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Clinical Investigation

Surveillance and Radiation Therapy for Stage I Seminoma—Have We Learned From the Evidence?

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Summary

Stage I testicular seminoma is a highly curable disease with several treatment modalities, including active surveillance, chemotherapy, and radiation therapy, demonstrating similar outcomes. This review of the National Cancer Data Base describes trends in treatment utilization as well as radiation therapy dose, including factors associated with treatment decision. Furthermore, we report on the impact of treatment modality on survival. This national review sheds light on changing practice patterns and confirms the results of smaller observational series and trials.

Purpose: To analyze, in the setting of stage I seminoma, the factors affecting adjuvant treatment decisions and resulting survival outcomes, using a national dataset.

Methods and Materials: We identified 33,094 stage I seminoma patients after orchiectomy from 1998 to 2012 from the National Cancer Data Base. Factors affecting treatment selection (active surveillance [AS] vs adjuvant treatment [AT]) were identified using a parsimonious multivariate logistic regression model. Propensity scores for treatment decision were generated and incorporated into a multivariate Cox regression analysis of overall survival. This process was then repeated within the AT cohort for factors predictive for chemotherapy [CT] versus radiation therapy [RT].

Results: Only 33% of patients received AS, and 65% received AT (89% RT and 11% CT). From 1998 to 2012 the proportion receiving AS increased from 23% to 60%, whereas RT utilization decreased from 73% to 21%, and CT utilization increased from 2% to 17%. Utilization of low-dose RT increased from 1.5% in 1999 to 34% in 2012. There was a small absolute overall survival advantage to AT over AS at 10 years (95.0% vs 93.4%, propensity adjusted hazard ratio 0.58, $P<.0005$).

Conclusions: There has been a significant increase in use of AS for stage I seminoma, influenced by both sociodemogrpahic and clinicopathologic factors. Between AT options, there has been significant increase in use of CT, mirrored by a decline in use of RT. Although overall survival remains high for all 3 treatment strategies, AT seems to be associated with a small absolute survival advantage over AS up to 10 years out from diagnosis.

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Introduction

Testicular cancer constitutes approximately 1% of all solid tumors but is the most common solid tumor in males aged 15 to 35 years (1). Approximately half of testicular tumors are seminoma, and three-quarters of these are diagnosed as stage I tumors (2). Historically, patients with stage I seminoma were treated with radical inguinal orchiectomy followed by adjuvant radiation therapy (RT) to the para-aortic and ipsilateral pelvic lymph nodes (3, 4). This resulted in relapse-free survival rates of more than 95%. With salvage chemotherapy (CT), disease-specific survival approached 100%. With such favorable outcomes, the focus began to shift toward minimizing late effects of adjuvant treatment (AT), by pursuing various treatment de-escalation strategies.

Efforts to decrease the intensity of RT included reducing field size and reducing dose to the lowest effective level (5-7). The Medical Research Council TE10 trial showed that the pelvic lymph nodes could be excluded from the RT field, thereby reducing dose to the remaining testicle and decreasing the risk of infertility (5). The Medical Research Council TE18 trial showed that the adjuvant RT dose could be safely lowered from 30 Gy to 20 Gy (7). With 6.5 years of median follow-up, a randomized trial comparing adjuvant RT with a single dose of carboplatin suggested noninferiority of carboplatin, along with decreased incidence of second germ cell tumor (8, 9). Accordingly, out of concern for the increased risk of radiation-induced malignancies, the European Association of Urology guidelines state that adjuvant RT should no longer be used in stage I seminoma patients (especially for those aged <40 years).

Contemporary to the investigation of de-escalation strategies, early reports on active surveillance (AS) began to emerge (10-13). After radical orchiectomy alone, only 15% to 20% of patients will experience disease recurrence. Nearly all of those who suffer recurrence can be successfully salvaged, leading to disease-specific survival approaching 100% in those initially managed with AS after orchiectomy (14, 15). Active surveillance has not been tested in a prospective, randomized trial, against either RT or CT, but it remains an attractive option owing to the potential to decrease the long-term effects associated with treatment (16-23). This has led to a lack of consensus as to which patients represent the ideal candidates for AS. On one hand, some advocate that AS should universally be the preferred management strategy for stage I seminoma patients. This approach, reflected in National Comprehensive Cancer Network guidelines, effectively spares 80% to 85% of patients the risk of adverse effects from AT but does require increased surveillance for all and requires the 15% to 20% who recur to undergo more intensive therapy than what AT would have been. Others have advocated for a risk-adaptive approach, because tumor size >4 cm or rete testis invasion have been shown to be risk factors for recurrence (24). The Spanish group (25) suggests that patients with both factors receive AT but that others receive AS. However, a recent study seeking to validate such a prognostic model was unable to do so (26). The overall lack of consensus has led to vigorous debate in the medical literature (27-29).

Given the changing paradigms in the treatment of stage I seminoma, lack of consensus, and limited phase 3 data, we sought to analyze the factors predictive of adjuvant treatment decisions and compare the overall survival (OS) among treatment groups using the National Cancer Data Base (NCDB).

Methods and Materials

Data source

The NCDB, a joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons, is a nationwide, facility-based, comprehensive clinical surveillance resource that captures 70% of all newly diagnosed malignancies in the United States annually (30, 31). The American College of Surgeons has executed a Business Associate Agreement that includes a data use agreement with each of its Commission on Cancer—accredited hospitals. Using deidentified data exempt from institutional review board oversight, we queried the NCDB database of testicular cancer patients from 1998 to 2012.

Patient selection

Of the 80,385 patients in the original NCDB testicular cancer database, a total of 33,094 stage I seminoma patients who had undergone orchiectomy were identified, as summarized in the CONSORT diagram (Fig. E1; available online at www.redjournal.org). All patients were newly diagnosed between January 1, 1998 and December 31, 2012 and had part or all of their initial treatment course within 6 months of diagnosis at a Commission on Cancer facility. All patients were between the ages of 18 and 90 years.

Definition of variables

Patients who received neither adjuvant RT or CT were defined as the AS group. The AT group is unlikely to contain early salvage cases, because the NCDB codes for the initial treatment course, and more than 90% of patients had their adjuvant treatment start within 90 days. Race was defined as non-Hispanic white, Hispanic white, black, or other. Insurance status was defined as private, government (including Medicare, Medicaid, other government), or not insured. Designation of residential setting was based on 2013 US Department of Agriculture Rural-Urban Continuum codes with "metropolitan" for counties in

Table 1 Baseline characteristics

Characteristic	All patients (n = 33,094)
Sociodemographic factors	
Year of diagnosis	
1998-2001	8994 (27.2)
2002-2005	8835 (26.7)
2006-2009	8882 (26.8)
2010-2012	6383 (19.3)
Age (y)	
≤30	8078 (24.4)
31-40	12,904 (39.0)
41-50	8435 (25.5)
≥51	3677 (11.1)
Charlson-Deyo comorbidity score	
0	20,760 (62.7)
1	1013 (3.1)
≥2	138 (0.4)
Unknown	11,183 (33.8)
Race	
Non-Hispanic white	26,445 (79.9)
Hispanic white	2319 (7.0)
Black	921 (2.8)
Other	828 (2.5)
Unknown	2581 (7.8)
Insurance status	
Private	26,265 (79.4)
Government	3181 (9.6)
None	2698 (8.2)
Unknown	950 (2.9)
Residential setting	
Metropolitan	27,658 (83.6)
Urban	3685 (11.1)
Rural	368 (1.1)
Unknown	1383 (4.2)
Median income (residential area) ($)	
<38,000	3988 (12.1)
38,000-47,999	6724 (20.3)
48,000-62,999	8675 (26.2)
≥63,000	12,881 (38.9)
Unknown	826 (2.5)
% Without high school diploma (residential area)	
<7	9973 (30.1)
7-12.9	11,034 (33.3)
13-20.9	7087 (21.4)
≥21	4207 (12.7)
Unknown	793 (2.4)
Distance from facility to residence (mi)	
≤5	10,247 (31.0)
5.1-10	7794 (23.6)
10.1-20	7486 (22.6)
>20	6817 (20.6)
Unknown	750 (2.3)
Facility type	
Community	3880 (11.7)
Comprehensive community	19,227 (58.1)
Academic/research	9938 (30.0)
Unknown	49 (0.1)
Facility location	
Northeast	7376 (22.3)
South	9924 (30.0)
Midwest	8950 (27.0)
Mountain	2066 (6.2)
Pacific	4778 (14.4)
Facility volume (no. cases)	
≤20	7298 (22.1)
21-40	11,051 (33.4)
41-60	6827 (20.6)
>60	7878 (23.8)
Unknown	40 (0.1)
Pathologic ractors	
T Stage	
1	22,566 (68.2)
2	6063 (18.3)
≥3	736 (2.2)
Unknown	3729 (11.3)
Tumor size (cm)	
≤2	6715 (20.3)
2.1-4	11,143 (33.7)
>4	12,213 (36.9)
Unknown	3023 (9.1)
Surgical margins	
Negative	31,199 (94.3)
Positive	371 (1.1)
Unknown	1524 (4.6)
Pathologic assessment of lymph node(s)	
Yes	914 (2.8)
No	31,647 (95.6)
Unknown	533 (1.6)

Values are number (percentage).

metropolitan areas, "urban" for counties with an urban population of 2500 or more but not in a metropolitan area, and "rural" for counties with an urban population of <2500. Residential median income quartiles and high school graduation rates were based on patient's ZIP code and 2008 to 2012 American Community Survey data. Distance from facility to residence was defined from facility mailing address to center of patient's ZIP code. Facility location was defined as follows; Northeast: CT, MA, ME, NH, NJ, NY, PA, RI, VT; South: AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV; Midwest: IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, WI; Mountain: AZ, CO, ID, MT, NM, NV, UT, WY; Pacific: AK, CA, HI, OR, WA. Radiation dose was classified as low (19-23.5 Gy), intermediate (23.51-26.5 Gy), or high (26.51-36 Gy).

Statistical analysis

IBM SPSS version 22 (IBM, Armonk, NY) was used for data analysis. Exploratory univariate analysis of factors

potentially predictive for AS versus AT was performed using a χ^2 test. Similarly, a separate, identical analysis was performed comparing both CT with RT and low-dose RT with intermediate/high-dose RT. For each of the 3 separate univariate analyses, a parsimonious multivariable binary logistic regression model was formed using hierarchical backwards selection of only factors significant for treatment selection on univariate analysis.

Overall survival was calculated in elapsed months from the date of diagnosis to the date of last contact or death. Kaplan-Meier curves were used to present the cumulative probability of survival; log−rank statistics were used to test statistically significant difference in the cumulative proportions between the groups. A Cox proportional hazards model was used for multivariable survival analysis, with factors significant on univariate analysis entered in a hierarchical fashion using backwards selection of the covariates' likelihood ratios. To adjust for potential indication bias (selection bias) between groups, a propensity score reflective of the probability that each patient received a particular treatment (AT vs AS, or CT vs RT) was calculated according to the factors that significantly (on multivariate logistic regression) affected which treatment was received (32, 33). The propensity score was then incorporated as a continuous covariate into multivariate Cox regression analyses for OS, which included only significant factors on univariate survival analyses not included in the propensity score, so as to avoid overcorrection. To further support the assumption of balance between groups, the propensity score was stratified into propensity score−based quintiles, and a standardized difference between the treatment groups of <0.10 was successfully validated. To account for potential immortal-time bias, the conditional landmark method was used with a cutoff of 6 months (the theoretical maximal time from completion of surgery and adjuvant therapy). Further confirming the strength of the findings, sensitivity analyses were conducted excluding time-biased covariates and covariates with $>5\%$ missing values, confirming the treatment effect (results not shown). Statistical significance was defined as an α level of <0.05.

Results

Patient characteristics

Baseline patient characteristics can be found in Table 1. Median age was 37 years, with an interquartile range of 31 to 44 years. Excluding unknowns, $<1\%$ of patients had a Charlson-Deyo comorbidity score of ≥ 2. The majority of patients were Caucasian (87%), had private insurance (82%), lived in a county that was part of a metropolitan area (87%), and were treated at a

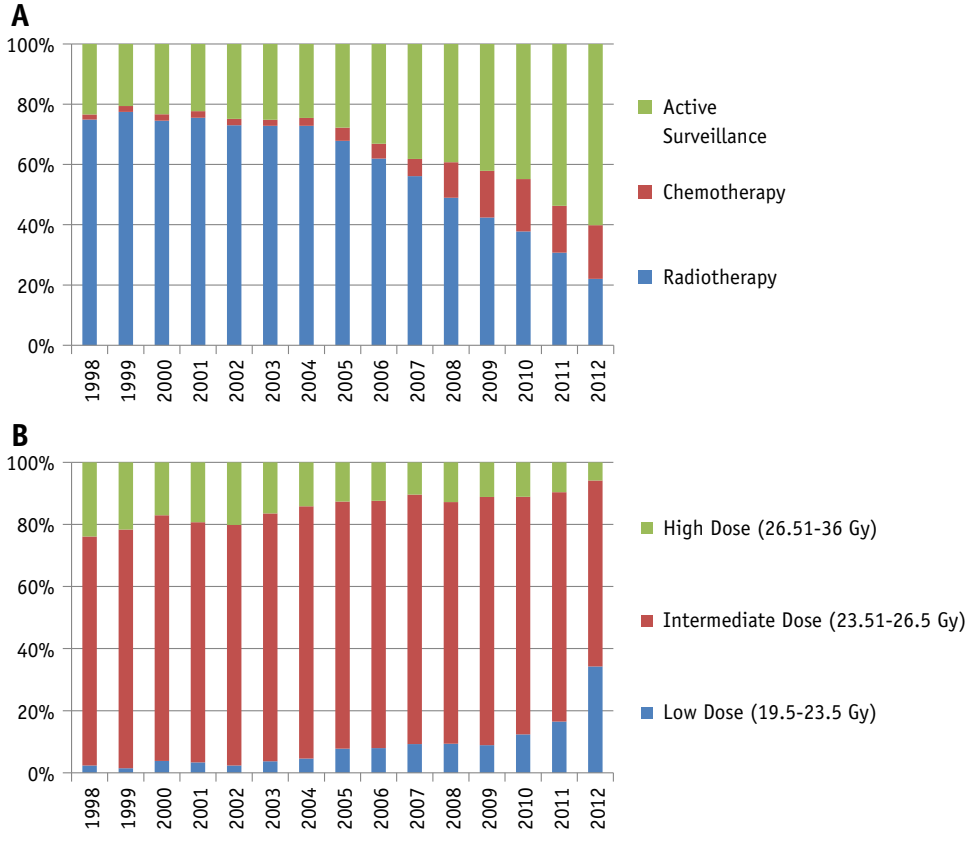

Fig. 1. Trends in treatment selection over time. (A) Treatment modality, and (B) radiation therapy dose.

Table 2 Comparative utilization of treatment versus surveillance by baseline characteristics

Factor	Active surveillance (n = 10,766), n (%)	Active treatment (n = 21,598), n (%)	Odds ratio	95% confidence interval	*P*
Sociodemographic factors					
Year of diagnosis*					<.0005
1998-2001	1963 (22.3)	6821 (77.7)	1	Reference	
2002-2005	2211 (25.5)	6444 (74.5)	0.84	0.78-0.90	
2006-2009	3311 (38.1)	5389 (61.9)	0.47	0.44-0.50	
2010-2012	3281 (52.7)	2944 (47.3)	0.26	0.24-0.28	
Age (y)					<.0005
≤30	2816 (35.6)	5093 (64.4)	1	Reference	
31-40	4122 (32.7)	8498 (67.3)	1.14	1.07-1.21	
41-50	2603 (31.6)	5645 (68.4)	1.20	1.12-1.28	
≥51	1225 (34.2)	2362 (65.8)	1.07	0.98-1.16	
Charlson-Deyo comorbidity score					.102
0	7811 (38.4)	12,528 (61.6)	1	Reference	
1	406 (38.3)	579 (58.8)	0.89	0.78-1.01	
≥2	58 (43.6)	75 (56.4)	0.81	0.57-1.14	
Race					<.0005
Non-Hispanic white	8421 (32.5)	17,464 (67.5)	1	Reference	
Hispanic white	902 (39.8)	1364 (60.2)	0.73	0.67-0.80	
Black	343 (38.3)	553 (61.7)	0.78	0.68-0.89	
Other	307 (38.5)	491 (61.5)	0.77	0.67-0.89	
Insurance status					<.0005
Private	8328 (32.4)	17,355 (67.6)	1	Reference	
Government	1120 (35.9)	1999 (64.1)	0.86	0.79-0.93	
None	1001 (37.9)	1638 (62.1)	0.79	0.72-0.85	
Residential setting*					<.0005
Metropolitan	9188 (34.0)	17,840 (66.0)	1	Reference	
Urban	992 (27.4)	2625 (72.6)	1.36	1.26-1.47	
Rural	113 (31.0)	251 (69.0)	1.14	0.91-1.43	
Median income (residential area)* ($)					<.0005
<38,000	1303 (33.4)	2602 (66.6)	1	Reference	
38,000-47,999	2053 (31.2)	4537 (68.8)	1.11	1.02-1.20	
48,000-62,999	2723 (32.0)	5785 (68.0)	1.06	0.98-1.15	
≥63,000	4412 (35.2)	8136 (64.8)	0.92	0.86-1.00	
% Without high school diploma (residental area)*					<.0005
<7	3309 (33.9)	6438 (66.1)	1	Reference	
7-12.9	3438 (31.8)	7373 (68.2)	1.10	1.04-1.17	
13-20.9	2267 (32.8)	4653 (67.2)	1.05	0.99-1.13	
≥21	1489 (36.3)	2616 (63.7)	0.90	0.84-0.97	
Distance from facility to residence* (mi)					<.0005
≤5	3209 (32.0)	6807 (68.0)	1	Reference	
5.1-10	2510 (33.0)	5100 (67.0)	0.96	0.90-1.02	
10.1-20	2402 (32.8)	4916 (67.2)	0.96	0.90-1.03	
>20	2394 (35.8)	4287 (64.2)	0.84	0.79-0.90	
Facility type*					<.0005
Community	1297 (34.6)	2456 (65.4)	1	Reference	
Comprehensive community	5887 (31.2)	12,963 (68.8)	1.16	1.08-1.25	
Academic/research	3551 (36.6)	6162 (63.4)	0.92	0.85-0.99	
Facility location*					<.0005
Northeast	2499 (35.0)	4633 (65.0)	1	Reference	
South	3600 (37.3)	6058 (62.7)	0.91	0.85-0.97	
Midwest	2455 (27.9)	6352 (72.1)	1.40	1.30-1.49	
Mountain	600 (29.8)	1414 (70.2)	1.27	1.14-1.41	
Pacific	1612 (33.9)	3141 (66.1)	1.05	0.97-1.14	

(*continued on next page*)

Table 2 (*continued*)

Factor	Active surveillance (n = 10,766), n (%)	Active treatment (n = 21,598), n (%)	Odds ratio	95% confidence interval	*P*
Facility volume* (no. cases)					<.0005
≤20	2576 (36.3)	4516 (63.7)	1	Reference	
21-40	3321 (30.7)	7488 (69.3)	1.29	1.21-1.37	
41-60	2170 (32.7)	4474 (67.3)	1.18	1.10-1.26	
>60	2691 (34.6)	5088 (65.4)	1.08	1.01-1.15	
Pathologic factors					
T Stage*					<.0005
1	7776 (35.3)	14,282 (64.7)	1	Reference	
2	1771 (29.9)	4153 (70.1)	1.28	1.20-1.36	
≥3	160 (22.4)	554 (77.6)	1.89	1.58-2.25	
Tumor size* (cm)					<.0005
≤2	2584 (39.4)	3976 (60.6)	1	Reference	
2.1-4	3663 (33.5)	7256 (66.5)	1.29	1.21-1.37	
>4	3750 (31.4)	8184 (68.6)	1.42	1.33-1.51	
Surgical margins*					<.0005
Negative	10,291 (33.7)	20,228 (66.3)	1	Reference	
Positive	87 (24.3)	271 (75.7)	1.58	1.24-2.02	
Pathologic assessment of lymph node(s)					.029
Yes	330 (36.8)	567 (63.2)	1	Reference	
No	10,307 (33.3)	20,640 (66.7)	1.17	1.02-1.34	

* Indicates variable that was significant on multivariate logistic regression analysis for treatment selection and thus included in the propensity score calculation.

comprehensive community facility (58%). Median distance from facility to residence was 8.6 miles, with an interquartile range of 4.0 to 17.5.

Excluding unknowns, 77% had T1 stage, 59% had a primary tumor of ≤4 cm, 99% had negative surgical margins, and only 3% had pathologic assessment of any lymph

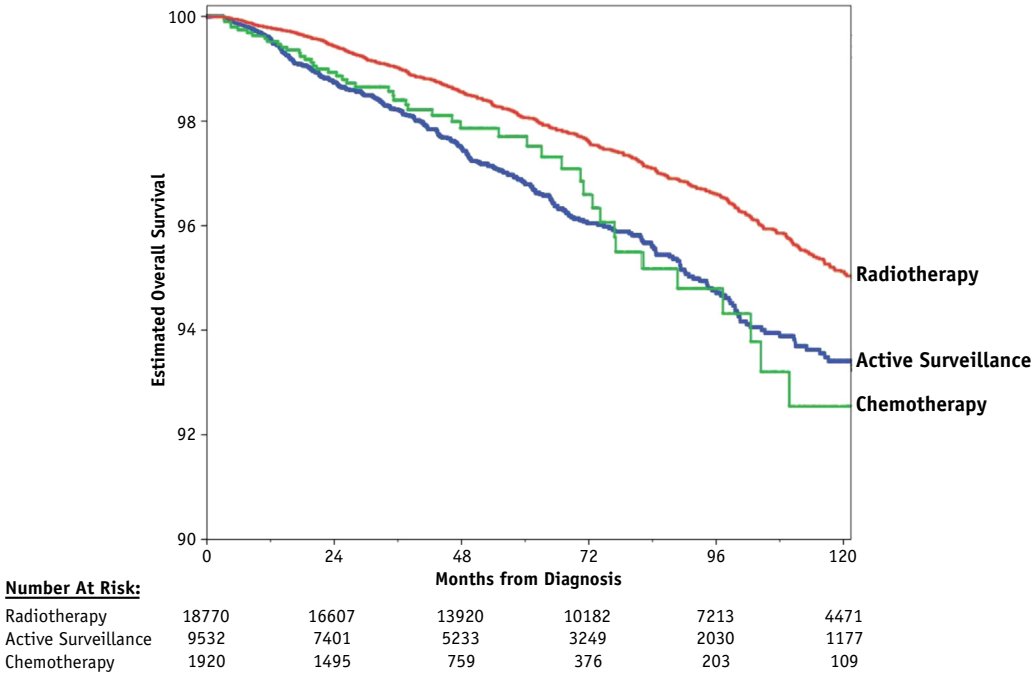

Fig. 2. Unadjusted Kaplan-Meier survival analysis.

node(s). Of the 33,094 patients identified, 32.5% received AS and 65.3% received AT (89.4% RT and 10.6% CT).

Trends in AS utilization

The proportion of patients receiving AS increased from 23% in 1998 to 60% in 2012 (Fig. 1A). The univariate analysis of factors associated with utilization of surveillance versus treatment can be found in Table 2. Factors independently associated with utilization of surveillance versus treatment on multivariate analysis included later year of diagnosis, lower facility volume, treatment at an academic center, increasing distance to home, living in a metropolitan area, increased residential area income, lower residential area high school graduation rate, facility region, lower T stage, smaller tumors, and negative surgical margins.

Trends in radiation versus chemotherapy utilization

Utilization of RT decreased from 73.2% in 1998 to 21.4% in 2012, mirrored by an increase in CT utilization from 1.6% to 17.3%. The univariate analysis of factors associated with utilization of RT versus CT can be found in Table E1 (available online at www.redjournal.org). Factors independently associated with utilization of RT versus CT on multivariate analysis included earlier year of diagnosis, private insurance, nonacademic center, facility region, lower T stage, and no pathologic examination of lymph nodes.

Radiation therapy dose

Radiation dose selection from 1998 to 2012 is described in Figure 1B. Utilization of low-dose RT peaked in the most recent year of analysis (2012) at 34%, up from a low of 1.5% in 1999, although it was not until 2010 that utilization of low-dose RT eclipsed 10%. Utilization of intermediate-dose RT remained in the range 73% to 81% from 1998 to 2011 and in 2012 dropped to 60%. Utilization of high-dose RT was highest in 1998 at 24% and lowest in 2012 at 5.9%. Univariate analysis of factors associated with the utilization of low-dose RT can be found in Table E2 (available online at www.redjournal.org). In multivariate analysis of factors significant on univariate analysis, factors predictive for low-dose RT included later year of diagnosis ($P<.0005$), treatment at an academic facility ($P<.0005$), and negative surgical margins ($P=.030$).

Survival outcomes

A Kaplan-Meier unadjusted survival analysis was performed (Fig. 2). At a median follow-up of 67 months the unadjusted 5- and 10-year OS rates were 96.8% (95% confidence interval [CI] 96.4%-97.2%) and 93.4% (95% CI 92.6%-94.2%) for the AS cohort versus 98.0% (95% CI 97.8%-98.2%) and 95.0% (95% CI 94.6%-95.4%) for the treatment cohort (log−rank $P<.0005$). When the treatment group was broken down into RT and CT the unadjusted 5- and 10-year OS rates were 98.1% (95% CI 97.9%-98.3%) and 95.1% (95% CI 94.7%-95.5%) versus 97.7% (95% CI 96.9%-98.5%) and 92.5% (95% CI 89.5%-95.5%) for RT and CT, respectively (log−rank $P=.003$). Statistically significant factors predictive for OS in a multivariate Cox proportional hazards model are detailed in Table 3.

Incorporating the propensity score for selection of AS versus AT into the multivariate Cox model resulted in a hazard ratio (HR) of 0.58 (95% CI 0.46-0.74; $P<.0005$) (Fig. 3A). This remained significant with a 6-month conditional landmark analysis (HR 0.59, 95% CI 0.46-0.76) to

Table 3 Unadjusted multivariable Cox proportional hazards model for overall survival (significant factors only)

Significant factor	Hazard of death (95% confidence interval)	*P*
Treatment strategy		<.0005
Active surveillance	Reference	
Chemotherapy	0.50 (0.29-0.85)	.011
Radiation therapy	0.60 (0.47-0.77)	<.0005
Age (y)		<.0005
≤30	Reference	
31-40	1.18 (0.79-1.76)	.412
41-50	2.13 (1.45-3.13)	<.0005
≥51	4.09 (2.78-6.01)	<.0005
Comorbidity score		<.0005
0	Reference	
1	1.81 (1.24-2.64)	.002
≥2	4.53 (2.38-8.64)	<.0005
Insurance status		<.0005
Private	Reference	
None	3.09 (2.15-4.43)	<.0005
Government	4.09 (3.12-5.35)	<.0005
% Without high school diploma (residential area)		.021
<7	Reference	
7-12.9	1.29 (0.93-1.79)	.122
13-20.9	1.59 (1.13-2.24)	.008
≥21	1.70 (1.17-2.48)	.006
Distance from facility to residence (mi)		.029
≤5	Reference	
5.1-10	1.57 (1.14-2.17)	.005
10.1-20	1.42 (1.02-1.99)	.039
>20	1.49 (1.06-2.08)	.022
Tumor size (cm)		.016
≤2	Reference	
2.1-4	0.85 (0.59-1.23)	.394
>4	1.27 (0.90-1.78)	.168
T Stage		.015
1	Reference	
2	1.41 (1.08-1.84)	.011
≥3	1.64 (0.96-2.81)	.070

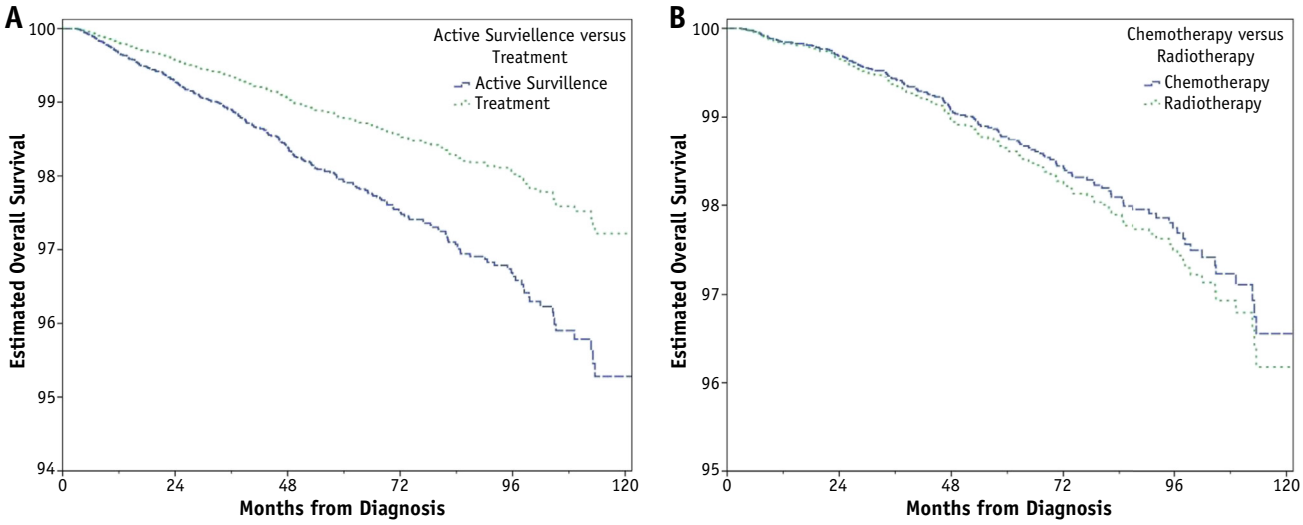

Fig. 3. Propensity score–adjusted overall survival probability on multivariate analysis. (A) Active surveillance versus treatment, and (B) radiation therapy versus chemotherapy.

account for potential immortal-time bias. Based on age, T stage, and tumor size, we were unable to identify a subset in which the propensity-adjusted survival curves overlapped or seemed to favor the surveillance group. The propensity-adjusted survival was similar between the RT and CT groups, with an HR of 0.90 (95% CI 0.51-1.58; $P = .715$) for CT (Fig. 3B).

There was no difference in survival between low-dose RT and intermediate/high-dose RT, with unadjusted 10-year OS of 93.7% (95% CI 89.5%-97.9%) versus 95.2% (95% CI 94.6%-95.8%), and a propensity-adjusted HR of 1.02 (95% CI 0.52-2.03; $P = .944$). Unadjusted Kaplan-Meier and propensity adjusted multivariate Cox survival plots were superimposable (data not shown).

Discussion

In this study we have shown that there has been a significant decline in the use of RT for stage I testicular seminoma from 1998 to 2012. At the same time, there has been a significant rise in both CT utilization and AS, such that in both 2011 and 2012, AS was the most common adjuvant management. Although radiation dose has decreased over time, incorporation of lower dosages has been slow, and there continues to be significant utilization of 30 Gy despite randomized evidence suggesting that this high of a dose is not necessary. Furthermore, the most commonly used dose continues to be in the intermediate range, with the most common fractionation schedule as 25.5 Gy in 17 fractions. There has not been a randomized trial comparing 25.5 Gy in 17 fractions with 20 Gy in 10 fractions, though these 2 fractionation schedules are similar radiobiologically. With the low side-effect rates seen at 20 Gy in 10 fractions, there is unlikely to be any benefit to delivering RT at 1.5 Gy per day instead of 2 Gy per day.

Paradoxically, patients in the uppermost quartile of residential area income had the highest rates of AS, as did those in the quartile with the lowest residential area high school graduation rate. This is likely the result of the interplay of health literacy with barriers to access to care. Likewise, patients who lived further from their treatment centers were more likely to receive AS, as were those who lived in metropolitan areas. Interestingly, even though minorities and patients without private insurance had an absolute 4% to 6% less likelihood of receiving surveillance, neither of these factors remained significant in the multivariate model, likely owing to the confounding influence of other sociodemographic factors that were significant in the multivariate model. Patients who were treated at an academic center were more likely to receive AS.

Radiation therapy was more frequently used than CT in Caucasians and those with private insurance. Radiation therapy was used less at centers with lower case volume. Chemotherapy was used more frequently with tumors of higher T stage and when there had been a pathologic assessment of lymph node(s). Chemotherapy was used more at academic centers.

With a median follow-up of 67 months, adjuvant treatment was associated with a small absolute survival advantage over AS (1.2% at 5 years and 1.6% at 10 years). Although this was statistically significant on multivariate analysis with propensity score adjustment for selection bias, the clinical relevance of this small survival advantage will undoubtedly be questioned. First, whether this survival advantage persists into the longer term is uncertain because the late effects of treatment could potentially bring survival curves back together or swing the pendulum all the way in favor of surveillance. Second, a potential explanation for this small survival benefit seen with treatment is that it was the result of bias from uncaptured variables. However, a more concerning possibility is that the rigorous follow-up

performed in trials or endorsed by clinical practice guidelines has not been strictly adhered to during the widespread adoption of AS and has thus compromised outcomes. Indeed, with our definition of AS as those who did not receive either CT or RT some patients may have received no tumor surveillance at all. In addition to adjuvant treatment, other factors associated with longer survival included younger age, lower comorbidity score, private insurance, living in an area with higher high school graduation rates, living closer to the treatment hospital, smaller tumor size (<4 cm), and lower T stage.

Other groups have looked into factors predictive of treatment decisions in stage I testicular seminoma. Hoffman et al (34) published a Surveillance, Epidemiology, and End Results analysis from 1990 to 2004 and showed a declining use of adjuvant RT. Gary et al (35) published an NCDB analysis looking at management trends and factors influencing those trends. Our findings were in line with these previously published analyses but augment the published body of knowledge by providing more recent data and numerous additional sociodemographic and pathologic variables, as well as radiation dose data and survival data, both of which were not described in the aforementioned publications.

The limitations to our study are similar to those of any retrospective national dataset. In particular, our follow-up period was limited, with a median follow-up of 67 months, making it impossible to draw conclusions on the long-term effects of treatment. Recurrence rates and subsequent salvage treatment are not captured by the NCDB, leaving OS as the only measurable clinical outcome. Without this information we are unable to calculate a disease-specific survival, which would be critically important in helping to understand the small absolute survival difference seen in this study. There is no information as to which CT regimen a patient received. Rete testis invasion and lymphovascular invasion were both poorly coded and only available for a small subset of patients and thus not included in our analysis. Only generalized ZIP code−based sociodemographic data were available for education level and income level, rather than patient-specific data. Despite these limitations, the vast depth of data captured nationwide by the NCDB allows for powerful analysis of management trends, and even the suggestion of a survival difference reinforces the importance of firm adherence to recommended AS follow-up regimens.

In conclusion, we have demonstrated a rapid increase in the utilization of AS and adjuvant CT, mirrored by a decrease in adjuvant RT utilization for stage I seminoma patients. Despite randomized evidence, radiation oncologists have been slow to adopt 20 Gy as a standard dose for stage I seminoma patients. We have also shown that in this large cohort of patients, there was a small absolute survival advantage during the first 10 years of diagnosis for those who received adjuvant treatment.

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