Protocol for the Examination of Specimens From Patients With Hematopoietic Neoplasms of the Ocular Adnexa

Kyle T. Bradley, MD, MS; Daniel A. Arber, MD; Michael S. Brown, MD; Chung-Che Chang, MD, PhD; Sarah E. Coupland, MBBS, PhD; Monica E. de Baca, MD; David W. Ellis, MBBS; Kathryn Foucar, MD; Eric D. Hsi, MD; Elaine S. Jaffe, MD; Michael C. Lill, MB, BS; Stephen P. McClure, MD; L. Jeffrey Medeiros, MD; Sherrie L. Perkins, MD, PhD; Jerry W. Hussong, MD, DDS; for the Members of the Cancer Committee, College of American Pathologists

The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations. The College regards the reporting elements in the ''Surgical Pathology Cancer Case Summary (Checklist)'' portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these protocols as an educational tool to assist pathologists in the useful reporting of relevant information. It did not issue the protocols for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the protocols might be used by hospitals, attorneys, payers, and others. Indeed, effective January 1, 2004, the Commission on Cancer of the American College of Surgeons mandated the use of the checklist elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, it becomes even more important for pathologists to familiarize themselves with these documents. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of these documents.

Accepted for publication November 4, 2009.

From the Department of Pathology and Laboratory Medicine, Emory University Hospital, Atlanta, Georgia (Dr Bradley); the Department of Pathology, Stanford University School of Medicine, Stanford, California (Dr Arber); Yellowstone Pathology Institute Inc, Billings, Montana (Dr Brown); the Department of Pathology, The Methodist Hospital, Houston, Texas (Dr Chang); the Department of Pathology, Royal Liverpool University Hospital, Liverpool, United Kingdom (Dr Coupland); the Department of Pathology and Laboratory Medicine, Physicians Laboratory Ltd, Sioux Falls, South Dakota (Dr de Baca); the Department of Anatomic Pathology, Flinders Medical Centre, Bedford Park, South Australia (Dr Ellis); the Department of Pathology, University of New Mexico, Albuquerque (Dr Foucar); the Department of Clinical Pathology, Cleveland Clinic, Cleveland, Ohio (Dr Hsi); the Department of Pathology, National Cancer Institute, Bethesda, Maryland (Dr Jaffe); the Departments of Medicine (Dr Lill) and Pathology and Laboratory Medicine (Dr Hussong), Cedars-Sinai Medical Center, Los Angeles, California; the Department of Pathology and Laboratory Medicine, Presbyterian Pathology Group, Charlotte, North Carolina (Dr McClure); the Department of Hematopathology, M. D. Anderson Cancer Center, Houston, Texas (Dr Medeiros); and the Department of Pathology, University of Utah Health Sciences Center, Salt Lake City (Dr Perkins).

The authors have no relevant financial interest in the products or companies described in this article.

Reprints: Jerry W. Hussong, MD, DDS, Cedars-Sinai Medical Center, 8700 Beverly Blvd, Room 4708, Los Angeles, CA 90048 (e-mail: hussongj@cshs.org).

PROTOCOL FOR THE EXAMINATION OF SPECIMENS FROM PATIENTS WITH HEMATOPOIETIC NEOPLASMS OF THE OCULAR ADNEXA

This protocol applies to primary hematopoietic neoplasms of the conjunctiva, orbital soft tissue, lacrimal gland, lacrimal drainage apparatus, and eyelid. Intraocular lymphomas and secondary hematopoietic neoplasms are not included. The 7th edition TNM staging system for ocular adnexal lymphomas of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended.

SURGICAL PATHOLOGY CANCER CASE SUMMARY (CHECKLIST)

Ocular Adnexa: Biopsy, Resection

Select a Single Response Unless Otherwise Indicated

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Specimen (select all that apply) (note **A**)
- ___ Conjunctiva
- ___ Orbital soft tissue (orbit)
- ___ Lacrimal gland
- ___ Lacrimal sac or nasolacrimal duct (lacrimal drainage apparatus)
- ___ Eyelid
- ___ Other (specify): _____
- ___ Not specified

Procedure
- ___ Biopsy
- ___ Resection
- ___ Other (specify): _____
- ___ Not specified

Lymph Node Sampling (select all that apply) (note **B**)
- ___ Not applicable
- ___ Regional lymph node(s) (preauricular/parotid, submandibular, or cervical)

___ Central lymph node(s) (lymph nodes from the trunk, eg, mediastinal, para-aortic)
___ Peripheral lymph node(s) (lymph nodes from distant sites other than central)
___ Other (specify): _____
___ Not specified

***Tumor Size (may be determined from radiographic studies)**

*Greatest dimension: ___ cm
*Additional dimensions: ___ × ___ cm
*___ Cannot be determined

Histologic Type (based on the 2008 World Health Organization [WHO] classification) (note **C**)

___ Extranodal marginal zone lymphoma (MZL) of mucosa-associated lymphoid tissue (MALT lymphoma)[#]
___ Follicular lymphoma
___ Diffuse large B-cell lymphoma, not otherwise specified (NOS)
___ Mantle cell lymphoma
___ Chronic lymphocytic leukemia/small lymphocytic lymphoma
___ Lymphoplasmacytic lymphoma
___ Other (specify): _____

[#] Included in this category are MZLs that lack key features associated with MALT-type MZL.

Pathologic Staging (pTNM)

TNM Descriptors (required only if applicable) (select all that apply) (note **D**)

___ b (bilateral)
___ m (multiple)
___ r (recurrent)
___ y (posttreatment)

Primary Tumor (pT)

___ pTX: Lymphoma extent not specified
___ pT0: No evidence of primary tumor

pT1: Lymphoma involving the conjunctiva alone without orbital involvement

___ pT1a: Bulbar conjunctiva involvement only
___ pT1b: Palpebral conjunctiva involvement (with or without fornix or caruncle involvement)
___ pT1c: Extensive conjunctival involvement (ie, both bulbar and nonbulbar conjunctiva involvement)

pT2: Lymphoma with orbital involvement with or without conjunctival involvement

___ pT2a: Anterior orbital involvement,[#] but no lacrimal gland involvement (with or without conjunctival involvement)
___ pT2b: Anterior orbital involvement with lacrimal gland involvement (with or without conjunctival involvement)
___ pT2c: Posterior orbital involvement (with or without anterior orbital involvement; with or without conjunctival involvement; with or without extraocular muscle involvement)
___ pT2d: Nasolacrimal drainage system involvement (with or without conjunctival involvement, but not involving nasopharynx)
___ pT3: Lymphoma with preseptal eyelid involvement[##] (with or without orbital or conjunctival involvement)

pT4: Lymphoma extends beyond orbit to involve adjacent structures (eg, bone, brain)

___ pT4a: Involvement of nasopharynx
___ pT4b: Osseous involvement (including periosteum)
___ pT4c: Involvement of maxillofacial, ethmoidal, and/or frontal sinuses
___ pT4d: Intracranial spread

[#] The anterior orbit is defined as the area between the orbital septum and the equator of the globe. The posterior orbit is defined as the area posterior to the equator of the globe, extending to the orbital apex.

[##] Eyelid involvement is said to exist when the ocular adnexal lymphoma infiltrates preseptal tissues (ie, tissues anterior to the orbital septum).

Lymph Node Involvement (pN)

___ pNX: Involvement of lymph nodes not assessed
___ pN0: No evidence of lymph node involvement
___ pN1: Involvement of ipsilateral regional lymph nodes (preauricular/parotid, submandibular, or cervical)
___ pN2: Involvement of contralateral or bilateral regional lymph nodes (preauricular/parotid, submandibular, or cervical)
___ pN3: Involvement of peripheral lymph nodes not draining ocular adnexal region
___ pN4: Involvement of central lymph nodes

Specify: Number examined: ___
Number involved: ___

Distant Metastasis (pM)

___ Not applicable
___ pM1a: Noncontiguous involvement of tissues or organs external to the ocular adnexa (eg, salivary glands, lung, liver)
*Specify site(s), if known: _____
___ pM1b: Bone marrow involvement
___ pM1c: Both pM1a and pM1b involvement

***Additional Pathologic Findings**

*Specify: _____

Immunophenotyping (flow cytometry and/or immunohistochemistry) (note E)

___ Performed, see separate report: _____
___ Performed
Specify method(s) and results: _____
___ Not performed

***Cytogenetic Studies (note F)**

*___ Performed, see separate report: _____
*___ Performed
*Specify method(s) and results: _____
*___ Not performed

***Molecular Genetic Studies (note G)**

*___ Performed, see separate report: _____
*___ Performed
*Specify method(s) and results: _____
*___ Not performed

***Comment(s):** _____

EXPLANATORY NOTES

A. Specimen.—The ocular adnexa are those anatomic structures that surround the eyeball, protect it from injury, and facilitate its functioning; this includes the conjunctiva (palpebral and bulbar), orbital cavity soft tissues, main lacrimal gland, accessory lacrimal glands, nasolacrimal drainage system (including the upper and lower canaliculi, lacrimal sac, and nasolacrimal duct), and the eyelid.

Ocular Adnexa Anatomy

Conjunctiva.—The conjunctiva is a mucous membrane that covers the inner surface of the eyelid (palpebral

conjunctiva) and the anterior surface of the eye (bulbar conjunctiva). The palpebral conjunctiva is contiguous with the bulbar conjunctiva, which is adherent to the periphery of the cornea. The deep recesses formed by the reflection of the palpebral conjunctiva onto the eyeball are known as the superior and inferior conjunctival fornices. The space between the palpebral and bulbar conjunctiva is referred to as the conjunctival sac. The caruncle is located at the inner canthus and represents a transition zone between the conjunctiva and the skin.

Orbit.—The orbit is defined as the soft tissues of the orbital cavity posterior to the orbital septum in the eyelid and includes the extraocular muscles. Thus, all lymphomas located posterior to the orbital septum are considered to involve the orbit. Orbital lymphoma is categorized as anterior and posterior according to its predominant location in relation to the equator of the globe. The anterior orbit is defined as the area between the orbital septum and the equator of the globe. The posterior orbit is defined as the area posterior to the equator of the globe, extending to the orbital apex.

Lacrimal Drainage System.—The main lacrimal gland is located in the superolateral part of the orbit. The accessory lacrimal glands of Krause and Wolfring are located in the region of the conjunctival fornices. The lacrimal glands secrete lacrimal fluid, which is drained by the lacrimal canaliculi into the lacrimal sac and then into the nasal cavity via the nasolacrimal duct.

Eyelid.—The eyelid is composed of multiple layers; these are, in order from outermost to innermost, epidermis, dermis, subcutaneous tissue including a thin layer of adipose tissue, orbicularis oculi muscle, orbital septum, levator muscle, tarsal plate, Müller muscle, and palpebral conjunctiva. For staging purposes, eyelid involvement is said to exist when the lymphoma infiltrates preseptal tissues (ie, tissues anterior to the orbital septum).[1–3]

Small populations of lymphocytes normally reside in the conjunctiva, particularly the conjunctival sacs and fornices, as well as in the main and accessory lacrimal glands. No lymph nodes exist in the ocular adnexa.

B. Lymph Node Sampling.—The regional lymph nodes of the ocular adnexa include the preauricular (parotid), submandibular, and cervical lymph nodes. ''Central'' nodes are defined as those located in the trunk (eg, mediastinal, para-aortic), whereas ''peripheral'' nodes refer to lymph nodes from other distant sites not draining the ocular adnexa.[2]

C. Histologic Type.—This protocol is to be used for primary hematopoietic neoplasms only. Histologic types should be assigned based on the WHO classification of tumors of hematopoietic and lymphoid tissues.[4] Although only the most common lymphoma types seen in the ocular adnexa are listed in the protocol, theoretically any lymphoma can involve this site as a primary neoplasm. The Table provides a list of the mature B-cell neoplasms, mature T- and NK-cell neoplasms, Hodgkin lymphomas, immunodeficiency-associated lymphoproliferative disorders, and histiocytic and dendritic cell neoplasms as defined in the 2008 WHO classification.[4] Hematopoietic neoplasms that are primarily restricted to blood and bone marrow (eg, myeloproliferative neoplasms, myelodysplastic syndromes, acute leukemias) are not included in the Table because, with the exception of rare cases of B lymphoblastic leukemia/lymphoma, they essentially never involve the ocular adnexa.

World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues[a]

Mature B-cell neoplasms
- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Splenic B-cell marginal zone lymphoma
- Hairy cell leukemia
- *Splenic B-cell lymphoma/leukemia, unclassifiable*
  - *Splenic diffuse red pulp small B-cell lymphoma*
  - *Hairy cell leukemia variant*
- Lymphoplasmacytic lymphoma
- Heavy-chain diseases
  - γ heavy-chain disease
  - μ heavy-chain disease
  - α heavy-chain disease
- Plasma cell neoplasms
  - Monoclonal gammopathy of undetermined significance (MGUS)
  - Plasma cell myeloma
  - Solitary plasmacytoma of bone
  - Extraosseous plasmacytoma
  - Monoclonal immunoglobulin deposition diseases
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma
  - *Pediatric nodal marginal zone lymphoma*
- Follicular lymphoma
  - *Pediatric follicular lymphoma*
  - *Primary intestinal follicular lymphoma*
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS)
- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the central nervous system
- Primary cutaneous DLBCL, leg type
- *Epstein-Barr virus (EBV)–positive DLBCL of the elderly*
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- Anaplastic lymphoma kinase (ALK)–positive large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
- Primary effusion lymphoma
- Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

Mature T- and natural killer (NK)–cell neoplasms
- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- *Chronic lymphoproliferative disorder of NK cells*
- Aggressive NK cell leukemia
- EBV-positive T-cell lymphoproliferative diseases of childhood
  - Systemic EBV-positive T-cell lymphoproliferative disease of childhood
  - Hydroa vacciniforme-like lymphoma
- Adult T-cell leukemia/lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30-positive T-cell lymphoproliferative disorders
- Primary cutaneous peripheral T-cell lymphoma, rare subtypes
  - Primary cutaneous γ-δ T-cell lymphoma
  - *Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma*

Continued

- *Primary cutaneous CD4-positive small/medium T-cell lymphoma*
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, ALK positive
- *Anaplastic large cell lymphoma, ALK negative*

Hodgkin lymphoma

- Nodular lymphocyte predominant Hodgkin lymphoma
- Nodular sclerosis classical Hodgkin lymphoma
- Mixed cellularity classical Hodgkin lymphoma
- Lymphocyte-rich classical Hodgkin lymphoma
- Lymphocyte-depleted classical Hodgkin lymphoma

Immunodeficiency-associated lymphoproliferative disorders

- Lymphoproliferative diseases associated with primary immune disorders
- Lymphomas associated with HIV infection
- Posttransplant lymphoproliferative disorders (PTLD)
  - Plasmacytic hyperplasia and infectious mononucleosis-like PTLD
  - Polymorphic PTLD
  - Monomorphic PTLD
  - Classical Hodgkin lymphoma type PTLD
- Other iatrogenic immunodeficiency-associated lymphoproliferative disorders

Histiocytic and dendritic cell neoplasms

- Histiocytic sarcoma
- Tumors derived from Langerhans cells
  - Langerhans cell histiocytosis
  - Langerhans cell sarcoma
- Interdigitating dendritic cell sarcoma
- Follicular dendritic cell sarcoma
- *Fibroblastic reticular cell tumor*
- *Indeterminate dendritic cell tumor*
- Disseminated juvenile xanthogranuloma

[a] Provisional entities in the 2008 World Health Organization classification are shown in italics.

In the largest review to date, 78% of lymphomas involving the ocular adnexa were primary, whereas 22% of cases involved the ocular adnexa secondarily.[5] Marginal zone lymphoma accounts for most of the primary ocular adnexal hematopoietic neoplasms. Other neoplasms that occur with notable frequency include follicular lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, and lymphoplasmacytic lymphoma. Rarely, B lymphoblastic leukemia/lymphoma, plasma cell neoplasms, and other types of non-Hodgkin lymphoma, including T- and natural killer–cell lymphomas, are seen.[1,5–20] Hodgkin lymphoma is extremely rare in the ocular adnexa.[5,14]

A recent study found that many MZLs involving orbital soft tissue lack key features associated with MALT-type MZL (eg, lack of lymphoepithelial lesions) and suggests avoiding the designation ''MALT lymphoma'' in the diagnosis.[14] Because this distinction is currently not recognized by the WHO classification, these lymphomas should continue to be categorized in this protocol according to the WHO designation ''extranodal MZL of mucosa-associated lymphoid tissue.''

D. TNM Descriptors.—As defined in the *AJCC Cancer Staging Manual*, descriptors are used to identify special cases within TNM classifications.[2] Descriptors are recorded as prefixes and precede the T stage when written.

The ''b'' prefix indicates bilateral lymphoma involving ocular adnexal structures.

The ''m'' prefix indicates the presence of multiple primary tumors in 1 ocular adnexal structure.

The ''r'' prefix indicates a recurrent tumor when staged after a documented disease-free interval.

The ''y'' prefix indicates those cases in which classification is performed during or following initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy).

E. Immunophenotyping (Flow Cytometry and/or Immunohistochemistry).—Immunophenotyping is essential to precisely diagnose and classify many of the hematologic malignancies and is important for identifying potential therapeutic targets such as CD20. Immunophenotyping can be performed using flow cytometry[21] or immunohistochemistry, each of which has its advantages and disadvantages. Flow cytometry is rapid (hours), is quantitative, and allows multiple antigens to be evaluated on the same cell simultaneously. However, antigen positivity cannot be correlated with tissue architecture or cytologic features. Immunohistochemistry requires hours or days to perform and quantitation is often subjective, but importantly it allows correlation of antigen expression with architecture and cytology, and the technique can be performed on archival tissue.

The AJCC has identified the tumor cell growth fraction as determined by Ki-67/MIB-1 immunohistochemistry as a clinically significant prognostic factor (site-specific factor), although it is not required for tumor staging.[2] The AJCC recommends ''counting the number of tumor cells with clear nuclear positivity for Ki-67 per 5 × 100 tumor cells using the 40× objective. A percentage value is therefore obtained, for example, a Ki-67 tumor cell growth fraction of 15%. Reactive cells, such as germinal center cells in extranodal MZLs, should not be included in the assessment.

If ancillary studies are referred to another laboratory, it is suggested that the date of the referral and the name of the reference laboratory be included in the report. If the results are not included in the initial report, the status and location of referral laboratory results should be given.

F. Cytogenetic Studies.—Cytogenetic analysis (including conventional karyotyping and fluorescence in situ hybridization [FISH]) is an integral part of the workup and classification of many hematologic malignancies.[22] Several mature B-cell lymphomas are associated with characteristic genetic abnormalities that are important in determining their biologic behavior and in establishing the diagnosis, for example, t(14;18) occurs in 70% to 95% of cases of follicular lymphoma.[4]

Extranodal MZL is the most common lymphoma subtype arising in the ocular adnexa. However, these lymphomas are somewhat unusual in that they show anatomic site–dependent variation in their cytogenetic findings. In 1 study that involved 6 cases of ocular adnexal MZL evaluated by metaphase cytogenetics (karyotyping), the following were identified: trisomy 3, 2 cases; trisomy 18, 1 case; del(4)(q24), 1 case; trisomy 10, 1 case; normal karyotype, 1 case.[23] Thirty-one cases evaluated for *MALT1* by FISH were all negative; however, 14 of 31 cases (45%) displayed gains of the *MALT1* signal consistent with +18q, and gains using a CEP3 probe consistent with +3 were found in 16 of 29 cases (55%).[23] In a separate study of 34 cases, FISH analysis revealed t(14;18)(q32;q21) (*IGH/MALT1*) in 1 case, trisomy 3 in 21 cases (62%), and trisomy 18 in 16 cases (47%).[24] A recent study by Lagoo et al[14] demonstrated a cytogenetic abnormality involving the

MALT1 locus in only 15% of ocular adnexal MZLs, and 0 of 20 cases showed a rearranged *MALT1* locus using FISH.

G. Molecular Genetic Studies.—Molecular analyses are being performed increasingly to evaluate for the presence of genetic abnormalities in all types of hematologic malignancies.[25,26] As with cytogenetic analysis, the detection of several specific genetic alterations gives both diagnostic and prognostic information and can also be used to aid in the detection of minimal residual disease. The most common molecular techniques available at the present time include Southern blot hybridization and polymerase chain reaction for determining rearrangements of the immunoglobulin heavy-chain genes and the T-cell receptor genes; FISH is also commonly used. Currently, molecular analysis is most helpful in assessing for clonality and detecting chromosomal translocations, but its role will undoubtedly increase in the future.

References

1. Knowles DM, Jakobiec FA, McNally L, Burke JS. Lymphoid hyperplasia and malignant lymphoma occurring in the ocular adnexa (orbit, conjunctiva, and eyelids): a prospective multiparametric analysis of 108 cases during 1977 to 1987. *Hum Pathol*. 1990;21(9):959–973.
2. Finger P, Albert D, Ainbinder D, et al. Ocular adnexal lymphomas. In: Edge SB, Byrd DR, Carducci MA, Compton CC, eds. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2009.
3. Coupland SE, White VA, Rootman J, Damato B, Finger PT. A TNM-based staging system of ocular adnexal lymphomas. *Arch Pathol Lab Med*. 2009;133(8): 1262–1267.
4. Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: IARC Press, 2008. *World Health Organization Classification of Tumours*; vol 2.
5. Ferry JA, Fung CY, Zukerberg L, et al. Lymphoma of the ocular adnexa: a study of 353 cases. *Am J Surg Pathol*. 2007;31(2):170–184.
6. Jenkins C, Rose GE, Bunce C, et al. Histological features of ocular adnexal lymphoma (REAL classification) and their association with patient morbidity and survival. *Br J Ophthalmol*. 2000;84(8):907–913.
7. Sharara N, Holden JT, Wojno TH, Feinberg AS, Grossniklaus HE. Ocular adnexal lymphoid proliferations: clinical, histologic, flow cytometric, and molecular analysis of forty-three cases. *Ophthalmology*. 2003;110(6):1245–1254.
8. Coupland SE, Krause L, Delecluse H, et al. Lymphoproliferative lesions of the ocular adnexa: analysis of 112 cases. *Ophthalmology*. 1998;105(8):1430–1441.
9. Auw-Haedrich C, Coupland SE, Kapp A, Schmitt-Gräff A, Buchen R, Witschel H. Long term outcome of ocular adnexal lymphoma subtyped according to the REAL classification. *Br J Ophthalmol*. 2001;85(1):63–69.
10. White WL, Ferry JA, Harris NL, Grove AS Jr. Ocular adnexal lymphoma: a clinicopathologic study with identification of lymphomas of mucosa-associated lymphoid tissue type. *Ophthalmology*. 1995;102(12):1994–2006.
11. McKelvie PA, McNab A, Francis IC, Fox R, O'Day J. Ocular adnexal lymphoproliferative disease: a series of 73 cases. *Clin Experiment Ophthalmol*. 2001;29(6):387–393.
12. Woog JJ, Kim YD, Yeatts RP, et al. Natural killer/T-cell lymphoma with ocular and adnexal involvement. *Ophthalmology*. 2006;113(1):140–147.
13. Coupland SE, Foss H, Assaf C, et al. T-cell and T/natural killer-cell lymphomas involving ocular and ocular adnexal tissues: a clinicopathologic, immunohistochemical, and molecular study of seven cases. *Ophthalmology*. 1999;106(11):2109–2120.
14. Lagoo AS, Haggerty C, Kim Y, et al. Morphologic features of 115 lymphomas of the orbit and ocular adnexa categorized according to the World Health Organization classification: are marginal zone lymphomas in the orbit mucosa-associated lymphoid tissue-type lymphomas? *Arch Pathol Lab Med*. 2008;132(9):1405–1416.
15. Medeiros LJ, Harris NL. Lymphoid infiltrates of the orbit and conjunctiva: a morphologic and immunophenotypic study of 99 cases. *Am J Surg Pathol*. 1989; 13(6):459–471.
16. Looi A, Gascoyne RD, Chhanabhai M, Connors JM, Rootman J, White VA. Mantle cell lymphoma in the ocular adnexal region. *Ophthalmology*. 2005; 112(1):114–119.
17. Jakobiec FA, Knowles DM. An overview of ocular adnexal lymphoid tumors. *Trans Am Ophthalmol Soc*. 1989;87:420–442, discussion 442–444.
18. Charlotte F, Doghmi K, Cassoux N, et al. Ocular adnexal marginal zone B cell lymphoma: a clinical and pathologic study of 23 cases. *Virchows Arch*. 2006;448(4):506–516.
19. Decaudin D, de Cremoux P, Vincent-Salomon A, Dendale R, Lumbroso Le Rouic L. Ocular adnexal lymphoma: a review of clinicopathologic features and treatment options. *Blood*. 2006;108(5):1451–1460.
20. Jakobiec FA. Ocular adnexal lymphoid tumors: progress in need of clarification. *Am J Ophthalmol*. 2008;145(6):941–950.
21. Craig FE, Foon KA. Flow cytometric immunophenotyping for hematologic neoplasms. *Blood*. 2008;111(8):3941–3967.
22. LeBeau MM. Role of Cytogenetics in the Diagnosis and Classification of Hematopoietic Neoplasms. Philadelphia, PA: Lippincott Williams & Wilkins; 2001:391–418.
23. Ruiz A, Reischl U, Swerdlow SH, et al. Extranodal marginal zone B-cell lymphomas of the ocular adnexa: multiparameter analysis of 34 cases including interphase molecular cytogenetics and PCR for Chlamydia psittaci. *Am J Surg Pathol*. 2007;31(5):792–802.
24. Tanimoto K, Sekiguchi N, Yokota Y, et al. Fluorescence in situ hybridization (FISH) analysis of primary ocular adnexal MALT lymphoma. *BMC Cancer*. 2006;6:249.
25. Bagg A. Role of molecular studies in the classification of lymphoma. *Expert Rev Mol Diagn*. 2004;4(1):83–97.
26. Johnson TE, Tse DT, Byrne GE Jr, et al. Ocular-adnexal lymphoid tumors: a clinicopathologic and molecular genetic study of 77 patients. *Ophthal Plast Reconstr Surg*. 1999;15(3):171–179.