

## Long-term follow-up results of no initial therapy for ocular adnexal MALT lymphoma

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**Background:** The majority of lymphomas in the ocular adnexa are low-grade B-cell lymphomas of mucosa-associated lymphoid tissue (MALT lymphoma). Although radiotherapy is the most frequently applied management, cataract and dry eye are problematic complications.

**Patients and methods:** Between 1973 and 2003, the clinical features of 36 patients with ocular adnexal MALT lymphoma with no symptoms who were managed with no initial therapy after biopsy or surgical resection were retrospectively analyzed.

**Results:** The median patient age was 63 years (range 22–84) and all patients had stage I disease, consisting of 31 unilateral cases and five bilateral cases. With a median follow-up of 7.1 years, 25 (69%) did not require treatment. The median time until the initiation of treatment in the remaining 11 patients (31%) was 4.8 years. Six patients (17%) died, and among them only two (6%) died due to progressive lymphoma. Seventeen patients (47%) progressed, but histologic transformation was recognized in only one (3%). The estimated overall survival rates of the 36 patients after 5, 10 and 15 years were 94%, 94% and 71%, respectively.

**Conclusions:** In selected patients with ocular adnexal MALT lymphoma, no initial therapy might be an acceptable approach, because 70% of patients remained untreated at a median of 8.6 years, and their survival was comparable to that of reports on immediate therapy.

**Key words:** MALT lymphoma, ocular adnexa, no initial therapy, prognosis

### introduction

An extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), first described in 1983 by Isaacson and Wright, was recognized in 1994 as a distinct entity of low-grade B-cell lymphoma in the revised European–American lymphoma (REAL) classification among marginal zone B-cell lymphomas, as well as in the most recent classification of the World Health Organization (WHO) [1–3]. Generally, the majority of MALT lymphomas have an indolent natural history and two-thirds of patients with MALT lymphoma have localized disease [4, 5]. For localized MALT lymphoma, radiotherapy is the most frequently applied management, and most patients show good response to radiotherapy, although several recent reports suggest that radiotherapy alone may not provide for a superior outcome [6–10].

For the management of lymphomas in the ocular adnexa, especially for localized disease, radiotherapy is a safe and effective form of local treatment [11–16]. Histology according to the

REAL or WHO classification can be used to accurately predict the prognosis of lymphomas in the ocular adnexa, and the MALT type has a more favorable prognosis than do malignant lymphomas of differing histology [17–20]. Although there have been few analyses of large numbers of MALT lymphomas in the ocular adnexa, its prognosis is thought to be better.

In general, low-grade lymphoma spontaneously regresses on several occasions. Conservative management by deferring treatment until disease progression is an acceptable option for selected patients with follicular lymphoma [21, 22]. This watch-and-wait strategy was initially applied to advanced-stage patients, but a recent retrospective study from Stanford University suggested that this conservative approach is applicable to selected patients with Stage I or II follicular lymphoma [23]. For the radiotherapy of ocular adnexal lymphoma, cataract and dry eye are problematic complications in some patients. From these points, it is controversial whether all patients with MALT lymphoma in the ocular adnexa should be treated with radiotherapy. There is only one report on a small number of patients according to the watch-and-wait approach for conjunctival MALT lymphoma [24]. Therefore, we conducted a retrospective analysis of

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36 patients with early stage disease for whom therapy was deferred after diagnosis at the National Cancer Center Hospital. The objective of this study was to analyze the outcome of the watchful waiting strategy after the diagnosis of early stage MALT lymphoma in the ocular adnexa in view of overall survival, time to treatment, the incidence of and outcome after disease progression, and cause of death.

## patients and methods

### patient selection

From 1973 to 2003, 36 patients who were diagnosed with primary MALT lymphoma in the ocular adnexa by biopsy or surgical resection were retrospectively analyzed. The criteria used for selection included patients who were diagnosed or reviewed with MALT lymphoma in the ocular adnexa and were managed with no initial therapy after diagnosis and a minimum follow-up of 6 months at the National Cancer Center Hospital, Tokyo, Japan.

The histopathologic diagnosis of MALT lymphoma was established by biopsy or surgical resection of the primary lesion. For all patients, the diagnosis was reviewed according to the REAL or WHO classification by two hematopathologists (Y.M. and A.M.).

### clinical features

For patients with a confirmed diagnosis of MALT lymphoma in the ocular adnexa, several sets of clinical data were analyzed based on their medical charts. Sex, age, clinical stages, involved sites, performance status (PS) according to the Eastern Cooperative Oncology Group scale, serum lactate dehydrogenase (LDH) at initial presentation and the degree of surgical resection were analyzed. The anatomically involved sites were determined using the classification of Knowles et al. [25] as previously reported. Physical examinations were performed on all patients. Chest X-ray, computed tomography of the head/eye, neck, chest, abdomen and pelvis, gallium scintigraphy, bone marrow aspiration and peripheral blood examinations were also carried out. The clinical stages were determined according to the Ann Arbor staging classifications.

### prognostic factor analysis

All eligible patients were exclusively followed-up at the National Cancer Center Hospital. If patients were lost during follow-up for more than 1 year, we personally contacted them via telephone for information regarding survival, progression and treatment after obtaining their informed consent. Survival was censored at the time of their last documented follow-up date. Overall survival, time to treatment and time to progression or recurrence were calculated from the diagnosis using the Kaplan–Meier method. We evaluated sex, age (<60 versus ≥60), involved site (orbit versus other sites), laterality (unilateral versus bilateral) and the degree of resection (complete resection versus partial resection or biopsy) using the log rank test. The statistical analysis was performed using SPSS for Windows version 11.0 (SPSS Inc, Chicago, IL).

## results

### patients' characteristics

From 1973 to 2003, 36 patients who had no symptoms or complaints were diagnosed with primary MALT lymphoma in the ocular adnexa and were managed with no initial therapy after biopsy or surgical resection. Their median time to treatment was 7.1 years, range 0.7–16.7 years. Two cases were identified between 1973 and 1982, 14 between 1983 and 1992,

and 20 between 1993 and 2003. The characteristics of the patients are shown in Table 1. Their median age was 62.5 years with a range of 22–84 years, and they consisted of 16 female and 20 male patients. Twenty-one patients (58%) were 60 years of age or older. The most frequently involved site was the orbit at 53%. In 31 patients (86%), their diseases were localized in the unilateral ocular region, whereas five patients (14%) had disease in the bilateral regions. All patients had stage I disease. The number of unfavorable factors according to the international prognostic index (IPI) was one in 19 of 21 patients 60 years or older, and 0 in 15 of 15 patients younger than 60 years, which were consistent with their low risk features.

### reasons for no initial therapy

The reasons for giving no initial therapy varied among the patients as shown in Table 2. Seven patients (19%) underwent no initial treatment based on patient preference. These patients had no symptoms such as diplopia, ptosis and swelling. When informed of the therapeutic options, they selected no initial therapy and close follow-up. Twenty-eight patients (78%) had no initial therapy based on physicians' suggestions. The reasons why the physicians recommended no initial therapy varied, including histopathologic diagnoses of low-grade lymphoma, complete surgical resection, and histopathologic diagnoses as benign process or borderline disease such as pseudolymphoma. One patient had no initial therapy because of advanced age.

### patient outcome

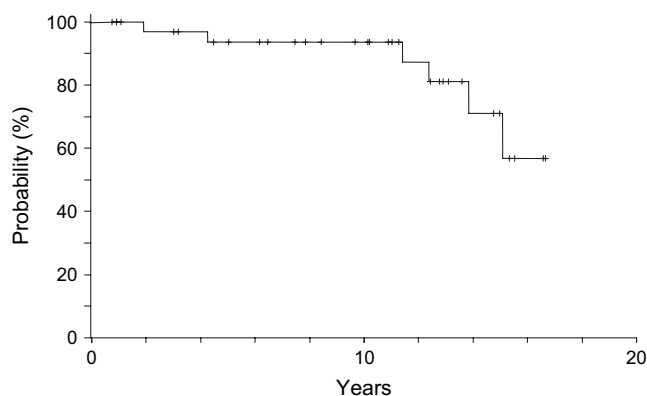
With a median follow-up of 10.5 years (range 0.7–16.7 years), the estimated median survival was not reached. The proportions of patients who remained alive after 5, 10 and 15 years were 94, 94 and 71%, respectively (Figure 1). There were no differences

**Table 1.** Patients' characteristics

	No. of patients ( <i>n</i> = 36)
Sex	
Male	20
Female	16
Age (years)	
Median	62.5
Range	22–84
Involved sites	
Conjunctiva	15
Orbit	19
Lacrimal gland	2
Laterality	
Right	15
Left	16
Bilateral	5
Stage I	36
LDH > normal	2
Degree of resection	
Complete resection	9
Partial resection	24
Biopsy	3

**Table 2.** Reasons for no initial therapy

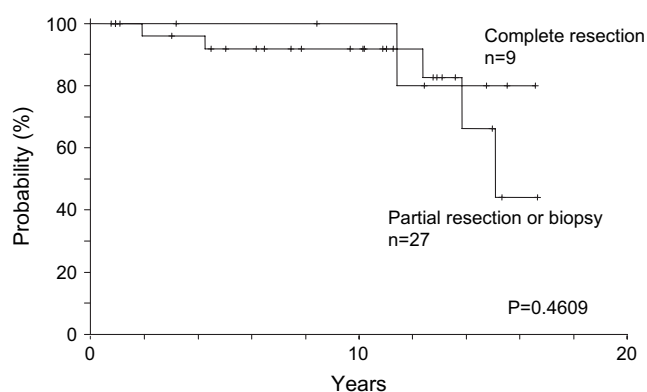
	No. of patients (n = 36)
Patient preference	7 (19%)
Physician preference	28 (78%)
Advanced age	1 (3%)

**Figure 1.** The estimated overall survival of 36 patients with ocular adnexal MALT lymphoma who were managed with no initial therapy. After 5, 10 and 15 years, the probability of overall survival was 94%, 94% and 71% respectively.

in overall survival according to age (<60 years versus  $\geq 60$  years), the involved sites and the degree of resection (Figure 2). Six patients died and only two deaths occurred because of progression of their lymphomas. One death was due to heart failure, two were due to pancreatic cancer, and the remaining was due to lung cancer.

Seventeen patients suffered from clinical recurrence or progression. Univariate analysis of patient characteristics and other variables affecting progression and the necessity of subsequent therapy are shown in Table 3. There were no clinical factors that influenced the progression and necessity of subsequent therapy. Only two patients progressed to systemic disease, while 15 showed recurrence or progression as local disease. In six of these 15 patients with local recurrence, further observation without any treatment was selected because of no manifestations of severe clinical symptoms. Only one patient was diagnosed with transformation to a higher-grade lymphoma.

As shown in Figure 3, 25 patients (69%) have not been treated for their diseases to date. At a median follow-up of 7.1 years, more than half have not received treatment for significant disease progression or transformation. The proportions of patients estimated to have not undergone treatment after 5, 10 and 15 years were 80, 63 and 57%, respectively. There were no differences in freedom from requiring treatment according to age (<60 years versus  $\geq 60$  years), the involved sites and the degree of resection (Figure 4). Eleven patients (31%) received treatment after recurrence or progression with a median time to treatment of 4.8 years (range 1.0–10.9 years). Nine patients received radiotherapy alone, one received combination radiation therapy and chemotherapy, and one underwent

**Figure 2.** Overall survival according to the degree of resection on initial diagnosis.**Table 3.** Univariate analysis of factors affecting progression and necessity of subsequent therapy

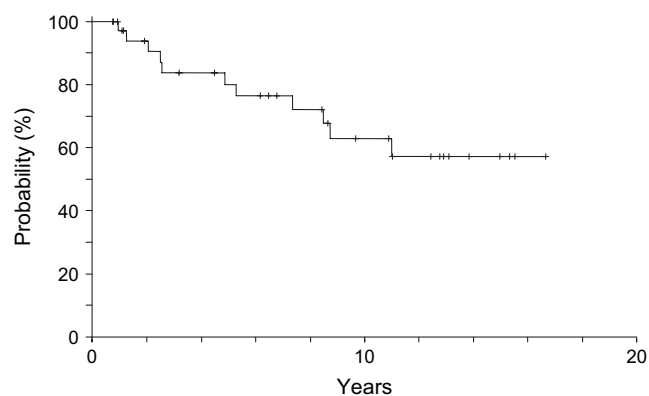
Characteristics	Probability (%)			
	5-year progression	P value	5-year subsequent therapy	P value
<b>Sex</b>				
Male	17.4	0.168	17.4	0.397
Female	39.1		14.9	
<b>Age (years)</b>				
<60	30.0	0.938	22.2	0.736
$\geq 60$	23.3		11.5	
<b>Involved sites</b>				
Conjunctiva/lacrimal gland	28.6	0.713	13.5	0.635
Orbit	31.0		18.4	
<b>Laterality</b>				
Unilateral	26.8	0.642	15.0	0.580
Bilateral	25.0		25.0	
<b>Degree of resection</b>				
Complete resection	28.6	0.224	0	0.787
Partial resection/biopsy	25.5		16.0	

complete surgical resection. These therapies were effective except for one patient who had progressed to systemic disease.

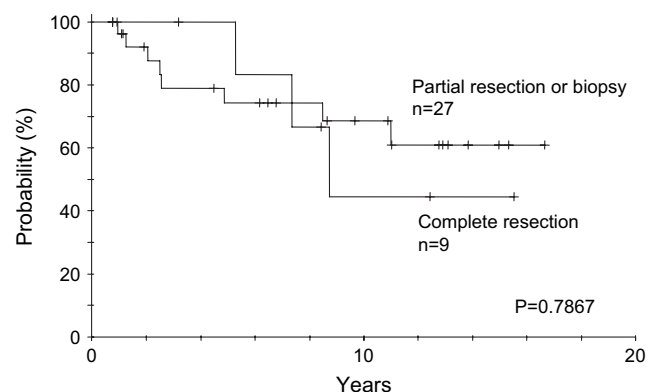
As initial therapy, we included nine patients who received complete surgical resection alone in the no initial therapy cohort, because it is not standard management for localized lymphoma, although conclusive evidence is lacking in indolent lymphoma, especially in MALT lymphoma. On the other hand, as salvage therapy after recurrence or progression, we categorized one patient who received complete surgical resection as the one who required treatment to avoid possible bias leading to our conclusion supporting no initial therapy.

## discussion

No initial therapy, often referred to as a watch-and-wait strategy, is recommended as an acceptable treatment option for patients with advanced-stage, low grade B-cell lymphoma,



**Figure 3.** Freedom from requiring treatment. After 5, 10 and 15 years, freedom from requiring treatment was 80%, 63% and 57%, respectively.



**Figure 4.** Freedom from requiring treatment according to the degree of resection on initial diagnosis.

especially for those with follicular lymphomas [21, 22]. However, the validity of the watch-and-wait strategy has not been evaluated using a large number of patients with MALT lymphoma. To assess the validity of this approach, we retrospectively analyzed our institutional records for the past 30 years. With a median follow-up of 10.5 years, the estimated overall survival rates after 5, 10 and 15 years were 94, 94 and 71%, respectively. Only 11 patients (31%) required treatment during the follow-up period, with 10 for local recurrence or progression and only one for distant disease. These results suggest that no initial therapy for MALT lymphoma may warrant evaluation.

In our series, six patients died and only two deaths occurred because of progressive disease; one died due to heart failure and two pancreatic cancer, and one died because of lung cancer. The cause of death was not limited to the progression of MALT lymphoma. It has been suggested that even if the start of therapy for MALT lymphoma in the ocular adnexa is delayed, the prognosis might not be worse in selected patients.

No prospective trials have compared immediate radiation or chemotherapy with no initial therapy for patients with MALT lymphoma in the ocular adnexa. To our knowledge, this report is the first to analyze deferred therapy for a large number of patients with stage I MALT lymphoma in the ocular adnexa. Matsuo and Yoshino [24] reported on the follow-up results

of observation or radiation for 13 patients with conjunctival malignant lymphomas. At a mean follow-up of 5.4 years, seven of eight patients under observation experienced spontaneous regression. Their conclusions were similar to ours where no initial therapy might be an acceptable therapeutic option. However, the patient population that was studied in their report was distinct from ours, because the initial site was limited to the conjunctiva in their study. In our analysis, the lymphomatous lesions were not limited to the conjunctiva, and there was no difference in patient outcome according to the initial site. In addition, the degree of surgical resection did not influence patient outcome as shown in Figures 2 and 4. These results suggest that no initial therapy is applicable to selected patients with ocular adnexal MALT lymphoma regardless of the degree of surgical resection.

Table 4 shows a comparison of the overall survival of patients with ocular adnexal lymphoma treated with immediate radiotherapy at several institutions and those of the present study who were managed with no initial therapy. Two previous reports focused on radiation for patients with MALT lymphoma [13, 16]. Table 4 reveals that the estimated overall survival rates in our series were not inferior to those of patients treated with immediate radiotherapy reported by other institutions, although the patient selection criteria might have differed among these studies.

Primary radiotherapy for localized MALT lymphoma in the ocular adnexa offers excellent local control with a prolonged clinical course [11–16]. However, recurrent disease can occur at local initial and distant sites. Uno et al. [16] described that responses to radiotherapy included a complete response in 26 of 50 patients, a partial response in 20 patients and no change in four patients. None of the patients who achieved a complete response experienced local recurrence, and five of the 20 who achieved a partial response exhibited recurrent disease 4–97 months after radiotherapy. Le et al. [13] indicated that local control by radiotherapy is 100% effective and that most of the failures arise in extranodal sites. In our series, there were 17 of 36 (47%) patients with clinical recurrence or progression. Among them, only two progressed to systemic disease, whereas 15 remained with local disease. In six of the 15 patients with local recurrence, further observation was selected because of the lack of manifestations of severe clinical symptoms. Only one patient showed histologic transformation to a higher-grade lymphoma. Although primary radiotherapy for localized MALT lymphoma in the ocular adnexa offers better local control than does no initial therapy, recurrence could have taken place in the immediate local radiotherapy group and no initial therapy group. There were few transformations to aggressive lymphoma in both groups, and there was probably no difference in the overall survival between these two therapeutic strategies as shown in Table 4. Considering these findings, no initial therapy may be an acceptable option in a fraction of patients with ocular adnexal MALT lymphoma.

In the present study, 25 of 36 patients (69%) have not been treated for their disease to date. At a median follow-up of 7.1 years, more than half of the patients had not received treatment for significant disease progression or transformation. This is notable because quality of life is an important issue for patients who wish to avoid early and late therapy-related complications.

**Table 4.** Overall survival in ocular adnexal lymphoma: comparison with other studies by immediate radiotherapy

Author	No. of patients	Histology	Stage	Median age (years)	5-year, 10-year survival (%)
Uno et al.	50	MALT	I	61	91, 76
Le et al.	31	MALT	I	54	100, 73
Bhatia et al.	47	Low/intermediate	I	69	74, NA
Martinet et al.	90	Low/intermediate/high	I–II	63.5	78, 70
Stafford et al.	48	Low/intermediate	I–IV	68	69, 40
Present study	36	MALT	I	62.5	94, 94

Recently, Conconi et al. [26] revealed that rituximab has clinical activity against MALT lymphomas. Also, Ferreri et al. reported that *Chlamydia psittaci*-eradicating antibiotics therapy resulted in an objective response in ocular adnexal MALT lymphoma [27, 28]. These therapeutic strategies would yield not only an effective response but also less therapy-related complications. It is clear that most MALT lymphomas in the ocular adnexa are indolent diseases. We believe that no initial therapy, rituximab and antibiotic therapy may be acceptable options for ocular adnexal MALT lymphoma.

More than half of the patients in our series have not yet been treated. These patients clearly benefited from a conservative management approach, although a minority of the patients showed a less favorable disease course. Clinical studies on no initial therapy for localized ocular adnexal MALT lymphoma are limited, and the reasons why most of the patients did not progress for a long period are unclear. Table 3 shows that no clinical factors influenced the time to progression and the necessity of subsequent therapy. Recently, cytogenetic studies have revealed that patients with MALT lymphoma have multiple karyotypic abnormalities,  $t(14;18)$  or  $t(11;18)$  translocation at diagnosis, and that these karyotypic abnormalities are useful for predicting the response to therapy and their prognosis [6, 29, 30]. There are no reports of cytogenetic or molecular genetic studies in relation to the prognosis of patients with ocular adnexal MALT lymphoma. If prediction of the clinical outcome of each patient is possible, more suitable therapeutic decisions including no initial therapy for each patient may be applicable.

In conclusion, survival in selected patients with localized MALT lymphoma in the ocular adnexa does not appear to be worse when no initial therapy is substituted for local radiotherapy. With the prediction of long median survival, quality of life is an important issue for patients who wish to avoid early and late therapy-related complications. Extended follow-up will be required to assess the impact of no initial therapy on overall survival and freedom from requiring treatment. Although the most frequently applied management of localized MALT lymphoma in the ocular adnexa is radiotherapy, we believe that no initial therapy is an acceptable option for selected patients.

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