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Vitreoretinal lymphoma: Central nervous system lymphoma risk with unilateral or bilateral ocular tumour. A multicentre collaboration

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OBJECTIVES: To investigate the risk of developing central nervous system (CNS) lymphoma in patients with vitreoretinal lymphoma (VRL) presenting with unilateral versus (vs.) bilateral ocular involvement.
METHODS: Retrospective, multicentre cohort study from January 1, 1984 to December 31, 2020.
RESULTS: There were 218 eyes of 127 patients with isolated VRL of the confirmed or presumed diffuse large B-cell subtype in the absence of known CNS or systemic lymphoma. Overall, mean patient age at presentation was 67 years (median 68, range 22–93 years), with 52 (40%) male, and 118 (90%) Caucasian. By univariate Cox regression analysis, two factors were predictive of decreased risk for development of CNS lymphoma, including initial presentation with unilateral VRL (versus bilateral VRL) (HR 0.5 [0.2–0.9], $p = 0.02$) and use of systemic chemotherapy for initial treatment of isolated ocular disease (HR 0.2 [0.1–0.6], $p = 0.002$). Both factors remained significant on multivariate and competing risk analyses. Progression from unilateral to bilateral VRL, patient age at presentation, and ocular structures involved (vitreous, subretinal space, subretinal pigment epithelial space) were not significantly associated with CNS lymphoma risk.
CONCLUSION: Initial presentation with unilateral VRL and treatment of isolated VRL with systemic chemotherapy were associated with lower risk of developing CNS lymphoma. Further study is required to determine whether select patients with isolated VRL might benefit from systemic chemotherapy in the prevention of CNS lymphoma.

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INTRODUCTION

Vitreoretinal lymphoma (VRL) is a rare, histologically aggressive, intraocular malignancy that can have serious implications for a patient's systemic health and survival [1–5]. Most commonly a diffuse large B-cell lymphoma (DLBCL), VRL can affect the vitreous, retina, and sub-retinal pigment epithelium (RPE) space [1]. While VRL can present in isolation, there is a well-established association with central nervous system (CNS) lymphoma [6, 7], and VRL can present preceding, concurrent with, or subsequent to CNS disease [8, 9]. Of all VRL patients, up to 90% may ultimately develop CNS lymphoma [1, 10], resulting in poor overall survival, with CNS lymphoma-related death in 65–85% of patients [4, 8, 11]. Due to the rarity of VRL, definitive conclusions regarding treatment regimens and outcomes from single centre data alone remain challenging.

There is currently no well-established standard of care for VRL. While intravitreal methotrexate and rituximab can achieve high rates of local tumour control or minimal residual disease within the eye [2, 3, 12–15], physicians often consider utilizing systemic therapies in an attempt to prevent development of CNS lymphoma and improve patient survival. However, the survival benefit of current first-line chemotherapy regimens remains uncertain. In a Mayo Clinic series of VRL patients, high-dose systemic methotrexate administered concurrently with intravitreal chemotherapy increased time to CNS lymphoma relapse but not overall time to death [16]. Studies from the International Primary Central Nervous System Lymphoma Collaborative Group and a collaborative European group similarly revealed no survival benefit of systemic chemotherapy, whole-brain radiotherapy, and/or peripheral blood stem cell transplantation compared with local ocular therapy alone [17, 18]. Improved treatment algorithms are desperately needed to improve patient survival, and clinical features may help identify high-risk patients who will derive the greatest benefit from more aggressive primary treatment. Herein, we present a multicentre collaboration investigating patients with VRL presenting initially with unilateral versus bilateral ocular involvement and explore associations with the development of CNS lymphoma.

METHODS

In this multicentre study, medical records were retrospectively reviewed to identify patients diagnosed with VRL on the Ocular Oncology Services at

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Table 1. Subanalysis of patients ($n = 127$) presenting with primary vitreoretinal lymphoma (unilateral versus bilateral involvement) in the absence of CNS or systemic disease.

Patient demographics	Unilateral VRL $n = 36$ patients (%)	Bilateral VRL $n = 91$ patients (%)	*p* values	Total $N = 127$ patients (%)
Age at presentation (years)	$n = 33$	$n = 90$		$N = 123$
Mean (median, range)	66 (71, 22–84)	68 (68, 28–93)	0.39	67 (68, 22–93)
Sex				
Male	17 (47)	31 (34)	0.22	48 (38)
Female	19 (53)	60 (66)		79 (62)
Race*				
Caucasian	33 (92)	82 (90)	1.00	115 (91)
African American	1 (3)	4 (4)		5 (4)
Asian	0 (0)	5 (5)		5 (4)
Hispanic	1 (3)	0 (0)		1 (1)
Indian	1 (3)	0 (0)		1 (1)

Groups are divided based on ocular involvement at time of initial presentation. Age variance 182 vs. 143, unilateral vs. bilateral.
VRL vitreoretinal lymphoma.
*The given *p* value reports Caucasian vs. other.

four major centres: Mayo Clinic, Rochester, Minnesota, USA, Wills Eye Hospital, Philadelphia, Pennsylvania, USA, University Vita-Salute-IRCCS Ospedale San Raffaele, Milan, Italy, and Hadassah-Hebrew University Medical Center, Jerusalem, Israel. Records were reviewed from January 1, 1984 to December 31, 2020. Patients with VRL were included regardless of CNS or systemic lymphoma status at date of presentation, but a subanalysis included only those who presented to the ocular oncologist with DLBCL subtype VRL in the absence of recent or remote CNS or systemic lymphoma history. Diagnosis of VRL was made via ocular biopsy or was presumed based on a fellow eye biopsy-proven diagnosis. This study was in compliance with the Health Insurance Portability and Accountability Act and adhered to the tenets of the Declaration of Helsinki. Institutional Review Board approval was obtained from Mayo Clinic with a waiver of written informed consent.

All patients underwent a complete, dilated eye examination by an ocular oncologist. Colour fundus photography, B scan ultrasonography, fluorescein angiography, indocyanine green angiography, and optical coherence tomography (OCT) were performed as available and as needed. Patients were managed in conjunction with a medical neuro-oncology/haematology team who directed workup for and treatment of CNS and systemic lymphoma. Brain MRI and lumbar puncture were recommended for all patients to exclude occult CNS lymphoma.

Retrospective review of clinical, photographic, and cytopathology records was undertaken at all four centres. Patient demographics (age, sex, race), prior pars plana vitrectomy, and duration of presenting symptoms were recorded. Clinical features included laterality (unilateral, bilateral), involved eye(s), presenting Snellen visual acuity, vitreous cellularity, subretinal infiltration, sub-RPE infiltration, and lymphoma subtype. For those with unspecified lymphoma subtype, DLBCL was presumed for the purposes of statistical analysis. Method of diagnosis was recorded, and the initial treatment approach was categorized as ocular therapy alone, concurrent ocular and systemic therapy for isolated ocular disease, or systemic therapy required for CNS and/or systemic lymphoma. Treatment modalities included systemic chemotherapy, whole-brain radiotherapy, intravitreal chemotherapy, and external beam radiotherapy (EBRT). Outcomes included follow-up duration, progression to bilateral ocular involvement (if initially unilateral), local ocular tumour control at date last seen (no regression, partial regression, or complete regression defined as absence of vitreous cell and resolution of any previous intraretinal or sub-RPE infiltration), requirement for enucleation, final visual acuity, development of CNS or systemic lymphoma, and death. Follow-up duration was defined as the time from initial ocular oncology evaluation to the date of last ocular oncology evaluation. Times from initial presentation on the Ocular Oncology Service to development of CNS or systemic lymphoma and death were recorded.

Statistical analysis was performed using SPSS Statistics Software Version 22 (IBM, Armonk, NY). Categorical variables were compared using Fisher's exact test or Chi-square test, and continuous variables were compared using Student's *t* test. Tests were performed in a two-sided fashion. Cox regression analysis was used to assess risk for CNS lymphoma, systemic lymphoma, or death based on presentation with unilateral versus bilateral VRL. For the subset of patients presenting initially with confirmed or presumed DLBCL and no CNS or systemic lymphoma, univariate and multivariate Cox regression analysis was used to determine risk factors for development of CNS lymphoma. Hazard ratios (HR) are reported as HR [95% confidence interval]. Competing risk analysis was performed using R statistical software. Statistical significance was defined as $p < 0.05$.

RESULTS

There were 470 eyes of 275 patients diagnosed with VRL during the study period. Patient demographics, presenting clinical features, treatment features, and outcomes for the entire cohort are listed in Supplemental Tables 1–4. A detailed subanalysis was performed for 218 eyes of 127 patients presenting initially with isolated VRL of the DLBCL subtype in the absence of known CNS or systemic lymphoma. Patient demographics are presented in Table 1. Mean patient age at presentation was 67 years (median 68, range 22–93 years), with 48 (38%) male and 115 (91%) Caucasian. Ocular involvement was unilateral in 36 (28%) or bilateral in 91 (72%) patients. A comparison (unilateral vs. bilateral) revealed no differences in demographics.

Clinical features at presentation for isolated VRL patients are listed in Table 2. Lymphoma subtype was confirmed DLBCL in 106 (83%) patients and presumed in 21 (17%) patients. A comparison (unilateral vs. bilateral) of features at the time of diagnosis revealed patients presenting initially with unilateral ocular involvement had worse logMAR visual acuity (1.05 vs. 0.54, $p = 0.003$), less frequent vitreous cellular infiltration (58% vs. 80%, $p = 0.01$), and more frequent use of combination diagnostic modalities of cytology, MYD88, and IL-10/IL-6 ratio (36% vs. 22%, $p = 0.01$).

Treatment features for isolated VRL patients are listed in Table 3. Of all eyes, 109 (50%) underwent pars plana vitrectomy and 38 (17%) had fine-needle aspiration biopsy to establish the diagnosis. A comparison (unilateral vs. bilateral) revealed that unilateral VRL eyes were more likely to have pars plana vitrectomy for diagnosis (72% vs. 46%, $p = 0.01$), and, unlike eyes in the bilateral VRL group, did not have presumed VRL based on a fellow eye diagnosis (0% vs. 34%, $p < 0.001$). For all 127 isolated VRL patients, initial approach to treatment included ocular therapy alone in 64 (50%), concurrent ocular and systemic therapy in the setting of isolated ocular disease in 21 (17%), initial systemic chemotherapy for CNS lymphoma development prior to starting ocular therapy in 41 (32%), and initial systemic chemotherapy for systemic extra-CNS

Table 2. Subanalysis of patients ($n = 127$) presenting with primary vitreoretinal lymphoma (unilateral versus bilateral involvement) in the absence of CNS or systemic disease.

Clinical features	Unilateral VRL $n = 36$ eyes of 36 patients (%)	Bilateral VRL $n = 182$ eyes of 91 patients (%)	*p* values	Total $N = 218$ eyes of 127 patients (%)
Prior vitrectomy	14 (39)	43 (24)	0.06	57 (26)
Duration of symptoms (months)	$n = 29$ eyes	$n = 112$ eyes		$N = 141$ eyes
Mean (median, range)	7 (5, 0–36)	10 (8, 0–49)	0.15	9 (7, 0–49)
Laterality	$n = 36$ patients	$n = 91$ patients		$N = 131$ patients
Unilateral	36 (100)	0 (0)	**<0.001**	36 (28)
Bilateral	0 (0)	91 (100)		91 (72)
Study eye	$n = 36$ eyes	$n = 182$ eyes		$N = 218$ eyes
OD	18 (50)	91 (50)	1.00	109 (50)
OS	18 (50)	91 (50)		109 (50)
Visual acuity	$n = 33$ eyes	$n = 154$ eyes		$N = 187$ eyes
≥20/40	15 (45)	80 (52)	0.57	95 (51)
20/50–20/200	8 (24)	61 (40)	0.11	69 (37)
<20/200	10 (30)	13 (8)	**0.002**	23 (12)
Visual acuity (LogMAR) Mean (median, range)	1.05 (0.40, 0.00–4.00)	0.54 (0.30, 0.00–4.00)	**0.003**	0.63 (0.30, 0.00–4.00)
Visual acuity (Snellen equivalent) Mean (median, range)	20/200 (20/50, 20/20-NLP)	20/70 (20/40, 20/20-NLP)	NA	20/80 (20/40, 20/20-NLP)
Ocular structures involved	$n = 36$ eyes	$n = 160$ eyes		$N = 196$ eyes
Vitreous cellular infiltration	21 (58)	128 (80)	**0.01**	149 (76)
Sub-retinal infiltration	18 (50)	51 (32)	0.05	69 (35)
Sub-RPE infiltration	14 (39)	57 (36)	0.85	71 (36)
Lymphoma subtype	$n = 36$ patients	$n = 91$ patients		$N = 127$ patients
Diffuse large B-cell (DLBCL)	31 (86)	75 (82)	0.79	106 (83)
Unspecified (presumed DLBCL)	5 (14)	16 (18)		21 (17)
Diagnostic modalities	$n = 36$ patients	$n = 91$ patients		$N = 127$ patients
Cytology with immunostains	14 (39)	52 (57)	0.56	66 (52)
Cytology + MYD88	9 (25)	19 (21)	0.06	28 (22)
Cytology + MYD88 + IL-10/6	13 (36)	20 (22)	**0.001**	33 (26)

Bold values indicate significant *p* value.
NLP no light perception, *RPE* retinal pigment epithelium.

lymphoma development prior to starting ocular therapy in 1 (1%) patient. Throughout the study, 87 (69%) patients received systemic chemotherapy, and a comparison (unilateral vs. bilateral) showed that patients presenting initially with unilateral ocular involvement were less likely to ultimately require systemic chemotherapy for all causes (50% vs. 76%, $p = 0.01$) or specifically for CNS lymphoma (28% vs. 58%, $p = 0.003$). There was no difference in use of whole-brain radiotherapy, intravitreal methotrexate, rituximab, or melphalan, or EBRT to the eyes between groups.

Outcomes for patients presenting with isolated VRL are described in Table 4. Mean follow-up for all 127 patients was 35 months (median 19, range 0–212 months), with no difference between groups. At final follow-up, complete local tumour control was achieved in 128 (74%) eyes. Of patients presenting initially with unilateral VRL, 6 (17%) ultimately developed bilateral VRL. A comparison (unilateral vs. bilateral) at the date of last ophthalmology follow-up revealed patients presenting initially with unilateral ocular involvement had worse logMAR visual acuity (1.12 vs. 0.65, $p = 0.02$) and were more likely to achieve complete local tumour control (88% vs. 71%, $p = 0.05$). Overall, CNS lymphoma developed after VRL in 63 (50%) patients, and systemic lymphoma developed after VRL in 8 (6%) patients. A total of 5 (4%) patients developed both CNS and systemic lymphoma. There were 55 (43%) patients who died, with 30 (55%) of 55 deaths due to lymphoma and 21 (38%) due to unknown cause. A comparison (unilateral vs. bilateral) revealed that patients presenting initially with unilateral VRL were less likely to develop CNS lymphoma (28% vs. 58%, $p = 0.003$). By Cox regression analysis, initial presentation with bilateral VRL was associated with increased risk of developing CNS lymphoma (HR 2.2 [1.1–4.3], $p = 0.01$) (Supplemental Fig. 1A, Kaplan–Meier curve in Supplemental Fig. 1B), but no increased risk of systemic lymphoma, all-cause mortality, or death due to CNS lymphoma.

Univariate and multivariate Cox regression analysis were performed to assess risk factors for development of CNS lymphoma. Results are presented in Table 5, and two protective factors were identified. Patients presenting initially with unilateral VRL (HR 0.5 [0.2–0.9], $p = 0.02$) and patients initially managed with systemic chemotherapy for isolated ocular disease (HR 0.2 [0.1–0.6], $p = 0.002$) (Supplemental Fig. 1C, Kaplan–Meier curve in Supplemental Fig. 1D) were less likely to develop CNS lymphoma. Both factors remained significant on multivariate analysis (unilateral VRL, $p = 0.03$; systemic chemotherapy, $p = 0.002$) and competing risk analysis (unilateral VRL, $p = 0.03$; systemic chemotherapy, $p < 0.001$). Progression from unilateral

Table 3. Subanalysis of patients ($n = 127$) presenting with primary vitreoretinal lymphoma (unilateral versus bilateral involvement) in the absence of CNS or systemic disease.

Treatment features	Unilateral VRL $n = 36$ eyes of 36 patients (%)	Bilateral VRL $n = 182$ eyes of 91 patients (%)	*p* values	Total $N = 218$ eyes of 127 patients (%)
Method of diagnosis				
PPV-based biopsy	26 (72)	83 (46)	**0.01**	109 (50)
FNAB-based biopsy	10 (28)	28 (15)	0.09	38 (17)
Unspecified	0 (0)	9 (5)	0.36	9 (4)
Diagnosis by fellow eye	0 (0)	62 (34)	**<0.001**	62 (28)
Initial treatment approach	$n = 36$ patients	$n = 91$ patients		$N = 127$ patients
Ocular therapy alone	21 (58)	43 (47)	0.33	64 (50)
Ocular therapy plus systemic therapy for isolated ocular disease	7 (19)	14 (15)	0.60	21 (17)
Required systemic therapy due to CNS lymphoma[a]	8 (22)	33 (36)	0.15	41 (32)
Required systemic therapy due to systemic lymphoma[a]	0 (0)	1 (1)	1.00	1 (1)
Overall treatment[b]				
Systemic treatment	$n = 36$ patients	$n = 91$ patients		$N = 127$ patients
Systemic chemotherapy	18 (50)	69 (76)	**0.01**	87 (69)
For ocular disease alone	7 (19)	14 (15)	0.60	21 (17)
For CNS lymphoma	10 (28)	53 (58)	**0.003**	63 (50)
For systemic lymphoma	1 (3)	7 (8)	0.44	8 (6)
Whole-brain radiotherapy	$n = 23$ patients	$n = 71$ patients		$N = 94$ patients
	1 (4)	7 (10)	0.67	8 (9)
Ocular treatment	$n = 36$ eyes	$n = 160$ eyes		$N = 196$ eyes
Intravitreal chemotherapy				
Methotrexate	21 (58)	80 (50)	0.46	101 (52)
Rituximab	8 (22)	41 (26)	0.83	49 (25)
Melphalan	0 (0)	4 (3)	0.60	4 (2)
External Beam Radiotherapy	7 (19)	44 (28)	0.40	51 (26)

Bold values indicate significant *p* value.
PPV pars plana vitrectomy, *FNAB* fine-needle aspiration biopsy, *CNS* central nervous system.
[a]Patients who progressed to CNS or systemic lymphoma before initiating therapy for isolated ocular disease.
[b]Patients may have received multiple treatment modalities in combination.

to bilateral VRL, patient age at presentation, ocular structures involved (vitreous, subretinal space, sub-RPE space), and incomplete local tumour regression were not significantly associated with CNS lymphoma risk. Initial management with systemic chemotherapy for isolated ocular disease was not associated with a decreased risk of all-cause mortality (HR 0.9 [0.4–1.6], $p = 0.64$) or death due to CNS lymphoma (HR 0.9 [0.4–2.2], $p = 0.87$). Vitrectomy prior to presentation was not associated with CNS lymphoma risk when analyzed as a possible marker for delay in diagnosis, However, diagnosis by cytology and immunostains alone compared with combination diagnostic methods incorporating MYD88 or IL-10/IL-6 ratio was associated with lower CNS lymphoma risk (HR 0.5 [0.3–0.9], $p = 0.01$).

DISCUSSION

VRL is a rare intraocular malignancy, most commonly of the DLBCL subtype, which can be associated with poor patient survival due to development of CNS lymphoma [1–5, 8, 9]. Given the rarity of this cancer and lack of randomized clinical trials, an effective, widely accepted standard of care approach to treatment remains elusive [11]. While improved survival has been reported in recent years [16], 5-year survival remains poor at 25–40% [11, 18–20], and the impact of current treatments on survival is questionable [11, 16, 17, 21–23]. In this multicentre, collaborative study, we investigated the impact of initial unilateral versus bilateral presentation of VRL on the risk of developing CNS lymphoma.

Approximately half of patients in this series presented with a known history of CNS or extra-CNS systemic lymphoma prior to VRL diagnosis. Among patients presenting with isolated VRL, initial presentation with unilateral ocular involvement was associated with approximately twofold decreased risk of developing CNS lymphoma compared with bilateral VRL. There was no increased risk of CNS lymphoma with subsequent development of bilateral VRL in patients presenting initially with unilateral disease, but with only six affected patients the study was likely underpowered to detect the significance of this rare event. Although unilateral patients were more likely to achieve complete local tumour regression, incomplete local tumour control was not associated with CNS lymphoma risk. When probing for additional risk factors for CNS lymphoma, initial treatment of isolated VRL with systemic chemotherapy was associated with approximately fivefold decreased risk of CNS lymphoma compared to treatment with local ocular therapy alone. However, neither unilateral VRL nor systemic chemotherapy reduced all-cause or disease-specific mortality. Previous studies have demonstrated a similar landscape

Table 4. Subanalysis of patients ($n = 127$) presenting with primary vitreoretinal lymphoma (unilateral versus bilateral involvement) in the absence of CNS or systemic disease.

Outcomes	Unilateral VRL $n = 36$ eyes of 36 patients (%)	Bilateral VRL $n = 182$ eyes of 91 patients (%)	*p* values	Total $N = 218$ eyes of 127 patients (%)
Follow-up (months)	35 (17, 0–212)	35 (21, 0–161)	0.99	35 (19, 0–212)
Mean (median, range)				
No follow-up	3 (8)	10 (11)	0.76	13 (10)
Progression to bilateral VRL	6 (17)	NA	NA	NA
Mean time to bilateral VRL (median, range)	27 (15, 9–87)	NA	NA	NA
Local ocular tumour control at DLS	$n = 33$ eyes	$n = 140$ eyes		$N = 173$ eyes
No regression (persistent/active disease)	0 (0)	12 (9)	0.13	12 (7)
Partial regression	4 (12)	29 (21)	0.33	33 (19)
Complete regression	29 (88)	99 (71)	**0.05**	128 (74)
Enucleation	2 (6)	2 (1)	0.13	4 (2)
Final visual acuity	$n = 29$ eyes	$n = 137$ eyes		$N = 166$ eyes
≥20/40	16 (55)	70 (51)	0.84	86 (52)
20/50–20/200	1 (3)	46 (34)	**0.001**	47 (28)
<20/200	12 (41)	21 (15)	**0.003**	33 (20)
Final visual acuity (LogMAR) Mean (median, range)	1.12 (0.30, 0.00–4.00)	0.65 (0.30, 0.00–4.00)	**0.02**	0.73 (0.30, 0.00–4.00)
Final visual acuity (Snellen equivalent) Mean (median, range)	20/260 (20/40, 20/20-NLP)	20/90 (20/40, 20/20-NLP)	NA	20/105 (20/40, 20/20-NLP)
Visual acuity loss ≥ 3 lines	5 (17)	37 (27)	0.80	42 (25)
	$n = 36$ patients	$n = 91$ patients		$N = 127$ patients[a]
CNS lymphoma after VRL	10 (28)	53 (58)	**0.003**	63 (50)
Mean time to CNS (median, range)	13 (9, <1–52)	18 (9, <1–135)	0.55	17 (9, <1–135)
Systemic extra-CNS lymphoma after VRL	1 (3)	7 (8)	0.44	8 (6)
Mean time to systemic (median, range)	<1 (<1, <1–<1)	22 (5, <1–88)	NA	19 (5, <1–88)
Death	12 (33)	43 (47)	0.17	55 (43)
Mean time to death (median, range)	51 (46, 3–111)	42 (31, 3–139)	0.55	43 (33, 3–139)
Cause of death	$n = 12$ patients	$n = 43$ patients		$N = 55$ patients
CNS lymphoma	5 (42)	25 (58)	0.35	30 (55)
Systemic lymphoma	1 (8)	0 (0)	0.22	1 (2)
Other confirmed cause	1 (8)	2 (5)	1.00	3 (5)
Unknown	5 (42)	16 (37)	1.00	21 (38)
Age at death (years) Mean (median, range)	70 (68, 58–87)	71 (72, 39–94)	0.72	71 (72, 39–94)
Cox regression analysis		**Hazard ratio [95% confidence interval]**	***p* values**	***p* value, adjusted**
Risk of CNS lymphoma		2.2 [1.1–4.3]	**0.01**	0.01[b]
Risk of systemic lymphoma		2.8 [0.3–22.7]	0.28	
Risk of death from any cause		1.4 [0.7–2.7]	0.28	
Risk of death from lymphoma		2.0 [0.8–5.2]	0.13	

Bold values indicate significant *p* value.
DLS date last seen, *CNS* central nervous system, *VRL* vitreoretinal lymphoma, *NLP* no light perception.
[a]A total of 5 (4%) patients developed both CNS and systemic lymphoma, with 0 (0%) patients in the unilateral group and 5 (5%) in the bilateral group.
[b]Adjusted for patient age at presentation and duration of symptoms prior to presentation as a time-dependent covariate.

for VRL patients. In 2016, Kim et al. reviewed 22 patients with primary VRL and found that 9 (41%) patients had concomitant CNS lymphoma [24]. Relapse rates were high, but two isolated ocular lymphoma patients and one VRL with CNS lymphoma patient managed with treatment regimens that included systemic chemotherapy had greater than 1 year of follow-up with no relapse [24].

A particularly challenging aspect of VRL is making a timely diagnosis, as VRL often mimics inflammatory uveitis, and small amounts of available tissue can lead to false-negative biopsy

Table 5. Subanalysis of patients ($n = 127$) presenting with primary vitreoretinal lymphoma (unilateral versus bilateral involvement) in the absence of CNS or systemic disease. Univariate and multivariate Cox regression analysis for risk of CNS lymphoma.

	Hazard ratio [95% confidence interval]	*p* values
Univariate analysis		
Unilateral ocular involvement at presentation	0.5 [0.2–0.9]	**0.02**
Progression to bilateral ocular involvement[a]	5.9 [0.8–43.4]	0.08
Patient age at presentation (per 1 year)	1.0 [1.0–1.0]	0.50
Patient race other than Caucasian	1.5 [0.6–3.8]	0.37
Vitreous involvement at presentation	0.8 [0.5–1.3]	0.37
Sub-retinal involvement at presentation	1.0 [0.6–1.8]	0.89
Sub-RPE involvement at presentation	0.8 [0.5–1.4]	0.46
Vitrectomy prior to presentation	0.7 [0.4–1.3]	0.32
Cytology and immunostains only for diagnosis	0.5 [0.3–0.9]	**0.01**
Incomplete local tumour regression	1.3 [0.7–2.4]	0.35
Initial treatment with prophylactic systemic chemotherapy	0.2 [0.1–0.6]	**0.002**
Multivariate analysis		
Unilateral ocular involvement at presentation	0.5 [0.2–0.9]	**0.03**
Initial treatment with prophylactic systemic chemotherapy	0.2 [0.1–0.6]	**0.002**

Bold values indicate significant *p* value. Ocular features were noted as positive for a given patient if one or both eyes had the feature of interest.
RPE retinal pigment epithelium, *CNS* central nervous system, *VRL* vitreoretinal lymphoma.
[a]Calculated as a time-dependent covariate.

results. While cytology with immunostaining is the mainstay of diagnosis, ancillary testing can be helpful, especially in cases of diagnostic uncertainty. Commonly employed ancillary tests for VRL include polymerase chain reaction to detect MYD88 mutation, cytokine analysis for IL-10/IL-6 ratio, and flow cytometry [4]. Santos et al. found flow cytometry to be of lower yield [25], and recent consensus recommendations for the diagnosis of VRL indicate IL-10/IL-6 ratio greater than 1, MYD88 mutation, and monoclonality as key indicators of VRL diagnosis [26]. Incorporation of these methods with cytology may reduce the false-negative biopsy rate, but it remains unclear whether delays in VRL diagnosis that result from false negatives impact likelihood of CNS lymphoma development. We attempted to use vitrectomy prior to presentation as a surrogate for delayed diagnosis and did not detect an association with CNS lymphoma risk. We did find that diagnosis using cytology with immunostains alone was associated with lower CNS lymphoma risk compared with diagnosis using combination methods incorporating MYD88 and IL-10/IL-6 ratio. However, given that all centres included in the study routinely employ ancillary testing as needed for diagnosis and that MYD88 testing has only more recently become available, it is difficult to understand the clinical importance of this result. Additional studies are required to determine the impact of diagnostic delay on CNS lymphoma risk.

Despite no proven standard of care for VRL, many physicians successfully employ intravitreal chemotherapy (methotrexate, rituximab, melphalan) to achieve a state of minimal residual disease [3, 27, 28]. In a large series describing 20 years of experience, 81 patients with VRL from Israel were successfully managed with single-agent intravitreal methotrexate using a standardized protocol with frequent induction injections followed by a consolidation phase [15]. Still, of 53 patients who presented with VRL in the absence of known CNS disease, 35 (66%) patients ultimately developed CNS lymphoma, which was a significant cause of mortality in the study cohort [15]. Thus, local ocular treatments may serve a quality of life function for VRL patients rather than conferring a survival benefit [11].

Methotrexate-based regimens are the current mainstay for systemic treatment of VRL and CNS lymphoma, and some centres use systemic chemotherapy for isolated VRL patients to prevent CNS disease. Unfortunately, relapse rates are high and the ability of such regimens to improve survival is questionable [1, 29]. In a recent French lymphoma oculo-cerebral (LOC) network study, 59 patients with isolated VRL received first-line treatment with intravenous high-dose methotrexate, and 8 of 59 patients received additional local treatment with ocular radiotherapy (6/59 patients) or intravitreal methotrexate (2/59 patients). A complete ocular response was achieved in 40 of 57 (70%) evaluable patients, but after median follow-up of 61 months, relapse occurred in 42 of 59 (71%), with 34 of 59 (58%) patients having at least one ocular relapse and 22 of 59 (37%) patients developing CNS lymphoma [30]. Despite high overall relapse rate, median overall survival in the study was 75 months with 66% overall 5-year survival, and on multivariate analysis, the authors found that high-dose initial systemic methotrexate (≥3 g/m^2) was associated with a fivefold improvement in overall survival ($p = 0.03$) in this cohort who presented with ocular only disease [30]. However, Habot-Wilner et al., in the 20-year experience study from Israel, found that median survival was 124 months for patients who developed CNS lymphoma after an initial diagnosis of VRL, with overall 5- and 10-year survival in VRL patients estimated at 84% and 61%, respectively. The Israel group did not use systemic chemotherapy in the absence of CNS disease but reported longer survival than the French LOC cohort. Thus, there may be population-based differences between these cohorts, and the utility of systemic chemotherapy for isolated VRL remains controversial.

Previous studies have failed to detect a survival benefit of systemic chemotherapy for VRL. In a Mayo Clinic series including 69 patients with DLBCL (33 primary isolated VRL, 18 concurrent VRL and CNS or systemic lymphoma, and 18 secondary VRL after CNS or systemic lymphoma), treatment with systemic high-dose methotrexate administered concurrently with intravitreal chemotherapy increased time to CNS lymphoma relapse but did not improve survival [16]. The International Primary Central Nervous System Lymphoma Collaborative Group evaluated 83 patients from 16 centres with isolated VRL and also found no survival benefit of systemic chemotherapy and/or whole-brain radiotherapy [17]. A collaborative European group evaluated 78 patients from 17 centres with isolated VRL and similarly found

no difference in 5-year survival, with CNS lymphoma development in 10 of 31 (32%) patients managed with local ocular therapy alone, 9 of 21 (43%) patients managed with systemic chemotherapy, whole-brain radiotherapy, and/or peripheral blood stem cell transplantation, and 9 of 23 (39%) patients managed with combination local and systemic therapy [18]. The authors of the French LOC network study [30] speculated that these studies may have failed to detect a survival benefit due to the variable nature of the administered CNS prophylactic regimens, with fewer than half of systemically-treated patients receiving a high-dose methotrexate-based regimen in two [16, 18] of the three studies. Insufficient number of patients to detect a difference should also be considered, as a prior study of 70 VRL patients from Wills Eye Hospital found no difference in time to CNS lymphoma for isolated VRL patients managed with systemic chemotherapy versus local ocular treatment alone (53 vs. 53 months, $p = 0.24$) [5]. However, when these patients were included in the larger, multicentre cohort for the present study, a significant benefit was detected despite heterogeneity of chemotherapy regimens. More research is required to draw definitive conclusions.

The landscape of VRL and CNS lymphoma treatment has been evolving, with newer, targeted treatments that were not well-evaluated within the period of this study. Of particular interest are Bruton tyrosine kinase inhibitors, such as ibrutinib. In 2017, Grommes et al. reported phase I trial results for 13 patients with relapsed or refractory CNS lymphoma managed with ibrutinib and found a 77% response rate [31]. In 2019, Soussain et al. reported phase II trial results for 44 evaluable patients with relapsed or refractory CNS lymphoma or primary VRL and found a 70% disease control rate [32]. Median progression-free survival and overall survival were 4.8 and 19.2 months, respectively [32]. In 2021, Renaud et al. retrospectively reviewed 22 patients with relapsed or refractory primary or secondary CNS lymphoma managed with both ibrutinib and temozolomide and found a 55% overall response rate [33]. Among responders, median progression-free and overall survival were 11.7 and 21.8 months, respectively [33]. Given the potential for survival improvement with newer agents, updated prospective trials are required to accurately represent the most current patient population.

Limitations to our study include its retrospective nature, variability of diagnostic methods and treatment patterns, changes in VRL management over time, and variable follow-up duration, with some patients lost to follow-up. Use of diagnostic imaging (autofluorescence, OCT) and methods of cytology, IL-10/IL-6 ratio, and MYD88 varied over the study period and with physician preference. Fellow eye diagnosis was often presumed without biopsy. Systemic workup and monitoring for CNS or systemic lymphoma was performed in conjunction with a neuro-oncology/haematology team, but details for each patient were not available. Ocular treatment and systemic chemotherapy regimens differed by centre, drug availability, and physician preference with insufficient records to discern agents, doses, and number of cycles administered for each patient. With a study period spanning over three decades, diagnosis and treatment of VRL have substantially evolved, with improved survival for VRL and CNS lymphoma patients in more recent years [11, 16]. Despite these limitations, the multicentre nature of this study resulted in a large patient cohort that permitted evaluation of the main outcomes of interest.

In summary, in this multicentre collaborative study, we found that initial presentation with unilateral VRL and treatment of isolated VRL with systemic chemotherapy were associated with reduced risk of developing CNS lymphoma. The use of systemic chemotherapy in isolated VRL remains controversial but could be considered for potential prevention of CNS disease in select patients. Patients presenting initially with bilateral VRL may be more at risk for CNS lymphoma development and, therefore, may require more strict systemic screening and could be more likely to derive benefit from an effective systemic treatment. However, given a lack of clear survival benefit associated with protective factors for CNS disease in this study and several prior studies showing no survival benefit of systemic chemotherapy for isolated VRL, larger, prospective randomized control trials are necessary to further evaluate the impact of standardized systemic chemotherapy regimens on lymphoma-related death. Strengthening collaboration between centres and structured investigation of current and emerging therapies are required to improve patient survival and define the standard of care for VRL.

SUMMARY

What was known before

- Vitreoretinal lymphoma can present with unilateral or bilateral ocular involvement.
- Vitreoretinal lymphoma has a strong association with CNS lymphoma development.
- Survival for CNS lymphoma is poor.

What this study adds

- Initial presentation with unilateral vitreoretinal lymphoma was associated with a decreased risk of CNS lymphoma development compared with bilateral vitreoretinal lymphoma.
- Treatment of isolated vitreoretinal lymphoma with systemic chemotherapy was associated with a decreased risk of CNS lymphoma development.

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AUTHOR CONTRIBUTIONS

All authors contributed to data collection and critical revision of the manuscript. Author L.A.D. was responsible for primary drafting of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

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