Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand

Ocular and Periocular Melanoma: Supplementary Document

1   Authors' Note

The Australian Cancer Network, in accordance with the National Health and Medical Research Council (NHMRC), has recently redeveloped the evidence-based Clinical Practice Guidelines for the Management of Melanoma. A previous edition of the guidelines published in 1999 had been used widely throughout Australia and New Zealand and translated into several languages for overseas use. The current guidelines, published by the Australian Cancer Network and approved by the NHMRC as a handbook and a web-based resource in 2008, contain a chapter and supplementary document on ocular and periocular melanoma (see www.cancer.org.au/skincancerguides, Ocular Melanoma; Chapter 24). The supplementary document appears below. This is the first NHMRC compilation of evidence-based guidelines for the management of ocular melanoma.

NHMRC guidelines are created by members of an expert working group from a broad range of disciplines each contributing a chapter. The guidelines are compiled according to NHMRC standards of quality and process. The aims are dual: to create concise recommendations for the management of ocular and periocular melanoma in the Australasian context and to grade the strength of the supporting evidence according to the level of the evidence base. Details regarding the process of the formation and grading of the guidelines may be found on the NHMRC website.

Uveal, conjunctival and cutaneous melanomas are malignant proliferations of melanocytes derived from neural crest cells. Despite similar origins they have different epidemiology, molecular biology, pathogenesis and metastatic pattern. This supplementary document focuses on evidence-based aspects of management. For detailed information regarding the basic science, epidemiology and pathogenesis of ocular, periocular and cutaneous melanoma, the reader is referred to the complete NHMRC document and the many excellent comprehensive reviews in the literature.

2   Introduction

The two principal types of primary ocular melanoma are uveal and conjunctival melanoma. Of the two, uveal melanoma is more common, with an incidence of four to six per million per year in most western countries.[2] 90 percent of uveal melanomas arise in the choroid, seven percent in the ciliary body and three percent in the iris.[3] Based on these data, the predicted Australian incidence is 90–100 cases per year of choroidal melanoma.[4] The frequency of conjunctival melanoma is one in 20 to one in 40 that of uveal melanoma, with an incidence of only 0.1–0.3 per million in most western populations.[5] Periocular melanoma includes eyelid and orbital melanoma. Primary eyelid melanoma has a similar incidence to conjunctival melanoma[6] whilst primary orbital melanoma is exceedingly rare. Melanoma metastatic to the eye or periocular sites is recognised, but also very rare.

The Collaborative Ocular Melanoma Study (COMS), undertaken in 1985, is the only source of level II evidence for the management of primary ocular melanoma. Participants were subdivided into three trials for small, medium and large choroidal melanoma. This trial has confirmed the role of brachytherapy in the treatment of medium-sized and small choroidal tumours, and has shown that pre-enucleation irradiation for large tumours has no survival benefit.[7-9]

Another recent advance in management is the identification of several risk factors for malignancy of small choroidal tumours.[10] This has led to improved clinical detection with more accurate selection of cases.

The management of ocular and periocular melanoma is a rapidly changing and expanding field. The aim of these guidelines is to highlight the various issues involved in the treatment of ocular and periocular melanoma.

3   Uveal melanoma

3.1 Precursor lesions (indeterminate lesions)

Uveal melanoma originates either de novo or from degeneration of an existing naevus, but the proportion of each is unknown. Six percent of individuals have choroidal naevi, of which one in 5000 is estimated to undergo malignant degeneration.[11] Much effort has been directed at determining which choroidal naevi have malignant potential or are small melanomas and require treatment, however diagnosis remains controversial. Specific precursor lesions for ciliary body and iris melanoma are less well studied, however are presumed to be similar to those for the choroidal melanoma.

In general, tumour growth over a short period (months) is considered a hallmark of choroidal melanoma. One arm of the COMS followed 204 patients with small choroidal melanocytic lesions (<3mm thick, <10mm in diameter) over five years to discover that 31% demonstrated growth, which has been found to be associated with a 3.2 relative risk of malignancy.[10,12,13] However, naevi may also demonstrate growth, usually slowly over a period of years.

Additionally a number of qualitative risk factors including tumour thickness (>2mm), orange pigment, absence of drusen, visual symptoms, proximity to the optic disc, subretinal fluid and absence of adjacent retinal pigment epithelial changes have been observed to be predictive of tumour growth.[10,12,13,14] Lesions which display such features have an elevated potential for malignant transformation and have been termed indeterminate lesions or naevomas (see table 1).

The management of indeterminate lesions remains controversial and may vary considerably from one centre to another. At some centres, definitive treatment for indeterminate lesions is preferred while at others, indeterminate lesions (especially if involving only one or two risk factors) are observed more often (usually three to six monthly) for growth using clinical photography and ultrasound. Transvitreal biopsy is used in some centres to improve diagnostic accuracy.[15] Treatment methods in relation to indeterminate lesions are similar to those for small melanoma (see *Primary choroidal and ciliary body melanoma*, below).

Uveal melanoma is more common in people with light coloured eyes with increasing frequency in older age groups, and with no sex predilection. Unlike cutaneous melanoma, the link to sunlight exposure is weaker. Certain conditions predispose to uveal melanoma, including oculodermal melanocytosis, neurofibromatosis type 1, familial cutaneous melanoma and cutaneous dysplastic naevus syndrome.

3.2 Primary choroidal and ciliary body melanoma

The clinical presentation of choroidal and ciliary body melanoma depends on the size and location of the lesion. Clinical diagnosis aided by ultrasound, which has characteristic features for uveal melanoma and can detect extraocular extension, has been demonstrated to have a very high level of accuracy in experienced hands.[16] Ultrasound biomicroscopy is particularly useful for the evaluation of ciliary body melanoma. Fluorescein angiography may provide useful ancillary information, while indocyanine green may be useful to detect complex microvascular patterns predictive of tumour growth.[17] CT or MRI imaging studies are useful to exclude extraocular extension and are used to plan radiotherapy at some centres.[3,5] In addition, a systemic evaluation is usually performed at presentation to assess for metastatic disease.

Biopsy is performed more liberally at some centres than others. It is generally indicated if other tests have failed to elucidate the diagnosis. The reported diagnostic accuracy varies depending on tumour size and location, diameter of needle, sampling technique and other factors .[18] With better techniques, fewer

complications and greater understanding of the importance of cytogenetics, some authors feel that it will become more common in the future, particularly if the cytogenetic profile is used in treatment planning.[19] There are risks, however, in terms of complications (e.g. vitreous haemorrhage) and the theoretical risk of spreading the tumour extra-ocularly. Sampling variability due to tumour cell heterogeneity with respect to the cytogenetic analysis of tumours also needs to be recognised.

The management of choroidal melanoma has changed considerably in recent years. Until the late 1970s, enucleation was the treatment of choice.[20,21] Today, eye-conserving plaque radiotherapy is the most common treatment. Other forms of treatment include periodic observation, transpupillary thermotherapy, charged particle irradiation, local tumour resection, enucleation and exenteration.[14,22,23]

The choice of treatment depends upon the size, location and growth of the tumour; the visual acuity, intraocular pressure and retinal changes in the affected eye; the patient's age, general health, wishes and psychological status; and the status of the other eye.[3,5,23] The various treatment options are outlined in Table 2 and are described in detail in the literature.

3.3 Iris melanoma

Ninety percent of iris melanomas are discrete circumscribed lesions with an excellent prognosis.[40] The remainder are diffuse or ring variants with a poorer prognosis. At many centres, suspicious circumscribed lesions are observed and intervention initiated if there is documented growth. Ultrasound biomicroscopy and clinical photography are particularly useful for documenting growth. Besides growth tendency, other factors that may initiate treatment include large size, multifocal tumours, tumour-related glaucoma, spontaneous hyphaema, involvement of the subjacent ciliary body or extrascleral extension. Primary treatment is usually surgical resection or various forms of radiotherapy (e.g. plaque brachytherapy or charged particle therapy). Enucleation remains the treatment of choice for tumours unsuited to conservative modalities. The majority of metastatic events occur when drainage procedures are inadvertently performed for tumour-induced raised intraocular pressure or ring melanomas, or when the iris melanoma is an extension of ciliary body or diffuse uveal melanoma.

3.4 Prognosis of treated uveal melanoma patients

Metastatic uveal melanoma is the cause of death in approximately 50% of all patients with the disease. The prognostic factors associated with this are as follows:

Size: Choroidal and ciliary body tumours are primarily divided into small (<3mm height, 5-10mm diameter), medium (3-5mm height, 10-15mm diameter) and large (>5mm height, >15mm diameter) subgroups.[47] Metastatic rate increases with the size of tumour, with the largest tumour diameter being more important than depth.[48] Small, medium and large tumours have 16%, 32% and 53% 5 year all-cause mortality, and 35%, 60% and 81% 10-year all cause mortality.[7] In addition, tumour size was found on meta-analysis to be the most important prognostic factor for survival in the COMS medium-sized tumour trial.[7]

Ciliary body involvement: Ciliary body tumours present later, larger and are more likely to invade the angle.[49] Ring melanoma involving the ciliary body and iris metastasis frequently has a poor prognosis.[50] In contrast, iris melanomas have a lower incidence of systemic metastases than other uveal melanomas, and have a <2% long-term tumour-related mortality.[2,5]

Cell type: Two melanoma cell types are common: epithelioid and spindle cell. Epithelioid cells have a worse prognosis than spindle cell, and a mixed pattern has an intermediate prognosis.[51]

Histopathology: Further histological poor prognostic markers include extravascular matrix patterns consisting of closed periodic acid-Schiff positive loops in the tumour, increased microvascular density, higher cell proliferation rate/mitoses, lymphocytic tumour invasion, and macrophage tumour invasion.[3]

Human Lymphocyte Antigen (HLA) class I and II expression: Expression of HLAs on melanoma cell membranes are associated with a poor prognosis, and may indicate a protective role of Natural Killer lymphocytes.[52]

Chromosomal abnormalities: Genomic changes of uveal melanoma have been studied using comparative genomic hybridisation.[53] Loss of chromosome three occurs early, and is highly predictive of metastatic risk. Other genetic changes have also been found to have prognostic significance and genetic profiling of tumours is now able to provide reliable prognostic information.

Local tumour recurrence after conservative treatment: Local tumour recurrence after conservative treatment is associated with a fourfold increase risk of metastasis. This may reflect a causal link between recurrence and metastasis, or a more aggressive cell line.[3]

3.5 Follow-up of treated uveal melanoma patients

There is currently no consensus on the ideal protocol for follow up and screening for metastatic disease from uveal melanoma and there is no evidence to date that any particular follow-up protocol influences long-term survival. Screening has been demonstrated to be associated with a slightly longer survival than symptomatic metastasis with treatment,[54,55] however probably represents earlier detection rather than true life extension. Additionally there is no effective treatment available for metastatic uveal melanoma (see *Metastatic uveal melanoma*), with the possible exception of the rare subgroup of patients with solitary or oligo liver metastases where there are anecdotal reports of extended survival after resection with or without intra-arterial chemotherapy.[56,57]

Following discussion of the risk-benefit ratio of screening with the patient, when screening is undertaken, some form of regular liver imaging (usually ultrasound) has been recommended by some authors[58] and given that metastases can present up to 25 years after the primary lesion is detected, long-term follow up is logical.

A reasonable consensus protocol is six-monthly follow up, with full clinical examination. Liver imaging, liver function tests and possibly a plain chest radiograph may be undertaken regularly or intermittently as clinically indicated.

3.6 Metastatic uveal melanoma

Today, choroidal melanomas can be controlled locally, with good preservation of vision in most patients.[3,59,60] Despite this, the survival rate for uveal melanoma has not changed over a 25-year period.[61] This may well reflect an inability to prevent or treat metastatic disease. Presuming exponential growth, the correlation of primary and metastatic uveal melanoma growth data suggests that micrometastases presumably seed early and can lay dormant for many years.[62] Only 2% of patients have detectable metastases at the time of diagnosis, however after local control metastases occur in 31% of cases at 5 years, 45% at 15 years, and 50% at 25 years.[54,63] It is unclear what factors activate the micro-metastases after such long dormant periods.

Metastases are invariably haematogenous, and 93% go to the liver.[55,64] Other organ sites once the liver is involved include lung (20%), bone (16%), skin (12%), kidney and brain.[55] Attempted treatment modalities include surgical resection, intra-arterial chemotherapy, chemoembolisation or combinations of these.

These rarely prolong survival and once symptoms occur, metastatic disease is often fatal within six months[65] (see www.cancer.org.au/skincancerguides, Clinical Practice Guidelines for the Management of Melanoma; Chapter 15).

4   Conjunctival melanoma

4.1 Precursor lesions

Seventy-one percent to 75% of conjunctival melanoma arise in an area of primary acquired melanosis (PAM) with atypia.[66-68] The remaining cases of conjunctival melanoma arise either de novo (12%) or from malignant degeneration of a naevus (12–17%). 13-50% of PAM with atypia will eventually become malignant,[69,70] however like choroidal naevi, most conjunctival naevi do not undergo malignant transformation.[67,68] The following lesions are suspicious: pigmented lesions that arise de novo in adulthood, lesions that increase in size, or lesions in a danger area (palpebral or forniceal conjunctiva, plica semilunaris, caruncle). However the rate of malignancy of these is under five percent.[71] A pigmented lesion of the conjunctiva that has any thickness (vertical growth) is highly suspicious for conjunctival melanoma until proven otherwise. Easily resectable suspicious lesions are often excised; extensive suspicious patches are more feasibly monitored regularly for growth (see Table 1). The method of resection is similar to that used for primary conjunctival melanoma (see below), however without wide margins. Topical mitomycin C may have a role for the management of widespread primary acquired melanosis with atypia.[72]

UV radiation has been implicated however has not been shown to be a causative agent in the formation of conjunctival naevi.[66] There are several case reports that suggest an association between conjunctival melanoma and xeroderma pigmentosum.[74]

4.2 Primary conjunctival melanoma

Conjunctival melanoma is more common in white, fair-haired individuals, arising in middle age and senior adults.[67] Like uveal melanoma, there is no sex predilection. Conjunctival melanoma typically arises within the bulbar conjunctiva and cornea, however it can be found on palpebral or forniceal conjunctiva, plica semilunaris, eyelid margins and caruncle (all of which have a poorer prognosis than bulbar conjunctival tumours).[75] Conjunctival melanoma is usually pigmented (occasionally amelanotic) and may be diffusely spreading or nodular. Conjunctival melanoma has a propensity to present as multifocal and recurrent disease with a tendency for local control to fail over time.[76]

The evaluation of any lesion suspicious for conjunctival melanoma includes full ophthalmic examination and systemic examination for metastasis. Preoperative mapping of the lesion using a slit lamp is essential for achieving adequate surgical margins.[77] Unlike uveal melanoma, locoregional lymph nodes need to be evaluated with clinical examination and imaging (such as ultrasound, CT or MRI) where locoregional metastatic disease is suspected. The role of sentinel lymph node biopsy is currently being evaluated.[78-80]

The diagnosis of conjunctival melanoma is based on biopsy and histopathological evaluation and is usually undertaken as part of the definitive primary treatment procedure (i.e. excisional biopsy with cryotherapy) unless disease is widespread and unresectable, in which case a staging incisional biopsy may be performed.

In a similar way to the management of uveal melanoma, there has been a movement to use eye-conserving treatment for conjunctival melanoma.[81] The management of conjunctival melanoma is predominantly surgical, with wide local excision and supplementary cryotherapy the most common treatment (see table 3).[73,77] Because diffuse, multifocal conjunctival involvement can occur, wide margins (5mm) are desired, however this should be balanced against preservation of ocular function. Topical chemotherapy and radiotherapy may have a role, but it is yet to be defined.[82,83]

Additional comments

Incisional biopsy and incomplete surgical excision are associated with a high recurrence rate when compared to complete surgical excision.[92] Mucosal grafts may be necessary for conjunctival defects. Options include an autologous contralateral conjunctival graft, autologous buccal membrane, or allogenic amniotic graft. Conjunctival grafts are sufficient for small defects. Amniotic membrane grafts are thin, transparent and non-immunogenic with higher take rates than mucosal grafts and allow easy post-operative tumour bed surveillance.[93]

4.3 Prognosis of treated conjunctival melanoma patients

A number of prognostic factors for recurrence and metastasis have been identified (see below). Additionally, there is a high likelihood of new ocular lesions. One study has estimated the incidence of recurrent or new ocular lesions to be 56% at 7.5 years after primary treatment.[76]

Tumour location: Most tumours arise on the bulbar conjunctiva, which has the best prognosis. Tumours in an unfavourable site such as the palpebral or forniceal conjunctiva, caruncle, plica semilunaris and eyelid margins are associated with a 2.2 fold greater risk of metastasis.[75]

Tumour extent: Thickness and diameter are important prognostic influences, although no clear threshold has been identified. According to the Swedish National Cancer Registry, tumours with thickness 10mm or more have a particularly poor prognosis.[68] Diffuse, multifocal tumours do worse than circumscribed ones.[5,68]

Cell type: Like uveal melanoma, epithelioid cells predict a poorer outcome than spindle cells, and their presence is associated with a three-fold increase in risk of metastasis compared to a pure spindle cell population.[5]

Features on histology: The most significant prognostic feature is involvement of surgical margins. Other poor prognosis factors include depth of invasion, pagetoid pattern or melanoma in situ pattern of growth, PAM *sine pigmento*, lymphocytic invasion (associated with a four-fold increased risk of metastasis), vascular invasion, and a high mitotic index (>5 mitoses per 10 high power fields).[5,68]

Local tumour recurrence after conservative treatment: Local tumour recurrence is associated with an increased risk of loco-regional and distant metastasis [76].

The origin of the melanoma (ie de novo, from PAM with atypia or nevus) does not effect the mortality rate.

4.4 Follow-up of treated conjunctival melanoma patients

Due to the high likelihood of recurrence or new ocular lesions indefinite biannual assessment is recommended (see table 4).

4.5 Treatment of node-positive disease

There is a paucity of specific data regarding the management of node-positive disease from conjunctival melanoma. The principles for management broadly correspond to those for loco-regional metastases from cutaneous melanoma (see www.cancer.org.au/skincancerguides, Clinical Practice Guidelines for the Management of Melanoma; Chapter 12). Management options for node-positive disease include lumpectomy with adjuvant ring radiotherapy, *enbloc* orbital exenteration with radical neck dissection, or radiotherapy alone. No method is proved more effective than another and results are generally poor, so a

conservative approach is recommended. Lumpectomy with adjuvant low dose ring radiotherapy is often undertaken, as it provides histological diagnosis and limits radiation-induced complications.[94] Sentinel lymph node biopsy techniques have been applied and may improve early detection of locoregional disease.[78,95]

4.6 Metastatic conjunctival melanoma

There is little specific data regarding the management of distant metastases from conjunctival melanoma (see www.cancer.org.au/skincancerguides, Clinical Practice Guidelines for the Management of Melanoma; Chapter x)

5   Eyelid melanoma

Management of cutaneous eyelid melanoma are to be considered within the guidelines of cutaneous melanoma (see www.cancer.org.au/skincancerguides , Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand). Cutaneous melanoma of the eyelid constitute less than 1% of all cutaneous melanoma, and previous studies generally present retrospective case series with NHMRC level of evidence Level IV.[96,97] However, the literature highlights special considerations in clinicopathologic and management features. Eyelid melanoma can occur as a primary lesion, or as a metastasis, but also as extension from conjunctival melanoma. The clinical and pathologic features of primary eyelid melanoma are broadly similar to those for primary cutaneous melanoma elsewhere in the body, although the lentigo maligna melanoma subtype is more common in this location. Eyelid melanoma has a similar prognosis to cutaneous melanoma and is managed in a similar way however have special considerations.[5] Complete surgical excision confirmed by histological examination of the entire specimen excision margin forms the basis of surgical treatment. Excision with wide margins is difficult to achieve without sacrificing important structures. Margin control by mapped serial excision or a modified Mohs' micrographic surgery using paraffin sections and delayed reconstruction are recommended and commonly used. Lymphatic mapping and sentinel lymph node biopsy for melanoma 1.0 mm and greater in thickness has an evolving role but remains controversial, noting the variable lymphatic drainage pattern of the eyelid.[8,97] The techniques of eyelid melanoma surgery and reconstruction, and of excision with histological control are outside the search criteria for this study.

6   Orbital melanoma

Orbital melanomas can be classified into primary and secondary melanomas. Primary orbital melanomas are extremely rare and often occur in association with melanosis oculi. Secondary orbital melanomas are seen more often and usually represent massive extrascleral extensions of uveal melanomas or distant metastases of cutaneous melanomas to the orbit. Presentation is typically with proptosis or diplopia from involvement of extraocular muscles. Prognosis is typically poor with a median survival ranging from six to 16 months.[5,98,99]

Treatment options include exenteration, surgical resection of focal lesions with or without adjuvant radiotherapy and/or chemotherapy. This approach does not seem to improve patient survival when compared with conservative treatment.[98] However, orbital exenteration is effective for local control of the disease.

7   Metastatic melanoma to the eye and periocular tissues

Metastatic melanoma to the eye and periocular region is rare; half involve the orbit, while the rest in order of frequency involve retina, vitreous, uveal tract, conjunctiva and anterior chamber.[5] It generally occurs in patients with disseminated metastases during the terminal stages of the disease, with a short life expectancy. Treatment is palliative and, among the various possible treatment options, circumscribed proton beam radiotherapy or global photon beam radiotherapy, at relatively high irradiation doses, seems to achieve the most favourable results.[100]

8   Psychological aspects of ocular melanoma

Many psychological issues are common to cutaneous melanoma in relation to risk of metastasis and death (see www.cancer.org.au/skincancerguides, Clinical Practice Guidelines for the Management of Melanoma; Section 16). Specific issues pertain to ocular and periocular sites, however, in regard to fear of visual morbidity and cosmetic concerns related to loss of an eye or facial deformity balanced against a treated tumour left in an eye requiring frequent follow up.[101-103]

The final decision about management should be made by the patient with guidance from the physician and other relevant health professionals (see table 5).

Acknowledgements

References

1.   Clinical Practice Guidelines, The management of cutaneous melanoma, NHMRC 1999.

2.   Char DH. Tumours of the eye and ocular adnexa. Toronto BC: Decker, 2001.

3.   Damato B. Treatment of primary intraocular melanoma. Expert Rev Anticancer Ther 2006; 6(4):493–506.

4.   Reader S, Grigg J, Billson FA. Choroidal melanoma: a review of the experience of the Sydney Eye Hospital Professorial Unit 1979–1995. Aust N Z J Ophthalmol 1997; 25(1):15–24.

5.   Char DH. Ocular melanoma. Surg Clin North Am 2003; 83(2):253–74, vii.

6.   Margo CE, Mulla ZD. Malignant tumors of the eyelid: a population-based study of non-basal cell and non-squamous cell malignant neoplasms. Arch Ophthalmol 1998; 116(2):195-198.

7.   The Collaborative Ocular Melanoma Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma II: initial mortality findings. COMS report no. 10. Am J Ophthalmol 1998; 125(6):779–796.

8.   Melia BM, Abramson DH, Albert DM, Boldt HC, Earle JD, Hanson WF et al. Collaborative ocular melanoma study (COMS) randomized trial of I-125 brachytherapy for medium choroidal melanoma. I. Visual acuity after 3 years COMS report no. 16. Ophthalmology 2001; 108(2):348–366.

9.   Diener-West M, Earle JD, Fine SL, Hawkins BS, Moy CS, Reynolds SM et al. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma, III: initial mortality findings. COMS Report No. 18. Arch Ophthalmol 2001; 119(7):969–982.

10.   Shields CL, Shields JA. Clinical features of small choroidal melanoma. Curr Opin Ophthalmol 2002; 13(3):135–141.

11.   Ganley JP, Comstock GW. Benign nevi and malignant melanomas of the choroid. Am J Ophthalmol 1973; 76(1):19–25.

12.   Factors predictive of growth and treatment of small choroidal melanoma: COMS Report No. 5. The Collaborative Ocular Melanoma Study Group. Arch Ophthalmol 1997; 115(12):1537–1544.

13.   Shields CL, Shields JA, Kiratli H, De Potter P, Cater JR. Risk factors for growth and metastasis of small choroidal melanocytic lesions. Ophthalmology 1995; 102(9):1351–1361.

14.   Shields CL, Shields JA. Recent developments in the management of choroidal melanoma. Curr Opin Ophthalmol 2004; 15(3):244–251.

15.   Augsburger JJ, Corrêa ZM, Schneider S, Yassin RS, Robinson-Smith T, Ehya H, Trichopoulos N. Diagnostic transvitreal fine-needle aspiration biopsy of small melanocytic choroidal tumors in nevus versus melanoma category. Trans Am Ophthalmol Soc 2002; 100:225-232.

16.   Accuracy of diagnosis of choroidal melanomas in the Collaborative Ocular Melanoma Study. COMS report no. 1. Arch Ophthalmol 1990; 108(9):1268–1273.

17. Mueller AJ, Freeman WR, Schaller UC, Kampik A, Folberg R. Complex microcirculation patterns detected by confocal indocyanine green angiography predict time to growth of small choroidal melanocytic tumors: MuSIC Report II. Ophthalmology 2002; 109(12):2207-2214.

18. Char DH, Miller T. Accuracy of presumed uveal melanoma diagnosis before alternative therapy. Br J Ophthalmol 1995; 79(7):692–696.

19. Damato B, Duke C, Coupland SE, Hiscott P, Smith PA, Campbell I, Douglas A, Howard P. Cytogenetics of uveal melanoma: a 7-year clinical experience. Ophthalmology 2007; 114(10):1925-1931.

20. Zimmerman LE, McLean IW, Foster WD. Does enucleation of the eye containing a malignant melanoma prevent or accelerate the dissemination of tumour cells. Br J Ophthalmol 1978; 62(6):420–425.

21. Zimmerman LE, McLean IW. An evaluation of enucleation in the management of uveal melanomas. Am J Ophthalmol 1979; 87(6):741–760.

22. Aarberg TM. Current clinical management options for uveal melanoma. Ophthalmol Clin North Am 1999; 12(2):177–182.

23. Bell DJ, Wilson MW. Choroidal melanoma: natural history and management options. Cancer Control 2004; 11(5):296–303.

24. Shields JA, Glazer LC, Mieler WF, Shields CL, Gottlieb MS. Comparison of xenon arc and argon laser photocoagulation in the treatment of choroidal melanomas. Am J Ophthalmol 1990; 109(6):647–655.

25. Barbazetto IA, Lee TC, Rollins IS, Chang S, Abramson DH. Treatment of choroidal melanoma using photodynamic therapy. Am J Ophthalmol 2003; 135(6):898–899.

26. Harbour JW, Meredith TA, Thompson PA, Gordon ME. Transpupillary thermotherapy versus plaque radiotherapy for suspected choroidal melanomas. Ophthalmology 2003; 110(11):2207–2214.

27. Shields CL, Shields JA, Perez N, Singh AD, Cater J. Primary transpupillary thermotherapy for small choroidal melanoma in 256 consecutive cases: outcomes and limitations. Ophthalmology 2002; 109(2):225–234.

28. De Potter P, Jamart J. Adjuvant indocyanine green in transpupillary thermotherapy for choroidal melanoma. Ophthalmology 2003; 110(2):406–413.

29. Shields CL, Naseripour M, Cater J, Shields JA, Demirci H, Youseff A, Freire J. Plaque radiotherapy for large posterior uveal melanomas (> or =8-mm thick) in 354 consecutive patients.Ophthalmology 2002; 109(10):1838-1849.

30. Bechrakis NE, Bornfeld N, Zöller I, Foerster MH. Iodine 125 plaque brachytherapy versus transscleral tumor resection in the treatment of large uveal melanomas. Ophthalmology 2002; 109(10):1855-1861.

31. Puusaari I, Heikkonen J, Summanen P, Tarkkanen A, Kivelä T. Iodine brachytherapy as an alternative to enucleation for large uveal melanomas.Ophthalmology 2003; 110(11):2223-2234.

32. Finger PT. Radiation therapy for choroidal melanoma. Surv Ophthalmol 1997; 42(3):215–232.

33. Char DH, Quivey JM, Castro JR, Kroll S, Phillips T. Helium ions versus iodine 125 brachytherapy in the management of uveal melanoma. A prospective, randomized, dynamically balanced trial. Ophthalmology 1993; 100(10):1547–1554.

34. Daftari IK, Char DH, Verhey LJ, Castro JR, Petti PL, Meecham WJ et al. Anterior segment sparing to reduce charged particle radiotherapy complications in uveal melanoma. Int J Radiat Oncol Biol Phys 1997; 39(5):997–1010.

35. Conway RM, Poothullil AM, Daftari IK, Weinberg V, Chung JE, O'Brien JM. Estimates of ocular and visual retention following treatment of extra-large uveal melanomas by proton beam radiotherapy. Arch Ophthalmol. 2006; 124(6):838-843.

36. Emara K, Weisbrod DJ, Sahgal A, McGowan H, Jaywant S, Michaels H, Payne D, Pintilie M, Laperriere NJ, Simpson ER. Stereotactic radiotherapy in the treatment of juxtapapillary choroidal melanoma: preliminary results. Int J Radiat Oncol Biol Phys 2004; 59(1): 94-100.

37. Histopathologic characteristics of uveal melanomas in eyes enucleated from the Collaborative Ocular Melanoma Study. COMS report no. 6. Am J Ophthalmol 1998; 125(6):745–766.

38. Damato B. Adjunctive plaque radiotherapy after local resection of uveal melanoma. Front Radiat Ther Oncol 1997; 30:123–132.

39. Char DH, Miller T, Crawford JB. Uveal tumour resection. Br J Ophthalmol 2001; 85(10):1213–1219.

40. Conway RM, Chua WC, Qureshi C, Billson FA. Primary iris melanoma: diagnostic features and outcome of conservative surgical treatment. Br J Ophthalmol 2001; 85(7):848–854.

41. Damato BE, Paul J, Foulds WS. Risk factors for residual and recurrent uveal melanoma after trans-scleral local resection. Br J Ophthalmol 1996; 80(2):102–108

42. Damato B, Wong D, Green FD, Mackenzie JM. Intrascleral recurrence of uveal melanoma after transretinal "endoresection". Br J Ophthalmol 2001; 85(1):114-115.

43. Damato B, Lecuona K. Conservation of eyes with choroidal melanoma by a multimodality approach to treatment: an audit of 1632 patients. Ophthalmology 2004; 111(5):977–983.

44. De Potter P, Shields CL, Shields JA, Cater JR, Tardio DJ. Impact of enucleation versus plaque radiotherapy in the management of juxtapapillary choroidal melanoma on patient survival. Br J Ophthalmol 1994; 78(2):109–114.

45. Rousseau AP. Uveal melanoma: update and future directions. Can J Ophthalmol 2004; 39(4):335–342.

46. Mortality in patients with small choroidal melanoma. COMS report no. 4. The Collaborative Ocular Melanoma Study Group. Arch Ophthalmol 1997; 115(7):886–893.

47. Shields JA, Shields CL, Donoso LA. Management of posterior uveal melanoma. Surv Ophthalmol 1991; 36(3):161-195.

48. Mooy CM, DeJong PT. Prognostic parameters in uveal melanoma: a review. Surv Ophthalmol 1996; 41(3):215-228.

49. Simpson ER. Ciliary body melanoma: a special challenge. Can J Ophthalmol 2004; 39(4):365-371.

50. Demirci H, Shields CL, Shields JA, Eagle RC Jr, Honavar S. Ring melanoma of the anterior chamber angle: a report of fourteen cases. Am J Ophthalmol 2001; 132(3):336-342.

51. McLean IW, Saraiva VS, Burnier MN Jr. Pathological and prognostic features of uveal melanomas. Can J Ophthalmol 2004; 39(4):343-350.

52. Ericsson C, Seregard S, Bartolazzi A, Levitskaya E, Ferrone S, Kiessling R, Larsson O. Association of HLA class I and class II antigen expression and mortality in uveal melanoma. Invest Ophthalmol Vis Sci 2001; 42(10): 2153-2156.

53. Naus NC, van Drunen E, de Klein A, Luyten GP, Paridaens DA, Alers JC et al. Characterization of complex chromosomal abnormalities in uveal melanoma by fluorescence in situ hybridization, spectral karyotyping, and comparative genomic hybridization. Genes Chromosomes Cancer. 2001; 30(3):267-273.

54. Kujala E, Makitie T, Kivela T. Very long-term prognosis of patients with malignant uveal melanoma. Invest Ophthalmol Vis Sci 2003; 44(11):4651–4659.

55. Singh AD, Borden EC. Metastatic uveal melanoma. Ophthalmol Clin North Am 2005; 18(1):143–50, ix.

56. Salmon RJ, Levy C, Plancher C, Dorval T, Desjardins L, Leyvraz S, Pouillart P, Schlienger P, Servois V, Asselain B. Treatment of liver metastases from uveal melanoma by combined surgery-chemotherapy. Eur J Surg Oncol 1998; 24(2):127-130.

57. Kodjikian L, Grange JD, Rivoire M. Prolonged survival after resection of liver metastases from uveal melanoma and intra-arterial chemotherapy. Graefes Arch Clin Exp Ophthalmol. 2005; 243(6):622-624.

58. Eskelin S, Pyrhönen S, Summanen P, Prause JU, Kivelä T. Screening for metastatic malignant melanoma of the uvea revisited. Cancer 1999; 85(5):1151-1159.

59. Gragoudas ES, Marie LA. Uveal melanoma: proton beam irradiation. Ophthalmol Clin North Am 2005; 18(1):111–8, ix.

60. Damato B, Kacperek A, Chopra M, Campbell IR, Errington RD. Proton beam radiotherapy of choroidal melanoma: the Liverpool–Clatterbridge experience. Int J Radiat Oncol Biol Phys 2005; 62(5):1405–1411.

61. Singh AD, Topham A. Survival rates with uveal melanoma in the United States: 1973–1997. Ophthalmology 2003; 110(5):962–965.

62. Singh AD. Uveal melanoma: implications of tumor doubling time. Ophthalmology 2001; 108(5):829–831.

63. Pach JM, Robertson DM. Metastasis from untreated uveal melanomas. Arch Ophthalmol 1986; 104(11):1624-1625.

64. The Collaborative Ocular Melanoma Study Group. Assessment of metastatic disease status and death in 435 patients with large choroidal melanoma in the Collaborative Ocular Melanoma Study (COMS): COMS report no. 15. Arch Ophthalmol 2001; 119(5):670-676.

65. Gragoudas ES, Egan KM, Seddon JM, Glynn RJ, Walsh SM, Finn SM et al. Survival of patients with metastases from uveal melanoma. Ophthalmology 1991; 98(3):383–389.

66. Seregard S. Conjunctival melanoma. Surv Ophthalmol 1998; 42(4):321–350.

67. Brownstein S. Malignant melanoma of the conjunctiva. Cancer Control 2004; 11(5):310–316.

68. Layton C, Glasson W. Clinical aspects of conjunctival melanoma. Clin Experiment Ophthalmol 2002; 30(2):72–79.

69. Folberg R, McLean IW, Zimmerman LE. Primary acquired melanosis of the conjunctiva. Hum Pathol 1985; 16(2):129–135.

70. Shields JA, Shields CL, Mashayekhi A, Marr BP, Benavides R, Thangappan A, Phan L, Eagle RC Jr. Primary acquired melanosis of the conjunctiva: risks for progression to melanoma in 311 eyes. The 2006 Lorenz E. Zimmerman lecture. Ophthalmology 2008; 115(3):511-519.

71. Shields CL, Fasiuddin AF, Mashayekhi A, Shields JA. Conjunctival nevi: clinical features and natural course in 410 consecutive patients. Arch Ophthalmol 2004; 122(2):167–175.

72. Chalasani R, Giblin M, Conway RM. Role of topical chemotherapy for primary acquired melanosis and malignant melanoma of the conjunctiva and cornea: review of the evidence and recommendations for treatment. Clin Experiment Ophthalmol 2006; 34(7):708–714.

73. Jakobiec FA, Brownstein S, Wilkinson RD, Katzin HM. Adjuvant cryotherapy for focal nodular melanoma of the conjunctiva. Arch Ophthalmol 1982; 100(1):115–118.

74. Aoyagi M, Morishima N, Yoshino Y, Imagawa N, Kiyosawa M, Ito M, et al. Conjunctival malignant melanoma with xeroderma pigmentosum. Ophthalmologica 1993; 206(3): 162-167.

75. Paridaens AD, Minassian DC, McCartney AC, Hungerford JL. Prognostic factors in primary malignant melanoma of the conjunctiva: a clinicopathological study of 256 cases. Br J Ophthalmol 1994; 78(4):252–259.

76. De Potter P, Shields CL, Shields JA, Menduke H. Clinical predictive factors for development of recurrence and metastasis in conjunctival melanoma: a review of 68 cases. Br J Ophthalmol 1993; 77(10):624–630.

77. Shields JA, Shields CL, De Potter P. Surgical management of conjunctival tumors. The 1994 Lynn B. McMahan Lecture. Arch Ophthalmol 1997; 115(6):808–815.

78. Baroody M, Holds JB, Kokoska MS, Boyd J. Conjunctival melanoma metastasis diagnosed by sentinel lymph node biopsy. Am J Ophthalmol 2004; 137(6):1147–1149.

79.   Esmaeli B, Reifler D, Prieto VG, Amir AM, Hidaji L, Delpassand E et al. Conjunctival melanoma with a positive sentinel lymph node. Arch Ophthalmol 2003; 121(12):1779–1783.

80.   Esmaeli B, Eicher S, Popp J, Delpassand E, Prieto VG, Gershenwald JE. Sentinel lymph node biopsy for conjunctival melanoma. Ophthal Plast Reconstr Surg 2001; 17(6):436–442.

81.   Paridaens AD, McCartney AC, Minassian DC, Hungerford JL. Orbital exenteration in 95 cases of primary conjunctival malignant melanoma. Br J Ophthalmol 1994; 78(7):520–528.

82.   Kurli M, Finger PT. Topical mitomycin chemotherapy for conjunctival malignant melanoma and primary acquired melanosis with atypia: 12 years' experience. Graefes Arch Clin Exp Ophthalmol 2005; 243(11):1108–1114.

83.   Stannard CE, Sealy GR, Hering ER, Pereira SB, Knowles R, Hill JC. Malignant melanoma of the eyelid and palpebral conjunctiva treated with iodine-125 brachytherapy. Ophthalmology 2000; 107(5):951–958.

84.   Shields JA, Shields CL, De Potter P. Surgical management of circumscribed conjunctival melanomas. Ophthal Plast Reconstr Surg 1998; 14(3):208–215.

85.   Brownstein S, Jakobiec FA, Wilkinson RD, Lombardo J, Jackson WB. Cryotherapy for precancerous melanosis (atypical melanocytic hyperplasia) of the conjunctiva. Arch Ophthalmol 1981; 99(7):1224–1231.

86.   Jakobiec FA, Rini FJ, Fraunfelder FT, Brownstein S. Cryotherapy for conjunctival primary acquired melanosis and malignant melanoma. Experience with 62 cases. Ophthalmology 1988; 95(8):1058–1070.

87.   Shields JA, Shields CL, Gunduz K, Cater J. Clinical features predictive of orbital exenteration for conjunctival melanoma. Ophthal Plast Reconstr Surg 2000; 16(3):173–178.

88.   Lommatzsch PK, Lommatzsch RE, Kirsch I, Fuhrmann P. Therapeutic outcome of patients suffering from malignant melanomas of the conjunctiva. Br J Ophthalmol 1990; 74(10):615–619.

89.   Demirci H, McCormick SA, Finger PT. Topical mitomycin chemotherapy for conjunctival malignant melanoma and primary acquired melanosis with atypia: clinical experience with histopathologic observations. Arch Ophthalmol 2000; 118(7):885–891.

90.   Finger PT, Czechonska G, Liarikos S. Topical mitomycin C chemotherapy for conjunctival melanoma and PAM with atypia. Br J Ophthalmol 1998; 82(5):476–479.

91.   Rodriguez-Ares T, Tourino R, De R, V, Becerra E, Capeans C. Topical mitomycin C in the treatment of pigmented conjunctival lesions. Cornea 2003; 22(2):114–117.

92.   Shields CL, Shields JA, Gunduz K, Cater J, Mercado GV, Gross N et al. Conjunctival melanoma: risk factors for recurrence, exenteration, metastasis, and death in 150 consecutive patients. Arch Ophthalmol 2000; 118(11):1497–1507.

93.   Paridaens D, Beekhuis H, van den Bosch W, Remeyer L, Melles G. Amniotic membrane transplantation in the management of conjunctival melanoma and primary acquired melanosis with atypia. Br J Ophthalmol 2001; 85(6): 658-661.

94. Tatla T, Hungerford J, Plowman N, Ghufoor K, Keene M. Conjunctival melanoma: the role of conservative surgery and radiotherapy in regional metastatic disease. Laryngoscope 2005; 115(5): 817-822.

95. Tuomaala S, Kivela T. Metastatic pattern and survival in disseminated conjunctival melanoma: implications for sentinel lymph node biopsy. Ophthalmology 2004; 111(4):816–821.

96. Chan FM, O'Donnell BA, Whitehead K, Ryman W, Sullivan TJ. Treatment and outcomes of malignant melanoma of the eyelid: a review of 29 cases in Australia. Ophthalmology 2007; 114(1):187-192.

97. Boulos PR, Rubin PA. Cutaneous melanomas of the eyelid. Semin Ophthalmol 2006; 21(3):195-206.

98. Liarikos S, Rapidis AD, Roumeliotis A, Angelopoulos AP. Secondary orbital melanomas: analysis of 15 cases. J Craniomaxillofac Surg 2000; 28(3):148-152.

99. Tellada M, Specht CS, McLean IW, Grossniklaus HE, Zimmerman LE. Primary orbital melanomas. Ophthalmology 1996; 103(6):929-932.

100. Zografos L, Ducrey N, Beati D, Schalenbourg A, Spahn B, Balmer A, Othenin-Girard CB, Chamot L, Egger E. Metastatic melanoma in the eye and orbit. Ophthalmology 2003; 110(11):2245-2256.

101. Brandberg Y, Kock E, Oskar K, af Trampe E, Seregard S. Psychological reactions and quality of life in patients with posterior uveal melanoma treated with ruthenium plaque therapy or enucleation: a one year follow-up study. Eye 2000; 14(Pt 6):839–846.

102. Cruickshanks KJ, Fryback DG, Nondahl DM, Robinson N, Keesey U, Dalton DS et al. Treatment choice and quality of life in patients with choroidal melanoma. Arch Ophthalmol 1999; 117(4):461–467.

103. Melia M, Moy CS, Reynolds SM, Hayman JA, Murray TG, Hovland KR et al. Quality of life after iodine 125 brachytherapy vs enucleation for choroidal melanoma: 5-year results from the Collaborative Ocular Melanoma Study: COMS QOLS Report No. 3. Arch Ophthalmol 2006; 124(2):226–238.

Tables

Table 1. Evidence summary and recommendations for choroidal and conjunctival precursor melanocytic lesions.

Evidence summary	Level	Reference
Choroidal pigmented lesions that display increased tumour thickness (>2mm), orange pigment, visual symptoms, absence of drusen, absence of retinal pigment epithelial changes and close proximity to the optic nerve are at risk of growth. Growth, in turn, is associated with an increased risk of malignant transformation.	II-IV	10,12,13
It is not known whether prompt treatment of indeterminate melanocytic lesions is associated with a better systemic prognosis than delaying treatment until growth is documented.		
Recommendation		
Recently diagnosed small choroidal melanocytic lesions which display any risk factors for growth undergo short interval ophthalmic follow-up with ultrasound and photography. Those lesions which display objective evidence of short term growth be treated and treatment considered for other lesions based on the number of risk factors, potential visual morbidity of the treatment and other patient factors (see *Primary choroidal and ciliary body melanoma*).		
Grade B		
Evidence summary	**Level**	**Reference**
Conjunctival pigmented patches may be PAM with atypia, which has a 13-50% risk of malignant subepithelial invasion.	IV	66,67,69,70, 73
Recommendation		
Conjunctival pigmented patches that arise de novo in adulthood, increase in size, increase in thickness or are found in a danger area (palpebral or forniceal conjunctival, plica semilunaris, caruncle) be excised for histopathologic examination when feasible, otherwise be observed frequently.		
Grade C		

Table 2. Evidence summary and recommendations for choroidal melanoma.

Evidence summary	Level	Reference
Most small choroidal pigmented lesions are benign and do not require specific treatment unless there is documented growth or risk factors for growth are present.	III	10,12-14,22
Xenon and argon arc lasers have superficial penetration and are associated with poor outcomes.	III	14,22,24,25
Transpupillary thermotherapy causes rapid tumour regression with precision of treatment; avoiding ocular irradiation. As primary treatment, compared to plaque brachytherapy, it has a higher recurrence rate and may also cause visual morbidity.	III	3,14,22,23,26-28
Plaque brachytherapy has a similar survival and visual outcome as enucleation for medium-sized tumours. Local control is achieved in 95% of medium-sized tumours. Radiation-induced visual loss commonly occurs, especially when treating tumours involving the optic disc or macula. Large tumours are a relative contraindication owing to sight threatening complications of radiation and higher recurrence rate.	II	3,7,9,14,22,23,26,29-31
Proton beam radiotherapy has a similar rate of survival and a slightly better rate of long-term local control compared to brachytherapy, however it causes slightly more anterior segment radiation-induced morbidity. It is useful for tumours with extensive optic nerve involvement, for which treatment with a notched plaque and transpupillary thermotherapy may result in greater visual loss, and for patients with large tumours who are unable or unwilling to pursue enucleation[†].	III	3,5,23,32-35
The majority of medium or large choroidal melanomas invade surrounding ocular structures and are unsuited to local resection. Transscleral resection of choroidal melanoma is associated with an increased risk of local recurrence compared with plaque brachytherapy, but fewer long-term complications and may better preserve vision. Endoresection is possible with a good visual outcome; although survival and recurrence data are limited.	III	3,14,22,23,30,31,37-42
Enucleation alone has a similar survival and recurrence rate as eye-conserving therapy for large tumours. Pre-enucleation radiotherapy does not provide any additional survival benefit for large tumours.	II	3,5,14,22,43-46

[†] Stereotactic radiosurgery is used as an alternative by some centres.[36]

Recommendations

Periodic observation be undertaken for benign choroidal naevi or small pigmented lesions of low or indeterminate risk of malignancy.
Grade B

Photocoagulation not be used in choroidal melanoma as it has a high recurrence rate and low tumour penetration.
Grade C

Transpupillary thermotherapy be recommended as adjuvant treatment for choroidal melanoma treated with radiotherapy. Transpupillary thermotherapy may be used as a sole therapy for select cases of choroidal melanoma or indeterminate lesions. Relative indications include small, heavily pigmented lesions in the extramacular posterior pole not touching the optic nerve head with minimal fluid, or recurrent lesions after radiation.
Grade B

Plaque brachytherapy be the first line treatment for most small and medium-sized choroidal melanoma, ciliary body tumours, tumours in monocular patients and mild cases of extraocular extension. Tumours encroaching the macula or optic disc can be treated with notched or eccentrically-placed plaques.
Grade B

Proton beam radiotherapy be recommended as a suitable alternative to plaque brachytherapy with similar tumour control and ocular morbidity outcome.
Grade C

Local transscleral resection is not recommended for most cases of choroidal melanoma, owing to a high rate of involvement of adjacent ocular structures. It is reserved for medium- or large-sized, anterior uveal tumours for which enucleation or radiation are undesired or contraindicated. It can be used as a second line treatment for recurrence after radiotherapy to salvage the eye.
Transscleral resection is a primary treatment for ciliary body and iris melanoma.
Grade C

Enucleation is recommended for large tumours, tumours invading ocular structures and the optic nerve, and eyes with poor visual prognosis.

Table 3. Evidence summary and recommendations for conjunctival melanoma

Evidence summary	Level	Reference
Conjunctival resection with wide margins[†] and alcohol corneal epitheliectomy[‡] provides local control of conjunctival tumours, with a 50% recurrence rate at ten years.	IV	77,81,84
Intra-operative cryotherapy[§] applied to the margins of resection reduces the rate of recurrence, however evidence does not support its role as a primary, secondary or adjuvant modality.	IV	73,76,85,86
Exenteration has no advantage over local resection in terms of rate of recurrence, metastasis and tumour-related death.	IV	81,87
Conventional radiotherapy is inferior to surgery for primary control of conjunctival melanoma, and should be reserved for eyes in which local resection is contra-indicated. Plaque brachytherapy has some benefit in the adjuvant setting and in treating recurrent tumours, however radiation-induced complications may result in visual reduction.	IV	68,83,88
Topical mitomycin C has a poor rate of local control as a primary treatment, and has not been shown to offer additional benefit as an adjuvant treatment[¶].	IV	72,89-91

[†]5mm margins are ideal, but in practice are rarely achievable in order to preserve ocular function.

[‡]Absolute alcohol epitheliectomy is a well-accepted and effective technique to destroy corneal atypical melanocytes before the tumour is excised.[77]

[§]Applied using a double freeze-thaw technique.[73,85,86]

[¶]Topical mitomycin C is occasionally used adjuvantly for incompletely excised tumours, after cryotherapy is given intra-operatively. The evidence for this is anecdotal. There is better evidence to support the use of topical mitomycin C for the management of widespread primary acquired melanosis with atypia.

Recommendations

Conjunctival resection be the first line management for conjunctival melanoma.
Grade C
Cryotherapy be performed using the double freeze-thaw technique on the under surface of conjunctival margins immediately after resection.
Grade C
Exenteration be reserved for unsightly, painful tumours for palliative purposes, and that eyelid sparing technique be used when possible, for better cosmesis.
Grade C
Radiotherapy be reserved for eyes in which local resection is contra-indicated, and for some recurrent tumours. Its role in the adjuvant setting be investigated further.
Grade C
Topical mitomycin C be reserved for select cases of conjunctival melanoma and for the treatment of primary acquired melanosis with atypia.
Grade C

Table 4. Evidence summary and recommendation for follow up of conjunctival melanoma.

Evidence summary	Level	Reference
Conjunctival melanoma has a high rate of primary recurrence and development of new ocular lesions. Distant metastases can occur years after local eradication of the primary tumour.	IV	66–68,76,86
Recommendation		
Conjunctival melanoma patients be followed up for life.		
Grade D		

Table 5. Evidence summary and recommendations for eyelid melanoma, orbital melanoma and psychological aspects of ocular melanoma.

Evidence summary	Level	Reference
Eyelid melanoma has a similar pathology, clinical presentation and prognosis to cutaneous melanoma and is managed in a similar way, noting special anatomical considerations.	IV	5,96,97
Recommendation		
Complete surgical excision and margin control with mapped serial excision or a modified Mohs' micrographic surgery be performed.		
Grade D		
Evidence summary	**Level**	**Reference**
Orbital melanoma typically represents local extention of uveal melanoma or metastasis from a distant site. Median survival ranges from six to 16 months.	IV	5,98,99
Recommendation		
A palliative approach be taken, with surgical resection offered when appropriate.		
Grade D		
Evidence summary	**Level**	**Reference**
Enucleation is probably associated with a higher rate of anxiety and poorer peripheral visual function than plaque brachytherapy for medium-sized choroidal melanoma.	III	3,14,101-103
Recommendation		
Patients receive appropriate counselling and be given adequate information to decide on their own management plan.		
Grade D		