ORIGINAL ARTICLE

Comprehensive analysis of orbital lymphoma in a Turkish cohort: clinical characteristics, histological subtypes, treatment modalities, prognostic factors, and implications for management

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Summary

The study analysed the clinical characteristics, treatment approaches, and survival outcomes of 97 consecutive patients with orbital lymphoma (OL) over a 25-year period at. The median age of the patients was 57.6 years, and 59.8% (n = 58) were male. Marginal zone lymphoma constitutes the most prevalent subtype, accounting for 67% of cases, whereas other common subtypes include diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, Burkitt lymphoma, and T-cell lymphomas. Unilateral involvement was observed in the majority of cases (72.3%). Common clinical presentations included mass (30.9%), swelling (26.8%), and epiphora (11.3%). Of the patients, 7.2% received rituximab alone, 14.4% received radiotherapy alone, 48.5% received chemotherapy, 27.8% received radiotherapy plus rituximab, 22.7% received radiotherapy plus chemotherapy, and 5.2% underwent surgery as the first-line treatment. During a median follow-up of 4.3 years, 15.5% of patients experienced relapse or disease progression. The 5-year and 10-year progression-free survival rates were 84.1% and 79.1%, respectively. This study contributes to our understanding of OLs and provides a foundation for further investigations in this field. Male gender, presence of B symptoms, advanced stage, secondary orbital lymphoma, aggressive histological subtype, and elevated serum lactate dehydrogenase levels were associated with poorer (either inferior or worse) progression-free survival.

Keywords Orbital lymphoma · Marginal zone lymphoma · Ocular adnexal lymphoma · Orbital neoplasms

Introduction

Orbital lymphomas (OLs) represent a subset of non-Hodgkin lymphomas (NHLs) that primarily affect the orbital tissues, including the eyelids, extraocular muscles, conjunctiva, lacrimal glands, or soft tissues of the orbital adnexa [1, 2]. OL is considered a distinct entity within the spectrum of lymphoid neoplasms due to its unique anatomical localization and clinical behaviour. OL accounts for more than half of all orbital tumors and constitutes approximately 1–2% of all NHL cases [3]. The majority of OLs originates from B cells, and extranodal marginal zone lymphoma (MZL) is the most prevalent histological subtype. Other subtypes, including follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and mantle-cell lymphoma (MCL), are less common but still contribute to the overall disease spectrum [1, 4]. The incidence of OL increases in the seventh decade of life [5, 6]. Although most cases are unilateral, approximately 7–24% of patients develop bilateral OL [1, 6].

OL may present with diverse signs including proptosis, palpable periocular mass or painless eyelid swelling [7]. Advanced age, clinical stage, histological subtype, lymph node involvement, and serum lactate dehydrogenase levels have all been reported as prognostic indicators in OL [8]. However, the prognosis of OL is especially influenced by the histological subtype and clinical stage. Low-grade lymphomas account for 84%, while high-grade lymphomas account for only 16% of all OL cases

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[9]. Furthermore, emerging evidence suggests a potential association between OL and certain microorganisms, most notably Chlamydia psittaci [10, 11]. Studies have implicated infectious agents in the development of OL, highlighting the complex interplay between infection and lymphomagenesis in the orbital region.

Despite the clinical significance of OL, research focusing on it is scarce. Therefore, the present study aimed to comprehensively characterize the histological subtypes of OL, determine the clinical stages at diagnosis, evaluate the treatment approaches, and assess the impact of these factors on survival outcomes in a cohort of Turkish patients. By providing insights into the unique characteristics and management of OLs in the Turkish population, this study aims to contribute to the existing knowledge and guide future research efforts in this field.

Methods

Study design and patient selection

This retrospective study aimed to analyse the clinical characteristics, treatment approaches, and survival outcomes of patients diagnosed with OL. The study was conducted at Hacettepe University Cancer Institute in collaboration with Hacettepe School of Medicine Department of Ophthalmology, including a total of 97 consecutive patients diagnosed with OL between January 2000 and May 2023. The study protocol was approved by the institutional review board of Hacettepe University, and written informed consent was obtained from all patients or their legal representatives.

Data collection

A comprehensive review of electronic medical records, pathology reports, and imaging studies was performed to collect relevant patient data. Demographic characteristics such as age and sex, relevant medical history, clinical presentation, symptom duration, lesion localization, and Eastern Cooperative Oncology Group performance status (ECOG-PS) were carefully documented. Imaging studies and laboratory tests, were reviewed to confirm the diagnosis of orbital lymphoma. Histological specimens, including biopsy or surgical resection samples, were evaluated by experienced pathologists to confirm the diagnosis of OL and determine the specific histological subtype according to the World Health Organization (WHO) classification system. Furthermore, the diagnosis was established in all patients through biopsy.

Clinical staging and treatment approaches

Clinical staging was determined based on a combination of imaging studies, including computed tomography (CT), magnetic resonance imaging (MRI), and fluorine-18 labeled fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) whenever available. Ann Arbor classification was used for staging. By definition, "primary" orbital lymphomas are stage IE since primary lymphomas are thought to be confined to the orbit. In "secondary" orbital lymphomas, on the other hand, where systemic illness may be present concurrently or prior, the orbit is the site of secondary extranodal involvement [3]. Treatment approaches were individualized based on the histological subtype, clinical stage, and patient-specific factors. Treatment modalities included systemic chemotherapy, radiotherapy, immunotherapy, and surgical excision. The choice and sequence of treatments were determined by a multidisciplinary team of medical oncologists, radiation oncologists, and ophthalmologists.

Follow-up and outcome measures

Patients were followed up at regular intervals after the completion of primary treatment. The duration of follow-up varied among patients depending on their treatment response and disease progression. The primary outcome measure was progression-free survival (PFS) which was defined as radiological evidence of disease recurrence or progression. The follow-up data were collected from electronic medical records, outpatient visits, and telephone interviews.

Data analysis

Statistical analyses were performed using IBM® SPSS software version 28. Descriptive statistics were presented as frequency (percent), mean ± SD, or median (min-max). Continuous variables were examined by visual and analytical methods to determine the normal distribution and analyzed with the Mann-Whitney U test. Survival estimates were calculated with the Kaplan-Meier method. The univariate and multivariate Cox regression analyses were used to identify the independent effects on PFS. An overall type-1 error level was used to infer statistical significance.

Ethical considerations

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The study

protocol was approved by the institutional review board, and patient confidentiality was strictly maintained. All patient data were de-identified and analyzed anonymously to ensure data privacy and confidentiality.

Table 1 Patient characteristics

Characteristics		Frequency (%), $n = 97$
Age at diagnosis, mean ± SD, years		57.6 ± 15.7
≤ 60 years		59 (60.8)
> 60 years		38 (39.2)
Sex	Female	39 (40.2)
	Male	58 (59.8)
Comorbidities	Hypertension	26 (26.8)
	Coronary artery disease	11 (11.3)
	Diabetes	8 (8.2)
	Autoimmune disease	8 (8.2)
	Malignancy	3 (3.1)
	Others	12 (12.4)
Local symptoms or signs	Mass	30 (30.9)
	Swelling	26 (26.8)
	Epiphora	11 (11.3)
	Proptosis	9 (9.3)
	Ptosis	7 (7.2)
	Blindness	4 (4.1)
	Diplopia	4 (4.1)
	Limited motility	3 (3.1)
	Displacement	3 (3.1)
Presence of B symptoms		14 (14.4)
Time to diagnosis, median (min-max), months		4 (0.5–180)
ECOG-PS	0	80 (82.5)
	1	15 (15.5)
	2	2 (2.1)
Laterality	Unilateral	92 (94.8)
	Bilateral	5 (5.2)
Localization	Orbita	57 (58.8)
	Lacrimal Gland	28 (28.9)
	Eyelid	12 (12.3)
Ann Arbor stage	IE	68 (70.1)
	IIE	10 (10.3)
	IIIE	5 (5.2)
	IV	14 (14.4)
Presentation	Primary OL	77 (79.4)
	Secondary OL	20 (20.6)
Histological subtypes	Indolent	78 (80.4)
	MZL	65 (67)
	FL	13 (13.4)
	Agressive	19 (19.6)
	DLBCL	13 (13.4)
	MCL	4 (4.1)
	T/NK-cell lymphoma	2 (2.1)

DLBCL: diffuse large B-cell lymphoma, ECOG-PS: Eastern Cooperative Oncology Group performance status, FL: follicular lymphoma, MZL: marginal zone lymphoma, MCL: mantle-cell lymphoma, OL: orbital lymphoma, SD: standard deviation

**Fig. 1** Histopathologic subtypes of the orbital lymphoma
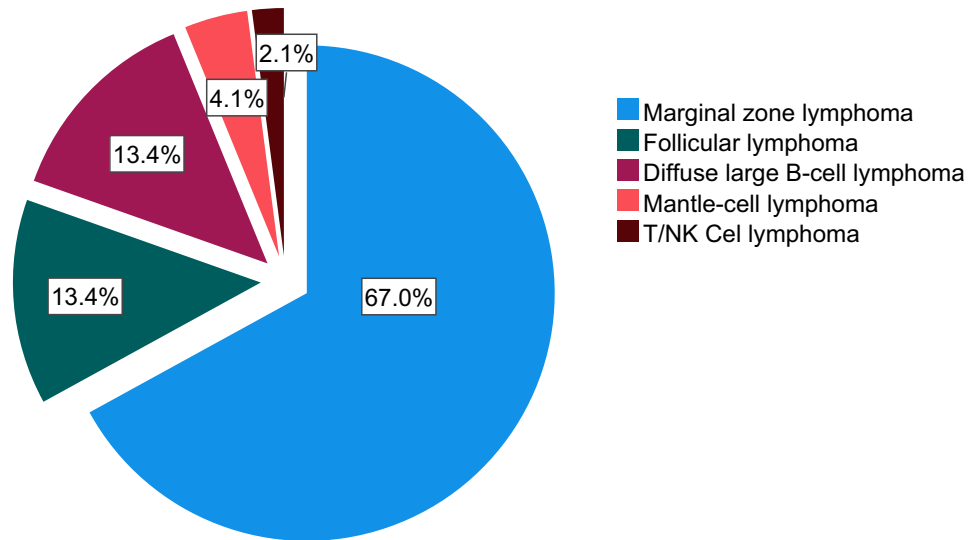
Results

Baseline characteristics

A total of 97 patients (59.8% male) were included in the study. The mean age at diagnosis was 57.6 ± 15.7 years. Forty-two (43.3%) patients had comorbid diseases, the most common of which was hypertension (26.8%). The most common local symptom or sign was mass (30 patients, 30.9%), while the others were swelling (26 patients, 26.8%), epiphora (11 patients, 11.3%), proptosis (9 patients, 9.3%), ptosis (7 patients, 7.2%), blindness (4 patients, 4.1%), diplopia (4 patients, 4.1%), limited ocular motility (3 patients, 3.1%), and paraxial globe displacement (3 patients, 3.1%) respectively. B symptoms, such as fever, weight loss, or night sweats, were present in 14 (14.4%) patients. The median time from symptom onset to diagnosis was 4 (0.5–180) months. While this time was 4 (0.5–180) months in MZL patients, it was 3 (1–14) months in non-MZL group
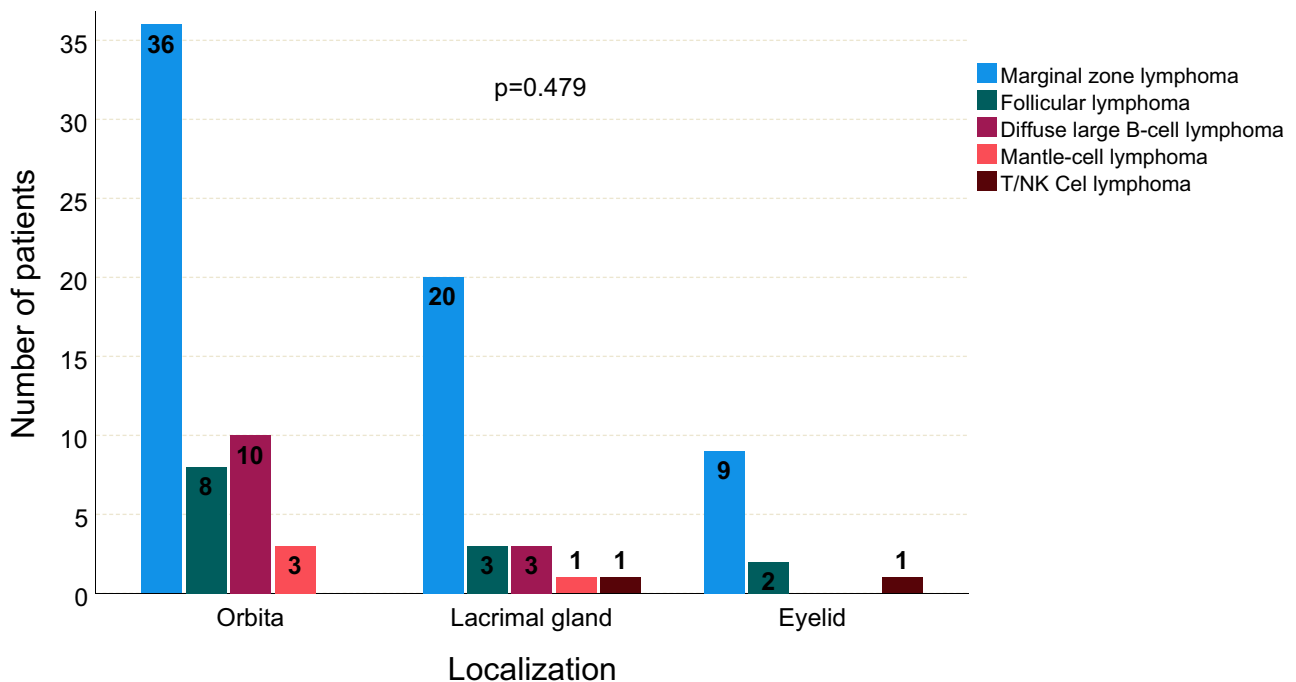
Fig. 2 Histological subtypes according to tumor localization

($p = 0.006$). ECOG-PS was 0, 1, and 2 in 80 (82.5%), 15 (15.5%), and 2 (2.1%) patients, respectively. The majority of cases presented with unilateral involvement (93 patients, 72.3%), while 4 patients (16.9%) had bilateral involvement. The tumor was localized in the orbit in 57 (58.8%) patients, in the lacrimal gland in 28 (28.9%) patients, and in the eyelids in 12 (12.4%) patients. Based on the Ann Arbor staging system, 68 (70.1%) patients were classified as stage IE, 10 (10.3%) patients as stage IIE, 5 (5.2%) patients as stage IIIE, and 14 (14.4%) patients as stage IV. The majority of cases presented with primary orbital lymphoma (77 patients, 79.4%), while 20 (20.6%) patients had secondary OL. Histopathologic subtypes of the OL were as follows: 65 (67%) patients had MZL, 13 (13.4%) patients had FL, 13 (13.4%) patients had DLBCL, 4 (4.1%) patients had MCL, and 2 (2.1%) patients had T/NK-cell lymphoma (Table 1, Fig. 1). There was no significant difference between histological subtypes according to tumor localization ($p = 0.479$, Fig. 2).

The median serum lactate dehydrogenase (LDH) level was 221 (115–1586) U/l and it was higher than normal in 36 (37.1%) patients. Laboratory examination results are detailed in Table 2. First-line treatment strategies employed in the study cohort included rituximab alone (7 patients, 7.2%), radiotherapy alone (14 patients, 14.4%), chemotherapy (47 patients, 48.5%), radiotherapy plus rituximab (27 patients, 27.8%), radiotherapy plus chemotherapy (22 patients, 22.7%), and surgical excision (5 patients, 5.2%) (Table 3).

Treatment response

Complete response (CR) was documented in 72 (74.2%) patients, 17 (17.5%) patients showed a partial response (PR), 6 (6.2%) patients had stable disease (SD), and 2 (2.1%) patients experienced progressive disease (PD). The objective

Table 2 Laboratory investigations

Blood tests	Mean ± SD
Hemoglobin, g/dl	13.9 ± 2
Neutrophils, × 10^3/mcl	4.1 ± 1.5
Lymphocytes, × 10^3/mcl	2.1 ± 0.9
Platelets, × 10^3/ml	238 ± 78.3
Albumin, g/dl	4.32 ± 0.54
Globulin, g/dl	2.98 ± 0.59
ESR, median (min-max), mm/hr	12 (2–82)
CRP, median (min-max), mg/l	0.4 (0.1–7.9)
LDH, median (min-max), U/l	221 (115–1586)
LDH > 1 × normal, n (%)	36 (37.1)
Beta-2 microglobulin, median (min-max), mg/l	1.75 (1.06–15.7)

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, LDH: lactate dehydrogenase, SD: standard deviation

Table 3 First-line treatment protocols

Treatment		Frequency (%), $n = 97$
Rituximab alone		7 (7.2)
Radiotherapy alone		14 (14.4)
Chemotherapy	R-CHOP	19 (19.6)
	R-CVP	6 (6.2)
	R-C	9 (9.3)
	R-Bendamustine	4 (4.1)
	Others	9 (9.3)
Radiotherapy plus rituximab		27 (27.8)
Radiotherapy plus chemotherapy		22 (22.7)
Surgery		5 (5.2)

C: cyclophosphamide, CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone, CVP: cyclophosphamide, vincristine, and prednisone, R: rituximab

response rate (CR + PR) was 91.7%, and the disease control rate (CR + PR + SD) was 97.9% (Table 4). Responses by first-line treatment types are detailed and visualized in Figs. 3, 4 and 5.

Survival outcomes

During a median follow-up of 4.3 (0.2–21.5) years, 15 (15.5%) patients experienced relapse or progression. Among these, 8 (53.3%) patients had MZL, 3 (20%) patients had DLBCL, 3 (20%) patients had MCL, and 1 (6.7%) had T/NK cell lymphoma. Five of the patients with recurrent MZL received rituximab re-treatment, while three patients received a rituximab and radiotherapy combination. One of the 3 relapsed DLBCL patients underwent enucleation, while the other two patients had systemic involvement and one of them died. All MCL and T/NK cell lymphoma cases had widespread disease and received combined chemotherapy along with radiotherapy.

The median PFS estimate could not be reached in the Kaplan-Meier analysis. The 5-year and 10-year PFS rates were 84.1% (95%CI: 76.1–92.1) and 79.1% (95%CI:

Table 4 Treatment response

Responses	Frequency (%), $n = 97$
Complete response	72 (74.2)
Partial response	17 (17.5)
Stable disease	6 (6.2)
Progressive disease	2 (2.1)
Objective response rate (CR + PR)	89 (91.7)
Disease control rate (CR + PR + SD)	95 (97.9)

CR: complete response, PR: partial response, SD: stable disease

68.9–89.3), respectively (Fig. 6). Factors affecting PFS were analysed with univariate and multivariate analyses. In univariate analyses, age at diagnosis (> vs ≤ 60 years, $p = 0.658$), ECOG-PS (≥ 1 vs. 0, $p = 0.713$), bilateral involvement ($p = 0.84$), and orbital localization ($p = 0.646$) were not associated with PFS; whereas male gender (HR: 11.05,

$p = 0.02$), presence of B symptoms (HR: 8.623, $p < 0.001$), stage IV disease (HR: 3.375, $p = 0.027$), secondary OL (HR: 4.875, $p = 0.002$), aggressive histological subtype (HR: 5.062, $p = 0.002$), and high LDH (< vs. > 1 × normal, HR: 3.625, $p = 0.029$) significantly affected PFS. Multivariate analysis revealed that male gender (HR: 12.632, $p = 0.017$)

Fig. 3 Treatment responses according to first-line protocols in different histological subtypes: **a**) Marginal zone lymphoma, **b**) Follicular lymphoma, **c**) Aggressive lymphomas (*a patient with stage IE diffuse large B-cell lymphoma refused chemotherapy). RT: radiotherapy, Rtx: rituximab, CT: chemotherapy
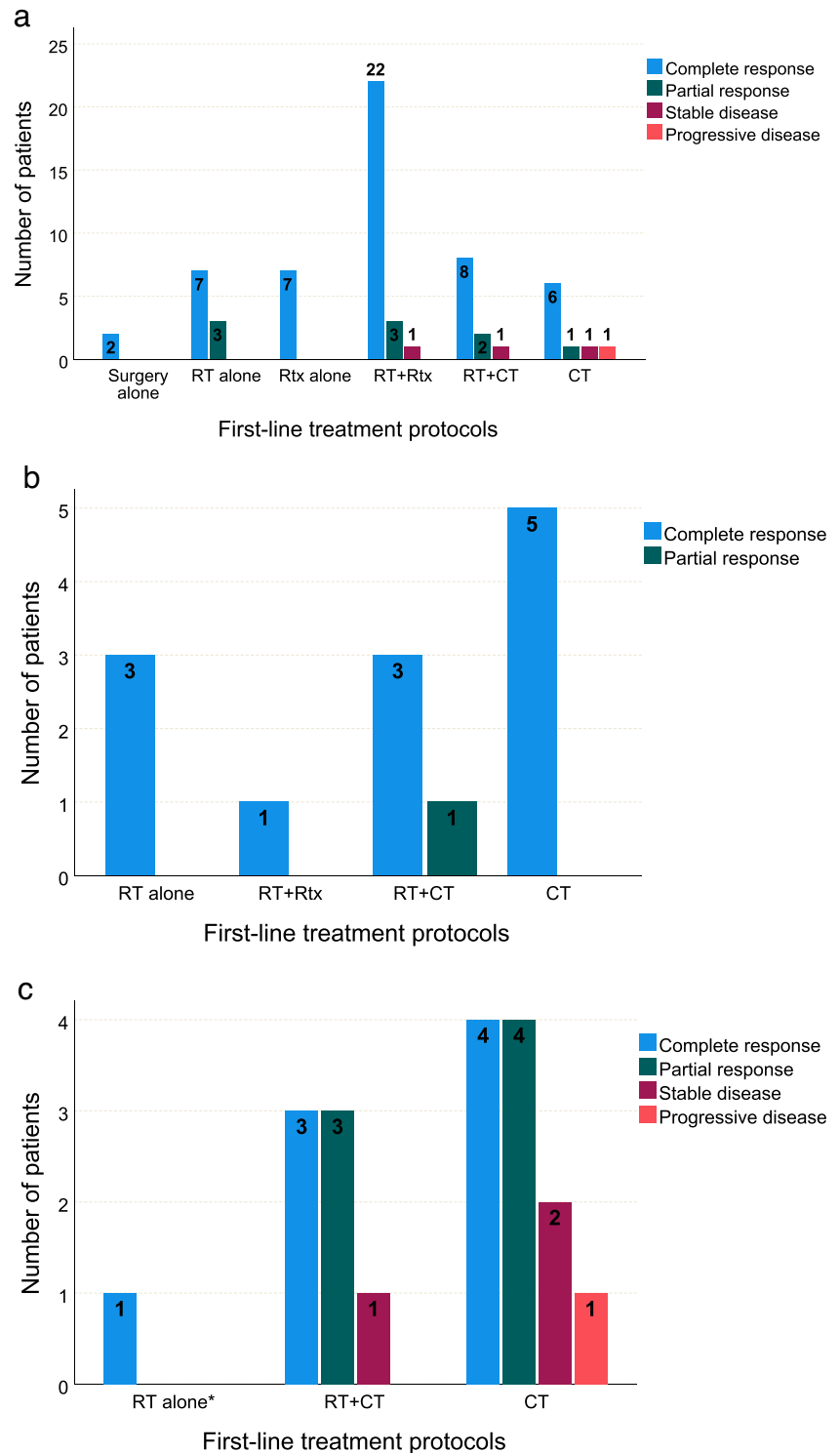
and presence of B symptoms (HR: 6.34, $p = 0.031$) were independent predictors of PFS (Table 5, Figs. 7 and 8).

Discussion

Our study provides a comprehensive analysis of OLs in a Turkish cohort. The study highlighted the long-term clinical outcomes in this specific subset of patients. The analysis included 97 consecutive patients diagnosed with OL, with MZL being the most prevalent histological subtype. Common symptoms observed were a visible and/or palpable mass, eyelid swelling, and proptosis. The mean age of patients was 57.6 ± 15.7 years, and a slight male predominance was noted. These findings contribute to our understanding of the demographic and clinical characteristics of OL. The study identified male gender and presence of B symptoms as poor prognostic factors for PFS. The findings provide important insights into the clinical characteristics, histological subtypes, treatment modalities, and outcomes of OL in a Turkish cohort. Understanding prognostic factors helps in predicting patient outcomes and tailoring treatment strategies.

Min et al., in 2022, conducted a single-center study involving treatment-naïve patients with orbital adnexal mucosa-associated lymphoid tissue (MALT) lymphoma [12]. Similar to our cohort, they identified male gender and the presence of B symptoms as poor prognostic factors for PFS [12]. In Savino's study, OL patients with the DLBCL subtype had a significantly higher risk of relapse, as indicated by an odds ratio of 7.7 (95% CI: 1.8–32.3) [13]. Similarly, patients treated with chemotherapy had a higher likelihood of relapse, with an odds ratio of 14.9 (95% CI: 2.6–83.7) [13]. Another study showed that patients treated with chemotherapy alone experienced an inferior PFS compared to those who received combined therapies ($p = 0.034$) [4]. These factors provide valuable information in predicting response to treatment and guiding personalized management.

As evident from our study, due to the indolent nature of the MZL subtype and the delayed diagnosis over several years, patients may remain under observation without receiving a definite diagnosis if not evaluated by an experienced ophthalmologist. Therefore, patients with ocular pathological findings without a confirmed diagnosis must be evaluated by ophthalmologists experienced in orbital lymphoma

Fig. 4 Images of pre (left) and post-treatment (right) physical examination findings. **a**) Proptosis due to marginal zone lymphoma in the left eye and response after 4 doses of rituximab. **b**) Follicular lymphoma mass in the right eye and response to 4 doses of R-CHOP treatment. **c**) Ptosis due to marginal zone lymphoma in the right eye and response to 2 doses of rituximab

and confirmed through biopsy. Additionally, MZL and FL subtypes present with indolent courses and fewer systemic manifestations, leading these patients to primarily seek care from ophthalmologists. Conversely, aggressive lymphomas such as DLBCL, T-NK cell lymphoma, Burkitt lymphoma, or secondary lymphomas are more likely to be referred to hematologist-oncologists rather than ophthalmologists initially. The course of the disease, the specific pathological subtype, and the evaluation by an experienced center can significantly impact the time to diagnosis and treatment for these patients.

Treatment approaches for OL vary depending on factors such as histological subtype, disease stage, and patient-specific considerations. Olsen et al., in 2019, conducted an international multicenter retrospective study to assess different treatment modalities and their outcomes [1]. The study emphasized the significance of histological subtype in determining treatment response and overall survival. Treatment modalities employed in OL management include rituximab alone, radiotherapy alone, and various chemotherapy regimens. The overall response rate reported across these studies was 91.7%. Furthermore, the use of radiotherapy as a primary treatment modality was explored in a systematic review by Oktariana et al. in 2022, further demonstrating its efficacy in managing OL [14].

Fig. 5 Images of pre (left) and post-treatment (right) radiological findings. **a**) Marginal zone lymphoma involvement in the right eye and response after 4 doses of Rituximab. **b**) Diffuse large B-cell lymphoma involvement in the left eye and response after 4 doses of R-CVP therapy. **c**) Secondary follicular lymphoma involvement behind the right eye and response with 4 doses of R-CVP
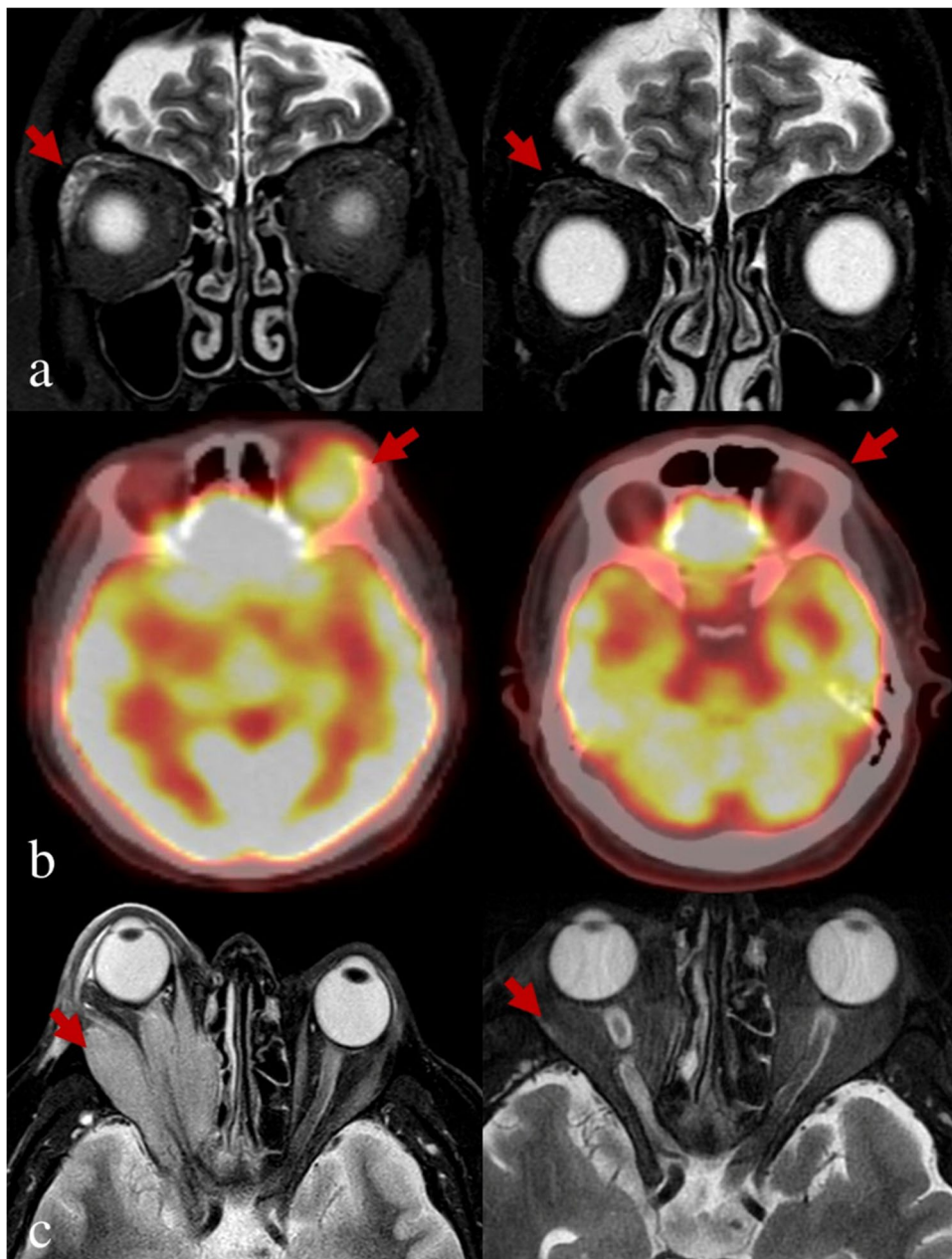
Fig. 6 Progression-free survival
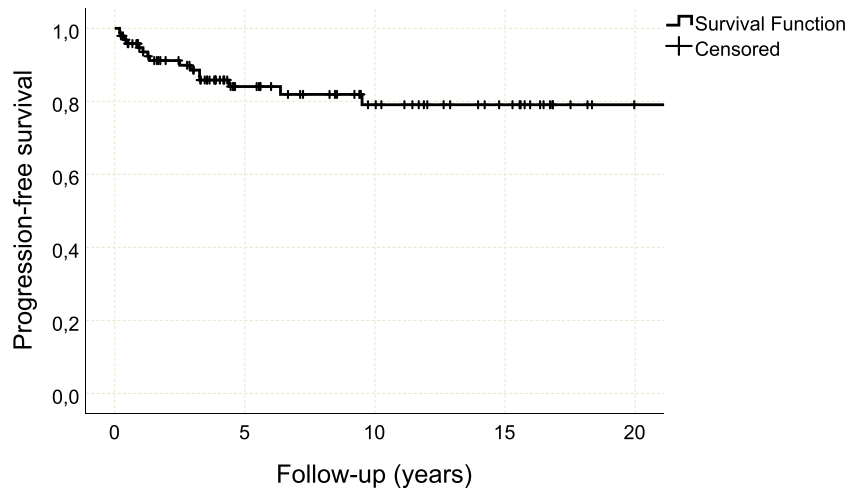
Table 5 Univariate and multivariate Cox regression analyzes of progression-free survival

Parameters	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p value*	HR (95% CI)	*p value*
Age at diagnosis > 60 years	0.785 (0.268–2.298)	0.658	-	-
Male sex	11.05 (1.452–84.12)	***0.020***	12.632 (1.57–101.66)	***0.017***
Presence of B symptoms	8.623 (3.049–24.39)	***< 0.001***	6.340 (1.179–34.094)	***0.031***
ECOG-PS ≥ 1	1.268 (0.357–4.510)	0.713	-	-
Bilateral involvement	1.233 (0.162–9.390)	0.840	-	-
Orbital localization	1.287 (0.440–3.766)	0.646	-	-
Ann Arbor stage IV	3.375 (1.148–9.927)	***0.027***	0.621 (0.140–2.749)	0.530
Secondary OL	4.875 (1.765–13.46)	***0.002***	1.599 (0.290–8.815)	0.590
Aggressive histological subtypes	5.062 (1.825–14.04)	***0.002***	2.042 (0.619–6.736)	0.241
LDH > 1 × normal	3.625 (1.138–11.55)	***0.029***	1.361 (0.355–5.224)	0.653

The italic bold text indicate statistical significance at $p < 0.05$ level. CI: confidence interval, ECOG-PS: Eastern Cooperative Oncology Group performance status, HR: hazard ratio, LDH: lactate dehydrogenase, OL: orbital lymphoma, SD: standard deviation

Before the discovery of rituximab, radiotherapy was more commonly used; however, it is known to be associated with ocular side effects, such as radiation retinopathy, optic neuropathy, and neovascular glaucoma [15, 16]. Since 2005, at our center, rituximab therapy has become a preferred treatment method due to its early response in MZL

Fig. 7 The effect of gender on progression-free survival


HR: 11.05 (95% CI: 1.452-84.12), p=0.02
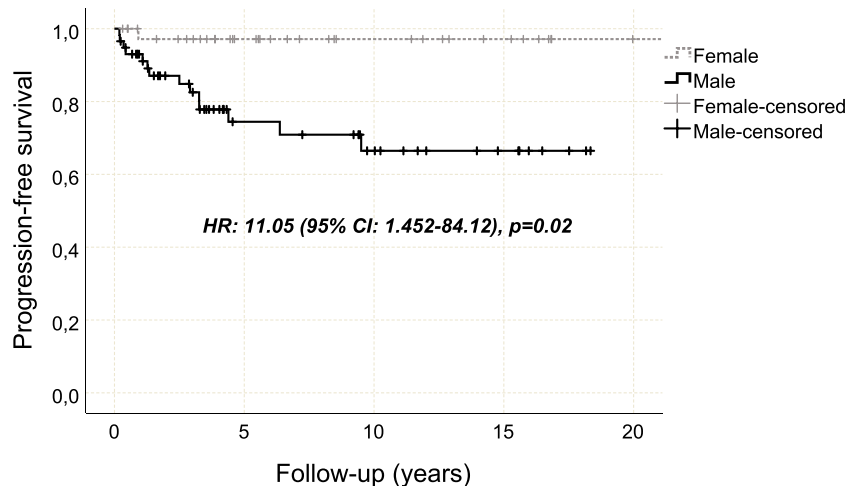
Fig. 8 Progression-free survival with the presence of B symptoms at diagnosis
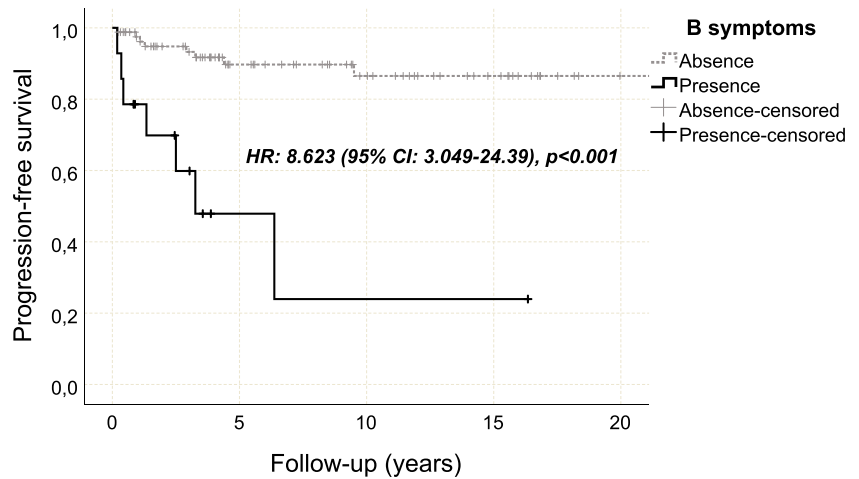
patients and high rates of complete response, along with being less toxic compared to radiotherapy. When patients are appropriately evaluated and monitored for infusion reactions and hepatitis B reactivation, rituximab is considered a more favorable agent in terms of side effects and response rates, especially in MZL patients compared to radiotherapy. Nevertheless, considering that orbital lymphoma is a rare tumor, we present an appropriate treatment algorithm for approaching these patients in line with our center's practices and the approaches of other centers in the literature (Algorithm 1).

However, our study has several limitations. Firstly, it was conducted in a single-center setting, which may limit the generalizability of our findings to other populations. Secondly, the retrospective nature of the study introduces the possibility of incomplete data. Thirdly, the sample size of our study was relatively small, which may impact the statistical power and precision of our results. Lastly, our study did not evaluate the cost-effectiveness or long-term side effects of different treatment modalities. Future research should address these limitations to provide more comprehensive and robust evidence in the field of orbital
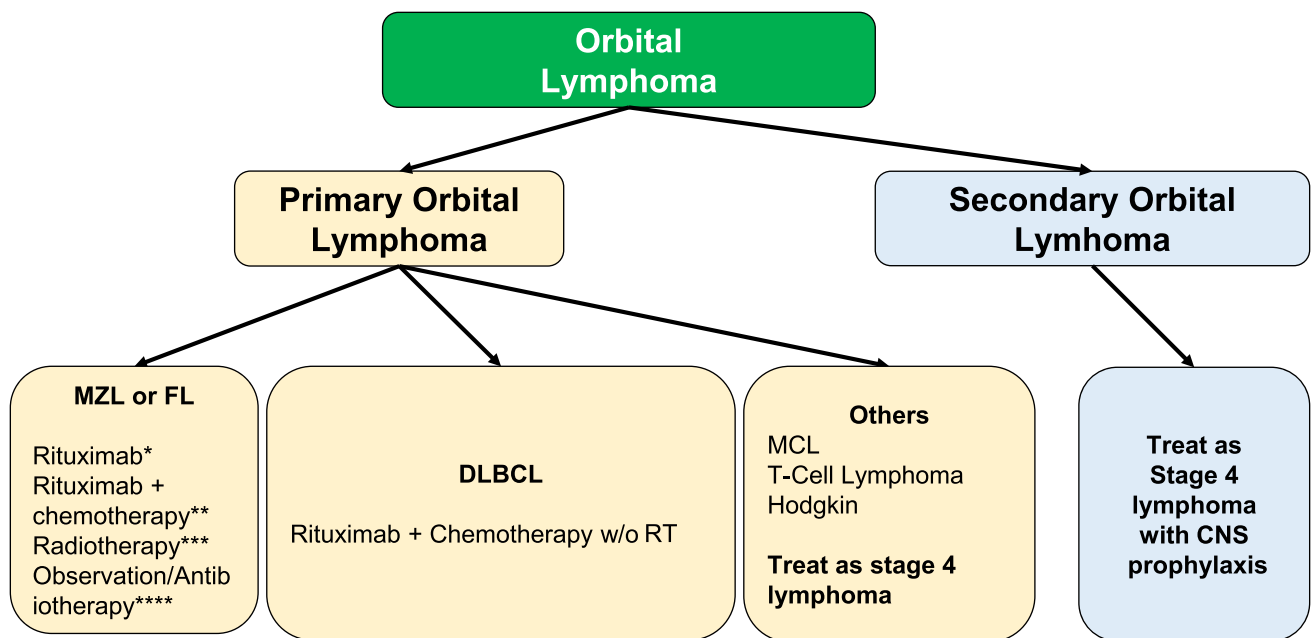
Algorithm 1 Approach to orbital lymphoma. CNS: central nervous system, DLBCL: diffuse large B-cell lymphoma, FL: follicular lymphoma, MZL: marginal zone lymphoma, MCL: mantle cell lymphoma, RT: radiotherapy. *For the majority of patients, rituximab monotherapy alone is adequate. **Bulky disease, visual disturbances, and the necessity for a rapid treatment response are considered. *** If the patient is frail and elderly (over 80 years of age) or if there are any contraindications to rituximab therapy. ****If the patient is asymptomatic, has no cosmetic concerns, or does not actively seek treatment

lymphoma management. Despite these limitations, our study contributes valuable insights into the understanding of OL and lays the foundation for future investigations in this field.

Conclusions

In conclusion, this study provides a comprehensive analysis of OL in a Turkish cohort, focusing on clinical characteristics, histological subtypes, treatment modalities, and prognostic factors. The findings contribute to our understanding of this rare lymphoma subtype and can guide clinicians in making informed decisions regarding diagnosis, treatment selection, and prognostic assessment. Further research is warranted to validate these findings and advance our knowledge of orbital lymphoma.

Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to publish Patients signed informed consent regarding publishing their data and photographs.

Conflict of interest The authors declare that they have no conflict of interest.

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