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Primary radiation therapy in stage I/II indolent orbital lymphoma – a comprehensive retrospective recurrence and toxicity analysis

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Abstract

Purpose or Objective: To provide a comprehensive recurrence and toxicity analysis of patients treated with radiotherapy alone for stage I/II (Ann-Arbor classification) indolent orbital lymphoma.

Material and Methods: We retrospectively reviewed the medical charts of 46 patients (and 51 orbits) treated at our centre with radiotherapy between 1995 and 2012 for biopsy-proven stage I/IIE primary orbital lymphomas. We evaluated treatment response and performed a comprehensive toxicity analysis with correlation to delivered radiation dose.

Results: At diagnosis, the median age was 63.5 years (range: 20–92). At initial diagnosis 43 and 3 patients had unilateral, synchronous bilateral involvement while there were 2 cases of contralateral metachronous failure. The predominant histological subtype was extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue in 42 (91.3%), follicular in 1 (2.2%), lymphoplasmacytic lymphoma in 1 (2.2%) and other indolent histology in 2 (4.3%) patients. Most lymphomas were located in the conjunctiva (18/35.3%) or eyelids (18/35.3%). Thirty-eight (82.6%) patients presented with stage I while 8/46 (17.4%) with stage II disease. The median radiation dose was 39.6 Gy (range: 21.6–48.6 Gy) delivered in 1.8–2 Gy single fractions.

At a median follow-up of 83 months (range: 7–258 months), the complete remission rate was 98%. A local relapse was observed in 2/51 (3.9%) orbits and 4/46 (8.7%) patients had systemic relapse. The 5- and 10-year PFS rates were 79.2% (95% CI: 73.0%–85.4%) and 67.6% (95% CI: 59.4%–75.8%); 5- and 10-year OS was 83.6% (95% CI: 77.9%–89.3%) and 76.5% (95% CI: 69.4%–83.6%), respectively. In total, 66 acute

Novelty statements:

- Radiotherapy alone is widely considered the standard of care for stage I/II (or stage II contiguous) indolent lymphoma.
- While several institutions have previously published their data on the management of indolent lymphoma, comprehensive patterns of relapse and toxicity analyses are lacking.
- Herein, we present the experience at our centre with particular emphasis on patterns of relapse and acute/late toxicity stratified by delivered radiation dose.
- We observed higher rates of severe toxicity in orbits receiving >36Gy vs. ≤36 Gy.
- Further research into ultra-low-dose radiotherapy and anti-CD20 monoclonal antibodies to further mitigate long-term sequelae in this setting is pertinent.

toxicity events (all-grade) were observed: 5/51 (9.8%) ≥G2 acute conjunctivitis, 2/51 (3.9%) cases of G2 acute keratitis, 1/51 (2%) cases of ≥G2 ophthalmagia and 12/51 (23.5%) cases of ≥G2 xerophthalmia. Furthermore, 45 chronic adverse events were observed in 34/51 (66.7%) irradiated orbits with 30 late adverse events attributed to cataract.

Conclusion: Our analysis confirms the role of radiotherapy alone at lower doses in the treatment of indolent orbital lymphomas. Further research is required to assess the efficacy of ultra-low-dose radiotherapy and anti-CD20 monoclonal antibodies to further mitigate long-term sequelae.

KEYWORDS
indolent non-hodgkin lymphoma, orbital lymphoma, radiotherapy, recurrence analysis, toxicity

1 | INTRODUCTION

Primary orbital lymphoma (OL) can arise in the eyelids, conjunctiva, and orbit including the lacrimal gland.[1] They constitute 50%–60% of malignancies of the ocular adnexa, comprise 5%–10% of all extranodal lymphomas and account for <1% of all Non-Hodgkin lymphoma (NHL).[2,3] They are most prevalent in the older adult population.[4] These types of lesions must be distinguished from intra-ocular lymphoma, a subtype of primary central nervous system lymphoma, that represents a high-grade process with a distinct therapeutic strategy.[5,6]

The first-line curative treatment for indolent orbital lymphoma in localised stage is radiotherapy alone with proven high response rates and manageable toxicity. Patients with OL have traditionally received radiotherapy (RT) at moderate to high doses ranging from 25 to 54 Gy with excellent local control rates in the order of 90%–100%.[7] Radiation-related side effects were tolerable but associated with increasing severe complications (grade 3–4) when more than 30–35 Gy was delivered.[8–11] Hence, some groups have proposed and published data on the efficacy of (ultra-)low-dose radiotherapy in an attempt to avoid unnecessary sequelae including cutaneous reactions, cataracts, dry eye, and more rarely macular degeneration, retinopathy, and corneal ulceration secondary to xerophthalmia.[8,12–15]

Herein, we present our institution's experience in the management of primary orbital lymphoma with radiotherapy. The purpose of this series is to provide a comprehensive recurrence and toxicity analysis in a cohort of patients treated with higher doses prior to the publication of the landmark trial establishing the role of lower dose radiotherapy in indolent NHL.[16]

2 | MATERIAL AND METHODS

2.1 | Patient and disease characteristics

Following institutional review board approval, we screened the medical records of 709 lymphoma patients treated between 1995 and 2012 in our department at the University Hospital of the Ludwig Maximilian University of Munich and identified 46 patients eligible for this retrospective study. The 46 patients had 51 biopsy-proven lesions presenting with stage I/IIE indolent orbital lymphomas. All lesions were treated with curative-intent radiotherapy. Patients were staged according to the Ann-Arbor staging system.

Conventional radiotherapy protocols were applied in all patients. Orbits treated in the earlier years were usually planned with an anterior electron field with a hanging lens block, whereas 3D conformal radiotherapy (3D-CRT) was applied in the latter years. All patients were monitored during and after completion of radiotherapy at least every 6 months with physical examination by a board-certified radiation oncologist and had surveillance imaging when indicated. Treatment response was assessed using the International Working Group (IWG) criteria published in 1999 and categorised into complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD).[17] No evidence of disease was defined as no loco-regional or distant disease at the time of follow-up based on physical and radiographic examinations. A comprehensive analysis of acute and late toxicity was performed and categorised according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

All Statistical analysis was performed using JMP version 13.0 software (SAS Institute,). The Shapiro-Wilk test was used to test for normality of the data set. The association of non-normally distributed variables was calculated using the Mann-Whitney *U*-test. The Fisher's exact test was used in the comparisons of acute/late toxicity. *p*-values below .05 were considered statistically significant. Progression-free survival (PFS) and overall survival (OS) were calculated from the date of initial pathological diagnosis and estimated using the Kaplan-Meier method.

3 | RESULTS

The median age at diagnosis was 63.5 years (range, 20–92 years). Forty-four (95.7%) patients had a favourable Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. At initial diagnosis, 20

(43.5%) lesions were located on the right, 23 (50%) on the left and 3 (6.5%) patients had synchronous bilateral involvement. Further, in 2/51 orbits metachronous contralateral recurrence was observed. Vis-à-vis localisation, the conjunctiva and eye lids each with 18 lesions were the most involved sites. The predominant histology was extranodal marginal zone lymphoma (EMZL) of mucosa-associated lymphoid tissue (MALT) in 42/46 (91.3%) patients with 1/46 patients (2.2%) presenting with follicular lymphoma, 1/46 (2.2%) patients with lymphoplasmacytic lymphoma and other indolent histological subtype with no further classification in the remaining 2/46 patients (4.3%). Thirty-eight (82.6%) patients presented with stage I vs. 8/46 (17.4%) with stage II disease which was attributed to bilateral or loco-regional lymph node involvement. Patient characteristics can be found in Table 1.

At initial clinical presentation, in 50/51 cases the most common complaints were swelling, conjunctivitis and exophthalmos in 30, 13 and 11 cases, respectively (Table 2). In addition, 31/51 (61%) cases had 1 symptom, whereas 14/51 (27%) and 3/51 (6%) reported 2 and 3 symptoms, respectively. In one case there were no complaints at initial clinical presentation.

The median follow-up (FU) duration was 83 months (range: 7–258 months). Of the 46 patients, 43/46 (93.5%) had a FU of at least 2 years after diagnosis. Moreover, 5-, 10- and 15-year FU rates were 73.9%, 41.3% and 21.7%, respectively.

TABLE 1 Patient and disease characteristics; *at diagnosis 46 patients presented with 49 involved orbits with metachronous contralateral failure occurring in 2 further orbits, hence 46 patients/51 orbits treated

Patients	Number (%)
Sex	46 patients (100)/51 orbits (100)
Male	12 (26.1)
Female	34 (73.9)
Age	
≤50	11 (23.9)
51–70	20 (43.5)
71–80	11 (23.9)
>80	4 (8.7)
ECOG-PS	
0	27 (58.7)
1	17 (37)
2	2 (4.3)
Laterality*	
Right	20 (43.5)
Left	23 (50)
Bilateral (synchronous)	3 (6.5)
Localisation	
Conjunctiva	18 (35.3)
Eyelid	18 (35.3)
Lacrimal structures	5 (9.8)
Retrobulbar	2 (3.9)
Non-specific	8 (15.7)
Histology	
MALT	42 (91.3)
Follicular lymphoma (FL)	1 (2.2)
Lymphoplasmacytic lymphoma	1 (2.2)
Other indolent lymphomas	2 (4.3)
Ann-Arbor classification	
I	38 (82.6)
II	8 (17.4)

3.1 | Radiotherapy

The median total delivered dose was 39.6 Gy (range: 21.6–48.6 Gy) delivered in 1.8–2 Gy single fractions. Most lesions (22/51 [43.1%]) in this study received a total irradiation dose of 45 Gy; 3D-CRT was applied in the majority of cases (35/51; 68.6%) and 35, 14 and 2 lesions were treated with photons, electrons or both, respectively (Table 2). A representative plan of a patient with right-sided manifestation treated to a dose of 36/1.8 Gy is presented in Figure 1.

3.2 | Treatment response

Following primary treatment, complete remission (CR) was observed in 50/51 orbits (98%). Only one lesion with MALT-lymphoma (2%) showed progressive disease. During the course of FU, 2/51 (3.9%) local recurrences were observed and 4/46 (8.7%) patients had a systemic recurrence, all in patients with MALT lymphoma. The 6 recurrences occurred in 4/46 patients. The 2 local failures occurred in a single patient who initially had a unilateral manifestation of the conjunctiva, which was successfully treated. However, 2 years later, the patient presented with a relapse in the form of contralateral conjunctival involvement, which was subsequently treated with radiotherapy. Subsequently, local failure occurred bilaterally after 83 and 118 months, respectively.

Of the 46 patients, 4 patients (8.7%) had systemic relapse after a median of 62.5 months (range 5–118 months). Vis-à-vis patient and treatment characteristics of the 4 patients with local/systemic recurrences, at initial diagnosis, 2 had manifestations in the eyelid, 1 in the lacrimal structures and the other in the conjunctiva. All patients received conformal radiotherapy with photons; all received ≥39.6 Gy. One patient developed a recurrence in the left breast and another in the palate region. The other two patients relapsed in the contralateral orbit (Table 3).

The 5- and 10-year PFS was 79.2% (95% CI: 73.0%–85.4%) and 67.6% (95% CI: 59.4%–75.8%), respectively. The median OS was not reached; 2-year OS was 97.8% (95% CI: 95.7%–100%) with 1 death recorded. The 5- and 10-year OS rates were 83.6% (95% CI: 77.9%–89.3%) and 76.5% (95% CI: 69.4%–83.6%), respectively (Figure 2A,B). Furthermore, the 5-year OS rate according to the Ann-Arbor classification was as follows: 88.3% (95% CI:

TABLE 2 Treatment characteristics; *only available for 50 orbits as one patient had no symptoms at initial diagnosis;** in a patient with bilateral involvement; [MeV=megaelectronvolt]

Initial symptoms	Number* (%)
Swelling	30 (60)
Conjunctivitis	13 (26)
Foreign body sensation	7 (14)
Exophthalmos	11 (22)
Change in visual acuity	4 (8)
Diplopia	2 (4)
Ptosis	5 (10)
Total dose (Gy)	Number (%)
≤36	18 (35.3)
>36	33 (64.7)
Remission status	Number (%)
Complete Remission (CR)	50 (98)
Progressive Disease (PD)	1 (2)
Partial Remission (PR)	0 (0)
Stable Disease (SD)	0 (0)
Radiation technique	
3D-CRT	35 (68.6)
Single anterior field	14 (27.5)
Single anterior field +opposing field**	2 (3.9)
Type of radiation	
Photons	35 (68.6)
Electrons (6-18MeV)	14 (27.5%)
Mixed	2 (3.9%)

82.8%–93.8%) and 68.6% (95%CI: 50%–87.2%) in the IE (36/46 pts) and IIE groups, respectively.

Of the 46 patients (first treatments for patients with bilateral involvement), 17 (37%) received radiation doses ≤36 Gy, whereas the other 29 (63%) patients received total radiation doses >36 Gy. 5-/10-year PFS rates were 81.3% (95% CI: 71.5%–91.0%)/81.3% (95% CI: 71.5%–91.0%) in the ≤36 Gy subgroup vs. 78.2% (95% CI: 70.3%–86.1%)/62.7% (95% CI: 52.4%–73.1%) in the >36 Gy subgroup, respectively ($p = .4$; Log-Rank test) (Figure 3A).

The 5-/10-year OS rates were 81.3% (95% CI: 71.5%–91.1%)/81.3% (95% CI: 71.5%–91.1%) in the ≤36 Gy subgroup vs. 85.3% (95% CI: 78.5%–92.1%)/75.9% (95% CI: 67.1%–84.7%) in the >36 Gy subgroup, respectively ($p = .9$; Log-Rank test) (Figure 3B).

3.3 | Acute toxicity

In total 42/51 orbits with a total of 66 acute adverse events (AEs) were observed (Table 4) and classified as detailed below. In 5/18 (27.8%) orbits irradiated with ≤36 Gy, a grade ≥2 acute AE was observed while in 14/33 (42.4%) orbits receiving >36 Gy, a grade ≥2 AE was observed ($p = .2$) (Table 5).

3.3.1 | Conjunctivitis

In 22/51 (43.1%) cases all-grade acute conjunctivitis was observed and only one case of grade 3 conjunctivitis. In 20/22 cases (90.9%), the symptoms completely resolved without the need of any intervention. All cases were irradiated with a radiation dose of 30–48.6 Gy. There was no significant correlation, but a trend between the occurrence of acute conjunctivitis and radiation dose ($p = .09$). In addition, in orbits treated with ≤36 Gy, 5/18 (27.8%) suffered from acute conjunctivitis, while orbits treated with >36 Gy, 17/33 (51.5%) had acute conjunctivitis ($p = .09$).

3.3.2 | Keratitis

In total, 2/51 (3.9%) cases of grade 2 acute keratitis were observed and was self-limiting within a couple of weeks post-radiotherapy. In both cases, a total dose of 30 Gy and 45 Gy was delivered. There was no correlation between the occurrence of acute keratitis and radiation dose ($p = .68$).

3.3.3 | Ophthalmagia

Ophthalmagia was observed in 7/51 cases (13.7%). Of the seven orbits, only one case was grade 3 and in all cases, symptoms resolved completely without any intervention. All cases received radiation doses ranging from 30.6 to 45 Gy. No significant correlation, but a trend between radiation dose and ophthalmagia was observed ($p = .08$). Furthermore, in the group treated with ≤36 Gy, 1/18 (5.6%) suffered from ophthalmagia while 6/33 (18.2%) treated with >36 Gy experienced ophthalmagia ($p = .21$).

3.3.4 | Xerophthalmia

In 35/51 cases (68.6%), xerophthalmia was observed. Of these, 23/35 (65.7%) were G1; 10/35 (28.6%) and 2/35 (5.7%) cases of G2 and G3 xerophthalmia were observed. Improvement of symptoms during the course of follow-up occurred in 22 (62.9%) orbits. Radiation doses ranging from 21.6 to 48.6 Gy were delivered. Also, there was no significant correlation between radiation dose and xerophthalmia ($p = .2$). In addition, 10/18 (55.6%) orbits treated with ≤36 Gy suffered from acute xerophthalmia; 25/33 (75.8%) orbits treated with >36 Gy experienced xerophthalmia ($p = .14$).

3.4 | Late toxicity

Of the 66 adverse events, resolution was observed in 51 cases (77.3%). A transition to chronic symptoms occurred in 15 cases (22.7%). In addition, there were 30 late AEs in the form of cataract.

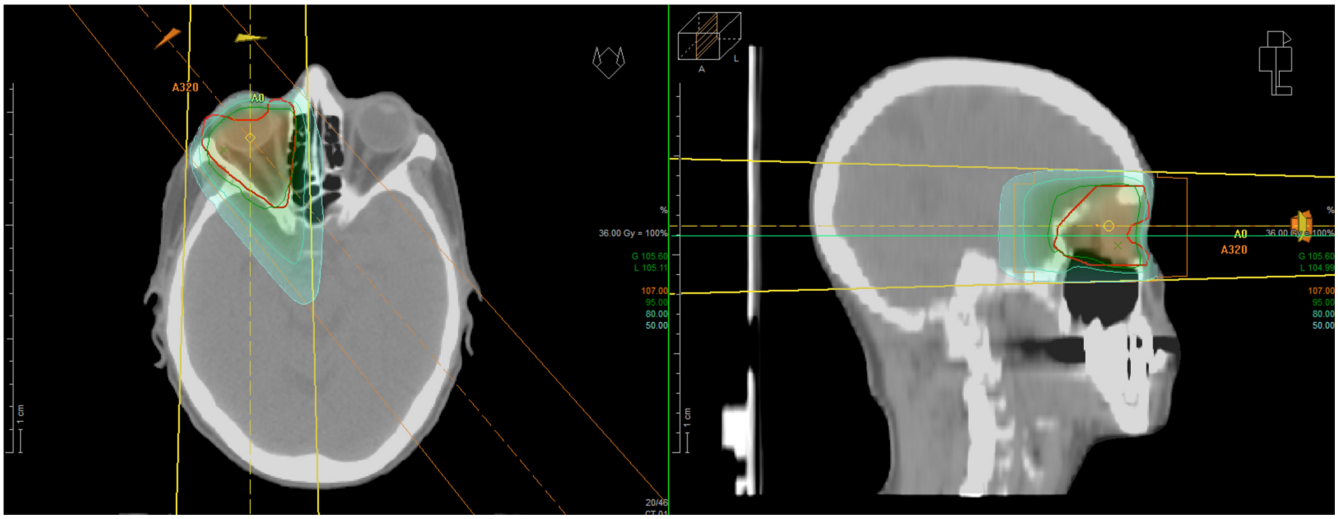


FIGURE 1 Representative plan in the transverse and sagittal plane of patient with OL in the right upper eye lid treated with a prescription dose of 36 Gy/20 fractions to the planning target volume (red line); 34.2 Gy/95% prescription dose (green isodose line with colour wash), 28.8 Gy/80% prescription dose (turquoise isodose line with colour wash) and 18.0 Gy/50% prescription dose (light blue isodose line with colour wash)

TABLE 3 Patient and treatment characteristics of patients with systemic recurrence; m = male, f = female

Pat	Sex	Age at diagnosis	Localisation	Type of radiation	Total dose (Gy)	Months to recurrence	Localisation of recurrence
1	m	65	Lacrimal structures	Photon	45	118	Contralateral orbit
2	f	57	Eyelid	Photon	45	5	Left breast
3	f	45	Eyelid	Photon	39.6	101	Palate
4	f	52	Conjunctiva	Photon	39.6	24	Contralateral orbit

Thus, 45 chronic symptoms were identified in 34/51 irradiated orbits (66.7%).

In addition, 7/18 (38.9%) orbits treated with ≤36 Gy suffered from a grade ≥2 chronic AE while 23/33 (69.7%) orbits treated with >36 Gy experienced a grade ≥2 chronic AE ($p = .03$) (Table 6).

In 2/22 (9.1%) suffering from acute conjunctivitis, a transition from acute to chronic conjunctivitis occurred. In 13/35 (37.1%) cases of xerophthalmia, transition from acute to late xerophthalmia was observed: 5/23 (21.7%) of G1, 6/10 (60%) of G2 and 2/2 (100%) G3 cases of acute xerophthalmia. In total, a quarter of all irradiated orbits were affected by chronic xerophthalmia. Vis-à-vis applied radiation dose, in the 13 cases of chronic xerophthalmia, radiation doses ranging from 30.6 to 48.6 Gy were delivered. There was no correlation between radiation dose and xerophthalmia ($p = .15$). Further, no secondary malignancies nor retinal pathologies were observed during the FU period.

3.4.1 | Cataract

In total, 30/51 (58.8%) cases of cataract were reported. Based on gender, 23/30 (76.7%) cases occurred in women while 7/30 (23.3%) occurred in men. Within the group of 34 women, cataract was observed in 23/38 orbits (60.5%) and 7/13 orbits (53.8%) in 12 men. Radiation dose ranged from 30 to 45 Gy. A significant correlation between dose and the occurrence of cataract was observed ($p = .01$).

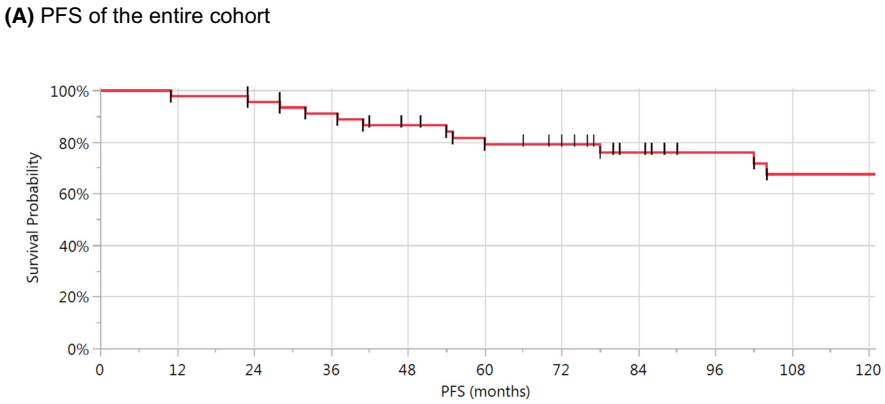
In addition, total radiation dose of ≤36 Gy vs. >36 Gy was significantly associated with the occurrence of cataract ($p = .03$). In 21/30 (70%) cases, cataract surgery was required.

The 21 patients who underwent cataract surgery received radiation doses ranging from 30.6 to 45 Gy, while the remaining 9 cases, which did not require surgery, received radiation doses ranging from 39.6 to 45 Gy. In addition, no significant statistical correlation between radiation dose and the need for surgical intervention was observed ($p = .12$).

4 | DISCUSSION

The present cohort of 46 patients with 51 indolent OL treated from 1995 to 2012 at a single tertiary cancer centre represents a modest number of patients treated exclusively for stage I-IIE OL. The results demonstrated that radiotherapy alone at a median dose of 39.6 Gy results in excellent local control. However, late sequelae following treatment cannot be overlooked.

The majority of our patients were female at a ratio of 2.8:1 and elderly (median age: 63.5 years). This finding is consistent with the previous studies.[11,18–20] and the predominant histology was MALT,



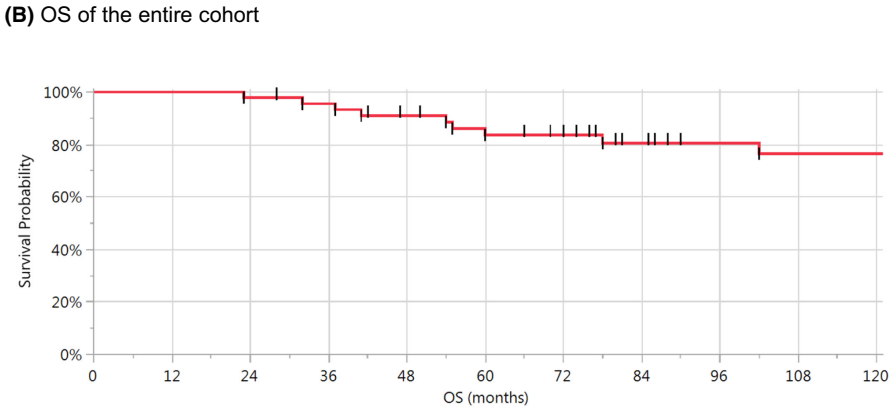
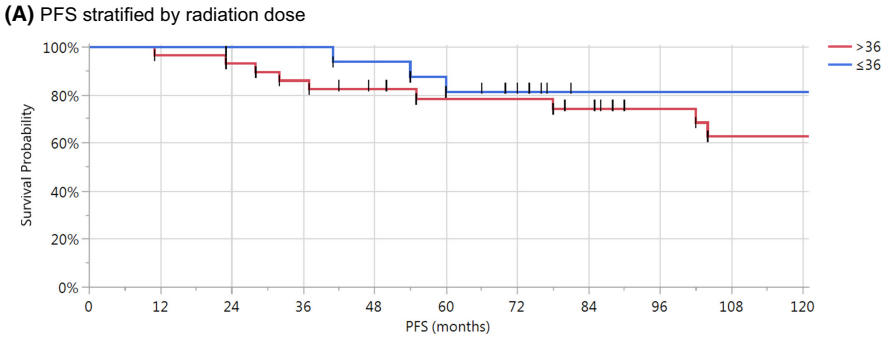


FIGURE 2 (A) PFS of the entire cohort. (B) OS of the entire cohort



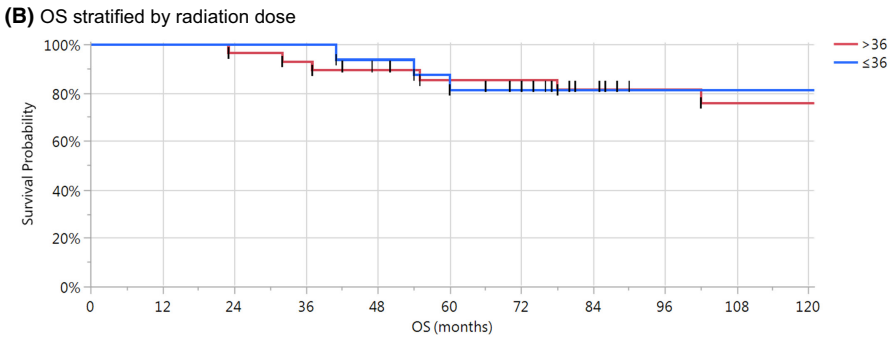


FIGURE 3 (A) PFS stratified by radiation dose. (B) OS stratified by radiation dose

accounting for 91.3% of cases. In our cohort a CR rate of 98% was achieved; 64.7% received more than 36 Gy. These results corroborate previous findings and are consistent with published literature.[8,11,14,21] A previous study in 89 patients with primary orbital MALT lymphoma treated with 25–30 Gy demonstrated a CR rate of 99%.[8] Zhou et al observed a local control rate of 98% at a median dose of 30.6 Gy in their cohort[21] and another analysis from Heidelberg observed an overall response rate of 97.7% in their conventional radiotherapy arm.[14] However, in comparison to the other studies, most of our patients received a total dose >36 Gy and no

inferior local control rates were observed for patients receiving ≤36 Gy. Importantly, a seminal multicentre randomised trial published in 2011 enrolled patients with any histological subtype and stage NHL including 361 sites of indolent NHL (predominantly FL and MZL) to receive at the time standard dose 40–45 Gy/20-23 fractions vs. lower dose 24 Gy/12 fractions. There was no significant difference in local control, PFS and OS. Of note, a significant increase in acute skin toxicity was observed in the standard arm of the indolent NHL group.[16] Thus it should be noted that international guidelines currently recommend 24–30 Gy for MZL, 24 Gy being widely used for sensitive sites like the orbit in this case. As such the doses delivered in our study were generally higher than contemporary dose recommendations.[22–24]

In the present study, the median FU of the 46 patients was 83 months, which allowed for an assessment of recurrences and long-term adverse events. In contrast, in the study by Zhou et al, the median FU was 46 months[21] and in another study which retrospectively analysed 89 patients with 110 OL, the median FU was 70.8 months.[8] The 2-year follow-up rate was 93.5% after diagnosis. 3/46 patients were lost to follow-up during this time. After 5 years, the follow-up was still 73.9%. The 5- and 10-year PFS rates were 79.2% and 67.6%, respectively. Previous studies have also reported similar 5-year PFS rates ranging from 65% to 95%.[21,25,26] In a study by Goda et al, the 5-year PFS was 76%[8] and more recently, another

TABLE 4 Acute toxicity per CTCAE version 4.03

Acute toxicity	Number (%)	Recovery (%)
Conjunctivitis (all-grade)	22 (43.1)	20 (90.9)
G1	17 (33.3)	17 (100)
G2	4 (7.8)	2 (50)
G3	1 (2)	1 (100)
G2 Keratitis	2 (3.9)	2 (100)
Ophthalmagia (all-grade)	7 (13.7)	7 (100)
G1	6 (11.8)	6 (100)
G2	0 (0)	-
G3	1 (2)	1 (100)
Xerophthalmia (all-grade)	35 (68.6)	22 (62.9)
G1	23 (45.1)	18 (78.3)
G2	10 (19.6)	4 (40)
G3	2 (3.9)	0 (0)

TABLE 5 Acute toxicity stratified by radiation dose; *per orbit i.e. a single orbit can present with ≥1 acute AE

Acute toxicity	≤36 Gy ($n = 18$)	>36 Gy ($n = 33$)	p-value (Fisher's exact test)
Conjunctivitis (total)	5 (27.8%)	17 (51.5%)	.09
Conjunctivitis ≥2 CTCAE	1 (5.6%)	4 (12.1%)	.41
Keratitis (total)	1 (5.6%)	1 (3.0%)	.88
Keratitis ≥2 CTCAE	1 (5.6%)	1 (3.0%)	.88
Ophthalmagia (total)	1 (5.6%)	6 (18.2%)	.21
Ophthalmagia ≥2 CTCAE	0	1 (3.0%)	.65
Xerophthalmia (total)	10 (55.6%)	25 (75.8%)	.12
Xerophthalmia ≥2 CTCAE	3 (16.7%)	9 (27.3%)	.31
All acute*	12/18 (66.7%)	30/33 (90.9%)	**.04**
All acute ≥2 CTCAE*	5/18 (27.8%)	14/33 (42.4%)	.23

TABLE 6 Late toxicity stratified by radiation dose; *per orbit i.e. a single orbit can present with ≥1 chronic AE

Late toxicity	≤36 Gy ($n = 18$)	>36 Gy ($n = 33$)	p-value (Fisher's exact test)
Conjunctivitis (total)	0	2 (6.1%)	.18
Conjunctivitis ≥2 CTCAE	0	2 (6.1%)	.41
Keratitis (total)	0	0	
Keratitis ≥2 CTCAE	0	0	
Ophthalmagia (total)	0	0	
Opthalmagia ≥2 CTCAE	0	0	
Xerophthalmia (total)	3 (16.7%)	10 (30.3%)	.44
Xerophthalmia ≥2 CTCAE	0	8 (24.2%)	**.02**
Cataract (total)	7 (38.9%)	23 (69.7%)	**.03**
Cataract ≥2 CTCAE	7 (38.9%)	18 (54.5%)	.22
All chronic*	8/18 (44.4%)	26/33 (78.8%)	**.02**
All chronic ≥2 CTCAE*	7/18 (38.9%)	23/33 (69.7%)	**.03**

study by König et al. showed a slightly more favourable 5-year local PFS of 88.6% and distant PFS of 89.9%.[20]

Furthermore, in the present analysis, 6 recurrences were observed in 4/46 (8.7%) patients. Two (3.9%) local recurrences and 4 (8.7%) distant failures, all in patients with MALT lymphoma. The 5- and 10-year OS rates were 83.6% and 76.5%, respectively. These results are well in accordance with the literature and attests to the favourable prognosis of primary indolent OL.[8,27,28] In the largest international, multicentre study to date reporting outcomes of patients with OL, 452/779 (58%) presented with EMZL (predominantly stage I/IIE disease) and 5- and 10-year OS was 80% and 62% across all disease stages.[28]

Of note, in the present analysis, emphasis was placed on patterns of relapse and toxicity given the higher doses applied and thus higher incidence of toxicity observed compared to that expected for patients receiving standard of care 24 Gy in the contemporary setting. In our analysis, no significant specific acute AE was associated with the delivered radiation dose. Acute AEs occurred in 42/51 (82.4%) orbits. The most frequent complaint was xerophthalmia in 35/51 (68.6%) cases. However, mild symptoms (G1) were observed in 23 cases (45.1%). Bischof et al also observed 74% mild (G1-2) acute AEs and no G3 acute AE despite a median radiation dose of 40 Gy in their cohort.[11] Only 6 (12.8%) cases of late AEs were observed in patients who received a radiation dose >36 Gy.[11] Some authors also report an increase in chronic xerophthalmia associated with radiation doses >40 Gy. Bessell et al. reported 23% chronic AEs in patients who received >40 Gy.[29] Another report specifically investigating ocular complications following radiotherapy in the craniofacial region showed a significantly higher incidence of xerophthalmia for eyes receiving a maximum dose >40 Gy and cataract when the lens received >5 Gy.[30] In another study by De Cicco et al, 44.4% of patients who received >36 Gy suffered more from chronic AEs as opposed to 20.7% in the group receiving ≤36 Gy.[25] Our data showed a similar correlation. In total, 34/51 (66.7%) orbits experienced chronic AEs. Orbits treated with ≤36 Gy, 7/8 (38.9%) suffered from ≥2 chronic AEs and 23/33 (69.7%) orbits treated with >36 Gy had ≥2 chronic AEs ($p = .03$). A quarter of all patients reported chronic dryness of the eyes; cataract occurred in 30/51 (58.8%) cases. Moreover, in 21/30 (70%) cases, cataract surgery was required. In our study, a significant increase in incidence of all-grade cataract in the >36 Gy vs. ≤36 Gy group was discerned, namely in 23/33 (69.7%) and 7/18 (38.9%) cases ($p = .03$), respectively. The higher incidence of cataracts may be attributed to the higher radiation dose compared to other studies.[14,21] Interestingly, in the Heidelberg study, cataract developed in 25.6% of cases, of which 10/11 were irradiated with more than 34 Gy.[14] In another study, 9/62 (14.5%) eyes had documented cataracts that required surgery and all 9 cases received photon irradiation to a total dose ranging from 30.6–40.6 Gy without lens block.[21] Moreover, Goda et al observed grade 3 cataract in 20/89 (22.5%) patients after a median duration of 3.6 years and confirmed the efficacy of lens shielding in their analysis.[8] However, of note, in a more contemporary analysis of patients treated to a median dose of 30 Gy (range: 30–36 Gy), the 5-year cumulative incidence of grade ≥2 cataract was 40%.[31]

This has led to a paradigm shift over the last decade with the initial shift to lower dose radiotherapy in the order of 24 Gy as a number of single institution studies reported excellent control rates >90%.[8,32–34] However, long-term toxicity still remained an issue in some reports.[8,32] As such transition to ultra-low dose (ULD) radiotherapy has been the subject of intense investigation.[12,13,35–37] As early as 2003, Haas et al. assessed ULD-RT in 109 patients (304 symptomatic sites) with recurrent B-cell indolent lymphomas with an ORR of 92% and median time to local progression of 25 months.[37] Further, a recent retrospective analysis in predominantly stage I/II OL did not observe any significant difference in PFS or OS in their ULD (4–6 Gy) vs. standard-dose (24–30.6 Gy) and high-dose (>30.6 Gy) RT arms. However, the ULD-RT arm was significantly underpowered (6/52 orbits). In addition, lower rates of grade 2 toxicity were observed in the ULD-RT and intensity-modulated radiotherapy arm.[36] Another retrospective study from Stanford reviewed 20 patients with 27 sites of OL. At a median FU of 26 months, ORR/CR rates were 96% and 85%, respectively. Importantly, only mild acute side effects were noted in 30% of treated sites and no long-term toxicity was reported.[12]

In another series from the MD Anderson Cancer Center (MDACC), ORR/CR rates of 100%/86% were observed in 22 patients treated with ULD RT and remarkably, only 1 grade 1 xerophthalmia was observed in the entire cohort.[13] Currently, the MDACC is investigating this concept in a prospective manner (NCT02494700). Furthermore, an open-label study was recently published assessing ultra-low-dose RT alone vs. ultra-low-dose RT +rituximab. Interestingly, there was no statistical difference in overall response and survival rates between the two groups.[38] Also, in the largest international multicentre retrospective cohort study to date of ocular adnexal MZL, stage IE patients treated with RT alone (median dose: 26 Gy) had a superior disease-specific survival (DSS) at 10 years (95%) compared to patients treated with chemotherapy (86%).[39]

While ULD radiotherapy is an interesting proposition, caution should still be warranted as evidenced by the recently published long-term results of the non-inferiority FoRT trial, which randomised patients with all-stage predominantly FL and MZL without specifically delving further into subtypes of MZL to 4 vs. 24 Gy radiotherapy (of which ~43% had stage I disease). At a median FU of 73.8 months, 2-/5-year local PFS rates were 94.1%/89.9% and 79.8%/70.4% (HR: 3.46; $p < .0001$) in the 24- and 4-Gy arm, respectively. Interestingly, 5-year local progression-free rates were 100% with 24 Gy and 88% with 4 Gy ($p = .015$) for MZL and higher than those seen in the follicular lymphoma subtype; 88% with 24 Gy and 68% with 4 Gy, respectively. The difference in local control at 2 years remained outside the non-inferiority margin of 10%, thus the authors concluded that 24 Gy in 12 fractions remain standard when durable local control is the paramount goal.[40]

Acknowledging the limitations of the current analysis, it should be noted that only patients from a single tertiary centre with a modest number of patients were included. The retrospective nature of this analysis is a caveat, and comparison with a more contemporary

cohort treated with ULD RT was not feasible. Nevertheless, the current analysis corroborates findings from previous studies. In addition, a comprehensive toxicity and pattern of recurrence analysis was performed supporting lower dose radiotherapy alone in these patients as a strategy for mitigating long-term high-grade sequelae. In primary RT to the orbit housing the eye, which is a fairly radiosensitive structure, attempts should be made to use the lowest total dose possible that is effective, and some sparing techniques, e.g. partial orbit irradiation, as well as ultra-low-dose RT in 2 fractions upfront, with higher dose salvage options should be considered.

5 | CONCLUSION

Our analysis confirms the role of radiotherapy alone at lower doses in the treatment of indolent orbital lymphomas. Further prospective studies are pertinent to assess the efficacy of ultra-low-dose radiotherapy and intravenous/intralesional anti-CD20 monoclonals in this setting.

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CONFLICTS OF INTEREST

On behalf of all authors, the corresponding author declares no conflict of interest related to this study.

DATA AVAILABILITY STATEMENT

Datasets analysed for the current study are available from the corresponding author on reasonable request.

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