



## Research Paper

# Comparison of Selection and Long-term Clinical Outcomes Between Chemotherapy and Radiotherapy as Primary Therapeutic Modality for Ocular Adnexal MALT Lymphoma<sup>☆</sup>

Young-Woo Jeon<sup>a</sup>, Hee-Jung Yang<sup>b</sup>, Byung-Ock Choi<sup>c</sup>, Seung-Eun Jung<sup>d</sup>, Kyung-Sin Park<sup>e</sup>, Joo-Hyun O<sup>f</sup>, Suk-Woo Yang<sup>b,\*</sup>, Seok-Goo Cho<sup>a,\*\*</sup>

<sup>a</sup> Department of Hematology, Catholic University Lymphoma Group, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

<sup>b</sup> Department of Ophthalmology, Catholic University Lymphoma Group, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

<sup>c</sup> Department of Radiation Oncology, Catholic University Lymphoma Group, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

<sup>d</sup> Department of Radiology, Catholic University Lymphoma Group, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

<sup>e</sup> Department of Pathology, Catholic University Lymphoma Group, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

<sup>f</sup> Department of Nuclear Medicine, Catholic University Lymphoma Group, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

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## ABSTRACT

**Background:** The choice of a primary treatment for ocular adnexal mucosa-associated lymphoid tissue lymphoma (OAML) depends on the extent of tumor spread. However, radiotherapy is commonly used as a first-line therapy despite ophthalmic complications, because most OAMLs are in a limited stage of progression. However, the initial therapeutic modality, including chemotherapy and treatment of the advanced stage, has not been fully established for OAML. Therefore, we evaluated the optimal therapeutic options and survival outcome-related parameters for patients with primary OAML.

**Methods:** We evaluated 208 consecutive patients with primary OAML who were diagnosed at the Catholic University Lymphoma Group between January 2004 and April 2015.

**Findings:** During a median follow-up of 70.0 months (range, 3.2–182.0 months) in 208 patients with primary OAML, most patients were female and the median age was 46 years old. Overall survival (OS) and progression-free survival (PFS) at 13 years were excellent (92.7% and 69.7%, respectively). Of the 117 patients who received the first-line radiotherapy, 92% achieved complete remission (CR), usually by being treated with less than 30 Gy. Radiation-related ophthalmic complications including dry eye syndrome (59%) and cataract (22%) caused a decline in the quality of life (QoL). Chemotherapy alone was used to treat 86 OAML patients, with 84.9% achieving CR and 12.8% achieving partial remission with tolerable toxicities. There were no differences in survival outcomes between patients treated with radiotherapy versus those treated with rituximab-containing chemotherapy, although the latter group had more advanced stages of OAML (OS,  $p = 0.057$ ; PFS,  $p = 0.075$ ).

**Interpretation:** OAML patients were predominantly female and relatively young, and radiotherapy as a primary therapeutic option was more likely to lead to radiation-related complications, resulting in lower QoL. On the other hand, frontline chemotherapy showed consistent therapeutic outcomes with tolerable toxicities compared to radiotherapy, and there were no long-term or delayed adverse events. Therefore, when considering therapeutic efficacy and therapy-related QoL, chemotherapy is recommended for younger patients, and radiotherapy is recommended for older and chemotherapy-ineligible patients.

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\* Correspondence to: S.-W. Yang, Department of Ophthalmology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, #505 Banpo-Dong, Seocho-Ku, Seoul 06591, Republic of Korea.

\*\* Correspondence to: S.-G. Cho, Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, #505, Banpo-Dong, Seocho-Ku, Seoul 06591, Republic of Korea.

E-mail addresses: [yswoph@catholic.ac.kr](mailto:yswoph@catholic.ac.kr) (S.-W. Yang), [chosg@catholic.ac.kr](mailto:chosg@catholic.ac.kr) (S.-G. Cho).

### Research in context

Primary ocular adnexal mucosa-associated lymphoid tissue lymphoma (OAML) generally has an indolent nature and excellent survival outcomes regardless of the primary therapeutic modality. According to the reported data, most patients with a limited OAML are primarily treated with radiotherapy (RT). However, as therapeutic outcomes for the primary therapeutic options increase, there is an associated increase in long-term or delayed radiation-related adverse effects such as dry eyes, retinopathy, and irreversible cataracts. We conducted a retrospective analysis of indirect comparative data on radiotherapy and chemotherapy as representative frontline therapies for OAML. Considering the disease characteristics of OAML, which occurs primarily in younger people but has excellent long-term survival, we conclude that it is better for some younger patients to consider early frontline chemotherapy, particularly for a rituximab-containing regimen, rather than undergoing radiotherapy even for a localized disease. Upfront RT is suggested for older patients who would not suffer from a deterioration in their quality of life due to ophthalmic complications or for those who are not suitable for systemic chemotherapy. Our results could be used as a basis for prospective clinical research for a tailored optimal therapeutic modality of OAML in the future.

## 1. Introduction

Since ocular involvement in lymphomatous diseases including primary ocular adnexal lymphoma (POAL) was first reported in 1952 [1], and defined as a malignant neoplasm involving lesions of the conjunctiva, lacrimal gland, orbit, and eyelid as orbital adnexal lesions, it has been found to occur in 1–2% of all non-Hodgkin's lymphoma (NHL) patients and in approximately 30–55% patients with orbital malignancies [2,3]. While POAL may present as different histological subtypes of NHL, including extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT), orbital or ocular adnexal MALT lymphoma (OAML) is the most frequent histological subtype, accounting for approximately 40–90% of POAL patients [4–6].

Numerous retrospective studies have described the pathophysiological and clinical characteristics of OAML [7,8]; it is a disease of the elderly population (median age of 65 years) with a female preponderance. The majority of OAML patients present with localized disease in the orbit area [9] and the incidence of bilateral involvement has recently increased. In addition, investigations of OAML pathogenesis have shown that autoantigen-related activation of the B-cell receptor results from chromosomal translocations and mutations with gene changes that regulate cell survival and apoptosis [10,11]. Patients with previous autoimmune diseases such as thyrotoxicosis or Sjogren syndrome have a much higher incidence of OAML [12]. Inflammatory conditions such as chronic conjunctivitis are risk factors for OAML [13,14]. Furthermore, the correlation between *Chlamydia psittaci* infection and OAML incidence is a controversial subject with geographic differences [10].

In therapeutic approaches, a practical therapeutic strategy for OAML includes surgery only, RT, and systemic chemotherapy. RT is adapted for localized OAML with excellent clinical outcomes of 85–100% complete remission (CR) and relatively excellent local control efficacy and treatment duration [15]. Several retrospective studies have reported on the adaptation of systemic chemotherapy with a favorable response and long duration of progression-free survival (PFS) [16]. A few cases of the “watch and wait” approach, or antibiotics administration alone have been reported but they show uncertain therapeutic outcomes [17].

Although significant advances have been made in elucidating the pathogenesis and clinical characteristics with therapeutic management in recent years, several significant aspects of OAML have still not been sufficiently addressed; initial therapeutic strategy is diverse, and there remains no consensus regarding the initial management of OAML. Despite high local control rates in first-line RT, the eyeball apparatus is a radiosensitive structure, so even small doses of radiation exposure of less than a single dose of 2 Gy are likely to increase the risk for cataracts [17,18]. RT-related cataract may lead to early loss of near vision and other ophthalmic complications including dry eye syndrome and keratitis, and it had increased the possibilities of cataract surgery. And these were resulting in a severe decline in the quality of life (QoL) [18, 19]. As another therapeutic option, systemic chemotherapy has hematological or non-hematological toxicities and relatively lower disease control efficacy than local therapy. Surgery alone or the “watch and wait” approach are not standard methods. To overcome these limitations, several studies have described the various clinical parameters between the natural disease courses and therapeutic options. However, most OAML-related studies have focused on upfront radiation therapy without addressing RT-related complications, and therapeutic outcomes of upfront chemotherapy have been overlooked.

Therefore, we performed a retrospective study of long-term follow-up survival outcomes using the uniformed therapeutic strategy according to standard staging systems on a large cohort of OAML patients. This study primarily focused on the disease characteristics and the efficacy of each therapeutic choice in ordinary clinical practice with a large cohort and an extended period of follow-up duration. Our purpose was ultimately to determine the overall responses for each therapy and the associated clinical parameters including upfront chemotherapy for primary OAML.

## 2. Materials and Methods

### 2.1. Patients

Between January 2004 and April 2015, we evaluated all consecutive OAML patients at the Catholic Bone Marrow Center, Seoul, the Republic of Korea who were diagnosed according to the morphological and immunophenotypic diagnostic criteria of lymphoma according to the World Health Organization (WHO) classification. All of the biopsy specimens were histologically confirmed by expert pathologists from the Catholic University Lymphoma Group (CULG), and all patients had consulted with expert ophthalmologists of CULG for the management of treatment modality-related complications during the follow-up period. Histologically advanced transformed-OAML subtypes (MALT lymphoma with diffuse large B cell lymphoma) and secondary OAL were excluded. We reviewed the patients' medical records, which included data on general physical examinations, geographic status, the Eastern Cooperative Oncology Group (ECOG) performance score, combined medical history, complete blood count (CBC) with serum chemistry, bone marrow (BM) tests with chromosomal data, primary therapeutic modalities, response to initial therapy, and treatment-related complications with survival outcomes. For staging, all patients underwent imaging of the orbital areas by computed tomography (CT), a chest CT, abdominopelvic CT, positron emission tomography (PET) CT, and magnetic resonance imaging (MRI).

### 2.2. Staging Workup and Definitions

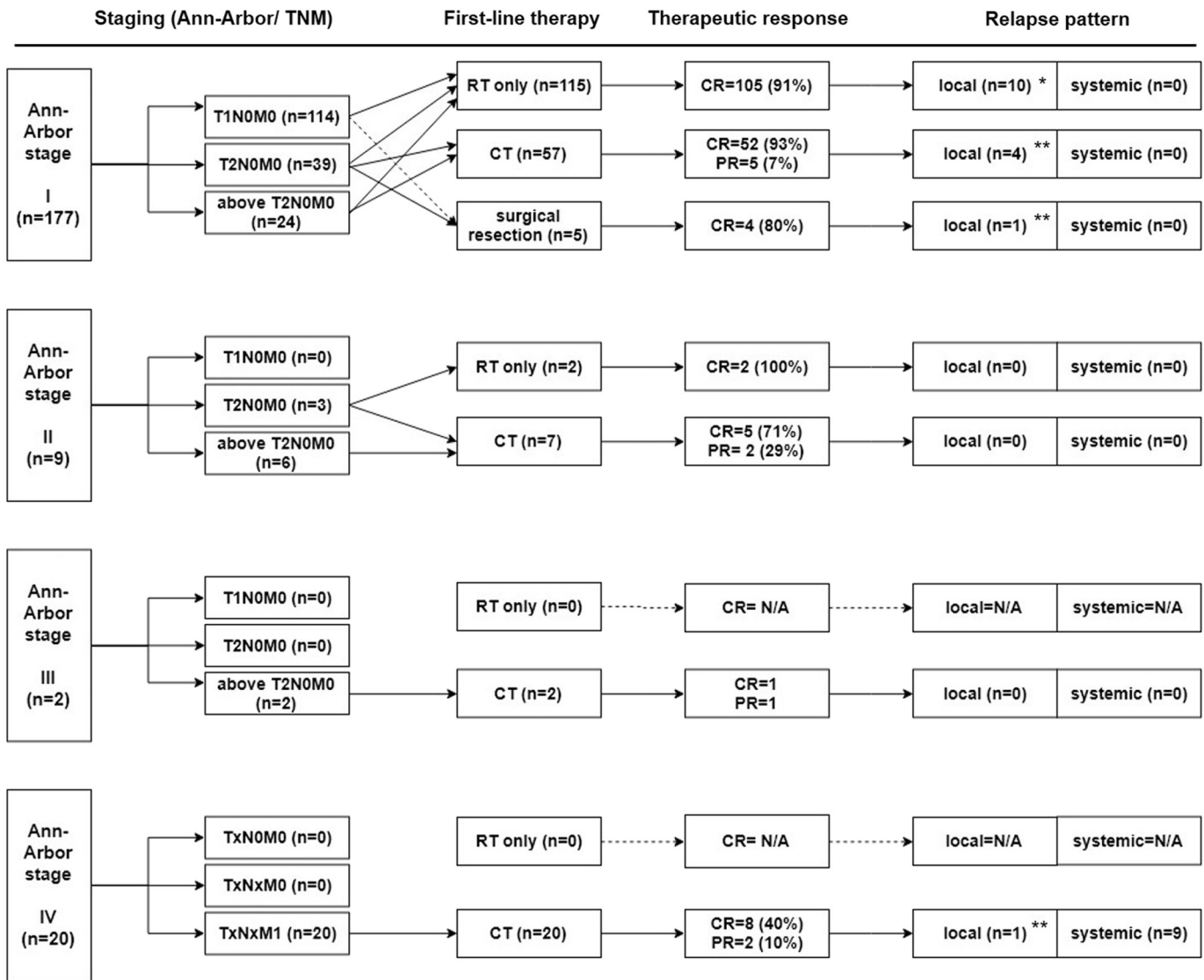
All of the enrolled patients were categorized using the International Prognostic Index (IPI) scoring system for non-Hodgkin lymphoma (NHL) with the Ann Arbor Classification. Primary OAL was defined as a malignant neoplasm involving lesions of the conjunctiva, lacrimal gland, orbit, and eyelid and bilateral ocular adnexal involvement was described as Ann Arbor stage IE rather than IVE [20]. Previously, our group had reported that the American Joint Committee on Cancer

(AJCC) TNM-based staging system (8th edition) was more applicable to patients with localized OAML for the selection of treatment strategies [21]. Hence, all patients were reclassified according to the AJCC TNM-staging system using orbital CT or MRI at the time of diagnosis: T1 was defined as lymphoma involving the conjunctiva alone without orbital involvement, T2 as lymphoma with orbital involvement with or without any conjunctival involvement, T3 as lymphoma with pre-septal eyelid involvement, and T4 as orbital adnexal lymphoma extending beyond the orbit to adjacent structures [22]. The confirmation of lymphoid malignancy involving BM was carried out through two processes in all cases, and was finally defined by positive immunohistochemistry (IHC) expression, a Hematoxylin and Eosin (H&E) positive stain, and definitive confirmation by IHC in all cases.

### 2.3. Therapeutic Strategy

Frontline therapeutic modalities involved curative surgery alone (RT alone, chemotherapy alone) or the combination of RT and chemotherapy. According to a previous study [21], primary therapeutic modalities were determined by combining the main TNM-staging system with

additional Ann Arbor staging. Patients diagnosed with the localized stage of T1-2N0M0 or most of Ann Arbor stage I-IE had generally undergone intensity-modulated radiation therapy (IMRT) as frontline therapy, and patients with advanced disease (which was categorized as TxN1-4M0 or TxNxM1 and all patients with malignant cells involving BM and bilateral involvement of the ocular adnexal area (based on retrospective and prospective research in our center) were treated with systemic combination chemotherapy with/without monoclonal antibodies such as rituximab as initial therapy. Patients with a partial response to frontline chemotherapy received an additional reduced-dose of radiotherapy, and particularly patients with lacrimal duct involvement and ongoing ductal obstructive symptoms or an encircled orbital area involvement with a relatively large mass were given low-dose consolidative radiotherapy. Symptomatic patients with direct optic nerve compression by the initial tumor were treated with primary radiotherapy as a priority for a rapid response. In addition, the group of gray zone was defined as in T3-4N0M0 was treated with mainly chemotherapy or RT. These therapeutic options were switched or combined, according to the patients' general status and the physicians' clinical judgment. These first-line therapeutic options are summarized in Fig. 1.



\* Relapse lesions are all of extra-radiation exposure-field or the other eye.

\*\* Relapse lesions are all of initially involved area.

Fig. 1. Therapeutic strategy and therapeutic responses after first-line therapy. All patients diagnosed with ocular adnexal mucosa-associated lymphoid tissue lymphoma (OAML) were classified according to combined Ann Arbor stage and tumor node metastasis (TNM) staging systems, and then an appropriate frontline therapeutic approach was selected for each patient.

A cyclophosphamide, vincristine and prednisone/rituximab with cyclophosphamide, vincristine, and prednisone (CVP/R-CVP) or cyclophosphamide, doxorubicin, vincristine, and prednisone/rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP/R-CHOP) regimen with 6 to 8 cycles each was adopted for these patients. The CVP or R-CVP chemotherapy regimen consisted of cyclophosphamide (750 mg/m<sup>2</sup>) and vincristine (1.4 mg/m<sup>2</sup>) on day 1 and prednisolone (60 mg/m<sup>2</sup>) on days 1 to 5 every 21 days with/without rituximab (375 mg/m<sup>2</sup>) on day 1. The CHOP or R-CHOP regimen consisted of cyclophosphamide (750 mg/m<sup>2</sup>), doxorubicin (50 mg/m<sup>2</sup>), vincristine 1.4 mg/m<sup>2</sup> on day 1, and prednisone (100 mg/m<sup>2</sup>) orally on days 1 to 5 every 21 days with/without rituximab (375 mg/m<sup>2</sup>) on day 1. Dose adjustment was performed based on hematological toxicity, neurological toxicity, and infusion-related reactions. All patients in the chemotherapy group were supported with granulocyte colony-stimulating factor for hematological toxicity.

#### 2.4. Assessment of Treatment Responses and Adverse Events

All patients underwent response assessments every 3 months for 1 year followed by every 4–6 months for 3 years, and then an annual check-up for local recurrence or systemic relapse. Response assessments were performed using the revised response criteria for malignant lymphoma: [23] CR was defined as the disappearance of all evidence of disease, partial remission (PR) as regression of measurable disease without new lesions, stable disease (SD) as the failure to attain CR or PR or PD, and relapse disease or progressive disease (PD) were defined as any new site-lesions that had increased by more than 50% of previously involved sites from the nadir status.

Chemotherapy-induced or RT-related adverse events were established according to the National Cancer Institute-Common Toxicity Criteria Adverse Events (NCI-CTCAE, version 4.0). Surveillance for ophthalmic complications was assessed by questioning patients for subjective symptoms, slit-lamp examination, visual field examination Schirmer's test, tear film break-up time, best-corrected visual acuity (BCVA) using the Snellen chart, and initial cataract status using the Lens Opacity Classification System III (LOCS III) in the radiotherapy group.

#### 2.5. Statistical Analyses

A response rate of primary therapeutic modalities, and the associated risk factors, OS, PFS, relapses and significant adverse events after each therapy were evaluated. OS was calculated from the date of initial diagnosis (time of biopsy) to the date of any cause of death or last follow-up, and PFS was defined as the period from the date of initial diagnosis until the time of the first progression, or last follow-up date, or the date of any cause of death, whichever occurred earlier. Time to best response (CR) was defined as the time from the date of treatment initiation to the date of the documented CR. Demographic and clinical characteristics were analyzed using the Student's t-test and chi-square test. Survival curves for OS and PFS were analyzed using the Kaplan–Meier method and compared to the log-rank test, and the Gray test used to analyze differences in the cumulative incidence curves of relapse incidences. To identify the risk factors for survival outcomes of OAML in our cohort, univariate and multivariate analyses were performed for the variables of age, sex, disease location, laterality, Ann Arbor stage, TNM stage, IPI score, BM involvement, Ki-67 index, and therapeutic modality. The prognostic significance of multivariate affecting therapy outcomes regarding OS, PFS, and relapse were determined using the Cox proportional hazard model with a variable of  $p \leq 0.2$  and hazard ratios (HRs) with 95% confidence interval (CIs) in univariate analyses. For all prognostic analyses, continuous variables were categorized and the median was used as a cut-off point. All interactions between each variable were investigated. Statistical significance was considered at a  $p$ -value  $< 0.05$  of the two-tailed likelihood ratio test, and each estimate

of the therapeutic methods was calculated with a 95% CI assuming an exact binomial distribution. All statistics were conducted using SPSS, version 20 (SPSS, Inc., Chicago, IL) and R-software (version 3.2.3, R Foundation for Statistical Computing, 2012, <http://cran.r-project.org/>).

This single-center retrospective study was approved by The Catholic Medical Center Institutional Review Board, and all of the analyses followed the Institutional Review Board guidelines and adhered to the Declaration of Helsinki.

The funders of the study had no role in the study design, data collection, data analyses, data interpretation, or writing of the report. Y.W. Jeon, and S.G. Cho had access to annotated patient clinical data. The corresponding author had full access to all of the anonymized results and final responsibility for the decision to submit for publication.

### 3. Results

#### 3.1. Patient Characteristics and Clinical Manifestations

Between January 2004 and April 2015, there were 214 patients diagnosed by the CULG at the Catholic University of Korea, Seoul. Two and four patients were excluded due to histologically advanced transformed-subtype and secondary OAML, respectively. Hence, a total of 208 patients with primary OAML were evaluated; the patient characteristics are summarized in Table 1. The median age of all patients was 46 years (range, 18–85 years) and females predominated (125 patients: 60.1%, ratio 1:1.5). This sex bias was due to a higher frequency of conjunctival OAML in females (72% of primary conjunctival OAML), while there were more male cases of non-conjunctival OAML (57%).

At presentation, 48 patients (23.1%) had bilateral involvement of ocular adnexal lesions. All patients except one had a good performance status (ECOG of 0 or 1). The majority of primary OAML was located in the conjunctivae (represented as T1 staging,  $n = 119$ , 57.2%), and in decreasing order of frequency, the initial location of the primary OAML was in the orbital area (represented as T2 staging,  $n = 59$ , 28.4%), eyelids (represented as T3 staging,  $n = 15$ , 7.2%), and extending beyond the orbit to adjacent structures (described as T4 staging,  $n = 14$ , 6.7%). Previously diagnosed autoimmune diseases were found in 10 (4.8%) patients, and these were Hashimoto thyroiditis in seven patients and Sjogren syndrome in three patients (Table 1). We previously reported a phase II study of R-CVP for 33 patients with limited-stage OAML with bilateral or beyond-conjunctival involvement [24]; all of these patients were included in this study as a frontline rituximab-containing chemotherapy group. The basic characteristics of our cohort were substantially different from most Western populations [25,26], with a younger median age at diagnosis and a low rate of prior diagnosis of autoimmune diseases.

#### 3.2. Clinical Manifestations at Time of Diagnosis

Symptoms and signs at the time of diagnosis were diverse and overlapped according to primary tumor lesions. The majority of symptoms and signs were in the conjunctival lesion ( $n = 119$ ); the most common presenting symptom was a lump or irritation ( $n = 93$ ), and the most common sign was a mass ( $n = 116$ ). At the other sites of lesions, such as the orbit, eyelid, and epi-bulbar areas, swelling and a mass were the most common presenting symptoms and signs, respectively. In particular, symptoms and signs by direct optic nerve compression were presented in three patients (two patients with 'ptosis' symptom and one patient with 'restricted eye movement' sign). None of the patients had B symptoms (data on B symptoms are not shown in Supplementary Table 1). The details are described in Supplementary Table 1.

#### 3.3. Staging Workup for Selecting First-line Therapies

The initial staging procedure revealed that 177 (85.1%) patients had Ann Arbor stage I/IE, 9 (4.3%) had Ann Arbor stage II, two (1.0%) had



**Table 1**  
Characteristics of 208 patients with primary ocular adnexal MALT lymphoma.

Factors	Total (n = 208)
Age, median, year (range)	46 (18–85)
Gender, male (%)	83 (39.9)
Tumor laterality (%)	
Unilateral	160 (76.9)
Bilateral	48 (23.1)
Anatomical location	
Conjunctivae	119 (57.5)
Orbit	59 (28.5)
Lacrimal duct and glands	16 (7.7)
Eyelid, nasopharynx	21 (10.1)
Bone marrow involvement (%)	
Positive	17 (8.2)
Number of extra-orbital involvement	
0	176
1	22
2	6
>2	3
LDH, U/L (range)	341 (164–911)
Elevated, n (%)	15 (7.2)
AJCC-TNM stage (%)	
T-	
T1	119 (57.2)
T2	59 (28.4)
T3	15 (7.2)
T4	14 (6.7)
N-	
N0	183 (88.0)
N1	9 (4.3)
N2	8 (3.8)
N3	4 (1.9)
N4	3 (1.4)
M-	
M0	177 (85.5)
M1	30 (14.5)
Ann Arbor stage (%)	
I/IE	177 (85.5)
II	9 (4.3)
III	2 (1.0)
IV	20 (9.6)
ECOG performance (%)	
0	203 (97.6)
1	4 (1.9)
2	1 (0.5)
ki-67 index, median (range)	
Assessed (n = 118)*	10 (1–90)
IPI risk classification (%)	
Low	172 (82.6)
Low-intermediate	23 (11.1)
High-intermediate	11 (5.3)
High	2 (1.0)
Previous autoimmune disease	10 (4.8)
Hashimoto thyroiditis	7 (3.4)
Sjogren disease	3 (1.4)
Primary therapeutic modality (%)	
Curative surgery alone	5 (2.4)
Radiotherapy	117 (56.2)
Chemotherapy	74 (35.6)
Chemotherapy + Radiotherapy	12 (5.8)

Abbreviations: MALT; mucosa-associated lymphoid tissue, IPI; international prognostic index.

\* 89 patients (43%) were excluded due to non-assessed ki-67 index at the initial diagnosis.

Ann Arbor stage III, and 20 (9.6%) had Ann Arbor stage IV disease. A total of 114 (54.8%) patients were T1N0M0, 42 (20.2%) were T2N0M0, 7 (3.4%) were T3N0M0, and 6 (2.9%) were T4N0M0 according to the AJCC-TNM staging system. Consequently, when all of the patients were reclassified according to the AJCC TNM-based staging system, 156 (75.0%) were considered to be in a limited stage, which involved orbital lesions with/without conjunctivae (from T1N0M0 to T2N0M0) and 39 (18.8%) were categorized as advanced stage TxN1–4M0 or TxNxM1. T1 staging involving the conjunctiva, T2 staging which involving the

orbit, T3 staging related to the eyelid, and T4 staging consisting of extra-orbital local spread were found in 119 (57.2%), 59 (28.4%), 15 (7.2%), and 14 (6.7%) patients, respectively. In all, 82.6% (n = 172), 11.1% (n = 23), 5.3% (n = 11), and 1.0% (n = 2) of cases in the IPI risk group were classified as low, low-intermediate, high-intermediate, and high risk, respectively (Table 1).

The BM study had been obligatorily performed for an initial baseline workup, combined with imaging studies in all patients with primary OAML according to CULG policies. Seventeen (8.2%) patients had malignant lymphoma cells involving BM, a relatively high rate compared to patients in Western societies. All patients with BM infiltration had more than one extranodal site, such as the spleen, lung, and skin (Table 1).

To confirm the disseminated status, most patients underwent a PET-CT scan. This revealed that seven (3.4%) patients had distant metastasis with significant fluorodeoxyglucose (FDG) uptake in the liver (n = 4), spleen (n = 5), intraabdominal lymph nodes (n = 2), kidney (n = 3), and cervical lymph nodes (n = 2). A core needle biopsy was performed on two patients with FDG uptake in cervical lymph nodes, and the results were confirmed histopathologically. Even if patients were initially diagnosed with distant spreading, there were no organ-related symptoms.

According to the Ann Arbor staging system and patient's status, each first-line therapy was applied to 117 (56.2%) patients consisting of radiation only, 86 (41.2%) patients had chemotherapy (including 12 patients with chemotherapy followed by low-dose radiation), and 5 (2.4%) patients had surgical resection only.

### 3.4. Brief Survival Outcomes

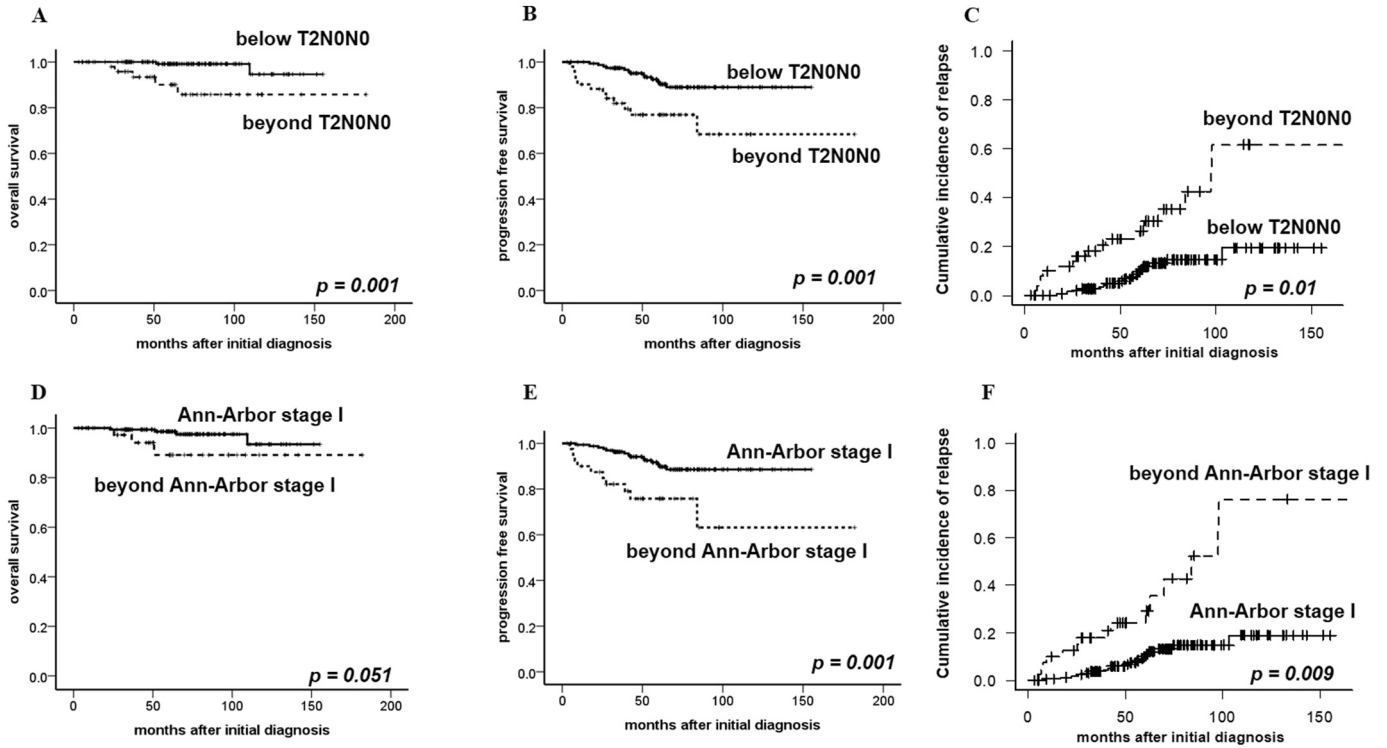
The median follow-up duration was 70.0 months (range 3.2–182.0 months) in all 208 patients with primary OAML. During this period, the median lymphoma-specific OS and PFS times were not reached. The 13-year lymphoma-specific OS and PFS were 92.7% and 69.7%, respectively (Supplementary Fig. 1A, B). The cumulative incidence of relapse (CIR) after first-line therapy was 29.3% at 13 years (Supplementary Fig. 1C).

The TNM staging system tended to reflect the survival outcome more precisely than the Ann Arbor staging system (Fig. 2): TNM classification clarified difference both OS and PFS (p-value 0.001 of OS and 0.001 of PFS, Fig. 2A, B), while Ann Arbor staging system was only associated with PFS, not OS (p-value 0.051 of OS and 0.001 of PFS, Fig. 2D, E). After initial therapy, patients beyond the T2N0M0 stage and beyond Ann Arbor stage I had high rates of CIR (Fig. 2C, F). The median time to response was 3.6 months across the whole cohort (range, 1.1–17.7 months) with no statistical differences between the upfront RT and primary chemotherapy group. Although these differences were not statistically significant, there was a trend towards a faster good response in the RT groups than in those treated with chemotherapy, as the median time to response was 3.0 months (range, 1.1–5.7 months) and 4.3 months (range, 1.6–17.7 months) in the RT and chemotherapy groups, respectively.

Seven (3.4%) patients died: four who had lymphoma progression and three due to non-lymphoma causes, such as intracranial hemorrhage (n = 1), advanced gastric cancer (n = 1), and prostate cancer (n = 1) without relapse of OAML.

### 3.5. Treatment Outcomes for Radiation Only as a First-line Therapy

A total of 117 (56.2%) patients had received RT only as the primary therapeutic modality, including 115 patients with Ann Arbor stage I/IE (reclassified as 113 patients with T1N0M0, one patient with T2N0M0, and one patient above T2N0M0) and two patients with Ann Arbor stage II (T2N0M0) (Fig. 1). It was possible to calculate the radiation dose and duration given during RT for 97 (83%) of 117 patients. The median RT dose was 26 Gy (range, 24–32 Gy), and the conventionally



**Fig. 2.** Survival outcomes according to staging systems in primary ocular adnexal mucosa-associated lymphoid tissue lymphoma (OAML). Kaplan-Meier estimates of overall survival (A), progression-free survival (B), and cumulative incidence of relapse (C) according to the TNM staging system. Kaplan-Meier estimates of overall survival (D), progression-free survival (E), and cumulative incidence of relapse (F) according to the Ann Arbor staging system.

fractionated method was used with a daily dose of 1.8–2.0 Gy five times per week. RT alone showed an excellent survival outcome with a 92% CR ratio (n = 107). The incidence of local relapse in the irradiated eye was significantly different (three patients with a dose of <26 Gy and no patients with a dose of ≥26 Gy; p = 0.02).

Relapses were observed from 17 to 65 months after RT. All relapsed patients (n = 10) who had received RT only showed a locally advanced relapse pattern without distant systemic relapse: three patients with an ipsilateral eye relapse and seven patients with a contralateral eye relapse. Even when relapse occurred in the ipsilateral eye with a radiation dose < 26 Gy, there was no infield-radiation-associated relapse pattern, and relapse sites were outside the field of radiation exposure or in the contralateral eye. None of the patients who received any dose of RT in limited stages experienced central nervous system (CNS) relapse. A radiation dose of ≥26 Gy was more effective against lymphoma.

**3.6. Treatment Outcomes of Chemotherapy as a First-line Therapy**

Chemotherapy alone was the primary treatment modality in 86 (41.3%) patients, including 57 with Ann Arbor stage I (34 patients

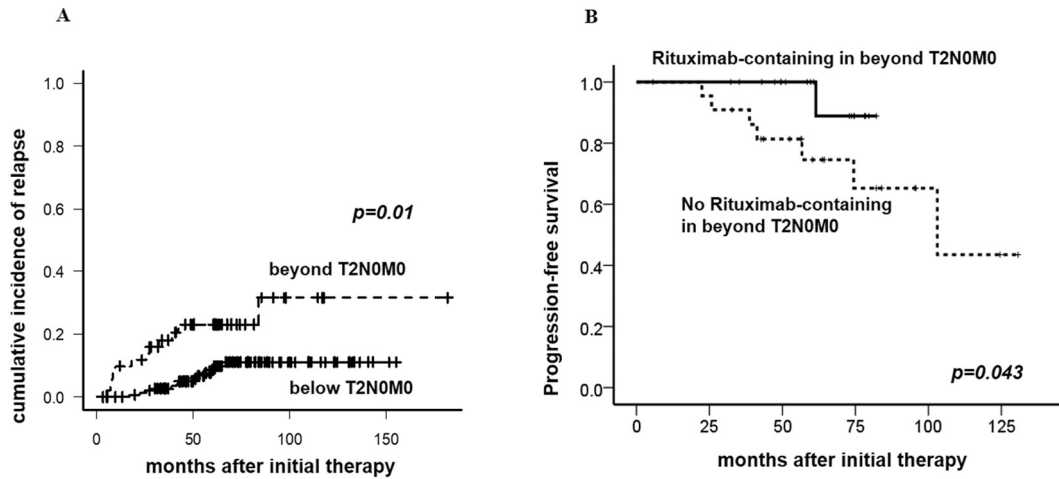
with T2N0M0, 23 patients above T2N0M0), 7 with Ann Arbor stage II (one patient with T2N0M0, six patients with above T2N0M0), two with Ann Arbor stage III (above T2N0M0), and 20 patients with Ann Arbor stage IV (TxNxM1) (Fig. 1). CVP, CHOP, R-CVP, and R-CHOP regimens were administered in 19, 14, 39, and 14 patients, respectively. Twelve patients who still displayed obstructive symptoms in the lacrimal duct or ocular irritative symptoms but with a PR disease status after they had completed systemic chemotherapy were treated with additional consolidative RT.

The median duration of follow-up was 66.1 months (range, 5.6--182.0 months) in the chemotherapy group. One month after chemotherapy, 73 (84.9%) patients were in CR and 11 (12.8%) patients were in PR. The CR rate differed varied from 71.4% to 92.3% and the PR rate varied from 7.7% to 28.6% in each chemotherapy regimen. Ultimately, 70 (81.4%) patients achieved CR and 16 (18.6%) relapsed after first-line chemotherapy. The response to each first-line chemotherapy regimen is summarized in Table 2. The CIR at 13 years was 18.5%, while there were statistically significant differences between staging groups: 9.8% vs. 30.9% for below T2N0M0 and beyond T2N0M0 (p = 0.01, Fig. 3A). Subgroup analyses were performed for chemotherapy alone

**Table 2**  
Response to first-line chemotherapy in patients with primary ocular adnexal MALT lymphoma.

	n	1 month after completion of chemotherapy				Final response to the first-line chemotherapy			
		CR (%)	PR (%)	SD (%)	PD (%)	CR (%)	PR (%)	SD (%)	Relapse (%)
CVP	19	15 (78.9)	4 (21.1)	0	0	15 (78.9)	0	0	4 (21.1)
CHOP	14	10 (71.4)	4 (28.6)	0	0	11 (78.6)	0	0	3 (21.4)
R-CVP	39	36 (92.3)	3 (7.7)	0	0	36 (92.3)	0	0	3 (7.7)
R-CHOP	14	12 (85.7)	2 (14.3)	0	0	8 (57.1)	0	0	6 (42.9)
Total	86	73 (84.9)	11 (12.8)	0	0	70 (81.4)	0	0	16 (18.6)

Abbreviations: MALT; mucosa-associated lymphoid tissue; CR, complete remission; PR, permanent remission; SD, stable disease; PD, progressive disease; CVP, cyclophosphamide, vincristine and prednisone; R = CVP, rituximab with cyclophosphamide, vincristine and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone.



**Fig. 3.** Survival outcomes for chemotherapy alone of advanced primary ocular adnexal mucosa-associated lymphoid tissue lymphoma (OAML). (A) Cumulative incidences of relapses according to TNM staging of the chemotherapy group. (B) Progression-free survival according to rituximab usage in the beyond T2N0M0 chemotherapy group.

and chemotherapy following RT: 60 patients achieved CR (82.2%) and 3 died due to disease progression in the chemotherapy alone group, whereas 10 patients (76.9%) reached CR status and 1 died from disease progression in the chemotherapy following RT group. The differences between groups were not significant (RR 1.9,  $p = 0.105$ ).

The pattern of relapse did not differ between local and systemic relapsed lesions in 14 patients ( $p = 0.592$ ); 5 patients relapsed in initially involved areas, and 9 recurred in distant areas (kidney, spleen, abdominal lymph nodes, and CNS). Locally relapsed patients ( $n = 5$ ) were treated with involved field radiation therapy (IFRT), and thereafter CR was achieved with no tumor-related deaths. Moreover, systemic relapsed patients ( $n = 9$ ) were treated with salvage chemotherapy followed by RT; one systemic relapse patient received ibrutinomab tiuxetan (ZEVALIN®) therapy and then achieved CR, while four of 9 patients with systemic relapse (29%) died due to disease progression. Moreover, among them, one patient with Ann Arbor stage IE (T4N0M0) died due to CNS relapse after R-CVP chemotherapy; this patient was previously reported [27].

### 3.7. Role of Rituximab in the First-line Chemotherapy Group

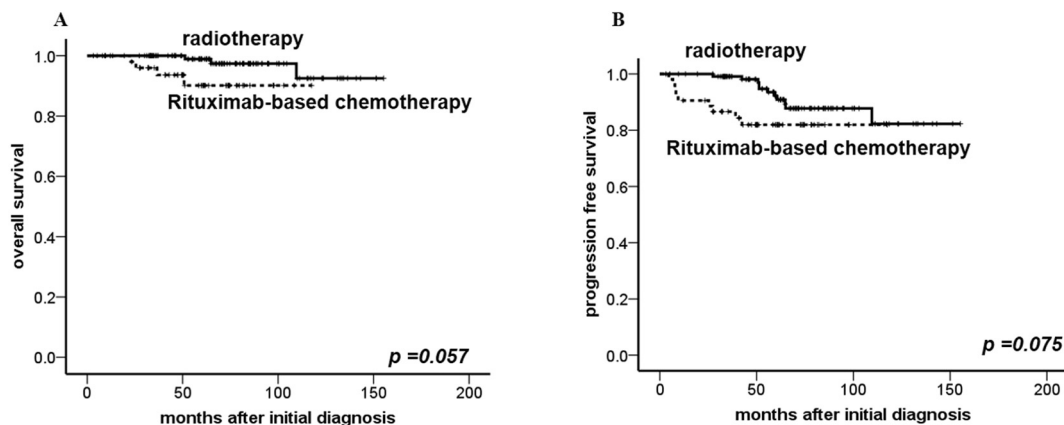
In the first line chemotherapy group, the rituximab-containing regimen was administered to 53 (62%) patients. The CR rate was significantly altered by rituximab usage at 1 month after chemotherapy, while no significant differences were identified at the last follow-up (75.8% vs. 90.6% CR at 1 month after chemotherapy in the non-

rituximab vs. rituximab regimen,  $p = 0.04$ ; 78.8% vs. 83.0% at the final response,  $p = 0.18$ ). To evaluate the efficacy of rituximab in the beyond T2N0M0 staging group, stratification analyses were undertaken. In a more advanced subgroup, there was a statistically significant difference of PFS between the rituximab and non-rituximab group ( $p = 0.043$ , Fig. 3B). OS and PFS did not show a statistical difference ( $p = 0.057$  and  $p = 0.075$ , respectively, Fig. 4), despite the fact that the advanced-stage patients and those with high IPI scores mostly belonged to the group that received a regimen containing rituximab.

### 3.8. Prognostic Factors Affecting Treatment Outcomes

CR rates and survival outcomes were diverse in each patient, so the identification of prognostic factors was performed to find out the risk factors which were affected by survival outcomes in all cohorts. Age, gender, initial tumor location, subgrouping of tumor location between conjunctival and orbital lesion alone, laterality, Ann Arbor stage, TNM-staging system, IPI risk classification, ki-67 index, and BM involvement status were evaluated for prognostic factors affecting PFS and OS (Table 3).

For PFS-related factors, univariate analysis showed statistical significance of poor prognosis in Ann Arbor stage III–IV (hazard ratio; HR = 3.30,  $p < 0.001$ ), beyond T2N0M0 (HR = 6.53,  $p = 0.003$ ), high-intermediate to high IPI classification (HR = 4.91,  $p = 0.001$ ), positivity of BM involvement (HR = 6.88,  $p < 0.001$ ), and first-line chemotherapy as therapeutic modality (HR = 2.85,  $p = 0.011$ ). Anatomically extra-



**Fig. 4.** Survival outcomes after radiotherapy and rituximab-containing chemotherapy. Kaplan–Meier estimates of overall survival (A) and progression-free survival (B) between frontline radiotherapy and primary rituximab-containing chemotherapy.

**Table 3**  
Prognostic factors affecting survival outcomes in patients with primary ocular adnexal MALT lymphoma.

Factor	Failure for PFS				Overall mortality				
	Univariate		Multivariate		Univariate		Multivariate		
	HR	p	HR	p	HR	p	HR	p	
Age									
≤46	1				1				
>46		0.432			5.47	0.116			
Gender									
Male	1				1		1		
Female	0.89	0.771			0.09	0.027	0.12	0.135	
Location									
Conjunctiva	1				1				
Extra-conjunctiva	2.42	0.014			8.04	0.054			
Location-subgroup									
Conjunctival lesion only	1				1				
Orbital lesion only	1.92	0.056			3.21	0.101			
Laterality									
Unilateral	1				1				
Bilateral	1.93	0.124			4.21	0.533			
Ann Arbor stage									
I-II	1				1				
III-IV	3.30	<0.001			2.87	0.012			
TNM-staging system									
T2N0M0	1		1		1		1		
Beyond T2N0M0	6.53	0.003	4.77	0.029	3.84	0.009	2.69	0.053	
IPI risk classification									
Low to low-intermediate	1				1				
High-intermediate to high	4.91	0.001			0.45	0.661			
BM involvement									
No	1		1		1		1		
Yes	6.88	<0.001	5.98	<0.001	2.73	0.003	2.03	0.059	
Ki-67 index (%)									
≤10	1				1				
>10	4.99	0.751			1.32	0.878			
Therapeutic modality									
Radiotherapy	1		1		1				
Chemotherapy	2.85	0.011	1.63	0.434	2.23	0.293			

Abbreviations: MALT; mucosa-associated lymphoid tissue, HR; hazard ratio.

orbital lesions (beyond T2N0M0) and lymphoma involved BM were independently correlated with shorter PFS in multivariate analysis (HR = 4.77, p = 0.029 and HR = 5.98, p < 0.001, respectively) (Table 3).

For OS-associated poor prognostic factors, univariate analysis showed that female gender (HR = 0.09, p = 0.027), Ann Arbor stage III-IV (HR = 2.87, p = 0.012), beyond T2N0M0 (HR = 3.84, p = 0.009), and positivity of BM involvement (HR = 2.73, p = 0.003) were associated with shorter OS. Multivariate analysis for OS showed no factors with statistical significances, however beyond

T2N0M0 (HR = 2.69, p = 0.053) and positivity of BM involvement (HR = 2.03, p = 0.059) only showed the negative tendency about OS (Table 3).

While including of the laterality was not associated with OS or PFS (p = 0.124, p = 0.533, respectively), patient's age, gender, ki-67 index were not associated with OS or PFS independently.

### 3.9. Adverse Events of Each Primary Therapeutic Modality

Table 4 lists the adverse events after primary RT or chemotherapy for primary OAML. In the first-line RT group, the most common adverse event was dry eyes at a level over grade 2 (59%, n = 68). Other ophthalmologic complications were occurred in the following order listed: adnexal inflammation (keratitis, blepharitis, conjunctivitis) (25%, n = 29, median 3 months after beginning RT; range 0.5 month to 7 months), cataract (22%, n = 26, median 34 months after beginning RT; range 17 months to 51 months), corneal ulceration (15%, n = 17, median 2.5 months after beginning RT; 2 to 3.5 months), and radiation retinopathy (9%, n = 10, median 3.2 months after beginning RT; 1 to 16 months), and nasolacrimal duct obstruction (3%, n = 3, median 1.5 months after beginning RT; 0.5 to 3 months). Twelve (10%) patients with cataracts were treated with cataract extraction surgery. There were no RT-related hematological complications over grade 2.

In the first-line chemotherapy group, significant toxicities were mainly hematological adverse events. The rates of Grade 3 or 4 neutropenia, anemia, and thrombocytopenia were 15%, 12%, and 16%, respectively. Other non-hematological complications were nausea (8%), hepatotoxicity (4%), and chemotherapy-related pneumonia (4%). All adverse events were tolerable and manageable with conservative treatment, and none lasted more than 3 months (median 28 days, range: 4-83 days). Moreover, there were no localized ophthalmic complications such as dry eyes, cataracts, or retinopathy.

### 3.10. Other Therapeutic Modalities Except for RT and Chemotherapy

Five patients with Ann Arbor stage I (T2N0M0) only received surgical resection. By the 150-month follow-up, four (80%) patients had achieved CR. However, only one patient relapsed at the same lesion site 19 months after surgical excision. This patient was treated with RT and achieved sustained CR thereafter.

A preliminary study of 50 patients with primary OAML showed no detectable *Chlamydia psittaci* in any titers of a polymerase chain reaction (PCR) assay using universal bacterial primers. Therefore, no additional consideration was needed to evaluate *C. psittaci* related-infection status in this study.

## 4. Discussion

Despite the increasing prevalence of primary OAL including OAML [28], large cohort analysis or multicenter prospective studies have

**Table 4**  
Adverse events by treatment modalities.

First-line radiotherapy (n = 116)		First-line chemotherapy (n = 86)			
Adverse events	n (%)	Adverse events	Grade 1-2, n (%)	Grade 3-4, n (%)	
Dry eyes (≥grade 2) <sup>†</sup>	68 (59)	Hematologic	Neutropenia	33 (38)	13 (15)
Cataract (≥grade 2) <sup>‡</sup>	26 (22)		Anemia	19 (22)	10 (12)
Cataract surgery	12 (10)		Thrombocytopenia	22 (26)	14 (16)
Others (≥grade 2)		Non-hematologic	Nausea	19 (22)	7 (8)
Radiation retinopathy	10 (9)		Hepatotoxicity	13 (15)	3 (4)
Corneal ulceration	17 (15)		General weakness	9 (11)	0
Adnexal inflammation (keratitis, blepharitis, conjunctivitis)	29 (25)		Infection (sepsis, pneumonia, UTI)	9 (10)	3 (4)
Nasolacrimal duct obstruction	3 (3)		Peripheral neuropathy	23 (27)	0
Therapy-related mortality	0	Therapy-related mortality		0	

<sup>†</sup> Dry eye was diagnosed by tear film break-up time and Schirmer's test.

<sup>‡</sup> Cataract was diagnosed by the Lens Opacities Classification System II (LOGS II).



practically been challenged because primary OAML itself is still one of the rare diseases. The majority of retrospective studies have focused on localized Ann Arbor stage IE OAML, which is usually treated with RT [25,26,29]. Therefore, the present study is one of the largest cohort analyses (208 subjects) of patients with a primary OAML histopathologic subtype that includes long-term follow-up and in which the patients were treated with a relatively homogeneous therapeutic strategy at a single center. Although a direct comparison between RT and chemotherapy could not be performed, a relatively large number of frontline chemotherapy treatments for OAML were included. We found several significant findings. First, long-term survival outcomes for OAML were favorable, at 92.7% and 69.7% for 13-year OS and PFS, respectively. Second, in locally limited OAML (staging below T2N0M0), RT was associated with excellent survival outcomes and local control (92% of the CR ratio) of lymphoma, although relapse in the contralateral eye was considerable and RT-related ophthalmic complication rates were high (59% with >grade 2 dry eye syndrome and 22% with cataract). Third, chemotherapy was still feasible with tolerable adverse events in locally advanced OAML (staging beyond T2N0M0 of Ann Arbor stage I or II) similar to RT, and rituximab-based chemotherapy was particularly effective in the distant advanced stage. Finally, BM and PET CT analyses were still needed for OAML, based on BM involvement as an independently poor prognostic factor for survival (HR 5.98,  $p < 0.001$ , PFS) and up-staging ( $n = 6$ , 3% of all patients) by PET CT.

As in Western societies [1,2,20,25,26,30–32], we observed that primary OAML is more common in female population as 1:1.5 of our male-to-female ratio. This was due to a higher prevalence of limited conjunctival OAML in females, while more males had the extraconjunctival disease. Notably, unlike previous studies that reported a median age at diagnosis in the mid-60s [17,30,32], the median age in our study was 46 years (range, 18–85). Comparative analyses according to age cutoffs of under and over 46 years of age indicated a pattern limited to ocular involvement (76.3% vs. 36.4%, respectively) while sex, laterality of eye involvement, and survival outcomes did not differ between the two groups. Therefore, most OAML patients were females with a locally limited stage.

In all, 4.8% ( $n = 10$ ) of our cohort had preexisting autoimmune diseases such as Hashimoto thyroiditis ( $n = 7$ ) and Sjogren syndrome ( $n = 3$ ), does not differ from the prevalence of the general population [33]. Thus, a positive correlation [25,34,35] between OAML and autoimmune disease could not be confirmed in our series. A phase II study by Ferreri et al. [13] reported that local immune stimulation by *C. psittaci* infection may play an important role in OAML pathogenesis. Antibiotics alone (doxycycline) as the initial therapeutic option was evaluated in several studies with an approximate 50% overall response rate [36,37]. However, we did not detect *C. psittaci* in any of 50 OAML patients analyzed by PCR. Autoantigen-related activation by autoimmune disease and local inflammatory processes did not directly contribute to the pathogenesis of OAML in our cohort.

Most of our patients presented with locally limited OAML (75.3%), which was limited to conjunctivae and orbital areas, as in most previous studies [3,19,25]. Similar to previous reports [9,16,24], we found a 7–25% incidence of bilateral ocular adnexal involvement in 23.1% of patients. The association between bilateral involvement and PFS and OS did not have significant statistical power in our large cohort (PFS: HR 1.93,  $p = 0.124$ ; OS: HR 4.21,  $p = 0.533$ ), similar to previous studies [30,38]. This is in contrast with Amrita et al. [25], who reported bilateral involvement as a clinical risk factor independently associated with PFS and OS in a large cohort. These different results may be due to our center's therapeutic strategy, which administers chemotherapy as a first-line therapy for patients with bilateral involvement.

While it is generally accepted that the initial staging workup for patients with primary OAML should include ophthalmic and complete physical examinations and a CT scan of the neck, chest, and abdominopelvic, the use of a PET CT scan and BM aspiration/biopsy

are controversial. Although 20% of OAML patients presented with advanced disease at the time of diagnosis [39–41] and BM involvement has been observed in 5–10% of patients with OAML in previous studies [3,8,17,25], BM aspiration and biopsy were performed in all 208 patients in our study and malignant lymphoma cells involving BM was found in 17 (8.2%) patients. Multivariate analyses revealed that lymphoma involving BM was independently correlated with a shorter PFS (HR = 5.98,  $p < 0.001$  and HR = 2.73,  $p = 0.003$ ) and slightly shorter OS (HR = 2.03,  $p = 0.059$ ). OAML is a low-grade type of B-cell NHL that typically has a relatively low FDG uptake in PET CT scans, leading to the inherent possibility of false-negative findings and low sensitivity (27%) [41,42]. Because OAML is an indolent disease with few distant lesions at initial diagnosis, many studies have not performed PET imaging at diagnosis [10,25]. However, in our cohort, PET CT scans indicated a change in Ann Arbor stage from I to IV in seven patients (3.4%) who had FDG uptake in the liver, spleen, kidney, cervical, and intra-abdominal lymph node; one had biopsy-proven extraorbital MALT lesions. All of these patients then received first-line chemotherapy, after which they achieved CR. Therefore, we suggest that both a BM study and PET CT scan are necessary components of initial OAML staging and diagnosis.

Overall, RT led to excellent local control (85–100%) in patients with Ann Arbor stage I OAML, achieving durable clinical remission [43,44]. However, RT may be insufficient to prevent distant recurrence (10–33%) over at least 10 years after RT [15,45,46]. Similar to previous studies, 91.5% of patients in our cohort achieved local control. There is no generally accepted radiation plan for patients with OAML, and no consensus on the optimal RT dose and fractionation. Although the International Lymphoma Radiation Oncology Group guidelines recommend doses of 24 to 25 Gy in 1.5 to 2 Gy fractions for primary OAML patients with high local control and minimal toxicity [47], in our cohort, a median dose of <26 Gy showed less lymphoma control than doses of >26 Gy and there were no statistical differences in RT-related local ophthalmic adverse events except for more dry eye complications. Similar observations were reported by Desai et al. [25] and Ejima et al. [48] with doses of 30 to 30.6 Gy. In our RT only cohort, a relapse pattern was observed in locally advanced relapsed patients alone: three local ipsilateral failures and five contralateral relapses. In addition, two relapsed patients who had received a dose of >26 Gy had contralateral eye relapse. However, no patients had a distant relapse; we only observed locally advanced relapse ( $n = 10$ ) in our series. Thus, RT only with a dose of >26 Gy achieved excellent local control with ipsilateral ex-radiation field relapses or contralateral eye relapses without distant recurrence in limited primary OAML patients.

Most previous studies have mainly focused on aspects of RT effectiveness, and thus RT-related complications that reduce QoL are often overlooked. We observed acute and chronic RT-related adverse events including dry eyes (59%), adnexal inflammations (25%), and retinopathy (9%) as acute RT-related complications, and cataract ( $n = 22\%$ ) and nasolacrimal duct obstruction (3%) as chronic complications. Similarly, Uno et al. [44] and Ejima et al. [48] reported that up to 50% of patients experienced long-term complications such as cataract (30–50%) and xerophthalmia (20–40%). Although we did not conduct a questionnaire to assess QoL, patients who had adverse events often complained about their decreased QoL; almost all patients with dry eye visited the hospital frequently as their lives were often disrupted by the pain and glare, and patients with post-RT cataracts had blurred vision and a fear of possible cataract surgery. Twelve patients (46%) with RT-related cataracts underwent cataract surgery. Patients with RT-related ophthalmic complications of grade 2 or higher, and those who underwent cataract surgery had a median age of 46 years and were mostly female, similar to our total cohort. These results suggest the possibility that surgical management for RT-related cataract was more common in relatively young patients, and that the surgery itself could be stressful and decrease QoL due to early loss of accommodation and near vision.

Regarding the use of chemotherapy in patients with OAML, few retrospective case series have reported single agent, immunotherapy, or combination immunochemotherapies [15,49,50]. Previous studies using rituximab alone or cytotoxic agents alone for MALT lymphoma have reported disappointing results [16,51] and recent trials have evaluated an immunochemotherapy regimen consisting of a cytotoxic regimen with/without rituximab for patients with Ann Arbor stages I to IV and have reported promising survival outcomes [52,53]. Rituximab therapy has the advantage of high activity in newly diagnosed and relapsed settings, but the disadvantages of early recurrence and lack of long-term data [51]. In our cohort, rituximab-containing regimens of R-CVP and R-CHOP, and non-rituximab regimens of CVP and CHOP were administered to 86 patients. They had advanced-stage OAML as bilateral T2N0M0, beyond T2N0M0. During approximately 66 months of follow-up, CR was achieved in 71.4–92.3% of patients at 1 month post-chemotherapy; long-term CR was achieved in 57.1–92.3% of patients. The early CR rate was high in patients treated with the rituximab-containing regimen, but this trend did not hold up for the long term. These results reflect the fact that all advanced-stage patients were treated with R-CHOP, and thus patients in this group had higher risk disease status. For this reason, when subgroup analyses of only relatively advanced stages beyond T2N0M0 were performed, the rituximab-containing group was characterized by a significantly longer PFS (Fig. 3B). Previous studies have reported local relapse as main problems after chemotherapy [16,51], but we observed a relapse pattern after first-line chemotherapy that differed depending on the initial lymphoma staging, with locally limited relapse in limited stage OAML and overwhelmingly higher systemic relapse rates in patients with advanced-stage OAML. In addition, CVP or CHOP regimens with/without rituximab is widely used for indolent NHL, these regimens resulted in tolerable hematological and manageable non-hematological complications similar to the previous studies, without any RT-related ophthalmic complications. Taken together, our results indicate that chemotherapy is effective even in locally advanced-stage OAML without localized ophthalmic complications, while relapses in distant advanced-staged OAML are similar to another subtype of NHL.

To date, it has generally been accepted that frontline RT is better than chemotherapy as a therapeutic option based on significantly higher response rates without complications. In our study, however, RT tended to have slightly better therapeutic outcomes than chemotherapy in terms of recurrence, but was not superior to rituximab-containing chemotherapy despite observations that most such patients were in a distant advanced stage ( $p$ -value 0.057 of OS, 0.075 of PFS, Fig. 4A, B) as well as compared to any chemotherapy regimens (RT vs. any type of CT regimen in OS,  $p = 0.281$ , Supplementary Fig. 2). Moreover, regarding adverse events, RT-related complications were mostly irreversible, whereas adverse events in the chemotherapy group were all temporary and reversible without therapy-related mortality.

Several studies have shown that advanced Ann Arbor stage, old age, having an extra-conjunctival lesion at diagnosis, B symptoms, and elevated serum levels of LDH are associated with poor prognoses in OAML patients [34,54]. However, in our cohort, the majority of these risk factors did not significantly affect survival outcomes. These results may stem from differences in the number of patients and the length of follow-up among studies. Multivariate analyses confirmed that the presence of extra-orbital lesions was an independent prognostic factor for shorter PFS and BM involvement. In addition, multivariate analyses showed that no factors were associated with shorter OS.

This study had some limitations. First, it had a retrospective design. Second, the median follow-up duration was only 70 months, which is insufficient to fully demonstrate the long-term course of this disease. Third, there was a relatively small probability of event occurrence and a large number of censored patients due to indolent disease characteristics of OAM or long time-to-event, which is likely to have introduced bias in our results, since as the final number of patients at the time point of comparative analysis of each therapeutic modality is reduced.

In conclusion, despite these limitations, our study confirms that primary OAML is an indolent, non-fatal disease that mostly affects younger females in our cohort, with excellent therapeutic responses and long survival outcomes for any therapeutic treatments. RT had a relatively high incidence of RT-related irreversible cataracts and other ophthalmic complications, even if it was modulated using a lens-shielding technique. This may significantly reduce the QoL of active young patients. Conversely, frontline chemotherapy showed similar or favorable OS and PFS rates, comparable to RT, as well as an absence of ophthalmic complications such as cataract and dry eye syndrome. Therefore, we recommend younger patients to consider early frontline chemotherapy, and especially a rituximab-containing regimen rather than RT, even if it is a localized disease. Upfront RT is suggested for older patients who are either unsuitable for systemic chemotherapy or who would not suffer from any deterioration in their QoL due to ophthalmic complications.

### Authors' Contributions

Conception and design: Y.W. Jeon, S.W. Yang, and S.G. Cho.

Development of methodology: Y.W. Jeon, S.W. Yang, and S.G. Cho.

Acquisition of data: Y.W. Jeon, H.J. Yang, B.O. Cho, S.E. Jung, K.S. Park, J.H. O, S.W. Yang, and S.G. Cho.

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y.W. Jeon, H.J. Yang, B.O. Cho, S.E. Jung, K.S. Park, J.H. O, S.W. Yang, and S.G. Cho.

Writing, review, and/or revision of the manuscript: Y.W. Jeon, S.W. Yang, and S.G. Cho.

Study supervision: S.G. Cho.

### Declaration of Interests

The authors declare that they have no personal or financial conflict of interest.

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### Appendix A. Supplementary Data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.eclinm.2018.10.001>.

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