

RESEARCH ARTICLE

Ocular Adnexal Lymphoma Classified using the WHO Classification: Not only Histology and Stage, but also Gender is a Predictor of Outcome

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ABSTRACT *Introduction:* Ocular adnexal lymphomas (OAL) belong to the most common malignancies of the orbit and eyelids and are now classified according to the WHO classification system. MALT lymphoma appears to be the most frequent OAL. Histology type and stage of OAL have been found predictors of patient survival. *Purpose:* To evaluate the outcome of a cohort of patients with OAL using the WHO classification and to compare outcome predictors with those of other studies using the WHO classification. *Design:* Retrospective, cohort study. *Materials and methods:* Clinical profile at presentation, initial complaints and findings, classification and stage, treatment and outcome of 54 patients with biopsy proven and re-analyzed OAL seen between 1 January 1992 and 1 January 2002 at the UMC Utrecht, NL, were evaluated. Kaplan-Meier survival analysis and multivariate Cox-regression survival analysis were applied to assess predictors of outcome. *Results:* Forty nine patients were found to have primary and five secondary lymphomas. Of those with primary OAL, 27 had MALT, eight diffuse large B-cell, six mantle cell and eight follicular cell lymphoma. Histology and stage showed a significant association with survival (Log-rank test: $p = 0.001$ and $p = 0.002$, respectively). A multivariate Cox-regression survival analysis showed histological type to be the only significant predictor for outcome. Looking at the dichotomy full remission versus not completely cured, gender was found to be a significant predictor (Log-rank test: $p = 0.005$). *Conclusion:* This study showed that not only histology type and stage, but also gender is a predictor of outcome.

KEYWORDS Non-hodgkin lymphoma; WHO-classification; MALT lymphoma; staging; histology

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INTRODUCTION

Ocular adnexal lymphoma (OAL) is the most common malignant tumor of the eyelids, conjunctiva and orbit, accounting for about 8% of all tumors seen in this area.¹

Patient care requires rapid explanation of diagnosis and prognosis of disease and the question is how this can be achieved in the management of a tumor as variable as AOL. Studies using the Revised European-American classification of Lymphomas (REAL) already showed that survival of patients with OAL is related to the stage and histology type of the disease.²⁻⁶ The introduction, however, of the World Health Organization (WHO) modification of the REAL classification,⁷ required a re-appraisal of these assessments. Studies using the WHO classification confirmed that histological subtype and stage are predictors of patient morbidity and survival.⁸⁻¹⁰ Jenkins et al.,⁹ in the largest series till present, assessed that also other factors, like deep localization (especially those lymphomas located in the lacrimal gland), the presence of a Relative Afferent Pupillary Defect and old age are related to a less favorable outcome. However, in none of these studies a relationship has been found between prognosis and gender. In this study, we evaluated the clinical profile at presentation including the time relapse between onset of complaints and diagnosis, initial complaints and clinical findings, classification, whether the tumor presented uni- or bilaterally, stage of the disease, treatment and outcome of 54 patients with OAL, referred to a tertiary referral center, classified and re-classified using the WHO classification, and compared our results with other studies using the WHO classification.

METHOD AND MATERIAL

We retrieved computer stored data from the Department of Pathology of all patients diagnosed with an OAL at the University Medical Center Utrecht, the Netherlands, between 1 January 1992 and 1 January 2002. We only included biopsy proven lymphomas with involvement of the orbit, eyelids, conjunctiva and lacrimal gland. For the purpose of this study, all biopsies were re-examined and reclassified according to the WHO classification system by one pathologist (DMDSS-G).

From the patients thus collected, we evaluated the time elapsed between onset of complaints and histological diagnosis, age, gender, initial complaints and signs and symptoms, mono- or bilaterality, the histological classification, the staging of the disease, the treatment given and the outcome in terms of survival and alive with disease. Clinical findings and CT- and MRI-scans served to determine localization of the tumor:

Retrospectal tumors predominantly outside the lacrimal gland were classified as 'orbital', predominantly within the lacrimal gland as 'lacrimal,' predominantly preseptal tumors as 'eyelid' and tumors largely confined to the conjunctiva, the classical 'salmon patch' lesions, as 'conjunctival'. The histological diagnosis was based on paraffin tissue biopsies and the use of immunohistochemistry.

For classification and staging, the WHO modification of the REAL classification was used. All patients were referred to a hemato-oncologist (EJP) for staging. For staging, the Ann Arbor classification was used. We classified patients with bilateral orbital, but without extra-orbital involvement as Ann Arbor stage I. We considered patients to have primary disease if there was no evidence of systemic disease prior to the diagnosis of OAL.

Treatment options applied were: observation, radiotherapy, chemotherapy or a combination of radio- and chemotherapy. Local radiotherapy treatment consisted of a total dosage of 30-40 Gy in multiple sessions in almost all cases. Chemotherapy treatment ranged from oral chlorambucil to C(H)OP (cyclofosfamide, doxorubicin, vincristine and prednisolone) regimens. The outcome measures we used were: alive with no remission, alive with remission (active disease), death due to lymphoma, death due to other cause and lost to follow-up.

Statistical Analysis

For statistical analysis, SPSS software, version 13.0 was used. To assess the predictive value of age, gender, presenting complaints and findings, histology type, stage, and treatment on the outcome, Kaplan-Meier survival and Cox-multivariate regression survival analysis were used.

RESULTS

Clinical Characteristics

Fifty four patients were diagnosed with OAL in the period between 1 January 1992 and 1 January 2002. Of these patients, 25 were male and 29 were female. Forty nine patients had primary disease; in five patients (9%) the orbital lymphoma developed secondary to systemic disease. At presentation, patients ranged in age from 24 to 89 years with a mean age of 64 years (Table 1). The mean follow-up period was 46 months (range 7-129). The interval between symptoms and the time of

TABLE 1 Comparison of different features of ocular adnexal lymphomas (Percentages between brackets, *n* = number, *y* = years, *mo* = months)

	MALT	Diffuse Large B-cell	Mantle Cell	Follicular	Secondary
Frequency (<i>n</i>)	27	8	6	Grade 1:3 Grade 2:3 Grade 3:2	5
Male/female (<i>n</i>)	16/11	1/7	4/2	2/6	2/3
Mean Age (<i>y</i>)	62	68	74	61	65
Complaints					
Swelling	21 (77)	7 (88)	5 (83)	6 (75)	5 (100)
Bulging eye	7 (26)	1 (13)	2 (33)	1 (13)	1 (20)
Double vision	7 (26)	3 (38)	2 (33)	4 (50)	3 (60)
Dropped eyelid	2 (7)	2 (25)	2 (33)	1 (13)	1 (20)
Irritation/tearing	18 (67)	5 (63)	2 (33)	4 (50)	0 (0)
Clinical features					
Mass	18 (67)	7 (88)	4 (67)	5 (63)	5 (100)
Proptosis	12 (45)	4 (50)	4 (67)	5 (63)	2 (40)
Motility imp.	4 (15)	4 (50)	3 (50)	2 (25)	0 (0)
Ptosis	5 (19)	1 (13)	2 (33)	3 (38)	2 (40)
Globe displ.	5 (19)	2 (25)	1 (17)	1 (13)	1 (20)
Localization <i>n</i> (5%)					
Eyelid	2 (7)	1 (13)	0 (0)	2 (25)	1
Orbit	9 (33)	4 (50)	2 (33)	5 (63)	3
Lacrimal gland	5 (19)	0 (0)	3 (50)	1 (13)	0
Conjunctiva	11 (41)	3 (38)	1 (17)	0 (0)	1
Laterality: uni/bi	22/5	8/0	5/1	7/1	5/0
Mean interval (<i>mo</i>)	18	12	12	9	2
Staging <i>n</i> (%)					
Ann Arbor I	19 (70)	6 (75)	2 (33)	3 (38)	—
Ann Arbor II	2 (7)	0 (0)	0 (0)	1 (13)	—
Ann Arbor III	1 (4)	1 (13)	0 (0)	3 (38)	—
Ann arbor IV	5 (19)	1 (13)	4 (67)	1 (13)	—
Treatment <i>n</i> (%)					
Observation	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)
Radiotherapy	17 (63)	4 (50)	1 (17)	1 (13)	1 (20)
Chemotherapy	7 (26)	2 (25)	4 (67)	4 (50)	2 (40)
Radio+chemo	2 (7)	2 (25)	1 (17)	3 (38)	2 (40)
Outcome <i>n</i> (%)					
Alive without disease	19 (70)	2 (25)	1 (17)	3 (38)	2 (40)
Alive with disease	2 (7)	4 (50)	1 (17)	3 (38)	1 (20)
Death lymphoma	2 (7)	1 (13)	3 (50)	1 (13)	2 (40)
Death other	2 (7)	1 (13)	0 (0)	1 (13)	0 (0)
Lost to FU	2 (7)	0 (0)	1 (17)	0 (0)	0 (0)
Follow-up (<i>mo</i>)	50	42	20	56	31

diagnosis ranged from one to 72 months, the mean interval being 13 months. There was no significant difference of the time period elapsed between the onset of complaints and the histological diagnosis between the histology subgroups of the primary OAL. For the whole group, the most common reason for seeking medical

help was swelling and or proptosis. The most common findings were palpable mass, proptosis, motility disturbance, ptosis and globe displacement. Localization of the tumor involved the orbit in 23 cases, the conjunctiva in 16 cases, the lacrimal gland in nine cases and the eyelid(s) in six cases. In 27 of 49 patients with primary

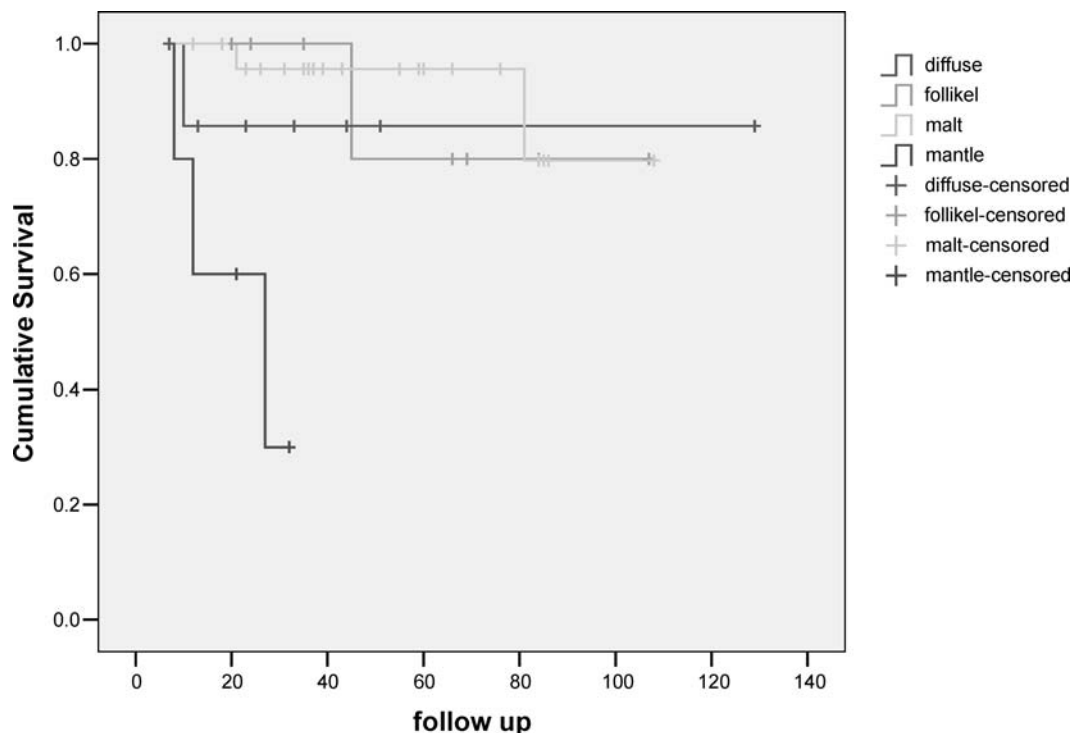


FIGURE 1 Survival function for different diagnoses.

disease the diagnosis according to the WHO classification was MALT lymphoma. Eight patients had diffuse large B cell lymphoma and another eight had follicular lymphoma (grade 1–3). In six patients the diagnosis was mantle cell lymphoma. Ann Arbor staging stage I was assessed in 61% of cases, whereas 22% of patients had stage IV disease. The following subtypes of OAL's in patients with secondary disease were found: one follicular lymphoma, grade 1, two follicular lymphomas, grade 3, one peripheral T-cell lymphoma, and one secondary multiple myeloma.

Treatment and Outcome

One patient with primary (MALT cell) lymphoma was observed. Twenty three patients with primary disease were treated with radiotherapy alone, 17 patients with chemotherapy alone, eight patients received a combination of radiotherapy and chemotherapy. Of the five patients with secondary disease, one patient was treated with radiotherapy alone, two patients received chemotherapy and two patients a combination of radio- and chemotherapy. Of all patients (primary and secondary), 27 (50%) responded well to treatment and showed complete remission after an average follow-up period of 46 months. At the end point of our study, 11 patients (20%) were alive with disease, nine patients (17%) died due to the lymphoma, while four patients

died due to other causes (Figs. 1 and 2). Three patients were lost to follow-up.

Of patients with secondary disease, two of them showed complete remission, one patient was alive with disease and two patients died of lymphoma. The mean follow-up in patients with secondary lymphoma was 33 months.

Patients with primary disease had an average follow-up of 45 months. Most patients ($n = 30$, 61%) were classified as stage I according to the Ann Arbor classification. Of these patients, 19 showed complete remission, five were alive with disease and one patient died of lymphoma (three died of a non-OAL related cause, two were lost to follow-up). Eleven patients had stage IV disease, of these patients one reached a remission, three patients were alive with disease and five patients died of lymphoma.

Statistical analysis of the following parameters, gender, age, time elapse between onset of complaints and final diagnosis, localization, whether the presentation was uni- or bilateral, WHO-subtype, and stage of the disease, of the 49 patients with primary disease revealed the following: Using univariate Kaplan-Meier survival analysis, diagnosis and stage showed a significant association with outcome (Log-rank test $p = 0.001$ and $p = 0.002$, respectively, see Figs. 1 and 2). A multivariate Cox-regression forward conditional survival analysis

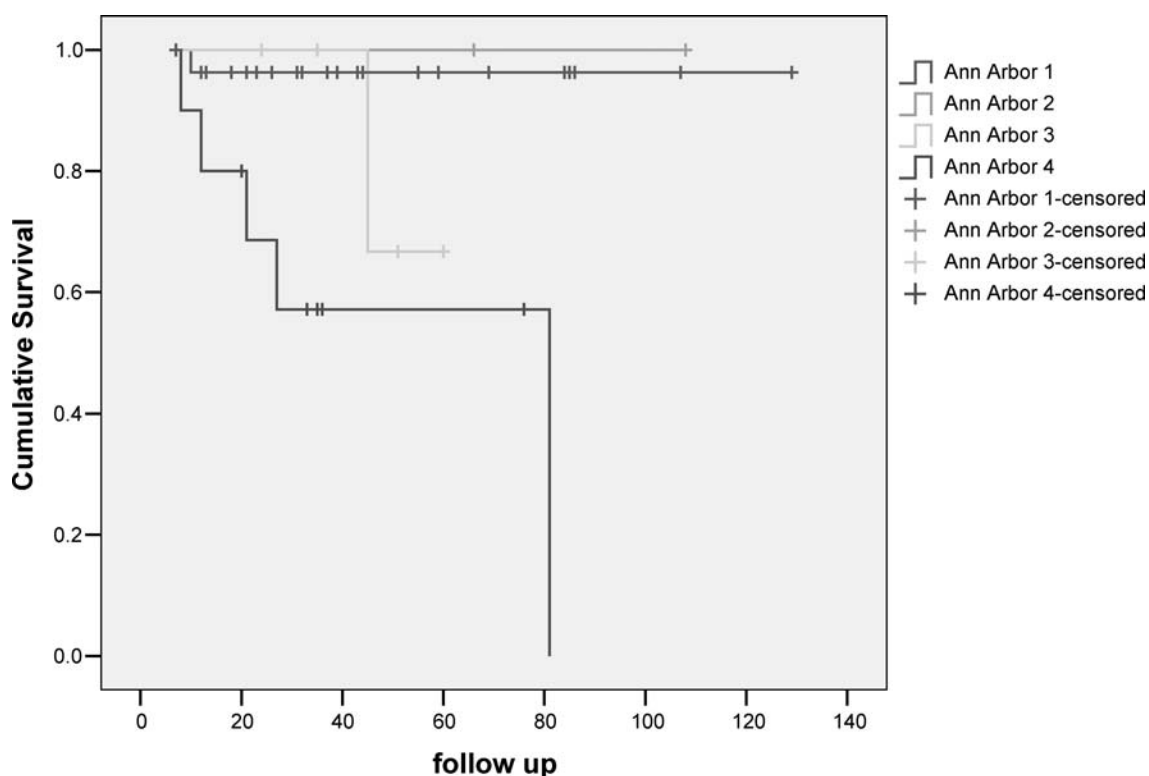


FIGURE 2 Survival function for different stages.

showed diagnosis to be the only independent significant predictor. We also looked at the dichotomy complete remission versus not completely cured (death due to OAL plus alive with OAL). Gender yielded to be the only significant predictor (Log-rank test $p = 0.005$. Lymphoma related death rate and/or recurrence rate was significantly higher in females than in males ($p = 0.03$).

DISCUSSION

This study confirms previous studies stating that tumor subtype (WHO classification) and stage of the disease (Ann Arbor classification) are decisive determinants of survival. With respect to the most common OAL subtypes, patients with a MALT type OAL have the best, patients with a mantle cell type the worst and those with a diffuse large B-cell or follicular cell type an intermediate prognosis. As far as we could retrieve, our study is the first to show that female patients with an OAL have a worse prognosis. Of 46 patients with primary disease at the final evaluation, 5 of 23 males versus 12 of 23 females had died of the lymphoma or were living with a recurrence ($p = 0.03$).

Whereas studies in the pre-WHO classification era,^{2,3,5,6} already showed that histological subtype and stage of the disease determined the outcome, these studies failed to demonstrate the role of gender, anatomic

site, and duration. Also, in a recent study with a limited number of patients ($n = 24$), no correlation of these parameters with survival could be assessed.¹¹ All these studies, however, were unanimous in their conclusion that OAL's are most frequently found within the orbit. Jenkins et al.,⁹ in the largest series described till present, found bilateral disease and lacrimal gland localization at presentation correlated with a higher rate of disseminated disease and systemic disease, bilateral disease, and deep orbital localization correlated with a worse prognosis. Relative old age and (slightly) worse prognosis were found to be related with each other. A long history of disease, however, was found to be related to a smaller chance of dissemination and a better prognosis, apparently because a long history of disease reflects milder pathology subtype. Sullivan et al.,¹⁰ in a series of 69 patients, found stage at presentation, tumor histology, primary or secondary status, and whether the tumor was uni- or bilateral, determinants of survival. In general, not unlike any malignant tumor, more aggressive tumor histology together with stage (bilateral disease can be considered as more advanced disease) determines the outcome of OAL. Old age, deep localization and female gender, as found in our series, may also influence the outcome in a worse direction. The fact that our study did not confirm that age, duration of the

disease prior to the diagnosis, localization and whether the presentation was uni- or bilateral were related to the outcome can be explained by the relatively small numbers as compared to some other studies.^{4,9}

It is therefore interesting, that—as far as we could retrieve—this study showed a relationship between outcome and gender for the first time. We assessed this relationship by grouping together patients who either had a tumor related death or a recurrence, which has not been done before.

Other studies have shown, that patients with a MALT or follicular cell OAL perform an excellent prognosis for life, although MALT lymphomas are known for their high distant relapse rate.^{8,12} In this study, relapse rates for primary MALT and follicular cell subtypes were 14 and 50% after a mean follow up of 50 and 56 months respectively. In spite of the normal protocol of local therapy of 30–40 Rad radiotherapy, two patients with a primary MALT lymphoma (7%), one with a B-cell, three with a mantle cell and one with a primary follicular cell lymphoma (13%) died following disseminated disease.

In conclusion, next to histological subtype and stage, and next to known clinical parameters as localization and uni- or bilateral presentation, gender seems to be a predictor of outcome in ocular adnexal lymphoma.

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