PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES

OCULAR ONCOLOGY

PERIOCULAR CUTANEOUS MALIGNANCY
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1. Introduction

**Periocular cutaneous malignancies** include basal cell carcinoma (BCC), squamous cell carcinoma (SCC), sebaceous cell carcinoma (SebCC), and cutaneous malignant melanoma (CMM). Five to 10% of all skin carcinomas occur on the eyelid. BCC is the most common skin cancer to affect the face and frequently involves the periocular region. It accounts for about 90% of malignant eyelid tumors. Although it carries a low metastatic potential, the carcinoma is locally invasive and destructive. Left inadequately treated, BCC can cause extensive tissue damage. This has serious functional and aesthetic implications, particularly when involving the eyelid and face.

2. Prevention

Smoking cessation and decreasing exposure to UV light (sunscreen, sunglasses, hats) are the most effective strategies to prevent periocular cutaneous malignancy and this is particularly important for fair-skinned persons. Immunocompromised patients must have their immune status optimized.

3. Screening and Early Detection

Patients with a personal or family history of cutaneous malignancy or pre-cancerous skin changes (i.e. actinic keratosis) are encouraged to undergo routine screening for early detection. Those who develop suspicious lesions should be evaluated as soon as possible. Patients with syndromic predisposition to cutaneous malignancy (i.e. xeroderma pigmentosum or basal cell nevus syndrome) are typically evaluated for new lesions every 2 to 6 months.

4. Diagnosis

Patients are referred to the Princess Margaret Hospital (PMH) ocular oncology service for localized periocular cutaneous malignancies. Those cases with orbital infiltration, regional or systemic metastasis, or cases co-managed with the PMH Head & Neck Oncology service are also evaluated.

**Clinical features.** Non-melanocytic lesions (BCC, SCC) may demonstrate malignant features including loss of eyelashes, distortion of the eyelid margin architecture, ulceration, pearly borders, telangiectatic vessels, induration, lack of tenderness, bleeding, or evidence of rapid growth. Melanocytic tumors (nevus, melanoma) may increase in size (vertical or radial growth), change in shape, increase in pigmentation, or demonstrate some of the features described above for non-melanocytic lesions. Adnexal lesions (SebCC) may masquerade as chronic, unilateral blepharitis or recurrent chalazion or demonstrate the features described above for non-melanocytic lesions. Any periocular cutaneous malignancy with orbital infiltration may cause vision loss, exophthalmos with or without double vision, decreased eye motility, or lack of trigeminal sensation.
During the initial assessment, a complete ophthalmological examination is performed including Snellen visual acuity, pupil reactivity, colour vision, slit-lamp evaluation, dilated funduscopy, assessment of extraocular motility, periorcular and facial skin assessment, retropulsion, exophthalmometry, dermatomal trigeminal sensation (V1 and V2), and head and neck lymph node palpation.

**Ancillary testing.** Any evidence of orbital involvement requires orbital neuroimaging (CT and MRI with and without contrast). A metastatic work-up is performed for biopsy-proven SebCC and sentinel lymph node biopsy may be considered for CMM.

**5. Pathology**

An incisional or excisional biopsy can be performed for non-melanocytic tumors. The specimen is sent in formalin for permanent histopathology. The common histomorphologic features of BCC seen with hematoxylin and eosin (H&E) staining include peripheral palisading, myxoid stroma, and artefactual clefting. Those for SCC include large, polygonal eosinophilic keratinocytes that may transform into nests or keratinous pearls with a surrounding inflammatory infiltrate. Poorly differentiated SCC contains more pleomorphic cells and no keratinization.

Pigmented or non-pigmented lesions suspicious for a melanocytic lesion (nevus or melanoma) are best treated by excisional biopsy with 1 to 2mm margins and a “no-touch” technique to avoid spillage of tumor cells. The histologic subtypes of CMM include superficial spreading melanomas, nodular melanomas, lentigo maligna melanomas, acral lentigious melanomas, and mucosal lentigious melanomas. More than 70% of CMMs are superficial spreading melanomas with haphazardly distributed atypical melanocytes at all levels of the epidermis. Immunohistochemical markers such as HMB-45 or S-100 are commonly used to confirm the diagnosis. Lesions suspicious for SebCC must be sent fresh so that fat stains such as oil-red-o can be used. Because these tumors can undergo pagetoid spread and commonly have multicentric involvement, map biopsies should be performed. SebCCs may grow in nests with central necrosis and foamy cytoplasm. Sometimes the lesion can mimic BCC, SCC, or a Merkel cell tumor.

The TNM classification system for cutaneous malignancy (AJCC, 7th edition) distinguishes non-eyelid and eyelid tumors.
TNM classification for eyelid carcinoma

PRIMARY TUMOR (T) FOR EYELID CARCINOMA
TX: primary tumor cannot be assessed
T0: no evidence of primary tumor
Tis: carcinoma in situ
T1: tumor less than or equal to 5mm in greatest dimension (not invading the tarsal plate or eyelid margin)
T2a: tumor 5-10mm in greatest dimension or any tumor that invades the tarsal plate or eyelid margin
T2b: tumor 10-20mm in greatest dimension or involves full-thickness eyelid
T3a: tumor greater than 20mm in greatest dimension or any tumor that invades adjacent ocular or orbital structures; any T with perineural tumor invasion
T3b: complete tumor resection requires enucleation, exenteration, or bone resection
T4: tumor is not resectable because of extensive invasion of ocular, orbital, craniofacial structures, or brain

REGIONAL LYMPH NODES (N) FOR EYELID CARCINOMA
NX: regional lymph nodes cannot be assessed
cn0: no regional lymph node metastasis based upon clinical evaluation or imaging
pN0: no regional lymph node metastasis based upon lymph node biopsy
N1: regional lymph node metastasis

DISTANT METASTASIS (M) FOR EYELID CARCINOMA
M0: no distant metastasis
M1: distant metastasis

ANATOMIC STAGE/PROGNOSTIC GROUPS FOR EYELID CARCINOMA

<table>
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<tr>
<td>IV</td>
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<td>Any N</td>
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Clark staging for cutaneous malignant melanoma
Level I: all tumor cells above basement membrane (in situ)
Level II: tumor extends into papillary dermis
Level III: tumor extends to interface between papillary and reticular dermis
Level IV: tumor extends into reticular dermis
Level V: tumor invasion of subcutaneous tissue
Breslow classification (thickness) for cutaneous malignant melanoma
I: less than or equal to 0.75mm
II: 0.76-1.5mm
III: 1.51-4mm
IV: greater than or equal to 4mm

TNM classification for cutaneous malignant melanoma

THICKNESS (T) CLASSIFICATION
TX: primary tumor cannot be assessed (shave biopsy, regressed primary)
Tis: melanoma in situ
T1: less than or equal to 1.0mm (a: without ulceration and mitosis less than 1/mm2,
    b: with ulceration and mitosis greater than or equal to 1/mm2)
T2: 1.01-2.0mm (a: without ulceration, b: with ulceration)
T3: 2.01-4.0mm (a: without ulceration, b: with ulceration)
T4: greater than 4.0mm (a: without ulceration, b: with ulceration)

REGIONAL LYMPH NODE (N) METASTASIS
N0: no evidence of regional lymph node metastasis
N1: one lymph node (a: micrometastasis—clinically occult) (b: macrometastasis—
    clinically apparent)
N2: 2 to 3 lymph nodes (a: micrometastasis, b: macrometastasis, c: in transit
    metastases/satellite(s), without metastatic lymph nodes (N2a: 2-3 nodes
    positive for micrometastasis; N2b: 2-3 nodes positive for macrometastasis;
    N2c: in transit met(s)/satellite(s) without metastatic nodes)
N3: 4 or more metastatic nodes or matted nodes or in-transit metastases/
    satellite(s) with metastatic node(s)

DISTANT METASTASIS (M)
M0: no evidence of distant metastasis
M1a: distant skin, subcutaneous, or nodal metastases, normal serum lactate
    dehydrogenase (LDH) level
M1b: lung metastases, normal LDH level
M1c: all other visceral metastases or any distant metastases with an elevated LDH
    level

MELANOMA STAGING

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6. Management

6.1 Management algorithms

There are many management options for periocular cutaneous malignancies, both surgical and non-surgical. Some non-surgical options include cryotherapy, radiation, photodynamic therapy, electrodissection and curettage, topical 5-fluorouracil, and topical immune modulators such as imiquimod. A problem with non-surgical management, however, is that no pathological specimen is reviewed to ensure complete tumor eradication.

6.2 Surgery

The primary management of BCC maybe surgical excision or radiotherapy. Surgical options may include primary excision with predetermined margins, frozen section (FS)-controlled excision, or Mohs micrographic surgery (MMS). The cure rates using these techniques for periocular BCC fall between 85 to 100%. Surgical resection of biopsy-proven SCC or melanoma is commonly performed in collaboration with Mohs’ surgeons at networked hospitals. The reconstruction is subsequently performed by an oculoplastic surgeon. Tumors with orbital infiltration who are not candidates for radiation treatment may require orbital exenteration.

6.3 Chemotherapy

There are many clinical trials underway for novel chemotherapeutic regimens to treat metastatic melanoma with limited efficacy.

6.4 Radiation therapy

Eyelid or orbital radiotherapy may be primary treatment for patients where surgical resections will likely be associated with significant tissue deficits, and quite often in elderly patients where comorbid conditions may increase surgical risks, or at patient discretion after consultation with both surgical and radiation teams. Radiation is also used as adjunctive therapy after tumor resection if clear margins are not achieved for an infiltrative, high-risk malignancy (i.e. morpheaform basal cell carcinoma). Local control rates are excellent in the 95% range in multiple reports.
Eyelid Tumours

Immobilization: neck rest
Simulation: clinical mark up
Technique: direct apposition with daily topical anesthetic
Energy: 75, 100, or 225 kv
Shielding: lead cut out for field definition
Dose: 3500 cGy/5, 4500 cGy/10, 5000 cGy/20, 6000 cGy/30

Orbital Tumours

Immobilization: neck rest and thermoplastic shell, relocatable GTC frame
Simulation: CT, possibly MRI on occasion
Technique: IMRT with daily Image Guidance with cone beam CT
Energy: 6 MV
Dose: 6000 cGy/30 for primary tumours
       2000 cGy/5, 3000 cGy/10 for metastatic tumours

6.5 Other therapy

In January 2012, the US Food and Drug Administration approved the first molecular-targeted therapy for metastatic or locally advanced BCC known as vismodegib (Erivedge). This therapy remains investigational.

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 pain, blurry vision, eye redness or discomfort, are treated with topical artificial tears or other medications 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. This occurs very rarely for patients with periocular cutaneous malignancy seen by the ocular oncology service.

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

Most patients are followed for tumor recurrence and functional and aesthetic rehabilitation post-surgery outside of the ocular oncology service at PMH (i.e. private office).