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Radiation therapy improves survival in patients with testicular diffuse large B-cell lymphoma

Jennifer C. Ho[a], **Bouthaina S. Dabaja**[a], **Sarah A. Milgrom**[a], **Grace L. Smith**[a], **Jay P. Reddy**[a], **Ali Mazloom**[b], **Ken H. Young**[c], **Lijuan Deng**[c], **L. Jeffrey Medeiros**[c], **Wenli Dong**[d], **Pamela K. Allen**[a], **Therese Y. Andraos**[a], **Nathan H. Fowler**[e], **Loretta J. Nastoupil**[e], **Yasuhiro Oki**[e], **Luis E. Fayad**[e], **Francesco Turturro**[e], **Sattva S. Neelapu**[e], **Jason Westin**[e], **Fredrick B. Hagemeister**[e], **Maria Alma Rodriguez**[e], and **Chelsea C. Pinnix**[a]

[a]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[b]Tacoma Valley Radiation Oncology, Tacoma, WA, USA

[c]department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[d]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[e]Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Abstract

In 120 Stage I–IV testicular diffuse large B-cell lymphoma (DLBCL) patients treated from 1964 to 2015, we assessed the benefits of prophylactic contralateral testicular radiation (RT) and prophylactic central nervous system (CNS) therapy on overall, progression free, testicular relapse free, and CNS relapse free survival (OS, PFS, TRFS, and CRFS, respectively). Seventy percent of patients received RT, 53% received anthracyclines and rituximab (modern therapy), and 61% received CNS prophylaxis. On univariate analysis RT was associated with improved TRFS, PFS, and trended toward improved OS. On multivariate analysis (MVA), RT was significantly associated with improved OS and PFS; the PFS benefit persisted among patients receiving modern therapy. CNS prophylaxis was associated with improved OS, PFS, and TRFS, but not CRFS on univariate analysis, and was not significant on MVA. RT is associated with improved survival, and should be considered for all testicular DLBCL patients, but additional strategies are needed to prevent CNS relapse.

CONTACT Chelsea C. Pinnix, CCPinnix@mdanderson.org, Department of Radiation Oncology, Unit 97, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA.

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Keywords

Testicular; lymphoma; radiation therapy; intrathecal chemotherapy; rituximab

Introduction

Primary testicular diffuse large B-cell lymphoma (DLBCL) represents 80–90% of all testicular lymphomas and is the most common testicular malignancy in men over the age of 50 years [1]. Nevertheless, testicular DLBCL is quite rare, representing 0.6% of all non-Hodgkin lymphomas [2]. Overall, the prognosis is poor, with a continuous risk of late relapses at extranodal sites, including the central nervous system (CNS) and contralateral testis.

Evidence regarding the optimal treatment of patients with testicular DLBCL is limited. The modern standard of care is radical unilateral orchiectomy followed by doxorubicin-based chemotherapy. Since the addition of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy resulted in a survival benefit in DLBCL patients, this regimen was also adopted for the management of testicular DLBCL [3–5]. Because of the risk of CNS relapse, CNS prophylaxis with intrathecal chemotherapy or high-dose systemic methotrexate has also become a component of standard therapy [6].

Another sanctuary site at risk for relapse is the contralateral testis, with one series showing a risk of 15% at 3 years and 42% at 15 years in the absence of radiation therapy (RT) [7]. Prophylactic RT to the contralateral testis is thus often recommended but has not been well studied, particularly in the modern era of rituximab and anthracycline-based chemotherapy [8].

In this study, we sought to examine the influence of prophylactic testicular RT and prophylactic CNS therapy on survival outcomes and patterns of relapse among patients with primary testicular DLBCL at a single institution over the course of several decades.

Materials and methods

Patient selection

After approval by our institutional review board, we retrospectively identified patients with testicular DLBCL between 1964 and 2015. All patients had a pathological diagnosis of DLBCL (all pathologic specimens reviewed at MD Anderson Cancer Center), and no prior treatment. Patients with late testicular involvement, no follow-up information, or who had disease progression during induction chemotherapy were excluded. Institutional records were used to obtain data on clinical, pathological and imaging characteristics, radiation treatment plans, recurrence and survival.

Between 1964 and 2015, 147 patients presented to MD Anderson for newly diagnosed testicular DLBCL. Thirteen patients were excluded for having not completed induction chemotherapy, and 14 patients were excluded for lack of follow-up, leaving 120 patients who met inclusion criteria and were included in this analysis.

Disease staging

Initial staging evaluations varied over time. Before 1993, staging evaluation included bone marrow aspirate and biopsy, lymphangiography, intravenous pyelography, gallium scanning, and/or computed tomography (CT) scans of the abdomen and pelvis. From 1993 to 2002, patients generally underwent bone marrow aspirate and biopsy, chest radiography, and CT of the chest, abdomen, and pelvis. Starting around 2002, positron emission tomography (PET) CT scans were consistently included in the staging evaluation. Information on Ann Arbor disease stage, performance status, and serum lactate dehydrogenase (LDH) levels was obtained from the pretreatment records. The International Prognostic Index (IPI) was calculated for all patients (retroactively for patients treated prior to the development of the IPI).

Treatment

RT was delivered after completion of chemotherapy. Prophylactic RT was typically given with a high-energy appositional electron beam targeting the entire scrotum, with custom lead skin collimation to limit dose to the surrounding structures. The most commonly used dose was 30.6 Gy in 17 daily fractions. CNS prophylaxis was typically administered during induction chemotherapy, and included either intrathecal chemotherapy, and/or high-dose methotrexate.

Follow-up and response

After therapy completion, patients were typically followed every 3–4 months for 2–3 years, then at 6-month intervals, and yearly thereafter. Surveillance radiographic studies were obtained at the discretion of the treating physician. Patients who were not followed at our institution were contacted annually to obtain information about survival, disease and treatment status. We used the definitions recommended by the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas to classify response [9]. For patients without PET/CT scans, CT scans alone were used to determine response.

Statistical analysis

Endpoints assessed included overall survival (OS), progression-free survival (PFS), testicular relapse-free survival (TRFS), and CNS relapse-free survival (CRFS). For PFS, relapse and death from any cause were considered events, and patients were censored at last followup. For TRFS and CRFS, testicular relapse and CNS relapse, respectively, were counted as events, and patients were censored at death or last follow-up. Survival rates were calculated from date of diagnosis. A subgroup analysis was done for patients who received modern systemic therapy (i.e. anthracyclineand rituximab-based chemotherapy).

Univariate associations between patient/tumor characteristics and therapy were tested using the chi-squared test and Fisher´s exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. Kaplan-Meier curves were estimated and stratified by RT and CNS prophylaxis. The log-rank test was used to test the survival difference between the patient and treatment characteristic groups. Univariate and multivariate Cox proportional hazard models were used to determine the effects of patient and treatment factors on survival outcomes, adjusted for covariates. The variables with p values of ≤.2 in the univariate

analysis were included in the full multivariable model. RT was forced in the multivariate model for OS and PFS, and CNS prophylaxis was forced into the multivariate model for CRFS. The reduced multivariate model was obtained using a backward selection approach, removing the least significant covariate from the full model one at a time, and p values of <. 05 was used as the limit for inclusion in this analysis. All tests are twosided. p Values less than .05 are considered statistically significant. All analyses were conducted using SAS 9.4 (SAS, Cary, NC) and S-Plus 8.0 (TIBCO Software Inc., Palo Alto, CA) software.

Results

Patient and treatment characteristics

Clinical and treatment characteristics are summarized in Table 1. Ann Arbor clinical stage was Stage I in 57 patients (49%), II in 26 (22%), III in 7 (6%), and IV in 27 (23%). Nearly all (97%) patients received orchiectomy; 105 (87%) received anthracycline-based chemotherapy; 64 (53%) received rituximab; and 102 (85%) received CHOP chemotherapy. Seventy-three (61%) patients received CNS prophylaxis, 72 with intrathecal chemotherapy, and 1 patient with high-dose methotrexate. Among the 84 patients (70%) who received RT, the median dose was 30.6 Gy (range, 24–40 Gy), at a median 1.8 Gy per fraction. Twenty-six (22%) patients who received testicular RT also received RT to other involved nodal regions, and 3 (3%) patients received nodal RT but not testicular RT. Patients receiving RT were more likely to have limited stage versus advanced stage (p = .004), to have received rituximab (p = .038), and to have received CNS prophylaxis (p < .001; Table 2). Patients treated with CNS prophylaxis were more likely to have a normal LDH level (p = .002), received anthracycline therapy (p < .001), CHOP chemotherapy (p < .001) and RT (p < .001; Table 2).

Survival and relapse

The median follow-up time was 5.1 years (range 0.3–39.7 years). The median PFS time was 5.3 years [95% confidence interval (CI) 3.9–6.5; Figure 1]. Patients who received RT had a significantly higher PFS time [median 6.3 years (95% CI 5.7–9.6) and 5-year PFS rate 65%] compared to those who did not [median 2.1 years (95% CI 1.1 −5.2) and 5-year PFS rate 30%] (p=.001; Figure 2). The median OS time was 7.7 years for all patients (95% CI 6.5–12.4; Figure 1). Patients who received RT had a median OS 8.3 years (95% CI 6.9–16.9; 5-year OS rate 73%) compared with a median OS of 5.9 years for those who did not (95% CI 2.6–13.3; 5-year OS rate 52%) (p = .065; Figure 2).

Ten (8%) patients experienced a testicular relapse. The median TRFS time was not reached; the 5-year TRFS rate was 93%, and the 10-year TRFS rate was 86% (Figure 1). Patients who received RT had a higher TRFS (5- and 10-year TRFS rates of 98% and 91%, respectively) compared to those who did not (5- and 10-year TRFS rates of 79% and 73%, respectively) (p = .001; Figure 2).

Twenty-three (19%) patients experienced CNS relapse, including 8 CNS parenchymal failures, and 2 orbital failures. The median CRFS time was not reached; the 5-year CRFS rate was 85% and the 10-year CRFS rate was 67% (Figure 1). Patients who received CNS

prophylaxis had a longer median OS time (9.3 years; 95% CI 6.6 to not reached) compared to those that did not (median OS 5.9 years; 95% CI 3.3–12.4) ($p = .017$; Figure 3). Patients who received CNS prophylaxis had a higher median PFS time (6.3 years; 95% CI 5.2–10.0) versus those who did not (3.4 years; 95% CI 1.9–5.9) ($p = .009$; Figure 3). CRFS was no different among patients who did or did not receive CNS prophylaxis (5-year CRFS rate 86% vs. 83%) ($p = .845$; Figure 3).

Univariate analysis

Several patient and treatment factors were evaluated in univariate analyses for potential associations with OS, PFS, TRFS, and CRFS (Table 3). For PFS, three factors were identified: LDH at diagnosis, CNS prophylaxis, and RT. Having an initial abnormal serum LDH level was associated with a higher risk of progression (HR 1.85, 95% CI 1.02–3.38, $p = .045$), whereas CNS prophylaxis (HR 0.56, 95% CI 0.36–0.87, $p = .010$), and RT (HR 0.48, 95% CI 0.31–0.75, $p = .001$) were associated with improved PFS. Increasing age, as a continuous variable, was of borderline significance for association with worse PFS (HR 1.02, 95% CI 0.99–1.03, $p = .064$).

On univariate analysis for OS, RT was of borderline significance for improved survival (HR 0.64, 95% CI 0.40–1.03, $p = .067$; Table 3). Three factors were significantly associated with OS on univariate analysis: increasing age (as a continuous variable) was associated with worse OS (HR 1.04, 95% CI 1.02–1.06, $p < .001$), whereas anthracycline chemotherapy and CNS prophylaxis were associated with improved OS (HR for anthracycline 0.45, 95% CI 0.24–0.84, $p = .013$; and HR for CNS prophylaxis 0.56, 95% CI 0.35–0.91, $p = .018$).

Patients who received RT were at lower risk of testicular relapse (HR 0.13, 95% CI 0.03–0.52, $p = .004$; Table 3). Receipt of CNS prophylaxis was also associated with decreased testicular relapse risk (HR 0.16, 95% CI 0.03–0.75, $p = .020$; Table 3). No factors were significantly associated with CRFS on univariate analysis, although there was a trend for an association with advanced stage (vs. limited stage) and worse CRFS [HR 2.22, 95% CI 0.92–5.36, $p = .077$].

Multivariate analysis

In multivariate analysis (MVA) for PFS, RT remained a significant predictor of improved PFS (HR 0.39, 95% CI 0.24–0.64, $p < .001$; Table 4), after adjusting for anthracycline chemotherapy (HR 0.39, 95% CI 0.20–0.76, $p = .005$), stage (HR 1.93, 95% CI 1.12–3.34, $p = .018$), and age (HR 1.03, 95% CI 1.01–1.05, $p = .013$). In MVA for OS, RT was associated with improved OS (HR 0.47, 95% CI 0.27–0.83, $p = .009$), in addition to anthracycline chemotherapy (HR 0.23, 95% CI 0.12–0.46, $p < .001$); whereas advanced disease stage (vs. limited stage) and increasing age (as a continuous variable) were associated with worse OS (HR for advanced disease 2.45, 95% CI 1.3–4.49, $p = .004$; HR for age 1.06, 95% CI 1.03–1.08, $p < .001$). The number of events was insufficient to analyze TRFS. No factors were significantly associated with CRFS in MVA, including CNS prophylaxis.

Subgroup analysis of patients given modern systemic therapy

To assess the added value of RT in the era of modern systemic therapy agents, we analyzed a subgroup of 64 patients who received rituximab and anthracycline chemotherapy (Table 2). The median follow-up time for these patients was 3.93 years (range 0.7–20.2 years). Compared with patients who did not receive modern systemic therapy, those who did were more likely to have intermediate- and high-risk IPI risk groups ($p = .008$), more likely to be advanced stage ($p = .027$), and more likely to have received CNS prophylaxis ($p < .001$) and RT ($p = .038$).

Among the 64 patients treated with modern therapy, on univariate analysis for PFS, RT was significantly associated with improved PFS (HR 0.23, 95% CI 0.11–0.50, $p < .001$), as was CNS prophylaxis (HR 0.21, 95% CI 0.09–0.48, $p < .001$). Advanced stage was marginally associated with worse PFS (HR 1.97, 95% CI 1.00–3.88, $p = .050$). On MVA, RT remained a significant predictor of improved PFS (HR 0.29, 95% CI 0.13–0.64, $p = .002$), after adjusting for CNS prophylaxis (HR 0.28, 95% CI 0.12–0.69, $p = .005$; Table 4).

On univariate and multivariate analyses for potential predictors of OS, increasing age was the only significant factor associated with worse OS (multivariate HR 1.05, 95% CI 1.02–1.09, $p = .004$). No treatment factors were associated with improved CRFS on univariate or multivariate analyses; advanced stage was the only predictor of worse CRFS (multivariate HR 3.31, 95% CI 1.07–10.26, $p = .038$). The number of events among patients who received modern systemic therapy was insufficient for a stable analysis of TRFS.

Patients who received RT had significantly improved median PFS (6.5 years vs. 2.2 years, $p < .001$) (Figure 4) and also had a significantly higher 5-year TRFS rate of 100% (vs. 82%, $p = .033$; Figure 4). Patients who received RT had a higher 5-year OS rate (80% vs. 69% in those who did not), but this difference was not significant ($p = .187$; Figure 4).

Discussion

In this large cohort of stage I–IV patients with testicular DLBCL, prophylactic testicular RT was associated with a decreased risk of testicular relapse and improved PFS and OS. The benefit in PFS remained among patients treated with modern-era rituximab and anthracycline-based chemotherapy. These results underscore the importance of treating this patient group with testicular RT, particularly as the natural history of this disease, in contrast to nodal DLBCL, has a propensity for late and sanctuary site relapses that are difficult to salvage with systemic therapy.

Our finding of an association between RT and improved survival is supported by other studies [7,8,10]. In one multi-institutional study of 373 patients with primary testicular DLBCL (79% stage I-II) treated in the pre-rituximab era, RT was associated with longer OS on MVA [7]. Another population-based study showed that patients who were not treated with surgical excision and RT had an inferior disease-specific survival [10]. Similar to the study by Zucca et al., we found that the OS benefit of RT was significant in a MVA accounting for stage, age, and anthracycline chemotherapy. In addition, RT was an independent predictor of improved PFS in all patients, including those receiving modern

systemic therapy. Although RT could be a surrogate for other favorable factors (patients receiving RT were more likely to have limited stage disease, and to have received rituximab and CNS prophylaxis), RT was statistically significant in multivariate analyses for OS and PFS accounting for several other patient and treatment characteristics, including stage. We also show that RT reduces testicular relapse, which is important given the continuous risk for late testicular relapse without RT, which can reach up to 42% at 15 years [7]. Because salvage therapies for relapse of testicular DLBCL are limited and prognosis after relapse is poor, with one study showing a median survival time of only 10 months [11], treatments to prevent relapse are imperative. Although data from prospective randomized studies are lacking, current evidence led to the inclusion of testicular RT in the recent International Extranodal Lymphoma Study Group (IELSG) phase II trial [6]. Despite increasing evidence in favor of RT, the rates of RT use have not changed over the past several decades, remaining at approximately 30–40% [10].

Prophylactic scrotal RT has limited acute toxicity. One expected side effect, dermatitis, can present as moist desquamation and typically resolves within a few weeks. The location of the treatment field far from critical structures and the relatively low RT dose make scrotal RT generally tolerable. At our institution, use of an appositional electron field with custom lead skin collimation also limits toxicity to nearby structures. A potential late effect of RT is hypogonadism, with continued declines in testosterone levels several years after treatment [12]; however, many patients are already at risk after orchiectomy and with increasing age. Patients should have their testosterone levels checked during follow-up and be referred to endocrinologists when necessary. Although secondary malignancies are a serious toxicity for other lymphomas affecting younger patients, this is considered of little concern given the generally older age of testicular DLBCL patients [13].

Interestingly, we found that CNS prophylaxis was not associated with decreased CNS relapse, but was associated with improved OS, superior PFS, and reduced testicular relapse (on univariate analysis in all patients), as well as improved PFS on MVA in the modern systemic therapy subgroup. Although our findings are limited by the retrospective design and long time span of this study, one possible explanation is that CNS prophylaxis is a surrogate for better overall treatment, as those patients who received CNS prophylaxis were also more likely to have received rituximab, anthracycline chemotherapy, CHOP, and RT. These findings suggest that CNS prophylaxis could be a surrogate for other treatment factors, further supported by the finding that receipt of CNS therapy reduced the testicular relapse risk in our dataset. Although intrathecal chemotherapy prophylaxis continues to be considered standard of care for patients with testicular DLBCL, several studies have not shown a benefit for intrathecal treatment with regard to CNS relapses, although there is an association with improved PFS. Zucca et al. reported a CNS relapse rate of 15%, most of which were brain parenchymal relapses. However, prophylactic intrathecal chemotherapy, although associated with improved PFS, did not have a significant effect on CNS relapse [7]. Also, in the recent IELSG phase II trial, which included intrathecal methotrexate, the rate of CNS relapse was 6% at 5 years. The lack of benefit from intrathecal chemotherapy for CNS relapse was confirmed by a report from the International Primary Testicular Lymphoma Consortium on 280 patients with DLBCL and testicular lymphoma treated at several institutions ($p = .918$) [11]. Further, in a retrospective study of DLBCL patients treated in

the rituximab era, receipt of CNS prophylaxis (with various regimens including both intrathecal and high-dose methotrexate) did not affect the rate of CNS relapse [14]. Because CNS relapses in testicular DLBCL more often occur in the brain parenchyma rather than the meninges, it is possible that intrathecal chemotherapy has inadequate parenchymal penetration. Another CNS prophylaxis option is systemic high-dose methotrexate; however, its use is limited by toxicity, especially among older patients. In our study, 72 patients had intrathecal chemotherapy, and only 1 patient received high-dose methotrexate, precluding analysis of differences between these two prophylaxis types. A newer prophylaxis type, liposomal cytarabine, maintains elevated drug levels in the cerebrospinal fluid; its safety and efficacy in high-risk DLBCL patients was recently reported in a prospective trial [15]. The currently ongoing IELSG 30 study includes both intrathecal liposomal cytarabine and systemic intermediate-dose methotrexate for CNS prophylaxis in an effort to decrease CNS relapses.

The adoption of anthracycline chemotherapy, in particular the CHOP regimen, based on standard treatment for patients with nodal DLBCL, has resulted in 5-year survival rates of 30–75% [1]. Because the addition of rituximab to CHOP resulted in a survival benefit relative to CHOP alone in trials of nodal DLBCL [3–5], an international prospective phase II trial of 53 patients with primary testicular lymphoma assessed the use of R-CHOP, along with intrathecal methotrexate and testicular RT for most patients, and reported a 5-year PFS rate of 74% and a 5-year OS rate of 85% [6]. However, in our analysis, rituximab was not associated with improved outcomes, a finding also noted in a large population-based study [10]. Possible explanations are that the biological characteristics of testicular DLBCL may make it less responsive to rituximab, or that rituximab does not effectively penetrate the extranodal sites commonly involved in the natural history of testicular DLBCL. The latter theory is supported by a large study of DLBCL patients with osseous involvement that showed that rituximab did not improve outcomes, although RT doubled their event-free survival [16]. If, in fact, rituximab does not have the same magnitude of benefit in testicular DLBCL as it does for nodal DLBCL, the role of RT may be even more important.

Our study has limitations, particularly its retrospective design and the heterogeneity of patient, diagnostic and treatment strategies over the long study period, which are important to note when considering our findings. Nevertheless, this report is one of the largest single-institution series to date with prolonged followup. The broad inclusion of patients allows us to study the general benefits of different treatment strategies in a rare disease where prospective randomized trials are unlikely to be feasible.

In conclusion, there is a continuous risk of late relapses in patients with testicular DLBCL often involving sanctuary sites such as the contralateral testis and CNS. We observed that the use of prophylactic testicular RT reduced the risk of contralateral testicular relapse, which seemed to translate into an improved OS and PFS. The improvement in PFS was also maintained even in the modern era of rituximab therapy. Therefore, given the aggressive nature of testicular DLBCL, the difficulty of salvaging failures, and the relatively low morbidity of RT, prophylactic testicular RT should be offered to all patients with this disease.

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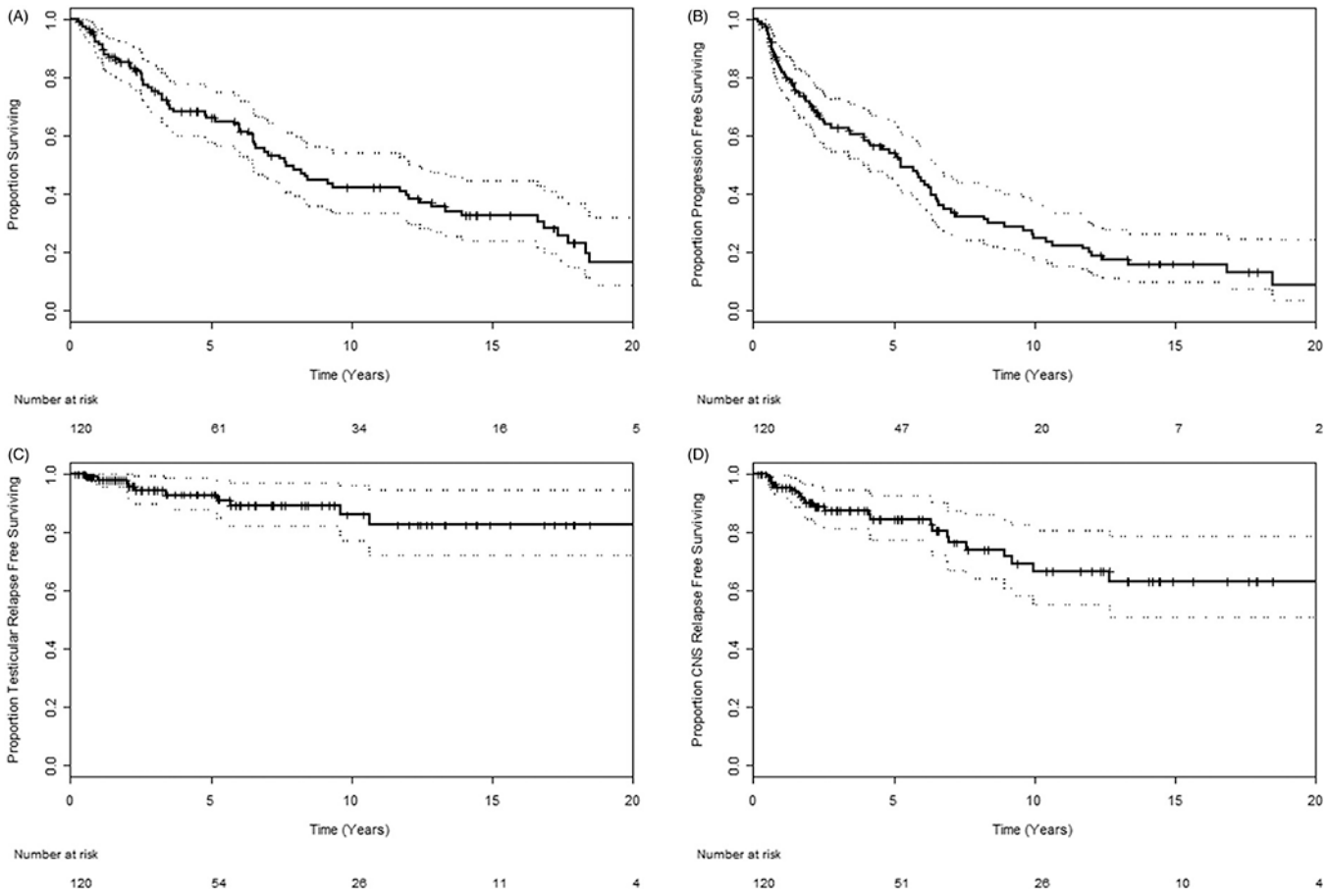

Figure 1.

(A) Overall survival, (B) progression free survival, (C) testicular relapse free survival, and (D) CNS relapse free survival among all 120 patients.

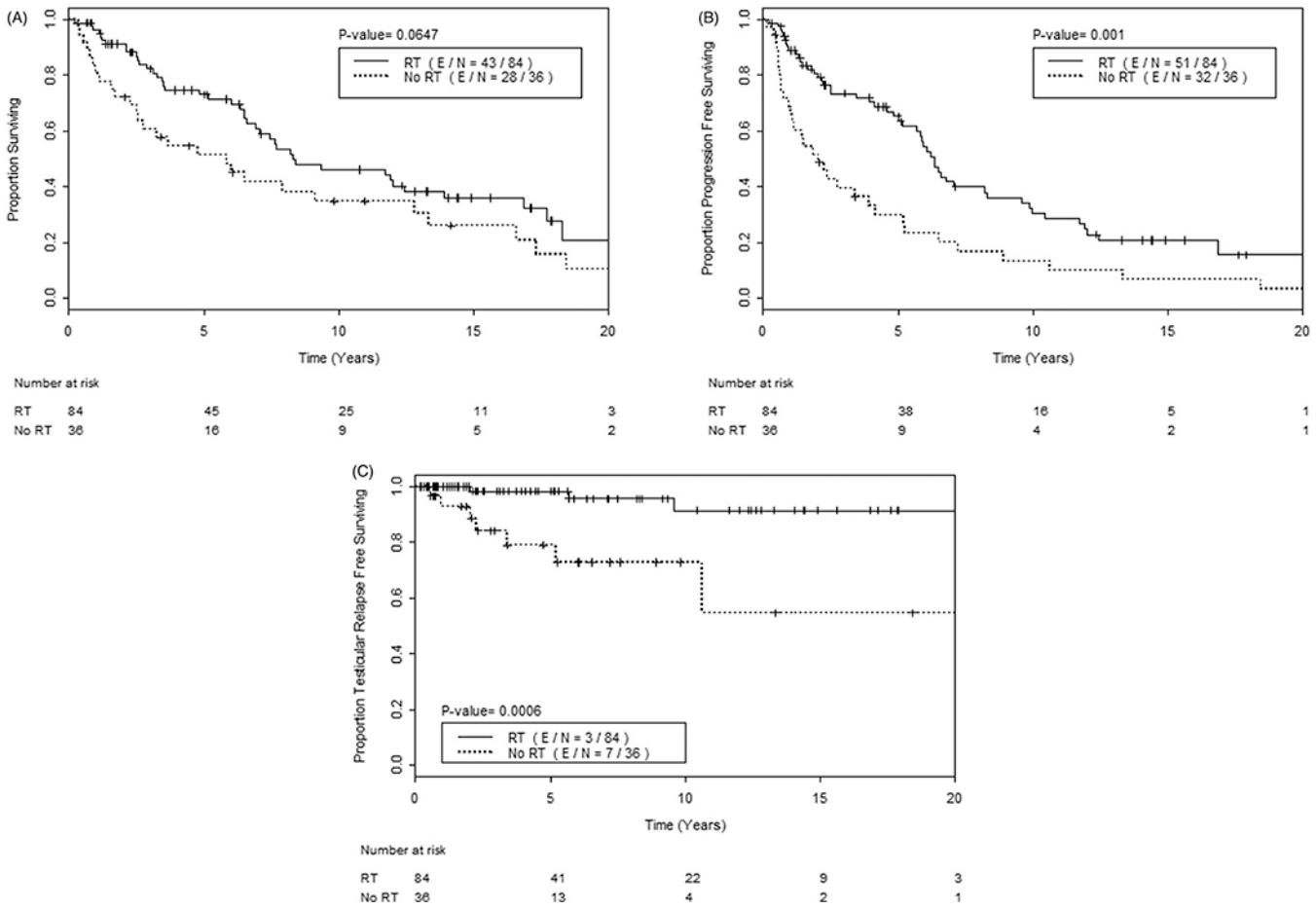

Figure 2.

(A) Overall survival, (B) progression free survival, and (C) testicular relapse free survival, among all 120 patients, comparing those who received testicular RT (solid line) versus those who did not (dashed line).

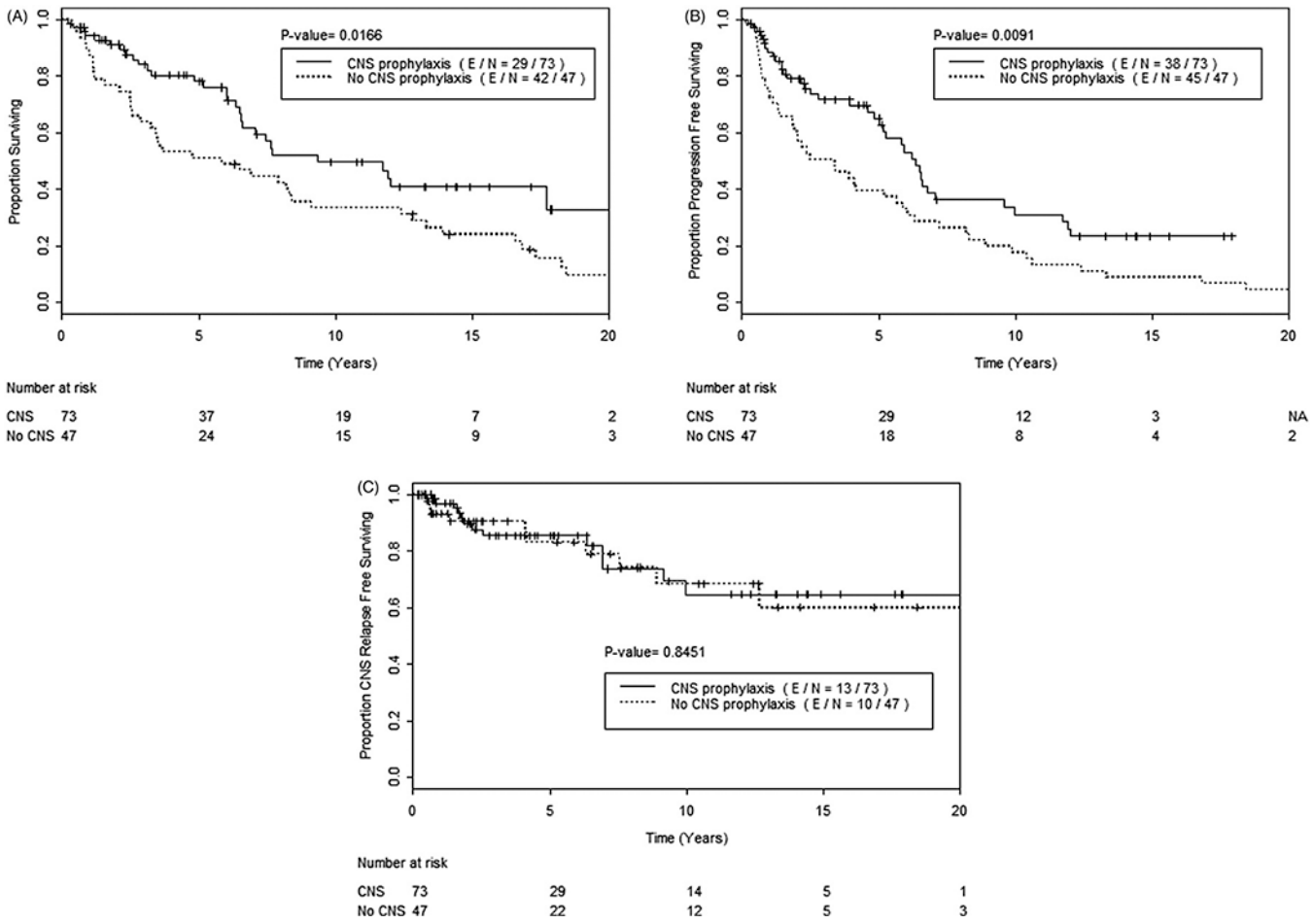

Figure 3.

(A) Overall survival, (B) progression free survival, and (C) CNS relapse free survival, among all 120 patients, comparing those who received CNS prophylaxis (solid line) versus those who did not (dashed line).

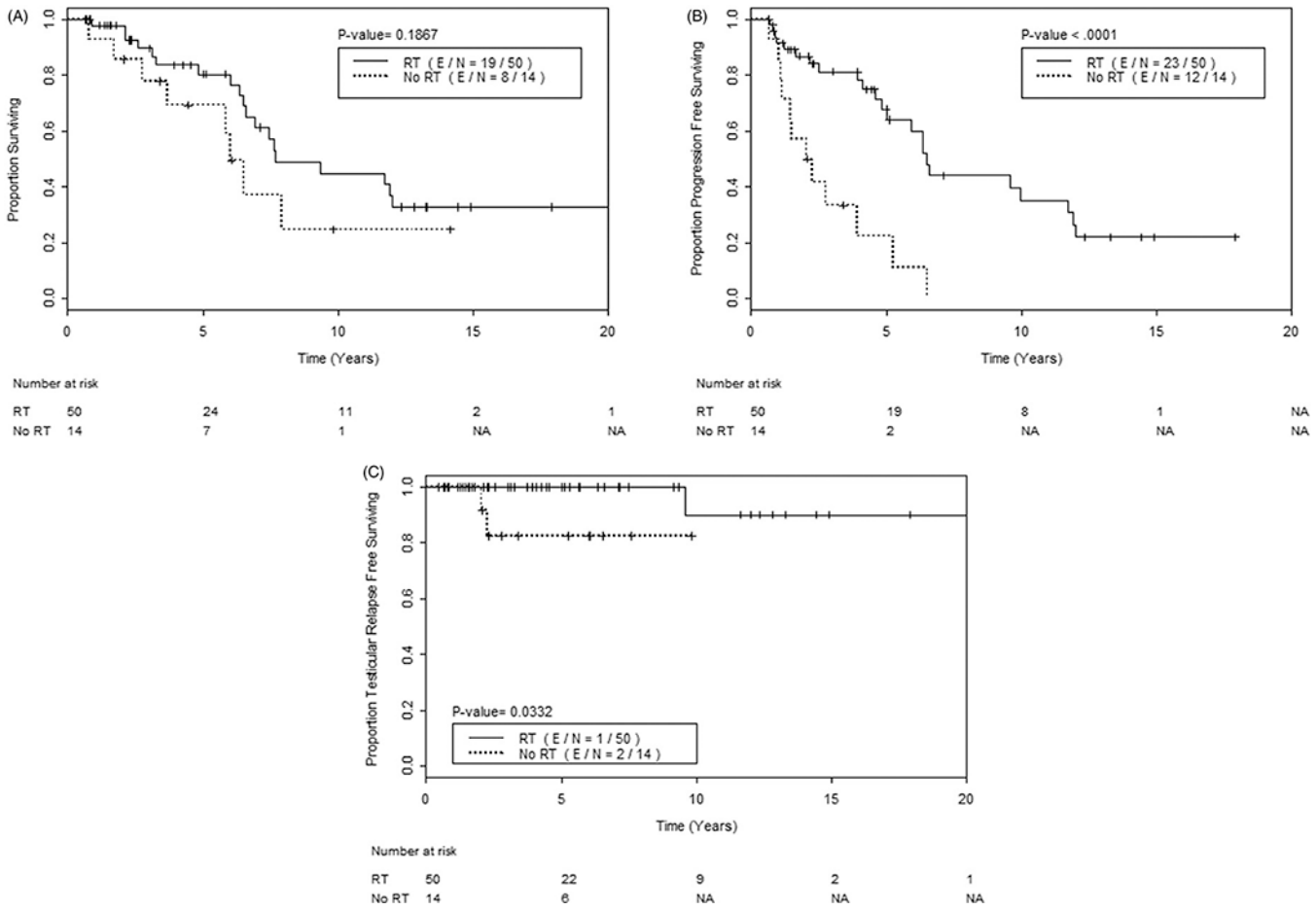

Figure 4.

(A) Overall survival, (B) progression free survival, and (C) testicular relapse free survival, among 64 patients who received modern systemic therapy, comparing those who received testicular RT (solid line)

Table 1.

Baseline patient and treatment characteristics among 120 patients.

Characteristic	Number	%
Stage		
I	57	49%
II	26	22%
III	7	6%
IV	27	23%
Age		
Median (range)	63 (22–96) years	
≥60	73	61%
<60	47	39%
LDH		
Elevated	24	20%
Not elevated	59	49%
Missing	37	31%
IPI risk category		
Low (0 or 1)	59	67%
Intermediate (2 or 3)	24	27%
High (4 or 5)	5	6%
Orchiectomy		
Yes	116	97%
No	4	3%
Anthracycline		
Yes	105	87%
No	13	11%
Missing	2	2%
Rituximab		
Yes	64	53%
No	56	47%
CHOP		
Yes	102	85%
No	16	13%
Missing	2	2%
CNS prophylaxis		
Yes	73	61%
No	47	39%
Testicular radiation		
Yes	84	70%
No	36	30%
Median dose (range)	30.6 Gy (24–40 Gy)	

IPI: international prognostic index; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; LDH: lactate dehydrogenase; CNS: central nervous system.

Table 2.

Patient characteristics stratified by receipt of modern therapy (rituximab and anthracycline chemotherapy), RT and CNS prophylaxis.

Characteristic	Modern therapy (*n* = 64) Number (%)	Non-modern therapy (*n* = 56) Number (%)	*p* Value	RT (*n* = 84) Number (%)	No RT (*n* = 36) Number (%)	*p* Value	CNS Tx (*n* = 73) Number (%)	No CNS Tx (*n* = 47) Number (%)	*p* Value
Stage									
I	27 (42)	30 (57)	.183	46 (55)	11 (33)	.020	35 (49)	22 (49)	.062
II	13 (20)	13 (25)		20 (24)	6 (18)		11 (15)	15 (33)	
III	5 (8)	2 (4)		5 (6)	2 (6)		6 (8)	1 (2)	
IV	19 (30)	8 (15)		13 (16)	14 (42)		20 (28)	7 (16)	
Age									
≥60	38 (59)	35 (63)	.726	52 (62)	21 (58)	.364	42 (58)	31 (66)	.356
<60	26 (41)	21 (38)		32 (38)	15 (42)		31 (43)	16 (34)	
LDH									
Elevated	16(25)	8 (14)	.281	13 (16)	11 (31)	.093	19 (26)	5 (11)	.002
Not elevated	31 (48)	28 (50)		46 (55)	13 (36)		40 (55)	19 (40)	
Missing	17 (27)	20 (36)		25 (30)	12 (33)		14 (19)	23 (49)	
IPI Risk category									
Low (0 or 1)	38 (55)	31 (84)	.008	47 (72)	12 (52)	.086	37 (60)	22 (85)	.068
Intermediate	18 (35)	6 (16)		16 (25)	8 (35)		20 (32)	4 (15)	
(2 or 3)									
High (4 or 5)	5 (10)	0		2 (3)	3 (13)		5 (8)	0	
Orchiectomy									
Yes	61 (95)	55 (98)	.622	82 (98)	34 (94)	.582	70 (96)	46 (98)	1.000
No	3 (5)	1 (2)		2 (2)	2 (6)		3 (4)	1 (2)	
Anthracycline									
Yes	64 (100)	41 (76)	.011	74 (89)	31 (89)	.926	71 (99)	34 (74)	<.001
No	0	13 (24)		9 (11)	4 (11)		1 (1)	12 (26)	
Missing		2		1	1		1	1	
Rituximab									
Yes	64 (100)	0	<.001	50 (60)	14 (39)	.038	56 (77)	8 (17)	<.001
No	0	56 (100)		34 (41)	22 (61)		17 (23)	39 (83)	
CHOP									
Yes	64 (100)	38 (70)	<.001	74 (89)	28 (78)	.185	71 (99)	31 (67)	<.001
No	0	16 (30)		9 (11)	7 (19)		1 (1)	15 (33)	
Missing	-	2		1	1		1	1	
Intrathecal chemotherapy									
Yes	56 (88)	17 (30)	<.001	60 (71)	13 (36)	<.001	-	-	
No	8 (13)	39 (70)		24 (29)	23 (64)				
Testicular radiation									

Characteristic	Modern therapy (*n* = 64) Number (%)	Non-modern therapy (*n* = 56) Number (%)	*p* Value	RT (*n* = 84) Number (%)	No RT (*n* = 36) Number (%)	*p* Value	CNS Tx (*n* = 73) Number (%)	No CNS Tx (*n* = 47) Number (%)	*p* Value
Yes	50 (78)	34 (61)	.038	-	-		60 (82)	24 (51)	<.001
No	14 (22)	22 (39)		-	-		13 (18)	23 (49)	

Abbreviations: IPI: international prognostic index; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; LDH: lactate dehydrogenase; CNS: central nervous system; RT: radiation therapy.

Table 3.

Univariate analyses of prognostic factors with PFS, OS, TRFS.

	PFS			OS			TRFS		
Variable	**HR**	**95% CI**	***p* Value**	**HR**	**95% CI**	***p* Value**	**HR**	**95% CI**	***p* Value**
Stage (advanced vs. early)	1.39	0.86–2.27	.183	1.43	0.83–2.44	0.195	0.96	0.20–4.66	.961
Age (continuous)	1.02	0.99–1.03	.064	1.04	1.02–1.06	**<0.001**	0.98	0.94–1.02	.333
LDH (elevated vs. normal)	1.85	1.02–3.38	**.045**	1.69	0.87–3.27	0.122	3.19	0.64–15.9	.157
IPI risk group (int. vs. low)	1.09	0.56–2.12	.800	1.82	0.89–3.69	0.099	0.94	0.10–8.69	.956
Anthracycline (yes vs. no)	0.64	0.34–1.20	.164	0.45	0.24–0.84	**0.013**	-	-	-
Rituximab (yes vs. no)	0.78	0.50–1.21	.266	0.78	0.48–1.29	0.333	0.39	0.10–1.52	.174
CNS Prophylaxis (yes vs. no)	0.56	0.36–0.87	**.010**	0.56	0.35–0.91	**0.018**	0.16	0.03–0.75	**.020**
Testicular radiation (yes vs. no)	0.48	0.31–0.75	**.001**	0.64	0.40–1.03	0.067	0.13	0.03–0.52	**.004**

Abbreviations: IPI: international prognostic index; int.: intermediate; PFS: progression free survival; OS: overall survival; TRFS: testicular relapse free survival.

p Values in bold indicate statistical significance.

Table 4.

Multivariate models of prognostic factors for PFS and OS, for all patients, and for those who received modern therapy (rituximab and anthracycline).

	PFS			OS		
Variable	**HR**	**95% CI**	***p* Value**	**HR**	**95% CI**	***p* Value**
All patients ($n = 120$)						
Age (continuous)	1.03	1.01–1.05	.013	1.06	1.03–1.08	<.001
Stage (advanced vs. early)	1.93	1.12–3.34	.018	2.45	1.33–4.49	.004
Anthracycline	0.39	0.20–0.76	.006	0.23	0.12–0.46	<.001
Testicular radiation	0.39	0.24–0.64	<.001	0.47	0.27–0.83	.009
Modern therapy patients ($n = 64$)						
Age (continuous)	-	-	-	1.05	1.02–1.09	.004
CNS Prophylaxis	0.28	0.12–0.69	.005	-	-	-
Testicular radiation	0.29	0.13–0.64	.002	0.50	0.21–1.18	.114