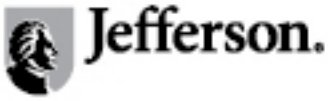

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Association of Disease Location and Treatment With Survival in Diffuse Large B-Cell Lymphoma of the Eye and Ocular Adnexal Region.

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Association of Disease Location and Treatment With Survival in Diffuse Large B-Cell Lymphoma of the Eye and Ocular Adnexal Region

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IMPORTANCE Primary diffuse large B-cell lymphoma (DLBCL) of the ocular region is rare, and the utility of surgery and radiation therapy remains unresolved.

OBJECTIVE To explore the clinical characteristics and determine factors associated with overall survival in primary vitreoretinal lymphoma (PVRL) and ocular adnexal (OA)–uveal DLBCL.

DESIGN, SETTING, AND PARTICIPANTS This retrospective analysis included 396 patients with ophthalmic DLBCL from January 1, 1973, through December 31, 2014, using the Surveillance, Epidemiology, and End Results database. The median follow-up was 39.0 months (interquartile range, 5.1-72.9 months). All patients diagnosed with primary DLBCL of the eye or retina (PVRL) or the eyelid, conjunctiva, choroid, ciliary body, lacrimal gland, or orbit (OA-uveal lymphoma) were included. Patients diagnosed at autopsy or with additional neoplastic disease were excluded.

MAIN OUTCOMES AND MEASURES Patient demographic characteristics, disease location, treatment modalities, and overall survival.

RESULTS Forty-seven patients with PVRL (24 women [51.1%] and 23 men [48.9%]) and 349 with OA-uveal DLBCL (192 women [55.0%] and 157 men [45.0%]) had a similar mean (SD) age at diagnosis (69.6 [12.3] vs 66.1 [17.7] years). No difference in the use of surgery or radiation therapy by location was found. For all PVRL and OA-uveal DLBCL, a Cox proportional hazards regression model affirmed that age older than 60 years was associated with increased risk for death (hazard ratio [HR], 2.7; 95% CI, 1.9-4.0; $P < .001$). Gross total resection was associated with a decreased risk for death (HR, 0.5; 95% CI, 0.3-0.9; $P = .04$), whereas radiation therapy was not. The 5-year overall survival among patients with PVRL was 41.4% (SE, 8.6%); among those with OA-uveal DLBCL, 59.1% (SE, 2.8%; Mantel-Cox test, $P = .007$). Median overall survival was lower in PVRL (38.0 months; 95% CI, 14.2-61.8 months) than in OA-uveal DLBCL (96.0 months; 95% CI, 67.3-124.7 months; Mantel-Cox test, $P = .007$). In addition, median overall survival in ophthalmic-only disease was higher (84.0 months; 95% CI, 63.2-104.8 months) than that in primary DLBCL that occurred outside the central nervous system and ophthalmic regions (46.0 months; 95% CI, 44.4-47.6 months; Mantel-Cox test, $P < .001$).

CONCLUSIONS AND RELEVANCE The 5-year survival in PVRL vs OA-uveal DLBCL differed by 17.7%, and overall survival was greater in ophthalmic DLBCL than in DLBCL located outside the central nervous system and ophthalmic regions. Younger age (≤60 years) and gross total resection were associated with increased survival.

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Diffuse large B-cell lymphoma (DLBCL) is a cancer of mature B lymphocytes. It is the most common subtype of non-Hodgkin lymphoma, representing 25% of cases.[1] In the United States, this malignant neoplasm has an incidence of 7 cases per 100 000 persons per year and occurs most frequently in white (85.5%) and male (56.0%) individuals.[2] The slight male predominance of DLBCL is similar to that of other non-Hodgkin lymphoma.[2]

The origin of DLBCL is nodal in approximately 58% of cases, extranodal in 42%, and extranodal extramedullary in 40%.[3,4] Diffuse large B-cell lymphoma can occur in various intraocular and ocular adnexal (OA) compartments, including the vitreous, retina, optic nerve, and subretinal pigment epithelium (primary vitreoretinal lymphoma [PVRL]), and in the uvea, conjunctiva, orbit, and eyelid (OA-uveal DLBCL).

The PVRL subtype is a primary central nervous system (CNS) lymphoma that can manifest in the eye, with commonly preceding, simultaneous, or sequential involvement of the CNS.[5,6] The intraocular malignant neoplasm involves the vitreous most commonly and the retina, subretinal pigment epithelium, and optic nerve.[7] The incidence of primary CNS lymphoma from 2005 through 2009 was 0.45 per 100 000 person-years, and 15% to 25% of patients with primary CNS lymphoma are estimated to manifest intraocular involvement (PVRL).[5,8,9] Most cases of PVRL prove to be DLBCL.[10-13] Owing to the rarity of PVRL and the small, heterogeneous study populations, the specific prognosis is somewhat unclear. One study of patients with PVRL demonstrated a 5-year cumulative survival rate of 35% among those with additional CNS extension and 68% among those without CNS extension.[14]

Primary DLBCL can also occur in the orbit, OA, choroid, ciliary body, and iris, collectively termed *OA-uveal regions*.[15-17] Orbital lymphoma is common and represents the most prevalent malignant orbital tumor in older adults.[18] Patients with orbital lymphoma generally present with painless, progressive orbital fullness or proptosis, dysmotility, and ptosis, whereas eyelid lymphoma manifests as a nontender, palpable mass, often with ptosis. By contrast, conjunctival lymphoma appears as a nontender, salmon-colored mass hidden in the fornix and occasionally with choroidal involvement.[19] Unlike PVRL, OA-uveal lymphoma does not generally extend into the CNS unless left untreated.[17,20] Diffuse large B-cell lymphoma represents 8% of all OA lymphoma and 3% of all conjunctival lymphoma and is more likely to have systemic involvement and to be aggressive.[15,21] Five-year overall survival rates in OA-uveal DLBCL, including all stages from localized to systemic involvement, range from 20% to 36%.[19,20,22]

The management for these 2 different clinical entities has limited to no overlap. Treatment of PVRL consists of high-dose vitreous methotrexate sodium, which forms the backbone of chemotherapy, often in combination with rituximab. Lymphoma of the CNS needs to be considered and examined.[23,24] Radiotherapy is the preferred treatment in some centers but carries risks for radiation-related cataract, retinopathy, and optic neuropathy as well as nontreatment of potential CNS disease.[25,26] For OA lymphoma, initial surgical resection for biopsy confirmation, followed by chemotherapy and/or radiotherapy, is performed.[19] For uveal lymphoma, confirmation is done with fine-needle aspiration biopsy, and treatment with radiotherapy, chemotherapy, and/or rituximab is administrered.[16]

The relative presentation, treatment, and outcomes of ophthalmic DLBCL are not well described in a large cohort. Thus, the purpose of this study was to delineate these features and overall survival characteristics using a national registry database, with focus on PVRL vs OA-uveal DLBCL.

Key Points

Question Which factors influence overall survival in ophthalmic diffuse large B-cell lymphoma?

Findings In this analysis of 396 patients with ophthalmic diffuse large B-cell lymphoma using the Surveillance, Epidemiology, and End Results database, older age (>60 years) was associated with increased risk for death, and gross total resection was associated with a decrease in this risk. A primary vitreoretinal location was associated with lower overall survival than an ocular adnexal–uveal location, and overall survival was greater in ophthalmic disease than non–central nervous system and nonophthalmic disease.

Meaning Patient age, disease location, and surgical excision may influence overall survival in ophthalmic diffuse large B-cell lymphoma.

Methods

We queried the November 2016 submission of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database for diffuse large B-cell lymphoma (DLBCL) (*International Classification of Diseases for Oncology* code 3 9680/3) diagnosed between January 1, 1973, and December 31, 2014, occurring primarily in the eye, not otherwise specified (NOS), and the retina to represent PVRL. The database was also queried for DLBCL that occurred with a primary site of the eyelid, conjunctiva, choroid, ciliary body, lacrimal gland, and orbit, jointly representing OA-uveal disease. Finally, DLBCL that occurred in non-CNS and nonophthalmic regions was queried. This study was approved by the institutional review board of Wills Eye Hospital, which waived the need for informed consent for use of data from the public registry.

Cases diagnosed at autopsy and cases involving secondary cancers were excluded. When available, data were extracted on patient age, sex, race, Ann Arbor stage (range, I-IV, with I indicating a single lymph node group; IV, multiple extranodal sites or lymph nodes), surgical resection, radiation therapy, survival time, and outcome (alive or dead due to any cause at the end of follow-up). Data on use of chemotherapy and the International Prognostic Index[27] were not available for analysis. Tumor grade and histologic trait data beyond diagnostic confirmation were sparse or unavailable.

Treatment designations considered to be surgical resection included partial resection and/or excision, gross total resection, surgery NOS, and local tumor destruction, which consisted of laser ablation or electrocautery. Treatment with external beam radiation represented radiation therapy.

Table 1. Characteristics of Primary DLBCL of the Eye and OA Regions[a]

Characteristic	OA-Uveal Lymphoma						PVRL (n = 47)	*P* Value[b]
	Eyelid (n = 28)	Conjunctiva (n = 26)	Lacrimal Gland (n = 27)	Orbit (n = 239)	Ciliary Body (n = 21)	Choroid (n = 8)		
Patient								
Age, mean (SD), y	68.1 (17.4)	61.6 (23.1)	61.2 (19.5)	67.1 (17.2)	63.3 (10.7)	68.4 (7.9)	69.6 (12.3)	.26
Age ≤60 y	10 (35.7)	12 (46.2)	14 (51.9)	83 (34.7)	8 (38.1)	1 (12.5)	9 (19.1)	.07
Age >60 y	18 (64.3)	14 (53.8)	13 (48.1)	156 (65.3)	13 (61.9)	7 (87.5)	38 (80.9)	
Sex ratio, female to male	1.00	2.25	2.00	1.03	3.20	1.67	1.04	.13
Race								
White	24 (85.7)	22 (84.6)	24 (88.9)	206 (86.2)	17 (81.0)	8 (100)	39 (83.0)	.86
Black	1 (3.6)	2 (7.7)	1 (3.7)	14 (5.9)	0	0	0	
Asian/Pacific Islander	1 (3.6)	1 (3.8)	1 (3.7)	16 (6.7)	4 (19.0)	0	6 (12.8)	
Native American or Alaskan	0	0	0	0	0	0	0	
Unknown	2 (7.1)	1 (3.8)	1 (3.7)	3 (1.3)	0	0	2 (4.3)	
Disease								
Laterality								
Unilateral	28 (100)	24 (92.3)	27 (100)	230 (96.2)	16 (76.2)	6 (75.0)	39 (83.0)	<.001
Bilateral	0	2 (7.7)	0	5 (2.1)	5 (23.8)	2 (25.0)	8 (17.0)	
Unknown	0	0	0	4 (1.7)	0	0	0	
Ann Arbor stage[c]								
I	19 (67.9)	19 (73.1)	17 (63.0)	121 (50.6)	15 (71.4)	5 (62.5)	30 (63.8)	.41
II	2 (7.1)	0	2 (7.4)	20 (8.4)	1 (4.8)	0	3 (6.4)	
III	0	3 (11.5)	3 (11.1)	47 (19.7)	0	0	0	
IV	2 (7.1)	3 (11.5)	2 (7.4)	32 (13.4)	4 (19.0)	2 (25.0)	6 (12.8)	
Unknown	5 (17.9)	1 (3.8)	3 (11.1)	19 (7.9)	1 (4.8)	1 (12.5)	8 (17.0)	
Treatment								
Surgery								
None or biopsy only	10 (35.7)	14 (53.8)	15 (55.6)	133 (55.6)	12 (57.1)	3 (37.5)	25 (53.2)	.14
Partial resection or excision	8 (28.6)	12 (46.2)	10 (37.0)	75 (31.4)	5 (23.8)	2 (25.0)	11 (23.4)	
Gross total resection[d]	1 (3.6)	0	0	7 (2.9)	3 (14.3)	1 (12.5)	3 (6.4)	
Surgery NOS	3 (10.7)	0	0	6 (2.5)	1 (4.8)	2 (25.0)	2 (4.3)	
Local tumor destruction[e]	2 (7.1)	0	1 (3.7)	5 (2.1)	0	0	1 (2.1)	
Unknown	4 (14.3)	0	1 (3.7)	13 (5.4)	0	0	5 (10.6)	
Radiation therapy								
None	10 (35.7)	13 (50.0)	15 (55.6)	99 (41.4)	11 (52.4)	3 (37.5)	19 (40.4)	.61
Administered	17 (60.7)	13 (50.0)	12 (44.4)	133 (55.6)	9 (42.9)	5 (62.5)	25 (53.2)	
Unknown	1 (3.6)	0	0	7 (2.9)	1 (4.8)	0	3 (6.4)	

Abbreviations: DLBCL, diffuse large B-cell lymphoma; NOS, not otherwise specified; OA, ocular adnexal; PVRL, primary vitreoretinal lymphoma.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and may not total 100.

[b] Calculated using 1-way analysis of variance or Kruskal-Wallis test.

[c] I indicates single lymph node group; IV, multiple extranodal sites or lymph nodes.

[d] Includes eye enucleation.

[e] Includes laser ablation and electrocautery.

We conducted a descriptive statistical analysis to determine demographic, tumor, and treatment characteristics, including 2-tailed *t* test, analysis of variance, and the Kruskal-Wallis test with a post hoc Dunn-Bonferroni approach. A Cox proportional hazards regression analysis was conducted to determine factors associated with death, controlling for age, sex, race, treatment with radiation, treatment with surgery, and disease location. Age was dichotomized (≤60 vs >60 years) as recommended by the International Prognostic Index model for non-Hodgkin lymphoma.[27] Laterality was not included as a covariate because of the low overall proportion of bilateral disease.

We conducted Kaplan-Meier survival analyses to determine overall survival and to compare survival by DLBCL disease location. Analyses were conducted with SPSS software (version 23.0; IBM), with $P < .05$ indicating significance.

Results

Forty-seven patients with PVRL had a mean (SD) age at diagnosis of 69.6 (12.3) years, with a female predominance (24 women [51.1%] and 23 men [48.9%]; sex ratio, 1.04). Three hundred forty-nine patients with primary OA-uveal DLBCL had a mean (SD) age at diagnosis of 66.1 (17.7) years that was not significantly different from patients with PVRL (*t* test, $P = .18$). Ocular adnexal-uveal DLBCL also had a female predominance (192 women [55.0%] and 157 men [45.0%]; sex ratio,

1.22), with no difference based on location (Kruskal-Wallis test, $P = .13$) (**Table 1**). The median follow-up was 39.0 months (interquartile range, 5.1-72.9 months).

When we compared PVRL and separate locations of OA-uveal disease, we found no difference in age (analysis of variance, $P = .26$) and proportion of patients older than 60 years (Kruskal-Wallis test, $P = .07$) (Table 1). We found no difference in patient race by location of disease, with each subgroup having mostly white patients (Kruskal-Wallis test, $P = .86$) (Table 1). As expected, most cases had a unilateral presentation. A higher proportion of bilateral disease occurred with primary DLBCL of the ciliary body (5 of 21 [23.8%]; Kruskal-Wallis test, $P < .001$) compared with no patients with primary DLBCL of the eyelid and lacrimal gland (post hoc Dunn-Bonferroni approach, $P = .02$) and orbit (5 of 239 [2.1%]; post hoc Dunn-Bonferroni approach, $P = .01$). We found no difference in proportions of Ann Arbor stage among disease locations. Data on extension into the CNS specifically were not available.

Among all locations of disease, treatment approaches included surgery, radiation therapy, both, or neither. We found no difference in the use or type of surgery by location (Kruskal-Wallis, $P = .14$) and no difference in the use of radiation therapy (Kruskal-Wallis, $P = .61$) (Table 1). Data on chemotherapy use were not available for analysis.

A Cox proportional hazard regression model revealed that increased age at diagnosis (dichotomized at ≤60 and >60 years) was associated with increased risk for death (hazard ratio [HR], 2.7; 95% CI, 1.9-4.0; $P < .001$). Patient sex and race were not associated with death. Ann Arbor stages and disease location were also not associated with death in this model. Although all surgical interventions were associated with decreased risk for death, most were not determinants. However, gross total resection, including eye enucleation and orbitotomy, was associated with a decreased risk for death (HR, 0.5; 95% CI, 0.3-0.9; $P = .04$). The use of radiation therapy was not associated with survival (**Table 2**).

Kaplan-Meier survival analyses revealed that overall survival differed by location (**Table 3** and **Figure 1**). Patients with PVRL had a 5-year overall survival rate of 41.4% (SE, 8.6%), and those with OA-uveal disease had a 5-year overall survival rate of 59.1% (SE, 2.8%) (Mantel-Cox test, $P = .007$). When we compared overall survival by Ann Arbor stages in PVRL, stage I had a median overall survival of 43.0 months (95% CI, 14.3-71.7 months); stages II to IV, 75.0 months (95% CI, 0-197.0 months) (Mantel-Cox test, $P = .17$). Median overall survival was higher for stage I (129.0 months; 95% CI, 95.0-163.0 months) than for stages II to IV (77.0 months; 95% CI, 47.1-106.9 months) in OA-uveal disease (Mantel-Cox test, $P = .02$).

Median overall survival was lower in PVRL (38.0 months; 95% CI, 14.2-61.8 months) than in OA-uveal disease (96.0 months; 95% CI, 67.3-124.7 months; Mantel-Cox test, $P = .007$) (**Figure 2**). In addition, median overall survival in ophthalmic (PVRL, uveal, and OA) disease was higher (84.0 months; 95% CI, 63.2-104.8 months) than in primary DLBCL that occurred outside the CNS and ophthalmic regions (46.0 months; 95% CI, 44.4-47.6 months; Mantel-Cox test, $P < .001$).

Table 2. Cox Proportional Hazards Regression Model of Factors Associated With Overall Survival of Primary DLBCL of the Eye and OA Regions

Characteristic	Hazard Ratio (95% CI)	*P* Value[a]
Patient		
Age ≤60 y	1 [Reference]	NA
Age >60 y	2.7 (1.9-4.0)	<.001
Sex		
Female	1 [Reference]	NA
Male	0.9 (0.7-1.2)	.49
Race		
White	1 [Reference]	NA
Black	4.2 (0.6-32.4)	.16
Asian or Pacific Islander	5.1 (0.6-46.4)	.15
Unknown	4.4 (0.5-35.2)	.16
Disease		
Ann Arbor stage[b]		
I	1 [Reference]	NA
II	0.9 (0.5-1.5)	.57
III	0.8 (0.4-1.6)	.53
IV	0.7 (0.4-1.5)	.40
Unknown	1.7 (0.9-3.1)	.08
Location		
Eyelid	1 [Reference]	NA
Conjunctiva	1.9 (0.5-6.9)	.33
Lacrimal gland	2.3 (0.6-8.9)	.21
Orbit	1.0 (0.2-3.9)	.96
Ciliary body	1.9 (0.6-6.2)	.31
Choroid	2.5 (0.7-8.7)	.14
Vitreoretinal	1.0 (0.2-3.9)	.96
Treatment		
Surgery		
None or biopsy only	1 [Reference]	NA
Partial resection or excision	0.6 (0.3-1.1)	.07
Gross total resection[c]	0.5 (0.3-0.9)	.04
Surgery NOS	0.5 (0.2-1.2)	.11
Local tumor destruction[d]	0.8 (0.4-1.8)	.58
Unknown	0.6 (0.2-1.5)	.28
Radiation therapy		
None	1 [Reference]	NA
Administered	1.2 (0.5-2.7)	.65
Unknown	0.8 (0.4-1.8)	.59

Abbreviations: DLBCL, diffuse large B-cell lymphoma; NA, not applicable; NOS, not otherwise specified; OA, ocular adnexal.

[a] Calculated using Cox proportional hazards regression.

[b] I indicates single lymph node group; IV, multiple extranodal sites or lymph nodes.

[c] Includes eye enucleation.

[d] Includes laser ablation and electrocautery.

Discussion

The present study represents a comprehensive analysis of primary DLBCL of the eye and OA regions and confirms pre-

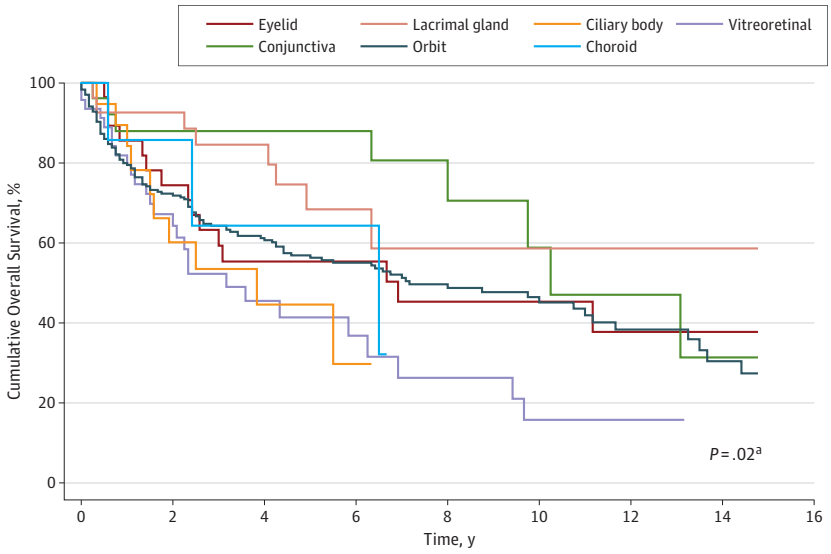
Table 3. Overall Cumulative and Median Survival of Primary DLBCL of the Eye and OA Regions After Diagnosis

Location	Survival Rate, Overall Cumulative (SE)[a]				Survival, Median (SE), mo
	1 y	2 y	5 y	10 y	
Eyelid	85.6 (6.7)	74.4 (8.4)	55.3 (9.6)	45.3 (10.2)	83 (56.1)
Conjunctiva	88.0 (6.5)	88.0 (6.5)	88.0 (6.5)	58.8 (14.9)	123 (23.1)
Lacrimal gland	92.6 (5.0)	92.6 (5.0)	68.4 (10.3)	58.6 (12.6)	(Not reached)
Orbit	79.5 (2.6)	71.8 (3.0)	56.3 (3.4)	45.1 (4.0)	86 (20.1)
Ciliary body	84.2 (8.4)	60.2 (11.8)	44.6 (13.0)	29.7 (14.9)	46 (19.2)
Choroid	64.3 (21.0)	64.3 (21.0)	32.1 (25.0)	32.1 (25.0)	78 (38.2)
PVRL	79.5 (6.1)	64.3 (7.5)	41.4 (8.6)	15.8 (7.8)	38 (12.1)

Abbreviations: DLBCL, diffuse large B-cell lymphoma; OA, ocular adnexal; PVRL, primary vitreoretinal lymphoma.

[a] Indicates cumulative proportion surviving at each time.

Figure 1. Overall Cumulative Survival for Primary Diffuse Large B-Cell Lymphoma (DLBCL) of the Eye and Ocular Adnexal Regions



No. at risk

Eyelid	28	20	13	10	7	6	4	2
Conjunctiva	25	18	15	12	8	5	3	1
Lacrimal gland	26	21	14	7	4	3	2	1
Orbit	229	146	105	73	47	31	17	7
Ciliary body	19	8	4	1	-	-	-	-
Choroid	7	5	3	2	-	-	-	-
Vitreoretinal	42	21	11	8	5	2	1	-

Data are stratified by anatomic site of disease. Disease of the conjunctiva and lacrimal gland showed a fair prognosis, whereas primary vitreoretinal lymphoma and disease of the ciliary body had a poor prognosis.

[a] Calculated using the Mantel-Cox test.

vious knowledge of this disease. Primary vitreoretinal lymphoma and OA-uveal disease occur most often in the sixth and seventh decades of life. Incidence is generally higher among women, an inverse of non-Hodgkin lymphoma found in other sites, for which men predominate.[19] This malignant neoplasm generally demonstrates a poor prognosis. From the perspective of location, the prognosis of primary DLBCL differs. We found the lowest median overall survival for PVRL and ciliary body disease, whereas the outlook for conjunctival and lacrimal gland disease was better. Disease of the orbit and eyelid had an intermediate prognosis. Poor prognosis for ciliary body disease was likely related to its increased bilateral manifestation.

A Cox proportional hazards regression model demonstrated that age greater than 60 years was associated with an increased risk for death. This association is well established in the non-Hodgkin lymphoma literature, and this cutoff is also a component of the International Prognostic Index.[27] In our model, Ann Arbor stage and disease locations were not determinants. However, Kaplan-Meier survival analysis demonstrated a difference for OA-uveal disease and not for PVRL. This effect of staging has been demonstrated previously for primary DLBCL of the ocular adnexa, including for overall and disease-specific survival.[20,22] The significance of the Ann Arbor staging system does not apply to primary CNS lymphoma, a subtype of which is PVRL, which corroborates these results.[28]

Decreased risk for death was associated with surgical treatment consisting of gross total resection, including eye enucleation. The role of surgery for the treatment of PVRL or OA-uveal DLBCL continues to be explored.[19] In a retrospective study of 34 patients with DLBCL of the ocular adnexa, only 1 was treated with complete surgical resection.[20] Surgery as the only treatment modality for orbital lymphoma is not typically used because of the difficulty with visualization of the entire infiltrating mass for resection and the concern for

residual tumor with the risk for recurrence.[29] More commonly, surgery is performed first for biopsy documentation or resection to prevent morbidity, and the backbone of treatment is chemotherapy and/or radiation therapy.[30] The use of surgery for PVRL is not well studied.

Radiation therapy has demonstrated a role in disease control of orbital lymphoma and PVRL.[25,31] Our model did not demonstrate that radiation therapy influences the risk for death; however, the SEER database does not differentiate between palliative and goal-directed radiation therapy. The relative efficacy of radiation therapy and chemotherapy continues to be debated for intraocular lymphoma.[32] Although radiation therapy is associated with cataract formation, retinopathy, and neuropathy, an intensive induction-consolidation-maintenance regimen of methotrexate chemotherapy is also associated with risk for keratopathy, maculopathy, and drug resistance.[25,33,34] This risk has led to the recommendation of fewer chemotherapy cycles with longer intervals and the addition of rituximab as a less toxic approach.[24,32] Whether ocular therapy affects overall survival is still unclear owing to the lack of randomized clinical trials.[25]

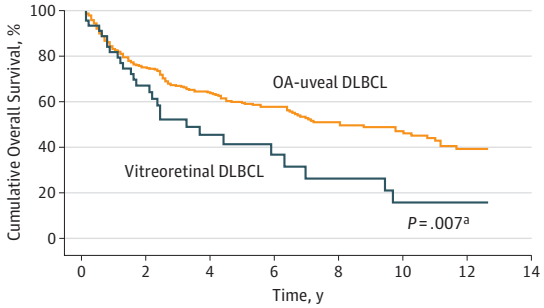
This study affirms that PVRL has a comparatively poorer prognosis than OA-uveal disease using a national database. This finding is likely attributable to the common association of PVRL with CNS disease. The most common cause of death in these cases is CNS lymphoma.[25] Ocular adnexal-uveal lymphoma can also extend to the CNS; however, the likelihood is relatively low, especially in unilateral disease.[17,20] The median overall survival for PVRL (38.0 months; 95% CI, 14.2-61.8 months) was similar to that of 31 months reported previously.[35] Primary DLBCL of the ophthalmic regions was documented to have a better prognosis than primary DLBCL of non-CNS and nonophthalmic regions. This finding is possibly attributable to extent of disease because primary DLBCL of the ophthalmic regions is often localized at presentation.

Limitations

The rarity of primary DLBCL of the eye and OA regions precludes prospective studies with high statistical power, making retrospective studies, such as this one, the next best approach. Retrospective data have intrinsic reporting biases. The SEER database is historically a surgery-based database, and surgery does not play a prominent role in this disease. Data on chemotherapy use are lacking, and because chemotherapy plays an important role in management, such data may have theoretically improved the predictive model in this study.

The SEER database does not have a primary site code for *vitreous*. The site designated *eye, NOS* was deemed to refer to the vitreous because of separate codes for adnexal regions. Data on the International Prognostic Index, serum lactate dehydrogenase level, centroblastic vs immunoblastic histopathologic findings, and recurrence were not available.[36] Of importance, the natural history of the disease in each case was not thorough.[20] The specific degree of extension of disease into the CNS, which is an important prognosticator for PVRL, was unknown.[25]

Figure 2. Overall Cumulative Survival for Primary Diffuse Large B-Cell Lymphoma (DLBCL) by Region



No. at risk							
OA-uveal	333	217	152	104	65	44	26
Vitreoretinal	42	21	11	8	5	2	1

Survival was higher for primary DLBCL of ocular adnexal (OA) regions than for primary vitreoretinal lymphoma.

[a] Calculated using the Mantel-Cox test.

Conclusions

Primary ophthalmic DLBCL can be classified into PVRL or OA-uveal subtypes, with both groups of patients presenting at a later age. Prognosis differs by disease location and was poor with PVRL, with a 58.6% mortality rate by 5 years, whereas OA-uveal DLBCL demonstrated a 40.9% mortality rate by 5 years. Patients with PVRL and OA-uveal DLBCL subtypes had greater overall survival compared with DLBCL located outside the CNS and ophthalmic regions.

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