Chapter 10
Management of Conjunctival Neoplasms

Stella K. Kim, Dan S. Gombos, and Bita Esmaeli

Abstract Melanocytic neoplasms of the conjunctiva include nevus, primary acquired melanosis (PAM) without atypia, PAM with atypia, and conjunctival melanoma. The most common nonmelanocytic tumors of the conjunctiva are squamous cell neoplasms. Surgical excision is the cornerstone of therapy for conjunctival tumors. Proper specimen handling is critical to ensure that lesion orientation is clear to the ocular pathologist. Adjuvant therapy for conjunctival tumors can include cryotherapy and/or topical chemotherapy with mitomycin C, 5-fluorouracil, or interferon, or adjuvant radiation therapy. Tumor thickness and ulceration are important prognostic factors for local control and survival for conjunctival melanomas. Sentinel lymph node biopsy is an important recent consideration for conjunctival melanomas that are thicker than 2 mm or those that have histologic evidence of ulceration.

10.1 Introduction

Neoplasms of the conjunctiva can be subdivided into melanocytic and nonmelanocytic subtypes. Melanocytic neoplasms include nevus, primary acquired melanosis (PAM) without atypia, PAM with atypia (which some equate as the ophthalmic equivalent of cutaneous melanoma in situ), and conjunctival melanoma. The spectrum of nonmelanocytic conjunctival lesions is broad and includes epithelial, vascular, fibrous, xanthomatous, choriostomatous, myxomatous, malignant epithelial, and lipomatous varieties. In this chapter, we will discuss melanocytic lesions, including nevus, PAM, and melanoma, and squamous cell neoplasms, including both conjunctival intraepithelial neoplasia (CIN) and invasive squamous cell carcinoma.

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10.2 Squamous Cell Neoplasms of the Conjunctiva

Squamous cell neoplasms are the most common nonmelanocytic tumors of the conjunctiva. Generally, squamous cell tumors are subdivided into cases of CIN and frank carcinomas with invasion beyond the conjunctival basement membrane. There are a series of reports implicating the human papillomavirus as a risk factor for squamous cell carcinoma of the conjunctiva [1]. Immunosuppression (due to infectious causes or pharmacologically induced) may also play a role in tumor development and is thought to increase the risk of regional and distant metastatic disease [2].

10.2.1 Conjunctival Intraepithelial Neoplasia

CIN can be thought of as a spectrum of disease ranging from mild to severe dysplasia. If a tumor has replaced the full thickness of the epithelial layer, it is referred to as a carcinoma in situ (CIS). CIN lesions are generally located at the limbus on the bulbar conjunctiva and have a flesh-like elevation (Fig. 10.1). Leukoplakia (a white plaque) may be seen on the surface of the lesion. CIN is not thought to carry a risk of metastasis and is generally treated with surgical excision and cryotherapy (see Section 10.2.3.1).

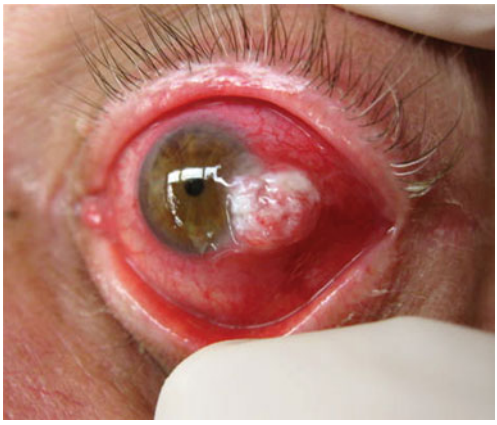

Fig. 10.1 A large perilimbal leukoplakic lesion, highly suggestive of squamous neoplasia

10.2.2 Invasive Squamous Cell Carcinoma

Squamous cell tumors with invasion beyond the conjunctival basement membrane are classified as carcinomas and have the potential for intraocular, orbital, and regional lymph node metastasis [3]. Tumors with a mucoepidermoid component noted on histopathology are generally more aggressive [4]. Clinically, squamous cell carcinomas tend to be larger than CIN lesions and require more extensive

surgical and adjuvant treatment. Squamous cell carcinomas also require increased surveillance for local and distant spread. Baseline neuroimaging of the head and neck region, including the regional lymph nodes in the parotid and cervical areas, is essential and may be done with computed tomography or magnetic resonance imaging. Ultrasound of the regional lymph nodes with possible fine needle aspiration is beneficial when done by experienced echographers.

10.2.3 Management

10.2.3.1 Local Excision and Cryotherapy

As is the case for other conjunctival tumors, surgical excision is the cornerstone of therapy for squamous cell tumors of the conjunctiva. Most surgeons employ a "no-touch" technique, in which the tumor is not manipulated with instruments, and use two sets of instruments, one for excision and the other for wound closure, to avoid contaminating the surgical field with "dirty" instruments.

Smaller and more localized lesions are treated with primary excisional biopsy performed using an operating microscope. Limbal lesions that extend onto the cornea are first treated with absolute alcohol, which is tumoricidal and helps loosen the adjacent corneal epithelium. The absolute alcohol is applied with a cotton applicator, and the loosened corneal epithelium is scrolled toward the limbus and the main tumor bed. The conjunctival portion is excised with a 2-mm margin of normal tissue and resected with a layer of underlying episclera using a beaver blade. Before the specimen is submitted for pathologic evaluation, it is essential that the surgeon labels the margins to orient the ocular pathologist. Placement of the specimen on nonadherent dressing or filter paper helps prevent the tissue from scrolling up.

Once the tumor has been excised in its entirety, a new set of surgical instruments is utilized for closure. Cryotherapy is generally administered to both the underlying bulbar conjunctival margins and the scleral bed. A double freeze–thaw cycle is indicated. The wound is generally reapproximated with absorbable sutures, although some surgeons prefer closure via secondary intention, which leaves the sclera bare. Large defects can also be covered with an amniotic membrane graft [5, 6].

10.2.3.2 Treatment of More Advanced Disease

In more advanced cases, local excision may not be possible or sufficient. Diffuse surface involvement or local recurrence can be treated with adjuvant topical chemotherapy with mitomycin C, 5-fluorouracil, or interferon [7–10]. Radiotherapy can be administered focally (with ocular plaque radiotherapy) or to the entire orbit with external-beam radiotherapy.

Intraocular extension can occur, with invasion into the anterior chamber and uvea [3]. Depending on the extent of invasion, a modified enucleation with en bloc excision of the globe and the overlying conjunctiva can be considered. However, cases of diffuse conjunctival involvement (Fig. 10.2), multiple recurrent tumors, or extensive

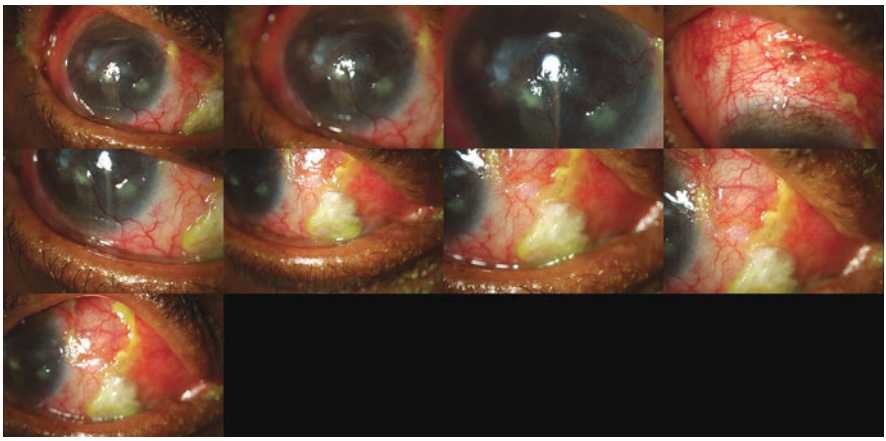

Fig. 10.2 Slit lamp photograph shows diffuse involvement of ocular surface with recurrent squamous cell carcinoma previously treated with multiple surgeries and brachytherapy. This patient underwent an orbital exenteration

orbital infiltration necessitate an orbital exenteration with or without a lid-sparing technique. If a lid-sparing technique is used, the eyelid skin can be used to line the orbital cavity [11, 12].

In high-risk patients—for example, in patients with detectable lymphadenopathy on clinical examination or imaging studies – a parotidectomy and neck dissection may be appropriate. The overall risk of lymph node metastasis from conjunctival squamous cell carcinoma is estimated to be less than 10% [13].

10.2.4 Surveillance

Patients should have follow-up visits at 3- to 6-month intervals depending on the extent of disease. Neuroimaging should be performed at the frequency of once a year, if indicated, and only for larger tumors with deep orbital or periorbital soft tissue extension and should include the head and neck region and adjacent lymph nodes.

10.3 Melanocytic Neoplasms

Melanocytic lesions of the conjunctiva behave similarly to melanocytic lesions of the skin because both types of lesions are derived from neural crest cells. Melanocytic lesions of the conjunctiva behave differently from iris and choroid lesions, which are derived from the neuroectoderm. Because conjunctival and skin melanocytic lesions have the same embryologic origin and because in clinical practice the patterns of metastasis for conjunctival melanomas are similar to cutaneous

melanoma, it is reasonable to apply principles of staging, diagnosis, pathologic evaluation, and clinical course for cutaneous melanocytic lesions to conjunctival melanocytic lesions with appropriate modifications based on the clinical experience with conjunctival tumors.

10.3.1 Nevus

Nevi are the most common conjunctival melanocytic lesions in infancy and childhood (Fig. 10.3), occurring most commonly around the time of puberty [14, 15]. Nevi are benign, but 15–30% of melanomas are derived from pre-existing nevi [16, 17]. On the other hand, the rate of conversion from a pre-existing nevus to a melanoma is reported to be less than 1% over 7 years, according to a large retrospective series of over 400 patients [18]. In children, pigmented lesions are most often benign, though there are reports of melanoma in patients younger than 20 years of age [19]. Therefore, the decision whether to observe or excise a nevus must be made carefully and take into account a variety of factors, including the rate of change in the lesion, its location, the age of the patient, and associated clinical signs such as vessels or cysts; a cystic proliferation within a melanocytic lesion of conjunctiva is more characteristic of a nevus than a melanoma [14, 20].

Observation of nevi involves serial examinations and careful photodocumentation. Change in color and size may be observed [14, 20]. Benign nevi are rarely

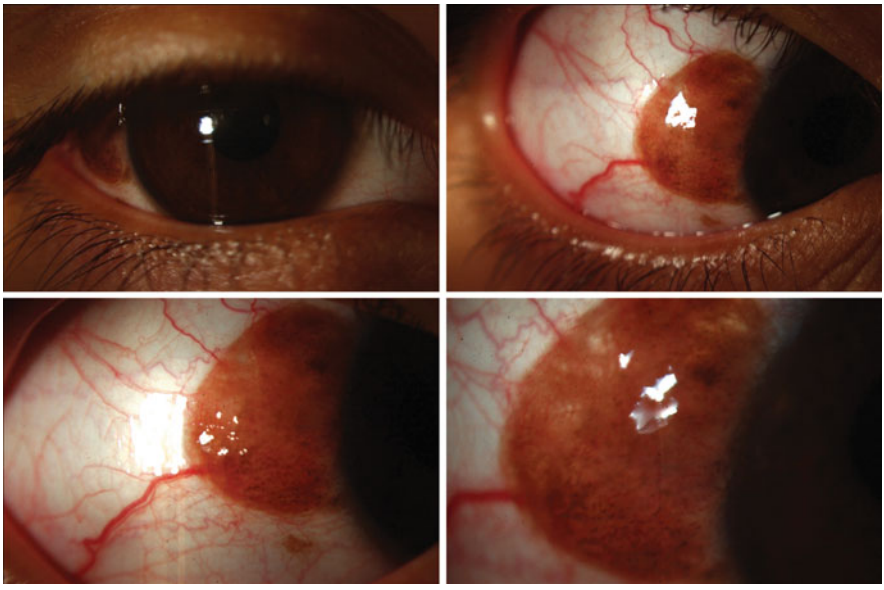

Fig. 10.3 Large conjunctival nevus in a 9-year-old boy. This lesion was surgically excised because of a history of recent enlargement

observed in the forniceal and palpebral conjunctiva; thus, biopsy of such lesions regardless of the patient's age has been advocated [14].

When a nevus is removed, careful attention to proper surgical technique is essential. It is important to avoid crush artifact by using conjunctival forceps, to excise the entire lesion with 2-mm margins when possible, to change instruments between excision and wound repair, and to handle the specimen in such a way so as to ensure that its orientation is clear to the ocular pathologist. As is true for all melanocytic lesions of the conjunctiva, frozen section evaluation of the specimen during surgery should be avoided as frozen section evaluation is not reliable for diagnosis and margin evaluation for melanomas.

Typically, if the probable diagnosis at the time of surgery is nevus, cryotherapy should be deferred. Adjuvant cryotherapy can be performed later if the diagnosis changes with the final pathology evaluation.

10.3.2 Primary Acquired Melanosis

PAM typically occurs in middle-aged Caucasians, presenting as a unilateral pigmented lesion at the limbus, on the bulbar conjunctiva, or elsewhere, including on the forniceal, caruncle, or tarsal conjunctiva [21–24]. In the ophthalmic literature, PAM is classified as PAM with atypia or PAM without atypia. Some clinicians feel that PAM with severe atypia is the ophthalmic equivalent of cutaneous melanoma in situ, and conceptualizing PAM with severe atypia as in situ disease may help patients and ophthalmic practitioners understand the severity of the diagnosis. In cases of PAM with atypia, it is helpful to have the degree of atypia (mild to severe) noted on the pathology report because the degree of atypia may be a predictor of the risk of progression to invasive melanoma [24]. In a recent large retrospective review of over 300 patients with PAM, no patients with PAM without atypia or PAM with mild atypia had progression to invasive melanoma, whereas 13% of patients with PAM with severe atypia had progression to invasive melanoma [24].

PAM with atypia and PAM without atypia typically cannot be differentiated on the basis of a clinical examination. Given the differences in the risk of progression and prognosis, some have advocated biopsy of all PAM lesions in high-risk individuals; others, though, have pointed out that one-third of middle-aged Caucasians have a unilateral pigmented lesion and have recommended against routine biopsies [25–27].

At the time of evaluation, the upper eyelids should be everted and evaluated to rule out pigmentary abnormalities, and the preauricular and cervical lymph nodes should be palpated.

The recommended treatment for PAM is complete excisional biopsy and adjuvant cryotherapy. It is important to avoid crush artifact by using conjunctival forceps, to excise the entire lesion with 2-mm margins when possible, to change instruments between excision and wound repair, and to handle the specimen in such a way so as to ensure that its orientation is clear to the ocular pathologist. It is important to

excise PAM lesions and document their size and the degree of atypia because the prognosis of patients with PAM that progresses to invasive melanoma is dependent on the size of the original lesion [24]. Cryotherapy is administered to the resection margins. For large defects, amniotic membrane may be useful in reconstructing the ocular surface [28]. For diffuse lesions, conjunctival map biopsy may be needed.

As previously indicated, fresh frozen section histopathologic evaluation is not recommended for melanocytic lesions. All specimens should be subjected to permanent section histopathologic evaluation with attention to the margins. Repeat excision to clear the margins is necessary in cases of PAM with severe atypia (melanoma in situ) at the surgical margins.

If the probable diagnosis at the time of surgery is PAM rather than invasive melanoma, decisions regarding further patient workup and adjuvant treatment can be made after the final pathology evaluation. In addition to cryotherapy, adjuvant therapy may include application of topical mitomycin C or interferon alpha [29–32].

10.3.3 Conjunctival Melanoma

In the ophthalmic literature, a distinction is made between PAM with atypia and melanoma. Conjunctival melanoma is rare, accounting for fewer than 2% of ocular melanomas and fewer than 1% of malignant tumors of the eye [33]. It is typically seen in patients 40–70 years of age and most commonly occurs in the intrapalpebral region near the limbus (Fig. 10.4) but may occur anywhere on the bulbar and palpebral conjunctiva as well as in the caruncle (Fig. 10.5) [34–36]. Factors associated with a worse prognosis include greater tumor thickness (depth), a non-limbal location, higher rate of mitosis, multifocality, and intralymphatic or intravascular spread [34–36]. In addition, ulceration was recently found by our group to be an important predictor of local recurrence and lymph node metastasis[37]. Studies of conjunctival melanoma describe 5-year survival rates between 74 and 93% and 10-year survival rates between 41 and 87% [34, 35, 38].

After a thorough ocular examination, including everted eyelid evaluation, gonioscopy, and regional lymph node palpation, a workup for systemic disease should be performed, including routine blood work; imaging studies of the lymph nodes, orbital structures, and brain; and possibly computed tomography of the chest, abdomen, and pelvis for melanomas that are thicker than 2 mm. If the workup for systemic disease is negative, then surgery for definitive local control can be carefully planned.

Complete wide local excision followed by application of cryotherapy to the resection margins and the surgical bed, first described by Jakobiec et al. [39] in 1980, remains the primary surgical approach for making the diagnosis and achieving local control. A margin of at least 2 mm outside of the lesion is achieved using the no-touch technique, in which the melanoma is not manipulated with instruments. Lesions that extend onto the cornea are first treated with absolute alcohol, which is tumoricidal and helps loosen the adjacent corneal epithelium. Epitheliectomy of

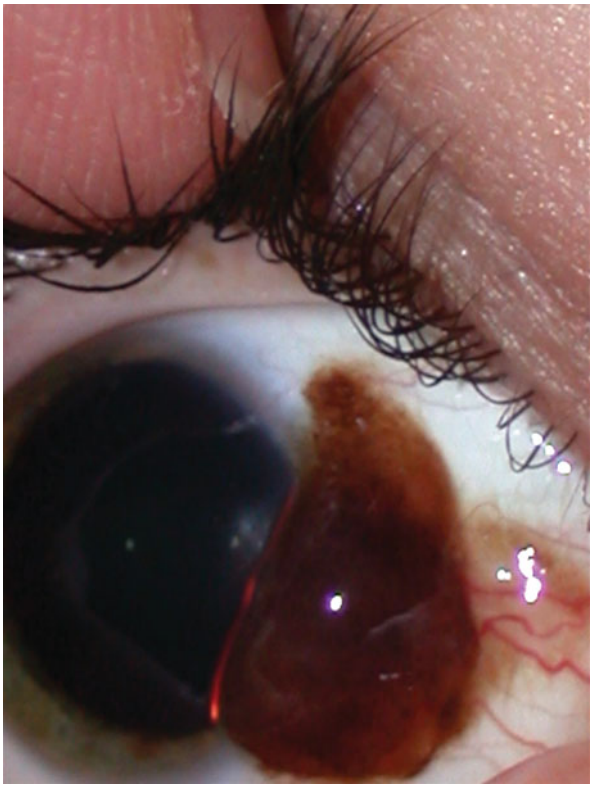

Fig. 10.4 Slit lamp photograph shows conjunctival melanoma at the limbus

corneal disease with absolute alcohol is performed. Excision is followed by double freeze–thaw cryotherapy of the conjunctival margins and the scleral bed. Proper handling of the surgical specimen is crucial to permit the pathologist to determine the true tumor thickness and to evaluate the margins [40]. Flattening of the surgical specimen and orientating the margins of interest for the pathologist are critical. A second set of clean instruments should be used for repair of the ocular surface to avoid contaminating the field with "dirty" instruments. Depending on the size of the defect, the conjunctival defect may be closed with primary closure or with amniotic membrane grafts. For widely disseminated disease on the surface of the eye, orbital exenteration with or without external-beam radiotherapy may be needed to achieve local control (Fig. 10.6). In some cases, judicious use of external-beam radiotherapy may obviate orbital exenteration [41].

If metastatic disease is found prior to surgical resection of conjunctival melanoma, the goal of surgery is to establish the definitive diagnosis as well as attempt to achieve local control by excisional biopsy and cryotherapy. However, because the patient will be treated with systemic modalities for metastatic disease, exenteration to achieve local control in such a setting is unwarranted.

For patients without evidence of metastatic disease on the initial workup, sentinel lymph node biopsy (SLNB) may be done in order to identify microscopic

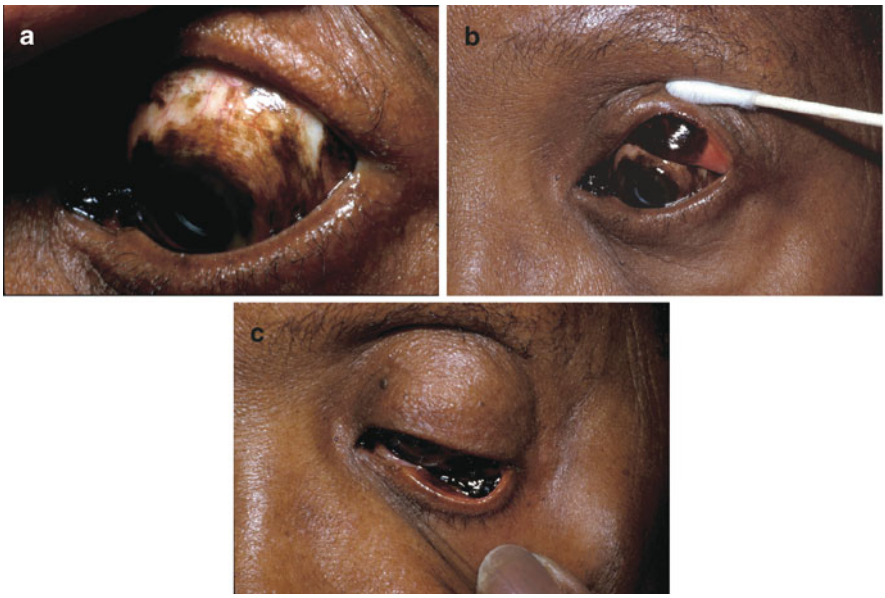

Fig. 10.5 (**a**) Bulbar conjunctival melanoma with extension onto the upper (**b**) and the lower (**c**) palpebral conjunctiva

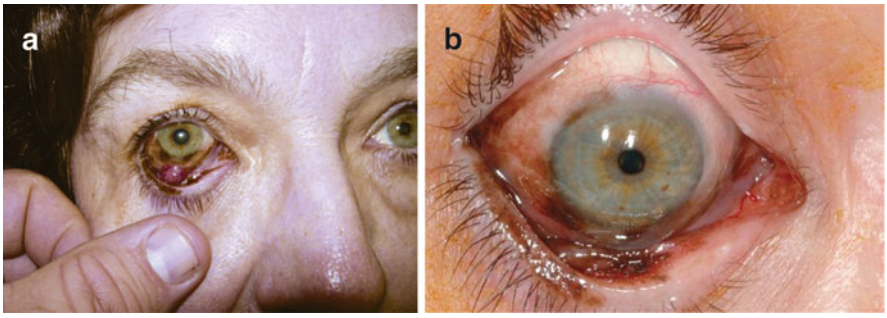

Fig. 10.6 Invasive melanoma of conjunctiva with diffuse involvement of lower eyelid margin, including an amelanotic nodule at the lid margin (**a**), as well as extensive involvement of the bulbar conjunctiva, caruncle, and parts of the upper palpebral conjunctiva (**b**). This patient had an orbital exenteration

disease in the primary ("sentinel") and secondary draining nodes [37, 42–44]. SLNB is widely accepted for evaluating whether there is microscopic lymphatic spread of cutaneous melanoma and other cancers, such as breast cancer. Our group has explored SLNB for conjunctival and eyelid melanomas in the last decade. The status of the regional lymph nodes is a crucial prognostic indicator, and SLNB can identify lymph node metastatic disease that otherwise would have gone undetected [37, 45]. At M. D. Anderson Cancer Center, a prospective trial is ongoing to evaluate the role

of SLNB in patients with conjunctival melanomas with clinically and radiographically negative regional nodes [37, 46, 47]. A recent analysis of the data from this trial showed that of 30 patients with ocular adnexal (conjunctival or eyelid) melanomas who underwent SLNB, 5 patients had a positive SLN (microscopic SLN metastasis) [37]. The analysis included 14 patients with bulbar conjunctival melanoma, 8 patients with palpebral conjunctival melanoma, 4 patients with melanoma involving both the bulbar and the palpebral conjunctiva, and 4 patients with eyelid skin melanoma. At least one SLN was identified in all patients. The median number of SLNs removed was 2. The most common basin sampled was the intraparotid, followed by submandibular (level I), preauricular, and superior cervical (level II). Among the 25 patients with negative SLNB finding, there were two false-negative events, although there were no false-negative events among patients treated during the last 4.5 years of the study. The mean Breslow thickness was 2.57 mm (range, 0.62–12 mm) among patients with negative SLNB findings and 4.86 mm (range, 2.0–7.2 mm) among patients with positive SLNB findings ($p = 0.055$). Ulceration was present in 11 patients (39%)—4 (80%) of 5 patients with positive SLNB findings and 7 (28%) of 25 with negative SLNB findings, including both patients with false-negative results. We concluded that SLNB is effective for identifying nodal micrometastasis in patients with ocular adnexal melanoma and provides important prognostic information and that the false-negative event rate in our series improved in the last 4 years, most likely due to a better technique and better patient selection for SLNB [37]. On the basis of this study, SLNB may be most appropriate in patients with conjunctival melanomas greater than 2 mm thick or when ulceration is present.

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