



## Radiation Therapy for Orbital Mucosa-Associated Lymphoid Tissue Lymphoma: What is the Optimal Radiation Dose?

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### Abstract

Primary orbital lymphoma is a rare malignancy that accounts for only 1% of all lymphomas, and more than half of orbital lymphomas present histology of marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT). MALT lymphoma is an indolent and slow growing disease that is very radiosensitive. Radiation therapy is thus the first choice of curative treatment for MALT lymphoma. The total dose of approximately 30 Gy in conventional fractions has been most frequently used for the treatment of MALT lymphoma, and has achieved an excellent local control rate of  $\geq 95\%$ . Recently, the total dose has been reduced to 24 Gy to 25 Gy in some institutions. Furthermore, low dose irradiation with 4 Gy in 2 fractions is also given, but the long-term efficacy is still unclear even though the initial response is good. In contrast, higher dose irradiation with  $>30$  Gy is not recommendable, because there is no evidence that such higher doses enhance the efficacy of local control, and because higher doses can cause unacceptable toxicities, such as severe retinopathy.

**Keywords:** Malignant lymphoma; Mucosa-associated lymphoid tissue lymphoma; Orbit; Orbital lymphoma; Radiation therapy

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### Introduction

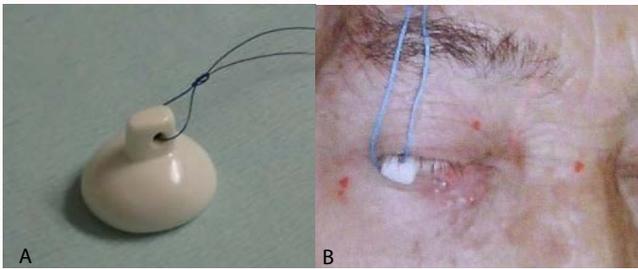
Primary lymphoma in the orbit, mainly ocular adnexa, is a relatively rare malignancy that accounts for only 1% of all lymphomas, and around 10% of extranodal lymphomas [1-3]. In more than half of patients with orbital lymphoma, the histological subtype presents marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) [3,4]. In 1983, Isaacson and Wright first described MALT lymphoma, which was subsequently classified by the World Health Organization [5,6]. MALT lymphoma is characterized by indolent and slow growing disease. Although approximately 30% of all MALT lymphomas are found to be accompanied with distant involvement at diagnosis, generally orbital MALT lymphoma is associated with a low malignant potential and a favorable prognosis in patients [7-9].

### Radiation Therapy

Radiation therapy has been applied in the treatment of orbital MALT lymphoma, and is now considered as the standard and most reliable curative treatment. We previously published a report on radiation therapy outcomes for orbital MALT lymphoma [10]. A total of 30 patients with orbital MALT lymphoma received external irradiation with the radiation fields including the gross tumor plus a 1 cm to 2 cm margin using 4 MV to 6 MV X-rays or 7 MeV to 13 MeV electrons. The typical dose distribution in the treatment planning with X-rays is shown in Figure 1. Clinical stages were stage I<sub>E</sub>A in 29 patients with tumors localized in the orbit, and stage II<sub>E</sub>A in one with cervical lymph node involvement. Three patients had tumors in the bilateral orbits. The median total dose of 30 Gy in 2 Gy fractions was delivered to the tumors, including the involved cervical lymph node. To protect the eye, a lead or tungsten shield was used for three patients treated with electrons. As a result, all irradiated tumors were completely controlled. All symptoms which patients had before treatment, including diplopia, proptosis, and lagophthalmos, disappeared or were markedly improved after treatment. Both the local control and overall survival rates at 5 years in all patients were 100%. Acute reactions, such as radiation-induced conjunctivitis, keratitis, and dermatitis,



**Figure 1:** Dose distribution curves on a computed tomography slice in the treatment planning of radiation therapy for a patient with mucosa-associated lymphoid tissue lymphoma in the right orbit. Six MV X-rays are delivered to the orbit through two antero-oblique ports using wedge filters.



**Figure 2:** Photographs of (A) an eye shield made of tungsten, and (B) a patient with the eye shield mounted on the right eye.

were mild and transient. Regarding late toxicities associated with radiation therapy, one patient developed severe retinopathy at 2 years after receiving radiation therapy of a moderate dose of 36 Gy in 18 fractions, which is usually considered to be safe [11]. Five patients developed symptomatic cataracts at 8-45 months after irradiation, but subsequently underwent successfully intraocular lens implantation. Three patients irradiated while wearing an eye shield had no cataracts at 77, 96, and 99 months after radiation therapy.

In many previous studies, including ours, patients presenting with orbital MALT lymphoma were treated with radiation therapy, which consisted of a total dose of approximately 30 Gy in conventional fractions [12-20]. Consequently, most studies have achieved excellent local control rates of  $\geq 95\%$  and overall survival rates of  $\geq 90\%$ , at 5 years. Based on these outcomes, the total radiation dose has been reduced to 24 Gy to 25 Gy in some institutions [21,22]. Furthermore, low dose irradiation with a total dose of 4 Gy in 2 fractions has been reported recently [23,24]. However, it is suggested that this treatment with low-dose irradiation results in a good initial response of the tumor, but is inferior to treatment with total doses  $\geq 24$  Gy for long-term local control. The use of low-dose irradiation may thus be limited to certain cases, such as patients in very poor general condition at this stage.

In our study, a patient treated with a total dose of 36 Gy in 18 fractions developed severe retinopathy [11]. Commonly, this moderate dose is considered to be safe, and causes no severe retinopathy, because it is much lower than 45 Gy, which is estimated to be a tolerable dose for the retina [25,26]. In addition, there is no evidence that a dose escalation to  $>30$  Gy improves the local control

of orbital MALT lymphoma. Considering such a risk and efficacy, a total dose of  $>30$  Gy is not recommended for the treatment of orbital MALT lymphoma any longer. On the other hand, a metallic shield is useful to protect the eye from radiation exposure, as well as irradiation to eyelid carcinoma (Figure 2) [27,28]. It may effectively prevent the incidence of radiation-induced cataracts, even though its use is limited to patients who are treated with electrons and present tumors that an eye shield has no risk of covering.

In fact, there is a report suggesting that aggressive treatment, including radiation therapy, contributes little to prolonged survival of patients with orbital MALT lymphoma, which has low malignant potential and is slow growing [29]. Although it cannot yet be concluded because a lack of data, watchful waiting may be one of the treatment options for patients with disease not presenting aggressive progression.

## Conclusions

Radiation therapy is effective in the treatment of orbital MALT lymphoma, and the total dose of 30 Gy is basically safe. It remains unclear at present whether a dose reduction to  $<30$  Gy is really suitable from the viewpoint of long-term disease control. It is expected that the optimal radiation dose will be determined by further studies in the near future, ideally randomized controlled trials.

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