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Original Article

Stage II Testicular Seminoma: Patterns of Care and Survival by Treatment Strategy☆

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Abstract

Aims: Stage II testicular seminoma is highly curable with radiotherapy or multi-agent chemotherapy (MACT). These modalities have not been compared in a randomised manner.

Materials and methods: Using the US National Cancer Data Base, we identified 2437 stage II seminoma patients (IIA = 960, IIB = 812, IIC = 665) treated with orchiectomy and either radiotherapy or MACT from 1998 to 2012. Factors affecting treatment modality (radiotherapy versus MACT) were studied using multivariable logistic regression. Propensity scores for treatment selection were incorporated into multivariable Cox regression analyses of overall survival.

Results: The median follow-up was 65 months (interquartile range 34–106). Rates of radiotherapy utilisation were: IIA = 78.1%, IIB = 54.4%, IIC = 4.2%. Rates of MACT utilisation were: IIA = 21.9%, IIB = 45.6%, IIC = 95.8%. For both IIA and IIB patients, later year of diagnosis, academic treatment facility and pathological confirmation of lymph node positivity were associated with increased utilisation of MACT. Also predictive for preferential utilisation of MACT were comorbidity score ≥ 1 and non-private insurance for IIA patients and T stage ≥ 2 for IIB patients. For IIA patients, survival was improved with radiotherapy compared with MACT with a 5 year survival of 99.0% (95% confidence interval 98.2–99.8) versus 93.0% (95% confidence interval 89.0–97.0). This advantage persisted on propensity-adjusted multivariate analysis (hazard ratio 0.28; 95% confidence interval 0.09–0.86; $P = 0.027$). For IIB patients, 5 year survival was 95.2% (95% confidence interval 92.8–97.6) for radiotherapy and 92.4% (95% confidence interval 89.2–95.6) for MACT (Log-rank $P = 0.041$), with no significant difference on multivariable analysis.

Conclusions: Radiotherapy is associated with improved survival over MACT for IIA patients, with no significant survival difference for IIB patients.

Key words: Chemotherapy; NCDB; patterns of care; radiotherapy; stage II; testicular seminoma

Introduction

Testicular seminoma is the most common solid tumour in men in their third or fourth decade of life, with about 70–80% diagnosed with stage I disease, 15–20% with stage II disease and less than 5% with more disseminated disease [1,2]. As this represents the most curable solid malignancy, recent efforts have focused on decreasing toxicity related to treatment, with active surveillance becoming the preferred treatment strategy after radical orchiectomy for stage I disease. Radiotherapy was historically the preferred treatment for stage II patients. For those with stage IIA–IIB disease (nodal disease $\leq$5 cm) treatment with radiotherapy has resulted in relapse-free survival rates of 90–95% and disease-specific survival approaching 100%, as even the rare patients suffering with relapse are highly salvageable with chemotherapy [3–6]. However, relapse rates for stage IIC disease (nodal disease >5 cm) treated with radiotherapy have been reported to be 25–55% [3,4,7], with most relapses being distant. Although, studies of more extensive radiotherapy fields lowered rates of relapse for stage IIC patients (10–20%), such treatment is no longer standard due to concerns of toxicity and the efficacy of chemotherapy [8,9]. Indeed, chemotherapy has been evaluated as an alternative to radiotherapy, with similar appearing efficacy

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in those with non-bulky disease and improved outcomes in those with stage IIC disease [2,10,11].

There is little controversy as to the preferred role of chemotherapy for those with stage IIC disease [7,10–12]. However, for patients with non-bulky nodal disease, significant controversy as to ideal treatment exists [11]. Radiotherapy and chemotherapy have never been prospectively compared for stage II seminoma. This controversy is reflected in consensus national guidelines with the National Comprehensive Cancer Network recommending radiotherapy as the preferred treatment for stage IIA, whereas European Association of Urology (EAU) guidelines equally allow for radiotherapy or chemotherapy. Both guidelines are equivocal for stage IIB and recommend chemotherapy for stage IIC. Other treatment strategies for stage II seminoma, such as single-agent carboplatin, have been shown to be inferior [13] or remain investigational, as is the case with combination carboplatin plus radiotherapy [14,15].

Due to the rarity of stage II seminoma, a sufficiently powered randomised trial comparing radiotherapy with chemotherapy is unlikely to be completed. Given the paucity of level I evidence and shifting treatment paradigms, we sought to analyse factors predicative for the utilisation of radiotherapy versus multi-agent chemotherapy (MACT) and corresponding overall survival among stage II seminoma patients on a national level using a hospital-based registry.

Materials and Methods

Data Source

Using de-identified data exempt from Institutional Review Board oversight, we queried the US National Cancer Data Base (NCDB) of testicular cancer patients from 1998 to 2012. The NCDB is a joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons. It is a nationwide, facility-based, tumour surveillance data set that encompasses more than 1500 hospitals and captures 70% of all newly diagnosed malignancies in the USA [16,17]. 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.

Patient Selection

Of the 80 385 patients in the original NCDB testicular cancer database, 2437 stage II seminoma patients who had undergone orchiectomy followed by either MACT or radiotherapy within 3 months of diagnosis were identified, as summarised in the CONSORT diagram (Figure S1). All patients were newly diagnosed between 1 January 1998 and 31 December 2012. All patients were between the ages of 18 and 90 years.

Table 1
Baseline characteristics ($n = 2437$)

Baseline characteristics	*n* (%)
Sociodemographic factors	
Year of diagnosis	
1998–2001	618 (25.4)
2002–2005	643 (26.4)
2006–2009	656 (26.9)
2010–2012	520 (21.3)
Age	
< 40 years	1350 (55.4)
≥ 40 years	1087 (44.6)
Charlson-Deyo comorbidity score	
0	1565 (64.2)
≥1	103 (4.2)
Unknown	769 (31.6)
Race	
White	2264 (92.9)
Non-White	142 (5.8)
Unknown	31 (1.3)
Insurance status	
Private	1791 (73.5)
Government	315 (12.9)
None	271 (11.1)
Unknown	60 (2.5)
Residential setting	
Metropolitan	2001 (82.1)
Urban	358 (14.7)
Unknown	78 (3.2)
Median income (residential area)	
<$38 000	337 (14.1)
$38 000–47 999	518 (21.6)
$48 000–62 999	690 (28.8)
≥ $63 000	849 (35.5)
Unknown	43 (1.8)
% without high school degree (residential area)	
< 7%	676 (27.7)
7–12.9%	816 (33.5)
13–20.9%	559 (22.9)
≥ 21%	346 (14.2)
Unknown	40 (1.6)
Distance from facility to residence	
< 10 miles	1292 (53.0)
≥ 10 miles	1108 (45.5)
Unknown	37 (1.5)
Facility type	
Community/comprehensive community	1600 (65.7)
Academic/research	834 (34.2)
Unknown	3 (0.1)
Facility location	
Northeast	516 (21.2)
South	691 (28.4)
Midwest	771 (31.6)
West	459 (18.8)
Facility volume	
< 5 cases	1190 (48.8)
≥ 5 cases	1247 (51.2)
Pathological factors	
T stage	
1	1353 (55.5)
2	745 (30.6)
≥ 3	210 (8.6)
Unknown	129 (5.3)

Table 1 (*continued*)

Baseline characteristics	*n* (%)
Tumour size	
< 4 cm	741 (30.4)
≥ 4 cm	1428 (58.6)
Unknown	268 (11.0)
Nodal Stage	
1	960 (39.4)
2	812 (33.3)
3	665 (27.3)
Surgical margins	
Negative	2172 (89.1)
Positive	86 (3.5)
Unknown	179 (7.3)
Pathologic confirmation of nodal positivity	
Yes	349 (14.3)
No	2037 (83.6)
Unknown	62 (2.1)
Therapeutic factors	
Treatment	
Multi-agent chemotherapy	1217 (49.9)
Radiotherapy	1220 (50.1)

Definition of Variables

Race was defined as White or non-White. Insurance status was grouped as private, government (including Medicare, Medicaid, other government) or not insured. Residential setting was based on 2013 US Department of Agriculture Rural-Urban Continuum codes with 'metropolitan' for counties in 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 less than 2500. The patient's zip code and 2008–2012 American Community Survey data were used to determine residential area median income quartiles and high school graduation rates. Distance from residence to facility was defined from the centre of the patient's zip code to the treating facility's mailing address. 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; West: AZ, AK, CA, CO, ID, HI, MT, NM, NV, OR,UT, WA, WY.

Statistical Analysis

IBM SPSS version 22 (IBM cooperation, Armonk, NY, USA) was used for data analysis. An exploratory univariate analysis of factors potentially predictive for radiotherapy versus MACT was carried out using a Chi-squared test separately for stage IIA and IIB patients. For each of these two 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. Given that there was essentially no variation in treatment for IIC patients, no such analysis predictive of treatment selection was completed; however, IIC patients were included to provide patterns of care and survival data in a large national cohort.

Overall survival was calculated 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, with Log-rank tests used to test the unadjusted overall survival for statistical significance. Cox proportional hazards modelling was used for multivariable survival analyses. Only factors significant on univariate analysis were entered with backwards conditional selection ($P < 0.10$ for inclusion). To adjust for potential selection bias between groups, a propensity score was calculated for each patient reflective of the probability of having received radiotherapy versus MACT based on the multivariate logistic regression [18]. Propensity scores were binned into quintiles and validated by assessment of standardised differences between treatment groups (<0.10 for validation). The propensity score was then incorporated as a continuous covariate into a multivariable Cox regression analysis of overall survival using backwards conditional selection ($P < 0.10$ for inclusion). In order to prevent overcorrection, factors incorporated into the model used to generate the propensity score were excluded from the final Cox model. The treatment effect was confirmed using sensitivity analyses excluding covariates with more than 5% missing values and time-biased covariates (results not shown). Statistical significance was defined as an alpha level of less than 0.05.

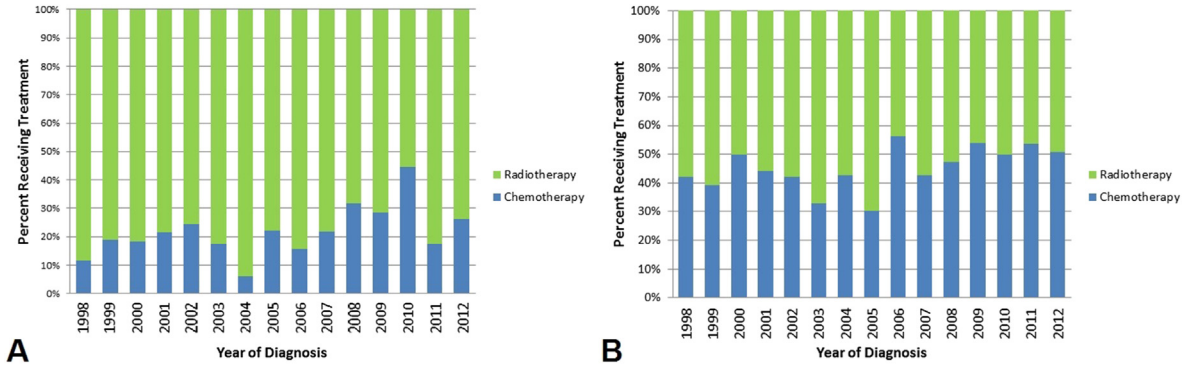

Fig 1. Trends in treatment selection over time: (A) stage IIA, (B) stage IIB.

Table 2
Comparative utilisation of multi-agent chemotherapy versus radiotherapy for stage IIA seminoma by baseline characteristics

	Chemotherapy ($n = 210$)	Radiotherapy ($n = 750$)	Odds ratio	95% confidence interval	*P*
Sociodemographic factors					
Year of diagnosis*					0.005
1998–2001	41 (17.4%)	194 (82.6%)	1	Reference	
2002–2005	44 (17.4%)	209 (82.6%)	1.00	0.63–1.60	
2006–2009	63 (24.2%)	197 (75.8%)	0.66	0.43–1.03	
2010–2012	62 (29.2%)	150 (70.8%)	0.51	0.33–0.80	
Age					0.290
< 40 years	132 (23.0%)	441 (77.0%)	1	Reference	
≥ 40 years	78 (20.2%)	309 (79.8%)	1.19	0.86–1.63	
Charlson–Deyo comorbidity score*					<0.0005
0	138 (21.7%)	497 (78.3%)	1	Reference	
1+	18 (48.6%)	19 (51.4%)	0.29	0.15–0.57	
Race					0.514
White	194 (21.6%)	704 (78.4%)	1	Reference	
Non-White	13 (25.5%)	38 (74.5%)	0.81	0.42–1.54	
Insurance status*					0.006
Private	145 (19.8%)	588 (80.2%)	1	Reference	
Government	37 (33.0%)	75 (67.0%)	0.50	0.32–0.77	
None	21 (25.0%)	63 (75.0%)	0.74	0.44–1.25	
Residential setting					0.371
Metropolitan	177 (22.3%)	618 (77.7%)	1	Reference	
Non-Metropolitan	25 (18.8%)	108 (81.2%)	1.24	0.78–1.97	
Median income (residential area)					0.004
<$38 000	42 (32.8%)	86 (67.2%)	1	Reference	
$38 000–47 999	29 (15.3%)	160 (84.7%)	2.69	1.57–4.63	
$48 000–62 999	61 (21.5%)	223 (78.5%)	1.79	1.12–2.84	
≥$63 000	75 (21.7%)	271 (78.3%)	1.76	1.13–2.77	
% without high school degree (residential area)					0.208
<7%	60 (21.3%)	222 (78.7%)	1	Reference	
7–12.9%	55 (18.3%)	245 (81.7%)	1.20	0.80–1.81	
13–20.9%	59 (25.4%)	173 (74.6%)	0.79	0.53–1.19	
≥21%	33 (24.6%)	101 (75.4%)	0.83	0.51–1.34	
Distance from facility to residence					0.627
<10 miles	112 (21.3%)	415 (78.7%)	1	Reference	
≥10 miles	95 (22.6%)	326 (77.4%)	0.93	0.68–1.26	
Facility type*					<0.0005
Community/comprehensive community	113 (17.9%)	519 (82.1%)	1	Reference	
Academic/research	96 (29.4%)	231 (70.6%)	0.52	0.38–0.72	
Facility location					0.052
Northeast	47 (22.9%)	158 (77.1%)	1	Reference	
South	74 (26.6%)	204 (73.4%)	0.82	0.54–1.25	
Midwest	50 (17.1%)	243 (82.9%)	1.45	0.93–2.26	
West	39 (21.2%)	145 (78.8%)	1.11	0.68–1.79	
Facility volume					0.429
< 5 cases	107 (23.0%)	359 (77.0%)	1	Reference	
≥ 5 cases	103 (20.9%)	391 (79.1%)	1.13	0.83–1.54	
Pathological factors					
T stage					<0.0005
1	110 (19.1%)	465 (80.9%)	1	Reference	
2	67 (22.9%)	226 (77.1%)	0.80	0.57–1.12	
≥ 3	26 (41.9%)	36 (58.1%)	0.33	0.19–0.57	
Tumour size					0.362
< 4 cm	70 (22.5%)	241 (77.5%)	1	Reference	
≥ 4 cm	113 (19.9%)	455 (80.1%)	1.17	0.84–1.64	
Surgical margins					0.044
Negative	174 (20.2%)	687 (79.8%)	1	Reference	
Positive	11 (35.5%)	20 (64.5%)	0.46	0.22–0.98	

Table 2 (*continued*)

	Chemotherapy ($n = 210$)	Radiotherapy ($n = 750$)	Odds ratio	95% confidence interval	*P*
Pathological confirmation of nodal positivity*					<0.0005
Yes	54 (57.4%)	40 (42.6%)	1	Reference	
No	150 (17.6%)	704 (82.4%)	6.34	4.06–9.89	

* Variable was significant on multivariable analysis and used to generate propensity score.

Results

Baseline Characteristics

Patient characteristics can be found in Table 1. The median age was 37 years, with an interquartile range (IQR) of 31–45. By stage, there were 960 IIA, 812 IIB and 665 IIC patients. Excluding unknowns, most patients were White (94%), had private insurance (75%), lived in a metropolitan area (85%), had a T1 primary (59%), had a primary tumour 4 cm or greater in size (66%) and had negative surgical margins (96%). Only 15% had pathological confirmation of nodal positivity. Overall for the 2437 patients identified, utilisation of radiotherapy and MACT was nearly evenly split. However, utilisation varied significantly by stage, with 78.1% of IIA, 54.4% of IIB and 4.2% of IIC having received radiotherapy. The median radiotherapy dose was 30.9 Gy (IQR 25.5–35.5) for stage IIA patients and 35.5 Gy (IQR 31.1–36.0) for stage IIB patients.

Trends in Radiation versus Chemotherapy Utilisation

Utilisation of radiotherapy decreased over time for both stage IIA and IIB patients, mirrored by an increase in the utilisation of MACT (with year of diagnosis as a continuous variable: IIA $P = 0.001$, IIB $P = 0.016$), as shown in Figure 1. The univariate analysis of factors associated with utilisation of radiotherapy versus MACT can be found in Table 2 for stage IIA patients and in Table 3 for stage IIB patients. Factors independently associated with utilisation of MACT over radiotherapy on multivariate analysis included later year of diagnosis, treatment at an academic facility and pathological confirmation of nodal positivity for both stage IIA and IIB patients. Also predictive for preferential utilisation of MACT were a Charlson-Deyo comorbidity score of 1+ and non-private insurance for stage IIA patients and T stage of 2+ for stage IIB patients.

Survival Outcomes

With a median follow-up of 65 months (IQR 34–106) the unadjusted 5 year survival by stage was: IIA = 97.1% (95% confidence interval 96.1–98.1), IIB = 93.9% (95% confidence interval 92.1–95.7) and IIC = 92.6% (95% confidence interval 90.6–94.6); Log-rank $P = 0.006$. Factors predicative of improved survival on multivariable analysis included age < 40 years, private insurance and comorbidity score of zero (Table 4). An univariate plot of overall survival by stage and treatment is given in Figure 2A. For stage IIA patients, overall survival was improved with radiotherapy compared with MACT, with a 5 year survival of 99.0% (95% confidence interval 98.2–99.8) versus 93.0% (95% confidence interval 89.0–97.0). This advantage persisted on multivariable analysis, with a hazard ratio of 0.22 (95% confidence interval 0.08–0.64, $P = 0.005$) and a propensity-adjusted hazard ratio of 0.28 (95% confidence interval 0.09–0.86, $P = 0.027$) (Figure 2B). For IIB patients, 5 year survival was 95.2% (95% confidence interval 92.8–97.6) for radiotherapy and 92.4% (95% confidence interval 89.2–95.6) for MACT (Log-rank $P = 0.041$). This was not statistically significant on multivariable analysis, with a hazard ratio of 0.74 (95% confidence interval 0.32–1.70, $P = 0.475$) and a propensity-adjusted hazard ratio of 0.77 (95% confidence interval 0.33–1.80, $P = 0.549$) (Figure 2C).

Discussion and Conclusions

In the largest published series of stage II testicular seminoma patients to date, we have shown strong adherence to published guidelines for stage IIC patients in that the overwhelming majority (96%) received MACT as opposed to radiotherapy. For non-bulky patients, for whom there is a lack of consensus as to the optimal treatment approach, we have reported on factors associated with treatment decision and have shown a small, but significant, trend away from treatment with radiotherapy in favour of MACT from 1998 to 2012. This trend was associated with a decreased 5 year overall survival for stage IIA patients, even after adjusting for all available indication bias, but resulted in no significant difference in overall survival for stage IIB patients. Potential explanations for the associated survival advantage seen with radiotherapy in stage IIA seminoma include better local control with radiotherapy, toxicities associated with MACT and the potential for incomplete treatment with MACT due to both the tolerability of the regimen and the comfortability of oncologists in treating this rare condition [19–21]. The increased risk of micrometastic disease outside the typical radiation fields for those with stage IIB disease probably increases the relative efficacy of MACT compared with radiotherapy in this subset, and could account for the similar overall survival seen for stage IIB patients. The decreased rate of radiotherapy utilisation for stage II seminoma patients is not unique to the USA [22].

The fear of late sequela, in particular second malignancies, gastrointestinal and cardiovascular events, is often

Table 3
Comparative utilisation of multi-agent chemotherapy versus radiotherapy for stage IIB seminoma by baseline characteristics

	Chemotherapy ($n = 370$)	Radiation ($n = 442$)	Odds ratio	95% confidence interval	*P*
Sociodemographic factors					
Year of diagnosis*					0.010
1998–2001	85 (43.1%)	112 (56.9%)	1	Reference	
2002–2005	72 (36.7%)	124 (63.3%)	1.31	0.87–1.96	
2006–2009	117 (50.2%)	116 (49.8%)	0.75	0.51–1.10	
2010–2012	96 (51.6%)	90 (48.4%)	0.71	0.48–1.06	
Age					0.306
< 40 years	210 (47.2%)	235 (52.8%)	1	Reference	
≥ 40 years	160 (43.6%)	207 (56.4%)	1.16	0.88–1.53	
Charlson-Deyo comorbidity score					0.287
0	248 (47.3%)	276 (52.7%)	1	Reference	
1+	18 (39.1%)	28 (60.9%)	1.40	0.75–2.59	
Race					0.738
White	342 (46.0%)	402 (54.0%)	1	Reference	
Non-White	24 (43.6%)	31 (56.4%)	1.10	0.63–1.91	
Insurance status					0.486
Private	269 (44.3%)	338 (55.7%)	1	Reference	
Government	51 (48.6%)	54 (51.4%)	0.84	0.56–1.28	
None	43 (50.0%)	43 (50.0%)	0.80	0.51–1.25	
Residential setting					0.341
Metropolitan	310 (46.3%)	360 (53.7%)	1	Reference	
Non-Metropolitan	49 (41.5%)	69 (58.5%)	1.21	0.82–1.80	
Median income (residential area)					0.392
<$38 000	53 (45.7%)	63 (54.3%)	1	Reference	
$38,000–47 999	70 (40.2%)	104 (59.8%)	1.25	0.78–2.01	
$48,000–62 999	101 (47.9%)	110 (52.1%)	0.92	0.58–1.44	
≥ $63 000	141 (47.8%)	154 (52.2%)	0.92	0.60–1.41	
% without high school degree (residential area)					0.059
<7%	100 (44.2%)	126 (55.8%)	1	Reference	
7–12.9%	117 (42.2%)	160 (57.8%)	1.09	0.76–1.55	
13–20.9%	87 (46.3%)	101 (53.7%)	0.92	0.62–1.36	
≥21%	61 (57.5%)	45 (42.5%)	0.59	0.37–0.93	
Distance from facility to residence					0.649
< 10 miles	201 (46.4%)	232 (53.6%)	1	Reference	
≥ 10 miles	164 (44.8%)	202 (55.2%)	1.07	0.81–1.41	
Facility type*					0.011
Community/comprehensive community	226 (42.2%)	309 (57.8%)	1	Reference	
Academic/research	142 (51.6%)	133 (48.4%)	0.69	0.51–0.92	
Facility location					0.595
Northeast	84 (49.7%)	85 (50.3%)	1	Reference	
South	111 (45.9%)	131 (54.1%)	1.17	0.79–1.73	
Midwest	114 (43.0%)	151 (57.0%)	1.31	0.89–1.93	
West	61 (44.9%)	75 (55.1%)	1.22	0.78–1.91	
Facility volume					0.318
< 5 cases	177 (43.8%)	227 (56.2%)	1	Reference	
≥ 5 cases	193 (47.3%)	215 (52.7%)	0.87	0.66–1.15	
Pathological factors					
T stage*					0.008
1	175 (40.2%)	260 (59.8%)	1	Reference	
2	125 (49.0%)	130 (51.0%)	0.70	0.51–0.96	
≥ 3	48 (55.8%)	38 (44.2%)	0.53	0.33–0.85	
Tumour size					0.167
< 4 cm	105 (49.5%)	107 (50.5%)	1	Reference	
≥ 4 cm	223 (43.9%)	285 (56.1%)	1.25	0.91–1.73	
Surgical margins					0.038
Negative	323 (43.9%)	412 (56.1%)	1	Reference	
Positive	18 (64.3%)	10 (35.7%)	0.44	0.20–0.96	

Table 3 (*continued*)

	Chemotherapy ($n = 370$)	Radiation ($n = 442$)	Odds ratio	95% confidence interval	*P*
Pathological confirmation of nodal positivity*					<0.0005
Yes	78 (63.9%)	44 (36.1%)	1	Reference	
No	284 (42.3%)	388 (57.7%)	2.42	1.62–3.61	

* Variable was significant on multivariable analysis and used to generate propensity score.

quoted as a motivational factor in reducing or eliminating radiotherapy from a treatment regimen in early-stage seminoma. This approach seems reasonable in certain situations, including stage I seminoma, where radiotherapy can be replaced with active surveillance [23,24]. Although there is little debate that treatment with radiotherapy increases risks of long-term morbidity/mortality [25–27], the notion that pelvic and para-aortic radiotherapy to a dose of 30–36 Gy carries a greater risk of morbidity/mortality than three to four cycles of MACT does not seem to be supported by the literature [5,11,28–32]. This is despite the bias of this body of literature against radiotherapy due to longer follow-up with radiotherapy and the antiquated radiotherapy techniques used and does not account for the ability of modern limited radiotherapy fields and techniques to widen the therapeutic ratio [33,34]. For example, in an analysis of 40 576 testicular cancer patients with 2285 second solid malignancies, Travis *et al.* [28] showed no statistically significant difference in risk between those who received radiotherapy alone versus chemotherapy alone (relative risk = 2.0 versus 1.8). Likewise, van den Belt-Dusebout *et al.* [30] reported on a cohort of 2707 testicular cancer patients with a median follow-up of 17.6 years and found a combined relative risk of second malignancy or cardiovascular disease of 1.8 after radiotherapy and 1.9 after chemotherapy.

Aside from more recent year of diagnosis, consistently across stage IIA and IIB subgroups MACT was favoured over radiotherapy for patients treated at academic treatment facilities and those undergoing pathological nodal assessment. A similar underutilisation of radiotherapy at academic treatment facilities has been noted in other hospital registry-based analyses [35] and may speak towards an increasing non-evidence based bias towards integration of novel therapies at such treatment facilities. Alternatively, patients at academic centres may have more advanced disease or unfavourable risk factors and thus be more likely to receive systemic therapy. Why patients who have had pathological confirmation of nodal positivity experience preferential use of MACT is less clear, but could be related to confounding variables such as size of lymph node, number of involved nodes and type of treatment facility. For stage IIA patients, MACT was increasingly implemented for those with higher comorbidity scores ($\geq$1), whereas for stage IIB patients there was a trend towards increased radiotherapy utilisation for patients with increased comorbidity scores. This is reflective of the overall tolerability of both MACT and radiotherapy [11,22]. Younger age and decreasing comorbidity score were predictive of improved survival as would be expected for a cohort of stage II seminoma with an expected high overall cancer-specific survival. Decreased survival for non-private insurance patients across stage II seminoma cohorts on multivariate analysis speaks to shortcomings in access to care in the USA and its potential strong negative impact on cancer cure rates; a trend also contemporaneously noted in other highly curable malignancies that afflict young otherwise healthy patients such as Hodgkin's lymphoma [36].

The limitations to our study have similarities to those of any retrospective national dataset, including potential

Table 4
Unadjusted multivariable Cox proportional hazard models for overall survival for all stage II seminoma patients

Significant factors	Hazard of death (95% confidence interval)	*P* value
Treatment strategy		0.059
Multi-agent chemotherapy	Reference	
Radiotherapy	0.58 (0.33–1.02)	
Age		0.049
< 40 years	Reference	
≥ 40 years	1.75 (1.00–3.06)	
Comorbidity score		0.001
0	Reference	
≥ 1	3.16 (1.56–6.40)	
Insurance status		<0.0005
Private	Reference	
None	2.87 (1.37–6.03)	
Government	4.30 (2.36–7.84)	

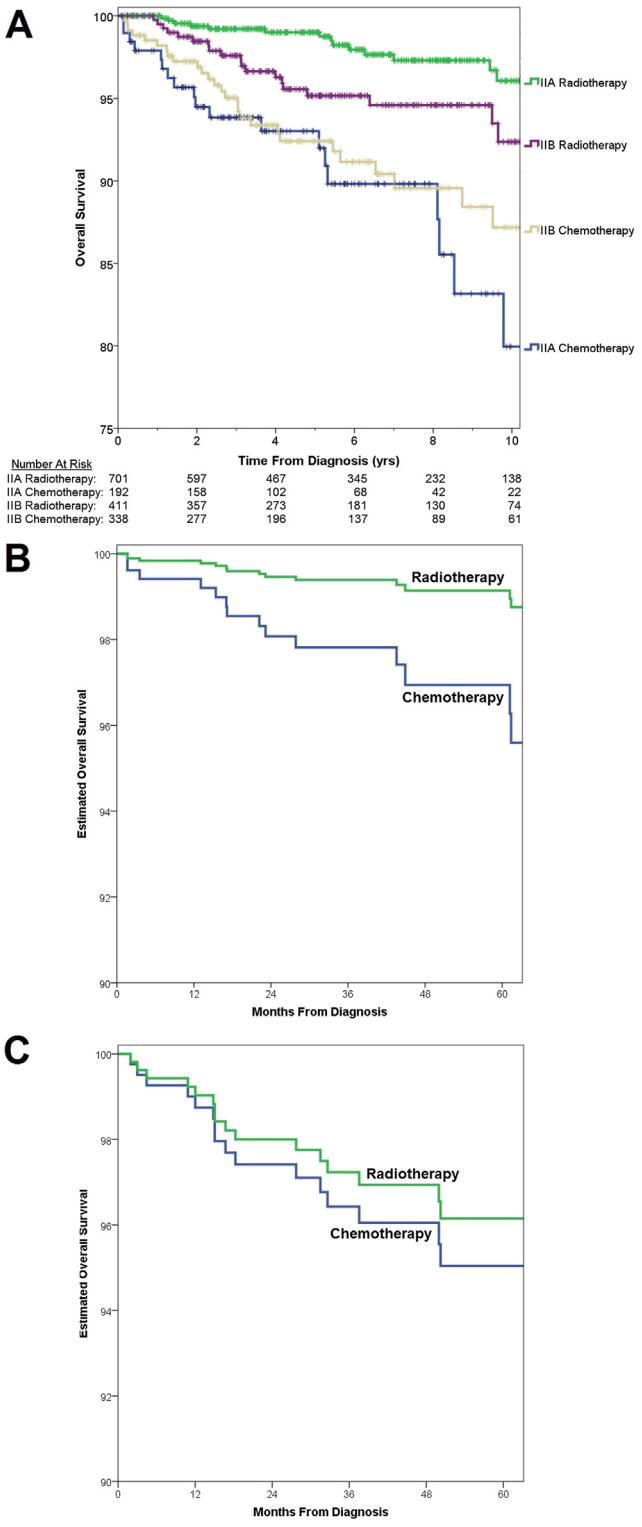

Fig 2. (A) Unadjusted Kaplan–Meier survival analysis by stage and treatment, (B) propensity score-adjusted overall survival probability on multivariate analysis for stage IIA, (C) propensity score-adjusted overall survival probability on multivariate analysis for stage IIB.

ascertainment bias and the inability to confirm results with individual patient data. Additionally, unobserved confounding variables potentially limit the analysis as there is no information as to specific comorbidities, extent of staging work-up, which chemotherapy regimen a patient received (i.e. Bleomycin Etoposide and Cisplatin (BEP) versus etoposide and cisplatin (EP)), number of cycles of chemotherapy, nor adherence to the chemotherapy regimen. This bias was reduced by excluding patients who received single-agent chemotherapy. Recurrence rates, subsequent treatment and cause of death are not captured by the NCDB, leaving relapse-free survival and disease-free survival incalculable and overall survival as the only measurable clinical outcome. Only non-specific zip code-based sociodemographic data were provided for education level and income level, rather than patient-specific data. Specific information related to the number of enlarged nodes and precise size of each was unavailable, which may bias the results of stage IIB patients in favour of radiotherapy if indeed patients with lower volume disease were more likely to receive radiotherapy and patients with higher volume disease were more likely to receive MACT. As with any large retrospective review most patients in this dataset were unlikely to have undergone a centralised pathological review. Although every attempt was made to exclude non-seminomatous histology based on pathological description and alpha-fetoprotein level, some patients' pathology may have been characterised differently had a centralised pathological review been carried out. Lastly, as these patients have excellent overall survival, we cannot exclude the potential for long-term toxicities leading to a convergence of the survival curves with extended follow-up. Despite these limitations, the large sample size and extensive data provided by the NCDB allow for an important analysis of outcomes and treatment trends that would otherwise not be possible.

In conclusion, we have shown a slow shift in the USA away from radiotherapy and towards MACT in the treatment of stage IIA/IIB testicular seminoma. For stage IIA patients, this was despite radiotherapy being associated with a small absolute survival advantage and being the preferred treatment modality by the National Comprehensive Cancer Network. Based on our findings, we would advocate for radiotherapy continuing to be the preferred treatment for stage IIA patients and for a risk-adapted approach for stage IIB patients where those with lower volume or solitary IIB disease receive radiotherapy and those with higher volume or multiple IIB nodes receive MACT.

Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.clon.2016.02.008.

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