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Ultra-low dose radiotherapy in the management of low-grade orbital lymphomas

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ABSTRACT

Background: Ultra-low dose radiotherapy (ULDRT) (2 × 2 Gy) has been used for symptomatic control of low-grade lymphomas with surprising local control rates, suggesting that these entities could respond to lower doses. These are particularly desirable for the treatment of orbital sites and some publications refer to high rates of complete responses. In this paper, we present our experience with the use of ULDRT for indolent orbital lymphomas.

Materials and methods: Electronic files and treatment plans of patients treated with ULDRT for low-grade orbital lymphoma were retrospectively reviewed. Oncological outcomes and toxicities were collected and described for each patient.

Results: Seven patients (median age of 75 years) with 8 lesions (3 follicular, 2 MALT, 1 marginal and 1 low-grade non-Hodgkin lymphoma) were considered for analysis. The majority had stage IE disease and one patient had bilateral disease. Six tumors were detected on imaging (median size of 20 mm). Involved orbital sites were periocular, conjunctival and palpebral; there was one case of intraocular (choroid) and one case of lacrimal gland involvement. One patient received consolidative rituximab after RT. The median follow-up time was 22 months. Two patients had partial response, one of them with persistent minimal choroidal disease and the other with partial response on CT. Five (71%) patients had clinical (n = 2) or radiologic (n = 3) complete response on treated sites. Reported late toxicities were minimal and included dry eye and pruritus.

Conclusion: In our experience, ULDRT achieved a local control rate of 100% and complete response rate of 71% with minimal toxicity.

Key words: radiotherapy; ultra-low dose; low-grade lymphoma; orbital lymphoma; extranodal lymphoma

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Introduction

Orbital lymphomas account for about 2% of all hematological malignancies, 5–15% of extranodal lymphomas and about 50% of orbital tumors [1]. The majority of orbital lymphomas such as follicular, mucosal associated lymphoid tissue (MALT) and marginal zone subtypes, have an indolent course; however, due to their location, they can compromise visual function and impact autonomy and quality of life.

The first line of treatment for low-grade localized orbital lymphomas is external beam radiotherapy (EBRT) [2]. Conventional doses (30–36 Gy) have been traditionally associated with local control rates of nearly 100% at 5 years [3]. In advanced

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stages, systemic treatment is mandatory and it can also be complemented with radiation in the case of persistent localized disease.

Supported by the high radiosensitivity of this entity and the results of a phase III trial [4] in 2011, low dose radiotherapy (24 Gy) has been endorsed in international guidelines [5] as standard of care in low-grade lymphomas. Various institutional-based reports confirm these results [6–8], both in nodal and in extranodal sites.

Ultra-low dose schemes (4 Gy in 2 fractions, every other day) have been used both for symptomatic and curative intent of low-grade lymphomas with surprising local control rates [9], suggesting that these entities could respond to even lower radiation doses. This hypothesis was tested in the FoRT trial [10], which compared 4 Gy versus standard of care 24 Gy for low grade lymphomas. This trial failed to prove non-inferiority of ultra-low doses, nevertheless being useful for symptomatic palliation.

Low and ultra-low dose radiotherapy are particularly desirable for the treatment of orbital sites and some publications refer to its excellent local control and high rates of complete responses (CR) [11, 12].

Due to its limited number of fractions, the ultra-low dose scheme is advantageous for fragile and elderly groups which are also the majority of patients presented with this malignancy. The use of ultra-low doses also carries minimal probability of toxicity, which is ideal for tumors localized in or near orbital structures or other radiosensitive areas.

The rarity of this entity presents a difficulty in reporting and comparing clinical outcomes. In this paper we present the experience of an oncological center in the use of ultra-low dose radiotherapy for the management of indolent orbital lymphomas.

Materials and methods

An institutional-based retrospective observational study was planned. Clinical electronic files and radiotherapy (RT) plans of patients treated for orbital lymphoma at our department between January 2010 and December 2020 were retrieved and reviewed. Ethical approval was obtained from the institutional ethics committee.

Twenty-one patients received EBRT for the treatment of orbital lymphoma. High grade histologies - mantle cell lymphoma (n = 5), T-cell lymphoma (n = 3), NK lymphoma (n = 1), lymphoplasmocytic lymphoma (n = 1) as well as indolent tumors treated with doses > 4 Gy (n = 3) were excluded from this analysis. One additional patient was excluded due to the lack of electronic file.

Patient characteristics, disease presentation and treatment details were collected. Histopathological diagnosis of the presenting lesion was performed, unless it was highly suggestive in the context of an advanced disease.

Each patient was staged according to Ann Arbor staging system and discussed in a multidisciplinary setting. Ultra-low dose radiotherapy was the treatment of choice in fragile patients with localized disease and also for palliative management in the cases of advanced stage lymphomas.

Radiation technique was chosen according to the disease location with electron beam RT used for superficial lesions. A planning Computed Tomography (CT) was acquired for all patients. When photon beam RT was planned, a thermoplastic mask for cranial immobilization was also used. Whole orbit irradiation was performed in the case of intraocular disease. When deemed necessary, planning images and radiotherapy plans were reviewed with an assistance of a radiologist and ophthalmologist. Visual registration with magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT) was also performed when available. All patients completed the prescribed ultra-low dose radiotherapy (2 × 2 Gy, every other day).

Patients underwent periodic follow-up with radiation oncology, hematology and ophthalmology; clinical or radiologic response was recorded. Local control was defined as partial or complete response. Acute and late toxicities were graded according to Common Terminology Criteria for Adverse Events (CTCAE) v.5.0. Follow up time was defined as time from the first day of EBRT to the last follow up or death, whichever first occurred.

Results

Seven patients with 8 lesions were considered for analysis. Patient characteristics and disease presentation are listed in Table 1.

Median age was 75 years (range 49–86 years) and 4 patients had an Eastern Cooperative Oncology Group (ECOG) performance status ≥ 1.

Table 1. Patient characteristics and disease presentation

Age (y), median (min–max)	75 (49–86)
Gender, male n (%)	4 (57)
ECOG PS, n (%)	
0	3 (43)
1	2 (29)
2	2 (29)
Histological subtype, n (%)	
Follicular	3 (43)
MALT	2 (29)
Marginal zone	1 (14)
Low-grade NHL, non-specified	1 (14)
Stage, n (%)	
I	4 (57)
II	1 (14)
IV	2 (29)
Primary disease, n (%)	
Yes	5 (71)
No	2 (29)
Image detected [A], n (%)	
Yes	6 (86)
No	1 (14)
Orbital symptoms, n (%)	
Impaired visual field	1 (14)
Ocular mass	2 (29)
Impaired visual acuity	1 (14)
Palpebral edema	1 (14)
Conjunctival injection	2 (29)
Diplopy	1 (14)
Proptosis	1 (14)
Involved orbital sites, n (%)	
Periocular	3 (43)
Conjunctival	2 (29)
Palpebral	2 (29)
Intraocular	1 (14)
Lacrimal gland	1 (14)
Laterality, n (%)	
Right	3 (43)
Left	3 (43)
Bilateral	1 (14)
Size [mm], median (min–max)	20 (15–28)

[A] — including ophthalmological examination; ECOG PS — Eastern Cooperative Oncological Score performance status; MALT — mucosal-associated lymphoid tissue; NHL — non-Hodgkin lymphoma

Most frequent histological subtype was follicular (n = 3), followed by MALT (n = 2) and marginal zone (n = 1); one patient was classified as non-specified low-grade non-Hodgkin lymphoma. The majority (n = 4) had localized disease (stage IE), 1 patient had a stage IIE disease and 2 remaining patients had stage IV at time of treatment. Two patients presented as a secondary orbital involvement of a previous diagnosed low-grade lymphoma.

Patients presented with one or many symptoms listed as: orbital mass (n = 2), conjunctival injection (n = 2), impaired visual field (n = 1), impaired visual acuity (n = 1), palpebral edema (n = 1), proptosis (n = 1) and diplopy (n = 1).

Six tumors were detected on imaging, namely contrast CT and PET/CT. Median size of measurable tumors was 20 mm (range 15–28 mm). Most frequent involved orbital sites were periocular (n = 3), conjunctival (n = 2) and palpebral (n = 2); other sites of involvement were intraocular (choroid) (n = 1) and lacrimal gland (n = 1). One patient had bilateral disease.

Treatment details and oncological outcomes for each patient are listed in Table 2. Two patients were planned with electrons. One patient had 4 cycles of rituximab after EBRT due to concomitant systemic disease relapse.

Median follow-up time was 27 months (range 10–44 months). Treatment response was documented on imaging (CT or PET/CT) in five patients; the remaining patients underwent clinical evaluation of response.

At the time of follow up, 4 patients (57%) were alive and with no signs of malignancy; one patient died with no signs of relapse; one patient had distant progression of lymphoma after six years and died due to malignancy; one patient was alive with persistent minimal choroidal disease that could not be differentiated from scarring; one patient had bilateral palpebral disease, with one lesion with complete resolution and the other with partial response. A case of CR is depicted in Figure 1.

Five (71%) patients had clinical (n = 2) or radiologic (n = 3) overall complete response. Six (75%) lesions had a complete resolution after treatment. The latest complete response was seen at 10 months.

There were no reported radiation-induced acute toxicities. Mild (CTCAE Grade 1) late toxicities were reported in two patients, including dry eye syndrome relived by lubricants and pruritus. Both patients had a visual compromise at diagnosis due

Table 2. Treatment details and oncological outcomes by treated patient

Patient	Presentation	Stage (Ann Arbor)	RT technique	Consolidative CT	Response	FU	Reported toxicity (CTCAE v.5.0)	Long-term outcome
#1	Isolated recurrence of follicular lymphoma as an infraorbitary mass causing impaired visual field	IV	Electrons	Rituximab × 4 cycles	Clinical CR	11 mo	None	Alive with no signs of malignancy
#2	MALT lymphoma presenting as a conjunctival fleshy mass	I	Electrons	–	Clinical CR	7 mo	None	Alive with no signs of malignancy
#3	MALT lymphoma of the conjunctival and choroid presenting with impaired visual acuity	I	3DCRT	–	Radiologic PR (minimal persistence in coroid)	27 mo	Dry eye syndrome (Grade 1)	Alive with minimal signs of malignancy
#4	Bilateral palpebral relapse of follicular lymphoma causing palpebral edema	IV	3DCRT/3DCRT	–	Radiologic CR/Radiologic PR	17 mo	None	Alive with signs of malignancy
#5	Extraocular NHL presenting with conjunctival injection and impaired visual acuity	I	3DCRT	–	Radiologic CR	15 mo	None	Deceased with no signs of malignancy
#6	Recurrence of marginal zone lymphoma of the lacrimal gland causing a mass and conjunctival edema	II	3DCRT	–	Radiologic CR	59 mo	None	Alive with no signs of malignancy
#7	Intraocular follicular lymphoma presenting with mass, proptosis and diplopia	I	3DCRT	–	Radiologic CR	79 mo	Dry eye syndrome (Grade 1) and pruritus (Grade 1)	Deceased with signs of malignancy (distance progression)

FU — follow-up; 3DCRT — 3D conformal radiation therapy; CR — complete response; CT — chemotherapy; CTCAE — Common Terminology Criteria for Adverse Events; NHL — non-Hodgkin lymphoma; RT — radiotherapy; PR — partial response

to the disease and had an overall improvement of baseline symptoms. No Grade 3 or 4 toxicities occurred.

Discussion

In this study, we present our experience with the use of ultra-low dose radiotherapy (2 × 2 Gy) in the management of orbital low-grade lymphomas. Our population was mainly composed of elderly patients and the intent was symptomatic local control of extended or localized disease. We report a local control rate of 100%, although only 5 patients had confirmatory image examination; minimal ocular toxicity was observed.

Other successful experiences with the use of ultra-low dose schemes for the management of orbital low-grade lymphomas are described in the literature, with similar local control and CR rates.

A retrospective study [13] reported on the use of 4 Gy to the orbit for palliation or reirradiation of low-grade lymphoma with an overall response rate of 96% and a CR of 85% at 2 years; there were no reported relapses among those who achieved CR, suggesting a sustained response.

A more recent publication reported the experience of MD Anderson [14], with a series of 22 patients treated with ultra-low dose; a CR rate of 65% was reported at 4 months, increasing to 86% at the end of follow up, emphasizing the possibility of late responses.

One comparative study [15] analyzed patients with low-grade orbital lymphoma treated with > 30.6 Gy, 24–30.6 Gy and 4–6 Gy; the 6 pa-

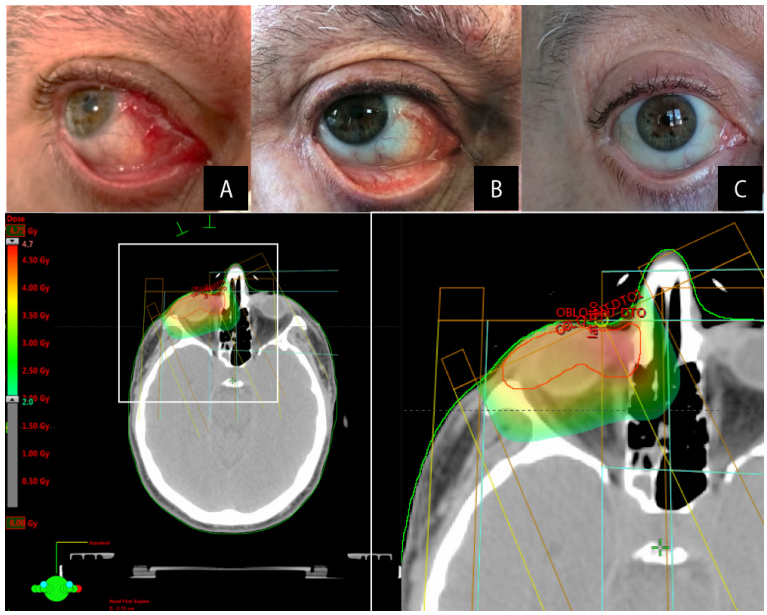

Figure 1. Example of patient #2 at presentation [A], at 4 months (partial response; PR) and at 10 months (complete response; CR) after radiotherapy. Bottom panel represents the dose distribution in color wash for the 3D conformal radiation therapy (3DCRT) treatment plan of the same patient. Planned tumor volume (PTV) is contoured in red

tients that were treated with 4–6 Gy were of advanced age or with comorbidities; still, there were no differences between groups, suggesting that ultra-low doses are also effective in terms of local control.

Nonetheless, the results of the long-term follow up of the FoRT trial [10] represented a setback in the implementation of ultra-low dose schemes for low-grade lymphomas as a new standard of care [16]. The authors concluded that ultra-low doses should be refrained from curative intent and offered for palliation in patients with short life expectancy.

This randomized phase III trial included an exploratory post hoc analysis in the subgroup of patients with orbital follicular lymphoma and non-inferiority of 4 Gy (2/13 progressions) could not be proven when compared to 24 Gy (0/20 progressions). Of note, the two progressive lesions (one follicular and one marginal zone, although grading was not provided) occurred at 5–6 years after treatment, suggesting the necessity of long term follow up in these patients.

Admitting that some late disease progression may occur (due to clones of unresponsive subtypes or latent viable tumor cells), patients with progressive or persistent disease are still able to undergo reirradiation. Consideration should be given to the possibility of late responses up until 6 months and for this reason reirradiation should not be initiated too early in the setting of a persistent disease. In the case of progression, both 24–30 Gy standard dose or a repeated 2 × 2 Gy course are feasible, with the latter having the aforementioned advantages [12]. This staged approach is gaining popularity in the management of low-grade lymphomas [17] and it is currently being tested on a prospective trial (MD Anderson — NCT02494700).

In our series, we report two cases of partial response. One patient had initial choroidal and conjunctival disease extension and maintained persistent minimal choroidal disease on ophthalmological examination in long term follow up. The other patient had bilateral palpebral disease, with persistent partial response in one of the sites on CT after 17 months. Both patients were asymptomatic, so further treatment was not pursued.

The excellent outcomes reported in the literature with orbital low-grade lymphomas after ultra-low dose radiotherapy may be justified by the confinement of the disease within the orbit socket and by the early symptoms of this disease location [13]. The median size of measurable tumors in our series was 20 mm, which advocates for a small localized lesion at presentation, even in the setting of stage IV disease.

The main advantage of lowering the dose in orbital lymphomas is the prevention of late toxicities. In fact, even with the use of low doses, late toxicities are commonly reported. A study from PMH [11] reports a CR over 90% with doses of 24–25.5 Gy; however, late toxicity occurred in 45% of patients, namely cataracts, dry eye, keratitis, macular degeneration and vitreous detachment. Although these effects can be surgically or medically managed, some degree of permanent toxicity was reported.

In the case of ultra-low doses, reported orbital toxicities are minimal, with dried eye being the most frequent observed late effect. In our study, 2/7 patients developed mild grade dry eye syndrome, one with associated pruritus.

In a recent study, ultra-low versus low dose courses for indolent orbital lymphomas were compared for 36 patients. Although similar oncological outcomes were reported between groups, with a local control of 100% and a CR and 50% in the ultra-low dose group [18], acute and late toxicities were more frequent in the 24 Gy group.

Moreover, some of the referred studies [14, 18] included mantle cell lymphomas in addition to follicular and marginal zone subtypes. Although not typically referred as an indolent lymphoma, there are reports that mantle cell could also be successfully managed with ultra-low dose radiotherapy due to its radiosensitivity; trials addressing the outcomes of this scheme in this particular histology are needed.

The authors acknowledge that the retrospective nature of this study introduces some subjectivity to the classification of acute and late toxicities, which can only be assessed thoroughly in a clinical trial setting. Also, radiologic evaluation of disease response was not routinely performed due to the palliative intent of the majority of the treatments, accounting for an overestimation of CR rate. Nevertheless, our results are in line with the described literature (Supplementary File — Tab. S1).

We could not emphasize enough the need for multicenter collaboration in the cases of rare disease entities such as orbital low-grade lymphomas, where the uniformization of treatment settings and reporting of outcomes could reveal more concise results.

Conclusion

In our experience, ultra-low dose radiotherapy (2 × 2 Gy) achieved a local control rate of 100% and a CR rate of 71%, with minimal toxicity for orbital low-grade lymphomas with the intent of symptomatic local control of extended or localized disease.

Our results are in line with the reported trend of excellent responses of this entity. The main advantage with the use of ultra-low doses to orbital lymphomas is the minimal probability of late ocular toxicities. In the case of persistent or progressive disease, a staged approach with reirradiation to a standard 24 Gy dose is gaining popularity. Multi-institutional collaboration is ultimately needed in order to collect and analyze experience in the management of this rare entity.

Conflict of interests

None declared.

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