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The outcome of radiation therapy as a primary treatment in orbital lymphoma: a systematic review

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ABSTRACT

Background: The extranodal marginal-zone B-cell lymphomas of mucosa-associated lymphoid tissue (MALT) is the most common orbital and adnexal lymphomas. Radiotherapy is one of the most preferred treatment options for orbital lymphomas since they are localized and radiation sensitive. The objective of this study is to evaluate how radiation therapy affected the outcome of orbital MALT lymphoma.

Materials and methods: PRISMA guideline was used to conduct this systematic review of electronic databases (PubMed, EMBASE and Cochrane Library), then we assessed the quality of evidence of each paper.

Results: Twenty-five studies were finally included. 94% studies were intended for definitive therapy and almost all of the studies used external radiation sources. The total doses given to the tumor bed ranged from 4 Gy to 55 Gy and were divided into three groups: ultra-low dose (4–6 Gy), standard-dose (24–30.6 Gy), and high-dose (> 30.6 Gy). 75–90% patients showed CR and local relapse was only reported at 3.5–5%. Higher 5-year PFS was reported in the patients group with lens shielding (90.1% *vs.* 82.1%) and an increase in Meiboscore after RT courses. Toxicities, including dry eye and cataract, were reported in several patients. Acute toxicities subsided gradually over a few months with artificial tears. The risk of early cataract formation increases in patients who received > 30 Gy and lower in the IMRT group.

Conclusion: RT is a successful primary definitive therapy for low-grade orbital MALT lymphoma, with a high survival rate, low recurrence rate, and typically acceptable toxicity.

Key words: radiation therapy; radiotherapy; orbital tumor; MALT; lymphoma

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Introduction

Non-lymphoma Hodgkin's was found in about 55% of primary orbital malignancies in adults. Extranodal marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue (MALT) type account for the majority of non-lymphomas Hodgkin's of the orbit and adnexa. The conjunctiva, eyelid, lacrimal gland, and retrobulbar region are commonly affected by orbital MALT lymphomas (OAML). It is characterized by an indolent course and a confined tumor that is predominantly radiation sensitive [1–3].

As an initial treatment for orbital MALT lymphoma, radiation therapy (RT) was known to be beneficial. For localized disease, radiotherapy has often been the treatment of choice. Compared to surgery, it provides superior local control and cure. Low to moderate radiation doses (25–36 Gy) are thought to be capable of achieving 95–100% lo-

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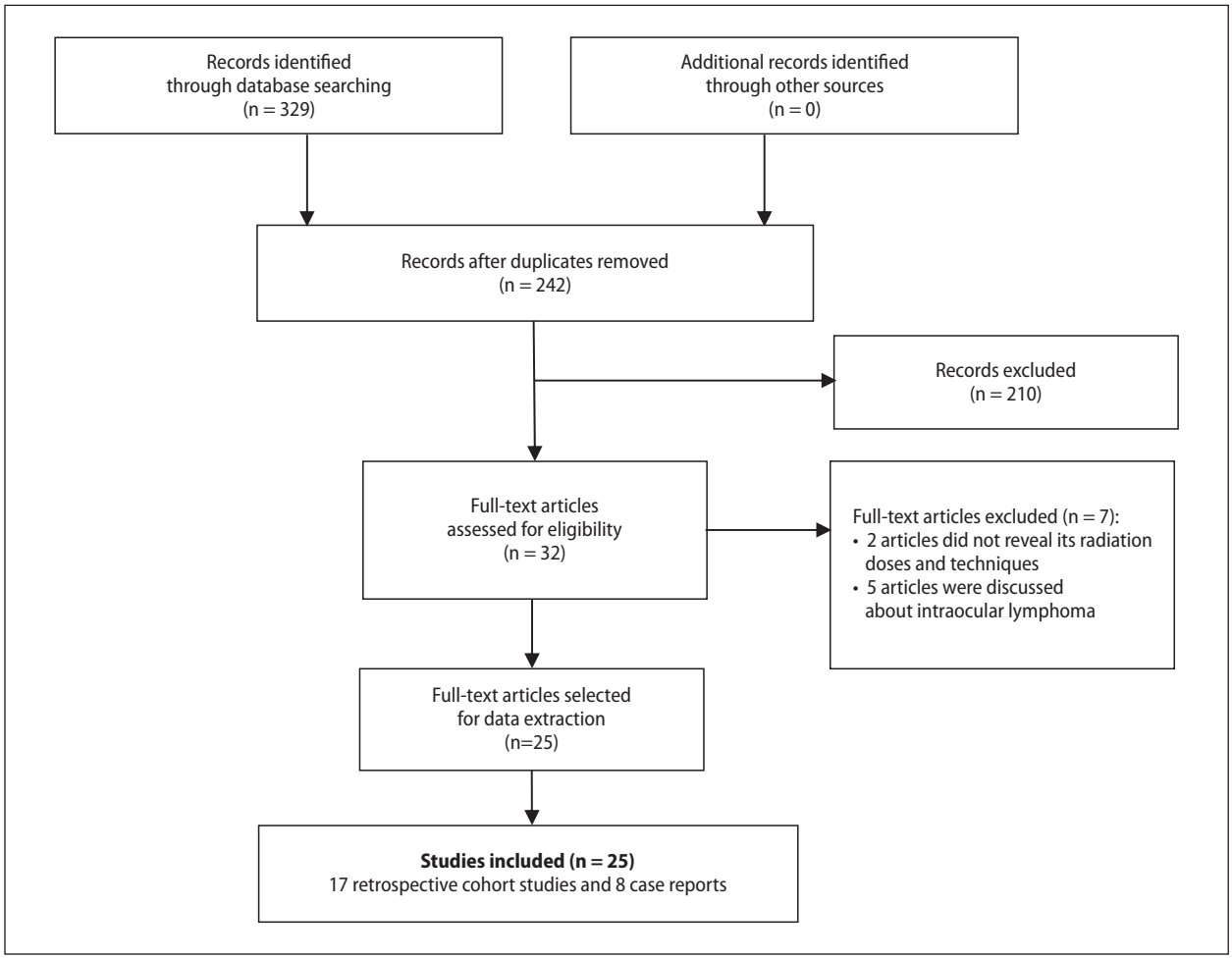

Figure 1. Flow diagram of study selection process

cal control. However, the ideal radiation dose for the treatment of orbital adnexal lymphoma that achieves a high local control rate with a low risk of visually noticeable sequelae is unknown. So, a variety of approaches, involving radiation dose, volume, and lens shielding, have been used [1–4].

Therefore, we conducted a systematic review to see how successful different doses and procedures of radiation therapy were for treating orbital MALT lymphoma.

Materials and methods

We conducted a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We searched the terms "Ocular Lymphoma", "Orbital Lymphoma", "MALT", "Radiotherapy", "Radiation therapy", and "IMRT" with time restriction from 2012 to 2022 in various electronic databases such as PubMed, EMBASE and Cochrane Library. The focus of the search was the outcome of the radiotherapy on the clinical application to the orbital lymphoma. We included full-text publications reporting orbital lymphoma at different ages. Literature which focused on orbital lymphoma that had been treated with radiotherapy, the doses of the radiotherapy used for treatment of orbital lymphoma, and also the response of radiation therapy to orbital lymphoma were searched and included. We considered only human-based topics and articles published in English. No full-text publications, duplicates, letters to editor, and articles with no radiotherapy effect on orbital lymphoma were excluded.

Two researchers evaluated the studies independently to determine the final articles to be included, and the final decision was reached by consensus with another author. All evidence was assessed by the Newcastle-Ottawa Scale (NOS) for cohort studies. The study is classified as high

quality if it gets 3 or 4 points in the selection domain AND 1 or 2 points in the comparability domain AND 2 or 3 points in the outcome domain [5]. The Joanna Briggs Institute (JBI) scale was used to evaluate the risk of bias from included case reports. It assessed demographic characteristics, past medical history, current condition, diagnostic assessment, treatment procedure, post-intervention condition, adverse events, and lessons to learn. The total score was categorized as low (0–3) and high quality (4–8) [6].

Results

Eligible studies

A total of 329 articles were identified through PUBMED, EMBASE, and Cochrane library. Eighty seven studies were removed because of duplication. The first selection was performed based on the title and abstract of the articles. We excluded 210 articles that did not meet the inclusion criteria. In further screening, 7 articles were omitted because of the lack of data. So, 25 studies were finally included in this systematic review.

Baseline characteristics

All included articles have a high score. The mean score of the NOS for the cohort studies was 7.4. The mean score of case reports in the JBI scale was 7.1. These results support that the 25 included studies were high quality on average. Baseline characteristics of the included studies are summarized in Table 1.

Purpose and RT methods

The purpose of the studies was mostly either definitive or curative for as many as twenty-four studies (96%), and one study (4%) has both a curative and palliative intent. In terms of palliative treatment, RT was used to control the symptoms in non-localized disease. In terms of radiation source, almost all of the studies used external radiation and just three cases, reported by Saria et al., 2020, used internal radiation also known as brachytherapy. Besides, several planning methods were used, such as conventional or IMRT. Unfortunately, not all the studies mentioned their planning method nor use of lens shielding.

The total doses that were given to the tumor bed ranged from 4 Gy to 55 Gy. It can be categorized into three major groups, which are high dose, standard dose, and ultra-low dose. Patients who received 4–6 Gy were considered ultra-low dose RT, those who received 24–30.6 Gy were considered standard-dose RT, and those who received > 30.6 Gy were considered high-dose RT. The dose received is also determined by the location of the tumor. Because the radiation regimen could be considerably divided according to the primary site of OAML: whether it is the orbit, lacrimal gland, and lacrimal sac, known as orbital-type lymphoma, or the conjunctiva. Higher energy was used in the orbital-type lymphoma compared to the OAML in the conjunctiva.

Results

Between 75% and 90% patients showed complete response after receiving a full dose of radiation therapy. While 11–25% patients resulted in partial response. In addition, four out of eight case reports stated that their patient achieved partial response and remained tumor-free until the end of the follow up. Local relapse only reported by Desai et al. 2017 and Woolf et al. 2015 at 3.5% and 5% consecutively. Higher 5-year PFS was reported by Kim et al. 2020 in the patients group with lens shielding (90.1%) than the group without lens shielding (82.1%).

Kim et al., 2020 also reported an increase in Meiboscore after RT courses. The ratio of the meibomian gland area to the overall analyzed area dropped as the meiboscore grew. It may contribute to the occurrence of side effects. Dry eye was one of the common side effects from RT. Artificial tears were used to alleviate the symptoms, which subsided gradually over a few months. Other acute toxicities reported were periorbital soft tissue swelling, conjunctivitis, tearing/watery eye, and photophobia. The late toxicities that were commonly reported are cataract, xerophthalmia, retinal problem, and nasolacrimal duct obstruction. Xu et al. reported the median cataract incidence period was longer in the lens shielding group. Dry eye and cataract were the most common long-term side effects. IMRT patients had less grade 2 late toxicities (9%) than those treated with conventional procedures (33%), according to Rehn et al., 2020. When compared to standard-dose and high-dose RT, grade 1 late adverse effects (59% and 65% *vs.* 33%) and grade 2 late

Table 1. Baseline characteristics

No	Study	Primary cancer sites	Purpose	RT method	Doses	Responses	Toxicities
Retrospective Cohort							
1	Xu et al., 2021	Orbital and ocular adnexal MALT	Definitive	EBRT (IMRT) + electron beam with or without lens-sparing method	A: 20 Gy/10 Fr EBRT+ 14 Gy/7 Fr Electron beam using lens shield B: 32 Gy/16 Fr or 34 Gy/17 Fr without lens shield	5-year & 10-year OS: 100% 5-year DFS: 96.7% 10-year DFS: 74.2% No local recurrence developed 3 patients developed distant metastasis	Acute: periorbital soft tissue swelling, dry eye, conjunctivitis Late: Patients aged ≥ 60 years had a 4.43-times higher risk of cataract incidence The median cataract incidence period was longer in the lens shielding group
2	Lee et al., 2021	Early-stage ocular adnexal MALT	Definitive	Electron beam with lens shielding	4 Gy in two fractions over 2 days	75% achieved CR 25% achieved PR	No adverse events reported
3	Leeson et al., 2021	Early stage ocular adnexal MALT	Definitive	EBRT (3D-CRT or VMAT)	20–30 Gy with 1.5–2 Gy fraction sizes	Excellent local disease control & no local recurrence	Acute : one patient experienced tearing and red eye Late : one patient experienced dry eye and cataract formation Both occurred in the same patient, who received 26Gy to the orbit using 3D-CRT
4	Rehn et al., 2020	Indolent ocular adnexal lymphoma	Definitive	EBRT (IMRT) EBRT (Conventional)	4–50.4 Gy in 0.5–2 Gy fraction sizes. High-dose RT: 29 patients Standard-dose RT: 17 patients Ultra-low-dose RT: 6 patients	Overall response rate : 94% High-dose CR: 90% Standard-dose CR: 82% Ultra-low-dose CR: 50% 10-year local control : 100%	Acute : conjunctivitis, dry eye, & tearing Late : dry eye, cataract Lower frequencies of adverse effect in IMRT group
5	Niwa et al., 2020	Ocular adnexal MALT	Definitive	EBRT	30–36 Gy in 15–18 fractions	69.1% had a CR 18.5% had a PR 3.7% had a stable disease	Acute : no acute morbidities Late : dry eye (3.7%), punctate keratitis(4.9%), cataract (2.5%)
6	Kim et al., 2020	Orbital lymphoma	Definitive	EBRT (IMRT) EBRT (3D-CRT) Electron beam	Orbital-type: 30.6-36 Gy in 17–20 fractions Conjunctival: 23.4–25.2 Gy in 13–14 fractions	Increase in meiboscore	No patient had development of severe dry eye with corneal erosion or vision compromise
7	Jeon et al., 2018	Ocular adnexal MALT	Definitive	EBRT	24–32 Gy in 1.8–2 Gy fraction sizes	92% achieved complete response	Acute: dry eye Late: dry eye (58%), cataract(22%)
8	Pinnix et al., 2017	Ocular adnexal lymphoma	Definitive	EBRT	4 Gy in 2 fractions over 2 days	86.4% patients had a CR and 13.6% patients had a PR	Acute: dry eye (4.5%) Late: no adverse effect reported
9	Li, 2018	Ocular adnexal MALT	Definitive	EBRT	Total dose ranged 30-55 Gy, mostly 34 Gy/17 fractions	Complete response and no progression	Dry eye syndrome (9%), cataract (4.5%), vision loss (4.5%)

Table 1. Baseline characteristics

No	Study	Primary cancer sites	Purpose	RT method	Doses	Responses	Toxicities
10	Platt, 2017	Ocular adnexal EMZL	Definitive	EBRT (3D-CRT, electron beam, & IMRT)	20–36 Gy in 1.5–2 Gy fraction sizes	No recurrence in the irradiation field. 86.66% visual acuity improvement.	Acute : no adverse event reported Late : cataract (31.6%), retinopathy (1.7%), retinal detachment (3.3%)
11	Park et al., 2017	Ocular adnexal MALT	Definitive	EBRT(single anterior field, 3D-CRT, IMRT) Electron beams with lens shield Electron beams with hanging block	22–45 Gy in 1.8–2 Gy fraction sizes	100% complete response 88.1% overall progression free survival 90.1% 5-year PFS in patients with lens protection 82.1% 5-year PFS in patients without lens protection	Acute: periorbital dermatitis (26.8%) Late: xerophthalmia (43.3%), cataract (11.9%), ptosis (4.5%), lacrimal duct obstruction (1.5%)
12	Shirota et al., 2017	Ocular adnexal MALT	Definitive	EBRT & electron beam	30 Gy in 15 fractions	5-year OS and local PFS were 100% 3-year disease PFS 100% 5-year disease PFS 93.3%	Acute: faint erythema, dry desquamation Late: cataract(25%)
13	Desai et al., 2017	Ocular adnexal MALT	Definitive	EBRT Electron & photon beam combination	— 22 to 45 Gy total dose — 36 Gy in 20 fractions — 30.6 Gy in 17 fractions	84.5% CR Median OS was 250 months Median PFS was 134 months 3.4% local relapse	No adverse event reported
14	Woolf et al., 2015	Ocular adnexal lymphoma	Definitive	EBRT & lens sparing technique	30-35 Gy in 15-20 fractions	OS 100%, 5% relapses	Acute: conjunctivitis, erythema, dry eye, photophobia, watery eye Late: cataract, diplopia
15	Harada et al., 2014	Ocular adnexal MALT	Definitive	EBRT Electron beam	30 Gy (30–46 Gy in 2 Gy per fraction)	5-year OS 97.6% 10-year OS 93.5% 5-year LRFS: 98.7% 10-year LRFS: 98.7% 5-year CRFS: 97.0% 10-year CRFS: 90.8%	Cataracts developed in 20% eyes treated without lens shielding
16	Fasola et al., 2013	NHL of the ocular adnexa	Definitive & palliative	Electron beams & EBRT	4 Gy in 2 fractions over 2 consecutive days	CR: 85% PR: 11% SD: 4%	Mild acute side effects including dry eye, conjunctivitis, and transient periorbital edema

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Table 1. Baseline characteristics

No	Study	Primary cancer sites	Purpose	RT method	Doses	Responses	Toxicities
17	Hashimoto et al., 2012	Ocular adnexal MALT	Definitive	EBRT Electron beam	36–50 Gy/18–25 fractions : 17 patients 30–32.4 Gy/15–18 fractions : 61 patients	5-year & 10-year OS: 98.1% and 95.3% 5-year RFS: 88.5% 10-year RFS: 75.9% No local recurrence developed 10 patients relapsed distant tumors	Acute : mild conjunctivitis, dry eye, periorbital erythema/edema Late : cataract, dry eye, glaucoma
Case reports							
1	Meng et al., 2021	Ocular adnexal MALT	Definitive	EBRT	4 Gy in 2 fractions over 2 days	2 months after RT: reduced tumor mass 4 months after RT: complete resolution of diplopia	No adverse events reported
2	Saria et al., 2020	Conjunctival MALT lymphoma	Definitive	Brachytherapy	14 Gy at 23 mm depth	Complete resolution of the lesion	No adverse events reported
3	Ahluwalia et al., 2020	Ocular adnexal MALT	Definitive	EBRT	25.2 Gy to the inferior fornix 29.2 Gy to nasal palpebral conjunctiva	Complete resolution of the lesion	No adverse events reported
4	Cetingul et al., 2020	Ocular adnexal EMZL	Definitive	Electron beam	36 Gy in 17 Fractions	Rapid remission of the tumor	Acute erythema
5	Bennet, 2019	Conjunctival lymphoma	Definitive	EBRT	25 Gy in 10 fractions	Tumor regression at 4 months after RT	Cataract on the left eye, 4 years after RT
6	Cham and Riad, 2016	Ocular adnexal MALT	Definitive	EBRT	17 Gy in 15 fractions	CR and no progression	Dry eye
7	İncesoy-Özdemir et al., 2014	Ocular adnexal MALT	Definitive	EBRT	36 Gy	No local or systemic recurrences after 4 years	No adverse event reported
8	Palavi and Popescu-Martinez, 2014	Ocular adnexal lymphoma	Definitive	EBRT	30.6 Gy with fractions of 18 Gy/day	CR in 2 months Remain tumor free at 8-month follow-up	No adverse event reported

CR — complete response; PR — partial response; RT — radiation therapy; EBRT — external beam radiation therapy; IMRT — intensity modulated radiation therapy; 3D CRT — three dimensional conformal radiation therapy; VMAT — volumetric modulated arc therapy; OS — overall survival; DFS — disease-free survival; PFS — progression-free survival; SD — stagnant disease; MALT — mucosa-associated lymphoid tissue; EMZL — extranodal marginal zone B-cell lymphomas

toxicities (6% and 31% *vs.* 0%) were less common after ultralow-dose RT.

Discussion

It is crucial to distinguish between intraocular lymphoma and orbital lymphoma since treatment and presentation are different. The most common sites for primary intraocular lymphoma are the retina or the uvea. Primary CNS lymphoma (PCNSL) is the most common type of the lymphoma in the retina, while the most common type of uveal primary lymphoma is the extranodal marginal zone also known as mucosa-associated lymphoid tissue (MALT) lymphoma. Intraocular lymphomas are usually localized in the eye, whereas orbital lymphomas do not affect intraocular tissue.

Orbital lymphoma or ocular adnexal lymphoma (OAL) is classified as primary if it affects only the ocular adnexa, and secondary if it is accompanied by another lymphoma of the same type. OAL is also classified by its location. It is classified as solitary if it just affects one or both orbits, extension if it affects nearby areas such as the sinuses, and systemic if it affects distant locations. About 55% of primary orbital tumors in adults were non-Hodgkin's lymphoma. Most of the non-Hodgkin's lymphoma of the orbit and adnexa are extranodal marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue (EMZL of MALT) type or usually called ocular adnexal MALT lymphoma (OAML). Most cases present in patients between the ages of 15 and 70 years, but it strikes around the seventh decade of life [2, 3, 7].

Orbital lymphoma is the most common orbital lymphoproliferative lesion, which involves a wide range of conditions, from reactive lymphoid hyperplasia to lymphomas. The lacrimal sac, orbital soft tissue, extraocular muscles, lacrimal glands, eyelids, and conjunctiva can all be affected separately or in combination by these lesions [8]. In this review we focus on the OAML. The time it takes to diagnose OAML is undoubtedly influenced by the gradual and varied evolution of clinical symptoms, which are reliant on the anatomic sites where lymphomatous tissue is present. The unique "salmon red patch" appearance is caused by conjunctival involvement, which occurs in roughly 25% of all cases. A pink conjunctival mass or conjunctival hyperemia is the most common symptom. The other 75% of the cases have an intraorbital mass. Orbital lymphoma usually presents with mass-effect symptoms such as exophthalmos, ptosis, epiphora, ophthalmoplegia, and metamorphopsia [1, 9–10]. OAML is indicated by an indolent course and most are localized tumors which are preferred and mostly sensitive to radiotherapy (RT) [8].

RT was known to be an effective therapy as the initial treatment in orbital lymphoma. Orbital lymphoma with radiotherapy shows better local control and cure than surgery. RT is the treatment of choice for solitary low-grade lymphomas [11]. Several studies that used RT as a primary treatment for stage IE orbital lymphoma, were given 25–35 Gy to the tumor bed [12–16]. Although RT has been shown to provide excellent local control in cases of OAML, a few studies showed that ophthalmologic outcomes may be unfavorable because decreased visual acuity and deterioration of lens opacity occur in a dose-dependent way after radiation[17]. Therefore, in 2013, a study reported that low-dose radiation (2 × 2 Gy) in the treatment of orbital lymphoma is effective and well tolerated, with high response rates, durable local control, and minimal side effects [18]. This finding sparked other studies to assess the effectiveness of low-dose radiation in orbital lymphoma.

As more and more studies appear with different doses of radiotherapy, Rehn et al. conducted a study to compare three dose groups. 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 [19]. Different radiation doses and volumes had no significant effect on progression-free or overall survival, according to the study. In comparison to standard-dose and high-dose RT, ultra-low-dose RT was associated with a significantly lower rate of late toxicities. In addition, IMRT patients had significantly fewer acute toxicities and a trend toward lower late toxicities, compared to 3D-CRT or electrons patients. Three cases of conjunctival MALT of the fornix were treated with a focused single dose of 14 Gy kilovoltage brachytherapy that prescribed to the maximum thickness of the lesion, and after 40 months of follow-up, none of the three patients treated had any acute or chronic toxicities and were disease-free locally and distantly [20].

Radiation caused minimal acute adverse effects such as dry eye, conjunctivitis, and momentary periorbital edema. Artificial tears were usually effective in alleviating the symptoms. Cataract is the most commonly reported late effect of radiotherapy [19, 21–25]. Individuals who had lens protection had a lower 5-year risk of cataract formation than patients who did not have lens protection[21,22]. Patients who got ≥ 30 Gy had a higher rate of cataract formation. There was no statistically significant link between underlying cataract risk factors such diabetes, hypertension, and contralateral cataract formation and symptomatic cataract formation [21].

Conclusion

RT is effective for treating low grade orbital MALT lymphoma as a primary definitive therapy with high survival rate, low recurrence rate, and generally acceptable toxicities. Until now, IMRT would be a better candidate for RT planning method because it provides lower toxicity. Different radiation doses and volumes have no significant effect on progression-free survival. However, ultra-low doses may result in a decreased rate of late toxicity.

Conflict of interest

The Authors declare that there is no conflict of interest.

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Ethical permission

Ethical approval was not necessary for the preparation of this article.

Authors contribution

All authors contributed equally to this work.

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