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ORIGINAL ARTICLE

Treatment-associated outcomes of patients with primary ocular adnexal MALT lymphoma after accurate diagnosis

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Abstract

Background Differentiation between primary ocular adnexal mucosa-associated lymphoid tissue (POA-MALT) lymphoma and reactive lymphoid hyperplasias sometimes may be difficult. We have examined the treatment-associated mortality of POA-MALT lymphoma after confirmed diagnosis and evaluated their proper treatments.

Patients and methods From 1991 through 2016, cases of POA-MALT lymphoma were retrospectively analyzed based on their pathological and molecular/immunological diagnoses.

Results A total of 78 cases with POA-MALT lymphoma with a median age of 66 years were analyzed over median/mean observations of 6.4/7.1 years. Forty-four patients (56%) were diagnosed with IgH gene clonality and 10 patients (13%) were diagnosed with flow cytometric analysis in addition to the pathological decision. The rest (24 patients, 31%) were diagnosed employing pathological decisions of hemato-pathologists and clinical decisions. All patients, except cases of watchful waiting, achieved complete remission. After initial treatment, 68 patients (87%) presented disease-free during the observation period. As treatment, a radiotherapy-based strategy was followed with 15 patients (19%, group A). Immuno-chemotherapy was administered to 24 patients (31%, B). Surgical extraction only was selected for 36 patients (46%, C). Watchful waiting was selected with three patients (4%). Recurrence after the initial treatment was found in one patient (7%) out of A, in three patients (13%) out of B, and in six patients (17%) out of C, respectively. Progression-free survivals at 5 and 10 years were 100 and 100% in A, 95 and 75% in B, and 88 and 81% in C, respectively. The recurrence rates between the patients who were diagnosed with only pathological decision ($n=24$) and the patients who were diagnosed with molecular and immunological procedures ($n=54$) did not show any statistical differences.

Conclusion Our results indicate that radiotherapy-based treatment strategies for patients with POA-MALT lymphoma show a low rate of recurrence and may improve their prognosis even after the accurate diagnosis. However, contamination of the cases with reactive (polyclonal) lymphoid hyperplasia into those with MALT lymphoma should be carefully removed to avoid unnecessary treatment for malignancies that do not exist.

Keywords Monoclonality · Non-Hodgkin lymphoma · POA-MALT lymphoma · Radiotherapy · Treatment-associated mortality

Introduction

Mucosa-associated lymphoid tissue (MALT) lymphoma is categorized into indolent B cell lymphoma, which occurs in extra-nodal sites affected by a long-standing inflammatory condition, such as allergies, auto-immune responses, or infections. For instance, gastric MALT lymphoma is strongly associated with infection with *Helicobacter pylori* (*H. pylori*), immune-proliferative small intestinal disease (IPSID; known as alpha chain disease [1]. In addition, MALT lymphoma in the bowel wall is associated with

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infection with *Campylobacter jejuni*, and MALT lymphoma in the salivary and thyroid glands after antigenic stimulation may be a component of auto-immune disease, such as Sjögren syndrome and Hashimoto thyroiditis [2–4].

MALT lymphoma also develops in the ocular adnexa, which consist of conjunctiva, the adjoining orbit, and the lachrymal gland. This primary ocular adnexal (POA) MALT is the third common type of MALT lymphoma, and discrimination of this disease from reactive lymphoid hyperplasia (pseudo-lymphoma) is always controversial. In 2004, an Italian group evaluated a set of MALT lymphomas in the ocular adnexa for infection with *Chlamydophila psittaci* (*C. psittaci*) using the PCR-based technique [5]. However, some groups including ours have reported a negative correlation between POA-MALT lymphoma and *C. psittaci* infection [6]. Moreover, in contrast with localized treatment (radiotherapy or surgical resection) for MALT lymphoma as an initial treatment, it is surprising that the patients with POA-MALT lymphoma who were managed with no initial therapy after biopsy or surgical resection had 94% overall survival at 5 years [7, 8]. Taking together the above observations and recent studies, reactive (polyclonal) lymphoid hyperplasia arising from various inflammations and infections may be included in the diagnosis of POA-MALT lymphoma at a certain rate as misdiagnoses, because clear immune-phenotypic and cytogenetic markers for the diagnosis of POA-MALT lymphoma have not been identified so far [9]. Accurate monoclonal diagnosis using IgH gene clonality with Southern blot or PCR amplification, and/or analysis of clonal cell surface antigens, would be necessary to discuss causative agents and proper treatments regarding the patients with POA-MALT lymphoma.

In this study, we have retrospectively accumulated cases of POA-MALT lymphoma, examined treatment-associated mortality, and discussed the diagnosis-associated treatment of this indolent B cell malignancy.

Materials and methods

Patients with POA-MALT lymphoma

Newly diagnosed patients with POA-MALT (primary disease sites; orbita, lacrimal gland and sac, conjunctiva, and eyelids) lymphoma had been retrospectively collected between June 1996 and June 2016 at Ehime University Hospital, Matsuyama Red Cross Hospital, Nagasaki University Hospital, Oita Prefectural Hospital, and Tokushima Prefectural Central Hospital (all hospitals are located in Shikoku or Kyushu, in the southern area of Japan). All cases were diagnosed by hemato-pathologists. When the tumor samples after surgical resection were large enough for additional procedures to confirm the accurate diagnosis of POA-MALT lymphoma, IgH gene clonality analysis with Southern blot or PCR analysis, and/or flow cytometric analysis of cell surface antigen density (FACS) were employed in some cases. In addition, clinical and laboratory data were collected from their medical records.

Pathological diagnosis, IgH gene clonality, and FACS

All patients were diagnosed by hemato-pathologists in each institute or reviewed by hemato-pathologists in other institutes based on their hematoxylin–eosin (HE) staining and immuno-histochemical analysis after the tumor biopsy. Regarding pathological decision, we have defined the following criteria for microscopic diagnosis. First, infiltrated tumor lymphocytes under the HE staining show small lymphocytes exhibiting plasmacytic and/or monocytoid differentiation. Second, the epithelium (glandular tissue) is invaded by infiltrated tumor lymphocytes resulting in the so-called lymphoepithelial lesion. Third, infiltrated tumor lymphocytes under immuno-histochemical staining show positive expressions of CD20 and CD79a, negative expressions of CD3, CD5, CD10, and cyclinD1, and negative expression of bcl-2 in the germinal center when the tumor shows reactive follicles. Based on above diagnostic criteria and clinical information, final diagnoses were decided after discussions among hemato-pathologists and clinicians. In addition, cryo-preserved primary tumor specimens obtained from patients at the time of tumor biopsy were analyzed with IgH gene clonality analysis (Doc S1) and/or FACS (Doc S2) to confirm their diagnoses.

Treatments

Treatments for patients with POA-MALT lymphoma were performed based on the decision of each physician after informed consent. Regarding radiotherapy, over 30 Gy (1.5 Gy × 20 or 2.0 Gy × 15 fractions) of radiation was administered. Regarding immuno-chemotherapy, eight cycles of R mono-therapy (375 mg/m^2), 4–6 cycles of R-CHOP (rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 (maximum 2 mg/body), day 1, and prednisolone 100 mg/body, days 1–5), and 4–6 cycles of R-CHOP-like regimen including R-CVP (rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2 (maximum 2 mg/body), day 1, and prednisolone 100 mg/body, days 1–5) were selected. No cases were treated with an R-bendamustine regimen, because the regimen including bendamustine as the first-line treatment had not been permitted before 2016 by Japanese health insurance programs. Clinical observation without any other treatment was selected after complete surgical extraction (operative therapy) at the time of tumor biopsy. In addition, 'watchful waiting' strategies were selected with some

patients based on their physician's choice after informed consent.

Statistical analysis

Survival time or progression-free time was defined as the interval between the date of enrolment in any treatment, including watchful waiting, and the date of the last follow-up (March 2016), death, or disease progression. Statistical analyses were performed using the SAS software package version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethics of study

This study was approved by the Ethics Committee for Clinical Studies at Ehime University Graduate School of Medicine (study #1604005).

Results

Diagnosis of POA-MALT lymphoma

After the removal of cases with insufficient data ($n=5$), a total of seventy-eight cases (34 females and 44 males, median age 66 years; range 21–87 years) with POA-MALT lymphoma was collected from Ehime University Hospital ($n=19$), Matsuyama Red Cross Hospital ($n=36$), Nagasaki University Hospital ($n=16$), Oita Prefectural Hospital ($n=6$), and Tokushima Prefectural Central Hospital ($n=1$). Patient characteristics in the current study are indicated in Table 1 Out of seventy-eight cases, 44 patients (56%) were diagnosed with IgH rearrangement and pathological decision, and 10 (13%) patients were diagnosed with FACS analysis and pathological decision. These total 54 cases were diagnosed with additional molecular/immunological studies. The rest of the 24 patients (31%) were diagnosed employing pathological decision and clinical observations (Fig. 1).

Treatment-associated outcomes of POA-MALT lymphoma

As an initial treatment, radiotherapy-based strategies (over 30 Gy) were adopted with 15 patients (19%, treatment group A). Immuno-chemotherapy (R, R-CHOP, or R-CHOP-like) was administered to 24 patients (31%, treatment group B). Surgical extraction alone was selected for 36 patients (46%, treatment group C). Watchful waiting was selected with three patients (4%, treatment group D) (Table 1). All patients except those where watchful waiting was employed ($n=75$) achieved complete remission after their initial treatments. Two patients died after the recurrence of disease (one; recurrence of original lymphoma, another; metastatic unknown lung tumor). A total of 65 patients (87%) presented disease-free during observation after their treatments (Fig. 2). Recurrence after the initial treatment was found in one patient (7%) out of group A (radiotherapy), in three patients (13%) out of group B (immune-chemotherapy), and in six patients (17%) (including two patients experiencing mortality) out of group C (operative therapy), respectively. Their progression-free survival at 5 years and 10 years was 100% and 100% in group A (radiotherapy), 95% and 75% in B (immune-chemotherapy), and 88% and 81% in C (operative therapy), respectively (Fig. 3).

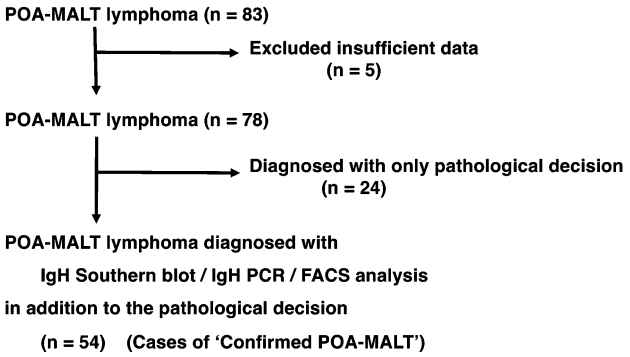

Fig. 1 Flow diagram of diagnostic procedures for patients with POA-MALT lymphomas ($n=83$)

Accurate diagnosis and treatment-associated outcomes involving POA-MALT lymphoma

We examined another treatment-base data analysis using cases of POA-MALT lymphoma which were diagnosed with molecular and/or immunological methods such as IgH gene clonality (Southern blot or PCR analysis) and/or FACS analysis in addition to pathological decision. We designated these cases as 'Confirmed POA-MALT' (Fig. 1). These were estimated to total 54 cases, and their patient characteristics based on treatment strategies are indicated in Table 2. Their progression-free survival at 5 years and 10 years were 100% and 100% in group A (radiotherapy), 93% and 67% in B (immune-chemotherapy), and 92% and 82% in C (operative therapy), respectively (Fig. 4). The recurrence rate between the patients who were diagnosed with only pathological decision ($n=24$) and the patients who were diagnosed with molecular and immunological procedures ($n=54$) did not differ (12.5% versus 13.0%) and they showed lower incidents, suggesting that our current study strictly selected patients with POA-MALT lymphoma even in both groups.

A total of seven patients experienced recurrence after their treatment. Four patients who had relapsed after their operation were treated with immune-chemotherapy, and two patients died. Two out of three patients who had relapsed after their immune-chemotherapy were treated with

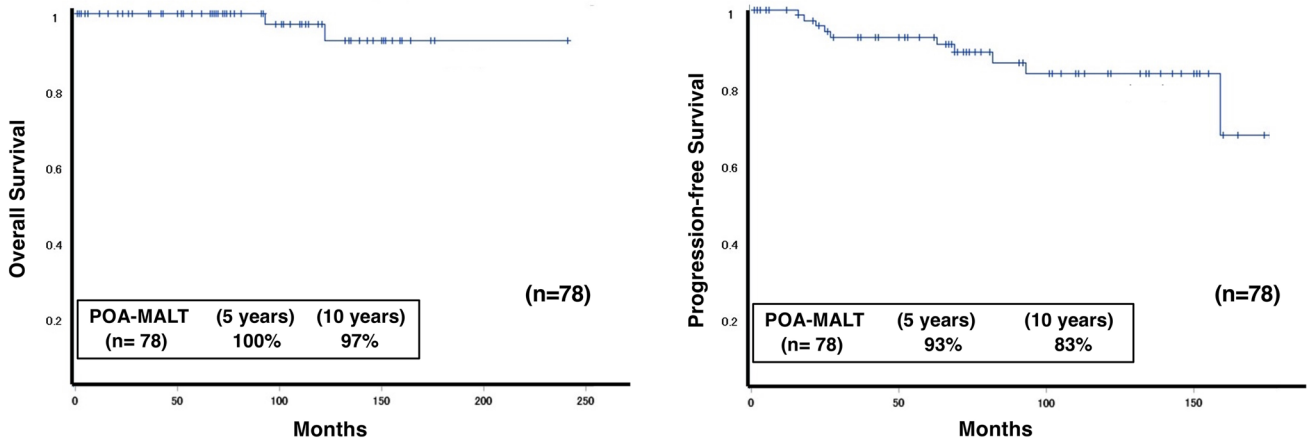

Fig. 2 Overall and progression-free survival of POA-MALT lymphoma patients ($n=78$)

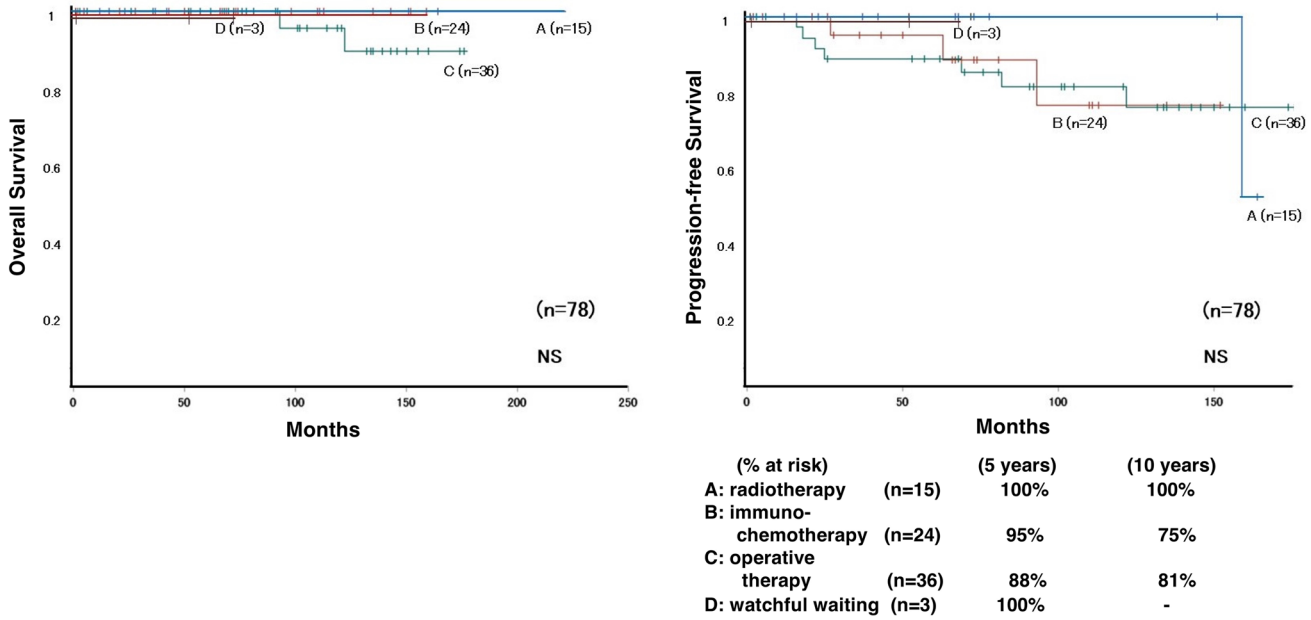

Fig. 3 Overall and progression-free survival of POA-MALT lymphoma patients based on treatment strategies ($n=78$). **a** Radiotherapy, **b** immune-chemotherapy, **c** operative therapy, **d** watchful waiting. *NS* not significant

R-bendamustine (RB) chemotherapy. They still have stayed in complete remission. Another patient had his tumor on the conjunctiva removed during an operation, because he did not accept chemotherapy. However, he is still in a disease-free status. The outcomes (overall and progression-free survival) of the patients who were diagnosed using only pathological decision for both groups, were somewhat better than those who were diagnosed with molecular and immunological procedures based on the Kaplan–Meier analysis, however, there were no statistical differences (Fig. 5).

Based on these observations (Figs. 3 and 4), a radiotherapy-based strategy for patients with POA-MALT lymphoma showed a low rate of recurrence overall, and it should be a promising strategy as an initial treatment for this type of indolent lymphoma.

Discussion

MALT lymphoma is the third most common NHL, and it develops in extra-nodal sites such as the GI tract, pharynx, salivary glands, lungs, and thyroid (The Non-Hodgkin's Lymphoma Classification Project, 1997) [10]. In this NHL, gastric MALT lymphoma is the most common and well characterized. Recent papers have reported that about 40–60% of cases of lymphoid tumors involving the ocular

Table 1 Lesions of the ocular adnexa-MALT lymphoma (n=78)

	(A) Radiotherapy		(B) Immuno-chemo-therapy		(C) Operative therapy		(D) Watchful waiting		All cases	
	(n=15)	(%)	(n=24)	(%)	(n=36)	(%)	(n=3)	(%)	(n=78)	(%)
Age (median)	64 y.o.		72 y.o.		59 y.o.		78 y.o.		66 y.o.	
Follow-up (median/mean)	5.6/5.9 years		5.9/6.2 years		9.1/8.7 years		4.4/3.5 Years		6.4/7.1 years	
Stage										
I	13	(87)	23	(96)	29	(81)	3	(100)	68	(87)
II	2	(13)	1	(4)	7	(19)	0		10	(13)
III	0		0		0		0		0	
IV	0		0		0		0		0	
PS										
0	14	(93)	24	(100)	36	(100)	2	(67)	76	(97)
1	1	(7)	0		0		1	(33)	2	(3)
2	0		0		0		0		0	
3	0		0		0		0		0	
4	0		0		0		0		0	
LDH										
Normal	14	(93)	22	(92)	36	(100)	2	(67)	74	(95)
> Normal	1	(7)	2	(8)	0		1	(33)	4	(5)
Site(s)										
Right	6	(40)	10	(42)	17	(47)	1	(33)	34	(44)
Left	7	(47)	13	(54)	12	(33)	2	(67)	34	(44)
Both	2	(13)	1	(4)	7	(20)	0		10	(12)
Organ										
Conjunctiva	4	(27)	3	(13)	14	(39)	0		21	(27)
Orbit	8	(53)	20	(83)	16	(44)	3	(100)	47	(60)
Lachrymal gland	2	(13)	1	(4)	4	(11)	0		7	(9)
Unknown	1	(7)	0		2	(6)	0		3	(4)
IPI										
0	7	(47)	3	(13)	19	(53)	1	(33)	30	(39)
1	7	(47)	19	(79)	17	(47)	1	(33)	44	(56)
2	1	(6)	2	(8)	0		1	(33)	4	(5)
3	0		0		0		0		0	
4	0		0		0		0		0	
sIL-2R										
Normal	7	(46)	11	(46)	11	(31)	1	(33)	30	(38)
> Normal	4	(27)	5	(21)	4	(11)	0		13	(17)
Unknown	4	(27)	8	(33)	21	(58)	2	(67)	35	(45)
Disease relapse	1	(7)	3	(13)	6	(17)	–		10	(13)
Disease death	0		0		2	(6)	0		2	(3)

adnexa are MALT lymphomas [11–14]. Taking into consideration these observations, POA-MALT lymphoma is not an excessively rare disease. However, POA-MALT lymphoma is somewhat unfamiliar for hematologists and oncologists, because the cases are first diagnosed by ophthalmologists and institutional pathologists, and the majority are treated by radiologists.

In our current study, we have tried to clarify two clinical questions. The first is what is the most promising treatment for localized POA-MALT lymphoma. The second is whether, after pathological diagnosis, reactive (polyclonal) lymph-proliferative diseases other than POA-MALT lymphoma also exist simultaneously.

Table 2 Patient characteristics of 'confirmed POA-MALT' lymphoma

	(A) Radiotherapy		(B) Immuno-chemo-therapy		(C) Operative therapy		(D) Watchful waiting		All cases	
	(*n* = 9)	(%)	(*n* = 18)	(%)	(*n* = 25)	(%)	(*n* = 2)	(%)	(*n* = 54)	(%)
Age (median)	74 y.o.		72 y.o.		55 y.o.		83 y.o.		66 y.o.	
Follow-up (median/mean)	2.1/4.7 years		6.1/6.1 years		11.0/9.4 years		2.2/2.2 years		7.6/7.3 years	
Stage										
I	7	(78)	17	(94)	18	(72)	2	(100)	44	(81)
II	2	(22)	1	(6)	7	(28)	0		10	(19)
III	0		0		0		0		0	
IV	0		0		0		0		0	
PS										
0	8	(89)	18	(100)	25	(100)	1	(50)	52	(96)
1	1	(11)	0		0		1	(50)	2	(4)
2	0		0		0		0		0	
3	0		0		0		0		0	
4	0		0		0		0		0	
LDH										
Normal	8	(89)	16	(89)	25	(100)	1	(50)	50	(93)
> Normal	1	(11)	2	(11)	0		1	(50)	4	(7)
Site(s)										
Right	3	(33)	8	(44)	11	(44)	0		22	(41)
Left	4	(44)	9	(50)	7	(28)	2	(100)	22	(41)
Both	2	(22)	1	(6)	7	(28)	0		10	(19)
Organ										
Conjunctiva	3	(33)	2	(11)	10	(40)	0		15	(28)
Orbit	4	(44)	16	(89)	12	(48)	2	(100)	34	(63)
Lachrymal gland	2	(22)	0		2	(8)	0		4	(7)
Unknown	0		0		1	(4)	0		1	(2)
IPI										
0	4	(44)	1	(6)	16	(64)	1	(50)	22	(41)
1	4	(44)	15	(83)	9	(36)	1	(50)	29	(54)
2	1	(11)	2	(11)	0		0		3	(6)
3	0		0		0		0		0	
4	0		0		0		0		0	
sIL-2R										
Normal	3	(33)	9	(50)	7	(28)	1	(50)	20	(37)
> Normal	4	(44)	3	(17)	3	(12)	0		10	(19)
Unknown	2	(22)	6	(33)	15	(60)	1	(50)	24	(44)
Disease relapse	0		3	(17)	4	(16)	–		7	(13)
Disease death	0		0		2	(8)	0		2	(4)

For the first question, several retrospective studies have been reported recently and have indicated the efficacy of radiotherapy for POA-MALT lymphoma [7, 15–17]. Our current results also support the conclusion that radiotherapy (over 30 Gy) should be a promising initial treatment for POA-MALT lymphoma to control the disease. However, the dose and the details of irradiation procedures in each case should be discussed carefully, because of adverse events, such as late damage to the lacrimal gland and duct, and cataracts after radiotherapy [18–22]. In our current analysis, immune-chemotherapy as an initial treatment shows a relatively high recurrence rate (7% recurrence in 5 years, 33% in 10 years), suggesting that the indication of immune-chemotherapy should be carefully discussed considering age and physical condition of the patients. Recently, intra-orbital injection of anti-CD20 antibody (rituximab) for POA-MALT lymphoma has been reported, however, after long-term observation efficacy is not assured because studies all dealt

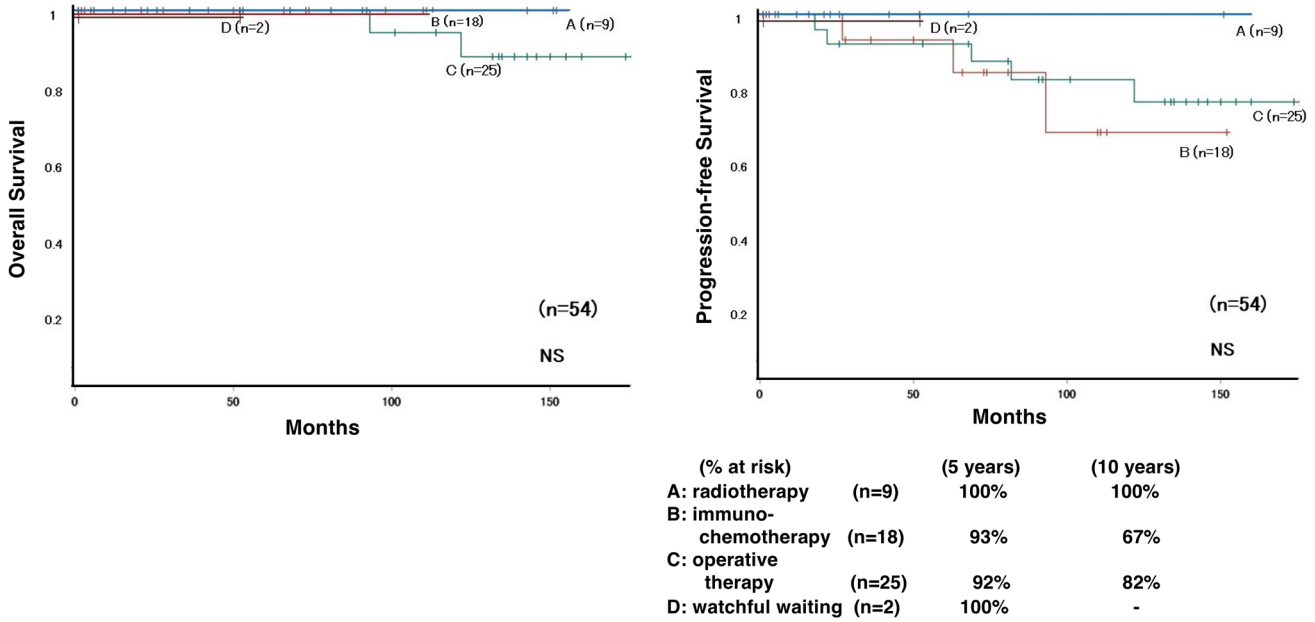

Fig. 4 Overall and progression-free survival of POA-MALT lymphoma patients who were diagnosed with molecular/immunological methods in addition to pathological decisions (cases of 'confirmed POA-MALT') based on treatment strategies ($n = 54$). *NS* not significant

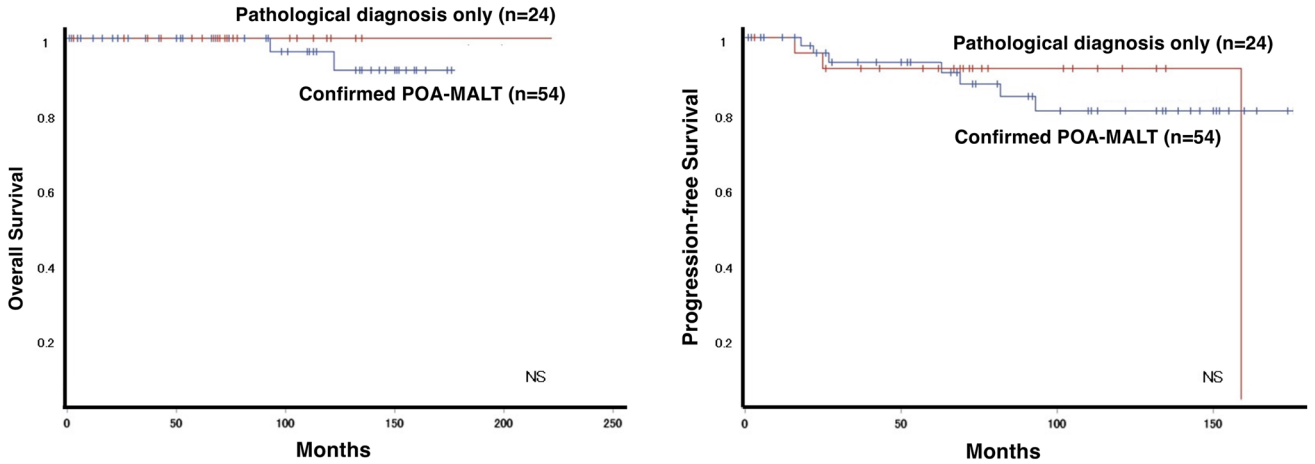

Fig. 5 Overall and progression-free survival of POA-MALT lymphoma patients who were diagnosed with molecular/immunological methods in addition to pathological decisions (cases of 'confirmed POA-MALT') ($n = 54$) and who were diagnosed with only pathological decisions ($n = 24$). *NS* not significant

with small numbers of cases [23–25]. Taking into consideration the above discussions together, surgical resection to provide enough material for a diagnosis of POA-MALT lymphoma, and then moving on to radiotherapy are recommended strategies for an initial treatment.

Another question, whether POA-MALT lymphoma includes reactive (polyclonal) lymphoid hyperplasia, still remained unresolved after this study.

The major lymphoid tumor disease in the ocular adnexa should be MALT lymphoma. In contrast, polyclonal lymphoid hyperplasias arising from various inflammations and infections are diseases that also occur in the ocular adnexa at a certain rate (20–30%) [7]. Molecular or immunological analysis, which we have done for adequate diagnoses, is necessary for the exclusion of other disease possibilities. However, it sometimes might be difficult to take sufficient amounts of tissue samples for such analyses because of the tumor size and primary onset. We sometimes refer to FISH or PCR analysis for an accurate diagnosis using *t* (14; 18) (q32; q21) involving IgH and MALT1 genes dominantly

expressed in ocular adnexal MALT lymphomas [26]. These analyses also may be difficult to do as routine work methods to reach accurate diagnoses. To accumulate the proper data about this type of NHL, it would be necessary to check on whether benign tumors caused by inflammatory diseases are excluded. In our current study, we have strictly selected suitable cases of POA-MALT lymphoma to analyze. A couple of cases were removed from this study, because they did not show IgH rearrangement with PCR analysis (data not shown) even if they were diagnosed after pathological decision. These patients are still alive with no recurrence, suggesting that molecular and immunological diagnosis should always be considered to avoid treating reactive lymphoid hyperplasias as malignancies.

In conclusion, POA-MALT lymphoma is an indolent disease, shows slow progression and has a relatively good prognosis. Radiotherapy-based initial treatment after clear diagnosis should improve the prognosis for patients with POA-MALT lymphoma. The number of study subjects was small and several methodological weaknesses of the present study have to be taken into account. We acknowledge that the current results must be confirmed by additional studies with a larger sample size.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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