Histological features of ocular adnexal lymphoma (REAL classification) and their association with patient morbidity and survival

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Abstract

***Background*—The histological characteristics of ocular adnexal lymphomas have previously provided only a limited guide to clinical outcome for affected patients. This clinicopathological relation was re-examined using the Revised European American Lymphoma (REAL) system to classify the tumours in a large cohort of patients.**

***Methods*—The biopsies and clinical follow up data for 192 patients with ocular adnexal lymphoma were reviewed, the biopsies being regraded in accordance with the REAL classification. For each of five histological groups, logistic regression analysis was used to determine the odds ratios (OR) for the presence of systemic disease at the time of orbital diagnosis and Cox regression analysis was used to assess the hazard ratios (HR) for disseminated disease and lymphoma related death. For 108 patients in whom extraorbital spread occurred, the histological category of lymphoma was compared with the sites of dissemination.**

***Results*—At presentation, the frequency of previous or concurrent extraorbital disease increased from marginal zone lymphoma (OR 1.0), diffuse lymphoplasmacytic/lymphoplasmacytoid lymphoma (OR 2.3), follicle centre lymphoma (OR 3.8), diffuse large B cell lymphoma (OR 4.0) to other histological lymphoma variants (OR 26.8). For all histological types, the estimated risk of extraorbital disease and lymphoma related death continued for many years and the proportion of patients with at least one extraorbital recurrence after 5 years was 47% for MZL, 48% for LPL, 64% for FCL, 81% for DLCL, and 95% for other lymphoma variants. The corresponding estimated rates for 5 year lymphoma related mortality were 12%, 19%, 22%, 48%, and 53% respectively.**

***Conclusions*—Patients with ocular adnexal lymphoma can be classified by REAL into five distinct groups, which show a progressive increase in the risks of extraorbital disease at diagnosis, of disease dissemination with time, and of tumour related death.**

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The histomorphological characteristics of lymphocyte recruiting diseases of the ocular adnexa have historically been regarded as a relatively poor guide to their prognosis, most lesions consisting of homogeneous sheets of well differentiated lymphocytes. Some authors had suggested that the presence or absence of germinal follicles might differentiate benign and malignant disease,[1–3] but while disseminated disease was less frequent in patients with germinal follicles,[4] their presence was no guarantee of a benign clinical course.[5]

The interpretation of the germinal centre was revised by Isaacson and Wright,[6] who put forward the concept of mucosa associated lymphoid tumours, in which the follicle represents a preceding inflammatory process which is subsequently involved by lymphoma.[7] These authors demonstrated that the neoplastic B cell population is initially located adjacent to the germinal centre (hence the name marginal zone lymphoma (MZL)) and later "colonises" the centre,[8] eventually destroying its architecture. The recognition of this group of extranodal lymphomas has resulted in fewer diagnoses of lymphoid hyperplasia, indeterminate or pseudolymphoma.[9] MZL has been reported to be the most frequent lymphoma in the ocular adnexa and accounts for between 38% and 64% of lymphomas at this site.[10 11] MZL generally respond well to local therapy,[12] but little information is available concerning the survival of patients with MZL affecting the ocular adnexa. Although a difference in survival between patients with low and high grade lymphomas has been demonstrated,[11–13] the relative morbidity and survival of patients with lymphomas classified according to the Revised European American Lymphoma (REAL) scheme[14] has not been reported.

We present an analysis of a cohort of patients, presenting to one institution between 1987 and 1996, that examines the relation between lymphoma histology and the presence of systemic disease at ophthalmic presentation, and the subsequent development of disseminated disease or tumour related death.

Methods

One hundred and twenty tissues biopsied between 1993 and 1996 were assessed prospectively and a further 98 archival specimens were retrospectively reviewed by two pathologists (IC and AN). Clinical follow up data were inadequate for 26 patients, leaving 192 patients in whom clinical and pathological data were available for detailed analysis. The associations between histology and the clinical outcome variables, spread and lymphoma related death were studied using logistic regression and Cox

Table 1 Characteristics and outcome for patients presenting with ocular adnexal lymphoma classified by histological type (REAL classification)

Characteristics		Histological category of lymphoma					
		MZL	*LPL*	*FCL*	*DLCL*	*H5*	*All*
	All patients	82/192 (43%)	44/192 (23%)	26/192 (14%)	19/192 (10%)	21/192 (11%)	192
Number	Solely adnexal disease	67/123 (54%)	29/123 (24%)	14/123 (11%)	10/123 (8%)	3/123 (2%)	123/192 (64%)
	All patients	68 (18–87)	63 (31–86)	65 (18–86)	73 (35–90)	60 (3–81)	66 (3–90)
Age at diagnosis (mean and range)	Solely adnexal disease	68 (18–87)	62 (31–86)	61 (18–86)	74 (39–85)	58 (3–80)	66 (3–87)
	All patients	35/82 (43%)	21/44 (48%)	12/26 (46%)	10/19 (53%)	16/21 (76%)	94/192 (49%)
Sex (proportion men)	Solely adnexal disease	29/67 (43%)	15/29 (52%)	6/14 (43%)	5/10 (50%)	2/3 (67%)	57/123 (46%)
Clinical outcome characteristics in all patients							
Systemic spread at diagnosis	Proportion	15/82 (18%)	15/44 (34%)	11/26 (42%)	5/19 (26%)	16/21 (76%)	62/192 (32%)
	Odds ratio	[1.0]	2.3 (1.0, 5.3)	3.3 (1.3, 8.5)	1.6 (0.5, 5.1)	14.3 (4.5, 45.1)	
Extraorbital spread at diagnosis	Proportion	15/82 (18%)	15/44 (34%)	12/26 (46%)	9/19 (47%)	18/21 (86%)	69/192 (36%)
	Odds ratio	[1.0]	2.3 (1.0, 5.3)	3.8 (1.5, 9.9)	4.0 (1.4, 11.6)	26.8(6.9,102. 7)	
Systemic spread at any time	Proportion	33/82 (40%)	25/44 (57%)	14/26 (54%)	19/19 (47%)	21/21 (100%)	102/192 (53%)
	Hazard ratio	[1.0]	1.0 (0.5, 2.0)	1.7 (0.7, 3.9)	2.0 (0.8, 5.1)	4.1 (1.9, 8.9)	
Extraorbital spread at any time	Proportion	33/82 (40%)	25/44 (57%)	16/26 (62%)	13/19 (68%)	21/21 (100%)	108/192 (56%)
	Hazard ratio	[1.0]	1.0 (0.5, 2.0)	1.9 (0.8, 4.3)	2.4 (1.0, 5.6)	4.1 (1.9, 8.9)	
All deaths	Proportion	24/82 (29%)	18/44 (41%)	10/26 (39%)	10/19 (53%)	14/21 (67%)	76/192 (40%)
Lymphoma related death	Proportion	11/82 (13%)	12/44 (27%)	8/26 (31%)	7/19 (37%)	11/21 (52%)	49/192 (26%)
	Hazard ratio	[1.0]	1.1 (0.5, 2.6)	2.0 (0.8, 5.0)	2.9 (1.1, 7.6)	3.9 (1.7, 9.2)	
*Clinical outcome characteristics in patients with solely adnexal disease at diagnosis**							
	Proportion	18/67 (27%)	10/29 (35%)	4/14 (29%)	4/10 (40%)	3/3 (100%)	39/123 (32%)
Future extra	Hazard ratio	[1.0]	0.9 (0.4, 1.9)	1.3 (0.5, 4.0)	1.9 (0.7, 5.8)	3.1 (0.9, 10.5)	
All deaths	Proportion	19/67 (28%)	10/29 (35%)	4/14 (29%)	5/10 (50%)	1/3 (33%)	39/123 (32%)
Lymphoma related deaths	Proportion	6/67 (9%)	4/29 (14%)	3/14 (21%)	3/10 (30%)	1/3 (33%)	17/123 (14%)
	Hazard ratio	[1.0]	0.5 (0.1, 2.3)	2.1 (0.5, 8.7)	2.5 (0.6, 11.2)	3.2 (0.4, 26.9)	

Lymphoma types: MZL = marginal zone lymphoma, LPL = diffuse lymphoplasmacytoid/lymphoplasmacytic lymphoma, FCL = follicle centre lymphoma, DLCL = diffuse large B cell lymphoma, H5 = rare histologic variants (see Table 2).
Lower and upper 95% confidence limits are given in parentheses after odds and hazard ratios. [1.0] is the reference datum.
"Systemic spread" refers to remote non-contiguous disease. "Extraorbital spread" refers to both remote disease and local extraorbital extension.
*These data refer to patients presenting without a previous history of lymphoma or without extraorbital lymphoma diagnosed (usually as a result of staging) within 3 months of biopsy.

proportional hazards. The site of spread of ocular adnexal lymphoma was also recorded and related to the histological classification outlined below.

HISTOPATHOLOGY

The tissues were classified in accordance with the REAL system[14] and allocated to one of five categories; marginal zone lymphoma (MZL), diffuse lymphoplasmacytic/lymphoplasmacytoid lymphoma (LPL), follicle centre lymphoma (FCL), diffuse large B cell lymphoma (DLCL), and other rare lymphomas (H5) (Table 1). For the regression analysis, the six patients with mantle cell lymphoma (MCL) were included in the H5 category.

The small sample sizes of some biopsies may prejudice the differentiation of MZL and lymphoplasmacytoid lymphoma (immunocytoma) as described in the REAL classification. MZL may consist of either centrocyte-like cells (Fig 1A) or lymphoplasmacytoid cells (Fig 1B) with or without lymphoepithelial and/or follicular invasion (Fig 1C).[8] In lymphoplasmacytoid lymphoma (immunocytoma), sheets of lymphoplasmacytoid cells may be observed without other architectural features and these cells cannot reliably be distinguished from MZL cells by either cytomorphology or immunohistochemistry. Neither consistently expresses CD5 or CD23 which have usefully distinguished other low grade B cell lymphomas[15] and although a polyclonal marker for marginal zone cells has been developed,[16] it has proved technically difficult to use and is not commercially available. In this study, tumours consisting of lymphoplasmacytoid/lymphoplasmacytic cells without evidence of either epithelial involvement or follicular remnants were classed as LPL.

Follicular architecture is also a feature of FCL, but in these cases the malignant population is inherent to the follicular structure (Fig 1D), consists of an admixture of centrocytic and centroblastic cells (Fig 1E), and stains with anti-bcl-2 antibody.[17] In DLCL, a high grade lymphoma, the malignant population consists of large cells with more cytoplasm than found in the lower grade lymphomas (Fig 1F). In mantle cell lymphoma, the malignant population consists of small to medium sized cells with irregular cleaved nuclei (Fig 1G) which stain with anti-cyclin D1 antibody (Fig 1H).[18] Together with mantle cell lymphoma, other rare variants placed into the H5 category were chronic lymphocytic leukaemia/small lymphocytic lymphoma, plasma cell myeloma, B precursor lymphoblastic leukaemia/lymphoma, T precursor lymphoblastic leukaemia/lymphoma, mycosis fungoides/Sezary syndrome, and angiocentric T cell lymphoma.

PATIENTS

The patients' sex, age at presentation, laterality of disease, and subsequent clinical course were obtained by review of notes.

Clinical questionnaires were sent to the patients' general practitioners and oncologist and, in 90 patients, the oncology notes were reviewed. Additional information or details of the death certificates were obtained from cancer registration agencies and the Office for National Statistics. The "follow up interval" was recorded as the interval from date of biopsy to the latest recorded clinical follow up

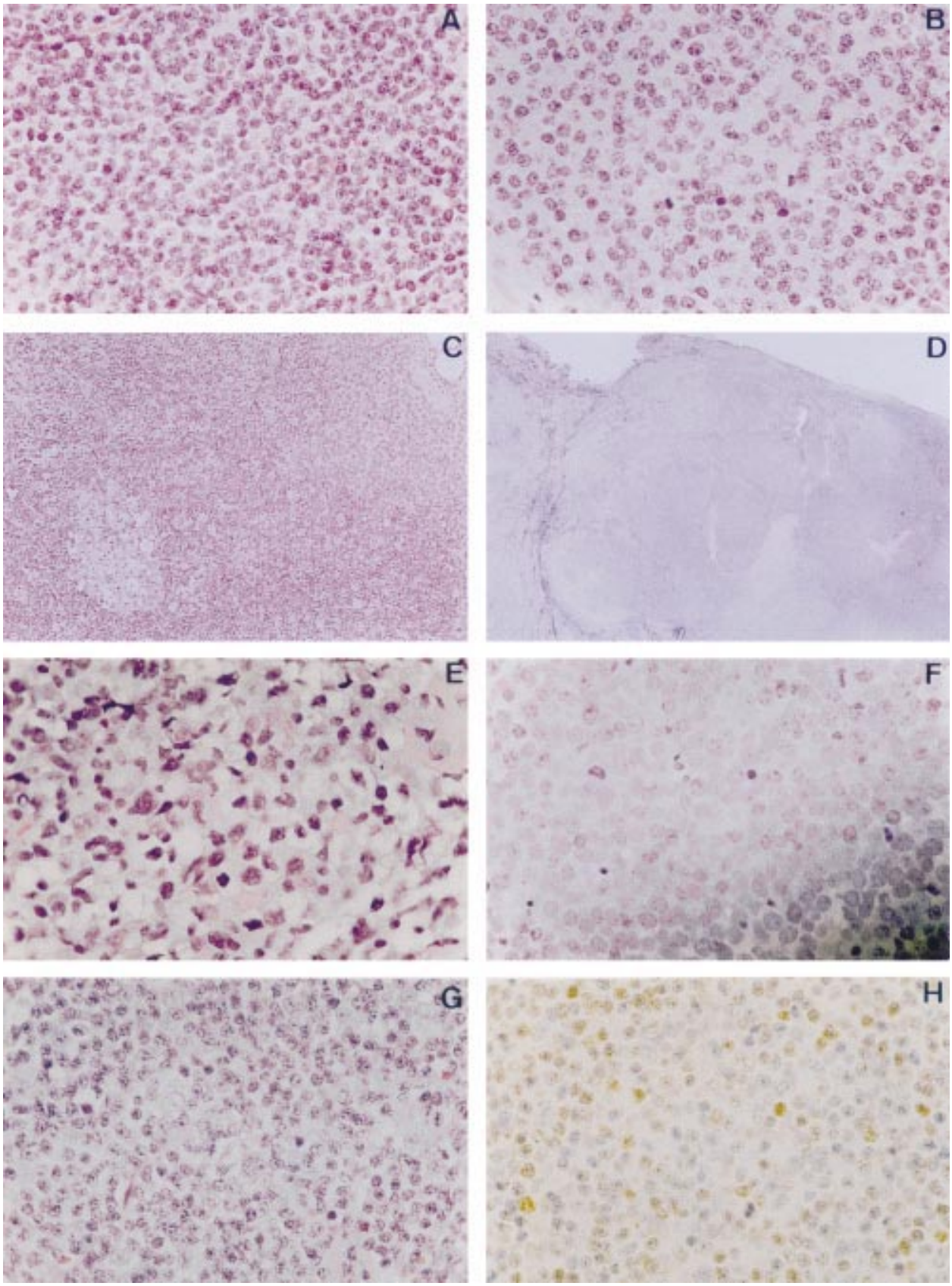

Figure 1 Typical histomorphology for lymphomas of the ocular adnexa (haematoxylin and eosin staining, unless otherwise stated). (A) Centrocyte-like cells in marginal zone lymphoma; (B) lymphoplasmacytoid cells in marginal zone lymphoma; (C) trapped reactive follicle in marginal zone lymphoma; (D) follicular architecture in follicle centre lymphoma; (E) centrocytes and centroblasts in follicle centre lymphoma; (F) centroblasts in diffuse large B cell lymphoma; (G) centrocytes in mantle cell lymphoma; (H) Cyclin D-1 staining in mantle cell lymphoma.

Table 2 Characteristics of 21 patients with rare variant lymphomas, categorised as "H5" for the analysis

Histology	Number of cases	Age at diagnosis (years)	Proportion of males	Proportion with extraorbital spread at diagnosis	Proportion with extraorbital spread at any time	Proportion with lymphoma related death
MCL	6	66 (median)	4/6 (67%)	5/6 (83%)	6/6 (100%)	1/6 (17%)
CLL	5	60 (median)	3/5 (60%)	4/5 (80%)	5/5 (100%)	5/5 (100%)
BPLL	3	3, 3, 9	3/3	2/3 (67%)	3/3 (100%)	1/3 (33%)
TPLL	1	3	1/1	1/1 (100%)	1/1 (100%)	1/1 (100%)
MF	3	58, 79, 81	2/3 (67%)	3/3 (100%)	3/3 (100%)	1/3 (33%)
PM	2	59, 74	2/2	2/2 (100%)	2/2 (100%)	1/2 (50%)
ATL	1	17	1/1	1/1 (100%)	1/1 (100%)	1/1 (100%)

MCL = mantle cell lymphoma; CLL = chronic lymphocytic lymphoma; BPLL = B precursor lymphoblastic leukaemia/lymphoma; TPLL = T precursor lymphoblastic leukaemia/lymphoma; MF = mycosis fungoides; PM = plasma cell myeloma; ATL = angiocentric T cell lymphoma.

and the "time to spread" as the time from surgery to the first record of extraorbital disease. The term "systemic spread" was used to describe non-contiguous (remote) disease, whereas the term "extraorbital spread" was used to describe either contiguous disease or non-contiguous disease or both; for example, a patient with contiguous disease of both the orbit and maxillary sinus without remote deposits would be considered to have "extraorbital spread" but not "systemic spread". Because only 24 patients (13%) had solely local extraorbital extension, this group of patients was not analysed separately in the statistical analysis. Death from lymphoma was confirmed by examination of death certificates and hospital records.

All but four patients received local radiotherapy (generally 30 Gy) and/or various regimens for chemotherapy and all such treated patients showed an initial response to therapy. Chlorambucil or fludarabine were most commonly prescribed for low grade lymphomas, whereas a combined regime of cyclophosphamide, doxorubicin, vincristine, and prednisolone was frequently used for high grade lymphomas.

STATISTICS

Using SPSS software, the associations between REAL histological type and (i) stage within 3 months of biopsy (previous or concurrent extraorbital spread—as defined above), (ii) time to extraorbital spread, and (iii) time to lymphoma related death (DOL) were assessed using regression analysis. The subsequent development of extraorbital spread (as defined above) and lymphoma related death in patients with solely adnexal disease at presentation were also examined. Logistic regression was employed for stage and Cox regression for the time related outcomes. Where death was unrelated to lymphoma, the data were censored. The MZL group was used as a baseline in these analyses, since it contained the greater number of observations and its selection favoured increased precision.

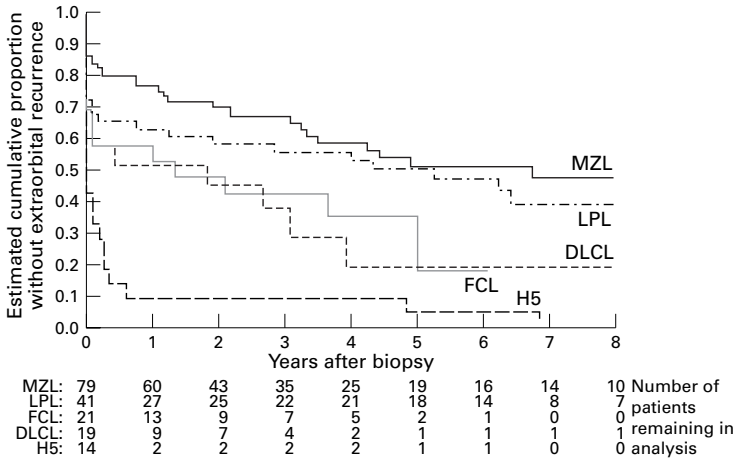

Figure 2 Cumulative proportion without extraorbital disease, based on 192 patients with ocular adnexal lymphoma: 82 marginal zone lymphomas (MZL), 44 lymphoplasmacytoid/lymphoplasmacytic lymphomas (LPL), 26 follicle centre lymphomas (FCL), 19 diffuse large B cell lymphomas (DLCL), and 21 other variants (H5). The data are censored for patients who, at time of last follow up, had not developed extraorbital disease. The figures refer, at a given time, to the number of survivors without recurrent extraorbital disease (classified by histopathological type).

Results

HISTOLOGICAL AND CLINICAL FEATURES

Biopsies from 94 men (49%) and 98 women were included in this study and MZL was the commonest type of lymphoma (82 cases; 43%) (Table 1). Twenty one patients had infrequent (<5%) diagnoses and were placed in the miscellaneous category H5 (Tables 1 and 2). The age at orbital biopsy varied from 3 to 90 years (median 66), although the childhood cases occurred exclusively in the miscellaneous category of rare variants (Table 2). The median follow up for the whole series was 46 months (range 0–243 months) compared with 50 months (3–243 months) for the 116 survivors. The median follow up for patients with LPL was greater than that for other histological diagnoses, which reflects the relatively greater frequency with which this diagnosis was made from archival as opposed to contemporaneous tissue sections (Table 1). Forty nine of the 76 deaths (64%) were tumour related.

EXTRAORBITAL (LOCAL AND/OR REMOTE SYSTEMIC) SPREAD AT DIAGNOSIS

In 17 patients, systemic lymphoma was known to be present outside the ocular adnexa at least 6 months before ophthalmic presentation. These occurred in patients with MZL (two cases), LPL (four cases), FCL (five cases), chronic lymphocytic leukaemia (two cases), MCL (two cases), mycosis fungoides (one case), and myeloma (one case).

The relative frequency of extraorbital spread, at or within 3 months of diagnosis, increased from MZL (the reference datum) through to H5 (Table 1). Four patients with DLCL had local extraorbital extension of lymphoma at diagnosis without widely disseminated disease; compared with patients

Table 3 Sites of spread for 192 patients with ocular adnexal lymphoma, classified by histological type. (Column percentages in parentheses)

	Histological category of lymphoma					
Site of spread	*MZL (82 cases)*	*LPL (44 cases)*	*FCL (20 cases)*	*DLCL (19 cases)*	*H5 (21 rare variants)*	*All (192 cases)*
Local extraorbital extension	2 (2%)	3 (7%)	5 (25%)	11 (58%)	3 (14%)	24 (13%)
Temporalis fossa	0	2 (5%)	4 (15%)	7 (37%)	3 (14%)	16 (8%)
Sinuses	1 (1%)	2 (5%)	1 (4%)	6 (32%)	1 (5%)	11 (6%)
Nasopharynx	1 (1%)	1 (2%)	1 (4%)	1 (5%)	3 (14%)	7 (4%)
Intracranial	1 (1%)	1 (2%)	0	2 (11%)	3 (14%)	7 (4%)
Nodes	22 (27%)	19 (43%)	13 (50%)	4 (21%)	10 (48%)	68 (35%)
Bone marrow	3 (4%)	7 (16%)	2 (8%)	0	11 (52%)	23 (12%)
Spleen	3 (4%)	7 (16%)	2 (8%)	2 (11%)	2 (10%)	16 (8%)
Liver	4 (5%)	0	1 (4%)	1 (5%)	2 (10%)	8 (4%)
Skin	12 (15%)	7 (16%)	7 (27%)	4 (21%)	6 (29%)	36 (19%)
Salivary gland	5 (6%)	1 (2%)	2 (8%)	0	1 (5%)	9 (5%)
Lung	4 (5%)	1 (2%)	1 (4%)	2 (11%)	1 (5%)	9 (5%)
Gut	2 (2%)	3 (7%)	0	1 (5%)	1 (5%)	7 (4%)
Breast	1 (1%)	0	2 (8%)	0	0	3 (2%)
Body cavity*	1 (1%)	3 (7%)	0	0	1 (5%)	5 (3%)
Kidney	1 (1%)	0	2 (8%)	1 (5%)	0	4 (2%)
Heart	1 (1%)	0	0	1 (5%)	0	2 (1%)
Muscle	1 (1%)	0	0	1 (5%)	0	2 (1%)
Bone	1 (1%)	0	0	0	1 (1%)	2 (1%)
Total	33 (40%)	25 (57%)	16 (62%)	13 (68%)	21 (100%)	108 (56%)

*Pericardial, peritoneal and pleural cavities.
MZL = marginal zone lymphoma; LPL = diffuse lymphoplasmacytoid/lymphoplasmacytic lymphoma; FCL = follicle centre lymphoma; DLCL = diffuse large B cell lympoma; H5 = rare histological variants.

with MZL, patients with DLCL had a higher frequency of extraorbital disease at diagnosis, although there was no difference in the frequency of widely disseminated disease between these groups (Table 1). Patients in the mixed category (H5) had the greatest risk of systemic disease at diagnosis, the wide confidence intervals (Table 1) reflecting the variety of diseases in this group.

EXTRAORBITAL (LOCAL AND/OR REMOTE SYSTEMIC) SPREAD AFTER TREATMENT

Overall, 53% of patients developed systemic lymphoma at some stage during their clinical course, a figure very similar to that recently reported by White *et al*.[9] Of patients with solely adnexal disease at diagnosis, the proportion developing systemic disease after treatment varied from 27% in patients with MZL, to all of the three patients in the rare miscellaneous category, H5 (Table 1). All types of lymphoma continued to present with recurrent disease beyond the orbit for many years after primary treatment and, at 5 years, the proportion with at least one such recurrence was 47% for MZL, 48% for LPL, 64% for FCL, 81% for DLCL, and 95% for other types (Fig 2).

Ocular adnexal lymphomas spread to many sites, the commonest being lymph nodes, skin, bone marrow, spleen, and locally to the temporalis fossa (Table 3). Although an extranodal lymphoma, MZL spread more frequently to lymph nodes than any other site, whereas patients with DLCL were more likely to exhibit local extension of the lymphoma mass, particularly to the paranasal sinuses and temporalis fossa. Dissemination to common sites of primary MZL, such as the salivary gland, lung, gut, and breast,[7 19 20] did not occur more frequently in patients with ocular adnexal MZL than in patients with other histological categories of lymphoma. Dissemination to the spleen was more frequently observed in LPL than in MZL. In the group of rare lymphomas (H5), the bone marrow was frequently involved by lymphoma, occurring in four cases of chronic lymphocytic leukaemia, two cases of mycosis fungoides, two cases of plasma cell myeloma, and one each of B precursor lymphoblastic lymphoma, T precursor lymphoblastic lymphoma, and angiocentric T cell lymphoma. In the six patients with MCL, dissemination occurred to lymph nodes only (two cases), gut (one case), liver (one case), nasopharynx (one case), and nodes, spleen, and pleural cavity (one case).

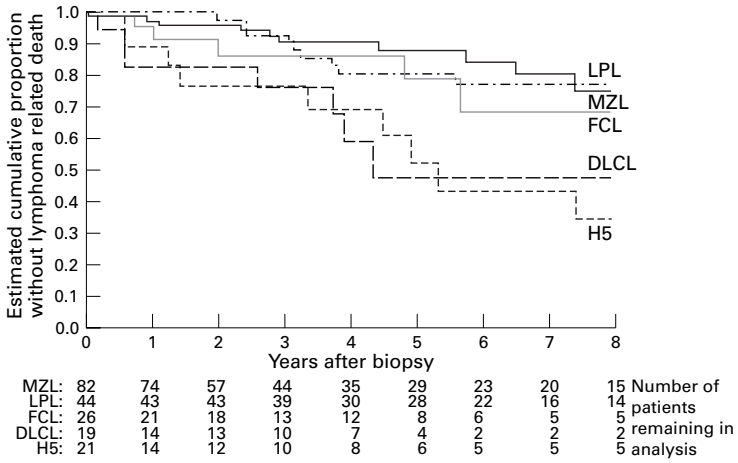

Figure 3 Cumulative proportion without lymphoma related death, based on 192 patients with ocular adnexal lymphoma (abbreviations and numbers as Fig 2). The data were censored for patients in whom the last follow up was before the end of the 8 year study period, either because of incomplete follow up or where death was unrelated to lymphoma. The numerical data refer to the number of patients alive at a given time.

LYMPHOMA RELATED DEATH

No significant difference in the risk of lymphoma related death was observed among patients with low grade lymphomas (MZL, LPL and FCL), but those with DLCL or the mixed group of rare lymphomas (H5) were estimated to have hazard ratios for lymphoma related death of 2.9 and 3.9 respectively (Table 1). Irrespective of histological type, lymphoma related deaths continued to occur for many years after ophthalmic diagnosis (Fig 3) and, at

5 years, the proportion of patients who had died of lymphoma was 12% for MZL, 19% for LPL, 22% for FCL, 48% for DLCL, and 53% for patients with rare variants (H5).

Discussion

This investigation has shown that the REAL classification, which was designed to reflect distinct morphological, immunological, cytogenetic, and molecular properties of lymphomas in general,[14] also usefully reflects differences in clinical behaviour of ocular adnexal lymphomas. The risk of extraorbital spread and of lymphoma related death increased progressively through the histological categories from MZL to LPL to FCL to DLCL but was greatest in patients with various other rare types of lymphoma.

Marginal zone lymphoma is usually regarded as a tumour of the elderly, but in the present series, adnexal MZL was detected in patients as young as 18 years and the median age at diagnosis was similar for all the categories studied (Table 1). As in other reports,[10] there was a slight predominance of females in patients with MZL (male:female 1:1.3).

This study does not support the widely held view that MZL of the ocular adnexa has a favourable outcome.[21] In contrast with previous reports,[10 21] in this investigation previous or concurrent systemic disease was present in 15/82 (18%) of patients with MZL, extraorbital spread occurred in 47% of our patients by 5 years (Fig 2) and, in those presenting with solely adnexal disease, there was no difference in the time to extraorbital spread between MZL and other histological categories of lymphoma (Table 1). Previous studies[10 22] suggested that relapses of most adnexal lymphomas occur early, whereas, in this study, the mean time to relapse for patients with solely orbital MZL was 63 months; this suggests that patients should be followed for much longer than the 5 years previously advocated.[22] The longest time to first dissemination of disease was 81, 103, 60, and 47 months for MZL, LPL, FCL, and DLCL respectively and deaths from lymphoma occurred as long as 125, 172, 170, and 52 months after diagnosis.

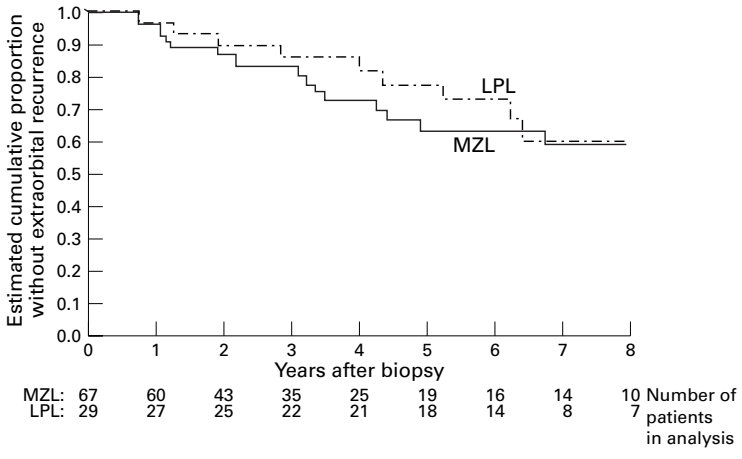

Figure 4 Cumulative proportion of patients, presenting with solely orbital disease, who remain without extraorbital spread—a comparison of marginal zone lymphoma (MZL; 67 cases) and lymphoplasmacytoid/lymphoplasmacytic lymphoma (LPL; 29 cases). The figures refer to the number of patients alive without recurrence at a given time.

As with lymphomas at other sites,[23 24] the rates of lymphoma related death among patients with the low grade lymphomas were similar (Table 1) and the risk of relapse of lymphoma or lymphoma related death continued for many years (Figs 2 and 3). There was no evidence that patients with low grade lymphomas of the ocular adnexa, including those with MZL, could be considered cured.

Marginal zone lymphoma, derived from lymphocytes with specific mucosal homing properties,[25] might be expected to spread preferentially to extranodal sites, but this was not observed for adnexal MZL, which like LPL and FCL, spread mainly to lymph nodes (Table 3). Despite limitations in differentiating LPL from MZL in small biopsies, a few of the patients classified as LPL in this study may truly have had MZL. As the clinical behaviour of the disease within these two categories differs, it is worthwhile applying a panel of antibodies to determine the cellular phenotype and thereby aid this differentiation; this panel ideally including CD5, CD10, CD23, cyclin D1, and bcl-2 antibodies, and others as indicated by the histomorphology, as these antibodies now work reliably with paraffin processed tissues. As in other anatomical locations,[24] systemic disease at diagnosis was commoner with adnexal LPL than with MZL (Table 1) and splenic involvement, reported in 40% of patients with lymphoplasmacytoid lymphoma,[24] was more common in adnexal LPL (16%) than MZL (4%). Furthermore, of the nine patients in whom monoclonal serum paraproteins were detected, five had orbital LPL and only one had MZL, these paraproteins usually being associated with nodal lymphoplasmacytoid lymphoma (immunocytoma). However, for patients presenting with solely adnexal disease, no significant difference in clinical behaviour was observed (Table 1; Fig 4).

Compared with patients with MZL, those with FCL were significantly more likely to have systemic disease at presentation (OR 3.3) (Table 1). FCL accounted for 11% of localised ocular adnexal lymphomas, which demonstrates that systemic nodal B cell lymphomas may first present in the ocular adnexa. Bcl-2 rearrangements in genomic DNA have previously been reported in patients with "lymphoid hyperplasia",[26 27] and it is possible that, in the absence of systemic disease to suggest neoplasia, the follicular changes in these biopsies were misinterpreted as "reactive".

Diffuse large B cell lymphoma is a high grade lymphoma, associated with an increased risk of systemic disease and lymphoma related death (Table 1). At diagnosis, 10/19 (53%) patients with DLCL had solely adnexal disease, 5/19 (26%) had contiguous local spread to neighbouring structures (maxillary or ethmoid sinuses, or subcutaneous tissue of the temporal fossa), and 5/19 (26%) had distant disease, one patient having both local extension and distant disease. Low grade gastric MALT lymphomas can undergo transforma-

tion to high grade tumours[28 29] and it has been suggested that DLCL may be derived from histological transformation of MZL.[10] However, only two cases of concomitant low grade and high grade lymphoma were observed in this study and patients with MZL and DLCL differed significantly in the site within the ocular adnexa involved by lymphoma. The high incidence of contiguous extraorbital spread of DLCL found in this investigation suggests that DLCL could be a manifestation of primary paranasal sinus lymphoma, which are frequently high grade tumours,[30] with secondary ophthalmic involvement.

Mantle cell lymphoma has only relatively recently been recognised as occurring in the ocular adnexa,[10] but was the commonest of the rare variants. The neoplastic B cell population of these lymphomas is composed of centrocytic cells[31] and it is possible that these lymphomas were previously underreported, especially in patients with ocular adnexal lymphoma, given the cytological similarity of these cells to the centrocyte-like cells found in MZL.[7] The advent of cyclin D-1 staining for formalin fixed material should improve the differentiation of these tumours.[18] The importance of the distinction is emphasised by the high frequency of systemic disease in patients with MCL, compared with MZL (Tables 1 and 2). Follow up for the six patients with MCL in this series was relatively short (40, 24, 9, 7, 4, and 129 months) and further study is required to determine whether these patients are at high risk of lymphoma related death, as reported for MCL arising at other sites.[24]

In conclusion, there is good evidence for an association between histological grade, as defined by the REAL classification system, and survival of patients with ocular adnexal lymphoma. Although marginal zone lymphomas are often thought to be indolent and have a good prognosis, this study found no difference in survival between patients with MZL and those with other low grade lymphomas of the ocular adnexa.

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