Original Investigation

Ocular Adnexal Diffuse Large B-cell Lymphoma
A Multicenter International Study

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IMPORTANCE The clinical features of diffuse large B-cell lymphoma (DLBCL) subtype of ocular adnexal lymphoma have not previously been evaluated in a large cohort to our knowledge.

OBJECTIVE To investigate the clinical features of ocular adnexal DLBCL (OA-DLBCL).

DESIGN, SETTING, AND PARTICIPANTS This retrospective international cooperative study involved 6 eye cancer centers. During 30 years, 106 patients with OA-DLBCL were identified, and 6 were excluded from the study. The median follow-up period was 52 months.

MAIN OUTCOMES AND MEASURES Overall survival, disease-specific survival (DSS), and progression-free survival were the primary end points.

RESULTS One hundred patients with OA-DLBCL were included in the study (median age, 70 years), of whom 54 (54.0%) were female. The following 3 groups of patients with lymphoma could be identified: primary OA-DLBCL (57.0%), OA-DLBCL and concurrent systemic lymphoma (29.0%), and ocular adnexal lymphoma relapse of previous systemic lymphoma (14.0%). Of 57 patients with primary OA-DLBCL, 53 (93.0%) had Ann Arbor stage IE disease, and 4 (7.0%) had Ann Arbor stage IIE disease. According to the TNM staging system, 43 of 57 (75.4%) had T2 tumors. Among all patients, the most frequent treatments were external beam radiation therapy with or without surgery (31.0%) and rituximab–cyclophosphamide, hydroxydaunorubicin, vincristine sulfate, prednisone (CHOP) or rituximab–CHOP-like chemotherapy with or without external beam radiation therapy (21.0%). The 5-year overall survival among the entire cohort was 36.0% (median, 3.5 years; 95% CI, 2.5-4.5 years). Relapse occurred in 43.9% (25 of 57) of patients with primary OA-DLBCL. Increasing T category of the TNM staging system was predictive of DSS (P = .04) in primary OA-DLBCL, whereas the Ann Arbor staging system was not. However, when taking all 100 patients into account, Ann Arbor stage was able to predict DSS (P = .01). Women had a longer median DSS than men (9.8 years; 95% CI, 1.9-17.7 years vs 3.3 years; 95% CI, 1.6-5.0; P = .03).

CONCLUSIONS AND RELEVANCE Most patients with primary OA-DLBCL were seen with Ann Arbor stage IE and TNM T2 disease. The 5-year overall survival was between 2.5 and 4.5 years, which is the 95% CI around the median of 3.5 years in this cohort. Increasing T category appears to be associated with decreased DSS among patients with primary OA-DLBCL. When taking all patients into account, sex and Ann Arbor stage also seem to be DSS predictors.

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Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma, accounting for 30% to 40% of all non-Hodgkin lymphomas.[1] It is a heterogeneous disease that is clinically, biologically, and molecularly diverse.[2] Extranodal lymphoma occurs in approximately 40% of patients with DLCBL, commonly involving the gastrointestinal tract, skin, and soft tissue.[1-3] Diffuse large B-cell lymphoma comprises 5% to 15% of ocular adnexal lymphomas (OALs), with the orbit being the most frequent site affected.[4-7]

Survival of patients with DLBCL in general has improved during the past decades following introduction of the anti-CD20 antibody rituximab, combined with anthracycline-containing cyclophosphamide, hydroxydaunorubicin, vincristine sulfate, prednisone (CHOP) or CHOP-like chemotherapy.[8] The 5-year survival outcomes are high in patients with DLBCL treated with rituximab-CHOP when stratified by age, different prognostic groups, and tumor bulk, but in refractory or progressive disease the prognosis remains poor.[3,9-12]

Two staging systems exist for OAL. The modified Ann Arbor staging system[13] is used for determining the clinical stage of patients with both nodal and extranodal lymphomas. When applied to lymphomas of extranodal sites (such as OALs), the Ann Arbor staging system has limitations. For example, two-thirds of OALs are designated as stage IE[14,15] independent of size, location, multicentricity, and unilaterality or bilaterality of the tumors. The site-specific American Joint Committee on Cancer TNM staging system differentiates between lymphomas of the eyelids, conjunctiva, orbit, lacrimal gland, and lacrimal sac[16] and allows for descriptors indicating whether an OAL is bilateral or multicentric. Briefly, the T category indicates the exact location of the primary tumor in the ocular adnexa. The N category indicates the extent of lymph node involvement, and the M category indicates involvement of extranodal tissues or organs external to the ocular adnexa.[14] Therefore, a more detailed picture of the local disease extent can be documented. In ocular adnexal DLBCL (OA-DLCBL), the prognostic utility of the Ann Arbor staging system and the TNM staging system for OAL needs to be further validated. Hence, the objectives of this international, multicenter study were to investigate the clinical and histopathologic features in patients with OA-DLBCL and to assess the usefulness of the Ann Arbor staging system and the TNM staging system in these tumors.

Methods

Study Design

The study followed the tenets of the Declaration of Helsinki, with institutional review board and health information privacy agency approval obtained from the Danish Data Protection Agency. The Danish National Ethics Committee did not require informed consent because most of the patients were deceased at the time of the study. Eligible patients with a histologic diagnosis of OA-DLBCL were identified from the databases of 6 participating eye cancer centers in a 30-year search period from January 1, 1980, through December 31, 2010.

Histopathology and DLBCL Subclassification

The pathologic specimens were evaluated by each center. Specimens were originally stained with hematoxylin-eosin and examined by immunohistochemistry (IHC) with the following panel of antibodies: CD3, CD5, CD79α, CD20, CD23, CD10, BCL2, BCL6, cyclin-D1, and MUM-1/IRF4 antibody.[2] The Ki-67 proliferative index was estimated by IHC in quartiles. Further IHC subgrouping was conducted to determine a surrogate for molecular subtypes (ie, germinal center B-cell [GCB]-like or activated B-cell-like[17]). Patients were divided into the GCB or non-GCB IHC subgroup according to the algorithm by Hans et al.[18]

Clinical Data

Clinical data were recorded. These included sex, age, symptoms, clinical findings, year of diagnosis, and serum lactate dehydrogenase level, as well as treatment, response to therapy, recurrence-free periods, time and localization of relapse, disease stage at the last follow-up time, and survival duration and cause of death. Also recorded was the International Prognostic Index (IPI), including age older than 60 years, Ann Arbor stage, more than 1 extranodal site, and performance status of 2 or higher.

Primary OAL was defined as clinically seen lymphoma that was limited to the ocular adnexal region (Ann Arbor stage IE) with or without involvement of unilateral preauricular or submandibular lymph nodes or adjacent structures such as the parotid gland (Ann Arbor stage IIE), and no history of lymphoma disease. Patients having OAL with concurrent advanced systemic lymphoma and initial symptoms outside the ocular adnexal region were considered to have disseminated OAL. A third group of patients had a history of systemic lymphoma in remission and were seen with a relapse of lymphoma in the ocular adnexal region (relapsed OAL). Assessment of disease extent was registered using the Ann Arbor staging system in all patients.[19] The extent of ocular adnexal involvement of primary OAL was also evaluated according to the TNM staging system for OAL.[12,16] Treatment response criteria were assessed as complete response, partial response, and stable disease.[20]

Statistical Analysis

Overall survival (OS), disease-specific survival (DSS), and progression-free survival were considered the primary end points. Overall survival was defined from the date of diagnosis to the date of follow-up or death from any cause. Disease-specific survival was defined as the date of diagnosis to the date of follow-up or death from lymphoma. Progression-free survival was calculated from the date of diagnosis to either the date of first relapse or progression after initial treatment to the date of last contact or death from any cause. Kaplan-Meier plots were used to visualize survival outcomes. The different risk groups were compared using log-rank test. Individual risk factors were compared using the Fisher exact test. A software program (SPSS version 20; IBM) was used for statistical calculations. $P < .05$ was considered significant.

Table 1. Clinical and Staging Characteristics of 100 Patients With Ocular Adnexal Diffuse Large B-cell Lymphoma

Characteristic	Total Patients, No. (%) (N = 100)	Disease Presentation, No. of Patients			*P* Value, Fisher Exact Test
		Primary (n = 57)	Disseminated (n = 29)	Relapsed (n = 14)	
Sex					.44
Male	**46** (46.0)	23	15	8	
Female	**54** (54.0)	34	14	6	
Age at presentation, y					.61
≤60	**29** (29.0)	19	7	3	
>60	**71** (71.0)	38	22	11	
Laterality					.70
Unilateral	**91** (91.0)	51	26	14	
Bilateral	**9** (9.0)	6	3	0	
Ann Arbor stage					<.001
IE	**56** (56.0)	53	0	3	
IIE	**15** (15.0)	4	8	3	
IIIE	**6** (6.0)	0	6	0	
IVE	**23** (23.0)	0	15	8	
Treatment					.04
EBRT with or without surgery	**31** (31.0)	20	9	2	
Rituximab					
In combination with CHOP or rituximab-CHOP-like with or without EBRT or ASCT[a]	**21** (21.0)	8	6	7	
In combination with other chemotherapy[b]	**9** (9.0)	5	2	2	
Only	**1** (1.0)	1	0	0	
Chemotherapy					
CHOP or CHOP-like with or without EBRT or ASCT[a]	**7** (7.0)	2	2	3	
Other chemotherapy[b]	**19** (19.0)	14	5	0	
Other treatment[c]	**12** (12.0)	7	5	0	
Recurrence or progression (n = 97)[d]					.001
No	**39** (40.2)	31	7	1	
Yes	**58** (59.8)	25	20	13	
Disease status at last follow-up					
Complete remission	**29** (29.0)	22	7	0	.02
Alive with disease	**8** (8.0)	3	4	1	
Dead from lymphoma	**44** (44.0)	20	14	10	.03
Dead from other cause than lymphoma	**19** (19.0)	12	4	3	

Abbreviations: ASCT, autologous stem cell transplantation; CHOP, cyclophosphamide, hydroxydaunorubicin, vincristine sulfate, prednisone; EBRT, external beam radiation therapy.

[a] One patient received ASCT.

[b] Other monotherapy or combination chemotherapy includes chlorambucil, cyclophosphamide, vincristine sulfate, etoposide, prednisone, cytarabine, methotrexate, and 5-fluorouracil.

[c] Other treatment includes surgery only, prednisone only, unknown, and no treatment.

[d] Three patients had unknown status.

Results

Clinical Features

In total, 106 patients with OA-DLBCL were identified from 6 eye cancer centers. Six patients were excluded from the study because of missing data, leaving 100 patients for analysis. The median follow-up period was 52 months. Thirty-four patients were from Copenhagen, Denmark; 25 patients were from Liverpool, England; 18 patients were from Houston, Texas; 15 patients were from Hyderabad, India; 6 patients were from Melbourne, Australia; and 2 patients were from Atlanta, Georgia. Selected patient data from the cancer centers in Copenhagen and Houston were previously published in local studies[7,21] on various histologic subtypes of OAL. Fifty-four patients (54.0%) were female (**Table 1**). The median age was 70 years (age range, 4-97 years). The median ages stratified by local eye cancer centers were 78 years in Copenhagen, 73 years in Liverpool, 64 years in Houston, 45 years in Hyderabad, 59 years in Melbourne; and 68 years in Atlanta. The ratios of women to men were 0.9 in Copenhagen, 1.5 in Liverpool, 1.6 in Houston, 0.5 in Hyderabad, 5.0 in Melbourne, and 2.0 in Atlanta.

Of 100 patients, 57 were diagnosed as having primary OA-DLBCL as defined above, 29 (29.0%) had systemic lymphoma with a secondary manifestation in the ocular adnexa, and 14 (14.0%) were seen with an ocular adnexal relapse of systemic lymphoma. These results are summarized in Table 1.

The orbit and conjunctiva were the most frequently involved ocular adnexal sites in all 3 groups. Tumor or swelling (75.0%) was the most common symptom (**Table 2**). The me-

Table 2. Location, Frequency of Symptoms, and Clinical Signs at Presentation of Ocular Adnexal Diffuse Large B-cell Lymphoma[a]

Variable	Total Patients, No. (%) (N = 100)	Disease Presentation, No. of Patients		
		Primary (n = 57)	Disseminated (n = 29)	Relapsed (n = 14)
Location in the ocular adnexal region				
Orbit	**49** (49.0)	26	16	7
Conjunctiva	**35** (35.0)	18	10	7
Lacrimal gland	**18** (18.0)	8	8	2
Eyelid	**15** (15.0)	7	6	2
Lacrimal sac	**1** (1.0)	0	0	1
Symptom				
Tumor or swelling	**75** (75.0)	35	24	16
Irritation or pain	**32** (32.0)	14	12	6
Epiphora	**23** (23.0)	7	11	5
Exophthalmus	**20** (20.0)	11	6	3
Diplopia	**16** (16.0)	7	9	0
Ptosis	**14** (14.0)	6	5	3
Decreased visual acuity	**5** (5.0)	4	0	1
Dry eye	**1** (1.0)	1	0	0
Not stated	**4** (4.0)	3	1	0
Clinical sign				
Mass	**82** (82.0)	38	29	15
Globe displacement	**39** (39.0)	21	14	4
Chemosis	**20** (20.0)	13	7	0
Restricted eye movement	**19** (19.0)	10	6	3
Resistance	**17** (17.0)	11	4	2
Edema	**14** (14.0)	8	5	1
Diplopia	**13** (13.0)	6	7	0
Ptosis	**12** (12.0)	9	2	1
Epiphora	**8** (8.0)	6	2	0
Not stated	**2** (2.0)	1	1	0

[a] Patients may have 1 or more locations, presentation symptoms, or clinical signs.

dian symptom duration was 9.6 months (range, 1-96 months). The most common clinical signs were a mass (82.0%) and globe displacement (39.0%) (**Figure 1**A and B). Serum lactate dehydrogenase level was available in 77 patients (77.0%). Among these, 19.5% (15 of 77) had an elevated serum lactate dehydrogenase level. The median IPI was 3 among 20 patients, all from Copenhagen, of whom 80.0% (16 of 20) had a high IPI (3 or 4) and 20.0% (4 of 20) had a low IPI (0 to 2).

Ann Arbor Staging System–Based and TNM-Based Staging of Primary OA-DLBCL

Of 57 patients with primary OA-DLBCL, 53 (93.0%) were seen with Ann Arbor stage IE disease and 4 (7.0%) with Ann Arbor stage IIE disease (Table 1). Of 57 patients with primary OA-DLBCL, 4 had involvement of the conjunctiva only (T1 disease), 43 had T2 disease (involvement of the orbit with or without the lacrimal gland), 3 had T3 disease (preseptal eyelid involvement), and 7 had T4 disease (extraorbital involvement) (**Table 3**). The posterior orbit (T2cN0M0) was the most frequently involved site in T2 disease, followed by the anterior orbit with or without the lacrimal gland (T2a-bN0M0). Lymph node (N1) involvement was present in 4 of 57 patients (7.0%).

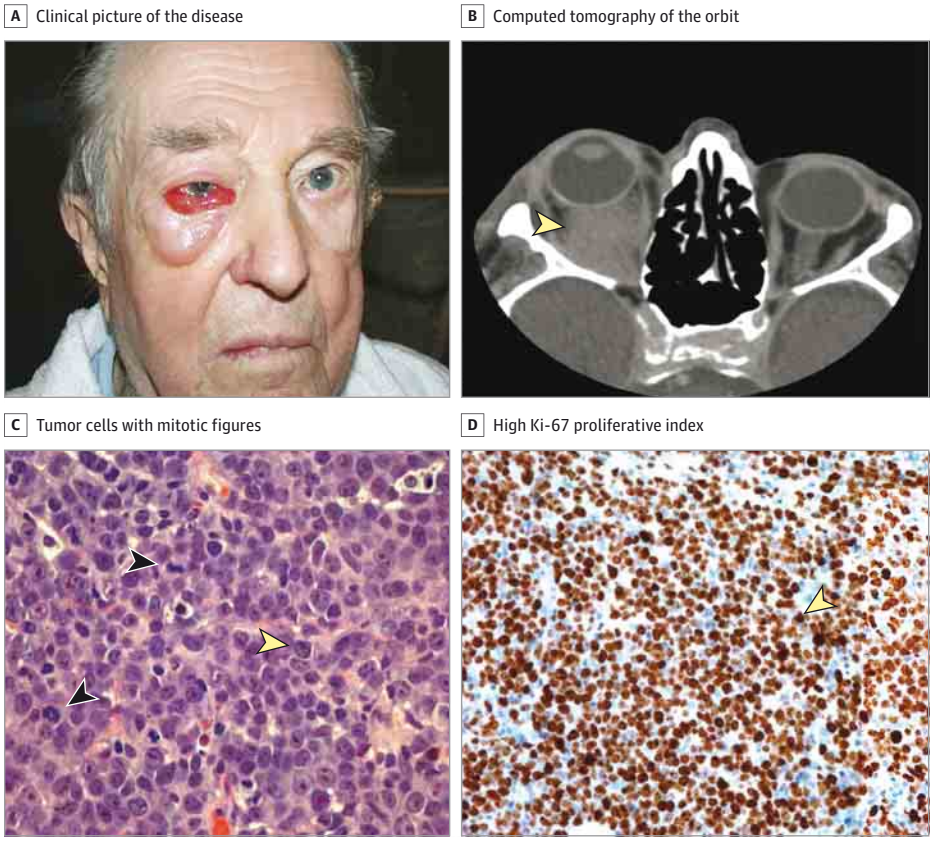
Histopathologic Findings

Information on morphologic details was available in 63 of 100 patients with OA-DLBCL. Centroblastic morphology was present in 57 specimens (90.5%), and 6 specimens (9.5%) had immunoblastic morphology (Figure 1C). Overall survival was unrelated to morphology (P = .90, log-rank test). The Copenhagen patients with centroblastic morphology had better DSS, as previously published.[7] Eighty-four OA-DLBCLs were subdivided further according to the algorithm by Hans et al.[18] Of these, 58 (69.0%) were categorized as non-GCB subtype, and 26 (31.0%) were categorized as GCB subtype. Information on the Ki-67 proliferative index was available in 94 patients (94.0%). The median Ki-67 proliferative index was 72.5% (range, 5.0%-100.0%) (Figure 1D). No difference in OS was identified in patients with non-GCB vs GCB subtype or with an increasing Ki-67 proliferative index (P = .14 and P = .10, respectively, log-rank test).

Treatment

Generally, high intracenter and intercenter variability in the treatment of OA-DLBCL was observed (eTable in the Supplement). External beam radiation therapy (EBRT) was the most frequently used treatment modality (31 of 100), followed by

Figure 1. Clinical and Histopathologic Findings of Ocular Adnexal Diffuse Large B-cell Lymphoma



A, Clinical picture of the disease. B, Computed tomography of the orbit showing the tumor mass (yellow arrowhead). C, Tumor cells (yellow arrowhead) with mitotic figures (black arrowheads) (hematoxylin-eosin, original magnification ×400). D, High Ki-67 proliferative index exceeding 90% (yellow arrowhead) (original magnification ×400).

rituximab-CHOP or rituximab-CHOP-like chemotherapy (21 of 100) and rituximab combined with other chemotherapy (9 of 100) (Table 1). Of 21 patients who received rituximab-CHOP or rituximab-CHOP-like regimens, 17 patients (81.0%) were in Houston. Among 15 of these, the mean (SD) number of cycles was 5.0 (2.2). These patients were all diagnosed as having OA-DLBCL after 2000 (ie, after Food and Drug Administration approval for rituximab in 1997). However, in the whole cohort, 79.0% of patients were diagnosed after 1997. Among the patients receiving rituximab-CHOP or rituximab-CHOP-like regimens, 10 of 21 (47.6%) received additional EBRT.

The mean (SD) radiation dose was 34 (14) Gy, and the mean (SD) dose per fraction was 2 (1) Gy. In 5 patients, the number of fractions per week was available, and all received 5 fractions per week. Data for the period in which EBRT was applied and the specific techniques were unavailable. Pathoanatomical targets were available for only 10 patients, all from Houston.

Among all patient groups, no differences were observed in treatment regimen or Ann Arbor stage ($P = .27$, the Fisher exact test). Similarly, no differences were seen in T category or treatment regimen among 57 patients diagnosed as having primary OA-DLBCL ($P = .49$, the Fisher exact test).

Treatment Outcomes and Survival

Recurrence or progression was observed in 25 of 57 patients (43.9%) with primary OA-DLBCL (Table 1). The time to relapse was known in 12 of 57 patients, with the median being 12.5 months (range, 1-191 months). The median progression-free survival was 5.0 years. All 25 patients with relapse had recurrence within the ocular adnexa, involving the orbit (n = 20), conjunctiva (n = 2), eyelid (n = 2), and lacrimal gland (n = 1).

In the entire study cohort, 63.0% of patients with DLBCL died. Of these, 44 (69.8%) died of lymphoma-related causes. The median time from initial diagnosis to lymphoma-related death was 33 months (range, 1-192 months). No differences in OS or DSS were observed among participating centers ($P = .25$ and $P = .75$, respectively, log-rank test). The OS rates at 3 and 5 years were 57.0% and 36.0%, respectively (median, 3.5 years; 95% CI, 2.5-4.5 years) for the entire cohort, whereas the DSS rates at 3 and 5 years were 64.0% and 47.0%, respectively (median, 4.8 years; 95% CI, 2.9-6.7 years).

Overall survival did not seem to be associated with treatment modality or date of diagnosis (before vs after 1997) ($P = .76$ and $P = .75$, respectively, log-rank test). No survival trends were identified among patients treated with rituximab-CHOP vs rituximab-CHOP-like chemotherapy when stratified by receipt of EBRT ($P = .93$, log-rank test). Of 20 patients treated with rituximab-CHOP or rituximab-CHOP-like chemotherapy with or without EBRT, 11 were alive at follow-up, and 8 of them were in complete remission. Patients older than 60 years had poorer median OS (3.3 years; 95% CI, 2.2-4.4 years) than patients 60 years or younger (8.3 years; 95% CI, 0.6-15.9 years) ($P = .03$, log-rank test). However, no difference was observed between the

2 groups with regard to progression-free survival and DSS (P = .91 and P = .26, respectively, log-rank test). Furthermore, the median DSS was significantly higher among women (9.8 years, 95% CI, 1.9-17.7 years) than among men (3.3 years; 95% CI, 1.6-5.0 years) (P = .03, log-rank test) (**Figure 2**A). This trend was also present when stratified by T category and Ann Arbor stage. The DSS did not differ among patients with primary, disseminated, and relapsed OA-DLBCL (P = .09, log-rank test). Among all groups, patients with Ann Arbor stage IVE disease had poorer median DSS (1.4 years; 95% CI, 0.2-2.6 years) than patients with Ann Arbor stage IE disease (8.3 years; 95% CI, 4.0-12.5 years), stage IIE disease (9.8 years; 95% CI, 2.6-17.0 years), and stage IIIE disease (5.0 years; 95% CI, 1.5-8.5 years) (P = .01, log-rank test) (Figure 2B).

Among 57 patients with primary OA-DLBCL, a marginal association between DSS and increasing T category was detected when patients were divided into overall T1, T2, T3, and T4 categories using the TNM-based system (P = .04, log-rank test). In this patient group, the median DSS was 9.8 years (95% CI, 6.9-12.4 years) for patients with T2 tumors and 4.4 years (95% CI, 2.4-5.2 years) for patients with T4 tumors (eFigure, A, in the Supplement). Further analysis of the association of T subcategories (eg, T1a, T1b, and T1c) with DSS showed no differences (P = .17, log-rank test). Furthermore, the Ann Arbor staging system did not predict DSS in patients with primary OA-DLBCL (P = .69, log-rank test) (eFigure 1, B, in the Supplement).

Table 3. Staging of 57 Primary Ocular Adnexal Diffuse Large B-cell Lymphomas According to the TNM-Based Staging System[a]

Ocular Adnexal Location and TNM Staging	Patients, No. (%)
Conjunctiva (n = 4)	
bT1bN0M0	2 (3.5)
bT1cN0M0	2 (3.5)
Orbit with or without lacrimal gland (n = 43)	
T2aN0M0	5 (8.8)
T2aN1M0	2 (3.5)
T2bN0M0	9 (15.8)
bT2bN0M0	1 (1.8)
T2cN0M0	23 (40.4)
T2cN1M0	1 (1.8)
bT2cN0M0	1 (1.8)
T2dN0M0	1 (1.8)
Preseptal eyelid (n = 3)	
T3N0M0	2 (3.5)
T3N1M0	1 (1.8)
Extraorbital (n = 7)	
T4bN0M0	1 (1.8)
T4cN0M0	3 (5.3)
T4cN1M0	1 (1.8)
bTcN0M0	1 (1.8)
T4dN0M0	1 (1.8)

[a] The TNM-based staging system according to the seventh edition by the American Joint Committee on Cancer.

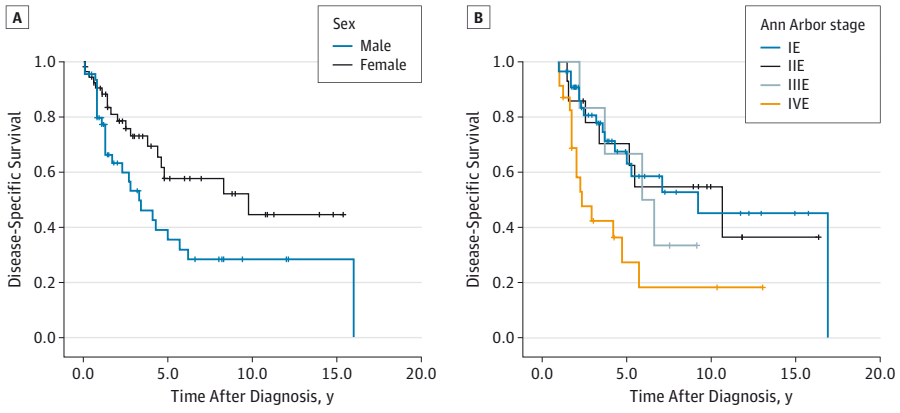
Discussion

To our knowledge, this international collaborative study represents the largest reported cohort of patients with OA-DLBCL with documented clinical characteristics. It is the first to date to analyze the usefulness of the American Joint Committee on Cancer criteria of the TNM staging system in OA-DLBCL only.

Most patients were approximately 70 years old, with a slight predominance of women, consistent with DLBCL at other nodal and extranodal sites.[3,22-25] Patients with low-grade OAL are generally 5 to 6 years younger, ranging from 63 to 65 years old.[5,21,22,26-30] Patients in Hyderabad had a younger median age and an overrepresentation of women. These variations may be related to differing demographic patterns among geographical regions[31] but are consistent with observations in a recently published international, multicenter study[32] of ocular adnexal follicular lymphoma. The OA-DLBCL herein generally involved the orbit and conjunctiva unilaterally, consistent with previous series of OA-DLBCL.[5,6,29,33]

The OS for the entire study group was between 2.5 and 4.5 years, which is the 95% CI around the median of 3.5 years in this population sample. Nevertheless, smaller series of OA-DLBCL with less demographic population heterogeneity have

Figure 2. Disease-Specific Survival Among 100 Patients With Ocular Adnexal Diffuse Large B-cell Lymphoma



A, Disease-specific survival was higher in women (median, 9.8 years) than in men (median, 3.3 years) (P = .03, log-rank test). B, Increasing Ann Arbor stage was associated with decreased disease-specific survival (P = .01, log-rank test). The crossed symbols indicate censored patients.

reported OS rates ranging from 50% to 56%.[26,34,35] In extranodal DLBCL elsewhere, survival outcomes depend on different variables, including anatomical site of the lymphoma, treatment, age, age-adjusted IPI, bulk of disease, toxicity, and comorbidity.[3,10-12,36] In particular, the addition of rituximab to CHOP treatment has improved survival for patients with DLBCL.[37] In a study[9] by the Groupe d'Etude des Lymphomes de l'Adulte among patients older than 65 years with nodal DLBCL, the 5-year OS was 58% in patients treated with rituximab-CHOP compared with 45% in patients treated with CHOP alone. Similar outcome results were obtained recently in a large database study[12] among patients older than 65 years with extranodal DLBCL. The effect of EBRT on outcomes in extranodal craniofacial (including orbital) lymphomas is unclear.[38,39] In the present study, the most common treatment modalities were EBRT and rituximab-CHOP and rituximab–CHOP-like chemotherapy, but treatment alone could not address the poor outcome. Our population was likely too heterogeneous and the patient groups too small to reach further conclusions on treatment and outcomes in OA-DLBCL. In particular, the lack of rituximab-CHOP or rituximab–CHOP-like chemotherapy and the differences in epidemiologic parameters and geographical treatment variations across time may in part explain our low survival rates. Furthermore, we could not fully assess reliable trends of other known prognostic risk indicators such as IPI, comorbidity, or treatment-related toxicity.[11,12] Additional inherent caveats of this study include selection bias of the retrospective design and variable allocation of patients into treatment regimens among the participating centers owing to demographic and socioeconomic differences.

Consistent with nodal DLBCL,[24,40,41] we found that men had poorer DSS than women. This sex-related adverse prognosis might be more pronounced in patients treated with rituximab-containing chemotherapy, suggesting that women respond better to immunotherapy.[40,41]

Most patients with primary OA-DLBCL had involvement of the posterior orbit (T2) according to the TNM staging system, consistent with previous evidence.[27] While no associations were observed between the specific site of the DLBCL within the ocular adnexa (as outlined by the TNM staging system) and local or systemic relapse or OS, we found that increasing T category is predictive of DSS in primary OA-DLBCL. Disease-specific survival was likely 6.9 to 12.4 years in patients with T2 disease, as opposed to 2.4 to 5.2 years in patients with T4 disease, which are the 95% CIs around the median survival of 9.8 and 4.4 years, respectively, in these subpopulations. These findings are consistent with evidence by Sniegowski et al,[21] who showed that the T category was highly predictive of DSS in patients with various subtypes of OAL. Yet, some overlap of patients with OA-DLBCL existed between their work and the present study. Herein, the TNM staging system was not predictive of DSS, which probably was owing to the paucity of patients within each T category when further subdivision into T subcategories (eg, T1a, T1b, and T1c) was applied. Similar problems have been described in previous studies[14,27,28,32] examining a wider range of subtypes of OAL.

When considering primary OA-DLBCL only and the predictive capacity of the Ann Arbor staging system, dissociation of prognostic curves could not be demonstrated. In agreement with previous studies,[5,6,29,33] when considering all patient groups herein, patients having Ann Arbor stage IVE OA-DLBCL appeared to have poorer DSS than patients having Ann Arbor stages IE through IIIE.

The present study represents the most patients to date with OA-DLBCL in whom molecular subtyping using IHC surrogate markers according to the algorithm by Hans et al[18] has been performed. Most peripheral DLBCLs are of GCB subtype, which have a prognosis almost twice as good as that of activated B-cell subtype.[17,42] In this study, no difference in outcomes was identified between the 2 subtypes, in line with previous investigations of OA-DLBCL.[43] Indeed, it has proven difficult to identify an IHC classifier for OA-DLBCL with consistent predictive values.[18,44] It would be useful to extract RNA to determine whether the algorithm by Hans et al[18] truly represents genuine molecular subtypes.[42] Additional biomarkers identified through newer technologies such as next-generation sequencing[45] may also be worthy of examination.

Conclusions

Most patients with primary OA-DLBCL were seen with Ann Arbor stage IE and TNM T2 disease. The median OS was 3.5 years. The findings of our study suggest that the TNM staging system for OAL may provide additional information to the Ann Arbor staging system when determining DSS in primary OA-DLBCL. Taking all lymphoma groups herein (primary, disseminated, and relapsed) into account, sex and Ann Arbor stage appear to be reliable DSS predictors. A larger cohort is required to assess whether T subcategories of primary OA-DLBCL, treatment, and histopathologic or clinical prognostic factors are possible predictors of outcomes.

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