Treatment Outcome of Radiotherapy for Localized Primary Ocular Adnexal MALT Lymphoma – Prognostic Effect of the AJCC Tumor-Node-Metastasis Clinical Staging System

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Abstract. *Aim: To analyze the treatment outcome of radiotherapy for localized primary ocular adnexal mucosa-associated lymphoid tissue lymphoma (POAML) and evaluate the prognostic effect of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) clinical staging system for POAML. Patients and Methods: Seventy-three patients with Ann Arbor stage IE POAML who were treated with radiotherapy alone were analyzed. T-Factor based on the AJCC staging system was T1 in 28, T2 in 33 and T3 in 12 patients. Results: Out of nine patients with relapse, six had distant and three had contralateral ocular adnexal relapse. One patient died of lymphoma progression. The 5-year local control and progression-free survival (PFS) rates were 100% and 81.5%, respectively. T-Factor was not significantly associated with PFS. Conclusion: Radiotherapy achieved excellent local control and survival rates for stage IE POAML. The AJCC TNM clinical staging system was not significantly predictive for PFS of stage IE POAML.*

Most cases of primary ocular adnexal lymphoma are extranodal marginal zone lymphomas of the mucosa-associated lymphoid tissue (MALT) type (1-3). MALT lymphoma was first presented in 1983 by Isaacson *et al*. (4). This disease is categorized as a low-grade lymphoma due to its slow progression. Because MALT lymphoma rarely metastasizes to distant sites and is sensitive to radiation in general, localized primary ocular adnexal MALT lymphoma (POAML) is frequently treated by radiotherapy alone and radiotherapy can achieve excellent local control (LC) (5). POAML affects the conjunctivae, orbits, eyelids, lacrimal glands *etc*. The Ann Arbor staging system has been widely applied for staging of POAML (6, 7). However, in the Ann Arbor staging system, ocular adnexal tumors without other lesions are categorized as stage IE, irrespective of their location. Bilateral ocular adnexal lesions are also classified into stage IE by the Ann Arbor system. Several investigators have reported that the specific disease locations of ocular adnexal lymphoma were associated with their prognosis (8-11). For example, poor prognosis was reported for MALT lymphoma in the eyelid or orbit with lacrimal gland involvement, lymphomatous involvement of the extraocular muscle and mass-forming type (8-10). In short, the Ann Arbor staging system does not precisely define the disease extent or site-specific prognosis of localized primary ocular adnexal lymphoma. There is thus a need for a staging system that can provide prognostic information for the treatment of POAML. More recently, a tumor-node-metastasis (TNM)-based clinical staging system for primary ocular adnexal lymphoma was developed under the guidance of the American Joint Committee on Cancer (AJCC). This staging system addresses many of the shortcomings of the Ann Arbor system and more precisely defines the disease extent (11, 12).

To date, there have been few reports analyzing the feasibility of the AJCC TNM clinical staging system for patients with Ann Arbor stage IE POAML who were treated by radiotherapy alone. In the present study, we analyzed the treatment outcome of radiotherapy for POAML and evaluated the prognostic effect of the AJCC TNM clinical staging system for Ann Arbor stage IE POAML.

Patients and Methods

Patients' characteristics. From 1997 to 2012, 92 patients with POAML were treated with radiotherapy alone at our Hospital.

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Eighteen patients with short follow-up and one patient with stage IIE disease based on the Ann Arbor staging system were excluded from this study. The remaining 73 patients with Ann Arbor stage IE POAML were analyzed. The median patient age was 63 years (range=22 to 90 years). Performance status (PS) was 0 in 41 and 1 in 32 patients according to the Eastern Cooperative Oncology Group (ECOG) criteria (13). In this study, tumors were divided into two categories by their morphology: superficial (SF) type and mass-forming (MF) type. SF-type tumors were defined as invisible on computed tomographic images, and MF-type tumors were defined as visible on computed tomographic images. Twelve patients had SF-type tumor and the others had MF-type tumor. The Ann Arbor stage IE tumors of all 73 patients were assessed by the AJCC TNM clinical staging system. In the AJCC TNM staging system, the T-factor of primary ocular adnexal tumors is used to divide them by anatomic location and tumor extent. T1 tumors are defined as conjunctival lesions and T2 as orbital lesions, irrespective of whether or not the conjunctiva is affected. T3 tumors are considered lymphoma with preseptal eyelid involvement. Finally, T4 tumors are classified as orbital adnexal lymphomas extending beyond the orbit to adjacent structures. By the AJCC TNM staging system, our patient group included 28, 33 and 12 patients with T1, T2 and T3 disease, respectively (Table I).

Table I. *Patient characteristics*.

Characteristic	Range (Median)	n
Age	22-90 (63)	
>60/<60 years		43/30
Gender		
Male/female		31/42
PS		
0/1		41/32
Tumor type		
Superficial/mass-forming		12/61
Stage*		
I		73
T stage#		
T1/T2/T3		30/31/12

PS: Performance status; *according to the Ann Arbor staging system; #according to the American Joint Committee on Cancer tumor-node-metastasis staging system for ocular adnexal lymphoma.

Treatment. The gross tumor volume (GTV) included the tumor extent. The entire anatomical region involved by the tumor was delineated as the clinical target volume (CTV). For example, the CTVs of T1 and T2 lesions were the conjunctiva and orbita, respectively. The PTV included the CTV with a 10 mm to 15 mm margin. Patients with POAML were treated with involved-field radiotherapy. The field did not include the regional lymphatic area. In this study, lens shielding and lacrimal gland shielding were performed, provided the shielding did not reduce the dosage to the tumor. Lens shielding was performed in 11 patients. Lacrimal gland shielding was performed in eight patients. The radiation dose was 24 Gy in 12 fractions for SF lesions, and 30 Gy in 20 fractions for MF lesions, with the exception of a single case treated with 18 Gy in 12 fractions. Thus the dose delivered ranged from 18 to 30 Gy (median=30 Gy).

Response. The initial response was evaluated according to the Cheson criteria at 3 months after the radiotherapy (14). The time to local and distant relapse was measured from the start of radiotherapy. Acute and late adverse events were evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v.4.0) (15).

Statistical analysis. Progression-free survival (PFS) and overall survival (OS) were calculated from the start of radiotherapy using the Kaplan–Meier method. Predictive factors for PFS and the difference in PFS between two T-factor groups were evaluated using the log-rank test. The predictive factors for PFS analyzed included the age, gender, PS, tumor type, radiation dose and initial response of patients. The associations between late adverse events and shielding were examined using Fisher's exact test. A *p*-value of less than 0.05 was considered statistically significant.

Results

The median duration of follow-up was 45 months. The 5-year LC rate was 100%. Nine patients experienced relapse. The median time to relapse was 43 months. Out of these nine patients, six had distant relapse and three had contralateral ocular adnexal relapse (Table II). The relapse sites of the six patients with distant relapse were the mesenterium, kidney, neck lymph nodes, tonsils, inguinum and multiple lymph nodes. Three out of these six patients were able to achieve a complete response (CR) by combined treatment with chemotherapy and local radiotherapy. Two patients achieved a CR by chemotherapy alone. However, one patient experienced further relapse after a second CR. At the third relapse, she underwent a biopsy of recurrent perirenal tumor. Pathological analysis confirmed that the tumor was diffuse large B-cell lymphoma. Although this patient underwent chemotherapy following peripheral blood stem cell implantation, she died of progression of lymphoma at 135 months after the start of treatment. One patient with multiple lymph node relapse received treatment at another hospital, therefore the treatment response was unknown. In all three patients with contralateral ocular adnexal relapse, the conjunctivae were the primary site. The conjunctivae were also the contralateral relapse sites. Among these three patients, one achieved CR by local radiotherapy for the relapsed site. The others were observed without additional treatment due to slow growth of tumor. One patient died of lung cancer at 94 months after the start of treatment.

The 5-year PFS and OS rates were 81.5% and 100%, respectively (Figure 1). Age, gender, PS, morphological tumor type, radiation dose and initial response of patients did not significantly associate with PFS (Table III). PFS by T-factor was 62.9% in T1, 85.4% in T2 and 100% in T3 patients. The T-factor was also not significantly associated with PFS (Table IV).

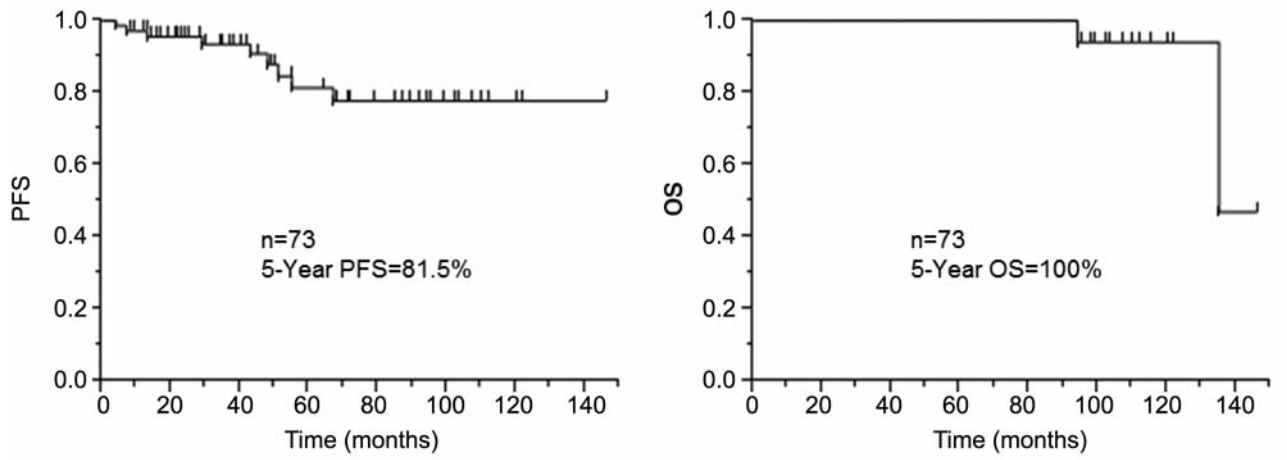

Figure 1. *Progression-free (PFS) and overall (OS) survival of 73 patients with Ann Arbor stage IE primary ocular adnexal mucosa-associated lymphoid tissue lymphoma.*

Table II. *Details of relapsed patients with Ann Arbor stage IE primary ocular adnexal mucosa-associated lymphoid tissue lymphoma after radiotherapy.*

T Stage	Age (years)	Gender	Tumor type	Radiation dose (Gy)	Initial response	Relapse site	Time to relapse (months)	Second-line therapy (response)	Dead/ alive
T1	36	M	SF	24	PR	C	48	Ob (SD)	Alive
T1	44	M	MF	30	CR	C	51	Ob (SD)	Alive
T1	86	M	MF	30	CR	C	4	RTx (CR)	Alive
T1	76	F	SF	24	PR	D	55	RTx+CTx (CR)	Alive
T1	75	F	MF	30	CR	D	7	RTx+CTx (CR)	Alive
T2	64	F	MF	30	CR	D	43	Unknown	Unknown
T2	62	M	MF	24	PR	D	13	RTx+CTx (CR)	Alive
T2	59	M	MF	30	CR	D	67	CTx (CR)	Alive
T2	56	F	MF	30	PR	D	29	CTx (CR)	Dead (lymphoma)

M: Male; F: female; SF: superficial; MF: mass-forming; CR: complete response; PR: partial response; SD: stable disease; C: contralateral; D: distant; Ob: observation; CTx: chemotherapy; RTx: radiotherapy.

Adverse events of radiotherapy are shown in Table V. The incidence of grade 2 or more late adverse events was 35.6% for cataracts, 15.1% for dry eye, 6.8% for keratitis and 4.1% for conjunctivitis. The 26 patients with grade 2 or more cataracts consisted of one patient with lens shielding and 25 without it. The incidence of grade 2 or more cataracts with lens shielding tended to be lower than that without lens shielding [1/11 (9%) *vs*. 25/65 (38.5%), p=0.084]. In all 11 patients with grade 2 or more dry eye, lacrimal gland shielding was not performed. However, dry eye was also not significantly associated with lacrimal gland shielding (p=0.600). One patient had grade 3 glaucoma and was treated by a radiation dose of 30 Gy.

Discussion

Excellent LC and survival by radiotherapy. In the present study, the 5-year LC, PFS and OS rates were 100%, 81.5% and 100%, respectively. The median radiation dose was 30 Gy in 20 fractions (SF type: 24 Gy in 12 fractions; MF type: 30 Gy in 20 fractions). Several authors have reported that excellent LC and survival rates were achieved by a moderate dose of radiotherapy in patients with Ann Arbor stage IE POAML (16-18). Uno *et al*. reported that the CR and OS rates of 50 patients with stage IE POAML by radiotherapy were 98% and 91% at 5 years, respectively. Their median radiation dose was 36 Gy in 18 fractions

Table III. *Predictive factors for progression-free survival in patients with Ann Arbor stage (log-rank test).*

Factor	n	5-Years PFS (%)	*p*-Value
Age, years			
>60	43	83.1	0.836
<60	30	80.8	
Gender			
M	31	76.8	0.737
F	42	84.6	
PS			
0	41	81.3	0.722
1	32	81.6	
Tumor type			
Superficial	12	60	0.591
Mass-forming	61	85.3	
Radiation dose			
>30	58	85.7	0.508
<30	15	69.6	
Initial response			
CR	35	73.9	0.591
PR+SD	38	81.5	

M: Male; F: female; PS: performance status.

Table IV. *Progression-free survival by T stage in the American Joint Committee on Cancer tumor-node-metastasis clinical staging system.*

T Stage	n	5-Years PFS (%)	*p*-Value	
T1	30	62.9		
			0.686	
T2	31	85.4		0.068
			0.167	
T3	12	100		

Table V. *Late adverse events after radiotherapy for 73 patients with localized primary ocular adnexal mucosa-associated lymphoid tissue lymphoma.*

Adverse event	Grade			
	1	2	3	4
Cataract	5	2	24	0
Dry eye	11	11	0	0
Keratitis	0	5	0	0
Conjuntivitis	1	3	0	0

(range=20-46 Gy) (19). Goda *et al*. treated 89 patients with stage IE primary orbital MALT lymphoma (POML) using a dose of 25-30 Gy in 10 fractions (25 Gy in 97% and 30 Gy in 3% of patients). The total radiation dose and fraction size were different from those in other reports. The 7-year OS, cause-specific survival, relapse-free survival and LC rates were 91%, 96%, 64% and 97%, respectively. Median time to relapse was 3.3 years (16). Harada *et al*. treated 90% of 86 patients with stage I POAML using a median dose of 30 Gy in 15 fractions (range=30-46 Gy). They reported that the 10-year local relapse-free survival and OS rates were 98.7% and 93.5%, respectively (17). Ejima *et al*. reported the treatment outcome of 42 patients with stage IE POAML. Thirty-eight patients were treated by radiotherapy alone and the other four underwent chemotherapy followed by radiotherapy. The 5-year LC, PFS and OS were 100%, 77% and 97%, respectively. The median radiation dose was 30.6 Gy in 17 fractions (20). Considering the excellent LC rates reported by many authors, POAML can be considered sensitive to radiotherapy as a local treatment. Although radiotherapy can achieve an excellent outcome for Ann Arbor stage IE POAML, the reported dose delivered varies from 20 Gy to 45 Gy among institutions. The optimal radiation dose is still controversial. There have been many reports on the excellent LC and survival rates achieved by radiotherapy as a first-line therapy. Indeed, some authors have reported PFS of 70-80% and OS of 90-100% (16, 20). Our results agree with these. Taken together, these findings indicate that 20% to 30% of patients treated with radiotherapy for stage IE POAML would experience relapse. Nonetheless, the OS of patients with stage IE POAML is still quite good. In the present study, six out of nine patients with relapse achieved CR by additional treatment, and two others with relapse were observed for slow growth of relapsed tumor. Goda *et al*. reported that only 1 out of 22 patients with relapse died of disease progression despite undergoing salvage treatment, and the others were alive after salvage treatment or simple observation (16). The reason for the good OS in Ann Arbor stage IE POAML seems to be that salvage treatment consisting of additional radiotherapy or chemotherapy is effective, or that the disease progression is very slow.

Failure pattern of POAML. Frequent distant and contralateral relapses are among the most challenging complications of POAML (5, 16, 17, 20-24). In the present study, out of 9 patients with relapse (12.3%), 6 (66.7%) had distant relapse. The other 3 relapsed patients had contralateral relapse. The failure pattern of POAML was distant and contralateral ocular adnexal relapse in the present study. Goda *et al*. reported that 20 out of 22 patients with relapse disease recurred at somewhere other than the original site. Fifteen of their patients experienced distant relapses, including local and distant relapses in two and contralateral and distant relapses in two. Five patients experienced relapse at the contralateral orbit alone, and two local relapse alone. The main failure pattern was distant and contralateral relapse

(16). Ejima *et al*. reported the outcome of 46 patients with stage IE POAML after radiotherapy alone or chemotherapy following radiotherapy. Of eight relapses, four patients experienced relapse at the contralateral site and the other four at a distant site (20). The main failure pattern after radiotherapy in Ann Arbor stage IE POAML was distant and contralateral relapse. This failure pattern could be explained by the presence of microscopic disease outside the treated area at first-line therapy (11, 25).

Hashimoto *et al*. showed that in 78 patients with stage IE POAML, combined treatment with radiotherapy and chemotherapy achieved a better relapse-free survival rate than mono-treatment with radiotherapy (21). However, combined treatment with radiotherapy and chemotherapy should not necessarily be used as a first-line therapy for localized POAML in order to control distant and contralateral relapse. This approach might constitute an over-treatment for patients without local or distant recurrence. In general, almost 70% of patients with stage IE POAML who were treated by radiotherapy experience no relapse. For these patients, the addition of chemotherapy to the first-line treatment may be overtreatment. For patients with local or contralateral relapse, the relapsed lesion can be controlled by local treatment including additional radiotherapy. For these reasons, combined treatment with radiotherapy and chemotherapy may not be appropriate as a first-line treatment for stage IE POAML.

AJCC TNM staging system and PFS. The AJCC TNM clinical staging system was not predictive for PFS in patients with Ann Arbor stage IE POAML in this study. The AJCC TNM clinical staging system defines disease extent more precisely within the anatomic compartment of the ocular adnexa than the Ann Arbor staging system (12). Several authors have suggested that tumor location is associated with relapse. Nam *et al*. suggested that primary lacrimal involvement may be related to future relapse more frequently than involvement at other subsites (26). Goda *et al*. suggested that the disease sub-site was an important prognostic factor associated with relapse rate, and that eventually the cumulative relapse rate at distant sites was higher in patients with lacrimal and soft-tissue disease than in those with conjunctival disease (16). Martinet *et al*. reported outcome and prognostic factors in orbital lymphoma. Their findings were similar to ours. In their study, conjunctival location was one of the favorable factors (9). On the other hand, Woo *et al*. concluded that in their study the recurrence rate of lymphoma in conjunctiva was significantly high (3).

Bayraktar *et al*. analyzed the impact of the initial presentation and staging outcome for POAML. In their study, the AJCC T-factor among 77 patients with Ann Arbor stage I was not effective for predicting the rate of freedom from progression. Treatment included radiotherapy, chemotherapy and surgery (27). Aronow *et al*. evaluated the usefulness of a TNM staging system in ocular adnexal lymphoma. Their study included 63 patients with not only primary ocular adnexal lesion but also nodal or distant metastasis. As in our present study, they found that the T-factor was not associated with relapse. However, they suggested that patients with N1-4 had marginally worse survival than those with N0, and the M1 patients had worse survival than the M0 patients (11). Graue *et al*. also concluded that the AJCC TNM clinical staging system is effective for patients with nodal positive and advanced stage disease (10).

In the present study, 73 patients with Ann Arbor stage IE POAML treated by radiotherapy alone were analyzed. To our knowledge, there have been no reports on the association between the AJCC TNM clinical staging system and PFS in a relatively large cohort of patients with Ann Arbor stage IE POAML treated by radiotherapy alone. We found the T-factor classification of the AJCC TNM clinical staging system was not a predictor for PFS. Because advanced cases such as T3 or T4 were small in number, this classification might not be effective for the prognostic prediction of localized ocular adnexal MALT lymphoma. In favorable prognostic POAML, the survival outcome in patients with T1, T2 and T3 stage disease could be significantly affected by only a slight difference in the number of patients with relapse. The ongoing accumulation of additional patients in future studies will be needed to precisely evaluate the utility of the AJCC TNM clinical staging system for the prediction of localized POAML.

Late adverse events. Cataract and dry eye are common late adverse events in radiotherapy for stage IE POAML (28). In the present study, the incidence of grade 2 or more late adverse events were 35.6% for cataract, 15.1% for dry eye, 6.8% for keratitis and 4.1% for conjunctivitis. One patient had grade 3 glaucoma. Cataract and dry eye were common late adverse events.

Harada *et al*. reported that cataract developed in 36 out of 65 patients treated without lens shielding and in 12 out of 39 patients with lens shielding. They concluded that lens shielding reduced the risk of cataract (17). Goda *et al*. reported that 20 out of 89 patients with stage IE POAML experienced grade 3 radiation-related cataract. However, in their study, the 7-year rate of radiation-related grade 3 cataract with lens shielding (15%) was lower than that without lens shielding (41%) (16). Son *et al*. reported that two (4.3%) out of 46 patients experienced radiation-related grade 3 cataract at 26 and 37 months after radiotherapy with a total dose of 36 Gy, and one of these patients was treated without lens shielding (18). Uno *et al*. reported that only two out of 50 patients experienced radiation-related grade 3 cataract without lens shielding, but none of 11 patients with

lens shielding experienced grade 3 cataract (19). In the present study, although the difference was not statistically significant, the incidence of grade 2 or more cataract in patients with lens shielding was lower than that in patients without lens shielding. Lens shielding thus seemed to be effective at preventing radiation-related cataract. The incidence of grade 2 or more dry eye was reported to be 4% to 17% (16, 18, 21). Our results were similar to these. There was no significant association between dry eye and lacrimal gland shielding. It might be that only a few patients received lacrimal gland shielding. Because lens or lacrimal gland shielding should be placed avoiding tumor extent, it is difficult to choose patients who are suitable for lens or lacrimal gland shielding.

Conclusion

Radiotherapy achieved excellent LC and good survival rates in patients with Ann Arbor stage IE POAML. The main failure pattern of this disease after radiotherapy was distant and contralateral relapse. The AJCC TNM clinical staging system for Ann Arbor stage IE POAML was not prognostic for PFS. Lens shielding appeared to be effective for preventing radiation-related cataract, and should be used whenever possible.

Conflicts of interest

The Authors have no conflicts of interest to report with regard to this study.

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