Invasive conjunctival melanoma has an incidence of less than one per million per year [1]. They tend to present in adulthood and the median age at diagnosis is 60 years. A proportion arise from ‘primary acquired melanosis’ (PAM), which histologically corresponds to conjunctival melanocytic intra-epithelial neoplasia (C-MIN) with atypia progressing ultimately to melanoma in situ [2]. Invasive melanomas tend to spread locally and to metastasize both to regional lymph nodes and systemically.

Previously, many patients were treated by primary orbital exenteration [3,4]. The impact of this radical treatment on survival was found to be less than previously believed, so it was generally superseded by local resection. Cryotherapy was popularized by Jakobiec in the 1980s for the treatment of diffuse intra-epithelial disease [5]. Shields et al., advocated cryotherapy as adjuvant therapy after local excision [6]. Topical chemotherapy with mitomycin C was introduced in the 1990s [7,8]. Adjuvant radiotherapy was reported by Treacher Collins as early as 1917, and subsequently by others [9,10]; however, it has not gained widespread popularity.

There is scope for improvement in the treatment of patients with conjunctival melanoma. First, the published literature reports that after treatment of invasive conjunctival melanoma more than 50% of patients develop local tumor recurrence, with 20% eventually requiring orbital exenteration and 20–30% developing fatal metastasis. Our results have improved since we replaced adjuvant cryotherapy with radiotherapy and topical chemotherapy. There is scope for multicenter clinical trials and translational research, but these require consistent staging and grading of disease. We propose that the term ‘primary acquired melanosis’ should only be used clinically, when the histology is not known. We have devised a clinical system for mapping conjunctival melanocytic lesions and a system for scoring the histological grade of atypia of conjunctival melanocytic intra-epithelial neoplasia/melanoma in situ. We anticipate that these measures will improve outcomes after treatment of conjunctival melanoma in situ and invasive melanoma.

Keywords: brachytherapy • conjunctiva • conjunctival melanocytic intra-epithelial neoplasia • cryotherapy • grading • melanoma • melanoma in situ • melanosis • mitomycin C • primary acquired melanosis • staging • treatment

Invasive conjunctival melanomas have an incidence of less than one per million per year [1]. They tend to present in adulthood and the median age at diagnosis is 60 years. A proportion arise from ‘primary acquired melanosis’ (PAM), which histologically corresponds to conjunctival melanocytic intra-epithelial neoplasia (C-MIN) with atypia progressing ultimately to melanoma in situ [2]. Invasive melanomas tend to spread locally and to metastasize both to regional lymph nodes and systemically.

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There is scope for improvement in the treatment of patients with conjunctival melanoma. First, the published literature reports that after ocular treatment more than 50% of patients get local tumor recurrence [11–13]. Second, approximately 20% of patients eventually require orbital exenteration because of local treatment failure [13]. Third, approximately 20–30% of patients develop metastatic disease and there is a possibility that some of this mortality is preventable [12–15]. Many, perhaps most, conjunctival melanomas are initially treated by a general ophthalmologist, who may not be familiar with the correct surgical technique. There is some evidence that such inexpert treatment contributes to morbidity and mortality [16].

Apart from therapeutic failure, there are several shortcomings in the terminology and histopathological assessment of conjunctival melanocytic neoplasia. First, the classification of conjunctival melanocytic lesions is vague (e.g., PAM, which encompasses a wide range of conditions). Second, the histological grading of intra-epithelial melanocytic neoplasia, including melanoma in situ, is imprecise and subjective, suffering therefore from poor reproducibility. Third, the clinical staging of invasive melanoma does not adequately reflect the severity of disease, although this should improve with the seventh edition (2009) of the tumor, node, metastasis (TNM) staging classification of the Union Internationale Contre le Cancer (UICC)/American Joint Committee on Cancer (AJCC) [17].
The aims of this article are to highlight the current weaknesses in nomenclature, grading, staging and treatment of conjunctival melanocytic lesions, and to predict how these problems will be addressed in the next few years.

Invasive conjunctival melanoma

Clinical features

Invasive conjunctival melanomas can be deeply pigmented, lightly pigmented or amelanotic (Figure 1). Their margins can be discrete or diffuse. They may be unifocal or multifocal. Approximately 50% are associated with diffuse C-MIN, consisting of pre-invasive melanoma in situ or, rarely, secondary spread into the epithelium from the underlying invasive tumor, or both [1].

Secondary effects of these tumors include dilated feeder vessels and corneal degenerative changes, if the tumor involves cornea. Approximately 45% of patients with metastatic disease also have regional lymph node metastases [18]. Median times to regional and systemic metastases are approximately 2.3 and 3.4 years, respectively [18].

Risk factors for metastasis include: thickness more than 2 mm, involvement of nonbulbar conjunctiva, caruncular disease, medial tumor location and recurrent tumor [11–13,16,19].

Pathology

Histopathological examination allows assessment of the cell type, deep invasion, intra-epithelial spread and tumor thickness, provided that sections are not cut tangentially. The cell type can be spindle or epithelioid. Staining with Melan-A, HMB-45 and MITF facilitates recognition of melanoma cells, firstly confirming that the tumor is melanocytic and, secondly, enhancing definition of tumor spread. The Ki-67 antibody gives an indication of tumor cell proliferation. Features suggestive of high grade malignancy include a high mitotic rate and lymphatic invasion [19,20].

Conventional treatment

The conventional approach to the treatment of invasive conjunctival melanoma is to excise any nodules en bloc, with a wide safety margin, together with a lamella of superficial sclera if the tumor is adherent to the wall of the eye [6,21]. This dissection may extend to the cornea. The diseased corneal epithelium is removed by debridement (i.e., scraping with a scalpel), this process being facilitated with the application of alcohol to the cornea. Once the tumor has been excised, adjuvant cryotherapy is administered to the deep surface of the adjacent conjunctiva, using a liquid nitrogen or carbon dioxide probe [6]. The defect is either closed by primary intention or patched with an amniotic membrane graft [21]. Fresh instruments are used for wound closure, to prevent iatrogenic tumor seeding. Further treatment is administered only if clinical or...
histological examination indicates extension of the tumor deeply and/or in the adjacent epithelium. Diffuse disease, if unresectable, is treated with adjuvant cryotherapy or topical chemotherapy, using mitomycin C [21]. Several authors have used various kinds of radiotherapy as an adjunct to surgery or for unresectable disease [22–25]. If the disease is too extensive for ocular conservation, then exenteration is performed. A few authors advocate sentinel lymph-node biopsy in high-risk cases [26,27].

Figure 3. Author’s method of treatment of bulbar conjunctival melanoma. Temporal bulbar conjunctival melanoma in the left eye of a 70-year-old man before treatment (A) and 2 years after local excision with cryotherapy, followed by adjuvant ruthenium plaque radiotherapy and topical mitomycin C chemotherapy (B). 4 years after treatment there was no recurrence and the visual acuity was 6/9.

Figure 4. Conjunctival melanoma before and after treatment.
Conjunctival melanocytic intra-epithelial neoplasia

Clinical features

Patients with C-MIN present in adulthood with a unilateral area of conjunctival melanosis (synonymous PAM) (Figure 2) [28,29]. This brown pigmentation is flat and irregular and can occur anywhere in the conjunctival or corneal epithelium. It can be unifocal or multifocal. The mean age at presentation is 56 years [29]. There is a slight preponderance of females [29]. The differential diagnosis of conjunctival melanosis includes: primary acquired melanosis; racial melanosis, which in dark-skinned individuals, mostly occurs in the interpalpebral area; congenital ocular melanocytosis, which is congenital, subconjunctival and slate-grey in colour; and secondary melanosis, caused by local abnormalities, such as cysts and squamous tumors, and systemic diseases, such as Addison’s syndrome and ochronosis. It is helpful to categorize melanosis as: congenital or acquired and primary or secondary.

Pathology

Conventionally, clinical PAM is classified histologically as ‘PAM without atypia’ or ‘PAM with atypia’ [28]. Normally, melanocytes are located only in the basal layer together with basal epithelial cells, which outnumber the melanocytes by approximately 50-to-one. PAM without atypia refers to

Figure 5. Diffuse residual intra-epithelial melanoma after excision and cryotherapy of a temporal bulbar conjunctival melanoma of the left eye of a 59-year-old man before topical chemotherapy with mitomycin C (A) and 2 years afterwards (B). 6 years after treatment there was no recurrence and the patient had a visual acuity of 6/9.

Figure 6. Limbal conjunctival melanoma in the left eye of an 80-year-old man before treatment with ruthenium plaque radiotherapy and topical chemotherapy (A) and 4 months afterwards (B). 2 years later, the patient died of unrelated disease without local tumor recurrence.
increased cytoplasmic melanin deposition and/or an increased density of melanocytes, these being confined to the basal layer of the epithelium and not showing any cellular atypia. With so-called PAM with atypia, the melanocytes show cellular atypia (i.e., large nucleus, prominent nucleolus and abundant cytoplasm), forming nests and also invading the more superficial layers of the epithelium and increasing in density until they may eventually replace the entire epithelium. Epithelioid melanocytic cytormophology and vertical invasion of epithelium are both associated with increased risk of invasive melanoma \[29-31\]. However, the term conjunctival ‘melanoma in situ’ is discouraged by some opinion leaders because of concerns that this might alarm patients \[29\].

Management

The main objective is to prevent invasive melanoma. There is a tendency to observe small lesions and to treat more extensive disease \[29\]. Some advocate excision and cryotherapy for larger lesions, which are associated with greater risk \[29\]. An amnion membrane or buccal mucosal graft is used after extensive excision \[29\]. Diseased corneal epithelium is scraped away with a scalpel, after devitalization with topical alcohol \[29\]. Residual disease is treated with cryotherapy and/or topical chemotherapy with mitomycin C drops \[29\]. Primary treatment with topical chemotherapy is gaining in popularity, but information on long-term outcomes is limited \[32\]. There is a lack of consensus regarding which patients should be treated, what concentration of mitomycin C should be administered and whether or not the puncta should be occluded with plugs to prevent canalicul stenosis and a watery eye. After treatment of an invasive conjunctival melanoma, any associated intra-epithelial disease needs to be eradicated in order to prevent the formation of another invasive tumor.

Expert commentary

Treatment

When the first author (Bertil Damato) specialized in ocular oncology in 1984, he followed conventional practice, excising any nodular melanoma and administering cryotherapy for superficial disease and to prevent deep recurrences after excision. The recommended cryotherapy protocols were followed, which suggested using a liquid nitrogen cryoprobe and checking the temperature with a thermocouple \[5\]. Nevertheless, the results were disappointing in terms of local tumor control and ocular morbidity.

In 1997, the first author replaced cryotherapy with ruthenium plaque radiotherapy as a method for preventing local recurrence from deep invasion. Initially, a dose of 100 Gy at 2.0 mm was administered, but when excessive vascular closure was noted in the conjunctiva this was reduced to 100 Gy at 1.0 mm. In 1999, cryotherapy for intra-epithelial disease was abandoned in favor of topical chemotherapy with mitomycin C. At first, a concentration of 0.04% was prescribed, but because of local toxicity, including stem cell failure, this was reduced to 0.02% in 2006.

With greater reliance on adjuvant brachytherapy and topical chemotherapy, the first author has altered his local resection technique, with a reduction in ocular morbidity and without any apparent increase in failure of local tumor control. His current practice with bulbar conjunctival melanomas is to perform local excision using a no-touch technique, with minimal lateral clearance and without superficial lamellar sclerectomy (Figure 3). Diathermy is applied to any areas where deep extension of the tumor is suspected. Using a fresh set of instruments, the conjunctiva is undermined as far as the fornices and closed with interrupted, absorbable sutures. If complete closure is not achieved, then the exposed part of the wound is allowed to heal by second intention. Here, 2 weeks postoperatively, once the conjunctiva has healed, adjuvant brachytherapy is administered, by means of a 15 mm ruthenium plaque, which is sutured to the sclera at the limbus. A mattress suture is used to ensure good apposition of the plaque and a bandage lens is inserted to reduce discomfort. A strontium applicator would be preferable, but
Brachytherapy is now administered to all patients with invasive melanoma (Figure 4). This is because histological examination of surgical clearance is considered unreliable, even if performed meticulously. If there is any clinical or histological evidence of intra-epithelial spread, then adjuvant mitomycin C chemotherapy is administered (Figure 5). Patients are reviewed every 6 months for 5 years, then annually. Any areas of recurrent pigmentation are biopsied.

Various modifications have been developed for unusual situations. If the adjuvant radiotherapy cannot be administered with a plaque, then proton- or external-beam radiotherapy is applied. Two patients with unresectable melanoma were treated with brachytherapy and proton-beam radiotherapy respectively, both successfully (Figures 6 & 7). Recurrent intra-epithelial disease is treated with further topical chemotherapy, or by cryotherapy and/or excision if the patient has already received more than one course of chemotherapy.

We have recently audited our results in 40 patients with invasive conjunctival melanoma who were referred to our hospital without prior surgical intervention (Figure 8) [16]. In total, three of these patients had multiple tumors and 20 had invasive melanoma and diffuse intra-epithelial disease. Invasive recurrence occurred in five out of 21 patients who were treated without adjuvant radiotherapy. By contrast, only one out of 19 patients with adjuvant radiotherapy developed a recurrence and this was located outside the irradiated field. None of these patients required exenteration. In total, four patients died of metastatic disease. Two of these fatal cases had recurrent disease and all showed caruncular involvement with tumor. In total 36 additional patients were referred for salvage therapy after treatment elsewhere (Figure 8). Here, 11 had no apparent residual disease; nine showed only intra-epithelial disease and 16 had invasive melanoma, with superficial spread in six patients. Several had iatrogenic ocular morbidity. One of these 36 patients eventually required exenteration. Metastatic disease occurred in five patients, all of whom were referred with recurrent, invasive melanoma. Interestingly the original melanomas of four of these patients apparently had only bulbar conjunctival involvement so they should have had a good prognosis [16].

The treatment of conjunctival melanomas is based on poor-quality evidence, consisting of case series from single institutions serving to promote the biases and beliefs of those centers (as indeed is the case with this article). As a result, there are many unanswered questions. Should adjuvant brachytherapy be
administered when histological examination indicates adequate surgical clearance? Should patients with so-called 'PAM with mild atypia' be observed or treated? What concentration of mitomycin C should be used? Is sentinel lymph node biopsy beneficial? Ideally, these questions should be addressed by multicenter, randomized, prospective studies. If randomization is not possible, then there is scope for merging outcomes data from several centers. Such multicenter collaboration is handicapped by vague terminology and inadequate documentation of the stage and grade of baseline disease, limitations that we have attempted to rectify.

Terminology & grading of melanocytic intra-epithelial neoplasia

The term 'PAM' is excessively vague. We have therefore proposed that histological terminology be revised to differentiate conjunctival hypermelanosis (i.e., without melanocytic proliferation) from C-MIN, the latter described as being either without atypia or with atypia [2]. We consider some stages of C-MIN with atypia to be analogous to melanoma in situ of skin and mucous membranes and, therefore, concur with the opinions of authors such as Ackermann et al [33]. Questioning of several patients with this condition has informed us that patients prefer to know the truth regarding their condition and are not unduly alarmed by the term melanoma in situ as long as it is explained to them that the threat to life is low in the absence of invasive disease. We suggest that PAM be used only as a clinical term, when the histology is not known.

Melanocytic intra-epithelial neoplasia with atypia tends to be described as 'mild', 'moderate' and 'severe'. We consider such terms to be imprecise and subjective, so that the same condition might be graded inconsistently by different pathologists or by the same pathologist on different occasions. Furthermore, the term mild may give a false sense of security so that the patient may receive inadequate care. We have devised a system for scoring the grade of atypia of C-MIN (Figure 9) [2]. This is based on the degree of cellular atypia, the density of melanocytic cells and the extent of epithelial invasion (Figure 10). Independent scoring of 40 specimens by three pathologists showed high degrees of repeatability (Coupland SE et al., Unpublished Data). By encouraging objectivity, our scoring system should enhance the surveillance of patients undergoing sequential biopsy of C-MIN, both in untreated cases and those who have had topical chemotherapy or cryotherapy. This scoring system should also be useful in multicenter studies, improving standardization.

We believe that all grades of atypia form part of the same spectrum of disease, ultimately resulting in melanoma in situ. We are aware, however, that this is a controversial topic because of concerns that patients with minimal disease might receive over-zealous treatment, thereby suffering unnecessary ocular morbidity. Our histological studies reveal a natural break between C-MIN scores, suggesting that it would be reasonable to label cases with a score less than five as C-MIN with atypia and those with a score greater than four as melanoma in situ. This categorization is in-keeping with previous studies reporting the incidence of invasive melanoma (presumably despite treatment) in patients with epithelioid morphology of melanocytes and vertical spread into the superficial layers of the epithelium (see previous). Despite initial resistance, we succeeded in incorporating the concept and category of conjunctival melanoma in situ into the seventh edition of the pathological TNM staging system (Box 1) [17].

Clinical mapping of conjunctival melanocytic neoplasia

At present, there is a lack of standardization in the way that clinical findings are documented. Some drawings fail to display the entire conjunctiva, because the eyes are drawn in a life-like fashion. We have devised a drawing that shows the entire conjunctiva which is divided into radial sectors and concentric regions (i.e., cornea, limbus, bulbar conjunctiva, fornix/plica, tarsal conjunctiva/caruncle and lid margin) [1]. The center of the cornea is regarded as being the most 'posterior' point, with the lid margins comprising the anterior limits. We have also developed a system that maps all lesions according to their

Box 2. Clinical tumor, node, metastasis staging of conjunctival melanoma.

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Regional lymph node (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumor (T)</td>
<td>TX: primary tumor cannot be assessed</td>
</tr>
<tr>
<td></td>
<td>T0: no evidence of primary tumor</td>
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<tr>
<td></td>
<td>T(is): melanoma confined to the conjunctival epithelium</td>
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<tr>
<td></td>
<td>T1a: ≤ 1 quadrant</td>
</tr>
<tr>
<td></td>
<td>T1b: &gt; 1 but ≤ 2 quadrants</td>
</tr>
<tr>
<td></td>
<td>T1c: &gt; 2 but ≤ 3 quadrants</td>
</tr>
<tr>
<td></td>
<td>T1d: &gt; 3 quadrants</td>
</tr>
<tr>
<td></td>
<td>T2: melanoma involving nonbulbar conjunctiva (palpebral, forniceal caruncular)</td>
</tr>
<tr>
<td></td>
<td>T2a: noncaruncular, ≤ 1 quadrant</td>
</tr>
<tr>
<td></td>
<td>T2b: noncaruncular, &gt; 1 quadrant</td>
</tr>
<tr>
<td></td>
<td>T2c: any caruncular, ≤ 1 quadrant</td>
</tr>
<tr>
<td></td>
<td>T2d: any caruncular, &gt; 1 quadrant</td>
</tr>
<tr>
<td></td>
<td>T3: melanoma invading nonconjunctival tissues</td>
</tr>
<tr>
<td></td>
<td>T3a: globe</td>
</tr>
<tr>
<td></td>
<td>T3b: eyelid</td>
</tr>
<tr>
<td></td>
<td>T3c: orbit</td>
</tr>
<tr>
<td></td>
<td>T3d: sinus</td>
</tr>
<tr>
<td></td>
<td>T4: melanoma invading CNS</td>
</tr>
<tr>
<td></td>
<td>NX: regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>Metastasis (M)</td>
<td>pN0: no regional lymph node metastasis, biopsy performed</td>
</tr>
<tr>
<td></td>
<td>cN0: no regional lymph node metastasis, biopsy not performed</td>
</tr>
<tr>
<td>Stage grouping</td>
<td>N1: regional lymph node metastasis</td>
</tr>
</tbody>
</table>

| Stage grouping | No stage grouping is presently recommended |

*Quadrants are defined by clock hour, starting at the limbus (e.g., 3, 6, 9, 12) extending from the central cornea, to and beyond the eyelid margins. This will bisect the caruncle.

7th Edition condensed by the authors [17].
postero–anterior extent and circumferential spread (in clock minutes) in each conjunctival region. A proforma has been designed for documentation of clinical findings [1].

Data on 76 patients were entered into a customized database and categorized with a statistical program so that cumulative plots could be generated using Excel (Microsoft) (Figure 10) [1]. These plots showed visually that involvement of medial conjunctiva correlated with local tumor recurrence and metastasis (Figure 11) [1].

**Clinical TNM staging of conjunctival melanoma**

Our study of 40 patients with invasive melanoma revealed a number of shortcomings in the sixth edition of the TNM staging of conjunctival melanomas [34]. First, this classification did not take account of coronal tumor location and particularly caruncular involvement, which correlate with survival. Second, it placed eyelid and brain involvement in the same category, even though intracranial spread is likely to represent more advanced disease and worse prognosis. Third, it did not consider basal tumor diameter, even though tumor size is probably of prognostic significance. Fourth, tumors with corneal involvement were given a worse grade than those confined to bulbar conjunctiva, even though the cornea, being devoid of lymphatics, is unlikely to be associated with a worse mortality. These errors have been rectified in the seventh edition of the staging, partly as a result of our study (Box 2) [17]. Some might criticize the omission of tumor thickness as a risk factor. However, first, this seems relevant only with tumors involving the nonbulbar conjunctiva, where clinical measurement with high-frequency echography is difficult, and, second, this information is provided in the pathological TNM section documenting histological measurements, which is more reliable. Further studies are required in order to correlate TNM staging with long-term survival.

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**Figure 8. Scoring system for conjunctival melanocytic intra-epithelial neoplasia, based on growth pattern, vertical intra-epithelial spread and melanocytic atypia.** The maximum score is 10.

sq.: Squamous.
Figure 9. Proforma for scoring conjunctival melanocytic intra-epithelial neoplasia.
Figure 10. Mapping of conjunctival melanomas referred to our center without prior treatment (A) and after previous surgical intervention elsewhere (B).
Reproduced with permission from [16].
**Translational research**

Why does more advanced TNM stage correlate with higher mortality? Is it because delay in treatment worsens prognosis or because TNM staging reflects more aggressive disease? Why are medial conjunctival melanomas associated with higher rates of metastasis? Is it because they are histologically and genetically distinct from temporal tumors or because the tissues in which they arise are different, for example, having higher vascular and lymphatic densities? We have investigated chromosomal abnormalities in conjunctival melanoma using a technique known as multiplex ligation-dependent probe amplification \[35\]. Our initial results indicate that these tumors show peculiar chromosomal abnormalities, particularly gains in chromosomes 7p and 12p and losses in chromosome 4q \[Lake S et al., Unpublished Data\]. How do these findings correlate with survival? Might genomic tumor typing be as useful for prognostication as it is with uveal melanomas? Translational studies such as this are required, but these depend on multicenter collaboration, long-term outcome data and adequate staging and grading of baseline disease.

**Five-year view**

We believe that in the next 5 years, the following changes will occur in the management of patients with conjunctival melanoma:

- More centers will treat invasive melanoma with adjuvant brachytherapy instead of cryotherapy, making it unnecessary to perform superficial lamellar sclerectomy. Adjuvant topical chemotherapy will reduce the need for wide excision margins;
- More centers will administer adjuvant radiotherapy to all patients with invasive melanoma, that is, even when histological examination suggests that deep clearance has been achieved;

**Figure 11.** Maps of (A) 40 conjunctival melanomas first treated at our center and (B) 36 eyes referred after treatment of conjunctival melanoma elsewhere. These show location and extent of disease. Each spot represents involvement of a sector of conjunctiva and not a separate tumor. See side of caruncle to determine whether left or right eye is involved. Reproduced with permission from \[16\].

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**Conjunctival melanoma & melanosis**

Translational research

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• Patients with involvement of medial and nonbulbar conjunctiva will be treated more aggressively, in view of the increased risk of local tumor recurrence and metastasis;
• The term PAM will be used only by ophthalmologists and then only when the histology is not yet known. Pathologists will no longer use PAM for histological conjunctival melanocytosis, which will be termed C-MIN to distinguish this condition from increased melanin deposition in the cytoplasm of conjunctival epithelial cells;
• C-MIN with atypia will no longer be labeled as mild, moderate and severe, but will be scored according to the severity of epithelial invasion, melanocytic density and cellular atypia. Disease with a score greater than four will be regarded as melanoma in situ and will be treated as malignant preinvasive disease;
• Patients referred to an oncology center only after their tumor has been excised will be regarded as having a high risk of multicentric tumor recurrence and will be more likely to receive prophylactic topical chemotherapy and radiotherapy;
• Multicenter studies will probably be in progress to evaluate the indications for adjuvant radiotherapy after apparently complete local excision of invasive melanoma. Patients with C-MIN scores less than five will be entered into clinical trials randomizing between treatment and observation. These studies will incorporate translational research correlating clinical disease with histological findings and cytogenetics, possibly identifying prognostic markers as found in uveal melanomas.

Financial & competing interests disclosure
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Key issues
• Invasive conjunctival melanomas arise from melanoma in situ, from a nevus or de novo. They can invade the eye, eyelids, orbit, sinuses, nasolacrimal duct and brain, as well as metastasize to regional lymph nodes and systemically.
• Local excision of invasive conjunctival melanoma is followed by high rates of local tumor recurrence, indicating that histological assessment of surgical clearance is unreliable and/or adjuvant cryotherapy is insufficient.
• Local tumor recurrence is associated with increased risks of uncontrollable disease, exenteration and metastatic death.
• Local tumor recurrence is rare in areas treated by adjuvant radiotherapy.
• The term ‘primary acquired melanosis’ is imprecise, encompassing increased melanin production and deposition without melanocytosis and various grades of conjunctival melanocytic intra-epithelial neoplasia (C-MIN) ranging from mild melanocytosis without atypia to advanced melanoma in situ.
• We have developed a system for scoring the grade of C-MIN with atypical/in situ melanoma and this should replace vague descriptors, such as ‘mild’, ‘moderate’ and ‘severe’, making histological reporting more objective and better standardized.
• The TNM system for staging conjunctival melanoma has recently been revised to take account of coronal tumor location, caruncular involvement and basal tumor diameter in terms of circumferential spread. Melanoma in situ has now been added to pathological TNM in the 7th edition.
• Multicenter studies are needed to evaluate systems for scoring C-MIN and staging invasive melanoma. Further studies are indicated to improve rates of local tumor control in patients with invasive melanoma and to determine which patients with C-MIN require treatment.

References
Papers of special note have been highlighted as:
• of interest
•• of considerable interest
•• Overview of the subject, including a novel method of grading conjunctival melanocytic intra-epithelial neoplasia (C-MIN).
•• Description of the most widely-used method of treating conjunctival melanoma.
Conjunctival melanoma & melanosis


Large study on risk factors.


Recent study correlating histological features of C-MIN with risk of invasive melanoma.


An argument in favor of considering C-MIN to be regarded as melanoma in situ.


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Report on outcomes after treatment of conjunctival melanoma.


Report on outcomes after treatment of conjunctival melanoma.


Large study reporting outcomes after treatment of conjunctival melanoma.


Study of outcomes after treatment of conjunctival melanoma, with patients treated primarily at an oncology center being distinguished from those referred after treatment elsewhere.


An early study correlating histological features of C-MIN with subsequent development of invasive melanoma.


A large study on C-MIN, correlating histological features with development of invasive melanoma.


An argument in favor of considering C-MIN to be regarded as melanoma in situ.


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