



PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES

OCULAR ONCOLOGY

CONJUNCTIVAL MALIGNANCY

Site Group: Ocular Oncology – Conjunctival Malignancy

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Authors: H. Krema, N. Laperriere, J. Waldron

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1. Introduction

Conjunctival malignancies may be divided into epithelial, melanocytic, lymphoproliferative, or secondary/metastatic lesions. When managed early, most will not invade other ocular structures or metastasize. However, left untreated they can become vision- and life-threatening.

A. Epithelial. Ocular surface squamous neoplasia (OSSN) comprises a spectrum of malignancy from dysplasia (mild, moderate, severe, carcinoma in situ) to invasive squamous cell carcinoma (SCC) arising from the non-melanocytic conjunctival epithelial cells. These tumors constitute the most common conjunctival malignancy in the United States. The incidence of OSSN has been reported between 0.02 and 3.5 persons per 100,000 each year, although there is wide geographic variation on the basis of solar exposure and the incidence of untreated AIDS. The tumor may arise from epithelial cells in the cornea, limbus, or conjunctiva.

B. Melanocytic. Abnormal melanocytic proliferations account for 50% of all conjunctival neoplasms. Conjunctival melanocytic proliferation appears to have a distinct pathway different from its cutaneous or uveal counterparts. Normal conjunctival melanocytes have a dendritic configuration and reside in the basal epithelium amongst the more numerous basal squamous cells. Their function is to secrete melanin, which provides protection from ultraviolet radiation. Increased proliferation of melanocytes results in a lesion that may be totally pigmented, partially pigmented, or non-pigmented. Whether or not a lesion is pigmented does not depend on the number of melanocytes, but rather the overall amount of melanin. Not all pigmented lesions are melanocytic tumors and not all melanocytic tumors are pigmented.

A melanocytic lesion may be benign (nevus), premalignant (primary acquired melanosis [PAM] with or without atypia) or malignant (melanoma). There are also some rare benign melanocytic tumors such as the Blue nevus and other variants. Pigmented lesions are also found on the caruncle or eyelid margin that are benign (i.e. nevus, oncocytoma) or malignant (melanoma). There is also *subconjunctival* melanocytic proliferation that may be associated with cutaneous, scleral and uveal pigmentation termed oculodermal or ocular melanocytosis. Melanoma can also secondarily involve the conjunctiva from cutaneous or uveal melanoma metastasis or from a continuous cutaneous melanoma. Any pigmented lesion that exhibits growth, change in shape or color, or involves the palpebral or forniceal conjunctiva is biopsied.

C. Lymphoproliferative. Lymphoproliferative lesions of the conjunctiva represent a spectrum of disease from reactive lymphoid hyperplasia (RLH) to malignant lymphoma. Lymphoid tumors can involve the conjunctival stroma, the eyelids, or the orbital structures (including lacrimal gland and sac) as a primary lymphoma or secondarily as part of a systemic lymphoma condition that affects multiple organs including the ocular adnexa. Together these are termed ocular adnexal lymphoid neoplasms (OALNs) and represent less than 10% of all extranodal non-Hodgkin lymphomas. Lymphoid proliferations constitute about 2% of conjunctival neoplasms, however the incidence of OALNs is increasing. The conjunctiva is involved primarily in about one third of cases,

which tends to result in a relatively better prognosis compared with other OALNs. Although non-Hodgkin lymphoma (NHL) of B-cell origin is most commonly encountered, T-cell or natural killer (NK)-cell lymphomas can also involve the ocular adnexa.

D. Secondary/Metastatic. Tumors that involve the eyelids, intraocular structures, or adjacent orbital tissues may spread by direct extension to the conjunctiva and are called “secondary” lesions. In contrast, tumors that involve the conjunctiva by distant spread are termed “metastatic” lesions.

2. Prevention

Extrinsic risk factors that predispose to conjunctival malignancy include smoking, ultraviolet (UV-B) radiation, and oncogenic infections such as human papillomavirus (HPV) and human immunodeficiency virus (HIV). Intrinsic risk factors include older age, immunosuppression, genetic predisposition, fair skin (for melanocytic tumors), and a personal history of cutaneous or other malignancy.

Solar damage and immunosuppression are the most important risk factors in non-syndromic patients (ie. xeroderma pigmentosa). For those who suffer from xeroderma pigmentosa, prevention involves avoidance of UV-light with sunglasses, hats, and staying indoors. HPV is a DNA virus and types 16 and 18 are implicated in cervical and conjunctival malignancy, although the association is more robust for the former. HPV types 6 and 11 are associated with most benign conjunctival papillomas. However, based on the available evidence, there is no role for routine testing of HPV DNA or mRNA in patients with conjunctival squamous neoplasia. There is an increasing incidence of conjunctival squamous neoplasia, about 10-fold, in HIV-positive patients. Overall, patients are counseled on strategies to address all modifiable risk factors including smoking cessation, use of sunglasses, and normalization of immune status. Early treatment of pre-cancerous lesions with close monitoring and follow-up is paramount.

3. Screening and Early Detection

Early recognition and treatment decreases tumor spread and improves prognosis for tumor control and visual preservation. Many conjunctival malignant tumors are difficult to distinguish from benign lesions based on the clinical examination alone. An excisional biopsy is recommended in such cases. Intraocular surgical procedures such as cataract extraction should not be performed simultaneously with biopsy until conjunctival malignancy is ruled out.

Conjunctival squamous neoplasia presents in younger patients who are HIV-positive. In an African patient, or one that is younger than 50 years of age that presents with conjunctival squamous neoplasia, an HIV test is mandatory. Similarly, patients with known HIV-seropositivity who have a conjunctival lesion should have a biopsy.

4. Diagnosis

Patients with suspicious conjunctival lesions are typically referred to the Princess Margaret Hospital (PMH) Ocular Oncology service by vision care specialists. Some patients are referred because an excised lesion was found to be malignant and there is a need for adjunctive therapy and ongoing follow-up. There is a wide spectrum of clinical features for conjunctival tumors but some common signs of malignancy include an abnormal appearance, size, shape, or location of pigmented or non-pigmented tissue with aberrant surrounding vasculature (e.g. feeder vessels). Lesions may be focal, multi-focal, diffuse, or infiltrative. Specific features of the four subtypes are described below.

Clinical Exam. All new patients will undergo a detailed ophthalmological examination of both eyes including Snellen visual acuity, pupil reactivity, intraocular pressure, and slit-lamp biomicroscopy. Detailed drawings and measurements as well as high-quality photographic documentation are performed. The base diameter of a conjunctival tumor is measured with the slit-lamp and tumor depth and presence of scleral penetration by ultrasound biomicroscopy (UBM).

A. Epithelial. Conjunctival squamous neoplasia usually involves the limbal conjunctiva with or without corneal involvement and rarely presents in the palpebral or forniceal areas. In most developed nations, conjunctival squamous neoplasia tends to present as a slow-growing mass of the interpalpebral conjunctiva in elderly, fair-skinned, males in the 7th or 8th decade. In Africa and parts of Asia, the disease presents quite differently. Patients are much younger (around 35 years of age), female, and have specific risk factors including a combination of high sun exposure, HIV pandemic, and high exposure to HPV resulting in earlier and more rapid presentation and a higher rate of recurrence (40% or higher). The appearance of squamous neoplasia is variable and the clinical features may not allow delineation between benign versus malignant lesions. These neoplasms may be isolated or coexist with corneal degenerations such as pingueculae or pterygia. The macroscopic appearance is most commonly leukoplakic, gelatinous, or papilliform. The growth pattern is nodular or diffuse and there may be visible intrinsic tumor vessels or feeder vessels.

The intratumor vascular pattern is often typical and its highly disordered appearance is quite distinct from the linear vessels noted in other conjunctival reparative or inflammatory processes. Early squamous cell carcinoma (SCC) presents similarly to dysplasia. Rarely, it can grow diffusely without tumefaction and masquerade as a sclerokeratitis, scleromalacia, or interstitial keratitis. Left untreated, SCC causes disfigurement, profound vision loss, loss of the eye, or rarely (in other areas of the world) fatal metastatic disease. Intraocular invasion is rare (0% to 7%). Clinical features of intraocular extension include an anterior chamber or ciliary body mass, broad anterior synechiae in the area of the tumor, neovascularization of the iris, scleritis, or scleral perforation. Invasion of orbital tissues is reported in 12% to 16% of invasive tumors.

Local recurrence, mainly a function of incomplete tumor removal, is reported in up to 15% of cases. Recurrent cases are more likely to progress and result in scleral invasion or

intraocular penetration. The main predictors for recurrence are older age, large lesion size, scleral involvement, positive surgical margins, or a high Ki-67 score (elevated proliferation index), and atypical features. Metastasis occurs in less than 1% of cases and mostly involves regional lymph nodes. Sites of metastasis include the parotid, submandibular and submaxillary glands, cervical lymph nodes, the lungs, and bone. Mortality from conjunctival SCC ranges from 0% to 8%, and mainly occurs in Middle Eastern and African countries. Variants of SCC (i.e. mucoepidermoid carcinoma, adenoid squamous cell carcinoma, spindle cell carcinoma, or clear cell carcinoma) tend to be more aggressive and the management involves wider local excision and closer follow-up. They are differentiated on the basis of their histopathological features.

B. Melanocytic. Conjunctival melanocytic nevus is the most common melanocytic tumor of the conjunctiva. It is a benign, well-circumscribed, flat proliferation of melanocytes often with inclusion cysts and is similar to its cutaneous counterpart. Both cutaneous and conjunctival nevi are classified similarly--*junctional, compound, and subepithelial*. Conjunctival melanocytic nevi typically involve the bulbar conjunctiva, the caruncle, or the plica semilunaris, and do not extend onto the cornea. Most bulbar conjunctival nevi are found at the nasal or temporal limbus but about 10% are seen in the superior or inferior quadrants. About 5% to 10% of nevi are junctional (intramucosal) and are found more commonly in younger patients. The vast majority are compound nevi, which account for 70% to 80% of all nevi and are deeper proliferations into the superficial substantia propria. The subepithelial nevi account for the remaining 5% to 10% and are found in older patients with proliferations completely within the substantia propria, without any intraepithelial component. Conjunctival melanocytic nevi may be congenital or acquired, but most will be evident within the first few decades of life. While typically non-pigmented earlier in life, about 70% of nevi become pigmented after puberty. This frequently results in a referral for biopsy of the lesion. About 50% to 60% of conjunctival nevi have intralesional cysts. It is very uncommon (less than 1%) for progression to malignant melanoma. Intralesional cysts are extremely rare in PAM and melanoma, and the clinical detection of an intralesional cyst suggests the tumor is a benign melanocytic proliferation.

Although there is congenital melanosis (i.e. racial melanosis) and secondary melanosis (related to certain systemic conditions like Addison's disease), the most common type is **primary acquired melanosis (PAM)** of the conjunctiva, as described initially by Algernon Reese. PAM is an acquired lesion that develops during middle-age in fair-skinned persons and tends to be unilateral, flat, conjunctival or limbal pigmentation. The cornea is involved in over 20% of PAM cases. **Conjunctival malignant melanoma (CMM)** is relatively rare compared with PAM and makes up only 1% to 2% of all eye cancer cases. The incidence may be increasing but remains less than 1 case per million persons per year in the United States. The incidence is about 0.8 cases per million for Whites and 0.2 cases per million for Asians or Blacks. Despite the rarity of the tumor, it remains important because the 10-year mortality rate is as high as 13% to 50%. CMM is more common in older, fair-skinned patients but may present in a person of any age or race. Clinically, CMM appears as a raised, pigmented lesion with increased vascularity or prominent feeder vessels and can be surrounded by a flat PAM lesion. Minimally

pigmented CMM is seen in 19% of cases. The majority of CMM cases (50% to 75%) arise from PAM with atypia, 20% to 30% arise de novo and 5% arise from a conjunctival nevus. Rarely, a conjunctival melanoma can present as a completely amelanotic lesion. It may be adherent to the sclera making it immobile, exhibit extension onto the cornea, or involve the canalicular system. CMM is more commonly found in bulbar conjunctiva but carries a worse prognosis when found in caruncular, forniceal or palpebral conjunctival locations. Caruncular melanomas have up to a 50% mortality rate at 3 years. Other poor prognostic features include large tumor size (especially thickness greater than 2mm), local tumor recurrence, epitheloid cell type, ulceration, multifocal presentation, positive surgical margins, and invasion into the eye, orbit, lymphatics or lacrimal system. Some limbal CMMs overlie the cornea, but intraocular extension is very uncommon. CMM that arise from PAM have a higher recurrence rate. CMM is often associated with local recurrence because of residual microscopic disease. The 10-year recurrence rate is about 50% and 25% of cases will exhibit metastasis. As expected based on lymphatic drainage patterns, nasal CMMs tend to spread to submandibular lymph nodes, while temporal CMMs tend to spread to preauricular and parotid lymph nodes. Regional metastases to lymph nodes in the face and neck and distant metastases to the liver, lung, gastrointestinal tract and brain have been described. Metastasis occurs by lymphatic or hematogenous spread. Patients can die of systemic metastases without any regional nodal involvement. Lesions thicker than 2 mm histologically, greater than 10 mm in basal diameter, those demonstrating ulceration, or those involving non-bulbar conjunctiva are shown to have relatively poor survival and so may be considered for initial sentinel lymph node biopsy.

C. Lymphoproliferative. Clinically, these sub-conjunctival lymphoid tumors tend to be diffuse, pinkish, slightly elevated lesions found more commonly in the fornices that grow over time in an indolent manner. Sometimes they are described as “salmon patch” lesions. The differential diagnosis includes those conditions that cause follicular conjunctivitis. Patients may be thought to have allergic or infectious conjunctivitis or scleritis that is unresponsive to conventional treatment and they are eventually discovered to have bilateral conjunctival lymphoma. Patients with conjunctival lymphoma may rarely present with upper eyelid swelling, or choroidal and other intraocular involvement. Conditions such as amyloidosis or sarcoidosis can simulate a lymphoproliferative disorder. Clinical or imaging examinations cannot differentiate benign from malignant lymphoproliferative lesions.

Reactive lymphoid hyperplasia (RLH) is benign but may develop monoclonal lymphocyte populations that evolve into lymphomas. It is sometimes multifocal and involves non-ocular sites including lung, parotid gland, and axillary nodes. **Mucosa-associated lymphoid tissue (MALT) lymphoma** is the most common conjunctival lymphoma and is also called extranodal marginal zone lymphoma of the mucosa-associated lymphoid tissue (MALT) type. MALT lymphoma arises predominantly in the gastrointestinal tract and less frequently in sites such as the lung, thyroid or salivary glands, and the ocular adnexa. Most MALT lymphoma subjects are adults, although children rarely present with conjunctival, eyelid, and systemic manifestations. Chronic exposure to infectious agents is believed to sustain immune system activation leading to malignant B-cell transformation in many locations. Although MALT lymphoma of the

stomach is associated with *Helicobacter pylori* infection causing chronic antigenic stimulation, this association has not been seen in conjunctival MALT. There are scattered reports of *Chlamydia psittaci* infection causing conjunctival MALT and systemic lymphoma with geographic variability. In most American centers this infective association has not been replicated. *Epstein-Barr virus (EBV)* is also associated with conjunctival lymphocytic infiltrates. Rarely, Burkitt lymphoma presents as a conjunctival mass. Conjunctival **follicular lymphoma (FL)** and **diffuse large B-cell lymphoma (DLBCL)** are less commonly seen than MALT lymphoma. FLs tend to involve the lacrimal gland more than conjunctiva. They also tend to have concurrent systemic involvement, although they may present with a primary conjunctival lesion in patients of all ages. Less commonly encountered are lymphoplasmacytic lymphoma (LPL) and T-cell lymphoma (TCL). Mantle cell lymphoma represents about 5% of NHLs but rarely manifests as a conjunctival lesion. A relatively new entity called the IgG4-related OALNs tend to preferentially affect lacrimal glands rather than conjunctiva. In patients who have undergone solid organ or bone marrow transplantation, an entity called posttransplantation lymphoproliferative disorder (PTLD) may rarely involve the eyes, including conjunctiva. Most of these cases are associated with an EBV infection during pharmacologic immunosuppression. Patients with confirmed conjunctival lymphoma require a systemic evaluation. Typically, this includes a physical examination, blood count, serum lactate dehydrogenase (LDH), bone marrow biopsy, and PET-CT.

The goal of treatment is complete remission of the lesion and or systemic condition. When classifying blood-derived tumors manifesting as a conjunctival lesion, the main cell types are lymphocytes (B-cells, T-cells), plasma cells, white blood cells, and histiocytes. **Leukemia** occurs with uncontrolled growth of immature white blood cells. Anterior chamber involvement may be the initial manifestation of leukemia relapse, but is uncommonly the initial presentation of systemic disease. It is more common for the retina, uveal tract or orbit to be involved but, rarely, leukemia can present as a pinkish mass lesion in the bulbar or forniceal conjunctiva. There are several reports of acute lymphoblastic leukemia and other leukemia subtypes in children and adults that manifest as a conjunctival mass. Once the diagnosis of leukemia is confirmed histopathologically, the patient is promptly referred to the hematology/oncology service for further work-up and treatment. **Histiocytic** tumors of the conjunctiva will present as fleshy or yellowish epibulbar lesions with prominent vessels around the base and can be confused with lesions such as pyogenic granuloma or pterygium. These include juvenile xanthogranuloma (JXG), fibrous histiocytoma, and rarer entities such as fibroxanthoma and reticulohistiocytoma. JXG is a benign disorder and cutaneous lesions typically present as painless, fleshy papules in infants and tend to resolve spontaneously. Intraocular, orbital, or conjunctival involvement is less common. When conjunctival JXG is suspected, the management options include observation, topical or subconjunctival steroids, and excision.

D. Secondary/Metastatic. While basal cell or squamous cell carcinomas of the eyelid tend to infiltrate deeply, **sebaceous cell carcinoma (SebCC)** may exhibit pagetoid extension into conjunctival epithelium. This malignant neoplasm arises from sebaceous glands within the eyelid (tarsal meibomian glands, Zeis glands), the caruncle, or eyebrow, and

spreads in a non-contiguous or multicentric fashion. Patients can be misdiagnosed with benign conditions such as chronic blepharoconjunctivitis or a chalazion, or malignant epithelial tumors, most commonly a diffuse conjunctival squamous cell carcinoma with contiguous eyelid involvement. Early diagnosis is crucial because, left untreated, the tumor carries a significant risk for metastasis and mortality. Tumor-related death is reported as high as 30%. Even with a histopathological specimen, SebCC cases can be misdiagnosed due to skip areas or an inexperienced pathologist. The definitive management is surgical excision with supplemental cryotherapy, radiation, or chemotherapy. Given the multicentric nature of SebCC, map biopsies of the conjunctiva are often performed including both epithelium and stroma or tarsus, unless an obviously small focal tumor is present. If a diffuse area of conjunctiva is found to be involved, topical mitomycin C (MMC) may be used if the entire tumor is intra-epithelial. Often if there is widespread conjunctival stroma involvement, with the tumor displaying extensive pagetoid spread, a larger resection and sometimes orbital exenteration is required. In patients with histopathological confirmation of SebCC, a systemic work-up to rule out visceral malignancies such as colon cancer, as seen in the Muir-Torre syndrome should be considered. SebCC of the tarsal or palpebral conjunctiva can occur.

Metastasis to the orbit and choroid occurs much more frequently than to conjunctiva. However, there are case reports of metastatic breast, lung, renal cell, and gastric cancers presenting as a conjunctival lesion. Metastatic conjunctival lesions do not need to be excised unless the patient is experiencing symptoms. The patient must, however, be referred promptly for full systemic evaluation and treatment.

Ancillary testing.

Ultrasonography – High-frequency ultrasound biomicroscopy (UBM) is useful to determine tumor thickness, shape, and scleral or intraocular penetration. The main limitation of ultrasonography is that it is highly dependent on the examiner's expertise and deep invasion may not be appreciated.

Neuroimaging – A magnetic resonance imaging (MRI) scan of the orbits and brain with contrast enhancement is indicated along with when orbital penetration is suspected. The head and neck region can also be imaged using MRI or PET-CT (positron emission tomography (PET) scanning) for possible regional nodal metastasis.

Sentinel Lymph Node Biopsy. Originally, sentinel lymph node biopsy (SLNB) was employed to improve prognostic accuracy in cutaneous melanomas. It was adapted for conjunctival melanoma management by some groups. It is useful only in lesions with a high risk of systemic spread. As an example, in conjunctival melanomas this would include thick tumors (>1.5 mm) involving the fornix or caruncle. Patients have a pre-operative lymphoscintigraphy with technetium Tc-99m sulfur colloid and blue dye injected into the tumor prior to SLNB. The area of the initial lymph node drainage of the tumor is identified and biopsied. There is a lack of consensus regarding its value for cutaneous and conjunctival malignancies including melanoma. Studies vary with respect to the false negative rate of SLNB. Overall, based on the available evidence, SLNB seems to be a safe procedure that may improve prognostic accuracy in some high-risk conjunctival malignancies. The decision to use this technique at PMH is made on a case-

by-case basis.

5. Pathology

A. Epithelial. When squamous neoplasia is confined to the conjunctival epithelium, it is called conjunctival intraepithelial neoplasia (CIN). The terms Bowen's disease and carcinoma in situ (CIS) have fallen into disfavor for several reasons. CIN is a premalignant dysplastic change in surface epithelium that can gradually progress to malignant invasive SCC. This occurs once tumor cells invade through the basement membrane into substantia propria, sclera, the orbit, or the eye. Lymphatic spread may occur with SCC but not with CIN. It is important to distinguish between tumor-free versus tumor-involved margins after excision if frozen section-controlled excision is not done. Several criteria will help classify the tumor based upon the new seventh edition of conjunctival carcinoma staging by the American Joint Committee on Cancer (AJCC) (see Table 1), including pleomorphism (mild, moderate, or severe), dyskeratosis (mild, moderate, severe), inflammation, actinic damage, mitotic rate, and the Ki-67 proliferation index.

Table 1. Carcinoma of the Conjunctiva Staging System (AJCC, 7th Edition)

TUMOR (T) SIZE

TX: primary tumor cannot be assessed

T0: no evidence of primary tumor

Tis: carcinoma in situ

T1: Tumor 5mm or less in greatest dimension

T2: Tumor more than 5mm in greatest dimension, without invasion of adjacent structures

T3: Tumor invades adjacent structures (excluding the orbit)

T4: Tumor invades the orbit with or without further extension:

T4a: tumor invades orbital soft tissues, without bone invasion

T4b: tumor invades bone

T4c: tumor invades adjacent paranasal sinuses

T4d: tumor invades brain

REGIONAL LYMPH NODES (N)

NX: regional lymph nodes cannot be assessed

N0: no regional lymph node metastasis

N1: regional lymph node metastasis

DISTANT METASTASIS (M)

MX: distant metastasis cannot be assessed

M0: no distant metastasis

M1: distant metastasis

HISTOPATHOLOGIC TYPE

* the classification applies only to carcinoma of the conjunctiva

- * CIN including in situ squamous cell carcinoma
- * squamous cell carcinoma
- * mucoepidermoid carcinoma
- * spindle cell carcinoma
- * sebaceous gland carcinoma including pagetoid (conjunctival) spread
- * basal cell carcinoma

HISTOLOGIC GRADE (G)

GX: grade cannot be assessed

G1: well differentiated

G2: moderately differentiated

G3: poorly differentiated

G4: undifferentiated

Biomarker:

Ki-67 growth fraction:

- * Is the Ki-67 growth fraction less than 5%?
- * Is the Ki-67 growth fraction between 5% and less than 10%?
- * Is the Ki-67 growth fraction between 10% and less than 20%?
- * Is the Ki-67 growth fraction between 20% and 50%?
- * Is the Ki-67 growth fraction greater than 50%?

B. Melanocytic. As many as 40% of conjunctival malignancies are misdiagnosed by non-ophthalmic pathologists. Distinguishing benign melanosis from melanoma is a concept unique to the conjunctiva. The term ‘melanosis’ encompasses all intra-epithelial melanocytic proliferations that are not nevi in addition to areas of excess melanin secretion. PAM is a neoplastic melanocytic proliferation that has not invaded the epithelial basement membrane into the substantia propria. The pigmentation may increase or decrease over time. It is relatively common and accounts for about 10% of all conjunctival melanocytic proliferative lesions. PAM is histologically differentiated as with or without atypia. **PAM without atypia** may be viewed as the conjunctival counterpart of cutaneous lentigo. It exhibits an increased number of normal-appearing melanocytes with overproduction of melanin within the basal layer and does not progress to malignant melanoma; however, it may progress to PAM with atypia.

PAM with atypia exhibits an increased number of melanocytes that have cytologic or architectural atypia (i.e. pleomorphism, nuclear hyperchromatism, prominent nucleoli) and is associated with up to a 75% risk of malignant progression. However, lesions will vary from those with only mild to those with severe cytologic atypia so the literature reports progression rates varying from 13% to 75%. The growth patterns in order of increasing severity are basilar hyperplasia, basilar nesting, intraepithelial nesting, pagetoid spread, and replacement of the entire epithelium. Again, the aggressiveness of the lesion can be ascertained most precisely by the degree of cellular atypia. Folberg and McLean observed that the presence of epitheloid cells is associated with a high risk of malignant progression. Other atypical melanocyte types include small polyhedral cells,

spindle cells, and dendritic cells. PAM with atypia can sometimes be difficult to distinguish histologically from a junctional nevus, but the clinical features and patient demographics usually make this differentiation straightforward. “Melanoma in situ” is not typically used although some dermatopathologists argue that this would more accurately reflect the risk of invasion for the “high-risk subset” of PAM with atypia.

C. Lymphoproliferative. Specimens should be sent fresh to the pathologist with a request for tissue processing according to a *lymphoma protocol*. This will include flow cytometry, immunohistochemical, and molecular studies, in addition to standard histology, in order to classify the lymphoproliferative lesion. Although light microscopy can often reliably diagnose a malignant lymphoma, tools such as immunohistochemistry and molecular genetic studies are invaluable to distinguish between the various types of both benign and malignant lymphoproliferative disease. These newer diagnostic techniques have obviated the need to classify lesions as “atypical lymphoid hyperplasia”, a term that was once commonly used. The B- or T-cell lineage of the tumor is determined by immunophenotyping that detects markers for B-cell antigens (CD20) or T-cell antigens (CD3, CD5). Follicular lymphomas demonstrate CD10 positivity. Cyclin-D1 protein staining is done if mantle cell lymphoma is suspected. Kappa or lambda light chain restriction will provide evidence of monoclonality, which is indicative of lymphoma. If polyclonal (mixed cell) populations are found, the lesion is more likely to be benign. Molecular genetic studies of immunoglobulin heavy chain gene rearrangement are done to look for clonal bands using polymerase chain reaction (PCR). For example, the MALT 1 gene demonstrates a t(14;18) rearrangement. Trisomy of chromosome 3 occurs in t(14;18)-positive MALT lymphomas.

A modified tumor-node-metastasis (TNM) clinical staging system of ocular adnexal lymphomas supersedes the previously used Ann Arbor staging system. The purpose is to more precisely stage OALNs, which are extranodal NHLs and show distinct dissemination patterns compared with the nodal lymphomas for which the Ann Arbor system was originally developed in the 1970s. The Ann Arbor classification places most OALNs into “stage 1E” making it difficult to distinguish the clinical course of patients within subgroups of this category. The Ann Arbor system failed to consider many clinical and histological features of prognostic significance, which has been greatly improved by the new TNM classification system (see Table 2). The limitations of this newer system are that secondary lymphomas or intraocular lymphomas are not part of the classification. Future classifications aim to incorporate histomorphologic, immunohistochemical, and molecular genetic information into staging for more predictive accuracy.

Table 2. TNM clinical staging for ocular adnexal lymphomas (OALs)

PRIMARY TUMOR (T)

TX: lymphoma extent not specified

T0: no evidence of lymphoma

T1: lymphoma involving the conjunctiva alone without orbital involvement

 T1a: bulbar conjunctiva only

 T1b: palpebral conjunctiva +/- fornix +/- caruncle

- T1c: bulbar and nonbulbar conjunctival involvement
- T2: lymphoma with orbital involvement +/- any conjunctival involvement
 - T2a: anterior orbital involvement but no lacrimal gland involvement (+/- conjunctival disease)
 - T2b: anterior orbital involvement with lacrimal gland involvement (+/- conjunctival disease)
 - T2c: posterior orbital involvement (+/- conjunctival involvement +/- any extraocular muscle involvement)
 - T2d: nasolacrimal drainage system involvement (+/- conjunctival involvement but not including nasopharynx)
- T3: lymphoma with preseptal eyelid involvement +/- orbital involvement +/- any conjunctival involvement
- T4: orbital adnexal lymphoma extending beyond orbit to adjacent structures, such as bone and brain
 - T4a: involvement of nasopharynx
 - T4b: osseous involvement (including periosteum)
 - T4c: involvement of maxillofacial, ethmoidal +/- frontal sinuses
 - T4d: intracranial spread

LYMPH NODE INVOLVEMENT (N)

- NX: involvement of lymph nodes not assessed
- N0: no evidence of lymph node involvement
- N1: involvement of ipsilateral regional lymph nodes
- N2: involvement of contralateral or bilateral regional lymph nodes
- N3: involvement of peripheral lymph nodes not draining ocular adnexal region
- N4: involvement of central lymph nodes

DISTANT METASTASIS (M)

- MX: dissemination of lymphoma not assessed
- M0: no evidence of involvement of other extranodal sites
- M1: lymphomatous involvement in other organs recorded either at first diagnosis or subsequently
 - M1a: noncontiguous involvement of tissues or organs external to the ocular adnexa (e.g. parotid glands, submandibular gland, lung, liver, spleen, kidney, breast)
 - M1b: lymphomatous involvement of the bone marrow
 - M1c: both M1a and M1b involvement

6. Management

6.1 Management algorithms

There are certain management principles unique to specific clinical entities but generally most conjunctival malignant tumors undergo local resection with or without supplemental cryotherapy and or topical chemotherapy. Surgical excision is preferred because it provides histopathologic confirmation of the diagnosis.

Primary acquired melanosis (PAM) and melanoma of the conjunctiva

The clinical management of PAM has been altered as the accuracy of histologic prognosis in PAM for malignant degeneration has been demonstrated. About 35% of lesions will progress clinically (i.e. increase in size or change in color or shape). Most ophthalmic oncologists biopsy PAM, especially if growth has occurred. In addition to high-risk histologic criteria, the size of PAM with atypia predicts the risk of progression to invasive melanoma. Lesions larger than 1 clock-hour should undergo surgical excision with negative margins and supplemental cryotherapy. Some prefer the use of topical chemotherapeutic agents like mitomycin C as primary therapy after an incisional biopsy of intraepithelial tumors.

For conjunctival melanoma, the definitive management is surgical excision with supplemental cryotherapy, radiation, or chemotherapy. Orbital exenteration is reserved for invasive melanoma into the eye or orbit. Exenteration does not confer a survival benefit, so orbital disease may also be managed by radiotherapy. However, the recurrence rate may remain high (up to 40% at 3 years).

Conjunctival lymphomas

The management of primary conjunctival lymphomas or other lymphoproliferative lesions is variable. Treatment options include chemotherapy with an anti-CD20 antibody (for B-cell lymphomas), external-beam radiation therapy (EBRT), surgical excision (with or without supplemental cryotherapy), or topical chemotherapeutic agents such as mitomycin C, 5-fluorouracil, or interferon alfa-2b. All of these modalities are effective with local tumor control rates greater than 75% and 5-year survival rates greater than 90%. Several groups note that fractionated photons to 20-30 Gy is sufficient for indolent orbital lymphoma to achieve a disease-free 5-year survival rate of 95%. Beta-ray brachytherapy using a Strontium-90-Yttrium-90 applicator is effective for conjunctival lymphomas but carries a risk for late corneal and lens complications. The side effects are mostly related to dry eye and cataract formation. This fractionated dose-delivery method allows a higher total treatment dose for the tumor and lower, safer doses to uninvolved tissues. One group uses three sessions of cryotherapy alone with liquid nitrogen spray in selected cases and reports a 98% cure rate. There are some reports of spontaneous regression of conjunctival lymphomas, suggesting that observation may be an option for some patients with minimal disease at presentation. In patients with active systemic lymphoma with ophthalmic involvement, the conjunctival lesion is treated with the local options described above, but the patient may also require multiple cycles of systemic chemotherapeutic (i.e. cyclophosphamide, vincristine, prednisone) or biologic (i.e. rituximab) agents. The role *chlamydia psittaci*, hepatitis viridae, or other infectious agents play in OALNs is still debated but seems to vary with geographical location.

6.2 Surgery

An excisional biopsy (“no-touch” technique) is always preferable and localized conjunctival tumors are most amenable to complete removal. Diffuse or multifocal malignant tumors that involve a large area of conjunctiva, or tumors such as sebaceous cell carcinoma (SebCC) with pagetoid spread are often not amenable to surgical excision alone and are best managed with primary or supplemental radiation and chemotherapy. An incisional biopsy may be acceptable for large tumors to confirm the diagnosis. Map biopsies can be done to determine the full extent of the neoplasm. The conjunctiva contains goblet cells and glandular structures important for normal tear film composition. When large areas are excised, or when both bulbar and palpebral conjunctiva is resected, this can be problematic for the ocular surface. Resection of extensive limbal tumors can result in stem-cell deficiency. When greater than 40% of limbal epithelium is resected, a free limbal autograft is taken from the contralateral eye.

Excision of conjunctival tumors without corneoscleral involvement:

The conjunctival neoplasm is excised to bare sclera and placed on a sterile telfa or paper drawing form orienting the specimen precisely relative to adjacent anatomical landmarks. A thin strip of conjunctiva surrounding the created defect is then excised and sent for intraoperative frozen section analysis. It is oriented precisely on the drawing form. All specimens are wetted with balanced salt solution (BSS) and sent “fresh” to the pathologist. This is because lymphoproliferative or sebaceous cell neoplasms need special stains that cannot be done if the specimen is sent in formalin. The corneal border for limbal tumors will not have a ‘margin’ to be sent for frozen section analysis, but is treated intraoperatively with cryotherapy. The frozen section analysis may provide a preliminary diagnosis and should be able to distinguish between benign and malignant lesions. Additional tissue can be sent as necessary if margins come back positive. Diathermy or wet-field bipolar cautery is used throughout the case for hemostasis as necessary. If a malignant neoplasm is confirmed, adjuvant double freeze-thaw cryotherapy is applied to the conjunctival margins and scleral bed. All clinically suspicious areas are treated. A hammerhead cryoprobe (set at -40 degrees Celsius) is used. The tissue is allowed to thaw before it is frozen for the second time. Gloves and instruments are changed prior to reconstruction. The method for reconstruction of the defect will depend upon its size and location. Smaller defects are closed primarily or with advancement flaps. Larger defects require either free autologous conjunctival grafts from the same or contralateral eye, free buccal mucosa grafts, or amniotic membrane grafts. Again, if greater than 40% of limbal epithelium is resected, a limbal autograft from the contralateral eye is required to prevent stem-cell deficiency. Castroviejo calipers are helpful to measure the size of the defect. The conjunctival graft should be about 25% larger than the defect size. This graft is sutured into position using 8-0 Vicryl or 10-0 Nylon suture. If the defect goes into the fornix, a vault conformer (also called a symblepharon ring conformer) is placed on the eye surface to avoid symblepharon formation. The eye is dressed with antibiotic ointment and a pressure-patch dressing. This dressing is removed the following day.

Excision of conjunctival tumors with corneal or scleral penetration:

When the conjunctival tumor extends into cornea, the involved cornea may undergo alcohol epitheliectomy or can be scraped with a blade. An effort is made to preserve Bowman's layer if possible because it acts as a barrier to intraocular tumor spread. The epithelium heals over a few days. Microscopic disease can extend beyond the clinical margins so supplemental cryotherapy (as described above), application of absolute alcohol, or adjunctive topical chemotherapy may be used. For lesions that have penetrated deeply, a superficial lamellar keratectomy is employed. Superficial scleral invasion is treated with partial lamellar sclerokeratoconjunctivectomy, although deeper invasion requires full-thickness eye wall resection with a free scleral graft.

Map biopsy technique:

This technique is mandatory for multicentric or diffuse tumors like sebaceous cell carcinoma (SebCC) that have pagetoid spread, or other large areas of involvement. For SebCC the specimen includes epithelium and stroma or tarsus. The biopsy sites are tarsal, palpebral/forniceal, bulbar, and limbal conjunctiva. These are submitted for permanent section analysis with each site independently analyzed.

Tumors with intraocular extension:

Enucleation surgery is usually required once there is intraocular extension. However, if this extension is localized to the iris or ciliary body, an eyewall resection including iridocyclectomy of the involved area may be considered. Otherwise, the conjunctiva is resected en bloc with the globe to avoid spreading tumor cells. For extensive conjunctival and ocular involvement or orbital penetration, a complete or anterior exenteration is often required.

Tumors with regional metastatic spread:

Although metastasis is uncommon, if it involves the regional lymph nodes, treatment typically includes parotidectomy, neck dissection, and radiation therapy.

6.3 Chemotherapy

Topical chemotherapy: Mitomycin C (MMC) is the most extensively studied of the topical chemotherapeutic agents and can be used as a primary treatment option in intraepithelial tumors since it reaches the neoplasm by first order pharmacokinetics; it is contraindicated in thick tumors. It is an alkylating agent cytotoxic both to proliferating and non-proliferating cells that is isolated from *Streptomyces caespitosus*. Treatment consists of four 2-week cycles of 1-week on MMC (0.02% to 0.04%) four times daily and 1-week on tobradex four times daily. Although highly effective, it carries the risk of complications such as conjunctival injection, keratopathy, punctal stenosis or rarely, limbal stem cell deficiency. In the series by Russell *et al.*, MMC 0.04% four times daily at three 3-week cycles is used for epithelial and melanocytic conjunctival tumors, and 52% of patients have short-term complications, 31% have long-term complications, 7% require treatment cessation, and 12% have limbal stem cell deficiency. Temporary punctal occlusion with plugs can be used while drops are administered to avoid damage to the lacrimal system. However, if there is a potential for tumor seeding in that area then

punctal plugs are best avoided. The other commonly used chemotherapeutic agents are 5-fluorouracil (5-FU) and interferon alfa-2b (IFN2b). Since these agents have different molecular mechanisms of action, failure with one adjuvant (assuming adequate drug diffusion) does not contradict the use of another drug. The topical chemotherapeutics are particularly useful for diffuse or multifocal intraepithelial malignancies. An advantage is that the entire ocular surface is treated so the importance of histologic control of tumor margins becomes less important. All three of the agents should remain part of the armamentarium because tumors exhibit a variable response to treatment. When planning to use these agents as supplemental therapy after surgical excision, a delay of 2 to 3 weeks will allow the conjunctival wound to heal. They can be used as primary treatment in select cases.

Systemic chemotherapy: Rituximab is a recombinant chimeric monoclonal antibody that targets the CD20 antigen. It is a systemic treatment option for B-cell lymphomas that exhibit CD20-positivity. Intravenous administration is used both as first-line and salvage therapy with moderate success. Rituximab is shown to be effective and safe for primary conjunctival lymphoma at a dose of 375 mg/m² given intravenously each week for one month. The therapeutic mechanism of action is probably a result of antibody-dependent cell-mediated and complement-mediated cytotoxicity. Intralesional therapy with either rituximab or chemotherapy has also been tried in a few cases.

6.4 Radiation therapy

Radiotherapy is an effective treatment option for lymphomas of the conjunctiva, eyelids, and orbit. For conjunctival lymphomas, a direct anterior electron beam with lens shielding is usually possible in most cases, whereas for orbital tumours with any retrobulbar component, a photon IMRT approach is preferred.

Anterior Electron

Immobilization:	neck rest and thermoplastic shell
Simulation:	CT
Technique:	direct anterior beam
Shielding:	hanging pencil eye shield just beyond eyelashes
CTV:	anterior 2/3 to 3/4 of orbit
Energy:	12, 16, or 20 MeV
Dose:	2000 cGy/10

Orbital RT

Immobilization:	neck rest and thermoplastic shell
Simulation:	CT
Technique:	IMRT with daily Image Guidance with cone beam CT
Energy:	6 MV
CTV:	whole orbit
Dose:	2500 cGy/10

Carcinomas that infiltrate bulbar conjunctiva cannot be treated with any external beam radiotherapy technique as doses required for tumour control are associated with a high likelihood of major toxicity to globe which would eventuate in enucleation. Occasional cases of relatively localized carcinomas may be treated with an iodine-125 plaque, but these are only rarely done.

6.5 Other therapy

Radioimmunotherapy using Y-90 ibritumomab tiuxetan (Zevalin) is a novel therapeutic approach that employs monoclonal antibodies such as rituximab given pre-treatment to deliver the radioisotopes to disease sites.

6.6 Oncology nursing practice

Patients seen at the Ocular Oncology clinic are invariably outpatients. The initial history and assessment of visual acuity and pupil reactivity is performed by the clinic RN. The RN is often used as an initial point of contact by patients when new symptoms develop or other questions arise.

6.7 Clinic Coordination/Management

The identification of a specific disease complex and the direction to appropriate subspecialty care is usually accomplished by a trained ocular oncology clinic coordinator/manager. This individual is frequently an experienced ophthalmic assistant. Knowledge of the vision care referral base and collection of investigational materials for new patients is of paramount importance as first steps to providing optimal patient care. The coordinator also serves an invaluable function in supporting both patient and family during investigation, therapy, and convalescence.

7 Supportive Care

7.1 Patient education

Patients and family members are educated on a one-on-one basis by a consultant during the initial assessment and at every follow-up visit.

7.2 Psychosocial care

When patients express or display emotional, psychological, or social concerns an effort is made to address these during the clinical encounter. In rare instances when this is insufficient to deal with all issues, the patient may be referred to the Department of Psychosocial Oncology.

7.3 Symptom management

Patients with conjunctival tumors who undergo local resection and or adjuvant therapy may present with redness, dry eye symptoms, blurriness, or pain. This is treated with topical artificial tears, corticosteroids, or other treatment as needed.

7.4 Clinical nutrition

The role of nutritional advice and support in the ocular oncology patient population is very limited. Patients with dry eye syndrome may be educated about the value of omega-3-fatty acid and flax seed intake while those with age-related macular degeneration may be encouraged to eat green leafy vegetables.

7.5 Palliative care

The medical oncology group facilitates end-of-life palliative care as needed for those patients with advanced metastatic disease. This occurs extremely rarely.

7.6 Other

Many patients travel from across Canada to the Ocular Oncology service of PMH. The clinic makes every effort to accommodate patients based on travel dates and facilitate lodging when required.

8. Follow up Care

Close monitoring for tumor recurrence is paramount. The rate of recurrence for OSSN after definitive treatment has been reported between 5% to 50%, mainly dependent on whether or not tumor margins were clear at the time of surgery. The key to treatment is prevention and close follow-up for suspicious lesions before they develop into SCC. Even after lesions are treated and appear to be in complete clinical remission, patients are followed annually for recurrence or development of new tumors, since the entire conjunctiva is exposed to risk factors such as UVB.

All treated patients with lymphoproliferative lesions must be monitored for local recurrence, which may present in the same or contralateral eye, and systemic involvement. Occasionally, patients with known systemic disease will have a conjunctival recurrence years later. In a study of 117 patients with conjunctival lymphoid tumors, the incidence of secondary lymphoma increased over time reaching 28% at 10 years. Systemic disease is less common in association with perilimbal lesions and non-bulbar conjunctival lesions or cases of multiple conjunctival lesions have the worse prognosis.

9. References

In preparation of this document, some data and tables were incorporated from the following publication.

Gill HS, Char DH, Cole TB. Malignancies of the conjunctiva and cornea. In *Cornea*; Eds. Copeland RA, Afshari N. Jaypee Brothers: Delhi, (in print).