# Clinical Atlas of Ocular Oncology

# Bertil E. Damato



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Dedicated to my wife, Frankanne, who made this atlas possible.

Bertil E. Damato

## Preface

When attempting to diagnose an ocular tumour, it can be difficult to find the relevant information in conventional atlases because these tend to order lesions according to diagnosis, which is just what is not known. Such atlases are designed mostly to prepare the reader for any future diagnostic conundrum and then, at the time of need, to help address the question, "Is this tumour what I think it is?".

I have therefore prepared this atlas, which organises tumours according to their colour and location in the eye so that readers without prior knowledge can quickly zoom in to the relevant section when asking themselves, "What could this lesion possibly be?"

This atlas should also serve as a teaching aid for trainees in ocular oncology and ophthalmology by presenting conditions in a seemingly random order, enabling self-assessment if the reader attempts to diagnose lesions from the images before reading the legends. Some repetition is unavoidable; however, trainees should find it useful to see subtle variations of the same tumour type.

This atlas is far from encyclopaedic, because of the vast number of tumours and variations. Furthermore, the range of clinical features is growing as new imaging tools are developed. This atlas therefore complements scientific articles, book chapters, and textbooks, including conventional atlases, which should be consulted for further information.

When not confirmed histologically, the diagnosis of several cases in this atlas is debatable. It should be useful for trainees to ponder over cases with an uncertain diagnosis, which reflect real-world difficulties. Even with histology, the diagnosis of a particular tumour can be termed differently by different experts. For example, what is termed 'PAM with atypia' by some is called 'in situ melanoma' by others.

I respectfully disagree with some of the terminology in general use, but I have retained the accepted terms in addition to proposing my preferred nomenclature.

The apparent colour of a tumour varies greatly between cameras. For example, a tumour that appears white with one apparatus can be yellow with another. The Optos camera can make amelanotic tumours appear pigmented. Some colours cannot be readily categorised so that whether a brownish-grey lesion is placed in a 'black-grey' or 'brown-tan' section is to some extent arbitrary.

Not all the cases in this atlas were treated by me. Any treatment selection is described non-judgmentally, respecting differences in opinion. The inclusion of cases from several hospitals serendipitously preserves the confidentiality of the healthcare providers as much as that of the patients. Many patients, some of whom I treated as long ago as the 1980s, would be managed differently today, because of the therapeutic advances that have taken place over the years.

Despite these limitations, I hope that this atlas will enhance the diagnosis of patients with ocular tumours so that individuals with harmless lesions can be spared the stress, expense, and inconvenience of unnecessary care whereas those needing urgent treatment can receive such therapy without delay.

Oxford and London, UK

Bertil E. Damato

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I wish to pay tribute to the colleagues I am privileged to have worked with at the Tennent Institute of Ophthalmology in Glasgow, Scotland (1980–1992); the Royal Liverpool University Hospital, England (1993–2013); the University of California San Francisco, USA (2013–2018); Oxford Eye Hospital, UK (2018–2021); Moorfields Eye Hospital, London (2018–); and the Nuffield Laboratory of Ophthalmology, Department of Clinical Neurosciences, University of Oxford (2018–).

I am grateful to Sonia Callejo, Guy Negretti, Roderick O'Day, Hibba Quhill, and Theodora Gkika for reviewing drafts of this manuscript. Not least, I would like to thank all the photographers and ultrasonographers who have obtained the images included in this atlas.

Finally, I am grateful to the staff at Springer for their expertise and effort in producing this atlas.

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### **Extraocular Lesions**

#### 1.1 Introduction

Extraocular tumours and pseudotumours include conjunctival and subconjunctival lesions, which can be categorised as congenital, inflammatory, neoplastic, traumatic, degenerative and idiopathic. Table 1.1 lists some of the more common conditions.

Systematic examination should include inspection of the facies, eyelids, tarsal conjunctiva, caruncle, plica, bulbar conjunctiva, cornea, episclera, sclera, as well as slit-lamp examination of the anterior chamber and ophthalmoscopy. It is important to examine the entire conjunctiva, including the fornices, by double-everting the eyelids or, less painfully, by gently pinching the eyelid skin and pulling the eyelid away from the globe while inspecting the area with a torch and loupe (or with a head-mounted binocular indirect ophthalmoscope using the 20D lens for magnification). The regional lymph nodes must also be palpated in all patients with conjunctival malignancy.

The following features should be documented: tumour location, colour, structure, dimensions and extent, as well as any effects on adjacent healthy tissues and any coexisting morbidity (Table 1.2). The author has designed a template for preparation of diagrams (Fig. 1.1). Imaging is useful for planning management and for surveillance and can include methods such as colour photography, optical coherence tomography and high-frequency ultrasonography. Depending on the suspected diagnosis, systemic investigations may be indicated to detect or exclude metastatic disease or an occult primary tumour.

In many cases, biopsy is required to establish the diagnosis, using methods such as incisional or excisional biopsy. Biopsy is also useful for distinguishing in situ from invasive tumours. As a rule, nodular tumours should be sampled by excisional biopsy, using a no-touch technique, a dry field, and fresh instruments for wound closure to prevent iatrogenic seeding of malignant cells to other parts of the conjunctiva and into the nasolacrimal system. Incisional biopsy is reserved for tumours that are too extensive for *en bloc* excision (e.g. conjunctival lymphomas) and for



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Congenital/	
developmental	
Hereditary	Hereditary benign intraepithelial dyskeratosis
Non-hereditary	Simple/complex choristomas (i.e., epibulbar dermoid, osseous choristoma, dermolipoma) Congenital ocular melanocytosis
Inflammatory	
Infectious	Tuberculosis Syphilis
Non-infectious	Sarcoid Juvenile xanthogranuloma
Neoplastic	
Benign	Conjunctival melanocytic naevus Conjunctival squamous papilloma Oncocytoma Conjunctival melanocytic intraepithelial neoplasia (CMIN) <sup>a</sup> without atypia Reactive lymphoid hyperplasia
Pre-malignant	Conjunctival melanocytic intraepithelial neoplasia (CMIN) with atypia Actinic keratosis Conjunctival squamous intraepithelial neoplasia (CSqIN) <sup>b</sup>
Malignant	J. J. M. J. M. M. L. M. M. L. M. M. C. M. J.
Primary	Melanoma Conjunctival squamous cell carcinoma Sebaceous carcinoma Lymphoma Kaposi sarcoma
Secondary	Intraocular tumours (e.g. melanoma, lymphoma) Orbital tumours (e.g. lymphoma) Eyelid tumours (e.g. sebaceous gland carcinoma)
Metastatic	Carcinoma (e.g. breast, lung) Sarcoma
Traumatic	Implantation cyst Foreign body granuloma Pyogenic granuloma
Degenerative	Pingueculum/pterygium Band keratopathy Retention lacrimal cyst (dacryops)
Idiopathic	Lymphangiectatic cyst

Table 1.1 Extraocular tumours and pseudotumours

<sup>a</sup>Widely termed 'primary acquired melanosis [PAM]'

<sup>b</sup>Generally termed *ocular surface squamous neoplasia* (OSSN) or *conjunctival/corneal intraepithelial neoplasia* (CCIN)

diffuse lesions such as primary acquired melanosis. Some favour imprint cytology even though this provides less information. It is important to liaise with the laboratory team to ensure that the specimen is placed in the correct transport medium and that it reaches the laboratory in a timely manner so that it is adequate for light microscopy with a variety of stains, immunohistochemistry and genetic studies (e.g. BRAF). Care should be taken to avoid crush artefact and scrolling of the specimen and to provide information that would enable the pathologist to orientate the specimen (e.g. by indicating the corneal edge of the specimen). 
 Table 1.2
 Documentation of conjunctival tumours

Tumour features

Eye (left, right) Suspected diagnosis (e.g. melanoma, squamous cell carcinoma) Tissue (e.g. conjunctiva, episclera, sclera) Shape (e.g. flat, dome, multinodular, multifocal, papillary) Colour (e.g. black, grey, brown, tan, yellow, white, pink, red, transparent) Vascularity (e.g. present, absent) Keratinisation (e.g. present, absent) Tumour size and extent Posterior margin (e.g. cornea, limbus, bulbar conjunctiva, fornix, plica, caruncle, tarsal conjunctiva) Anterior margin (e.g. cornea, limbus, bulbar conjunctiva, fornix, plica, caruncle, tarsal conjunctiva, evelid skin) Circumferential extent (clock mins) (e.g. 10-30) Caruncle involved (e.g. no, partial, complete) Plica involved (e.g. no, partial, complete) Longitudinal diameter (mm) Transverse diameter (mm) Thickness (mm) Lymph node involvement (yes, no; if yes, specify location(s)) Secondary effects Secondary effects (e.g. feeder vessels, haemorrhage)



Fig. 1.1 Conjunctival templates: (a) right eye; (b) left eye. Unlike some other templates, these display the entire conjunctiva

The author's preferred terminology merits explanation. Conventionally, terms such as 'squamous cell carcinoma' and 'melanoma' imply invasion of the lamina propria unless otherwise specified by qualifiers such as 'in situ' or 'intraepithelial'. The term 'primary acquired melanosis (PAM)' is widely used to describe histological findings but is imprecise because it does not distinguish between hyper-melanosis (i.e. increased melanin production by a normal melanocytic population) and melanocytic neoplasia. The author therefore recommends restricting 'PAM' to increased conjunctival pigmentation on slit-lamp examination, with such melanosis not being present congenitally and not secondary to topical medications or systemic disease. Similarly, the term 'conjunctival and corneal intraepithelial neoplasia (CCIN)' does not specify the type of cell that is neoplastic and 'ocular surface squamous neoplasia (OSSN)' is inappropriate for non-bulbar squamous neoplasia. The author prefers 'squamous intraepithelial neoplasia (SIN)', specifying the location separately (i.e. conjunctival, corneal, tarsal).

As with other cancers, malignant conjunctival tumours should, if possible, be staged according to the latest Cancer Staging Manual of the American Joint Committee on Cancer (AJCC).

#### 1.2 Black–Grey Conjunctival Lesions

Most black/grey extraocular lesions are melanocytic proliferations, comprising congenital ocular melanocytosis, naevus, melanoma, and primary acquired melanosis, but pigmented squamous neoplasms and scleral atrophy should also be considered (Figs. 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 1.10, 1.11, 1.12, 1.13, 1.14, 1.15, 1.16, 1.17, 1.18, 1.19, 1.20, 1.21, 1.22, 1.23, 1.24, 1.25, 1.26, 1.27, 1.28, 1.29, 1.30, 1.31, 1.32, 1.33, 1.34, 1.35, 1.36, and 1.37).

**Fig. 1.2** Conjunctival naevus (histologically proven) in a 27-year-old man. The ubiquity of high-quality digital photography in the general population has enhanced scope for self-monitoring of such lesions



Fig. 1.3 Conjunctival naevus in a 91-year-old woman of Asian origin. There is also an area of faint complexionassociated melanosis superiorly





**Fig. 1.4** Conjunctival melanoma at the temporal limbus of the left eye in a 69-year-old man. Note the large size, the feeder vessel and the extensive conjunctival melanosis. Histology showed an invasive nodular melanoma and conjunctival melanocytic intraepithelial neoplasia (CMIN) with severe atypia [also known as 'primary acquired melanosis (PAM) with atypia']. The author's preferred treatment is tumour excision with adjunctive brachytherapy and topical mitomycin-C chemotherapy

**Fig. 1.5** Dome-shaped, deeply pigmented, limbal conjunctival melanoma in a 79-year-old woman, who noticed the lesion 5 months previously. Note the adjacent primary acquired melanosis and the feeder vessels



**Fig. 1.6** Extraocular extension of a ciliary body melanoma in an 86-yearold old man. Note the sentinel vessels, which are episcleral





**Fig. 1.7** Deeply pigmented, limbal conjunctival naevus in the left eye of an 18-year-old man. The lesion was present since infancy. Note the absence of feeder vessels and the multiple clear cysts. The tumour was excised, using the no-touch technique in case any malignant change had occurred. Enlargement of a naevus during the first three decades of life is common without malignant change

**Fig. 1.8** Nodular conjunctival melanoma arising in an area of primary acquired melanosis in a 69-yearold man



**Fig. 1.9** Deeply pigmented conjunctival squamous intraepithelial neoplasia in a 33-year-old Black man. Note the frothy keratin, with discrete irregular margins, on the surface of the lesion. There is complexion-associated melanosis in the adjacent conjunctiva. (Reprinted with permission from: Damato, B. Ocular Tumours: Diagnosis and Treatment. Butterworth Heinemann, Oxford 2000)





**Fig. 1.10** Pigmented conjunctival squamous intraepithelial neoplasia (carcinoma in situ) in a 49-year-old man of Hispanic origin. The lesion had been noticed 1 year previously and had been misdiagnosed as melanoma. Note the large feeder vessels. Diagnostic clues include the grey keratin on the tumour surface. Treatment was by excision, using the no-touch technique, followed by adjunctive topical 5-fluoro-uracil (5-FU) chemotherapy. Some would prefer interferon drops instead of 5-FU

**Fig. 1.11** Conjunctival naevus with an unusually large cyst in a 11-year-old boy from the Indian subcontinent. Note the absence of feeder vessels. The lesion was excised and found to be a compound naevus





**Fig. 1.12** Nodular conjunctival melanoma involving cornea in a 52-year-old man. The lesion was excised using the no-touch technique, taking care not to perforate Bowman's membrane, which acts as a barrier to intraocular spread of any residual tumour. Once the surgical wound had healed, this was followed by adjunctive proton beam radiotherapy and topical mitomycin-C. Instead of proton beam radiotherapy, other centres may have administered adjunctive brachytherapy, using a strontium, ruthenium or iodine applicator. (From Kao et al. 2016; with permission)



**Fig. 1.13** Conjunctival melanoma in a 39-year-old man from the Indian subcontinent. The lesion had been present since birth, growing slowly over many years, then rapidly over 6 months. The tumour was excised. Histology showed an invasive melanoma with incomplete excision. The patient declined adjunctive therapy and developed a recurrence in the inferior fornix 5 months after the excision. Genetic analysis showed the tumour to have a BRAF mutation, with implications for treatment with a systemic BRAF inhibitor should metastatic disease develop

**Fig. 1.14** Subconjunctival pigmented Axenfeld loop in the right eye of an 11-year-old boy. This is a long-posterior ciliary nerve that exits and re-enters the globe around 3–4 mm from the limbus. Pressure on this loop can cause pain, which is a diagnostic feature. These loops are common but not usually pigmented. They may have a cystic appearance, as in this case. No treatment is indicated



**Fig. 1.15** Subconjunctival pigmented Axenfeld loop in the right eye of a 54-year-old woman. Unlike the lesion in Fig. 1.14, this loop appears solid not cystic



**Fig. 1.16** Subconjunctival foreign body in the right eye of a 77-year-old man, who had previously worked as a coal miner. (Reprinted with permission from: Damato, B. Ocular Tumours: Diagnosis and Treatment. Butterworth Heinemann, Oxford 2000)



**Fig. 1.17** Conjunctival squamous intraepithelial neoplasia in a 36-year-old Black man. Note the large keratin plaque. Excision biopsy excluded deep invasion. There are areas of complexion-associated melanosis elsewhere





**Fig. 1.18** Lightly pigmented, grey/brown, conjunctival squamous intraepithelial neoplasia in a 38-year-old woman of African origin. Note the keratin plaque in the central area of the lesion. Note also the feeder vessels. There is complexion-associated melanosis elsewhere. Histology excluded deep invasion and showed the lesion to be completely excised

**Fig. 1.19** Scleral necrosis after ruthenium plaque radiotherapy for a choroidal melanoma in a 68-year-old woman. This complication occurred because of exposure of irradiated sclera following dehiscence of the conjunctiva after plaque removal



**Fig. 1.20** Conjunctival metastatic melanoma in a 61-year-old man, who had undergone excision of a cutaneous melanoma on the shoulder 14 months previously. The conjunctival tumour had been noticed by the patient only 1 week previously. Despite immunotherapy, the patient subsequently developed metastases elsewhere

#### Fig.

**1.21** Subconjunctival, extraocular extension of a uveal melanoma in an 83-year-old man with a ciliary body melanoma with a basal diameter of 24 mm and a thickness of 13 mm. Note the dilated and tortuous episcleral 'sentinel' vessels, which are almost always present over ciliary body tumours

**Fig. 1.22** Scleral thinning in an 81-year-old woman with rheumatoid arthritis. This lesion shines brightly on transpupillary transillumination







**Fig. 1.23** Scleral necrosis in a 75-year-old woman developing 15 months after ruthenium plaque radiotherapy for a cilio-choroidal melanoma. This complication occurred because of a non-healing conjunctival defect. The eye was enucleated by the attending ophthalmologist because the scleral defect was considered too extensive for a scleral graft

**Fig. 1.24** Nodular, bulbar, conjunctival melanoma overhanging the limbus in a 69-year-old woman. An optometrist had noticed a pigmented lesion 2 years previously. The tumour had a basal diameter of 10 mm and a thickness of 6 mm. Histology showed deep invasion and adjacent conjunctival melanocytic intraepithelial neoplasia with severe cytological atypia

Fig. 1.25 Transparent age-related scleral degeneration in an 89-year-old man







**Fig. 1.26** Congenital ocular melanocytosis in the supero-nasal quadrant of the left eye, with pigmentation of the sclera. The conjunctiva is normal and transparent. Note the melanocytosis in the adjacent sector of the iris





**Fig. 1.27** Extensive congenital ocular melanosis in the right eye of a 35-year-old White man. The pigmentation is most marked in the anterior sclera. The overlying conjunctiva is transparent. (a) Low-magnification photograph, showing pigmentation in all quadrants. (b) Magnified view of the inferior aspect of the globe, showing the slate-grey colour and two pigmented Axenfeld loops. These patients require long-term surveillance because of a risk of uveal melanoma

Fig. 1.28 Plicar naevus in an 8-year-old girl. The lesion was first noticed 3 years previously. Note the smooth surface and the apparent absence of clear cysts (some of which may be revealed by anterior segment optical coherence tomography). Naevi of the non-bulbar conjunctiva are usually excised, by some surgeons at least, because malignant transformation, although rare, is associated with an increased risk of metastasis



Fig. 1.29 Conjunctival melanoma in a 68-year-old man, who noticed the tumour 3 months previously



**Fig. 1.30** Caruncular naevus in a 12-year-old girl. The photograph was e-mailed by the patient's mother following a video consultation with the author. This case shows the high quality of the images that can be obtained with some smart phones



**Fig. 1.31** Caruncular naevus of the right eye, without cysts, in a 42-year-old woman. The lesion was excised because of a history of growth. No malignancy was found



**Fig. 1.32** Oncocytoma of the left caruncle in an 83-year-old woman, which is black because of a haemorrhage into a cystic space. Most oncocytomas are red or tan coloured. The diagnosis was established by excision biopsy, which also excluded malignancy



Fig. 1.33 Caruncular melanoma in a 57-year-old man. Despite successful treatment of this lesion, the patient developed metastatic disease, which was fatal. Note the intrinsic tumour vascularity. (Reprinted with permission from: Damato, B. Ocular Tumours: Diagnosis and Treatment. Butterworth Heinemann, Oxford 2000)

**Fig. 1.34** Primary acquired melanosis of the right inferior fornix





**Fig. 1.35** Palpebral conjunctival naevus with cysts in a 56-year-old man, confirmed by excision biopsy





**Fig. 1.36** Large inferior forniceal conjunctival melanoma in the left eye of a 79-year-old woman, with an adjacent seedling supero-temporal to the main tumour. (**a**) View with eyelid retraction. (**b**) Appearance without eyelid retraction

**Fig. 1.37** Diffuse tarsal conjunctival melanoma in the left eye of a 34-year-old woman. Note the spread across the lid margin to adjacent skin. The patient was treated successfully with proton beam radiotherapy (see Fig. 1.181). (Reprinted with permission from: Damato, B. Ocular Tumours: Diagnosis and Treatment. Butterworth Heinemann, Oxford 2000)



#### 1.3 Brown–Tan Conjunctival Lesions

Apart from some carcinomas, most brown-tan lesions are melanocytic, and these include complexion-associated melanosis, primary acquired melanosis, naevus and melanoma (Figs. 1.38, 1.39, 1.40, 1.41, 1.42, 1.43, 1.44, 1.45, 1.46, 1.47, 1.48, 1.49, 1.50, 1.51, 1.52, 1.53, 1.54, 1.55, 1.56, 1.57, 1.58, 1.59, 1.60, 1.61, 1.62, 1.63, 1.64, 1.65, 1.66, 1.67, 1.68, 1.69, 1.70, 1.71, 1.72, 1.73, 1.74, 1.75, 1.76, 1.77, 1.78, 1.79, 1.80, 1.81, 1.82, 1.83, 1.84, 1.85, 1.86, 1.87, 1.88, and 1.89).

**Fig. 1.38** Conjunctival naevus in the left eye of a 67-year-old woman, confirmed by excision biopsy, which also showed features of a pingueculum in some areas





**Fig. 1.39** Conjunctival melanoma in the left eye of a 47-year-old woman. (**a**) Colour photograph, showing a nodular lesion with adjacent primary acquired melanosis. (**b**) Superior tarsal conjunctiva, with diffuse melanosis, which appeared about 6 years after excision of the limbal tumour. This case shows the importance of lifelong surveillance, with examination of the entire conjunctiva at every visit and palpation of regional lymph nodes

**Fig. 1.40** Amelanotic, bulbar compound naevus in a 15-year-old female, confirmed by excision biopsy. Note the feeder vessels, which can be present in young patients even when the tumour is benign





**Fig. 1.41** Nodular melanoma arising from primary acquired melanosis in a 36-year-old man. The patient had noticed pigmentation in this area at the age of 13 years. Treatment consisted of excision with adjunctive cryotherapy, strontium brachytherapy and mitomycin-C topical chemotherapy. This case shows how a long history does not exclude malignancy

**Fig. 1.42** Conjunctival carcinoma in a 65-year-old man of African origin, who was treated by tumour excision followed by adjunctive strontium brachytherapy. The lesion had been noticed 2 years previously but had not been treated by his ophthalmologist because of a misdiagnosis of pterygium



**Fig. 1.43** Conjunctival squamous intraepithelial neoplasia in an 87-year-old man from the Indian subcontinent, who noticed the lesion almost a year previously. Note the white tumour spreading circumferentially around the peripheral cornea, with a pigmented area medially. Histology showed full-thickness dysplasia amounting to carcinoma in situ





**Fig. 1.44** Temporal bulbar conjunctival melanocytic intraepithelial neoplasia amounting to melanoma in situ in a 28-year-old woman, treated by excision with adjunctive topical mitomycin-C chemotherapy. The lesion had grown slowly since first detected at the age of 10 years. This case shows how a dark complexion and a long history do not exclude malignancy. This case also shows that thickening of the lesion does not necessarily indicate deep invasion into lamina propria

**Fig. 1.45** Temporal bulbar conjunctival naevus, with clear cysts, in the right eye of a 55-year-old woman, who reported recent thickening. Excision biopsy excluded malignancy. The apparent growth was probably the result of enlargement of the cysts



**Fig. 1.46** Enlarging conjunctival naevus in a 14-year-old boy of Indian descent. Note the multiple cysts, filled with clear fluid. Naevi commonly enlarge during the first two decades of life



Fig. 1.47 Conjunctival melanocytic intraepithelial neoplasia with severe atypia in the left eye of a 51-year-old man, who reported growth of the lesion over several years. Note the dilated feeder vessels, which can develop even with tumours that have not invaded the lamina propria. The tear meniscus is yellow because of fluorescein administration just prior to the photography



Fig. 1.48 Corneal and conjunctival squamous intraepithelial neoplasia in the right eye of a 72-yearold woman of Asian descent. The patient's daughter became aware of the lesion 6 months previously but referral had been delayed by the Covid-19 pandemic. Note the thickened tumour, the papillary appearance centrally, the feeder vessels and the tumour pigmentation, consistent with the patient's dark complexion





**Fig. 1.49** Subconjunctival, extraocular extension of a uveal melanoma in the left eye of a 58-yearold man. (a) Slit-lamp view, showing a pigmented nodule with diffuse margins. (b) Fundus photograph, showing a large, medial, cilio-choroidal tumour. The eye was enucleated



**Fig. 1.50** Conjunctival melanoma arising from primary acquired melanosis in a 76-year-old woman. The patient had noticed pigmentation 15 years previously. Her ocular oncologist treated her by excision, cryotherapy and brachytherapy. Several months later, she developed recurrences in the medial bulbar conjunctiva and supero-temporal fornix, which may have been prevented if adjunctive mitomycin-C had been administered in the first instance. Recurrent conjunctival melanoma is associated with an increased mortality