate for stage IIA disease was 97% for RT compared with 96%, 92%, and 92%, respectively, for other management approaches ( $P = 0.30$ ).

Improved OS ( $P = 0.03$ ; Figure-2) was noted in patients with stage IIB disease who received RT (5-, 10-, and 15-year OS rates of 98, 96%, and 88%, respectively) as opposed to no RT (5-, 10-, and 15-year OS rates of 90%, 86%, and 86%, respectively). The 5-, 10-, and 15-year CSS rate was 98% for stage IIB patients who received RT compared with 98%, 96%, and 96%, respectively, for those who underwent other management approaches ( $P = 0.60$ ).

**Univariate and Multivariate Analyses**

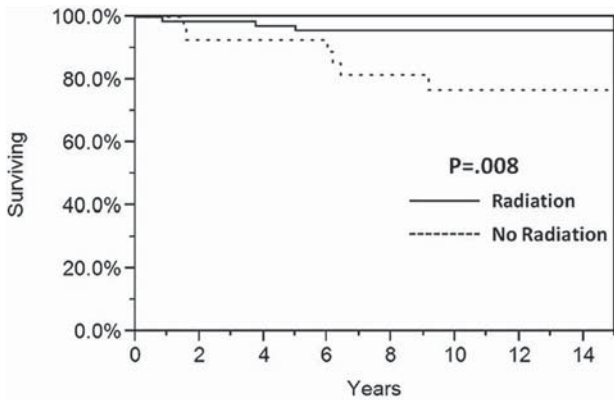
On univariate analysis, race, educational level, marital status, treatment year, and T and N

stage were not associated with OS or CSS. Increasing age was associated with worse OS ( $P = 0.009$ ), but not CSS ( $P = 0.11$ ). Age was associated with worse OS on multivariate analysis as well, adjusting for race, T and N stage, year of treatment, use of RT, marital status, and educational level. The use of RT correlated with improved OS (HR 0.30; 95% CI: 0.12-0.74;  $P = 0.008$ ) but not CSS ( $P = 0.35$ ) on univariate analysis. The use of RT correlated with improved OS on multivariate analysis as well (HR 0.40; 95% CI: 0.15-0.90;  $P = 0.02$ ).

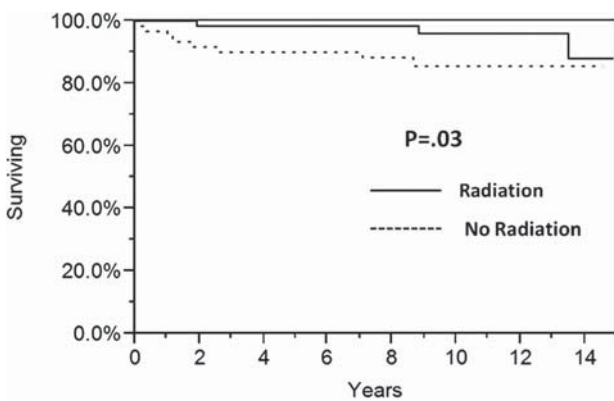
**DISCUSSION**

The bulk of retroperitoneal adenopathy is the most important prognostic factor in stage II disease (5). There have been no prospective, randomized trials involving stage IIA or IIB testicular seminoma due to the rarity of such patients. As a result, treatment recommendations have commonly been guided by reports from single institutions (3).

**Figure 1 - Overall survival for stage IIA testicular seminoma patients managed with radiation therapy vs. other approaches.**



**Figure 2 - Overall survival for stage IIB testicular seminoma patients managed with radiation therapy vs. other approaches.**



One limitation of the SEER database is a lack of randomization with regards to treatment. Other limitations include a lack of treatment details in the no RT group such as chemotherapeutic agents and doses.

In a highly curable disease such as stage IIA and IIB testicular seminoma, prevention of long-term complications of treatment is a priority. Retroperitoneal RT increases the relative risk (RR) of second non-germ-cell malignancies, including gastric (RR 4.1), pancreatic (RR 3.8), and colon (RR 1.9) cancers (10). Also, several groups have reported that retroperitoneal RT results in a twofold or greater risk of cardiovascular disease beyond 15 years, particularly when prophylactic mediastinal/

supraclavicular RT is added (11-13). Late effects are less well-defined for chemotherapy than they are for RT (10). The deleterious effects of 3-4 cycles of cisplatin-based chemotherapy on fertility are transitory, reversible, and dose-dependent (14). Huyghe et al. (14) suggested that RT has a more deleterious effect on fertility than chemotherapy in testicular cancer patients. However, RT in that study was antiquated by today's standards. Fertility can be preserved when the RT dose to the remaining testis is reduced to less than 2 Gy (15, 16). The cumulative incidence of spermatogenesis as a function of time appears to be similar after modern RT and cisplatin-based chemotherapy (16-18). A low but increased risk of development of acute myeloid leukemia is associated with chemotherapy, especially when etoposide is administered in high cumulative doses (19). Travis et al. (10) observed significantly increased risks of solid cancers among testicular cancer patients treated with RT alone (RR = 2.0, 95% CI = 1.9 to 2.2), chemotherapy alone (RR = 1.8, 95% CI = 1.3 to 2.5), and both (RR = 2.9, 95% CI = 1.9 to 4.2). Huddart et al. (12) observed an increased incidence of cardiovascular events in germ cell tumor patients treated with cisplatin-based chemotherapy. van den Belt-Dusebout et al. (20) reported that retroperitoneal RT strongly increases the risk of second malignancies but not of cardiovascular disease, whereas chemotherapy increases the risks of both second malignancies and cardiovascular disease. In addition, cisplatin-based chemotherapy has been associated with nephrotoxicity, ototoxicity, and neuropathy (21), especially when a large number of cycles of cisplatin is given. Fossa et al. (22) observed that men treated with chemotherapy (with or without RT) in 1975 or later had higher mortality from all non-cancer causes (standardized mortality ratio (SMR) = 1.34, 95% CI = 1.15 to 1.55), all circulatory diseases (SMR = 1.58, 95% CI = 1.25 to 2.01), all infections (SMR = 2.48, 95% CI = 1.70 to 3.50), and all respiratory diseases (SMR = 2.53, 95% CI = 1.26 to 4.53). Active surveillance is not a management option post-orchiectomy for stage IIA and IIB disease; however, it is the preferred approach for stage IA and IB disease (23).

This report is the largest study of stage IIA and stage IIB testicular seminoma in the litera-

ture. The 5-year OS and CSS rates of 96-98% for RT are comparable with other reports (5, 8). Based on a median follow-up of 10 years in this study, RT was associated with improved OS in stage IIA (Figure-1) and IIB (Figure-2) disease. Patients who underwent RT had similar known characteristics such as age to those who did not undergo RT (Table-1). However, this study was not randomized. As a result, the improved OS in patients who received RT may be due to selection bias. Also, patients in the RT group could have received a single cycle of neoadjuvant carboplatin chemotherapy prior to RT, which reduces the risk of relapse (21). In addition, stage IIA and stage IIB testicular seminoma patients in the no RT group may have been treated with 4 cycles of single-agent carboplatin chemotherapy, which results in worse OS and progression-free survival than cisplatin-based chemotherapy (24, 25). In this report, no patients died of acute myeloid leukemia or infection in the RT group, whereas 2 patients died of these causes in the no RT group based on a median follow up of 10 years (Table-2). Most second malignancies and major cardiac events occur more than 15 years after RT (8, 13). As a result, longer follow-up is necessary to assess late toxicity and OS. Only 7 of 22 (32%) deaths in this study were due to testicular seminoma (Table-2). Consequently, statistical power was limited for the assessment of CSS.

Chung et al. (5) reported 5-year relapse-free survival rates of 92% and 90%, respectively, for stage IIA and stage IIB testicular seminoma patients who underwent RT. Similarly, Classen et al. (6) reported 6-year relapse-free survival rates of 95% and 89%, respectively, for stage IIA and stage IIB patients who were treated with RT.

Modified dog-leg RT to 30 Gy in 15 fractions remains the preferred approach by most investigators for stage IIA testicular seminoma in the absence of a horseshoe kidney, inflammatory bowel disease, or a history of RT (3, 4, 26, 27). If one of these 3 contraindications to RT is present, then cisplatin-based combination chemotherapy is recommended (3, 4, 26, 27). Prophylactic mediastinal/supraclavicular RT is no longer given for stage II testicular seminoma due to its late toxicity (13, 28).

In most studies, more than 80% of stage IIA patients received RT (5, 7, 29). Similarly, 82%

of stage IIA patients in this report received RT. Nevertheless, cisplatin-based chemotherapy for good-risk testicular seminoma patients as defined by the IGCCCG (9) has gained in popularity over the past decade (30). One advantage of cisplatin-based chemotherapy is that it can eradicate carcinoma in situ in the remaining testis and prevent or postpone the development of an invasive cancer in some patients (17).

The Spanish Germ Cell Cancer Group conducted the first study of cisplatin-based chemotherapy as frontline therapy in stage IIA testicular seminoma patients (30). None of the 19 stage IIA patients relapsed. Also, in the Swedish and Norwegian Testicular Cancer Project (SWENOTECA) study (29), none of the 6 stage IIA patients who received cisplatin-based chemotherapy relapsed. Based on the impressive progression-free survival in these two studies, the European Society for Medical Oncology (31) recommends cisplatin-based chemotherapy or modified dog-leg RT to 30 Gy in 15 fractions, with no preference for one treatment option over another, for stage IIA testicular seminoma.

Cisplatin-based chemotherapy used to be reserved for stage IIB patients with high-volume disease, e.g., multiple lymph nodes measuring 3.1-5.0 cm (3, 4). The Spanish Germ Cell Cancer Group conducted a study that included 54 patients with low-volume, e.g., a solitary retroperitoneal node measuring 2.1-3.0 cm, or high-volume stage IIB disease. Patients were treated with three cycles of cisplatin, etoposide, and bleomycin (PEB) or four cycles of cisplatin and etoposide (PE) (30). Median follow up was 72 months. The 5-year progression-free survival rate for stage IIB patients was 87%. The SWENOTECA study included 67 stage IIB patients with low-volume or high-volume disease who were treated with cisplatin-based chemotherapy (29). None of them relapsed based on a median follow-up of 5.2 years. Based on the excellent progression-free survival in the SWENOTECA study, version 1.2014 of the National Comprehensive Cancer Network Clinical Practice Guidelines (32) and the European Society for Medical Oncology (31) recommend three cycles of PEB chemotherapy for all stage IIB patients, regardless of tumor burden. If there is a contraindication to bleomycin

such as a reduction in lung capacity, emphysema, current or a history of heavy smoking, or poor renal function, then four cycles of PE may be used (31). Modified dog-leg RT to 36 Gy in 18 fractions also constitutes a treatment option for stage IIB patients in whom chemotherapy would be unsuitable (31) or who have a solitary retroperitoneal node measuring 2.1-3.0 cm (32).

One treatment that has been investigated for stage IIA and IIB testicular seminoma is a single course of neoadjuvant carboplatin chemotherapy followed by para-aortic RT to 30-35 Gy. In a series involving 51 patients, there have been no relapses after a median follow up of 55 months (21). Eight per cent of patients experienced grade 3 hematological toxicity and 2% developed grade 3 nausea. These results are promising; however, additional investigation is needed (3, 30).

## CONCLUSIONS

Stage IIA testicular seminoma patients in the U.S. underwent RT more often than stage IIB patients between 1988 and 2003. There was no significant change in RT utilization for stage IIA or IIB disease during this time period. Cisplatin-based chemotherapy has produced excellent progression-free survival and, as a result, may eventually become the most popular treatment approach for both stage IIA and IIB testicular seminoma.

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