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# Radiotherapy Dose and Volume De-escalation in Ocular Adnexal Lymphoma

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**Abstract.** *Aim: Modern radiotherapy (RT) technique and therapy de-escalation have led to encouraging results in lymphoma management. In this study, we aimed to describe the oncological and toxicity outcome in patients with ocular adnexal lymphoma. Patients and Methods: A total of 45 patients with 52 orbital lesions who were treated at our Institution between 2003 and 2019 were considered. Clinical characteristics, treatment outcomes, and toxicity were assessed. Patients receiving 4-6 Gy were categorized as receiving ultra-low-dose RT, 24-30.6 Gy as standard-dose RT, and >30.6 Gy as high-dose RT. Results: The predominant histological subtype was marginal zone lymphoma in 39 lesions (75%). Radiation dose ranged from 4-50.4 Gy. In the whole cohort, 11% of the lesions were treated with ultra-low-dose RT, 33% with standard-dose RT, and 56% with high-dose RT; 60% of lesions were treated using intensity-modulated RT (IMRT), while 44% of lesions were treated with partial orbital RT. The median duration of follow-up was 33 months. The overall response rate was 94% (complete response rate=83%). The 5-year local control rate, progression-free survival, and overall survival were 100%, 76%, and 92%, respectively. We did not detect any significant difference in progression-free or overall survival regarding different radiation doses and volumes. Ultra-low-dose RT was associated with a significantly lower rate of grade 2 late toxicities (0% vs. 6% and 31%, p=0.05) in comparison with standard-dose and high-dose RT, respectively. Patients who received IMRT had a significant fewer acute grade 2 (16% vs. 43%, p=0.05) and a trend towards lower late grade 2 toxicities (9% vs. 33%, p=0.06). Conclusion: Radiation dose and volume de-escalation seem to be safe and effective, with excellent local control and survival in the management of ocular adnexal lymphoma. IMRT seems to be associated with less toxicity.*

Indolent non-Hodgkin lymphomas (NHL) are the most common primary orbital and ocular adnexal malignant neoplasms. Marginal zone B-cell lymphoma (MZL) of mucosa-associated lymphoid tissue type and follicular lymphoma are the most frequent histological subtypes (1-3). The lesions can occur in the eyelid, conjunctiva, orbital soft tissue and the lacrimal gland (4). Indolent NHLs are sensitive to radiotherapy (RT); therefore, external-beam RT is considered to be the gold standard, achieving excellent outcomes. In the past decades, lowering the applied RT dosage in patients with hematological malignancies/indolent lymphoma was investigated in order to minimize toxicities (5-12). Additionally, several studies demonstrated less toxicity and better local control rates when using intensity-modulated (IM) RT compared to conventional techniques such as 2D or 3D conformal RT for head and neck cancer (13-15).

Since the use of modern techniques results in an improved treatment of patients with neck and head cancer, those methods might be as effective when treating lesions in other regions such as the orbit. With its complex anatomy and putative severe RT side-effects affecting vision and quality of life, sparing structures at risk in the orbit is of keen importance. The aim of this study was to analyze the influence of treatment volume, technique, and applied dosage on local control and complication rates.

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*Key Words:* Low-dose, ultra-low, intensity-modulated radiotherapy, toxicity, moderate-dose RT.

## Patients and Methods

We retrospectively reviewed the medical charts of 45 patients (44% males, 56% females) with 52 lesions treated at our center between 2003 and 2019 for histologically confirmed indolent ocular adnexal lymphoma (Table I). Patients receiving 4-6 Gy were categorized as receiving ultra-low dose RT, 24-30.6 Gy as standard-dose RT, while those receiving >30.6 Gy were categorized as receiving high-dose RT. Seven patients (16%) received antibody to CD20 rituximab with/without chemotherapy before or after RT. The median duration of follow-up was 33 (range=2-170) months. Treatment response was assessed at a 2- to 3-month follow-up appointment with a clinical examination and radiologically (computed tomography or magnetic resonance imaging). Complete remission (CR) was defined as complete clinical regression of ocular adnexal lymphoma, while partial response (PR) represented any sub-CR response exceeding 50% regression. Local progression was defined as a >25% expansion of the lesions. Otherwise, the ongoing presence of lesions was classified as stable disease (SD). Overall response rate (ORR) was defined as the proportion of patients who had a CR or PR to RT.

*Statistical analysis.* Time-dependent event curves were generated by the Kaplan–Meier method and compared with log-rank tests. Overall survival (OS) was calculated from the first day of RT. Progression-free survival (PFS) was calculated from the initiation of RT therapy to documented relapse or death. Local control was calculated from the initiation of RT until the time of documented local relapse. Differences were considered statistically significant at a $p$-value of less than 0.05. Independent variables were first analyzed with univariate analysis. Variables shown by univariate analysis to be associated with PFS or OS at $p \le 0.1$ were entered into a Cox proportional hazards regression model for multivariate analysis. Chi-squared or Fisher exact tests were performed to investigate the relationships between pairs of categorical variables. The two-sample $U$-test was used to study the relationship between categorical and continuous variables. Student's t-tests were used to analyze differences between paired samples. All statistical analyses were conducted with IBM SPSS Statistics 25.0 software (IBM, Armonk, NY, USA).

## Results

The median age at diagnosis was 63 years (range=30-91 years). Twenty-one lesions (40%) were on the right and 31 (60%) on the left side. Seven patients presented (16%) with bilateral involvement (5 synchronous and two metachronous). The predominant histological subtype was marginal zone lymphoma in 39 lesions (75%) and 8 lesions were follicular lymphomas (15%). Most lymphomas were intraorbital (46%), or in the conjunctiva/eyelid (43%). The majority of patients presented with stage I-II disease (94%).

The RT dose ranged from 4 to 50.4 Gy (median=36 Gy) in daily fractions of 0.5-2.0 Gy (median fraction dose=1.8 Gy). A total of 21 superficial lesions (44%) were treated with partial orbital irradiation. In the whole cohort, 31 lesions were treated with IMRT (60%), while 21 lesions were treated with conventional techniques (25% with electron and 15% with 3D conformal RT). Most intraorbital lesions (75%) and lacrimal gland lesions (50%) received IMRT, while 50% of conjunctival/eyelid lesions were treated with electrons ($p$=0.005). Twenty-nine lesions (56%) were treated with high-dose RT and seventeen (33%) lesions with standard-dose RT, while only six lesions (11%) were treated with ultra-low-dose RT as individual therapy with shorter treatment time due to comorbidities or advanced age. The median follow-up of the high-dose group was significantly longer with a median of 40 months (interquartile range=57) compared to the ultra-low-dose RT group (median=4 months, interquartile range=35) and the standard-dose RT group (median=14 months, interquartile range=62). The overall response rate was 94% (CR=83%). The CR was significantly higher following high-dose and standard-dose RT (90% and 82% *vs.* 50%, $p$=0.03) compared with ultra-low-dose RT.

During follow-up, seven patients (13%) developed out-of-field relapse. There was only one documented in-field relapse (2%) which occurred 12 years following 45 Gy RT of MZL in the right eye. The local control rate at 5 and 10 years was 100%. The median time to progression was 36 (range=15-148) months. Except for two, all patients were alive at the end of analysis.

The 5-year PFS rate was 76% and the 10-year PFS rate was 61%. Patients with MZL or follicular lymphoma had higher 5-year PFS (89% and 67%, respectively) in comparison with those with other types of lymphoma (25%, $p$=0.003). In these patients, intraorbital lymphoma showed a trend towards conferring inferior 5-year PFS compared to that in other sites (71% *vs.* 100%, $p$=0.1). No 5-year PFS difference ($p$=0.7) was detected between the group which was treated with ultra-low-dose RT (100%) *versus* standard-dose (86%) and high-dose (71%) groups. There was no significant difference in PFS between patients with unilateral and bilateral ocular adnexal lymphoma (73% *vs.* 83%, respectively, $p$=0.9). Furthermore, no difference in PFS in terms of radiation volume (partial orbital irradiation 87% *vs.* whole orbital irradiation 70%, $p$=0.9) was noted. In subgroups analysis, patients with intraorbital lesions treated with IMRT had a trend towards higher 5-year PFS in comparison with those treated with conventional techniques (75% *vs.* 25%, respectively, $p$=0.08), while patients with conjunctival/eyelid manifestations had similar 5-year PFS regardless of the irradiation technique used (100% with IMRT *vs.* 88% with electrons, $p$=0.5).

The 5- and 10-year OS rates were 92%. No OS difference was detected between different RT techniques ($p$=0.9) nor between different RT dosages ($p$=0.7). There was no significant difference in OS between patients with unilateral and those with bilateral ocular adnexal lymphoma ($p$=0.4). Moreover, no significant difference in OS in terms of radiation volume ($p$=0.9) was detected.

In univariate analysis, young age ($p$=0.03), MZL/follicular lymphoma histology ($p$=0.01), and CR to RT ($p$=0.003), were associated with a significant improvement in PFS. Young age ($p$=0.06) and CR to RT ($p$=0.04) may be associated with better OS. In a multivariate analysis, young age ($p$=0.03), MZL/follicular lymphoma histology ($p$=0.008), and CR to RT ($p$=0.004) were associated with PFS improvement but only age ($p$=0.06) seemed to be clinically meaningful in terms of OS (Table II).

Table I. *Patient and treatment characteristics.*

| Characteristic | Value |
|---|---|
| Age, years | |
| Median (range) | 63 (30-91) |
| Gender, n (%) | |
| Male | 20 (44%) |
| Female | 25 (56%) |
| Lymphoma maximal diameter, cm | |
| Median (range) | 2.8 (1.1-6) |
| Stage | |
| I | 34/45 (76%) |
| II | 8/45 (18%) |
| III-IV | 3/45 (6%) |
| Lymph node enlargement | |
| Yes | 4/45 (9%) |
| No | 41/45 (91%) |
| LDH | |
| Normal | 25/45 (56%) |
| Elevated | 4/45 (9%) |
| Unknown | 16/45 (35%) |
| Histology | |
| MZL | 39/52 (75%) |
| Follicular | 8/52 (15%) |
| Small cell | 2/52 (4%) |
| Mantle cell | 2/52 (4%) |
| Unknown | 1/52 (2%) |
| Primary tumor site | |
| Intraorbital | 24/52 (46%) |
| Conjunctiva/eyelid | 22/52 (43%) |
| Lacrimal gland | 6/52 (11%) |
| Radiation parameters | |
| Total RT dose, Gy | |
| Median (range) | 36 (4-50.4) |
| Fraction dose, Gy | |
| Median (range) | 1.8 (0.5-2) |
| Radiation dose, n (%) | |
| High-dose (>30.6) | 29/52 (56%) |
| Standard-dose (24-30.6 Gy) | 17/52 (33%) |
| Ultra-low-dose (4-6 Gy) | 6/52 (11%) |
| Technique, n (%) | |
| IMRT | 31/52 (60%) |
| 3D-CRT | 8/52 (15%) |
| Electrons | 13/52 (25%) |
| Radiation volume, n (%) | |
| Whole orbit | 29/52 (56%) |
| Partial orbit | 23/52 (44%) |
| Systemic treatment, n (%) | |
| Rituximab alone | 5/45 (11%) |
| Rituximab + chemotherapy | 2/45 (5%) |
| None | 38/45 (84%) |
| Response to RT, n (%) | |
| Complete | 43/52 (83%) |
| Partial | 6/52 (11%) |
| Stable disease | 3/52 (6%) |
| Relapse, n (%) | |
| Local | 1/52 (2%) |
| Distant | 7/52 (13%) |
| None | 44/52 (85%) |

MZL: Marginal zone lymphoma; IMRT: intensity-modulated radiotherapy; 3D-CRT: three-dimensional conformal radiotherapy.

Table II. *Univariate and multivariate analyses for progression-free (PFS) and overall (OS) survival.*

| Risk factor | PFS | | OS | |
|---|---|---|---|---|
| | HR | *p*-Value | HR | *p*-Value |
| Univariate model | | | | |
| Age | | | | |
| Years | 1.074 | **0.03** | 1.17 | **0.06** |
| Gender | | | | |
| Male | 0.87 | 0.75 | 0.015 | 0.47 |
| Diameter of the lesion | | | | |
| cm | 1.013 | 0.9 | 1.99 | 0.2 |
| Stage | | | | |
| 1 *vs*. 2-4 | 0.376 | 0.16 | 0.36 | 0.48 |
| Lymph node involvement | | | | |
| Yes *vs*. no | 20.90 | 0.14 | 50.41 | 0.23 |
| LDH | | | | |
| Elevated *vs*. normal | 10.63 | 0.6 | 250.9 | 0.8 |
| RT dose | | | | |
| Ultra-low *vs*. standard | 0.51 | 0.8 | 0.62 | 0.9 |
| Histology | | | | |
| MZL/FL *vs*. other | 0.13 | **0.01** | 0.27 | 0.35 |
| Orbital RT | | | | |
| Partial *vs*. whole | 0.95 | 0.9 | 0.02 | 0.5 |
| Technique | | | | |
| IMRT *vs*. other | 0.84 | 0.81 | 0.91 | 0.9 |
| Response to RT | | | | |
| CR *vs*. PR/SD | 0.049 | **0.003** | 0.057 | **0.04** |
| Systemic therapy | | | | |
| Yes *vs*. no | 0.41 | 0.3 | 0.04 | 0.7 |
| Multivariate model | | | | |
| Age | | | | |
| Years | 10.085 | **0.03** | 10.17 | **0.06** |
| Histology | | | | |
| MZL/FL *vs*. other | 0.02 | **0.008** | - | - |
| Response to RT | | | | |
| CR vs. PR/SD | 0.006 | **0.004** | - | - |

HR: Hazard ratio; LDH: lactate dehydrogenase; MZL/FL: marginal zone lymphoma/follicular lymphoma; RT: radiotherapy; IMRT: intensity-modulated radiotherapy. CR: complete remission; PR: partial remission; SD: stable disease. Bold values indicate statistical significance.

*Toxicities*. During RT courses, all patients experienced mild toxicities. Treatment was in general well tolerated with acute adverse effects (AEs; 83% grade 1 and 27% grade 2 toxicities) but without grade 3/4 toxicities occurring. The most frequent acute AEs were conjunctivitis, dry eye, and tearing. Patients who received IMRT showed a trend towards lower frequency of acute grade 1 AEs (77% *vs*. 90%, $p=0.2$) and significant fewer grade 2 AEs (16% *vs*. 43%, $p=0.05$). Regarding radiation dose, following ultra-low-dose RT, we detected less frequent acute grade 1 AEs (33% *vs*. 94% and 86%, $p=0.1$) and grade 2 toxicities (0% *vs*. 18% and 38%, $p=0.09$) compared with standard-dose and high-dose RT, respectively.

Late toxicity included grade 1 in 60%, grade 2 in 19%, and grade 3 in 8%. The most common long-term toxicities were eye dryness and cataract. We detected fewer grade 2 late AEs in those treated with IMRT (9% *vs.* 33%, $p$=0.06) compared with conventional techniques. Following ultra-low-dose RT, grade 1 late toxicities (33% *vs.* 59% and 65%, $p$=0.3) and grade 2 late toxicities (0% *vs.* 6% and 31%, $p$=0.05) were less frequent compared with standard-dose and high-dose RT, respectively.

In terms of radiation volume, there were no differences in acute or late toxicities between those who received partial and those who received whole orbital irradiation.

## Discussion

RT remains the standard treatment for patients with indolent primary orbital NHL. Over the decades, there has been an ongoing search for the optimal therapeutic dose, field definition and RT techniques. The analysis presented here revealed the safety and feasibility of dose de-escalation below the standard dose. The actual dose recommendation from the guidelines of the International Lymphoma Radiation Oncology Group (ILROG) is 24-25 Gy (16). The advice is supported by a large prospective randomized study by Lowry *et al.* comparing 24 *versus* 40 Gy to 45 Gy for indolent lymphoma, which showed equivalent disease control in both groups (9). It remains unclear though how many patients with ocular adnexal lymphoma in this trial were included. Furthermore, the prospective FORT-Trial compared 24 to 4 Gy for patients with follicular lymphoma and showed an inferiority regarding local PFS of the low-dose RT group (4 Gy) (11). Nevertheless, there were no differences regarding response rate in those with mucosa-associated lymphoid tissue lymphoma in a sub-group analysis. Recently, Lee *et al.* confirmed the above dose recommendation for orbital MZL of mucosa-associated lymphoid tissue of their multicenter cross-sectional cohort study of Korea with a median total dose of 25.2 Gy (17).

According to the ongoing trend towards lowering the radiation doses we additionally compared lesions treated with moderate dose RT (≤30.6 Gy) *versus* conventional RT doses (>30.6 Gy). The resulting complete response rate was 83% which is in line with the current international data (9, 17-19). Notably there was a non-significant trend towards a slightly better PFS following use of the IMRT technique, but only for patients with intraorbital lesions ($p$=0.08). Our data show equivalent adequate outcome with ultra-low doses (4-6 Gy). There was no significant difference in PFS or OS between the different RT dose groups. The only significant determinant of OS in our multivariate analysis was age, which was already reported recently by Olsen *et al.* (3). Moreover, histology, and response to RT tended to have an impact on PFS in our analysis. The rate of acute grade 2 AEs was obviously lower in the IMRT group when compared with patients treated with 3D-conformal RT or electrons (16% *vs.* 43%, $p$=0.05), while there was a trend towards a lower late toxicity rate ($p$=0.06). Minehan *et al.* (8) and Stafford *et al.* (20). already described considerable late toxic effects including keratitis, severe dry-eye syndrome, glaucoma, retinopathy, optic atrophy, corneal ulceration and cataract formation when patients were treated with doses greater than 35 Gy. Goda *et al.* reported grade 1 to 3 late toxic effects in 45% of patients who only received 25 Gy (21).

This has resulted in an ongoing attempt to lower the RT doses further while maintaining equivalent OS and PFS. Multiple single-institutional series have demonstrated adequate response rates for the treatment of indolent NHL with doses as low as 4 Gy (1, 22-25). König *et al.* reported 90% CR in patients with low-grade lymphomas of various locations treated with 2×2 Gy (25). Nevertheless, the median follow-up period in their retrospective analysis was comparatively low at only 21 months, and the sample size was small. The FORT-Trial that compared conventional RT doses (24 Gy) to low-dose RT (4 Gy) showed inferiority regarding PFS in the low-dose RT group but also stated no difference in OS between the arms. The fact that local relapses can be salvaged with re-radiation with conventional doses makes that approach promising in the future. Local disease recurrence cannot necessarily be prevented by dose-escalation, as in our study, the only in-field recurrence appeared after RT of 45 Gy. In 2018, a German prospective multicentered study was initiated to investigate ultra-low-dose RT (2×2 Gy) for nodal indolent follicular lymphoma in combination with the CD20 antibody obinutuzumab (Clinicaltrials.gov NCT03341520). Thus, it may be a reasonable concept to minimize the rate of distant relapse after RT.

None of the available studies interpreted their results regarding the various techniques or were mainly using 2D or 3D techniques (9-11, 17, 18, 26). In terms of the ongoing advances in RT techniques, IMRT is gaining increasing importance in the treatment of head and neck malignancies (13-15, 27). To our knowledge, this is the first study to compare a modern technique (IMRT) with conventional techniques (3D-conformal RT and electrons) and different RT doses and volumes regarding outcome. Moreover, there is a lack of consensus regarding the choice between whole orbital irradiation *versus* partial orbital irradiation. The ILROG recommends a clinical target volume covering the entire orbit in the case of intraorbital lymphoma and one encompassing only the conjunctival sac and the eyelid in the case of local restriction to the conjunctiva (16). In accordance with several studies, no difference was detected regarding local control or PFS (28-30). However, Pfeffer *et al.* reported a local relapse rate of 33% after partial orbital irradiation (31).

Our study had some limitations commonly occurring in retrospective studies. Firstly, there was a potential selection bias regarding the chosen technique, in particular whether electrons were used or photons. The nature of the superficial lesions of a conjunctival lymphoma requires the use of electrons and therefore disqualifies use of photons in many cases. About 43% of our patients had a conjunctival/eyelid manifestation, whereas 46% of the lesions were located intraorbitally. The comparison of side-effect rates between conjunctival and intraorbital lesions treated with different modalities therefore has to be interpreted with caution. Secondly, the retrospective setting of this study and the small sample size does not offer evidence as good as that of a prospective trial. Thus, there is an urgent need for prospective randomized trials addressing different RT techniques with consequences on OS, PFS and toxicities.

## Conclusion

Reduction of RT dose or volume seems to be a safe and effective modality with excellent local control and survival in the management of ocular adnexal lymphoma. Young age, MZL histology, and complete response to RT are associated with improved PFS and IMRT seems to be associated with less toxicity.

## Conflicts of Interest

All Authors declare no conflicts of interest.

## Authors' Contributions

Conceptualization, S.R., K.E., N.E., G.L., and H.T.E.; data curation, S.R. and K.E.; formal analysis, K.E. and S.R.; methodology, K.E, M.O., A.B., and U.H.; writing—original draft, S.R. All Authors have read and agreed to the published version of the article.

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