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Management of conjunctival malignant melanoma: a review and update

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Abstract

Conjunctival malignant melanoma is a pigmented lesion of the ocular surface. It is an uncommon but potentially devastating tumor that may invade the local tissues of the eye, spread systemically through lymphatic drainage and hematogenous spread, and recur in spite of treatment. Despite its severity, the rarity of available cases has limited the evidence for diagnosis and management. This review will provide an overview of the epidemiology, presentation, diagnosis, management, and surveillance of conjunctival melanoma, with an emphasis on recent advances in biological therapies to treat this disease.

Keywords

Conjunctival malignant melanoma; melanoma; ocular neoplasm; BRAF inhibitors; mitomycin C; interferon alpha-2b; ipilimumab; vemurafenib; dabrafenib

Epidemiology and Risk Factors

Conjunctival malignant melanoma (CMM) is a rare but potentially life-threatening cancerous growth of the eye. It arises from melanocytes located amongst the basal cells of the conjunctival epithelium. It is an uncommon tumor which comprises about 2% of all eye tumors, 5% of melanomas in the ocular region [1] and 0.25% of all melanomas overall [2]. Cutaneous melanoma is 360 to 900 times more common than CMM [2,3]. Overall incidence is between 0.24 to 0.8 cases of CMM per million, based on population data from the national registries of Finland, Sweden, Denmark, the Netherlands and the United States over several decades [4–8]. Incidence is increasing [4–8]. Over a 27-year period between 1973 and 1999, the age-adjusted incidence of CMM in the United States increased by 101%, and by 295% in white males older than 60 [5]. Studies in Finland and Sweden, which possess relatively

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homogeneous populations, have noted the increasing incidence of CMM in tandem with cutaneous melanoma, suggesting a possible association between CMM and ultraviolet (UV) light exposure [4,6].

The risk factors for CMM are not well understood. While there are known risk factors for cutaneous melanoma, including family history, fair skin and hair, high density of freckles [9], UV light exposure especially during childhood [10,11], and genetic syndromes such as familial melanoma syndromes [12], xeroderma pigmentosum [13], Hodgkin lymphoma and hereditary retinoblastoma [14], the risk factors for CMM are not yet established. Tumor rarity and the limited number of population-based studies restrict any strong conclusions. Even the data regarding the association between UV light exposure and ocular melanoma has been equivocal [15]. Familial risks have been investigated, with a possible association with retinoblastoma and breast cancer [16]. Amongst ethnic groups, Asians & Pacific Islanders are the least affected (0.15 cases per million). In comparison to that ethnic group, American Indians are 1.1 times more likely to be affected, Blacks 1.2 times, Hispanics 2.2 times, and White, non-Hispanics 3.3 times [17]. Various studies have shown no predilection for either gender [18,19], while some have shown a greater association with male gender [4].

Despite the lack of evidence regarding risk factors, the association between CMM and two related conditions, primary acquired melanosis (PAM) and nevi is well documented [19–21]. Fifty seven to seventy six percent of CMM arises from primary acquired melanosis (PAM) [6,8,20,22]. PAM with severe atypia can transform into a melanoma at a frequency of 13 to 50% [21]. PAM without atypia or mild atypia is unlikely to progress to melanoma [21]. PAM should be differentiated from racial or complexion-associated melanosis (CAM), which is a condition without malignant potential [23]. Less commonly, CMM may arise de novo (16-25%) or from nevi (1-6%) [8,20,22,24].

Presentation

Conjunctival melanoma commonly presents as a thickened, raised, pigmented lesion with prominent feeder vessels and surrounding areas of melanosis (Figures 1A-1D). It is usually unilateral and presents in adulthood [25]. Although melanoma typically has some degree of pigmentation, amelanotic CMM can occur (15-19%) [19,20] and be mistaken for ocular surface squamous neoplasia (OSSN) or lymphoma (Figure 1D). Most patients simply complain of noticing a pigmented spot but on rare occasions, the tumor can be associated with ocular pain and irritation [19]. The most common location is on the bulbar conjunctiva (60-92%) [8,19,20], most likely because this area is directly exposed to sunlight. The limbus is often involved (48- 61% of cases) [6,8,19,20]. No particular quadrant appears to be favored, with the following ranges reported: superior (16-34%), inferior (22-39%), nasal (17-34%), and temporal (26-63%) [19,20]. Less frequently, CMM may present on the palpebral and forniceal conjunctiva, plica semilunaris and caruncle. CMM located in these latter areas is associated with worse prognosis [20]. Multifocal lesions are present in 22-28% of patients [8,26] and are also associated with increased mortality [27].

Rarely, CMM may present with invasion (1% of cases), usually spreading first through lymphatic drainage [20]. Tumors of the nasal conjunctiva appear to drain to the

submandibular lymph nodes [28] while tumors of the rest of the conjunctiva primarily drain to the preauricular and deep cervical lymph nodes [28,29]. Tumors may also invade secondary structures [30–32] through direct extension or hematogenous spread [3], such as the orbit (2% of cases) [20], eyelids (1%) [20], and the nasolacrimal duct, nasal cavity or paranasal sinuses (1-5% cases) [20,33]. CMM with limbal involvement may invade the cornea; however, Bowman's membrane acts as an important natural barrier, restricting the tumor to superficial layers [3].

Diagnosis

History & Physical Exam

The diagnosis of CMM is usually made by careful clinical examination and slit lamp biomicroscopy. Clinical examination should include a thorough history (age, symptoms, sun exposure, evolution of lesion, previous cancers, symptoms, and review of old photographs) and physical examination (lymph node palpation, gross examination of ocular surface, changes in eyelids and adjacent skin). On slit lamp, the examiner should inspect the ocular surface carefully for pigment, nodularity, and feeder vessels, remembering to examine intertriginous areas such as the fornix and tarsal conjunctiva by everting both the lower and upper eyelids. The presence of pigment, particularly on the tarsal conjunctiva should heighten suspicion for CMM. The anterior chamber should also be examined and a dilated fundus examination performed to inspect the interior surfaces of the eye. Slit lamp photographs should be taken to document the size and extent of the lesion.

Differential Diagnosis

Differential diagnosis includes the progenitors of CMM: PAM and conjunctival nevi. Like CMM, PAM is typically unilateral but presents as a flat, asymmetric, noncystic, pigmented patch on the conjunctiva or cornea. The lesion may be multifocal [23,34]. CAM may resemble PAM, but is usually bilateral, and is found in patients of darker complexion [35]. Conjunctival nevi can usually be differentiated by history as they are mostly stable, unilateral, focal pigmented lesions, and often have cystic spaces [34]. Other differential diagnoses include local extension of uveal melanoma or melanocytoma, and distant metastasis of cutaneous melanoma. Amelanotic melanoma may resemble pyogenic granulomas [19], lymphomas, or squamous lesions such as pterygia, pingueculae, or OSSN. Though rarer, staphylomas, subconjunctival hematomas, mascara, foreign bodies, and hematic cysts have all been mistaken for CMM [25].

Histopathologic Diagnosis

Histopathologic evaluation by a trained pathologist is used to confirm the diagnosis (Figure 2). An excisional biopsy is preferred over concerns of tumor cell seeding [19]. Histological sections should be made perpendicular to the epithelial surface to allow measurements of tumor thickness. Specimens are oftentimes bleached because the melanin granules can obscure cell morphology and underlying architecture, and interfere with antibody-antigen interaction during analysis by immunohistochemistry [36]. Four types of atypical melanocytes exist in CMM lesions: spindle cells, balloon cells, small polyhedral cells, and round epithelioid cells [37]. Spindle cells are elongated melanocytes with hyperchromatic

nuclei and eosinophilic nucleoli [38]. Balloon cells have a larger, rounder morphology, centrally placed nuclei, with altered melanogenesis that leads to numerous clear vacuoles in the cytoplasm that compress nuclei into a “scalloped” appearance [39]. Small polyhedral cells are named for their typical shape, and have clear cytoplasm, prominent nucleoli, and homogenously staining nuclei [40]. Round epithelioid cells have morphology as named, contain prominent nucleoli, marked nuclear pleomorphism, and abundant eosinophilic cytoplasm [37]. However, each of these cells can be found in a variety of other conditions, including PAM and conjunctival nevi [35,37]. In particular, PAM with atypia is characterized by epithelioid cell morphology [35]. Thus, other histological features are used to correlate with clinical findings in order to solidify the diagnosis of malignancy. These are: pagetoid spread, radial extension of the intraepithelial component, bandlike inflammation of the basal layer, mitotic activity, decreased maturation of basal cells, and invasion of sclera, or cornea past Bowman's membrane [37]. PAM with atypia, by contrast, is characterized by intraepithelial growth of atypical melanocytes, without the vertically invasive pattern of CMM [35]. Certain histologic features may predict prognosis of CMM. Purely spindle cell type lesions have been associated with a more favourable prognosis than mixed cell type lesions [27], while pagetoid growth [41], mitotic figures greater than five per high powered field [27], and absence of inflammatory response may be associated with a worse prognosis [42]. The pathologist's report should include pertinent information to decision-making regarding the treatment of the patient such as tumor thickness, and adequacy of lateral and deep margins [40].

Adjuvant Tools

Histopathology remains the gold standard for definitive diagnosis of CMM. It provides unparalleled resolution and the ability to visualize all layers of tissue. CMM can sometimes be difficult to distinguish from nevi, and excised tissue may miss lesions present elsewhere [43]. Prior to surgical removal, the clinician often will want to evaluate the tumor in a non-invasive fashion to help plan in the management and approach to the tumor. Adjuvant diagnostic techniques provide an opportunity to evaluate the tumor, although each comes with their own set of disadvantages (Table 1). Reported adjuvant tools include impression cytology, exfoliative cytology, ultrasound biomicroscopy, anterior segment optical coherence tomography, and confocal microscopy.

In impression cytology (IC), filter strips or sterile glass slides with polished edges are used to gently shave off superficial cells from the CMM (Table 1). Cells are graded based on features indicative of malignancy and invasion, such as degree of atypia. Samples possessing the highest proportions of atypical melanocytes are diagnosed as malignant. This technique is based upon the concept that in CMM and PAM, atypical melanocytes ascend to the surface as they mature, unlike in other benign pigmented lesions [44–46], mimicking the maturation process of epidermal stem cells into their various lineages. Abnormal maturation is therefore reflected in abnormal superficial epithelial cells [46]. This technique has a high positive predictive value, but the nature of its application makes it difficult to use in narrow locations such as the fornix or tarsal conjunctiva. Additionally, the cytologic profile of superficial epithelial cells may not always correlate with that of deeper layers [44,47,48].

A related technique, exfoliative cytology, uses a cotton-tipped applicator in order to collect cells from the epithelial layer (Table 1). The sensitivity, specificity, positive predictive value, and negative predictive value of this technique has been reported as 85%, 78%, 59%, and 93%, respectively [45]. However, as with IC, the accuracy of superficial epithelial cells for the diagnosis of a primarily basal epithelial tumor has been questioned [44,45,47,48].

In recent years, a great number of non-invasive imaging techniques have also become available, with the goal of producing images in the office that correlate with histopathologic findings.

Another useful technique is ultrasound biomicroscopy (UB). In UB, the patient is reclined back, local anesthetic drops are applied, and an eyebath filled with water or methylcellulose solution is placed on the ocular surface to provide an interface with the instrument [49]. High frequency sound waves are emitted, and an image is generated based on the echo pattern. UB can penetrate pigmented tumors and estimate tumor thickness. This is useful primarily for pre-surgical planning. It may also assist in decision making regarding sentinel lymph node biopsy (SLNB), as some proponents recommend that procedure based on tumor thickness. UB does not provide as good resolution as other imaging techniques [50–52].

Anterior segment optical coherence tomography (AS-OCT) uses light, rather than sound waves to generate images. This technique does not require a water bath, and can provide better resolution than UB. However, it has been found to have difficulty penetrating pigmented lesions, resulting in shadowing posterior to the tumor [51]. Ultra high resolution OCT (UHR AS-OCT) improves on AS-OCT by increasing scan depth and axial resolution [53], allowing it to penetrate moderately pigmented and keratinized epithelial layers, and visualize all layers of conjunctival and corneal surfaces. In CMM, one can see a thin, normal layer of epithelium (ruling out superficial lesions such as OSSN), and some epithelial cleavage indicating involvement of epithelium with atypical melanocytes, but the majority of the lesion is subepithelial, with basal epithelium that is normal thickness and hyper-reflective [53] (Figure 3). Nevertheless, as the instrument still utilizes light as its source, penetrance in thick lesions is an issue, making it difficult to determine the posterior limits, let alone any detail of such lesions [53].

With in-vivo confocal microscopy, anesthesia and lubricating gel are applied, and the patient is seated in front of the instrument as the microscope is brought forwards. For the highest resolution images, the microscope must make contact with the eye. This technique accomplishes excellent resolution, at the level of individual cells by ensuring that the source of light and the instrument detector receiving reflected light are focused on the same point on the ocular lesion [54]. It has been most useful in imaging the cornea and assessing various features such as corneal thickness, nerve densities, and density of stromal and endothelial cells [54]. In conjunctival melanoma, atypical, highly reflective cells with prominent nuclei and large nucleoli can be seen [55]. However, the instrument has limitations in terms of depth perception, as it produces images of en-face, horizontal optical sections, but it cannot create a vertical image showing all layers [54,55]. This is particularly important with CMM, as management decisions are impacted by thickness of tumor and

depth of invasion. Training is also required as image depth must be calibrated and image intensity must be standardized prior to each case [54].

Various techniques have also been developed to assist ocular pathologists with histopathologically equivocal melanocytic lesions, such as fluorescent in-situ hybridization (FISH) and pump probe microscopy [56,57]; however, these are beyond the scope of this review.

Management

Management options are based on a number of case reports and limited case series, as the rarity of this tumor has made it difficult to conduct clinical trials to determine the best therapy. The current standard of care is wide local excision, followed by double freeze-thaw cryotherapy to the margins. This is often followed by a variety of adjuvant therapies in order to prevent recurrence and metastasis. We have developed an algorithm for approaching the management of CMM (Figure 4). SLNB may be used to detect regional metastasis. Developments in our understanding of the underlying genetic abnormalities in CMM may lead to new, targeted therapies and greatly expand initial medical management.

Surgical

When conjunctival melanoma was first treated, radical techniques such as enucleation and exenteration were considered for eradication of particularly diffuse melanoma [58]. Such approaches have since been shown to provide no improvement in survival; furthermore, intrinsic to them are the consequences of disfigurement and blindness [59]. Currently, these techniques are only performed as palliation for tumors that invade the orbit or completely involve the conjunctiva [19], with most patients eventually developing metastasis or dying [59–61].

Currently, the mainstay of treatment of conjunctival melanoma in the majority of centers is wide local excision and biopsy with “no-touch” technique and cryotherapy to the margins. The use of a “no-touch” surgical technique was originally recommended by Shields, et al. [62] due to concerns of seeding, tumor dissemination, and recurrence, and continues to show a positive trend amongst different centers [25,63]. For similar reasons, a wide excisional biopsy is preferred over incisional [19]; however, incisional biopsy may be performed in the case of extensive lesions [64].

As previously described [34], our surgical approach consists of excising the tumor with wide margins of 4 mm using a “no-touch” technique (Figure 5). In the case of scleral invasion or corneal involvement, partial sclerectomy with fresh instruments, or alcohol epitheliectomy to the cornea are performed. It is important that Bowman's layer remains intact, as it is a natural barrier to deep tumor invasion. A dry surgical field is also maintained to avoid tumor cell seeding. The excised specimen is carefully mounted on paper, taking great care to maintain orientation, and avoid generating histopathologic artifact (Figure 5C). [31]. Cryotherapy in a double freeze-slow thaw mode is then delivered to the margins (Figure 5F), taking care to lift the conjunctiva to avoid administering cryotherapy to the sclera. Adjuvant cryotherapy induces necrosis of tumor cells during the thawing portion due to the efflux of

intracellular contents [65], and reduces recurrence in comparison to excision alone [8]. An amniotic membrane is placed over the bare scleral defect using clean instruments (Figure 5G), after which a symblepharon ring may be inserted. We recommend using an amniotic membrane allograft to cover the bare sclera, as amniotic membrane has anti-inflammatory and anti-scarring properties which aid in healing, promote epithelialization and prevent fibrosis, symblepharon and subsequent diplopia, suppress angiogenesis, and are immunologically well tolerated [66–70]. The techniques used to harvest these grafts are well established [71]. Additionally, the use of such grafts helps with cosmetic appearance by covering up large-sized defects. For small defects, primary closure is an option and is less expensive. Variations on this step exist at other centers with some recommending primary closure without the use of amniotic graft [25], or the use of mucosal allografts (buccal, inner lip) [66,72]. In the postoperative course, antibiotics and steroids should be given to reduce inflammation and prevent infection. If a symblepharon ring is inserted after surgery, frequent lubrication and use of ointment are recommended, with removal of the ring after 2 weeks or as clinically indicated.

A total of 4 case series were found in the literature evaluating outcomes of the surgical technique of wide excision with cryotherapy, covering 457 patients (Table 2) [8,20,29,73]. Overall, 72% (314/434) of cases experienced complete resolution, 29% (134/457) of cases experienced local recurrence, 19% (81/434) of cases experienced metastasis, 10% (43/434) of cases required exenteration, and 6% (28/434) of cases were fatal, all over a mean follow-up time of 52 months [8,20,29,73].

Possible complications from surgery include symblepharon formation, non-healing epithelial defects, hyphema, limbal stem cell deficiency (LSCD), corneal scarring, infection, and diplopia [66,67,74]. Possible adverse effects of cryotherapy include inadvertent and often temporary damage to ocular structures, most commonly the conjunctiva, cornea or iris, resulting in chemosis, subconjunctival hemorrhage, scleral and corneal tissue loss, corneal endothelial damage, iritis, hyphema and iris atrophy [75,76]. If the ciliary body is affected, intraocular pressure alterations including hypotony may occur [76]. Less commonly, damage to the eyelids, uvea, and extraocular muscles may result in ectropion, uveitis, and possible paralysis of extraocular muscles especially if muscle insertion sites are involved [75,76]. Rarely, aggressive administration may damage palpebral conjunctiva, resulting in long-lasting dry eye symptoms or the limbus causing limbal stem cell deficiency [76]. Rare occurrences of scleral melting have been reported [77].

Nonexcisional Adjuvant Therapy

Surgical excision is generally considered the primary therapy for CMM. None of the adjuvant therapies we will discuss have an established role in the primary treatment of the disease. However, they are commonly used following surgical excision in order to improve long-term local control and reduce local recurrence, as patients with CMM are prone to recurrences throughout their lifetime [19,20]. The decision to pursue adjuvant treatment is at the discretion of the ophthalmologist, but is especially recommended in cases of inexcisable disease, where histology reveals tumor presence at surgical margins. There is no consensus on the preferred adjuvant therapy [64]. Reported therapies include cryotherapy, mitomycin

C, interferon alpha-2b, brachytherapy, external beam radiotherapy and proton beam radiotherapy. Focal cryotherapy may also be used to manage local recurrent disease. The use of sentinel lymph node biopsy for CMM remains under considerable debate; however, its ostensible use is in the detection of metastasis.

Topical chemotherapy

Topical chemotherapy is valued for its ability to treat the entire ocular surface, and convenience for the patient. Reported chemotherapeutic agents for CMM include mitomycin C [78–82], and interferon alpha-2b [82–85]. Mitomycin C is the more studied agent, and is currently the preferred adjuvant therapy of most ophthalmologists.

Mitomycin C (MMC) is a quinone antibiotic with anti-tumor properties. Primarily, it acts as a potent alkylating agent and inhibits DNA synthesis in tumor cells. However, it also generates free radicals that damage DNA and proteins through lipid peroxidation [86], inhibits cell proliferation, and induces apoptosis in tumor cells [87]. MMC is most commonly administered in a concentration of 0.04% four times a day in 1-3 week-long cycles. Notably, a short regimen of MMC may be useful prior to surgical excision if there is particularly diffuse PAM as MMC has been reported as a primary treatment for PAM with atypia with good response [79]. The regimen in this case is most commonly 0.04% four times a day for cycles of 14 consecutive days with 1-week intervals in between cycles to avoid toxicity from prolonged exposure to MMC [88,89]. Punctal occlusion or applying gentle pressure to the puncta while the patient's eyes are closed can help to increase absorption while also preventing passage through the nasolacrimal ducts and potential punctal stenosis. While MMC is an established treatment for PAM, its use in the management of CMM is limited to pre- and post- excisional adjuvant therapy. The outcomes of MMC as primary and adjuvant therapies will be compared here in order to demonstrate the poor outcomes in its use for primary CMM.

A total of 6 case series (50 patients) were found in the literature which used MMC for ocular surface diseases. Of these, a cohort of 10 patients had MMC used as primary therapy for CMM. (Table 2) [79–81,90–92]. In 6 case series (112 patients) describing MMC, a cohort of 48 patients were found in which MMC was used as adjuvant therapy following surgical excision. (Table 3) [66,78–81,93].

The regimen when MMC was used as primary therapy was 0.04% MMC four times a day 28 consecutive days [80], or 28 days consisting of 2 cycles of 14 consecutive days split by 14 days without any chemotherapy [79,81] o5ver an average of 1.9 cycles. Overall, 40% (4/10) of cases experienced complete resolution, 20% (2/10) of cases experienced partial resolution without recurrence or metastasis, 40% (4/10) of cases experienced local recurrence, 10% (1/10) cases experienced metastasis, and 20% (2/10) required exenteration, all within a mean follow-up time of 19.4 months [79–81,90–92]. The poor results of MMC when used as a primary therapy for CMM strongly underscore the importance of avoiding its use as primary treatment for CMM. MMC does not cross the basement membrane, limiting its use to surface lesions. Additionally, subepithelial nests of neoplastic melanocytes, and nodular tumors may be resistant to topical application [79,80].

The regimens when MMC was used as adjuvant therapy following surgical excision of CMM, were 0.04% MMC four times a day for 1 week [79–81], for three weeks followed by one week of topical corticosteroid [78], for 4 weeks [92], or for 3 weeks followed by 3 weeks without MMC [93] over an average of 2.0 cycles. Overall, 73% (35/48) cases experienced complete resolution, 26% (13/48) of cases experienced local recurrence, 6% (3/48) cases experienced metastasis, and 2% (1/48) required exenteration, all within a mean follow-up time of 37.8 months [66,78–81,93]. These results suggest that the most effective role for MMC in CMM is as an adjuvant therapy.

MMC has been associated with a variety of adverse effects, especially with prolonged use; subsequently, patient compliance may become an issue. In a study of 15 patients with CMM, the most common complaints were injection (13/15 or 87%), tearing (10/15 or 67%), pain (9/15 or 60%) and irritation (9/15 or 60%). In a study of 91 patients with OSSN treated with 0.04% MMC four times a day for 1-3 cycles of 7 consecutive days, patients most commonly complained of an allergic reaction (31/91 or 34%) after the second or third cycle, and epiphora secondary to punctal stenosis after a median of 2 months (14/91 or 15%) [100]. Limbal stem cell deficiency is potentially a serious complication of MMC, especially with prolonged or high-dose exposure [101]. Other commonly reported side effects include tearing, hyperemia, irritation, pain, keratoconjunctivitis, blepharospasm and punctate epithelial keratopathy [102,103]. Rarer side effects include corneal haze, cataract, epithelial defects, limbal stem cell deficiency with keratopathy, disciform keratitis and contact dermatitis [78,104]. Though usually transient, these effects can be uncomfortable for the patient, and have been reported to last up to 6 months [78,100].

Interferon alpha-2b (IFN-α2b) is a naturally occurring cytokine released by immune cells that has been found to be of use in numerous antiviral, antimicrobial, and anti-tumorogenesis applications, including condyloma acuminatum, hepatitis B and C, hairy cell leukemia, and chronic myeloid leukemia [105,106]. It interferes with tumor cell proliferation by prolonging the length of the cell cycle, down-regulating oncogenes and promoting tumor suppressor genes. However, in ocular lesions, it is believed to act by enhancing the immune response by increasing MHC class I cell surface antigen expression [106,107]. It has been applied both topically and in subconjunctival/perilesional injections. Topical application is preferred due to reduced side effect profile and avoidance of systemic effects, while subconjunctival application may be useful if compliance or expense is an issue [108]. There is no consensus on the concentration or dosing regimen. Topical application of IFN-α2b for the treatment of OSSN is typically given in concentrations of 1 million IU four times a day, and continued for 1 month after clinical resolution of the lesion [109].

The data using IFN for CMM is limited. A total of 3 case series were found with IFN-α2b as adjuvant therapy following surgical excision of CMM, covering 11 patients (Table 3) [83–85]. The regimens were 1 million IU four times a day for three months [85], 1 million IU five times a day for six weeks [84], and 3 million IU (of interferon-β) total over 22 subconjunctival injections [83] over an average of 1.3 cycles. Overall, 91% (10/11) cases experienced complete resolution, 9% (1/11) of cases experienced local recurrence, 0% experienced metastasis, and 0% required exenteration, all within a mean follow-up time of 16.4 months [83–85].

None of these 10 patients reported any systemic side effects such as flu-like symptoms that have been associated with associated with IFN-α2b [110], only mild, transient symptoms: 30% (3/10) reported a mild chemical conjunctivitis, and 10% (1/10) reported corneal edema and punctate epithelial erosions [84,85]. In the case of IFN-β subconjunctival injections only transient local side effects were noted, including injection, irritation, corneal punctate epithelial erosion, and corneal and eyelid edema [85]. Although its role remains unclear, with its minimal side effect profile, IFN-α2b may be considered as an alternative in patients intolerant of MMC adjuvant therapy [85]. However, it is important that the data on IFN for CMM is limited, and further studies are required to examine its efficacy.

It is important to reiterate that despite their use as adjuvant therapies, topical chemotherapies do not have an established role in primary treatment of CMM.

Radiotherapy

CMM is generally not considered radiosensitive; thus radiotherapy should not be used as primary therapy [111]. As adjuvant therapy following surgical excision, it should be delayed until the conjunctiva has healed [112]. Radiotherapy options consist of brachytherapy (internal radiotherapy) and teletherapy (external beam radiotherapy). Radiotherapy is usually given in multiple small fractions. This allows normal tissue time to repair itself, while also sensitizing target tissues by allowing time for reoxygenation and reassortment of cells in the cell cycle [112].

Brachytherapy involves the use of plaques, rings, seeds, or other various custom-designed applicators to provide radioactive sources that interface with the tumor site while limiting radiation of the rest of the remaining ocular surface [113]. It is a non-invasive treatment that can be done in-office under local anaesthetic [94]. Plaques may be reverse-mounted to administer radiation to the tarsal conjunctiva [94]. The use of numerous isotopes, including Ru^{106} [114,115], I^{191} [113], or I^{125} [95], or Sr^{90}-beta or Y^{90} [94,116] has been explored. As opposed to teletherapy, which can require several weeks of treatment, brachytherapy can be completed in less than a week [113].

A total of 4 case series were found with brachytherapy as adjuvant therapy following surgical excision of CMM, covering 74 patients (Table 3) [8,94–96]. The radioisotope used was Sr^{90} in 3 cases [8,94,96] and I^{125} in 1 [95]. The mean dose was 47.4 Gy, from an average of 8.3 Gy over 6.7 fractions at a depth of 1.5-3.0mm. Overall, 80% (59/74) of cases experienced complete resolution, 20% (15/74) of cases experienced local recurrence, no cases experienced metastasis, and no cases required exenteration, all within a mean follow-up time of 63.9 months [8,94–96,116,117]. Kaplan-Meier 5- and 10- year estimates of complete resolution without recurrence or metastasis were both 82% [94]. Brachytherapy has also been reported to reduce recurrence in comparison to excision alone, excision with cryotherapy, or excision with MMC, although results were only statistically significant when compared against excision with cryotherapy [8].

Brachytherapy appears to be well tolerated, with minimal adverse effects [94]. In a composite of 4 case series, 96 patients with CMM treated with adjuvant brachytherapy after surgical excision experienced the following side effects: transient dry eye syndrome (49% or

47/96), transient corneal ulcers (12% or 11/96), reduced peripheral corneal vascularization (4% or 4/96), descemetocele (1% or 1/96), transient episcleritis (1% or 1/96), and scleral necrosis (1% or 1/96) [94,95,116,117]. The corneal ulcers resolved with the use of bandage contact lenses, and the case of scleral necrosis occurred in a patient who had prior excision of sclera. However, scleral necrosis has been reported in brachytherapy for uveal melanoma, occurring in 1% of cases after a median of 79 months [118]. One limitation of brachytherapy is its susceptibility to movement of the eye which may decrease the calculated dose of radiation to the target area [113]. Additionally, these applicators are not actively produced due to low demand [94].

External beam radiotherapy (EBRT) is a common adjuvant therapy for head and neck cancers. However, use of EBRT has been minimal in CMM due to concerns about damage to other ocular structures. Consequently, data is limited. In the literature, it has been used as an alternative to exenteration in high-risk tumors (increased thickness, recurrent, multifocal, unfavorable location, ineligible for brachytherapy) [98]. EBRT involves the use of a high voltage X-ray machine to deliver focused beams of electrons, photons, or protons to the tumor [97]. The procedure is usually completed in 15-20 minutes but may require the patient to return for several sessions over several weeks [97]. Proton beam radiotherapy (PBRT) is a form of EBRT which is able to concentrate ionizing radiation to the tumor site while minimizing its effects on surrounding tissues. This is because a proton is a relatively heavy and charged particle, thus it gradually loses speed and stops and delivers its maximum dose at a predictable depth in the target tissue [112].

A total of 3 case series were found with EBRT or PBRT as adjuvant therapy following surgical excision of CMM, covering 51 patients (Table 3) [97–99]. The mean dose was 51.5 Gy, from an average of 4.7 Gy over 9.6 fractions. Overall, 85% (17/20) of cases experienced complete resolution, 37% (19/51) of cases experienced local recurrence, 22% (11/51) cases experienced metastasis, 15% (4/26) cases required exenteration, and 8% (2/26) cases were fatal, all within a mean follow-up time of 34.8 months [97–99]. Kaplan-Meier 5- and 10-year estimates of complete resolution without recurrence or metastasis were 86% (CI 73-99%) and 80% (CI 64-96%), respectively [99]. While EBRT appears to have poorer outcomes than brachytherapy, a study of 56 patients comparing EBRT using electrons (X-Rays), brachytherapy, and PBRT following surgical excision of conjunctival melanoma concluded that there were no obvious differences regarding resolution and systemic metastasis [115]. Further studies are required to bolster these conclusions.

EBRT has been associated with numerous adverse effects. In the 51 patients treated with adjuvant EBRT after surgical excision of CMM, 96% (25/26) reported dry eye syndrome, 77% (20/26) reported local eyelash loss in the area of irradiation, 27% (7/26) reported focal cataracts, 15% (4/26) reported limbal stem cell deficiency with corneal vascularization, and 4% (1/26) reported keratinization of the conjunctiva [97–99]. Dry eye syndrome occurs due to atrophy of all sources of tear film production: lacrimal acinar cells, goblet cells, and meibomian glands, in response to prolonged radiation [119]. Trichiasis, blepharitis, exposure keratopathy [97,120], neovascular glaucoma [98], radiation retinopathy [97], optic neuropathy [121], and nasolacrimal duct blockage have also been reported [122] when EBRT has been used for other ophthalmic and adnexal complications.

Focal Cryotherapy

Cryotherapy is itself an adjuvant therapy, typically administered at the time of excision to the surgical margins, as described above. Recurrent lesions that are large or multifocal, or new presentations of CMM generally necessitate surgical re-excision with cryotherapy to the margins [19]. However, for patients who are followed carefully and present with local recurrent pigment, management with focal cryotherapy alone may be sufficient. Although this has been reported in the literature over the last 20 years [19,73,123,124], formal published data on the prognostic outcomes of recurrent CMM managed solely by focal cryotherapy is sparse. Cryotherapy can be performed in the office under local anesthetic, and is administered in a double freeze-thaw cycle that induces necrosis via the mechanism previously described. Dispersion of pigment granules may be seen in the treated tissue shortly afterwards, the characteristic appearance of “coffee granules” [34,123].

A total of 2 case series were found with focal cryotherapy used as supplemental treatment in recurrent CMM after surgical excision, covering 4 patients. Overall, 75% (3/4) of cases experienced complete resolution, 25% (1/4) of cases experienced local recurrence, and 0% of cases experienced metastasis, exenteration or fatality, within a mean follow-up time of 9.5 months [123,124].

Sentinel Lymph Node Biopsy

Sentinel lymph node biopsy (SLNB) preceded by lymphoscintigraphy is predicated upon the idea that micrometastasis to regional lymph nodes may indicate clinically undetectable systemic spread. This may provide an early opportunity to treat disease before distant or further systemic metastasis can develop. SLNB is a formal surgical procedure usually performed during or after removal of the primary lesion. Preoperative lymphoscintigraphy involves injection of a tracer radioisotope such as technetium (Tc-99m) subconjunctivally near the conjunctival tumor. Dynamic lymphatic imaging follows until the first sentinel lymph node is detected. A handheld γ-probe may be used to confirm the location of this node in addition to other foci of radioactivity. The skin overlying the node is marked, careful surgical dissection at the time of excision of the tumor follows, and the lymph node(s) are sent to pathology [125]. Proponents of intraoperative SLNB believe that this ensures the best chance of finding a sentinel node [126,127]. However, other centers recommend SLNB after surgical excision of the tumor in order to minimize the risk of dissemination with injection of radiotracer, and to measure tumor thickness for better selection of candidates [125].

Currently, the use of SLNB remains highly debated. There is a lack of consensus in what high risk pathologic features warrant such an invasive procedure. Studies show utility in detecting metastasis for tumors thicker than 2 mm [8,59,125,128], diameter greater than 10 mm [8], and tumors with histologic ulceration [129].

The pertinence of SLNB with respect to conjunctival melanoma may be underscored by its established role in cutaneous melanoma. There is a growing body of evidence demonstrating similarities in patterns of metastasis between these two entities. For cutaneous melanoma, tumor thickness appears to be the best predictor of lymph node involvement [130], with sentinel lymph node biopsy detecting nodal metastases to a greater extent than through

clinical examination in cutaneous melanoma tumors of intermediate thickness (1.2 to 3.5 mm) [131–135] or significant thickness (>3.5 mm) [134,135]. Subsequent lymphadenectomy in those patients has demonstrated benefits of prolonged distant disease-free survival and overall survival in comparison to the respective cohort of melanoma patients found to be node-positive on clinical examination a median of 19.2 months after excision of the melanoma [134,135]. SLNB has also been shown to detect regional lymph node spread not found on clinical examination or preoperative imaging [136].

A total of 5 case series, covering 56 patients, were found evaluating SLNB as a technique for detecting clinically undetectable metastasis in CMM (Table 4) [125,129,136–138]. Lymph nodes were not palpable in all cases, and preoperative imaging such as PET and MRI scans were within normal limits in all cases. SLNB was performed after CMM excision in the majority of cases. Preoperative lymphoscintigraphy was positive in 93% (52/56) cases for at least 1 node. Thus, only 52 cases continued onto SLNB. It should be noted that patients in these studies met certain enrollment criteria such as Breslow thickness > 1mm [129,139], or the presence of histologic ulceration [139]. The lymphatic drainage basin was the parotid lymph nodes in 34% (19/56) of cases, the submandibular lymph nodes in 27% (15/56), the lymph nodes alongside the internal jugular vein at levels II-IV [139] in 18% (10/56), and the preauricular lymph nodes in 58% (32/56).

Histologically positive lymph nodes for tumor metastasis were discovered in only 17% (9/52) of cases, the mean Breslow thickness of those with positive nodes was 5.42 mm, from a range of 2.2-10mm, and frequency of recurrence, metastasis, and death were 56%, 56%, and 44% respectively in these cases. Histologically negative lymph nodes for tumor metastasis were discovered in 83% (43/52) of cases, the mean Breslow thickness of those with negative nodes was 2.31 mm, from a range of 0.84-2.57mm, and 93% (39/43) of these cases were truly negative with the patients remaining free of recurrence or metastatic disease, while 7% (3/43) eventually developed systemic disease. The mean follow-up time overall was 1.9 years, and the only complications noted were a transient blue stain in 31% (5/16) of patients, and transient facial nerve palsy in 6% (1/18) [125].

Nonetheless, despite the apparent utility of SLNB, up to 25% of patients have distant metastasis without clinically detectable regional lymph node involvement [140]. Most of the data regarding SLNB is based on small case series due to the rarity of CMM. Multicenter controlled trials may help to determine uniform techniques for SLNB [127] and assess prognostic benefits. A trial is currently underway to evaluate SLNB through the outcome measures of: frequency of SLNB positivity in CMM, false negative rate for this measure, and identifying any ocular or periocular complications of the technique and risk of facial nerve damage (ClinicalTrials.gov Identifier: NCT00386906).

Systemic Work-up

Although there are no strict guidelines for systemic workup, any patient with conjunctival melanoma is at high risk for metastasis, and should be referred to a medical oncologist for detection and targeted therapy [3,34,141]. PET/CT scans, commonly used to detect

metastasis in other malignancies may potentially be used for CMM. However, the current literature is sparse, and further studies are required to truly assess their efficacy [142,143].

Prognosis

Metastasis and recurrence are unfortunately common for patients with CMM. In this section we will consider the main prognostic outcomes of local recurrence, regional lymph node metastasis, systemic metastasis, and melanoma-related mortality (Table 5).

Local Recurrence

A composite of six large studies involving a total of 770 cases revealed an overall average local recurrence of 40% (307/770) over a mean interval of 2.4 years. Kaplan-Meier 5-and 10- year percentage estimates of recurrence following surgical excision ranged from 36-45%, and 31-59%, respectively [6,8,20,22,29,140]. Risk factors for recurrence include: thickness of primary tumor, subsequent local recurrences, incomplete excision at the time of surgery, and non-limbal tumor location [6]. The last is one of the most important; in particular, location of the tumor in plica semilunaris, or non-epibulbar locations such as the forniceal conjunctiva, caruncle, or eyelid margins is associated with the greatest frequency of recurrence [8,144]. On the other hand, epibulbar tumors show a lower frequency of local recurrence and distant metastases [8].

Lymphatic Spread

A composite of five large studies covering 734 cases revealed an average frequency of lymph node metastasis of 19% (140/734) over a mean interval of 3.4 years [8,22,29,128,140]. Kaplan-Meier 5- and 10- year percentage estimates of lymph node metastasis following surgical excision were both 11% reported in one of the studies, covering 85 cases. When staged according to the American Joint Committee on Cancer (AJCC) guidelines, 5- and 10- year percentage estimates range from 17-52% and 27-57%, respectively [22]. The regional lymph nodes are the most common initial site of metastasis, and the most common lymph nodes affected are the preauricular, parotid, submandibular, and cervical nodes. Temporal conjunctival melanomas show a tendency to metastasize to preauricular lymph nodes, while nasal conjunctival melanoma tends to metastasize to the submandibular lymph nodes [28]. Risk factors for lymph node metastasis include: tumor thickness, histologic ulceration, and mitotic figure count > $1/mm^2$ [145]. These are already known prognostic factors for cutaneous melanoma, having been incorporated into the AJCC's primary tumor classification for cutaneous melanoma [133].

Metastatic Disease & Mortality

A composite of five large studies covering 734 cases revealed an average frequency of systemic metastasis of 19% (141/734) over a mean interval of 3.4 years. Kaplan-Meier 5- and 10- year percentage estimates of systemic metastasis following surgical excision ranged from 11-16%, and 18-26%, respectively [8,19,22,29,128,140]. When tumors were stratified according to the AJCC classification, reported 5- and 10- year percentage estimates were 11-42%, and 20-52%, respectively. Metastatic disease from CMM affects the liver, lungs, brain, and skin but has also been reported in the bones and gastrointestinal tract

[8,19,21,146]. It can also spread directly towards the eyeball and orbit, and nasolacrimal system and sinuses [147,148].

A composite of five large studies covering 734 cases revealed an average frequency of melanoma-related death following surgical resection with tumor-free margins of 18% (114/649) over a mean interval of 4.9 years. Kaplan-Meier 5- and 10- year survival rates ranged from 74-86%, and 41-78%, respectively [6,8,19,22,29,140], with one study reporting 5- and 8- year estimates of melanoma related-death as 7% and 13%, respectively [19]. When tumors were stratified according to the AJCC classification, reported 5- and 10- year percentage estimates of melanoma-related death were 5-23%, and 14-20%, respectively.

Risk factors for metastatic disease and mortality include: disease recurrence, involvement of non-bulbar conjunctiva, medial bulbar conjunctiva, caruncle and plica semilunaris, tumour thickness of more than 2 mm, de novo origin, and nodular growth pattern [8,19,20,26,59,128]. Caruncular involvement in particular has demonstrated poor prognosis [19,144]. Despite only 16-25% of conjunctival melanomas arising de novo, these are associated with the greatest risk for metastasis and death [20]. CMM originating de novo has estimated 10-year risk of orbital invasion, 10-year risk of metastasis, and 10-year mortality rates of 17%/49%/35%; from PAM: 16%/25%/9%, and from nevus: 9%/26%/9% [20] (Table 6).

Staging

The Tumor Node Metastasis (TNM) staging system is used to classify CMM lesions. Staging guidelines are published by the American Joint Committee on Cancer (AJCC) (Table 7) [149]. T(is) describes tumors that are roughly equivalent to PAM with atypia, describing a lesion containing atypical melanocytes that does not invade past the conjunctival epithelium. T1 describes CMM affecting the bulbar conjunctiva while T2 describes CMM affecting the palpebral and forniceal conjunctiva and the caruncle. T1 and T2 tumors are further subdivided by number of quadrants affected. T3 describes CMM that locally invades the globe, eyelid, orbit, or paranasal sinuses. T4 describes CMM with invasion of the central nervous system. Lymph node metastasis is subdivided into three general categories: unable to be assessed (Nx), no regional lymph node metastasis (N0), and positive lymph node metastasis (N1). The designation of no regional lymph node metastasis (N0) is further divided depending on whether this was proven by biopsy (N0a), or deduced solely on clinical examination without biopsy (N0b). Systemic metastasis is divided into negative (M0) or positive (M1) metastasis.

Genetics and Molecular Therapies

There is a growing body of evidence demonstrating a common genetic kinship between conjunctival and cutaneous melanoma, while also differentiating it from uveal melanoma [150– 153]. The treatment of cutaneous melanoma has been revolutionized by the discovery of unique genetic mutations in affected tissues, and the novel biological therapies that have been developed to target the downstream effects of these mutations. Early research appears to show that CMM may share some of these genetic patterns. In this section we will discuss the development of these biological therapies in cutaneous melanoma, then expand upon the

considerable efforts underway to translate these exciting discoveries into the management of CMM.

Cutaneous Melanoma

Prior to mid-2011, dacarbazine, an alkylating chemotherapeutic drug, was the only agent approved by the FDA for the treatment of metastatic cutaneous melanoma. Research into immune pathways and genetic mutations involved in the disease eventually led to the FDA approval of ipilimumab (marketed as Yervoy) in March 2011 [154,155], vemurafenib (marketed as Zelboraf) in August 2011, and dabrafenib (marketed as Taflinar) in May 2013, for the treatment of metastatic and unresectable melanoma [156]. Recent research on the inhibition of mitogen-activated protein kinase kinase (MEK) may lead to further biological therapies [157].

Ipilimumab is a monoclonal antibody that blocks cytotoxic T-lymphocyte-associated antigen 4 (CLTA4) on lymphocytes, a negative costimulatory molecule of T-cells, allowing CD28, a major positive costimulatory molecule of T-cells to function unopposed and stimulate immune response. Vemurafenib and dabrafenib are highly selective BRAF-kinase inhibitors, a mutation found in 60 percent of cutaneous melanomas, primarily at the V600E position [158]. BRAF is an oncogene that encodes a serine/threonine protein kinase within the mitogen-activated protein (MAP) kinase pathway involved in signal transduction. In its mutated form, this protein kinase is constitutively active, promoting both inhibition of apoptotic processes and unregulated cellular growth and proliferation [159]. Vemurafenib, in particular, has demonstrated prognostic benefits in both untreated and previously treated BRAF V600 mutant metastatic cutaneous melanoma [156,160].

Conjunctival Melanoma

Reported genetic mutations in CMM include BRAF, KIT and NRAS. Numerous other genetic mutations have also been investigated in CMM, the significance of which is ambiguous as they are generally much rarer than BRAF. Furthermore, it is worth cautioning that although a mutation may be present in patients with CMM, this mutation may simply be coincidental, effectively neutral and not necessary to the pathogenic drive underlying the disease [161]. Table 8 summarizes the new therapies.

BRAF has received the most attention, due to a high level of concordance in the BRAF mutation between cutaneous and conjunctival melanoma. A total of 6 case series were found in the literature assessing the presence of BRAF mutations in CMM, covering a total of 163 cases (Table 9) [150,151,153,162–164]. When classified according to source, BRAF was found in 33% of primary CMM, 67% of CMM secondary to metastasis, and 22% of CMM of unknown origin. To date, there are no completed clinical trials specifically assessing the efficacy of BRAF inhibitors vemurafenib and dabrafenib in CMM. However, a trial is currently underway to assess efficacy and safety of ipilimumab in patients with metastatic melanoma, including conjunctival melanoma (ClinicalTrials.gov Identifier: NCT01355120). Interestingly, the idea has been proposed that there is the potential for synergistic effect should ipilimumab and vemurafenib be combined, as BRAF inhibitors can cause higher tumor recognition by T-cells which would be activated by the effects of ipilimumab [165],

and this treatment may be explored in clinical trials in the future. At present, it would be reasonable to perform routine testing for BRAF mutation at position V600E as this may open up further options for those patients who are BRAF positive. In particular, BRAF inhibitors may be considered in cases of CMM with regional and systemic metastasis. Clinical trials of BRAF-selective inhibitors for advanced cutaneous or mucosal melanoma are ongoing; however, inclusion of patients with CMM should be considered.

KIT gene encodes CD117, a receptor tyrosine kinase involved in growth and survival, and is commonly found in mucosal and acral melanomas. A highly-selective anti-CD117 agent, imatinib is widely used for the treatment of chronic myeloid leukemia and acute lymphoblastic leukemia. However, KIT mutations have only rarely been found in CMM samples. A total of 3 case series were found in the literature assessing the presence of KIT mutations in CMM covering 45 cases [164,166,167]. KIT was found in 2.2% of CMM tumors. Imatinib has been associated with side effects of headache, diarrhea, nausea and vomiting, fluid retention and edema, rash, fever and muscle pain.

NRAS is an oncogene in the Ras family that encodes a GTPase which, when mutated, activates a signal transduction pathway that leads to unregulated cell division. NRAS has been detected in 15% of cutaneous melanomas [168,169]. A total of 2 case series covering 89 patients found NRAS in 16% (14/89) of CMM samples [151,164].

Similar to cutaneous melanoma, a number of phosphorylated proteins in the mTOR pathway have been found in CMM, suggesting that mTOR inhibitors such as rapamycin may be beneficial [170]. Other genetic patterns in CMM reported include amplification of copy numbers CDKN1A and RUNX2 in primary tumors, and amplification of MLH1 and TIMP2, and deletion of MGMT and ECHS1 in metastasis-origin tumors [153].

Additionally, CMM appears to have a different genetic identity from that of uveal melanoma. Dratviman-Storobinsky, et. al. found the GNAQ mutation in uveal melanomas but not in CMM [171]. Griewank, et. al. found that monosomy 3 was found in uveal melanoma whereas losses in 9p, gains in chromosome 7 or amplifications of CCND1 centromere proximal chromosomal areas of chromosome 11 favored CMM [151].

At this time, BRAF and MEK seem to be the most promising to test in patients with conjunctival melanoma, and the research trends mirror this. As further genetic patterns and molecular targets emerge, future studies may target several pathways (Table 8).

Expert commentary

Conjunctival malignant melanoma (CMM) is a rare tumor with an increasing incidence. A thorough history should be performed including details of sun exposure, previous skin cancers, and family history of melanoma. A significant amount of CMM arises from primary acquired melanosis (PAM) with atypia. De novo and nevus etiologies are rarer. CMM typically presents as a pigmented lesion on the bulbar conjunctiva, often involving the limbus. Although history and slit lamp exam are usually sufficient for clinical diagnosis, advances in imaging techniques such as ultra high resolution optical coherence tomography (UHR AS-OCT) offer the ophthalmologist the ability for in-vivo analysis help with pre-

surgical planning. The current standard of care is wide local excision using a “no-touch” technique with tumor-free margins and double freeze-thaw cryotherapy to the margins. Adjuvant therapies, most often in the form of MMC, can be considered for inexcisable or recurrent disease. All cases should be referred to an oncologist for detection of systemic metastasis and continued monitoring. The role of lymphoscintigraphy and sentinel lymph node biopsy is highly debated to date, as improvement in survival with this technique has not yet been established. The exciting advent of tumor specific mutations, and biological therapies that combat these mutations, have yielded promising results in cutaneous melanoma and this approach is currently being mirrored in CMM. The most common mutation/therapy in CMM is BRAF/vemurafenib/dabrafenib, and are considered in cases of regional or systemic metastasis. Despite these new advances, the prognosis of CMM is guarded with frequency of local recurrence up to 45% in 5 years, lymph node metastasis up to 52%, systemic metastasis up to 42%, and mortality up to 23% during this time period.

5 year view

The authors suspect that UHR OCT and confocal microscopy have the potential to improve the accuracy diagnosis and aid with surgical planning. With regards to treatment, genetic evaluation of tumor and tumor specific biological therapies to combat mutations are an exciting new frontier. Given the emerging genetic similarities between cutaneous and CMM, future therapies for metastatic cutaneous melanoma will likely be evaluated more fully in CMM.

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List of abbreviations

CMM	Conjunctival malignant melanoma
PAM	Primary acquired melanosis
CAM	Complexion associated melanosis
IC	Impression cytology
UB	Ultrasound biomicroscopy
AS-OCT	Anterior segment optical coherence tomography
UHR AS-OCT	Ultra high resolution optical coherence tomography
LSCD	Limbal stem cell deficiency
MMC	Mitomycin C
IFN-α2b	Interferon alpha 2 beta
OSSN	Ocular surface squamous neoplasia
EBRT	External beam radiotherapy

PBRT	Proton beam radiotherapy
SLNB	Sentinel lymph node biopsy
AJCC	American Joint Committee on Cancer
TNM	Tumour Node Metastasis
FDA	Food & Drug Administration

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Key Issues

- Conjunctival melanoma is an uncommon but increasingly important and potentially fatal tumor of the eye.

- Prognosis is poor, with recurrence and metastasis commonly occurring despite excision with tumor free margins. Recurrences are associated most strongly with a non-limbal location. The percentage of patients with local metastasis, distant metastasis, and melanoma-related death approach 52%, 42% and 23%, respectively within 5 years.

- Diagnosis is generally by clinical examination and slit-lamp findings. However, high resolution imaging such as UHR OCT and confocal microscopy may offer assistance with making the diagnosis, and assisting in surgical planning.

- Current management is wide local excision with cryotherapy to the margins. Adjuvant therapies include topical chemotherapy, cryotherapy, and radiotherapy.

- Follow-up should include referral to an oncologist. In spite of some controversy, lymphoscintigraphy should be performed for tumors >2mm in thickness

- Advances in characterizing conjunctival melanoma at a genetic level are offering insight into potential biological therapies that are already in use for the treatment of cutaneous melanoma. This is the new frontier for management of conjunctival melanoma.

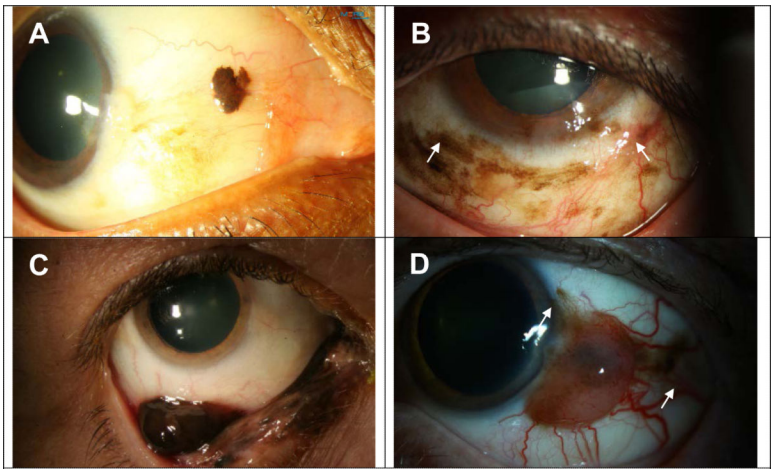

Figure 1. Various presentations of conjunctival malignant melanoma (CMM)

(A) Discrete, raised, pigmented lesion (B) Multifocal CMM (white arrows) in the setting of diffuse primary acquired melanosis (PAM) (C) Large, raised, pigmented CMM originating from inferior fornix (D) Large, raised, amelanotic/mildly pigmented CMM with surrounding PAM (white arrow), referred as ocular surface squamous neoplasia (OSSN).

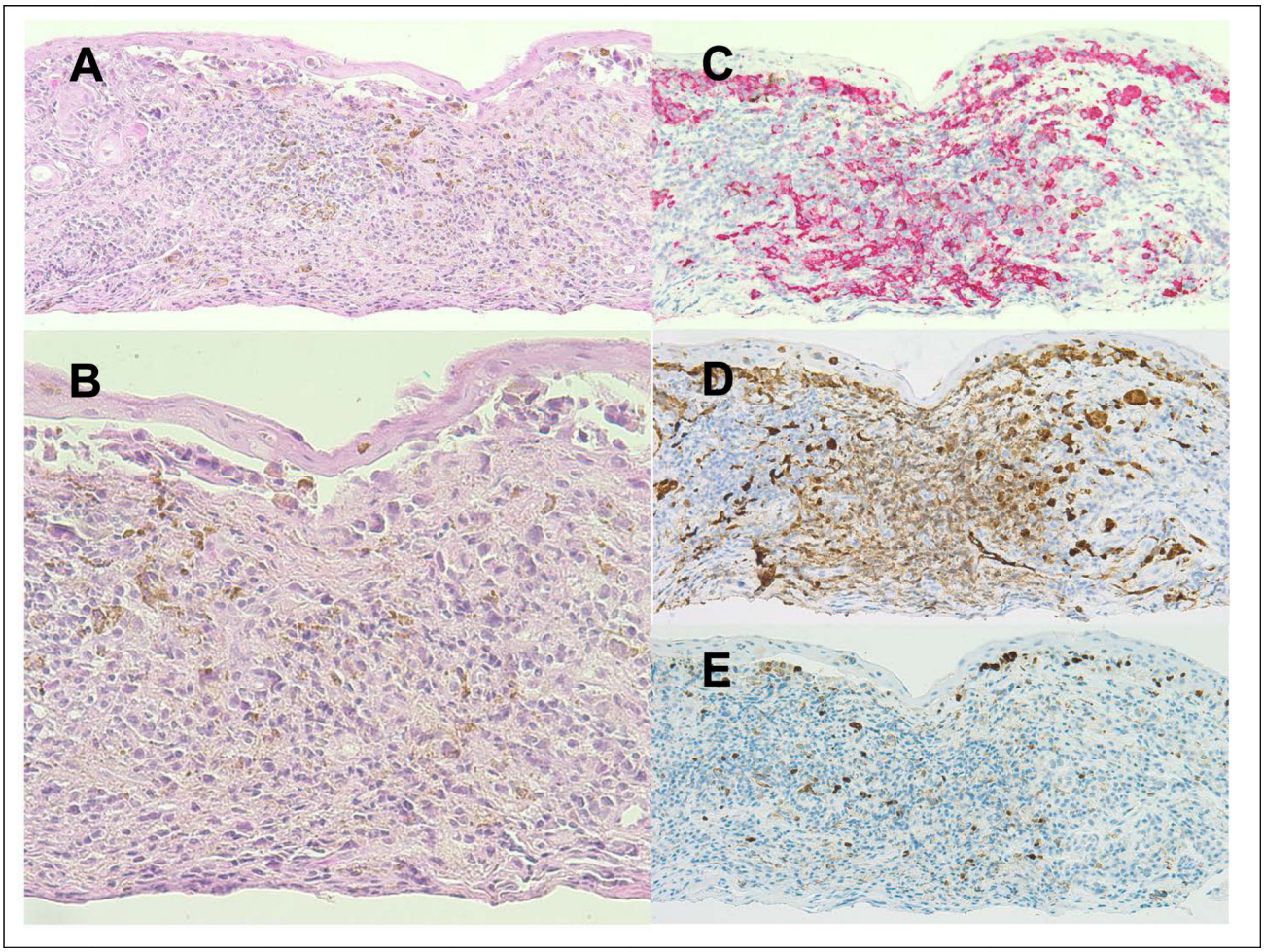

Figure 2.

Histopathology of a conjunctival melanoma arising in primary acquired melanosis. Low (A) and high (B) magnification images disclose conjunctiva that contains atypical melanocytes located within the basal epithelium as well as within the substantia propria that extends up to full thickness to the deep margin. The atypical melanocytes stain positive for Melan-A (C) and S-100 (D). The Ki-67 stain demonstrates a moderate amount of cells cycling within the tumor (E). (A, Hematoxylin-eosin, original magnification x200; B, Hematoxylin eosin, original magnification x400; C, Melan-A, original magnification x200; D, S-100, original magnification x200; E, Ki-67, original magnification x200)

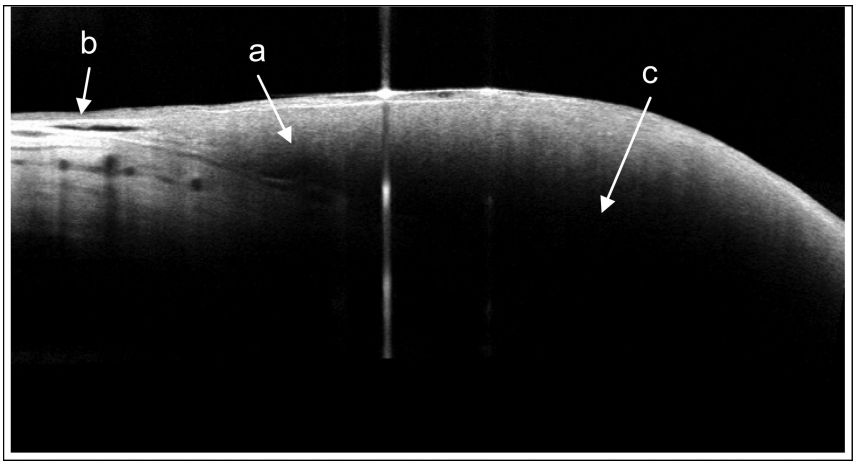

Figure 3. Ultra high resolution optical coherence tomography (UHR AS-OCT) images of conjunctival malignant melanoma

(a) subepithelial lesion (b) mildly hyperreflective normal-thickness epithelium, (c) shadowing of tissue

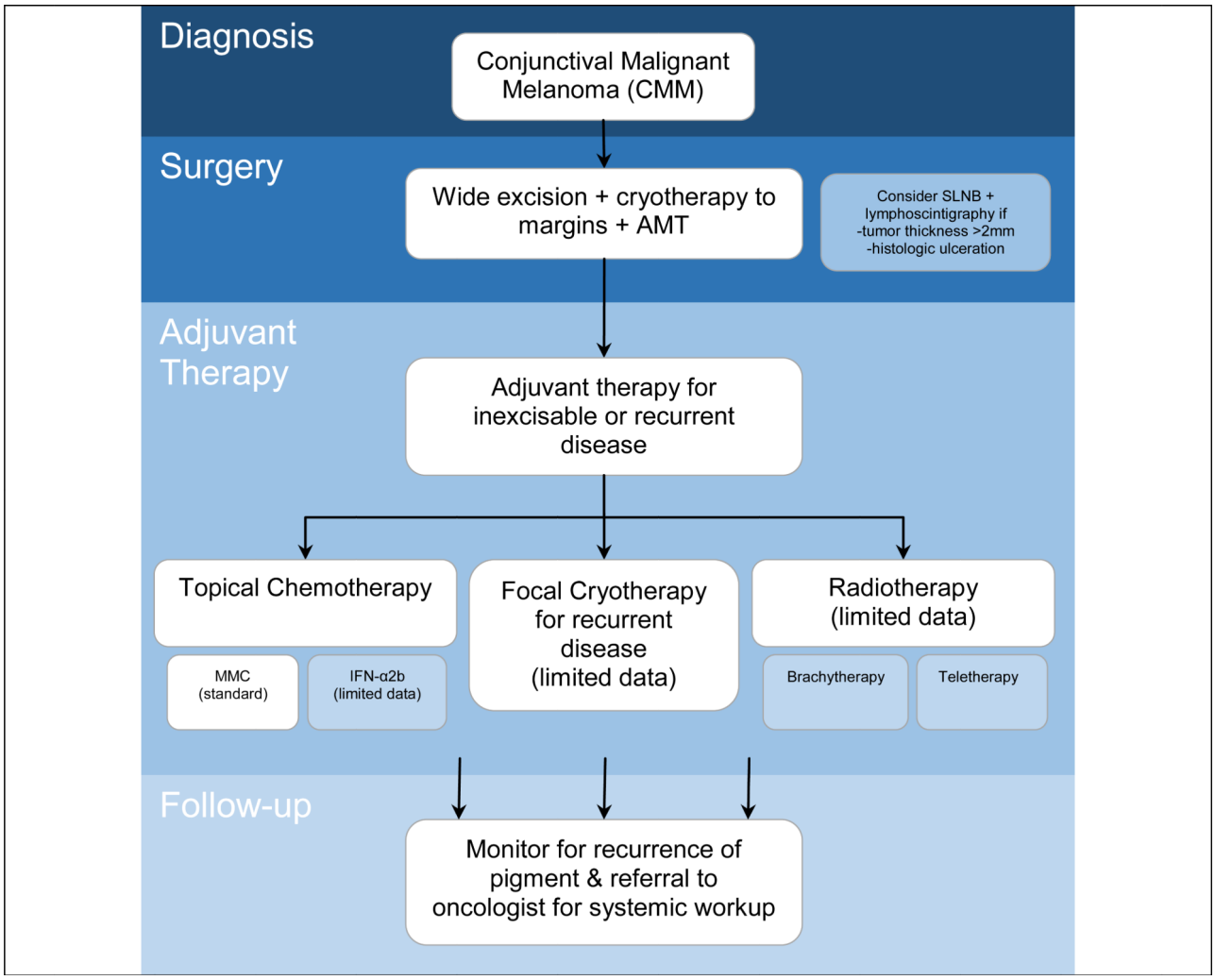

Figure 4. Algorithm for management of conjunctival malignant melanoma

After clinical diagnosis is made based on history, slit lamp findings, and imaging, the current standard of care is surgical excision. A trial of mitomycin C (MMC) can be considered prior to excision if there is significant primary acquired melanosis (PAM) for chemoreduction. Surgical excision includes wide margins (~4mm), cryotherapy to the margins, and closure or placement of amniotic membrane transplant (AMT). Sentinel lymph node biopsy (SLNB), if done, is usually done at time of excision but may be done afterwards. Adjuvant therapies include topical MMC or interferon alpha-2b (IFN-α2b), internal radiotherapy (brachytherapy) or external radiotherapy (teletherapy). All cases should be referred to an oncologist for detection of metastasis.

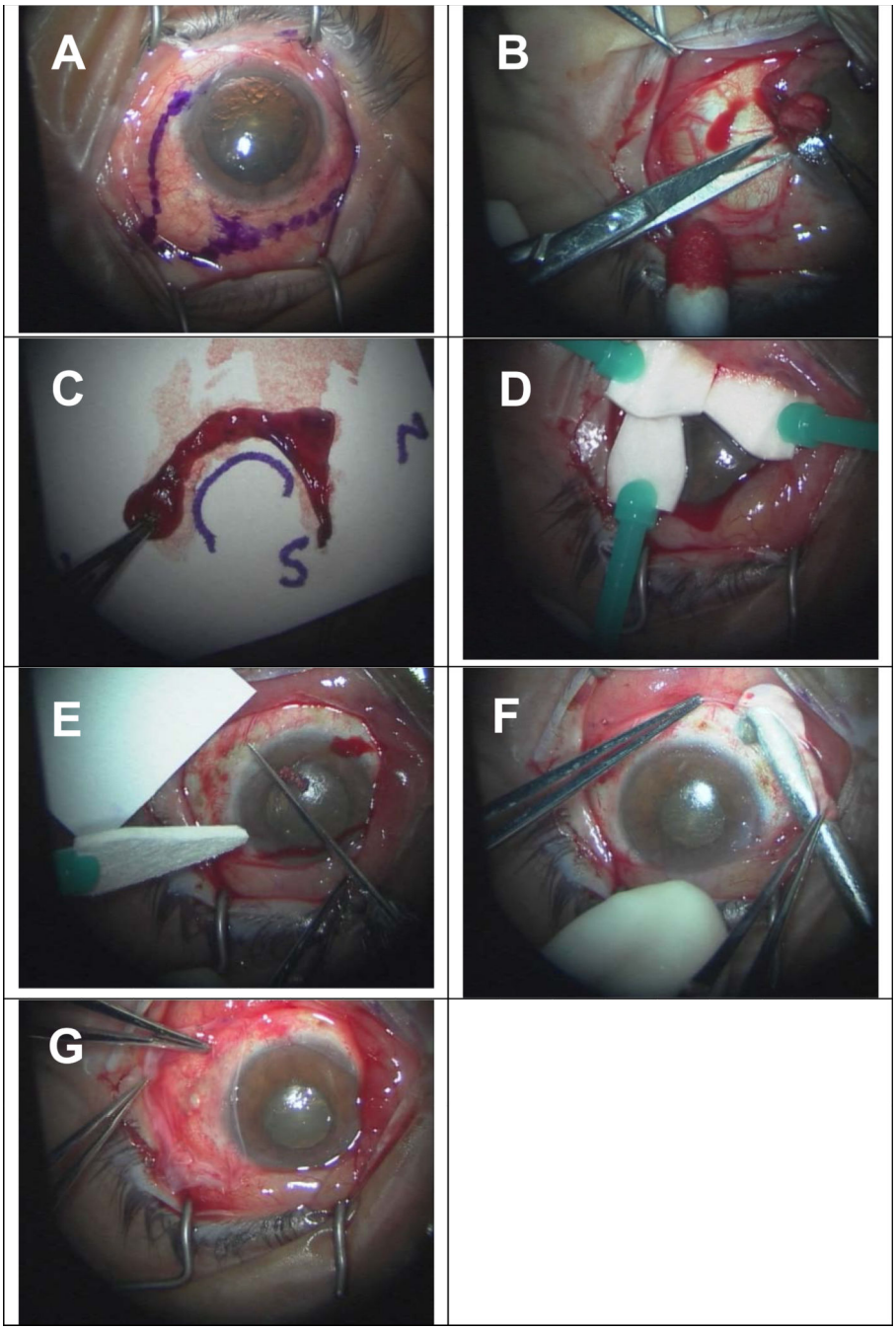

Figure 5. Surgical excision of conjunctival malignant melanoma

(A) 4-mm wide surgical margins are marked, (B) Surgical excision of tumor in no touch technique. Note the dry surgical field. (C) Specimen is carefully oriented for margin control. (D) Swabs soaked in absolute alcohol are placed on involved areas of the cornea for 1 minute for epitheliectomy. (E) Corneal epithelium is debrided and cells sent for evaluation. (F) Cryotherapy is administered to surgical margins, with the conjunctiva raised to avoid damage to the sclera. (G) Amniotic membrane graft placement.

Table 1

Summary of adjuvant diagnostic tools

Technique	Findings	Advantages	Disadvantages
Impression cytology and Exfoliative cytology	-Melanocytes amongst various epithelial cells (keratinocytes, goblet cells, etc.) are graded based on level of cellular atypia [44]. -Samples with the highest proportions of atypical melanocytes are diagnosed as malignant [44].	-Quick, efficient, painless -Exfoliative cytology parameters [45]: -sensitivity: 85% (95% CI: 77-93%) -specificity: 78% (95% CI: 73-84%) -positive predictive value: 59% (95% CI 49-68%) -negative predictive value: 93% (95% CI: 90-97%)	-Difficult to apply in narrow locations [48] -Superficial epithelial cells may not be representative of cells from deeper layers [48] -Unable to determine thickness or invasion [48]
Ultrasound biomicroscopy (UB)	-Assesses thickness, tumor properties (degree of homogeneity) [50]	-Excellent penetrance and depth perception [51]	-Low resolution [49] -Contact methodology [49]
Anterior segment and ultra high resolution optical coherence tomography (AS-OCT and UHR AS-OCT)	-Assesses thickness, tumor properties [51,53] -UHR AS-OCT has higher detail than AS-OCT [51,53]	-Non-contact [51,53] -Better resolution than UB [51,53]	-Difficulty penetrating thicker lesions [51,53]
In-vivo confocal microscopy	-Horizontal sections [54] -Atypical, highly reflective cells with prominent nuclei and large nucleoli [55]	-Excellent resolution, comparable to histopathology [54]	-Requires training [54] -Contact methodology in some devices [55] -No cross sectional/vertical images [55]

Table 2

Efficacy of primary therapies for conjunctival malignant melanoma

	Surgery	**Mitomycin C**
Number of studies	4 [8,20,29,73]	5 [79–81,90–92]
Total number of cases	457	10
Dose		0.04%
Frequency		Four times a day
Duration		14 days or 28 days
Average number of cycles		2.0
% complete resolution	72% (314/434)	40% (4/10)
% recurrence	29% (134/457)	40% (4/10)
% metastasis	19% (81/434)	10% (1/10)
% exenteration	10% (43/434)	20% (2/10)
% mortality	6% (28/434)	
Mean follow-up time (months)	52	19.4

Table 3

Efficacy of adjuvant therapies for conjunctival malignant melanoma

	Topical chemotherapy		**Radiotherapy**	
	Mitomycin C	**Interferon alpha-2b**	**Brachytherapy**	**External Beam Radiotherapy**
Number of studies	6 [66,78–81,93]	3 [83–85]	4 [8,94–96]	3 [97–99]
Total number of cases	48	11	74	51
Dose	0.04%	1 million IU		
Frequency	Four times a day	Four times a day		
Duration	-1wk or -3wks + 1wk topical steroid or -3wks + 3wks OFF or -4wks	-6wks -3mo		
Average number of cycles	2.0	1.3		
Radioisotope			Strontium-90 (3), Iodine-125 (1)	
Grays per fraction			8.3	4.7
Total number of fractions			6.7	9.6
Total Grays			47.4	51.5
Depth			1.5-3.0mm	
% complete resolution	73% (35/48)	91% (9/11)	80% (59/74)	85% (17/20)
% recurrence	26% (13/48)	9% (1/11)	20% (15/74)	37% (19/51)
% metastasis	6% (3/48)	0%	0%	22% (11/51)
% exenteration	2% (1/48)	0%	0%	15% (4/26)
Mean follow-up time (months)	37.8	16.4	63.9	34.8

Table 4

Use of sentinel lymph node biopsy (SLNB) for conjunctival malignant melanoma

Number of studies	5 [125,129,136–138]
Number of cases of CMM	56
Clinically negative (palpation) lymph node	100% (2/2)
MRI negative for lymph met	100% (53/53)
SLNB at same time as CMM excision	4% (1/25)
SLNB after CMM excision	96% (24/25)
Preoperative lymphoscintigraphy positive (for at least 1 node)	93% (52/56)
Preoperative lymphoscintigraphy positive for more than 1 node	0% (0/3)
Histologically positive (evidence of micrometastasis)	17% (9/52)
Histologically negative (No evidence of micrometastasis)	83% (43/52)
Drainage basin parotid	34% (19/56)
Drainage basin lymph nodes along internal jugular vein (level II, III and IV)	18% (10/56)
Drainage basin submandibular nodes	27% (15/56)
Drainage basin preauricular	58% (32/56)
Mean Breslow tumor thickness among SLNB positive (mm)	5.42
Mean tumor thickness among SLNB negative (mm)	2.31
Of the histologically negative, % complete resolution (no recurrence/metastasis)	93% (40/43)
False negatives (histologically negative but developed recurrence or metastasis)	7% (3/43)
% recurrence of those histologically positive	56% (5/9)
% metastasis	56% (5/9)
% death	44% (4/9)
Mean follow-up time	1.9y
Complications	Transient blue stain 5/16 (31%), transient facial nerve palsy 1/18 (6%)

Table 5

Prognosis of Conjunctival Melanoma

	Local Recurrence	Lymph Node Metastasis	Systemic Metastasis	Mortality
Number of studies	6 [6,8,20,22,29,140]	5 [8,22,29,128,140]	5 [8,22,29,128,140]	5 [6,8,19,22,29,140]
Total # of cases	770	734	734	734
Risk of prognostic event	28-67%	12-41%	12-52%	6-44%
Average risk	40% (307/770)	19% (140/734)	19% (141/734)	18% (114/649)
Time to prognostic event (years)	1.4-2.5	2.3-4.4	3.1-6.5	4.8-6.5
Mean time to prognostic event (years)	2.4	3.4	3.4	4.9
5-year estimate	36-45%	11-52%	11-16% T1: 11% T2: 35% T3: 42%	74-86% (survival) 7% (death) T1: 5% T2: 20% T3: 23%
10-year estimate	31-59%	11-57%	18-52% T1: 20% T2: 52% T3: n/a	41-78% (survival) 13% (death, at 8 years) T1: 14% T2: 20% T3: n/a

Table 6

Relationship between origin of melanoma and subsequent prognosis

Origin	Frequency	Orbital invasion [20]	Metastasis [20]	Mortality [20]
PAM	57-76% [6,8,20,22]	16% (16%)*	19% (25%)	5% (9%)
De novo	16-25% [8,20,22,24]	17% (17%)	35% (49%)	17% (35%)
Nevus	1-6% [8,20,22,24]	9% (9%)	10% (26%)	0% (9%)

*5-year risk (10-year risk)

Table 7

American Joint Committee on Cancer (AJCC) classification of conjunctival malignant melanoma [149]

Primary Tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T(is)	Malignant melanoma confined to conjunctival epithelium
T1	*Malignant conjunctival melanoma of the bulbar conjunctiva*
T1a	≤ 1 quadrant
T1b	>1 but ≤ 2 quadrants
T1c	>2 but ≤ 3 quadrants
T1d	>3 quadrants
T2	*Malignant conjunctival melanoma of the nonbulbar (palpebral conjunctiva, forniceal conjunctiva, caruncular)*
T2a	≤ 1 quadrant, no caruncular involvement
T2b	>1 quadrant, no caruncular involvement
T2c	≤ 1 quadrant, any caruncular involvement
T2d	>1 quadrant, any caruncular involvement
T3	*Any malignant conjunctival melanoma with local invasion*
T3a	Globe
T3b	Eyelid
T3c	Orbit
T3d	Sinus
T4	Tumor invades the central nervous system
Regional Lymph Node (N)	
Nx	Regional lymph nodes cannot be assessed
N0a (biopsied)	No regional lymph node metastasis, biopsy performed done
N0b (not biopsied)	No regional lymph node metastasis, no biopsy performed
N1	Regional lymph node metastasis
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Table 8

New Biological Therapies

Agent	Target
Ipilimumab	Anti-CTLA4
Vemurafenib	B-RAF kinase
Dabrafenib	B-RAF kinase
Imatinib	Kit/CD117
Trametinib	MEK

Table 9

Summary of selected genetic targets in conjunctival melanoma

Gene	Suspected role	Source (# studies)	Overall Detection rate	Other findings
BRAF	Serine/threonine kinase that, when mutated, inhibits apoptosis and promotes cellular proliferation	Unknown (4) [150,162–164]	22.2% (14/63) at V600E, V600R, V599E and E585K positions	BRAF+ tumors tended to have larger diameter and greater depth of invasion [162], presence of BRAF mutations in conjunctival nevi but not PAM suggest that oncogenic events orchestrated by BRAF mutations may lead to conjunctival nevi as much as to conjunctival melanoma. Additionally, conjunctival melanomas arising from nevi may have a high probability of a BRAF mutation [163].
		Primary (2) [151,153]	33% (31/94) at V600E position	
		Metastasis (1) [153]	67% (4/6) at V600E position	
		Uveal melanoma (1) [150]	0% (0/88)	
		Conjunctival nevi (1) [163]	50% (14/28)	
		Conjunctival PAM (1) [163]	0% (0/15)	
KIT	Receptor tyrosine kinase that promotes cell survival and growth.	Unknown (3) [164,166,167]	2.2% (1/45)	20% (1/5) tumors were positive for CD117 expression, suggesting that CD117 immunoreactivity is not a good predictor of KIT mutation. Patients should simply undergo mutational analysis to determine if imatinib therapy is appropriate [166], c-kit immunostaining positive in 48% (13/27) but no KIT mutations detected suggesting immunostains are not good predictors of KIT mutation [167].
NRAS	GTPase that, when mutated, promotes unregulated cell division.	Unknown (1) [151]	16% (14/89) tumors	