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ORIGINAL ARTICLE

Examining the utility of lower dose radiotherapy for localised primary ocular adnexal MALT lymphoma

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Abstract

Introduction: Most primary ocular adnexal lymphomas are those involving mucosa-associated lymphoid tissue (MALT). Radiotherapy (RT) dose regimens in the literature vary from the historically used high doses (up to 56 Gy) to lower dose RT. We aimed to examine our institution's experience with the use of orbital RT for treating early-stage primary ocular adnexal MALT lymphoma (POAML). **Methods:** Patients treated for stage I or II POAML over a 12-year period (July 2006 to June 2018) were identified through institutional databases. Data were retrospectively collated through review of patient records. Descriptive statistical methods were employed to analyse the data. **Results:** Eighteen patients (median age of 67; range 44-87yrs) with localised POAML (3 cases of bilateral disease) were identified, resulting in a total of 21 evaluable orbits. Eight (44%) patients were female, and all were documented to be of good performance status (ECOG 0-1). The median follow-up was 34 months (range 8-75 months). The commonest dose fractionation used was 20 Gy in 10 fractions (n = 13 orbits) and a 3D conformal or volumetric modulated arc therapy (VMAT) technique was used in the majority of cases. None of the patients experienced an in-field recurrence. One patient had experienced a contralateral orbital recurrence two years post-unilateral orbital RT for orbital MALT lymphoma. Three patients experienced distant relapse. **Conclusion:** The use of lower dose orbital RT such as 20 Gy in 10 fractions (or radio biologically equivalent) yields excellent local disease control in the management of ocular adnexal MALT lymphoma. The durability of the response appears to be favourable. Given the indolent nature of the disease and the low levels of toxicity associated with lower dose orbital RT, this regimen remains our favoured approach to the management of localised POAML.

Introduction

Primary ocular adnexal lymphomas account for approximately 10% of all extranodal non-Hodgkin lymphoma (NHL).[1] Of these, mucosa-associated lymphoid tissue (MALT) lymphoma is the most common subtype[1] and represents up to 90% of the cases, known herewith as Primary Ocular Adnexal MALT Lymphomas (POAML).[2,3] Although POAML is largely an indolent disease, it can cause significant local morbidity if left untreated. In addition, the presence of genetic aberrations of *p53* or *p16* may result in its progression to more aggressive subtypes of lymphoma (such as Diffuse Large B Cell Lymphoma) in a minority of cases.[2] The average age of diagnosis for all extranodal MALT lymphoma is 6,6 and it occurs evenly across the genders.[4] Within the ocular adnexa, the most common site of origin is the orbit (40%), followed by the conjunctiva (35-40%), the lacrimal gland (10-15%), and the eyelid (10%).[2] Bilateral orbital involvement is not uncommon and is seen in 10-15% of cases.[2]

The treatment of choice for localised (stage I) POAML remains definitive local radiotherapy, with studies generally demonstrating local control rates over 85%.[2,5,6]

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The literature documenting the use of radiotherapy for POAML, however, is very varied in terms of radiotherapy techniques, and importantly, the dose. This is likely a reflection of the evolution in radiotherapy techniques and dose regimes over time. Studies evaluating the utility of orbital radiotherapy using older radiotherapy techniques and doses, while reporting good local control, have also reported a range of acute and late side effects associated with the treatment. These include dry eye, keratitis, cataract formation, and retinal damage. Goda et al[5] documented the late side effects of 89 POAML patients who received radiotherapy to their orbit where most (98%) received a dose of 25 Gy in 10#. They found that almost half of the cohort experienced cataract formation (cumulative incidence of grade 3 cataract requiring surgery was 18% at 5 years and 25% at 7 years).[5] A third of their patients experienced other late sequelae including dry eye and keratitis.[5] Although most patients experienced a full resolution of their side effects with appropriate treatment, 10% suffered with symptomatic non-reversible persistent late effects.[5] More recent studies have assessed the efficacy of lower doses of radiotherapy, in an attempt to minimise radiotherapy related side effects to the orbit without compromising local control.[7,8]

The current study aimed to examine a decade of practice at our institution of using orbital radiotherapy in the management of POAML, in order to determine the disease control outcomes achieved with contemporary radiotherapy techniques and dose regimes.

Methods

A retrospective study design was employed to examine all cases of POAML treated by our lymphoma multidisciplinary team and radiation oncology service (across two hospital sites) over a 12-year period from July 2006 till June 2018. All cases of MALT lymphoma diagnosis in adult patients were identified by searching our institution's electronic cancer patient medical record database (ARIA) using ICD-10 codes for non-Hodgkin lymphoma and then further identifying those with MALT lymphoma using manual review of medical records, reports of investigations and correspondence. Cases where orbital radiotherapy was employed in patients with a clear histopathological diagnosis of MALT lymphoma were included in this study. Other cases of low-grade NHL were excluded. All patients also had to have been adequately staged to ensure a diagnosis of stage I or II (E). Patient, tumour and treatment details were then collated from the patient's cancer care record (ARIA) and main hospital records (paper and electronic- CERNER Powerchart). Similarly, disease outcomes including local (ipsilateral) relapse, contralateral orbital relapse, and overall survival were collected. Patients were followed up clinically, with imaging as indicated, generally on a 3-6 monthly schedule for the first year, and variable schedules thereafter. Descriptive statistics were employed for data analysis. This research had institutional ethics approval from Western Sydney Local Health District within the scope of a quality improvement project.

Results

Eighteen patients with a median age of 67 (range 44-87) met the eligibility criteria. The patient, tumour and treatment characteristics of the eligible patients are presented in Table 1. Of the 18, three patients had presented with bilateral orbital involvement with MALT lymphoma, resulting in a total of 21 evaluable orbits. Two out of the three cases of bilateral involvement were treated simultaneously. The third case presented with bilateral involvement but each orbit was treated individually, one month apart. All patients were of a good performance status (ECOG 0-1).

Most orbits were treated with a 3D conformal (n = 12) or volumetric modulated arc therapy (VMAT) (n = 8) technique using 6MV photons Figures 1 and 2. One instance of a parallel opposed beam arrangement with prescription dose delivery at midpoint was used in the treatment of bilateral orbital MALT lymphoma Figure 3.

Table 1. Patient, disease and radiation treatment details.

Characteristics	Number of patients (% of total)
Gender	
M	10 (56%)
F	8 (44%)
MALT lymphoma location within the Ocular adnexa	Number of orbits (% of total)
Inner canthus/eyelid	5 (23%)
Orbit	11(52%)
Conjunctiva	4 (19%)
Inferior rectus muscle	1 (5%)
Bilateral cases	3 (14%)
Dose to tumour in 2 Gy equivalent ($\alpha\beta$ = 10)	
4 Gy	2 (9.5%)
20 Gy	13 (62%)
24-26 Gy	5 (24%)
30 Gy	1 (5%)
Treatment technique	
VMAT	8 (38%)
3DCT	12 (57%)
Parallel opposed	1 (5%)

VMAT - Volumetric modulated arc therapy; 3DCRT – three-dimensional conformal radiation therapy

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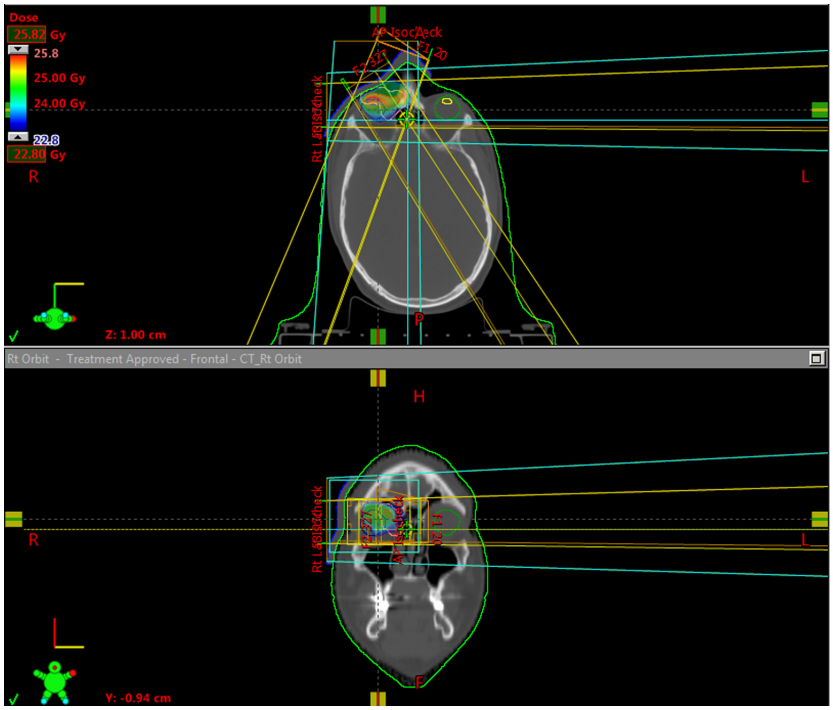

Figure 1. Single Orbit 3DCT; orbital lesion; 95% isodose volume is highlighted

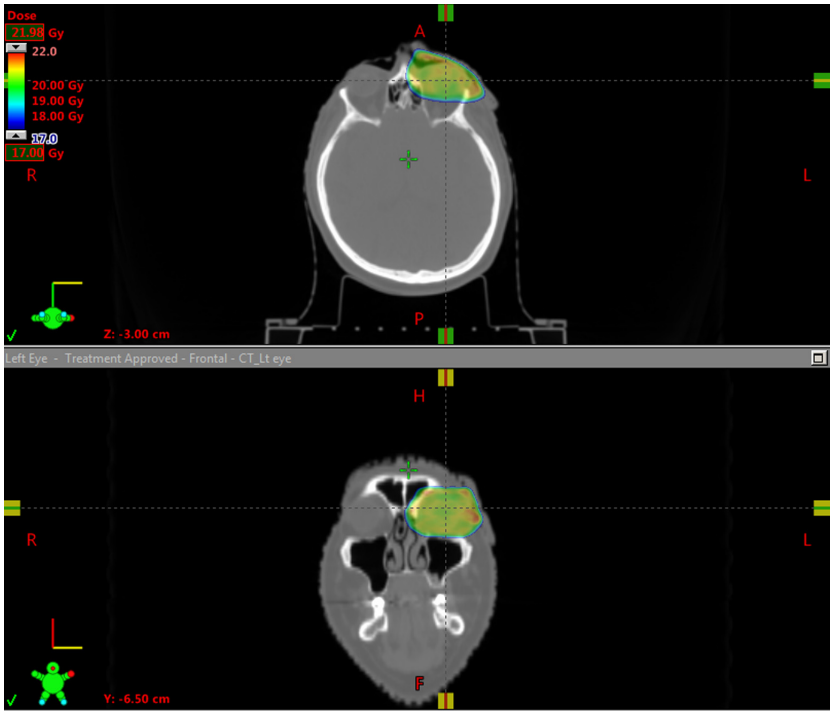

Figure 2. Single orbit VMAT; lower eyelid lesion; 95% isodose volume is highlighted

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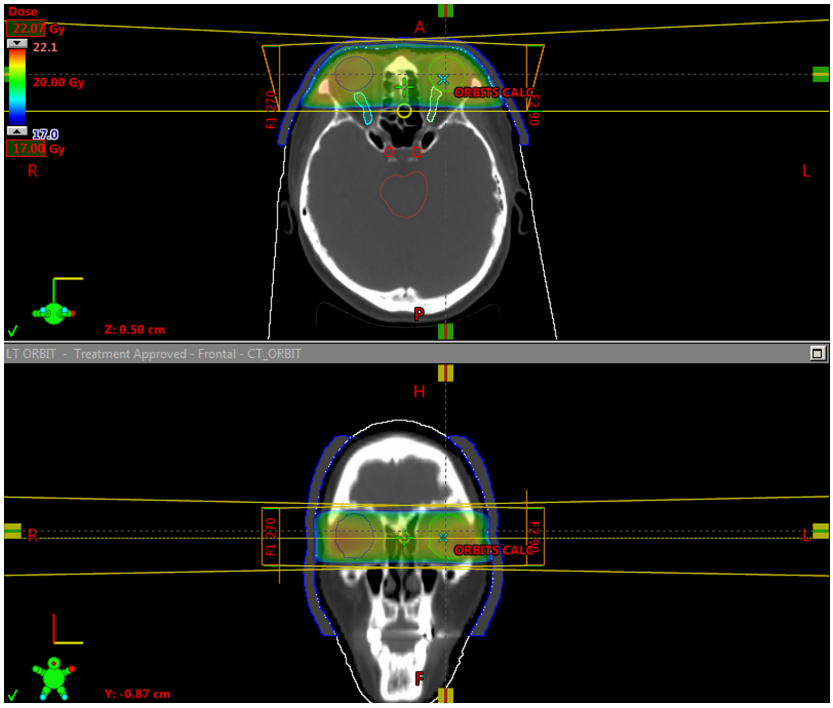

Figure 3. Bilateral Orbits 3D-conformal parallel opposed technique; conjunctival lesions; 95% isodose volume is highlighted

The commonest dose fractionation used was 20 Gy in 10 fractions (n = 13 orbits). With the exception of one patient, all of the patients received treatment with 1.5-2 Gy fraction sizes and received total doses between 20-30 Gy. One patient received a dose schedule of 4 Gy in 2 fractions and this patient had bilateral involvement and had both orbits irradiated concurrently. This dose schedule was specifically chosen in this case due to the patient's age (87) and ECOG (1); He was demographically the outlier in the data.

At median follow-up of 34 months (range 8–75 months), 17 of the 18 patients were known to be alive. One patient did not attend scheduled follow-ups with any of their specialists nor their general practitioner and was lost to follow-up. All remaining patients had excellent local disease control with none experiencing a local recurrence. There was only one case of contralateral orbital relapse of MALT lymphoma at two years following initial treatment. This patient was treated successfully with systemic treatment. Three patients (16%) experienced distant relapse. These occurred at 6-month, 24-month, and 48-month post-initial orbital radiotherapy for MALT lymphoma. At last follow-up, 16 patients were in remission, with one patient having active but stable lymphoma which was under observation.

There was only one documented instance of acute toxicity in the form of tearing and red eye, and similarly one documented instance of late toxicity in the form of dry eye and cataract formation - these both occurred in the same patient, who received 26Gy15# to the orbit using a 3D conformal technique.

Discussion

Historically, the radiotherapy dose schedules employed for POAML have ranged from 24-54Gy[7,8]. Our experience suggests that lower radiotherapy doses equivalent to 20-24 Gy in 1.8-2 Gy fractions provide excellent local control rates. Given that the higher doses used historically have not been associated with any additional benefit to local control rates, yet have higher rates of side effects,[9] the International Lymphoma Radiation Oncology Group (ILROG),[10] in 2015 published radiotherapy guidelines for the treatment of extranodal lymphomas and suggested that orbital lymphomas be treated with 24-25 Gy in 1.5-2 Gy fractions. Our experience is in line with these guidelines and the current study findings support the use of lower dose orbital radiotherapy (equivalent to 20 Gy in 10 fractions) for POAML.

It is recognised that current studies are focused on further reductions to the radiotherapy dose in this disease and have assessed the effectiveness of ultra-low doses of radiotherapy: 4 Gy in 2 fractions; colloquially known as the 'boom boom'. Pinnix et al[7] conducted a retrospective

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review of 22 patients treated at MD Anderson Cancer Centre over a five year period after treatment with 4 Gy in 2 fractions of orbital radiotherapy for low-grade ocular adnexal lymphoma. Whilst they included all ocular adnexal lymphomas, MALT lymphoma comprised over 60% of these 22 cases and they were followed up for a median of 14 months. They recorded freedom from local recurrence at two years to be 75%, with no significant acute or late toxicities.[7] Considering the indolent nature of low-grade lymphomas, the follow-up data on these cases are short and therefore future reports of long term outcomes will be of considerable interest.

The current study was a retrospective observational analysis, with the associated limitations of such a process. The overall number of cases was small. Although, this may be reflective of changes in histopathological classification of the entity of MALT lymphoma over time, it is also reflective of the uncommon nature of POAML. The number of cases identified is also in line with the incidence of POAML as documented in the literature. A key limitation is the lack of accurate and reliable data on the side effects of radiotherapy, given that the study period spanned over a whole decade during which there was transition from paper-based medical records to an electronic one, there was fragmentation of record keeping across the cancer service and the wider hospital, and major changes were implemented to the processes around the recording and reporting of such information. As such, the available information was not sufficient to meaningfully offer insights into the toxicity profiles of different radiotherapy dose fractionation regimens. One of the strengths of this case series is that, even with the study period spanning 12 years, all the cases of orbital MALT lymphoma were managed within a single lymphoma multidisciplinary team and radiation oncology service (across two hospital sites), with little variation in radiotherapy technique and with only small variations in dose fractionations consistent with evolving treatment paradigms reflected in the current ILROG guidelines.[10]

This study confirms that low dose orbital radiotherapy equivalent to 20-24 Gy in 2 Gy equivalents yields excellent local disease control in orbital MALT lymphoma and supports the current ILROG guidelines on the management of indolent lymphomas. Future studies may lead to further decreases in radiotherapy doses with the aim of preserving adequate local disease control whilst minimising side effects.

Conflict of Interest

The authors declare no conflict of interest.

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