Localized Ocular Adnexal Mucosa-Associated Lymphoid Tissue Lymphoma Treated With Radiation Therapy: A Long-Term Outcome in 86 Patients With 104 Treated Eyes

（放射線治療された局所眼付属器原発マルトリンパ腫：86 人 104 個の眼の長期治療成績）

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Introduction

The incidence of ocular adnexal lymphoma is reported to be less than 10% in all extranodal lymphomas [1]. More than half of the cases of ocular adnexal lymphoma are mucosa-associated lymphoid tissue (MALT) lymphomas [2]. MALT lymphoma, first described in 1983 by Isaacson and Wright [3], is believed to have a tendency to remain localized to the primary site for a long time [4]. Therefore, local therapy has usually been applied for this disease [5, 6]. Among several treatments, radiotherapy has been generally considered the most effective for the localized disease [1, 4, 5, 7-10]. The objective of our study is to analyze the characteristics of primary ocular adnexal MALT lymphoma (POAML) including its natural history, behavior of progression, prognostic factors and treatment-related adverse effects.

Materials and Methods

Eighty-six patients with histologically proven stage I POAML treated with radiotherapy at National Cancer Center Hospital

between 1990 and 2010 were retrospectively reviewed. Median age was 56 years (range,18-85 years). There were 49 male (57%) and 37 female (43%) patients. The pathological diagnosis of MALT lymphoma was established by biopsy or surgical resection sample. Staging work-ups included physical examination, complete blood counts, magnetic resonance imaging (MRI) or computed tomography (CT) of both orbits, CT of the neck, thorax, abdomen and pelvis, and bone marrow biopsy. Tumors classified as stage I in this study were unilateral or simultaneous bilateral diseases that did not have extraorbital extensions. Twelve patients had simultaneous bilateral lesions. These bilateral lesions were both treated by radiation therapy, and the total number of the eyes undergoing radiation as a primary therapy was 98. Additionally, all the 6 relapses in the contralateral eyes underwent radiation therapy. Therefore, the total number of eyes treated by radiation was 104 (unilateral primary:74, bilateral pimary:12×2, contralateral relapses:6). As for subsites of the 104 eyes, conjunctiva and eyelid involvement was seen in 46 eyes, lacrimal

gland was 7 and non-conjunctival/eyelid/lacrimal gland involvement in 51 eyes.

The total of 77 patients including 66 of unilateral and 11 of bilateral lesions were treated by radiotherapy alone (Table 1). Among unilateral tumors, 3 patients received chemotherapy followed by radiotherapy, and other 5 patients underwent surgery (maximal excision) before radiation. Also, one of bilateral tumors was treated with radiation and chemotherapy. Among those treated with radiation and chemotherapy, 2 patients had four or six cycles of CHOP (cyclophosphamide, hydroxydaunorubicin, oncovin, and prednine), and 1 patient had four cycles of R-CHOP (rituximab + CHOP) and 1 patient had one cycle of COP (cyclophosphamide, oncovin, and prednine). Total of 4 patients received chemotherapy.

The radiation dose varied between 30-46Gy in a conventional fractionation, and the median dose was 30Gy. No eyes were treated by dose lower than 30 Gy. Direct appositional electron irradiation with 3-12MeV was used in 41 eyes. The remaining 63

eyes were treated with 4 or 6 MV photon beams with a single anterior field or a wedged pair of anterior and oblique fields. A lens block was used in 39 of 104 eyes (photon beam:27, electron beam:12), and a bolus was used in 41of 104 eyes (photon beam:13,electron beam:28).

Local relapse free survival (LRFS) was calculated from the last day of radiotherapy until the date of the first documented relapse with death and last follow-up without local relapse considered as censored. Contralateral relapse-free survival (CRFS) was defined as time period from the last day of radiation therapy until the date of the first documented contralateral relapse with death and last follow-up without contralateral relapse considered as censored. In the analysis of contralateral relapses, 24 eyes of simultaneous bilateral diseases were not included, because there was no contralateral eye for primary bilateral lesions. Overall survival was defined as time period from the first day of radiotherapy until the date of death due to any cause or until the date of the last follow-up for patients who were alive. Cataract incidence was

calculated from the last day of radiotherapy to the date of cataract diagnosis. All survival curves as well as the cataract incidence were calculated by the Kaplan-Meier method with a statistical difference tested by log-rank test. A p value of less than 0.05 was considered as statistically significant. All the statistical analyses were performed using Predictive Analytic Software (PASW), version 18.0 (SPSS Inc., Chicago, IL, USA).

Table 1. Patient characteristics		
Characteristics	Number	
Sex		
Male	49patients (57%)	
Female	37patients (43%)	
Age		
median/range	56/18-85years	
Bilateral Presentation	12patients	
Contralateral relapse	6patients	
No. of Irradiated Eyes	104eyes	
Unilateral Involvement	74eyes	
Bilateral Involvement	24eyes	
Contralateral relapse	6eyes	
Primary Site		
conjunctiva and eyelid	46 eyes	
lacrimal gland	7 eyes	
non-conjunctiva/eyelid/lacrimal gland	51 eyes	
Treatment RT only/Chemo＋RT/Surg + RT	94/5/5eyes	
Radiation Dose		
median/range	30/30-46Gy	
Treatment (Total number of treated eyes: 104)		
X-ray	63eyes	
Electron beam	41eyes	
Shield		
yes/no	39/65eyes	
Bolus		
yes/no	41 (photon beam:13, electron beam:28)/63eyes	

Results

The median follow-up duration of all patients was 9 years (range, 0.9-22 years).The 5- and 10-year OS rates were 97.6% and 93.5%, respectively (Fig.1). Also, the 5- and 10-year LRFS rates were

98.7% and 98.7%, and CRFS rates were 97.0% and 90.8%, respectively. None died of the disease; the deaths of 6 patients were from non-lymphoma-related causes. The number of total relapses was10. Among them, one case relapsed locally in the irradiated eye, while contralateral relapses were seen in 6 patients. The other 3 patients had a distant relapse. The patient who developed local relapse had had simultaneous bilateral tumors at the presentation and both tumors were treated by radiation therapy. Only her right eye lymphoma in the conjunctiva relapsed 45 months after electron beam irradiation of 30Gy. The 6 contralateral relapses were also treated by radiation therapy alone, and all those lesions were controlled with a follow-up length of 3 to 12 years. Patients with tumor size≧4cm showed a greater risk of contralateral relapses with 5- and 10-year CRFSs of 100% and 55.6%, respectively, for the tumors≧ 4 cm, and 96.7% and 94.3%, respectively, for the tumors < 4 cm (p=0.012) (Fig.2). Other factors, such as gender, age, tumor location were not significant for relapse in the contralateral orbit.

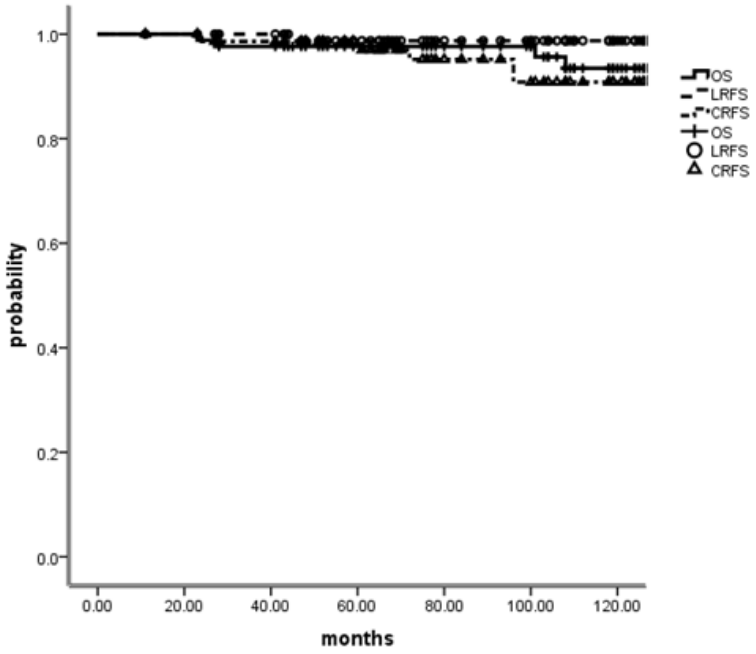

Fig.1. Overall survival(n = 86), local relapse free survival (n = 104), and contralateral relapse-free survival (n = 74) in patients with primary ocular adnexal MALT lymphoma (5- and 10-year OS rates: 97.6% and 93.5%,LRFS rates: 98.7% and 98.7%, and CRFS rates: 97.0% and 90.8%, respectively)

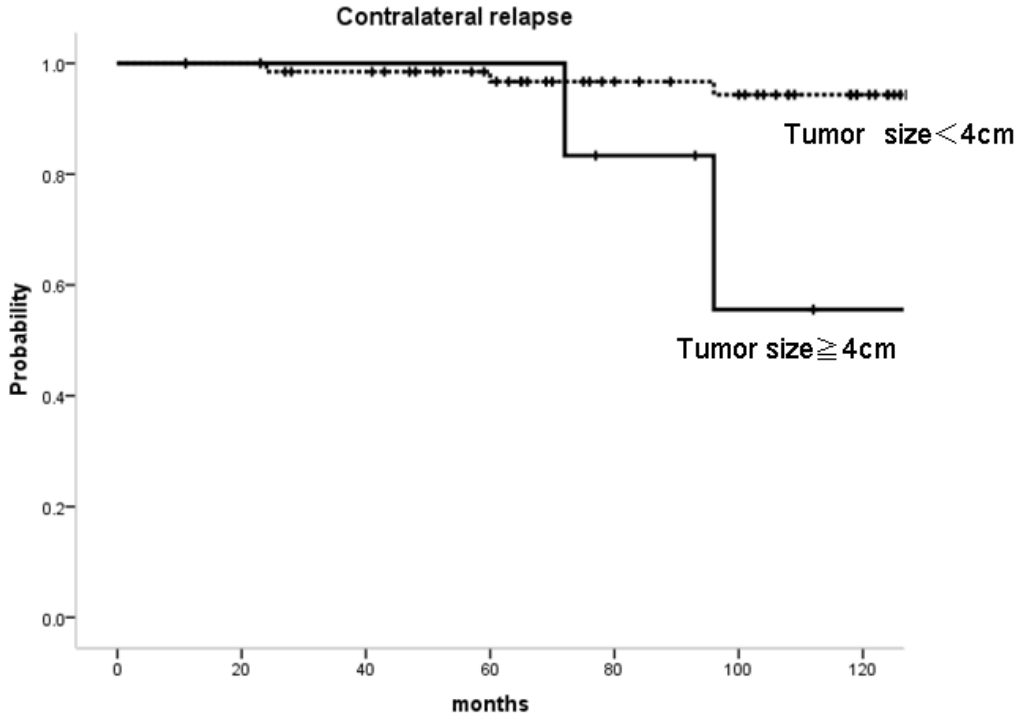

Fig. 2. Contralateral relapse free survival rates according to tumor sizes

The clinical characteristics of simultaneous bilateral lesions are shown in Table 2. No clinical factors affected bilateral lesions except for tumor size. Bilateral lesions were seen in 6.9% of the patients with tumors larger than or equal to 1 cm, while in 28.6% of the patients with tumors less than 1 cm. ($p = 0.007$)

Table 2. Clinical features of unilateral and bilateral lesions.				
		Unilateral	Bilateral	P value
Age		53.8	50.7	p=0.51
Gender				
	Male	42	7	p=0.919
	Female	32	5	
Size				
	<1cm	20	8	p=0.007
	≧1cm	54	4	
Location				
	Conjunctiva	30	8	p=0.091
	Other than conjunctiva	44	4	

Among patients who developed distant relapses, initial therapy was radiation alone for two patients, and surgery followed by radiation for one patient. Of those, two relapsed at mediastinum, and one relapsed at left pleura. All of them underwent additional treatment. One patient with mediastinum was treated with 6 cycles of R-CHOP, and another patient with mediastinum underwent 6 cycles of R-CHOP followed by 30Gy of radiation. The patient with pleural disease underwent surgery. All the patients achieved CR and no evidence of disease at additional 24-132 months of follow-up. There were no statistically

significant influencing prognostic factors for distant relapse (Table 3).

Table 3. Clinical features of distant metastasis.				
		Distant relapse	Others	P value
Age		50.3	53.5	p=0.725
Gender				
	Male	2	47	p=0.730
	Female	1	36	
Size				
	<4cm	3	77	p=0.629
	≧4cm	0	6	
Location				
	Lacrimal gland	1	5	p=0.068
	Other than lacrimal gland	2	78	

Risk factors for cataract were retrospectively evaluated in 104 eyes including eyes treated for the primary diseases and 6 eyes treated for the contralateral relapse. Cataracts occurred in 48 of 104 eyes. Of those, 31 eyes underwent surgery. A lens-shielding technique was used in 39 of 104 eyes. Thirty-six of the 65 eyes without lens shielding developed a cataract with 5-year cataract incidence of 50.9%, whereas 12 of the 39 patients with lens shielding developed a cataract with 5-year cataract incidence of

27.4% (p=0.037) (Fig.3). The radiation dose was not a risk factor (65 eyes were treated with 30Gy vs. 39 eyes were treated with >30Gy; p =0.843). Also, the use of a bolus did not influence upon risk of cataracts.

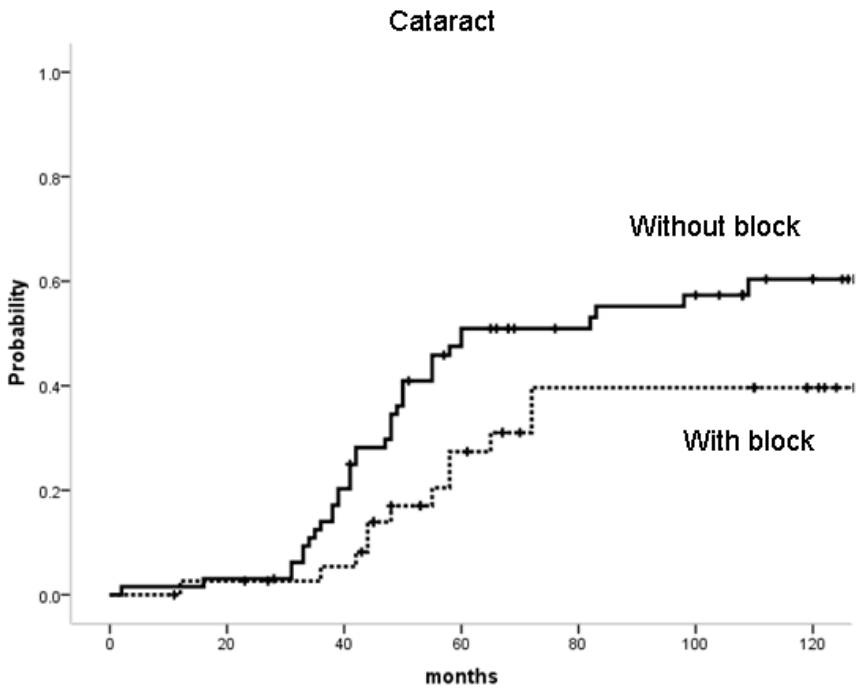

Fig. 3. Cumulative incidence of cataract according to whether lens shielding was used

Discussion

In this study, excellent LRFS of 98.7% in 5 and 10 years was achieved, and moderate dose of 30 Gy was effective for stage I

POAML [11-14].The predominant site of relapse was a contralateral orbit. However even those contralateral relapses were controlled well by radiation therapy alone.

Most previous studies had analyzed the prognostic significance of tumor subsite at either a conjunctiva or other locations [1, 10, 15]. Some studies have suggested that tumor at conjunctival location may have a better prognosis than at other anatomic subsites of the orbit, while other studies did not find a difference between conjunctival location and other sites. In our study, we did not see any differences of prognosis between conjunctival and the other sites. Also, Nam stated that primary lacrimal involvement may be related to future relapse more frequently than other orbital subsites [16]. In our study, there were 6 patients with lacrimal primary. One patient had bilateral lacrimal involvements, and the total number of eyes with lacrimal involvement was 7 in 6 patients. Among them, only one patient with lacrimal tumor developed a distant relapse 12 years after the radiation therapy. Because of the small number of the patients with distant relapse

statistically significant influence of the primary orbital subsite upon distant relapse could not be seen..

Some reports of POAML showed distant relapse other than the ocular relapse, and the possible role of immunochemotherapy reducing the distant relapse was suggested. Hashimoto et al. reported that 30.6Gy combined with rituximab successfully decreased the risk of systemic relapse [14]. However, our study demonstrated after the extensive staging, distant relapse of stage I POAML is rare, and there seems to be only a small role of immunochemotherapy in stage I POAML. Additionally, most reported series have demonstrated excellent OS with only exceptional death due to POAML, delivering cost demanding immunochemotherapy in all patients with localized POAML is out of consideration. Contralateral orbital relapse was seen most often, but the median time to the contralateral relapse was as long as 84 months after radiation therapy. Therefore, patients with stage I POAML must be followed longer than 5 years with a

meticulous attention to the contralateral eye. There are few reports on the management and prognosis of contralateral relapse of POAML. In our study, all the 6 contralateral relapses were treated by radiation therapy, and all were controlled for 3-12 years without local as well as extraorbital relapses. Goda et al. also stated that an isolated contralateral relapse of MALT lymphoma in the paired organ could be successfully managed with another course of RT and often did not result in further disease relapse in distant sites [17]. Solitary contralateral relapse of stage I POAML should be treated by repeated course of radiation therapy.

Although anatomic site of tumor location, gender and age were not significant for relapse in the contralateral orbit, the patients with tumor size $\geqq$ 4 cm showed a greater risk of contralateral relapse more than 5 years after the treatment. Therefore, long term follow-up is mandatory for patients with a larger tumor with attention to the contralateral eye.

In our series, primary bilateral lesions were small in their size at the presentation. POAML often presents as a salmon-pink lesion

that was sometimes misdiagnosed as other ocular surface diseases, such as allergic or chronic conjunctivitis, and it is sometimes challenging to recognize the small tumor [18].There is a possibility that patients with bilateral lesions might draw attention of the ophthalmologists to the symptoms including irritation, epiphora, and mass sensation compared to those with unilateral lesions. This might have resulted in an early diagnosis with relatively small size in our bilateral lesions. All of the bilateral lesions were controlled well by radiation except for one case of local relapse. Also, the NCCN Guidelines Version1.2013 recommends [19] radiation therapy to both lesions in the bilateral POAML.

Total dose of around 30 Gy in a conventional fractionation seems to be the present standard in radiotherapeutic management of POAML. Hashimoto reported that 30.6Gy combined with rituximab successfully decreased the risks of systemic relapse. In contrast, Tsang and coworkers reported that for local control of POAML results from the use of a slightly lower dose of 25Gy of

30 patients in orbital lymphomas remained excellent [13].

Recently, low-dose radiation has become increasingly used in the management of indolent non-Hodgkin lymphoma (NHL) [20-25]. Fasola et al. recommended 2Gy ×2 as excellent treatment of NHL of the ocular adnexa for the purpose of disease control in patients with advanced stage with the option of reirradiation in the case of locoregional relapse [26] However, there are few data regarding how much the dose could be reduced safely in radical radiation therapy of POAML. Therefore, future clinical trials seem to be necessary to reduce the optimal deses in the radiation therapy for POAML.

The employment of the shielding-block reduced the incidence of cataract with a statistically significant difference. However, because cataract was effectively managed by surgery with a resultant restoration of vision, shielding block must be inserted only in the lesions which would be treated with easy insertion of the shielding block.

Conclusion

Local radiation therapy up to 30 Gy can attain excellent local control and overall survival of POAML. Predominant site of relapse was a contralateral eye, which can be also controlled by local radiation. Because median time to contralateral relapse was 84 months, long term follow-up of POAML is mandatory.

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