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Extranodal Marginal Zone Lymphoma of Ocular Adnexa: Outcomes following Radiation Therapy

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Key Words
Adnexal tumors · Lymphoma · Radiation damage

Abstract
Aim: The aim of this study was to report outcomes following radiation therapy in patients with biopsy-proven extranodal marginal zone lymphoma of the ocular adnexa and uvea. ***Methods:*** Records from a single institution were retrospectively reviewed from January 1997 to December 2015. The mean follow-up duration was 38 months (range 0–194). Radiation therapy was administered to 77 eyes (60 patients); 57 of the 77 eyes (74%) were treated with radiation only (range 20–36 Gy, median 15 fractions). Radiation cataract, radiation retinopathy, and optic neuropathy assessments were performed on all eyes treated with radiation. ***Results:*** 100% of the 47 patients treated with radiation therapy only had local control with an average dose of 26.5 Gy (median 25.2 [range 20–36] Gy; 150–200 cGy per fraction). Four patients lost 2 lines or more of vision after radiation. The most common complication of radiation therapy was cataract formation/progression in 19 eyes (25%). Radiation retinopathy was observed only in 1 patient (1%). ***Conclusion:*** Our results confirm that radiation therapy (median 25 Gy) for extranodal marginal zone lymphoma of the ocular adnexa is associated with high local control and low risk of visually significant complications.

Introduction

Marginal zone B-cell lymphomas (MZL) are a group of lymphomas that originate from B-cell lymphocytes in the marginal zone of secondary lymphoid follicles [1]. MZL accounts for between 5 and 17% of all non-Hodgkin lymphomas (NHL) [2–6]. The International Lymphoma Study Group classified 3 subtypes of MZL. This includes extranodal marginal zone B-cell lymphoma (EMZL), splenic marginal zone B-cell lymphoma, and nodal marginal zone B-cell lymphoma [1, 2, 7, 8]. EMZL is the most frequent, low-grade, indolent, small B-cell lymphoma with a prolonged course of the ocular adnexa [9, 10]. Ocular adnexal lymphomas (OAL) of the EMZL type have a high response rate to various treatment modalities, such as radiation therapy, chemotherapy, and immunotherapy [2, 9–13].

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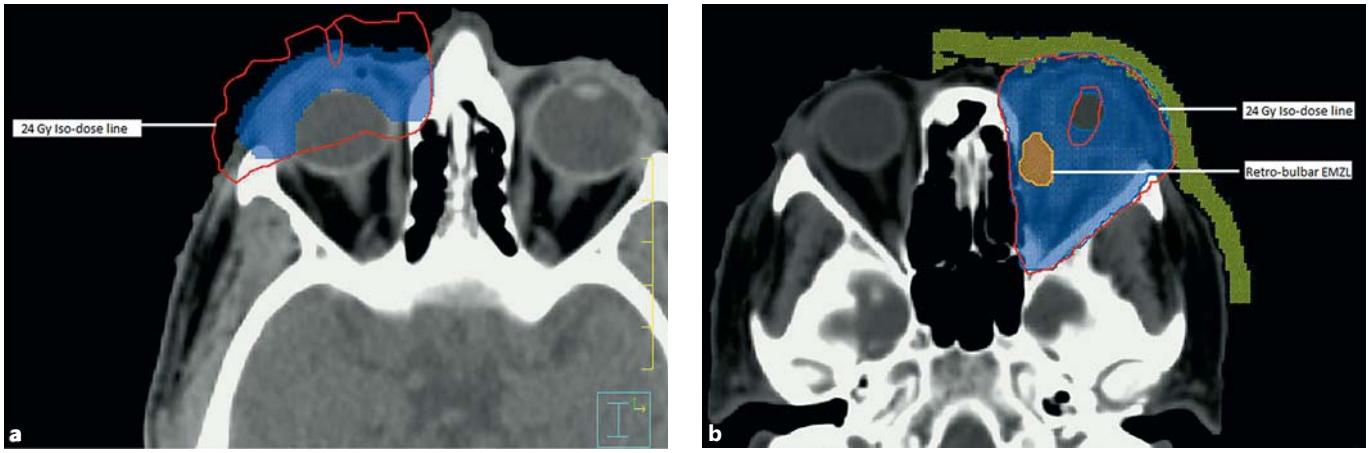

Fig. 1. Radiation fields using image-guided intensity-modulated radiation therapy techniques. **a** Patient with conjunctival ocular adnexal lymphoma undergoing partial orbital radiation therapy using direct anterior electron beam. This results in sparing of the posterior pole. **b** Patients with retrobulbar ocular adnexal lymphoma require total orbital radiation therapy.

As EMZL is an indolent form of lymphoma, radiotherapy has long been the treatment of choice for localized disease [14–16]. Long-term survival and excellent local control have been documented with radiotherapy alone [4, 9, 10, 14, 15]. It is estimated that using low to moderate radiotherapy doses (25–36 Gy) can obtain 95–100% of local control [4, 11, 17]. Few authors have advocated radiotherapy doses of 25 Gy or less [16, 18, 19]. A recent British National Lymphoma Investigation randomized trial confirmed excellent local control rates at 24 Gy for indolent NHL and 30 Gy for aggressive NHL [20].

However, the optimal radiation dose that will achieve a high local control rate with a minimal risk of visually significant complications for the treatment of EMZL type OAL is not well known. We investigated the dose-response relationship vis-à-vis radiation complications in published studies and evaluated outcomes of a single institution cohort followed using a standard protocol.

Patients and Methods

Patient Selection

After approval by our institutional review board, the study patient population was identified from our patient database at the Cleveland Clinic from January 1st, 1997, to December 31st, 2015 (19 years). The diagnosis was established in all patients by tissue biopsy performed at the Cleveland Clinic or reviewed by our pathology department if biopsy was performed elsewhere. In the setting of concurrent systemic involvement, biopsy from another involved site was considered adequate for diagnosis of ocular involvement. A complete history and ophthalmic exam was performed on all patients. Our assessment included best-corrected visual acuity, intraocular pressure, external examination (exophthalmometry and motility testing), slit-lamp examination, and dilated fundus exam. Slit-lamp, external, and fundus photography were routinely performed. B-scan ultrasonography and optical coherence tomography were obtained in patients with uveal involvement. All patient charts were reviewed for clinical features (age, sex, age at diagnosis, and details of lymphoma involvement), treatment type, radiation dose, fractionation, recurrence (local vs. distant), and complications from the radiation treatment. All information was placed on a secured, password-protected, encrypted database.

Treatment

Since 2005, the Cleveland Clinic protocol for the EMZL type of OAL has been to treat unilateral ocular-only involved eyes with radiotherapy and bilateral ocular-only disease or systemic disease with single-agent rituximab. The average and median doses of radiation were 26.5 and 25.2 Gy, respectively. The range was 20–36 Gy delivered in fractions (150–200 cGy per fraction). Over the years, concomitant with innovations in the field of radiation oncology, radiation therapy was administered using 3 different techniques: external-beam radiation therapy, involved-field radiation therapy, and image-guided intensity-modulated radiation therapy (IGIMRT). Indolent lymphomas anterior to the orbital septum underwent partial orbital irradiation using a direct electron field and daily bolus; retrobulbar and lacrimal-gland OAL underwent whole orbital irradiation utilizing 3-dimensional conformal radiation therapy techniques (Fig. 1). Since 2014, we have employed IGIMRT based on the International Lymphoma Radiation Oncology Group consensus report [21].

Local Control

Local control was defined as resolution of symptoms/signs at presentation supported by imaging studies. Recurrence was defined as lymphoma relapse after local control had been achieved and was divided into 2 categories: local and distant. Any recur-

Table 1. Radiation parameters: a review of the published studies for extranodal marginal zone lymphoma of the ocular adnexa

First author [ref.]	Year	*n*	Follow-up, months	Median radiation dose, Gy	Radiation dose, range, Gy	Location	Local control[a], %	Cataracts, %	Rad. retinopathy, %
Galieni [22]	1997	7	51	n/a	36–40	OAL	100	0	n/a
Baldini [23]	1998	8	73	n/a	26–40	OAL	100	15[b]	0
Hasegawa [24]	2003	20	71	34	20–45	OAL	95	45[b]	n/a
Matsuo [25]	2004	6	34	30	30	OAL	100	n/a	n/a
Tsang [16]	2003	31	58	25	25	OAL	93	10[b]	n/a
Uno [26]	2003	46	50	36	20–46	OAL	95	12[b]	4
Ejima [27]	2006	38	42	30.6	30–50	OAL	100	33[b]	2
Suh [28]	2006	52	70	30.6	5.4–30.6	OAL	94	4[b]	0
Monzen [29]	2007	21	47	40	30–54	OAL	100	14[b]	n/a
Nam [30]	2009	50	66	30	20–45	OAL	98	16[b]	3
Goda [31]	2010	89	71	25	25–35	OAL	97	n/a	n/a
Son [32]	2010	32	46	30.6	21.6–45	OAL	98	4	0
Bayraktar [33]	2011	73	57.5	30.6	23.5–45	OAL	95	15	3
Lim [4]	2011	73	42.2	n/a	30.6–45	OAL	100	0[b]	n/a
Hashimoto [12]	2012	58	74	30.6	30–50	OAL	100	47[b]	8
Hata [34]	2011	30	35	30	28.8–45.8	OAL	97	17[b]	0
Paik [35]	2012	8	50	36	30–40	OAL	100	n/a	n/a
Cho [8]	2013	41	n/a	37.8	30.6–45	OAL	n/a	20[b]	n/a
Harada [15]	2014	77	47	30	30–46	OAL	99	46[b]	n/a
Ohga [14]	2013	53	n/a	30	24–30	OAL	98	27[b]	0
Our study	2016	47	38	26.5	20–36	OAL	100	25[b]	2

Any radiated eye was included for cataract or retinopathy calculations. When graded, cataract was included if it was of grade 2 or more. When graded, retinopathy was included if it was of grade 3 or more. Rad., radiation-induced; n/a, not available; OAL, ocular adnexal lymphoma. [a] Radiation therapy-only cases were analyzed for local control calculations. [b] Lens shielding was used in some of the cases.

rence that was in the field of radiation was considered a local recurrence. Any recurrence out of the field of radiation was considered a distant recurrence, which can further be categorized as the contralateral untreated eye or systemic. Patients who received radiation therapy only were included to control for the effects of chemotherapy or immunotherapy in combination with radiation therapy on the tumor recurrence data. A review of the literature for patient outcomes related to radiation treatment was performed (Table 1). Local control rate versus median dose and local control rate versus average follow-up were plotted.

Visual Acuity Outcomes

All patients who were treated with radiation for EMZL type of OAL and who had at least 6 months of follow-up were included in this analysis.

Visually Significant Complications

Acute reactions to the radiation were not assessed in this study, which included common findings of radiation dermatitis, keratitis, and dry eyes, as these conditions are self-limiting and symptoms are easily treated by noninvasive measures. Visually significant complications analyzed were cataract formation/progression, radiation retinopathy, and optic neuropathy.

Radiation Cataracts

All eyes treated with radiation therapy were included in this analysis. Radiation cataract was defined as a latent response to any form of radiation, which may cause an early progression of the lens in any layer. Included patients were documented to have asymmetric, visually significant lenticular changes in the treated eye when compared to the contralateral eye. The presence of posterior subcapsular opacity in the absence of other causes was considered adequate to diagnose radiation-induced lenticular changes. By including patients who only had radiation therapy in 1 eye and excluding patients who had prior cataract surgery we could establish a control group. Here, we analyzed the incidence of cataract formation in the treated phakic eye versus the untreated phakic eye of the same individual.

Radiation Retinopathy/Optic Neuropathy

All eyes treated with radiation were included in this analysis. Findings of radiation retinopathy included retinal microaneurysms, retinal hemorrhages, retinal exudates, cystoid macular edema, cotton-wool spots, retinal neovascularization, or vitreous hemorrhage.

Retinal Tear/Detachment

Patients who sustained a rhegmatogenous retinal detachment after radiation treatment were identified.

Radiation Parameters

A review of the literature for patient outcomes related to radiation treatment was performed. Twenty peer-reviewed articles were identified with similar patient populations (randomized tri-

al for EMZL of the ocular adnexa). Local control rate versus median dose and local control rate versus average follow-up were plotted.

Statistical Analysis

Outcomes were recorded from the date of tissue diagnosis to the date of the first event or, if no events occurred, the last follow-up time. For treatment-related analysis, outcomes were recorded from the date of treatment start to the date of the first event. The entire statistical analysis was conducted in R, version 3.2.3. Control rate was plotted against dose, as well as follow-up time. Each data point, i.e., study, was weighted by the number of patients included. Based on these weights, the line of best fit was estimated and plotted.

Results

Patient Characteristics

A total of 81 patients with 103 involved eyes seen at the Cleveland Clinic from January 1997 to December 2015 were identified with biopsy-proven EMZL type of OAL. Twenty-one patients were excluded because the patient was lost to follow-up after treatment or the patient continued treatment elsewhere after diagnosis. In total, 77 eyes of 60 patients were treated with radiation, which included 6 eyes with simultaneous uveal involvement (8%). Of the 60 total patients treated with radiation, there was a predominance of male patients; 39 patients were male (65%) and 21 patients were female (35%) with a mean age of 65 years. The average length of follow-up was 38.6 months with a range of 1–94 months and a median of 27 months (Table 2).

Table 2. Patient characteristics: extranodal marginal zone lymphoma of ocular adnexa

Total number of patients	70
Total number of patients treated with RT	60
Total eyes treated with RT	77
Total number of patients treated with RT only	47
Total eyes treated with RT only	57
Mean age at diagnosis (range), years	65 (23–88)
Male, *n* (%)	39 (65)
Female, *n* (%)	21 (35)
Average length of follow-up, months	38
Site of involvement per eye, *n* (%)	
OAL only	71 (92)
Both OAL and uvea	6 (8)
Radiation dose, Gy	
Range	20–36
Average	26.5
Median	25.2

RT, radiation therapy; OAL, ocular adnexal lymphoma (orbit, eyelids, conjunctiva, and lacrimal gland).

Local Control

Forty-seven of the 60 patients (57 eyes) who were treated with radiation therapy only were analyzed for local control. All these were staged as IE (Ann Arbor staging system) at initial evaluation. None of these patients were identified with local recurrence during their follow-up period. However, 6 patients (13%) subsequently developed recurrence at a distant site; either systemic only ($n = 5$) or contralateral eye and systemic recurrence ($n = 1$).

Visual Acuity Outcomes

The charts of 60 patients with OAL only who were treated with radiation therapy and who had at least 6 months of follow-up were reviewed to compare the visual outcomes. Phakic and pseudophakic patients were included. Three patients had 20/100 or worse vision at presentation. This includes 1 patient each with amblyopia, central retinal artery occlusion, and compressive optic neuropathy. Only 5 patients had 2 or more lines of vision loss after radiation therapy. In 3 of these patients, the visual decline was associated with cataract formation/progression and in 1 was due to dry eye.

Visually Significant Complications

Radiation Cataract

Radiation-induced cataract was the most common complication after radiation therapy to the globe and orbit. Nineteen of the 77 eyes (25%) that underwent radiation therapy developed a radiation-induced cataract. Mean radiation dose and fractions were 29.27 Gy and 16, respectively. The average number of months from treatment start to diagnosis of a radiation cataract was 40 months with a range of 2.5–147 months. The average change in logMAR from treatment start to diagnosis of radiation cataract was 0.26. To adequately assess the degree of radiation effect on the lens, we grouped our patients into those who were phakic in both eyes and only received radiation therapy to only 1 eye. There were 25 patients that fitted this description, and 10 patients developed a visually significant cataract in the treated eye compared to 1 cataract in the untreated eye. The average change in logMAR in the treated eye was 0.31 compared to 0.05 in the untreated eye group.

Radiation Retinopathy/Optic Neuropathy

After a careful review of the charts, only 1 patient out of 77 included patients that received radiation therapy was observed to have radiation retinopathy. This patient devel-

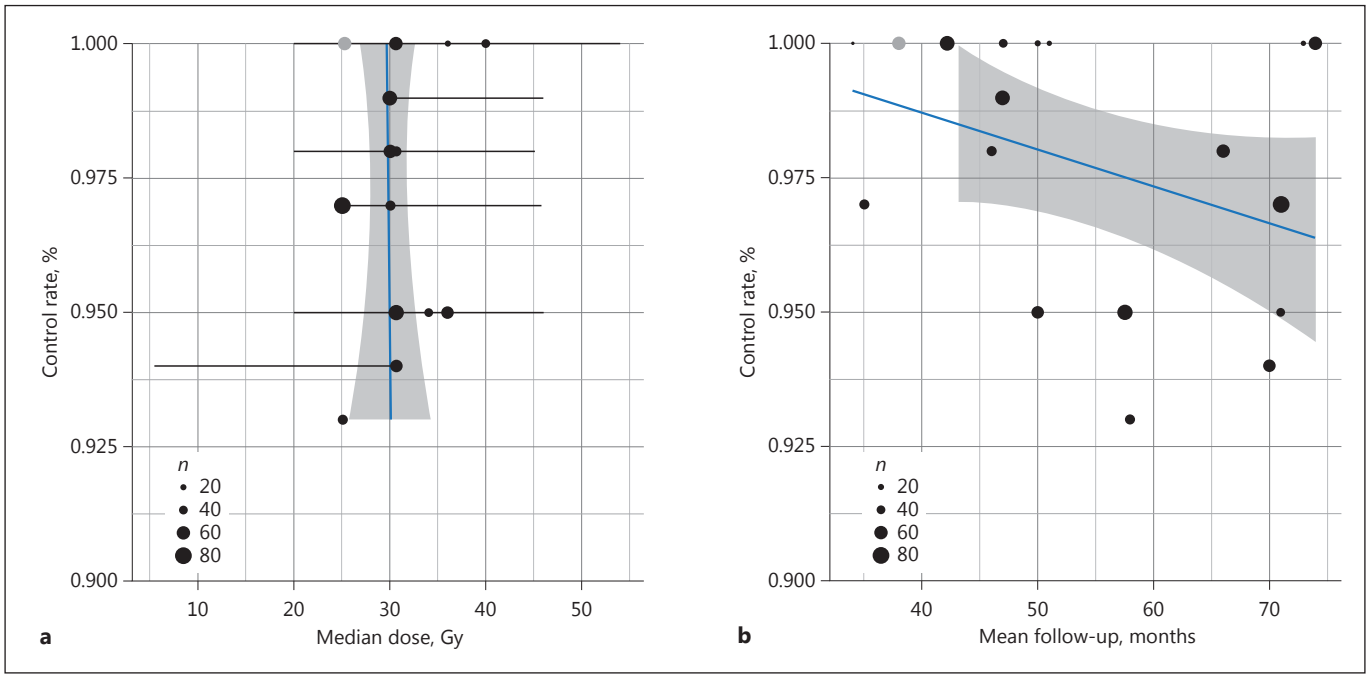

Fig. 2. Published studies. **a** Association between median dose and control rate. The x-axis shows the radiation dose in Gy. Points represent the median dose reported in a study and the whiskers the range of radiation dose in the study. The size of the point corresponds to the number of subjects in the study. The y-axis is the reported local control rate of the study. **b** Association between mean follow-up duration (months) and control rate. The x-axis represents the reported follow-up time of the study, the y-axis the reported control rate. The size of the point represents the number of subjects in the study. The blue line represents the line of best fit, weighted by the number of subjects in the study. The grey areas represent the standard error associated with the line of best fit.

oped cystoid macular edema, retinal hemorrhages, and neovascularization of the iris and was subsequently treated with panretinal photocoagulation and bevacizumab injections. Although this patient was a poorly controlled diabetic, similar findings were not seen in the untreated eye, confirming the presence of radiation retinopathy. Six years after radiation therapy, visual acuity was counting fingers with chronic cystoid macular edema, hard exudates, and atrophic scar. Anti-VEGF injections were discontinued 3.5 years prior because of poor response to therapy.

Retinal Tear/Detachment

Five patients were identified who sustained a rhegmatogenous retinal detachment after radiation treatment. Three patients were excluded, 1 patient developed a retinal detachment after cataract surgery, 1 in the untreated eye, and the other patient developed a retinal detachment attributable to ciliary body biopsy. Two patients developed a retinal tear/detachment during the radiation treatment and in the absence of an intraocular biopsy.

One patient had a new posterior vitreous detachment, and the other patient had a preexisting posterior vitreous detachment. A complete dilated exam was performed in both patients, and no retinal tears or other peripheral retinal abnormalities were observed prior to radiotherapy treatment. Both patients had hyperopia. One patient had OAL, and the other patient had concomitant OAL and uveal lymphoma. There was no significant difference in radiation dosages (24–25.2 Gy) between these cases and the rest of the cohort.

Radiation Parameters

Twenty peer-reviewed articles were reviewed from 1997 to 2013 [4, 8, 12, 14–16, 22–35]. All patients treated with radiation therapy only were recorded. When control rate was plotted against radiation dosage (Gy), the estimated line of best fit (when weighted by number of subjects in the study) was 30 Gy (Fig. 2a). When the control rate was plotted against follow-up time, an inversely proportional relationship was observed (Fig. 2b). Fractionation range for ophthalmic radiation varies from 150 to 200 cGy per fraction in standard clinical practice. Published reports did not all provide fractionation information.

Discussion

In our study, we analyzed our 19-year radiation therapy treatment outcomes for biopsy-proven EMZL type OAL. We identified 77 eyes that were treated with radiation therapy, and 57 were treated with radiation therapy only. Local control rate was 100% in eyes treated with radiation therapy only with the mean dose of 26.5 Gy (median 25.2 [range 20–36] Gy). Results for local control are given only for those that received radiation therapy *only*, removing confounding effects of systemic therapy. When we plotted the control rate against the average dose data from 20 peer-reviewed articles with a similar patient population, our line of best fit, weighted by the number of subjects in the study, was at 30 Gy (Fig. 2a). When we plotted the local control against follow-up time, the line of best fit demonstrated an inverse trend (Fig. 2b). In our study sample, we achieved 100% of local control with an average dose of 26.5 Gy and a median of 25.2 (range 23.4–36) Gy. Fractionation range for ophthalmic radiation varies from 150 to 200 cGy per fraction in standard clinical practice. Published reports did not all provide fractionation information. Lower radiation doses (such as 4 Gy in 2 fractions) have also been evaluated for patients with indolent lymphomas, such as marginal zone lymphoma and follicular lymphoma of nonocular sites [36]. In a randomized phase 3 noninferiority trial, local progression-free survival was inferior with 4 Gy (2 fractions) compared to 24 Gy (12 fractions), establishing the higher dose as the standard of care [37].

Overall, there was a minimal risk of visually significant complications. Visual outcomes after radiation therapy for EMZL type OAL demonstrate the minimal effect of the radiation on visual potential. Only 4 patients lost 2 lines or more of vision after radiation. Few studies have reported severe radiation retinopathy with a total radiation dose of <40 Gy as observed in 1 of our patients (34 Gy in 20 fractions) [6, 38]. Radiation-induced toxicity to the retina has been documented in 5 and 50% of patients at 5 years with fractionated doses of 45–50 and 55 Gy, respectively [39]. Our patient, who was diabetic, lost vison (final acuity of counting fingers) due to cystoid macular edema, cotton-wool spots, retinal hemorrhages, and neovascularization of the iris requiring full panretinal photocoagulation treatment and despite multiple anti-VEGF intravitreal injections. Diabetes has been reported to increases the risk of radiation retinopathy [38]. In our patient, development of unilateral radiation retinopathy may have been exacerbated by diabetic status.

Radiation-induced retinal tear or detachment is not a recognized risk from radiation therapy. Two (2%) of our patients were diagnosed with a new retinal tear or detachment during radiation therapy. None of the patients were myopic or had evidence of peripheral retinal abnormalities considered as risk factors for retinal tears at baseline examination. Even though the effects of radiation therapy on the vitreous are not known, our data suggest that the risk of a retinal tear or detachment from radiation treatment should be discussed with the patient given its potential for vision loss.

A limitation to our study is that this is a retrospective review rather than a prospective study. Our oncology service at the Cleveland Clinic was created in 2002. Prior to this time, many patients were lost to follow-up or they obtained treatment elsewhere (16 out of 97 patients), which is a significant proportion of our initial population. As shown in Figure 2b, there is an inverse relationship between local control rates and average length of follow-up time. Our average follow-up was 38 months and 100% local control. Longer follow-up times will be needed to see if our local control data follow a similar trend.

Over the years, concomitant with innovations in the field of radiation oncology, radiation therapy was administered using 3 different techniques: external-beam radiation therapy, involved-field radiation therapy, and IGIMRT. Strictly on theoretical grounds, IGIMRT, the current standard in the US and Europe, is not expected to influence disease control but is expected to reduce associated short- and long-term morbidity [40].

In conclusion, our data suggest that 25 Gy (median dose) is an effective (fractionated) radiation dose providing high local control and low risk of visually significant complications. Our findings are consistent with the recently published results of a phase III randomized trial [20] and guidelines from the International Lymphoma Radiation Oncology Group recommendations for extranodal lymphoma of all sites [21].

Statement of Ethics

The study complied with the guidelines for human studies and animal welfare regulations. The subject gave informed consent, and the study protocol was approved by the institute's committee on human research.

Disclosure Statement

The authors have no conflicts of interest to declare.

References

1 Thieblemont C: Clinical presentation and management of marginal zone lymphomas. Hematology Am Soc Hematol Educ Program 2005:307–313.
2 Thieblemont C, Coiffier B: Management of marginal zone lymphomas. Curr Treat Options Oncol 2006;7:213–222.
3 Freeman C, Berg JW, Cutler SJ: Occurrence and prognosis of extranodal lymphomas. Cancer 1972;29:252–260.
4 Lim SH, Kang M, Son J: Extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue type of the ocular adnexa: retrospective single institution review of 95 patients. Indian J Ophthalmol 2011;59:273–277.
5 Fung CY, Tarbell NJ, Lucarelli MJ, et al: Ocular adnexal lymphoma: clinical behavior of distinct World Health Organization classification subtypes. Int J Radiat Oncol Biol Phys 2003;57:1382–1391.
6 Hata M, Kaneko A, Tomita N, Inoue T: Severe retinopathy following radiation therapy with a moderate dose for orbital mucosa-associated lymphoid tissue lymphoma. Hematol Oncol 2014;32:212–214.
7 Isaacson P, Wright DH: Malignant lymphoma of mucosa-associated lymphoid tissue. A distinctive type of B-cell lymphoma. Cancer 1983;52:1410–1416.
8 Cho WK, Lee SE, Paik JS, Cho SG, Yang SW: Risk potentiality of frontline radiotherapy associated cataract in primary ocular adnexal mucosa-associated lymphoid tissue lymphoma. Korean J Ophthalmol 2013;27:243–248.
9 Aronow ME, Portell CA, Sweetenham JW, Singh AD: Uveal lymphoma: clinical features, diagnostic studies, treatment selection, and outcomes. Ophthalmology 2014;121:334–341.
10 Portell CA, Aronow ME, Rybicki LA, Macklis R, Singh AD, Sweetenham JW: Clinical characteristics of 95 patients with ocular adnexal and uveal lymphoma: treatment outcomes in extranodal marginal zone subtype. Clin Lymphoma Myeloma Leuk 2014;14:203–210.
11 De Cicco L, Cella L, Liuzzi R, et al: Radiation therapy in primary orbital lymphoma: a single institution retrospective analysis. Radiat Oncol 2009;4:60.
12 Hashimoto N, Sasaki R, Nishimura H, et al: Long-term outcome and patterns of failure in primary ocular adnexal mucosa-associated lymphoid tissue lymphoma treated with radiotherapy. Int J Radiat Oncol Biol Phys 2012;82:1509–1514.
13 Fuller ML, Sweetenham J, Schoenfield L, Singh AD: Uveal lymphoma: a variant of ocular adnexal lymphoma. Leuk Lymphoma 2008;49:2393–2397.
14 Ohga S, Nakamura K, Shioyama Y, et al: Radiotherapy for early-stage primary ocular adnexal mucosa-associated lymphoid tissue lymphoma. Anticancer Res 2013;33:5575–5578.
15 Harada K, Murakami N, Kitaguchi M, et al: Localized ocular adnexal mucosa-associated lymphoid tissue lymphoma treated with radiation therapy: a long-term outcome in 86 patients with 104 treated eyes. Int J Radiat Oncol Biol Phys 2014;88:650–654.
16 Tsang RW, Gospodarowicz MK, Pintilie M, et al: Localized mucosa-associated lymphoid tissue lymphoma treated with radiation therapy has excellent clinical outcome. J Clin Oncol 2003;21:4157–4164.
17 Smitt MC, Donaldson SS: Radiotherapy is successful treatment for orbital lymphoma. Int J Radiat Oncol Biol Phys 1993;26:59–66.
18 Goda JS, Le LW, Lapperriere NJ, et al: Localized orbital mucosa-associated lymphoma tissue lymphoma managed with primary radiation therapy: efficacy and toxicity. Int J Radiat Oncol Biol Phys 2011;81:e659–e666.
19 Stafford SL, Kozelsky TF, Garrity JA, et al: Orbital lymphoma: radiotherapy outcome and complications. Radiother Oncol 2001;59:139–144.
20 Lowry L, Smith P, Qian W, et al: Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: a randomised phase III trial. Radiother Oncol 2011;100:86–92.
21 Yahalom J, Illidge T, Specht L, et al: Modern radiation therapy for extranodal lymphomas: field and dose guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys 2015;92:11–31.
22 Galieni P, Polito E, Leccisotti A, et al: Localized orbital lymphoma. Haematologica 1997;82:436–439.
23 Baldini L, Blini M, Guffanti A, et al: Treatment and prognosis in a series of primary extranodal lymphomas of the ocular adnexa. Ann Oncol 1998;9:779–781.
24 Hasegawa M, Kojima M, Shioya M, et al: Treatment results of radiotherapy for malignant lymphoma of the orbit and histopathologic review according to the WHO classification. Int J Radiat Oncol Biol Phys 2003;57:172–176.
25 Matsuo T, Yoshino T: Long-term follow-up results of observation or radiation for conjunctival malignant lymphoma. Ophthalmology 2004;111:1233–1237.
26 Uno T, Isobe K, Shikama N, et al: Radiotherapy for extranodal, marginal zone, B-cell lymphoma of mucosa-associated lymphoid tissue originating in the ocular adnexa: a multiinstitutional, retrospective review of 50 patients. Cancer 2003;98:865–871.
27 Ejima Y, Sasaki R, Okamoto Y, et al: Ocular adnexal mucosa-associated lymphoid tissue lymphoma treated with radiotherapy. Radiother Oncol 2006;78:6–9.
28 Suh CO, Shim SJ, Lee SW, Yang WI, Lee SY, Hahn JS: Orbital marginal zone B-cell lymphoma of MALT: radiotherapy results and clinical behavior. Int J Radiat Oncol Biol Phys 2006;65:228–233.
29 Monzen Y, Hasebe H: Radiotherapy for localized orbital mucosa-associated lymphoid tissue lymphoma. Ophthalmologica 2007;221:233–237.
30 Nam H, Ahn YC, Kim YD, Ko Y, Kim WS: Prognostic significance of anatomic subsites: results of radiation therapy for 66 patients with localized orbital marginal zone B cell lymphoma. Radiother Oncol 2009;90:236–241.
31 Goda JS, Gospodarowicz M, Pintilie M, et al: Long-term outcome in localized extranodal mucosa-associated lymphoid tissue lymphomas treated with radiotherapy. Cancer 2010;116:3815–3824.
32 Son SH, Choi BO, Kim GW, et al: Primary radiation therapy in patients with localized orbital marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). Int J Radiat Oncol Biol Phys 2010;77:86–91.
33 Bayraktar S, Bayraktar UD, Stefanovic A, Lossos IS: Primary ocular adnexal mucosa-associated lymphoid tissue lymphoma (MALT): single institution experience in a large cohort of patients. Br J Haematol 2011;152:72–80.
34 Hata M, Omura M, Koike I, et al: Treatment effects and sequelae of radiation therapy for orbital mucosa-associated lymphoid tissue lymphoma. Int J Radiat Oncol Biol Phys 2011;81:1387–1393.
35 Paik JS, Cho WK, Lee SE, et al: Ophthalmologic outcomes after chemotherapy and/or radiotherapy in non-conjunctival ocular adnexal MALT lymphoma. Ann Hematol 2012;91:1393–1401.
36 Haas RL, Poortmans P, de Jong D, et al: High response rates and lasting remissions after low-dose involved field radiotherapy in indolent lymphomas. J Clin Oncol 2003;21:2474–2480.
37 Hoskin PJ, Kirkwood AA, Popova B, et al: 4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomised phase 3 non-inferiority trial. Lancet Oncol 2014;15:457–463.
38 Kaushik M, Pulido JS, Schild SE, Stafford S: Risk of radiation retinopathy in patients with orbital and ocular lymphoma. Int J Radiat Oncol Biol Phys 2012;84:1145–1150.
39 Emami B, Lyman J, Brown A, et al: Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991;21:109–122.
40 Goyal S, Cohler A, Camporeale J, Narra V, Yue NJ: Intensity-modulated radiation therapy for orbital lymphoma. Radiat Med 2008;26:573–581.