Patterns of Outcome and Prognostic Factors in Primary Large-Cell Lymphoma of the Testis in a Survey by the International Extranodal Lymphoma Study Group

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Purpose: **To determine clinical features and patterns of outcome of primary testicular diffuse large B-cell lymphomas (DLCL).**

Patients and Methods: **A retrospective international survey of 373 patients with primary testicular DLCL.**

Results: **Most patients presented with localized disease (stage I to II), and the median age at diagnosis was 66 years (range, 19 to 91 years). Anthracycline-based chemotherapy was administered to 255 patients (68%), and prophylactic intrathecal chemotherapy was given to 68 patients (18%); 133 patients (36%) received prophylactic scrotal radiotherapy. Median overall survival was 4.8 years, and median progression-free survival was 4 years. The survival curves showed no clear evidence of a substantial proportion of cured patients. A favorable international prognostic index score (IPI), no B-symptoms, the use of anthracyclines, and prophylactic scrotal radiotherapy were significantly associated with longer survival at multivariate analysis. However, even for patients with stage I disease and good-risk IPI, the outcome seems worse than what was reported for DLCL at other sites. At a median follow-up of 7.6 years, 195 patients (52%) had relapsed. Extranodal recurrence was reported in 140 cases. Relapses in CNS were detected in 56 patients (15%) up to 10 years after presentation. A continuous risk of recurrence in the contralateral testis was seen in patients not receiving scrotal radiotherapy.**

Conclusion: **Testicular DLCL is characterized by a particularly high risk of extranodal relapse even in cases with localized disease at diagnosis. Anthracycline-based chemotherapy, CNS prophylaxis, and contralateral testicular irradiation seem to improve the outcome. Their efficacy is under evaluation in a prospective clinical trial.**

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PRIMARY TESTICULAR lymphoma represents 1% to 2% of all non-Hodgkin's lymphomas, with an estimated incidence of 0.26/100,000 per year. Approximately 85% of patients are older than 60 years of age. Even though lymphomas account for only 1% to 7% of all testicular malignancies, they represent the most common testicular tumor in men older than 50 years of age.[1-4] Histologically, 80% to 90% of primary testicular lymphomas are of diffuse large-cell type with B-cell immunophenotype,[1,2,4-6] but isolated cases of other histologic subtypes have been reported.[6-10] Peculiar histologic and molecular features have been described in diffuse large-cell lymphomas (DLCL) of the testis, including plasmacytoid differentiation and somatic hypermutation of immunoglobulin heavy-chain gene, indicating a possible antigen-driven stimulation, analogous to what is seen in extranodal marginal zone lymphoma.[9] In addition, primary testicular lymphoma shows a tendency to disseminate systematically to several extranodal sites, including the contralateral testis, central nervous system (CNS), skin, Waldeyer's ring, lung, pleura, and soft tissues.[2-6,10-12] Over the years, treatment for primary testicular lymphoma has been variable. Treatment using radiation therapy alone provides suboptimal disease control, even for patients with clinically stage I disease.[13-15] Chemotherapy without anthracyclines was shown to produce inferior results compared with regimens with anthracyclines.[2,11,12] Thus,

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chemotherapy with anthracycline-containing regimens is the recommended therapy after orchiectomy.[2,16,17] However, despite the administration of aggressive chemotherapy regimens, prognosis is often still poor, even in localized disease, with the 2-year relapse rate exceeding 50% in most series.[11,17,18] Current published series, in general, tend to be small and often have a short follow-up to define the optimal management. Therefore, the optimal management of this disease remains undefined. A retrospective international survey of patients with primary DLCL of the testis from 23 institutions was coordinated by the International Extranodal Lymphoma Study Group (IELSG) to better define the specific clinical features at presentation, the prognostically important clinical variables, the response to therapy, and patterns of failure. This was performed to possibly provide a comprehensive basis for a prospective international therapeutic trial.

PATIENTS AND METHODS

All patients were either enrolled onto prospective clinical trials or were consecutive patients treated at participating centers between 1968 and 1998. To overcome the difficulties generated by the different histologic classifications used for the initial diagnosis over that time, we considered eligible for the study the patients with non-Hodgkin's lymphoma included in the groups G-H of the Working Formulation,[19] diagnosed as having centroblastic or immunoblastic lymphomas according to the Kiel classification[20] or as DLCL according to the REAL classification,[21] and presenting with a clinically dominant testicular mass. This relaxed definition of primary large-cell lymphoma of the testis also allowed the inclusion of patients ultimately shown to have advanced-stage disease. Initial diagnosis was revised at each institution when the original histologic material was obtainable; a subset of 55 cases (randomly selected among those with available paraffin-embedded material) was further reviewed by a pathology panel of IELSG to assess the diagnostic reproducibility. Patients with lymphoblastic and Burkitt lymphoma were excluded.

Standardized forms were submitted to participating institutions to obtain information on age, Eastern Cooperative Oncology Group performance status, Ann Arbor stage, presence and location of extranodal disease, B symptoms, bulky disease (defined as any mass at any site with a diameter larger than 10 cm), serum lactate dehydrogenase (LDH), and beta-2 microglobulin levels. The International Prognostic Index (IPI) score was determined according to the published criteria.[22] Because of the retrospective nature of the study, not all variables were available for each patient. We also obtained data on initial treatment, including irradiation to the contralateral testis, prophylactic intrathecal chemotherapy, response to treatment, site and time of failure, cause of death, and status at last follow-up.

All patients were clinically staged according to the Ann Arbor criteria.[23] The staging procedures were not standardized but varied depending on different centers and periods and included chest and abdomen imaging investigations (computed tomography scans or lymphangiogram) and bone marrow biopsy. Bilateral testicular involvement at diagnosis was considered to represent stage I disease. The final stage of patients with bilateral disease was determined by the degree of involvement of other nodal and extranodal sites.

Complete remission (CR) was defined as the disappearance, for at least 1 month, of all clinical evidence of the disease, including the normalization of all laboratory values and radiographs that were abnormal at presentation, including that of bone marrow if initially involved. Partial remission (PR) was defined as a greater than 50% reduction in the largest dimension of involved sites. Objective response rate was defined as the sum of the CR and PR rates. No response was defined as a less than 50% regression or stable or progressive disease. All early deaths caused by disease progression or treatment-related toxicity were considered as treatment failures and were included in the no response group. All evaluations of clinical stage and response to treatment were based on the original data recorded by local physicians. Patients with stage I disease who had no evidence of disease after orchiectomy (with or without subsequent adjuvant chemotherapy or radiation) were not considered for response evaluation but only for overall survival (OS), cause-specific survival (CSS), and progression-free survival (PFS) analysis. According to the National Cancer Institute criteria,[24] OS was calculated from time of diagnosis to time of either death from any cause or of last follow-up. PFS was measured from time of diagnosis to the time of primary treatment failure, relapse/progression, or death from lymphoma. CSS was measured from time of diagnosis to the time of death from disease or treatment-related causes. The median follow-up was computed by the reverse Kaplan-Meier method.[25] Survival probabilities were calculated using the life-table method, survival curves were estimated by the Kaplan-Meier method, and differences between curves were analyzed using the log-rank test.[26] Binomial exact 95% confidence intervals (CIs) were calculated for percentages. Either the χ^2 test or the Fisher's exact test was used for testing associations in two-way tables, as appropriate. The Cox proportional hazards model was used for multivariate analysis of OS, CSS, PFS, and estimation of relative risk (hazard ratio) and its CI.[27] *P* values of .05 or less (two-sided test) were considered to indicate statistical significance. Statistical analysis was conducted using the STATA 5.0 software package (Computing Resource Centre, Santa Monica, CA).

RESULTS

Patient Population Characteristics

The study population included 381 patients from 23 institutions (22 cancer centers and one cooperative group). We excluded eight patients from the study for the following reasons: revised histology (lymphoblastic lymphoma) in two patients and incomplete data or inadequate follow-up in six patients. The final analysis included 373 patients.

Table 1 lists the main clinical features at presentation. The median age at presentation was 66 years. Two hundred fourteen patients presented with disease localized to the testis, whereas 80 patients had involvement of locoregional lymph nodes (including inguinal in 16, iliac in 10, lumboaortic in 42, and unspecified locoregional lymph nodes in 12 patients). Lymphomatous involvement of the testis was documented pathologically in 366 patients. In the remaining seven patients, presentation was clinical but histologic documentation was performed on a lymph node biopsy because of the disease dissemination. Synchronous bilateral testicular involvement at diagnosis was reported in eight patients (2%); in four of them, the disease was limited to the testes, and these patients were considered as stage I. B symptoms were documented in 34 patients, 11 of whom had limited-stage disease. Serum LDH level was elevated in 59 patients (28%) with Ann Arbor stage I/II disease who had LDH measured at presentation. Sixty-nine patients presented with additional involvement of other extranodal sites.

Treatment and Outcome

Three hundred fifty-three patients (95%) underwent orchiectomy as first therapeutic and diagnostic intervention. In 41 patients, no further treatment was delivered because of the patient conditions or preferences. Primary treatment included chemotherapy in 134 patients, radiotherapy in 51 patients, or a combined-modality approach (chemoradiotherapy) in 145 patients (39%). Because patients were treated according to the current policy of each institution at the time of diagnosis, there is a wide range of radiotherapy doses (from 18 to 50 Gy) and fields (from scrotal only to a variety of extended fields with or without contralateral testis) among the 196 patients who received radiotherapy. Two cases lacked information about radiotherapy. Two hundred seventy-nine patients (75%) were treated with combination chemotherapy, and 255 (68%) received an anthracycline-containing regimen. Sixty-eight patients (18%) were also subjected to prophylactic intrathecal chemotherapy, with only 51

Table 1. Clinical Characteristics at Presentation

Characteristic	No. of Patients	%
Age, years		
Median	66	
Range	19-91	
IPI		
Low to low/intermediate risk	292	78
Intermediate/high to high risk	70	19
Unknown	11	3
Performance status		
ECOG score 0-1	323	86
ECOG score 2-4	44	12
Unknown	6	2
Stage		
I-II	294	79
III-IV	79	21
B symptoms		
Absent	336	90
Present	34	9
Unknown	3	1
Bulky disease		
Absent	353	95
Present	20	5
Serum LDH		
Normal	176	47
Elevated	100	27
Unknown	97	26
Serum beta-2 microglobulin		
Normal	48	13
Elevated	28	7
Unknown	297	80
No. of extranodal sites		
1, ie, testis only	304	82
>1	69	18
Additional extranodal sites involved at diagnosis		
Bone marrow	18	5
CNS	11	3
Adrenal glands	9	2.5
Skin	9	2.5
Bone	8	2
Kidney	7	2
Soft tissue	6	1.5
Lung	6	1.5
Gastrointestinal tract	6	1.5
Liver	4	1
Other locations, each < 1%	17	4.5

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 2. First-Line Therapy

Treatment Modality	No. of Treated Patients	% of the Entire Cohort
Orchiectomy	353	95
Unilateral	350	94
Bilateral	3	1
Systemic chemotherapy	279	75
Aggressive regimens	255	68
CHOP or 2nd generation regimens	191	51
MACOP-B, ProMACE/CytaBOM, or other 3rd generation regimens	45	
High-dose chemotherapy and/or autotransplantation	19	
Nonanthracycline-based regimen (CVP) or single alkylating agent	24	6
Intrathecal chemotherapy	73	20
Prophylactic	68	18
Therapeutic	5	2
High-dose intravenous methotrexate	29	8
Radiotherapy	196	53
Combined with chemotherapy	145	39
Prophylactic to the contralateral testis	133	36
Aggressive anthracycline-based chemotherapy plus intrathecal prophylaxis and scrotal irradiation	34	9

Abbreviations: MACOP-B, methotrexate, doxorubicin, cyclophosphamide, vincristine, predisone, and bleomycin.

of them receiving at least four doses (median number of intrathecal injections, four; range, one to 12 injections). In five patients, therapeutic intrathecal chemotherapy was delivered because of CNS involvement at diagnosis. One hundred thirty-three patients (36%) received prophylactic radiotherapy to the contralateral testis; locoregional radiotherapy was delivered to 49 stage I and 43 stage II patients. A subset of only 34 patients (9%; median age, 58 years; 22 patients with stage I, 10 patients with stage II, one with stage III, and one with stage IV disease) received all modalities and were treated with anthracycline-containing chemotherapy regimens, together with prophylactic irradiation of the contralateral testis and prophylactic administration of at least four doses of intrathecal methotrexate. Table 2 lists the front-line therapeutic approaches used. Treatment policies may have been changed at each institution during the time; however, a comparison of OS, CSS, and PFS of cases in this series treated before 1980, from 1980 to 1989, and after 1989 did not show any significant difference.

One hundred sixty-two patients who did not undergo surgery or had postorchiectomy residual disease received additional therapy (chemotherapy or radiotherapy or both). One hundred fifty-five of these patients were assessable for response to therapy; 110 patients (71%) achieved a CR, and 15 (10%) achieved a PR. Among the stage II to IV patients receiving chemotherapy, the objective response rate was 80% with 70% CRs, and the response rate was higher (87% *v* 53%, $P < .0001$) in the group of patients treated with anthracycline-containing regimens.

Median OS was 4.8 years for the whole group and 5.8 years for the patients presenting with stage I/II disease. Table 3 lists the results of the survival analysis by Ann Arbor stage. The 5- and 10-year OS rates were 48% (95% CI, 42% to 53%) and 27% (95% CI, 21% to 33%), respectively, in the whole series (Fig 1). One hundred seventy-two patients (46%) have died from lymphoma or lymphoma-related therapy (Table 4), most of them within 3 years from diagnosis. However, lymphoma-related deaths showed a continuous pattern of occurrence up to 14 years from diagnosis. The 5- and 10-year CSS rates were 55% (95% CI, 49% to 61%) and 43% (95% CI, 36% to 50%), respectively. The 5- and 10-year PFS rates were 48% (95% CI, 42% to 54%) and 33% (95% CI, 26% to 40%), respectively, with a median PFS of 4 years (Fig 1).

Pattern of Relapse and Analysis of Prognostic Factors

Good performance status, limited stage, absence of B symptoms, absence of a bulky mass, normal serum LDH and beta-2 microglobulin, absence of additional extranodal involvement, and favorable IPI were the main clinical features significantly associated with better OS, CSS, and PFS at univariate analysis (Table 5). Among stage I patients, the group of those with normal LDH, age less than 60 years, and a performance status $\leq$ 1 had a significantly better outcome, with an OS rate of 81% and

Table 3. Survival Patterns by Ann Arbor Stage

Survival	Stage I (n = 214) %	Stage I (n = 214) 95% CI	Stage II (n = 80) %	Stage II (n = 80) 95% CI	Stage III-IV (n = 79) %	Stage III-IV (n = 79) 95% CI	Whole Series (n = 373) %	Whole Series (n = 373) 95% CI
OS								
Median, years	6.1		3.9		1.1		4.8	
Surviving at 5 years	58	50-65	46	34-57	22	13-33	48	42-53
Surviving at 10 years	29	21-37	29	18-41	19	10-30	27	21-33
CSS								
Median, years	9.9		6.5		1.2		6.6	
Surviving at 5 years	66	58-73	53	40-64	27	17-38	55	49-61
Surviving at 10 years	48	38-58	43	29-55	27	17-38	43	36-50
PFS								
Median	5.9		4.5		0.8		4.0	
Surviving at 5 years	54	46-61	48	36-59	30	19-42	48	42-54
Surviving at 10 years	36	26-46	32	18-47	27	16-39	33	26-40

PFS rate 68% at 5 years (with median PFS of 11.7 years, median CSS of 12.6 years, and median OS of 8.9 years).

Combination chemotherapy with anthracycline-containing regimens significantly improved the outcome in all patients (5-year PFS, 35% *v* 55%; $P = .0005$; and 5-year OS, 39% *v* 52%; $P = .02$). Even when the analysis is limited to stage I to II patients, the benefit of anthracycline-containing chemotherapy was statistically significant for PFS ($P < .0001$) and OS ($P = .006$). Patients receiving six or more cycles of chemotherapy had a better long-term outcome than those treated for a shorter period (10-year OS, 44% *v* 19%; $P = .03$). Among the prognostic factors that were statistically significant at the univariate analysis, IPI, B symptoms, anthracycline-containing chemotherapy, and prophylactic scrotal irradiation retained statistical significance at multivariate analysis of OS, CSS, and PFS (beta-2 microglobulin was not included in the multivariate analysis because it was available only in a small subset of patients).

Patients receiving radiotherapy have a significantly longer OS (median OS, 5.9 *v* 2 years; $P = .0008$), but most of them have a favorable IPI score. Among patients receiving radiotherapy locoregional to the primary testicular site of involvement, the OS was longer for those receiving an irradiation dose of at least 30 Gy ($P = .02$).

In 41 patients, orchiectomy was the sole treatment; 36 of them were stage I disease who achieved a surgical CR after orchiectomy. Their PFS and CSS were significantly shorter than those of patients receiving additional chemotherapy and/or radiotherapy (median PFS, 1.0 *v* 5.4 years; $P = .0012$; and median CSS, 2.9 *v* 9.2 years; $P = .031$); OS was also shorter, but the difference did not reach statistical significance (median OS, 2.1 *v* 6.4 years; $P = .070$).

At a median follow-up of 7.6 years, 195 patients (52%) relapsed. The duration of survival after relapse was poor (median, 4.5 months). Extranodal recurrence, with or without nodal disease, was reported in 140 (72%) of 195 cases (Table 6). More frequent extranodal sites of involvement at relapse, other than testis or CNS, included bone, skin, bone marrow, lung, soft tissue, adrenal glands, liver, gastrointestinal tract, and spleen. Isolated contralateral testis relapse was observed in 11 stage I to II patients and in one stage IV patient; in 31 further patients, a testis relapse was associated with other nodal and extranodal sites of localization. Anthracycline-based chemotherapy reduced

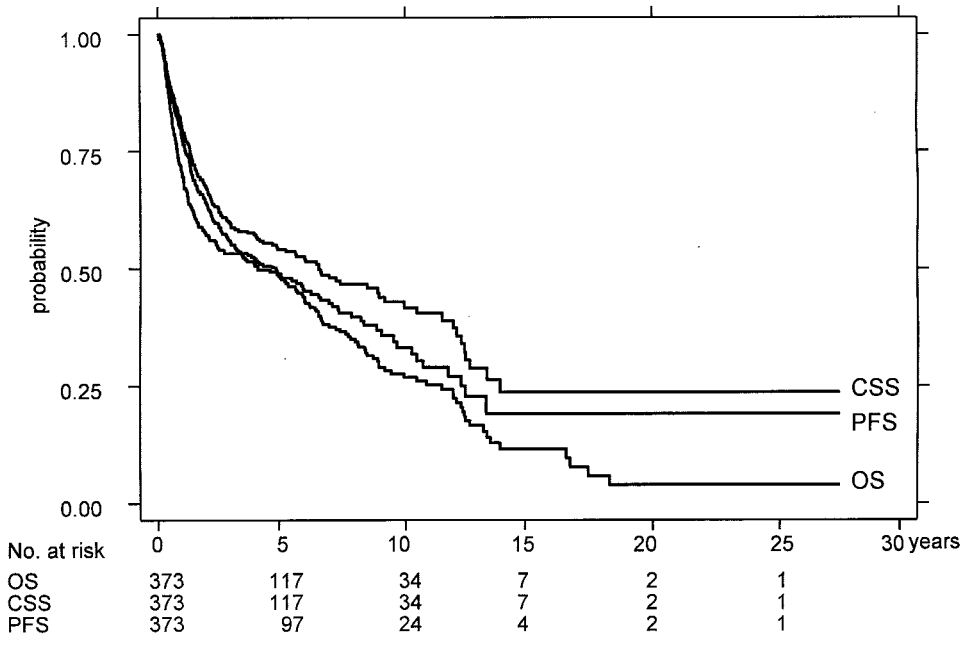

Fig 1. Kaplan-Meier estimate of overall survival, cause-specific survival, and progression-free survival in the whole series of 373 patients with primary testicular large-cell lymphoma.

Table 4. Causes of Death

	No. of Patients			
	Stage I (n = 214)	Stage II (n = 80)	Stage III-IV (n = 79)	Overall (n = 373)
Lymphoma progression	75	37	44	156
Treatment toxicity	6	3	7	16
Second tumor	8	2	1	11
Cardiac disease	8	4	1	13
Other	22	8	7	37
Unknown	1	—	—	1
Total	120	54	60	234

the rate of relapse in the contralateral testis ($P = .02$). A continuous risk of recurrence in the contralateral testis (15% at 3 years, 42% at 15 years) was present in patients not receiving radiotherapy to the contralateral testis ($P = .003$; Fig 2). Prophylactic radiotherapy to the contralateral testis was also associated with better PFS (5-year PFS, 36% *v* 70%; $P = .00001$) and OS (5-year OS, 38% *v* 66%; $P = .00001$) rates.

CNS relapses and/or progressions, occurring continuously up to 10 years after presentation, were observed in 56 patients (15%); the majority were parenchymal brain relapses (Table 6). An isolated CNS relapse was reported in 23 stage I to II patients and in 11 stage III to IV patients. Whole-brain irradiation was given to 15 of them, with only four responses. The estimated 5- and 10-year risk of CNS relapse were 19% (95% CI, 14% to 25%) and 34% (95% CI, 25% to 46%), respectively (Fig 3). Only 20% of the patients relapsing in the CNS had intrathecal CNS prophylaxis as part of their front-line therapy. Prophylactic intrathecal chemotherapy, including at least four doses of therapy, was associated with an improved PFS rate (5-year PFS, 46% [95% CI, 40% to 52%] *v* 72% [95% CI, 55% to 83%]; $P = .02$); however, its specific effect on the CNS recurrences was not statistically significant.

In the present series, only 29 patients (8%), 16 of whom had stage IV disease, received high-dose intravenous methotrexate as part of their initial treatment, apparently with no evidence of any benefit in either reducing CNS relapses or prolonging survival. On the contrary, the subset of 34 patients who received aggressive systemic chemotherapy and complete prophylaxis (intrathecal chemotherapy and scrotal irradiation) at median follow-up of 2 years seemed to have a significantly better outcome, with a 3-year OS rate of 88%. This therapeutical approach was tested, controlling for IPI and B symptoms, in a Cox model, which confirmed a significantly better outcome for patients who received such a treatment.

Table 5. Univariate Analysis of Prognostic Factors for OS, CSS, and PFS

Features	*P* (log-rank test)		
	OS	CSS	PFS
Ann Arbor stage, I/II *v* III/IV	< .0001	< .0001	< .0001
ECOG Performance status (0/1 *v* ≥2)	< .0001	.0001	.011
Presence of B symptoms	.001	< .0001	.0003
LDH, 1 × normal *v* > 1 × normal	< .0001	< .0001	.0065
Extranodal involvement other than testis	< .0001	< .0001	< .0001
Age > 60 years	.04	NS	NS
CNS involvement	.0005	< .0001	.003
Beta-2 microglobulin, 1 × normal *v* > 1 × normal	< .0001	.0001	.006
Bulky disease, > 10 cm	.003	.0008	.015
IPI score low/low-intermediate *v* intermediate/high-high risk	< .0001	< .0001	< .0001
Anthracycline-based chemotherapy	.021	.042	.0005
Intrathecal chemotherapy, ≥ 4 cycles	NS	NS	.018
Prophylactic scrotal radiotherapy	< .0001	< .0001	< .0001
Aggressive anthracycline-based chemotherapy plus intrathecal prophylaxis and scrotal irradiation	.0001	.0006	.0003

Abbreviations: NS, not significant; ECOG, Eastern Cooperative Oncology Group.

Table 6. Sites of Initial Failure

	No. of Patients			
	Stage I (n = 214)	Stage II (n = 80)	Stage III-IV (n = 79)	Overall (n = 373)
Failing patients	102	44	49	195
Contralateral testis plus other nodal and extranodal sites	19	5	7	31
Isolated contralateral testis	10	1	1	12
Total CNS relapse	27	12	17	56
Brain	16	8	6	30
Meninges	3	2	8	13
Brain + meninges	3	0	3	6
Unspecified	5	2	0	7
Isolated CNS relapse	17	6	11	34
Brain	11	4	4	19
Meninges	1	0	5	6
Brain + meninges	3	0	2	5
Unspecified	2	2	0	4
Isolated extranodal sites other than testis or CNS	47	12	24	83
Total extranodal sites	76	25	39	140

DISCUSSION

Because primary testicular presentation of DLCL is rare, only the international cooperation among several referral cancer centers has allowed this review of 373 cases. Some of these patients have been already included in previous reports.[16-18,28-31] Thus far, no prospective studies of testicular lymphomas have been conducted. Therefore, despite its retrospective nature, this study represents a unique tool for defining the presentation and outcome of primary testicular lymphoma, a peculiar subset of DLCL, differing from its nodal counterpart in several respects.[9]

The poor outcome of most patients with testicular large-cell lymphoma is confirmed by this study; the long-term survival curves show no clear evidence of a substantial proportion of cured patients (Fig 1). Even for patients with stage I disease and good-risk IPI, the outcome seems worse than what is reported for DLCL at other sites.

Our series also confirms the previously reported high rate of extranodal recurrence and the frequent involvement of unusual sites. The duration of survival after relapse seems to be poor. Failures usually occurred within 1 to 3 years after the initial therapy. However, several late relapses have been observed up to 14 years after diagnosis, especially in the CNS and the contralateral testis, the latter raising the problem of distinguishing a new primary disease versus a late recurrence. The possibility of late CNS relapses has been reported in other studies as well and is in marked contrast with the median time to CNS relapse of less than 1 year in patients with aggressive nodal lymphomas.[32]

A continuous occurrence of lymphoma-related deaths up to several years after treatment has also been seen in other patients with localized DLCL;[33] however, the extranodal pattern of

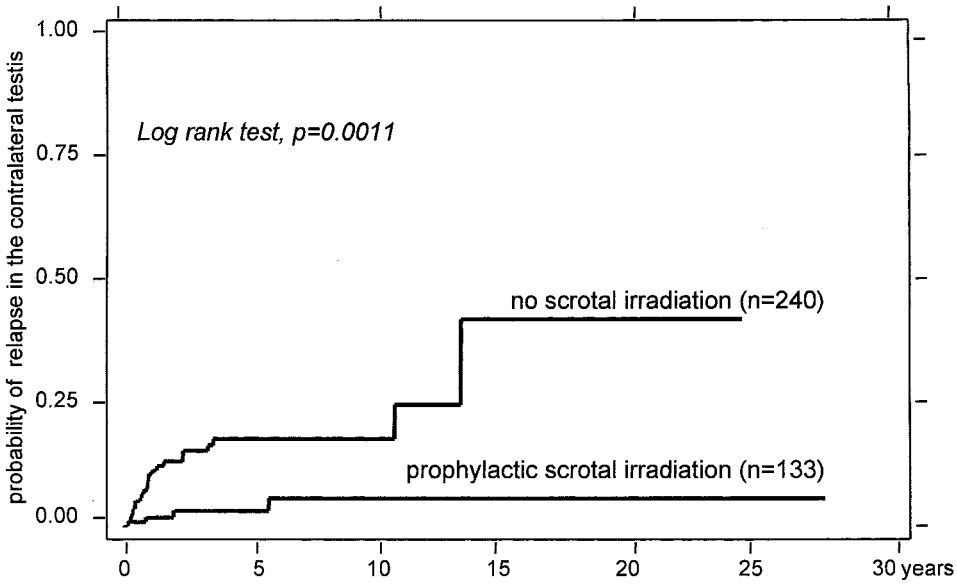

Fig 2. Continuous risk of recurrence in the contralateral testis in patients not receiving prophylactic scrotal radiotherapy (*P* = .0011).

relapse is more unusual in DLCL primarily arising outside the testis. The cause of the consistently observed high rate of extranodal relapses in primary testicular lymphoma remains undefined.[29] A particular pattern of expression of adhesion molecules, resulting in poor adhesion of lymphoma cells to the extracellular matrix, may contribute to this behavior.[34,35] In addition, both testis and CNS have been considered immune-privileged sites where lymphoma cells may escape from T lymphocyte–mediated immunosurveillance,[36] and both testis and CNS have been considered sanctuary sites where chemotherapy may have reduced efficacy.

Adjuvant chemotherapy after orchiectomy and retroperitoneal irradiation was introduced, similar to the other presentations of DLCL, in the early 1980s, and some reports showed a reduced relapse rate and, more importantly, an improved overall survival for patients treated with chemotherapy.[16,37] However, the benefit from aggressive chemotherapy for early-stage testicular lymphoma is controversial.[17,18,37-39] In the present series, even patients with localized disease had a significantly longer PFS and OS when treated with anthracycline-containing chemotherapy regimens. The recent reports of improved survival with the addition of rituximab to the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy regimen in elderly DLCL patients support the hypothesis that this combination also may be of benefit in the subset of primary DLCL of the testis.[40]

Before the widespread use of anthracycline chemotherapy, patients with stage I and II testis lymphomas were managed mainly with postorchiectomy radiotherapy to the para-aortic and pelvic lymph nodes.[13-15] At present, radiotherapy to the retroperitoneal nodes has largely been abandoned in stage I patients,[41] but it is generally given to stage II patients as part of the combined-modality approach recommended in stage II DLCL presenting in other sites.[42] Unfortunately, the wide variability of doses and fields in our retrospective analysis prevented a reliable study of the impact of retroperitoneal radiotherapy in localized testis lymphomas, although the prognostic impact of this strategy seems to be dose-dependent.

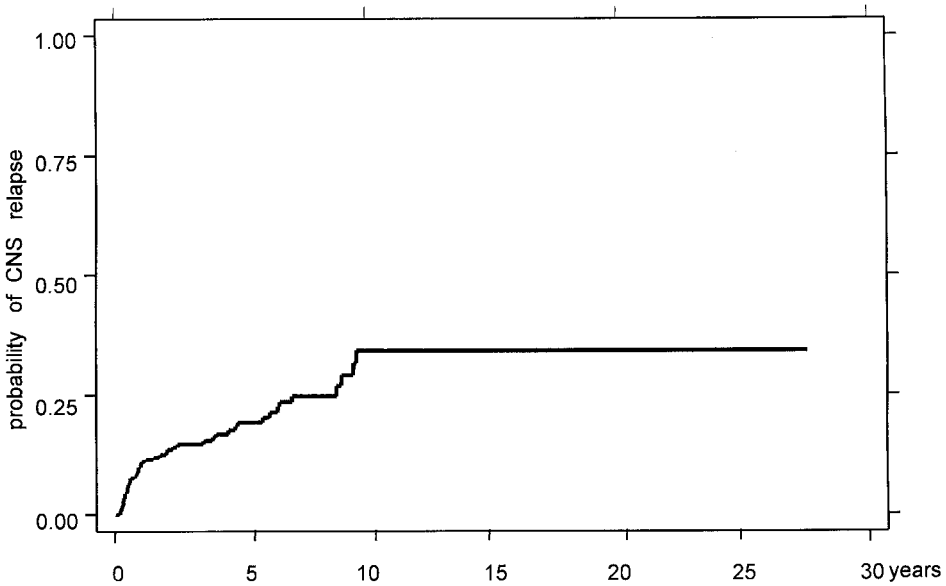

Fig 3. Continuous risk of recurrence in the central nervous system in the whole series of 373 patients with primary testicular large-cell lymphoma.

A substantial rate of failure in the contralateral testis has been reported in the literature, and it has been confirmed in our cases where continuous high risk of recurrence in the contralateral testis is documented in patients not receiving prophylactic scrotal radiotherapy (Fig 2). Our data confirm that low-dose radiotherapy to the contralateral testis, which has been recommended by some authors for all patients with primary testis lymphoma,[3,18,37,38] could reduce the risk of failure at this site.

Distant extranodal failures, especially in the CNS, remain a major problem, even in patients who receive a full course of doxorubicin-based chemotherapy. The issue of optimal treatment of patients at the time of isolated CNS relapses is unresolved. Whole-brain radiotherapy is most often used; however, this treatment has substantial potential neurotoxicity, especially in the elderly. A recent report indicates that high-dose intravenous methotrexate alone might be a feasible and effective alternative to whole-brain radiotherapy.[32] The high rate of CNS progression observed in historical series has led to a recommendation for routine CNS prophylaxis with at least intrathecal chemotherapy.[18,29,38] The value of intrathecal chemotherapy, introduced as a prophylactic measure in the 1990s, is still controversial because CNS failures occur more frequently in brain parenchyma than in meninges,[32,43] and CNS relapses have been observed also in patients who received intrathecal chemotherapy. A clear propensity for parenchymal involvement is confirmed in our study (Table 6) and is in marked contrast to primary nodal DLCL, where the CNS relapse rate is below 5% and the leptomeninges are the dominant site of involvement.[43,44] In our series, intrathecal chemotherapy was associated with an improved PFS; however, its direct effect on preventing CNS relapses was not statistically significant, possibly because of the low number of patients who received such treatment (80% of CNS relapses did not receive any intrathecal prophylaxis).

The use of high-dose methotrexate to deliver parenchymal CNS prophylaxis has been shown to be effective among patients with primary nodal lymphomas[44] but is not always practical or feasible in elderly patients, and even the delivery of standard intrathecal chemotherapy is often problematic. In this series, only 29 patients (8%) received high-dose intravenous methotrexate as CNS prophylaxis, apparently with no evidence of any benefit in either reducing CNS relapses or prolonging survival; but again, the small number of treated cases does not allow any conclusions to be drawn. On the contrary, the small subset of patients who received aggressive systemic chemotherapy and complete prophylaxis (intrathecal chemotherapy and scrotal irradiation) showed a significantly better outcome, with a 3-year actuarial OS rate of 88%. However, their median follow-up is short, a possible selection bias cannot be ruled out, and the efficacy of this policy has yet to be validated in prospective clinical trials.

In conclusion, this retrospective IELSG survey represents the largest body of information on outcomes of patients with testis lymphoma to date. It confirms the findings of smaller studies and provides interesting data concerning the best treatment strategy, but because of its retrospective nature, it does not provide a definitive answer as to the optimal approach to this disease.

The management of patients with testicular lymphoma presents several challenges. Because of the poor prognosis, an aggressive treatment approach is warranted. However, testicular lymphoma is predominantly a disease of older men who often have limited ability to tolerate aggressive treatment. Improved understanding of the genetic and molecular characteristics of testicular lymphoma may help in the future to identify patients at risk of CNS failure and to tailor the treatment to the individual patient.

The rarity of the disease makes randomized trials virtually impossible. Hence, an international collaboration is crucial to properly address the management of testicular lymphoma. On the basis of the results of this study, an international prospective trial has been launched by the IELSG to assess the feasibility and efficacy of prophylactic radiotherapy to the contralateral testis and intrathecal methotrexate in addition to rituximab plus CHOP chemotherapy. This study should test the results of this retrospective analysis and can provide further evidence to support the use of systemic chemotherapy and complete prophylaxis (intrathecal chemotherapy and scrotal irradiation), thus helping to define some standard guidelines for the management of testicular DLCL. We are aware that the potential benefit of rituximab for a lymphoma arising in immune privileged sites remains questionable (despite data suggesting its crossing of the blood-brain barrier, it does not seem to penetrate into CNS well when administered intravenously, and its intrathecal administration is poorly studied). However, the association of rituximab plus CHOP has been shown to be significantly better than CHOP alone,[40] and it is considered the standard treatment of DLCL at any site in several institutions. Given the observed propensity for parenchymal involvement of CNS relapses, other regimens, capable of circumventing the blood-brain barrier,[45] might be more appropriate in view of the CNS penetration of methotrexate and cytarabine, but it may be difficult to test an aggressive regimen in a large multicentric study of mainly elderly patients.

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APPENDIX

The appendix is available online at www.jco.org.

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