

Management of malignant and benign eyelid lesions

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Purpose of review

The management of benign and malignant eyelid neoplasms has been extensively examined. This paper offers an overview of the most common eyelid lesions and their management based on a review of the relevant bibliography.

Recent findings

Recent studies have focused on the results of nonsurgical approaches for benign and premalignant lesions that are routinely surgically excised. In the malignant group, a consensus has been reached over the preferred method of tumor excision for basal cell carcinoma: Mohs surgery or complete surgical excision with frozen-section control of the margins offers the lowest tumor-recurrence rate. Important acquisitions have been made on squamous cells for which sentinel node biopsy may reveal early metastatic cancer. Intraepithelial tumor growth is a peculiar feature of sebaceous gland carcinoma that seems to indicate an increased risk for orbital invasion. Recent reports regarding the rare tumor, Merkel cell carcinoma, recommend a wide surgical excision with 5 mm margins; this may reduce the incidence of lymph-node metastasis, haematogenous spread and local recurrences.

Summary

Although treatment of the most common benign and malignant tumours affecting the eyelids has not radically changed over the years, recent reports have significantly improved the standard of care for affected patients.

Keywords

benign eyelid lesion, malignant eyelid tumor, medical management, periocular neoplasm, surgical management

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Abbreviation

BCC basal cell carcinoma

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Introduction

A wide variety of lesions can affect the skin in the periocular region and they can be benign, premalignant and malignant. Although only 15–20% of periocular skin lesions will actually be malignant, it can be challenging for the general ophthalmologist to accurately identify and diagnose malignancy. The benign lesions most commonly encountered by the ophthalmologist are chalazia, epidermal inclusion cysts, seborrheic keratoses and apocrine hydrocystomas. The premalignant conditions include actinic keratosis, Bowen's disease and keratoacanthoma. In the malignant group, basal cell carcinomas (BCCs) and squamous cell carcinomas are the most common, whereas sebaceous gland and Merkel cell carcinomas are the most aggressive (Table 1).

Benign tumours

Although the clinical diagnosis of benign eyelid tumour is rather simple in most cases, histopathologic confirmation of the excised lesion is recommended in every case. Kersten *et al.* [1] reported a total 2.3% risk of misdiagnosing a clinically benign lesion with a biopsy-proven malignant or premalignant lesion. Ozdal *et al.* [2] reported a discrepancy between the clinical diagnosis and the histology on a large number of chalazia, with a 1.4% risk of misdiagnosing the chalazion as sebaceous gland tumor (1.1%) or basal cell tumour (0.3%).

Chalazion

A chalazion is a lipogranulomatous inflammation affecting the meibomian glands of the tarsal plate or the glands of Zeis, or both, and it appears as a chronic, localized swelling of the eyelid. The treatment consists of transconjunctival incision with curettage of the lipogranulomatous tissue followed by excision of the surrounding pseudocapsule. Recently, Ben Simon *et al.* [3^{*}] suggested intralesional triamcinolone injection to avoid a surgical procedure. Although this option is interesting, in many cases it requires multiple injections and it carries the potential risk of serious visual complications due to central retinal artery embolization. Corticosteroid injections can be used for long-standing, fibrotic chalazia after resecting part of the lesion for histopathological confirmation.

Epidermal inclusion cyst

These cysts appear as round or oval, dome-shaped lesions filled with keratin, localized superficially under the eyelid skin. Since their natural tendency is to progressively enlarge, complete surgical excision is recommended.

Table 1 Classification of benign and malignant periocular tumors

Benign	Premalignant	Malignant
Chalazion	Actinic keratosis	Basal cell carcinoma
Epidermal inclusion cyst	Bowen's disease	Squamous cell carcinoma
Seborrheic keratosis	Keratoacanthoma	Sebaceous gland carcinoma
Apocrine hydrocystoma		Merkel cell carcinoma

The cyst can be removed with two different modalities: it can be dissected by the surrounding skin and orbicularis muscle, keeping the capsule intact, or it can be marsupialized, decapitating the top half of the cyst and allowing the bottom half to granulate in the defect. Recurrence of the cyst after surgical excision is rare and occurs if cyst material is buried under the skin.

Seborrheic keratosis

Seborrheic keratosis is the most common benign eyelid lesion that affects elderly patients. Seborrheic keratosis has a typical stuck-on appearance with varying degrees of pigmentation and, despite its progressive growth, it remains superficial and can be shaved off at the dermal-epidermal junction, leaving the skin defect granulate. Although Neuhaus *et al.* [4] described a peculiar entity of seborrheic keratosis with basal clear cells that histologically resembles a melanoma *in situ* and some of the pigmented lesions may be clinically confused with lentigo maligna or melanoma, seborrheic keratosis is entirely benign and carries no risks of malignant transformation.

Apocrine hydrocystoma

Apocrine hydrocystomas are cystadenomas that arise from the sweat glands of Moll, associated with a hair follicle along the eyelid margin. A distinctive feature of hydrocystomas, due to the fact that they have a very thin wall and contain clear fluid, is that they transilluminate. Marsupialization of the cyst is curative and recurrence is rare. A nonsurgical option reported by Dailey *et al.* [5] consists of intralesional injection of trichloroacetic acid, especially useful for large or confluent lesions.

Premalignant lesions

Premalignant lesions are not true skin cancer yet, but, if left untreated, can give rise to squamous cell carcinoma; these include actinic keratosis, keratoacanthoma and Bowen's disease.

Actinic keratosis

Actinic keratosis is a common precancerous skin lesion and occurs in the exposed areas (head, neck, arms and dorsum of hands) of older individuals with a fair complexion who have had excessive sun exposure. The lesion appears typically as a round, scaly, hyper-keratotic plaque and on palpation has the texture of sandpaper. The size and

number of keratotic plaques increase and decrease proportionally with the intensity of the sun exposure. The risk of malignant transformation for a given actinic keratosis plaque is only 0.24% per year, but over an extended period of time, a patient with multiple lesions has a 12–16% incidence of squamous cell carcinoma. Spontaneous regression of the actinic keratosis is frequently observed, especially if the patient discontinues the UV exposure; therefore, observation of the keratotic lesions is a reasonable option. Surgical excision is preferable to remove individual keratosis and cryotherapy or imiquimod 5% cream is used when treating multiple lesions or extended areas of affected skin.

Bowen's disease

Bowen's disease refers to squamous cell carcinoma *in situ*, with full-thickness epidermal atypia, but no deeper dermal involvement on histopathology. These lesions appear as elevated, round or oval nonhealing erythematous plaques. Complete surgical excision is advised as Bowen's disease may progress to a vertically invasive squamous cell carcinoma. Patel *et al.* [6**] conducted a randomized study to evaluate the efficacy of imiquimod 5% cream to treat biopsy proven squamous cell carcinoma *in situ* and they achieved 73% of resolution with no relapse during the 9-month follow-up period. Although imiquimod is not approved by the US Food and Drug Administration for the treatment of periocular lesions due to the potential risk of contact with the globe, Brannan *et al.* [7*] described a patient who was cured after completing a 3-month treatment; the lesion disappeared and no recurrence was noted 6 months postoperatively, but the patient developed a cicatricial lower-lid ectropion that required correction with a skin graft. Although imiquimod seems to be effective for the treatment of Bowen's disease, its use in the periocular area is still controversial.

Keratoacanthoma

Keratoacanthoma has been considered benign in the past, but many authors now regard and treat it as a low-grade squamous cell carcinoma. It appears initially as a flesh-colored papule on the lower eyelid and rapidly develops into a dome-shaped nodule with elevated margins and a central crater filled with keratin. Given the potential for spontaneous involution (usually over a 3–6-month period), there is a strong argument for conservative management. Although intralesional chemotherapy, radiotherapy and cryotherapy have all been suggested as useful options, incisional biopsy to confirm the diagnosis followed by complete surgical excision with frozen-section control or Mohs micrographic surgery remains the preferred treatment [8].

Malignant eyelid tumours

The malignant lesions that affect the eyelids are BCC and squamous cell carcinoma and, less often, sebaceous cell and Merkel cell carcinoma. In general terms, since

90% or more of malignant eyelids tumors are represented by BCC, the ophthalmologist should know how to recognize a BCC-suspect lesion at first sight.

Basal cell carcinoma

BCC is the most common of all malignant eyelid tumors, accounting for 90–95% of cases. They occur more frequently on the lower eyelid (50–60%) and at the medial canthus (25–30%) and less frequently on the upper eyelid (15%) and the lateral canthus (5%). Based on their clinical appearance, BCCs are classified as nodular, noduloulcerative and morpheaform; the nodular and noduloulcerative BCCs are more common and they appear as firm, raised, pearly nodules with fine teleangectasias on the borders (nodular) or a central ulceration (noduloulcerative). A less common, but more aggressive BCC is the morpheaform type, which appear as an indurated and slightly elevated lesion with ill-defined borders. More recently, two new clinical entities of BCC have been reported: a nodular form with an infiltrative component that may extend beyond the clinically obvious margins and a linear form that seems to have more aggressive behaviour [9,10]. Mortality rate from ocular BCCs is estimated to be 3% and usually occurs secondarily to intracranial extension of tumors that have been inadequately treated or clinically neglected [11–14]. BCCs arising in the medial canthal region are at particular high risk for intraorbital and intracranial extension.

For the treatment of BCC, many different modalities have been reported and include cryotherapy, radiotherapy and photodynamic therapy, but surgical excision is generally regarded as the definitive method of treatment. Mohs micrographic surgery is considered the gold standard for the complete excision of the tumor because theoretically it preserves the maximal amount of healthy tissue while providing the best assurance of complete cancer removal [15]. This greatly depends on the ability and the experience of the dermatopathologist that performs the Mohs procedure, however, and many surgeons prefer to excise the BCC with clinically free margins (2 mm) and to control the margins histologically with frozen or permanent sections [16]. The recurrence rate for primary BCCs excised with margin control is very low, ranging from 0 to 2% [17,18]. Following the excision of the tumor the eyelid should be reconstructed by standard oculoplastic procedures and should be performed expeditiously. Despite the fact that cryosurgery has been considered suboptimal for the treatment of periocular BCCs in the past, a high success rate, with the recurrence rate near 0% and minimal side effects, has been reported by several authors using a double freeze-and-thaw technique with a standard cryprobe directly applied to the BCC [17,18]. Cryotherapy might be a reasonable choice for the treatment of periocular nodular or noduloulcerative BCC in patients who are poor candidates for surgery.

Squamous cell carcinoma

Although squamous cell carcinoma is less common than BCC, it is biologically more aggressive. It can arise *de novo* or from areas of actinic keratosis, Bowen's disease, keratoacanthoma or radiation dermatosis. Clinically it appears very similar to BCC, and can be difficult to differentiate, but, unlike BCC, squamous cell carcinoma has a potential for metastatic spread through direct extension or indirectly via lymphatic and hematogenous routes [19]. Surgical excision with margin control and reconstruction similarly to BCC is the treatment of choice, but squamous cell carcinoma has a greater tendency than BCC to recur locally. Perineural infiltration facilitates spread into the orbit, intracranial cavity and periorbital structures along the branches of the trigeminal nerve, the extraocular motor nerves and the facial nerve [20]. Faustina *et al.* [21] reported an incidence of regional lymph-node metastasis in patients with squamous cell carcinoma of the eyelids of 24%, a 6% risk of distant metastasis and an 8% risk of perineural invasion, and they suggest including sentinel lymph-node biopsy as a standard procedure in patients with recurrent, large or invasive squamous cell carcinomas. A nonsurgical alternative treatment for periocular squamous cell carcinoma is photodynamic therapy with topical 5-aminolevulinic acid after application of a Frost suture in order to protect the globe. Although only one case has been reported, Rossi *et al.* [22] achieved a very good result with rapid healing without the use of local anesthesia. There was no evidence of scar formation and no signs of recurrence at 6 months follow-up.

Sebaceous gland carcinoma

Sebaceous gland carcinoma is a highly malignant and potentially lethal tumor that can originate from the meibomian glands of the tarsal plate or from the glands of Zeis associated with the eyelashes. The most common location is the upper eyelid, but multicentric origin is common and separate upper- and lower-eyelid tumors occur in 6–8% of patients. Often this neoplasm has a grossly visible yellow discoloration due to lipid content within the neoplastic cells. According to a paper from Shields *et al.* [23] sebaceous gland carcinoma can often mimic blepharoconjunctivitis (25%), chronic chalazia (20%), BCC (13%) or squamous cell carcinoma (10%). Loss of cilia and of the normal anatomy of the eyelid margin is common. A nodule that initially simulates a chalazion but later causes loss of eyelashes and destruction of the meibomian orifices or a chronic unilateral blepharoconjunctivitis warrants biopsy. Sebaceous gland carcinomas tend have an intraepithelial growth phase (pagetoid spread), which may extend over the palpebral and bulbar conjunctiva. Intraepithelial conjunctival extension has been reported to be present in 44–80% of patients with sebaceous gland carcinoma and the epithelium of the conjunctiva can display multifocal involvement with skip areas [24]. The skin might initially be intact or only inflamed because

sebaceous carcinomas originate in the tarsal plate, and a superficial skin biopsy may be normal or reveal only the chronic inflammation that goes along with sebaceous gland carcinoma, but miss the underlying tumor. A pentagonal full-thickness eyelid excision or alternatively a punch biopsy is necessary to make the correct diagnosis. Multiple map biopsies of adjacent palpebral and bulbar conjunctiva should be obtained because of the potential for pagetoid spread and the multifocal origin of the tumor [25]. Local recurrences and distant metastases of the tumor have been reported to be similar for sebaceous gland carcinomas with and without intraepithelial invasion of the conjunctiva, while orbital invasion was found in 36% of tumors with intraepithelial invasion compared with 7% of tumors without invasion, suggesting that when it is present, intraepithelial involvement is a risk factor for more invasive behavior of the tumor [26].

Merkel cell carcinoma

Merkel cell carcinoma is a rare but highly malignant tumor, with two-thirds of patients presenting with lymph-node metastasis at diagnosis or within 18 months from initial therapy and one-third with local recurrences and satellite lesions [27,28]. Merkel cell carcinoma occurs more often in women of advanced age (70–80 years old), occurs more often in the upper eyelid and usually appears as a painless, reddish or purplish, vascularized solitary nodule, without ulceration of the overlying epidermis. The duration of symptoms is relatively short and the tumor shows a rapid growth pattern to a significant size (>10 mm) within 2–3 months. It is often clinically confused with other periocular neoplasms, such as BCC, cyst or chalazion, because of its low incidence [29]. A biopsy should be performed to avoid inappropriate surgical procedures (curettage, cauterization, etc.) because of the elevated risk of clinical misdiagnosis. Most authors agree that wide surgical excision, with 5 mm clear margins, followed by frozen-section control of the margins, confirmed in definitive paraffin sections, is the gold standard for the management of Merkel cell carcinoma [29,30]. A recent report on Merkel cell carcinomas affecting the head and neck region indicated that surgery plus local adjuvant irradiation, even in presence of free surgical margins, is associated with significantly lower rates of local and regional recurrence of Merkel cell carcinoma than surgery alone [31[•]]. According to another study, sentinel lymph-node biopsy in patients with biopsy-proven Merkel cell carcinoma revealed occult nodal involvement in 32% of cases. The recurrence rate for patients with a positive lymph-node biopsy proved to be three times higher and for these patients adjuvant nodal therapy significantly improved the prognosis [32[•]].

Conclusion

Through a careful review of the literature this paper has outlined the most relevant advances for the treatment of

the most common benign and malignant eyelid tumors. New clinical entities with their peculiar behavior have only lately been described. Significant advances in the management of malignant eyelid tumors have been made, and important lessons have been learned on aggressive periocular eyelid carcinomas.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 491–492).

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