

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

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.

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Procedures

- Biopsy
- Resection

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CAP Ocular Adnexa Protocol Revision History

Version Code

The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: OcularAdnexa 3.0.0.0

Summary of Changes

No changes have been made since the March 2010 release.

Surgical Pathology Cancer Case Summary

Protocol web posting date: March 2010

OCULAR ADNEXA: Biopsy, Resection

Select a single response unless otherwise indicated.

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: ___ x ___ cm
- + ___ Cannot be determined

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

- Extranodal marginal zone lymphoma 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 marginal zone lymphomas that lack key features associated with MALT-type marginal zone lymphoma.

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 pre-septal 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: ___

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Distant Metastasis (pM)

Not applicable

pM1a: Non-contiguous 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's 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 World Health Organization (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 (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues

Mature B-cell Neoplasms

Chronic lymphocytic leukemia/small lymphocytic lymphoma
 B-cell polymorphocytic 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
 Gamma heavy chain disease
 Mu heavy chain disease
 Alpha 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
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 Castlemann 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 NK-cell Neoplasms

T-cell prolymphocytic leukemia
 T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
 Aggressive NK cell leukemia
 Epstein-Barr virus (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 lymphomas, rare subtypes
 Primary cutaneous gamma-delta T-cell lymphoma
 Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma
 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
 Post-transplant 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

Note: Provisional entities in the 2008 WHO 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 (MZL) accounts for the vast majority of 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 NK-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 Since 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 American Joint Committee on Cancer (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 cytometry²¹ or immunohistochemistry, each of which has its advantages and disadvantages. Flow cytometry is rapid (hours), 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/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 5x100 tumor cells using the 40x objective. A percentage value is therefore obtained, eg, a Ki-67 tumor cell growth fraction of 15%.” Reactive cells, such as germinal center cells in extranodal marginal zone lymphomas, 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 work-up 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 (eg, t(14;18) occurs in 70% to 95% of cases of follicular lymphoma).⁴

Extranodal marginal zone lymphoma 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 one 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 the 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 al¹⁴ demonstrated a cytogenetic abnormality involving the *MALT1* locus in only 15% of ocular adnexal MZLs, and zero 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 (PCR) 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.

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