Under the microscope—

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The usual suspects in eyelid malignancies

First submitted: October 13, 2024
Revision submitted: October 17, 2024
Revision accepted: October 23, 2024
Published: Winter 2024

Peer reviewed

Abstract

When evaluating an eyelid lesion, the physician tries to determine the diagnosis and whether the lesion is benign or malignant. Malignant eyelid lesions include basal cell carcinoma, squamous cell carcinoma, sebaceous carcinoma, melanoma, and Merkel cell carcinoma. Basal cell carcinoma is the most common eyelid malignancy and has the lowest metastatic potential. The goal in evaluating eyelid lesions is to detect malignancies early to improve the chance of cure.

Evaluation of an eyelid lesion is one of the most common referrals to an oculoplastic surgeon. First and foremost, the oculoplastic surgeon tries to determine whether the eyelid lesion is benign or malignant. This is based on the history and exam. Children rarely have malignant eyelid lesions.[1] In evaluating adults, history is very useful in helping to determine whether a lesion is benign or malignant. Lesions that have been present for years and have not changed are likely to be benign. Pain is an indicator of an inflammatory, and usually benign, process. On examination, the size and location of the lesion should be documented, and photographs should be obtained. Malignant lesions are destructive, and the architecture of the eyelid is often disrupted with eyelash loss. Ulceration and irregular borders are also hallmarks of malignancy.

If the lesion is thought to be benign, the patient is informed of this, and observation or excision can be performed. However, the patient should know that a lesion cannot be diagnosed as benign with 100% certainty without a biopsy. If the patient elects for observation, the photographs provide a baseline, and the patient should return if any change is noted. If the lesion is thought to be malignant or if any question exists, an incisional biopsy should be performed. This is to confirm whether the lesion is benign or malignant, and if malignant, what type of malignancy it is.

Other useful historical information includes the amount of sun exposure the patient has had throughout their life and if any systemic medical issues exist. Immunosuppressed patients (e.g., solid organ transplant, leukemia) are predisposed to developing eyelid malignancies.[2] Asking whether family members have developed skin cancers, especially early in life (before age 55 years), is also useful.

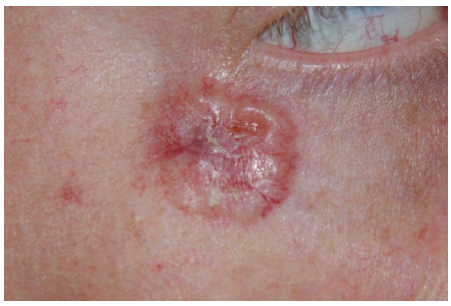


Figure 1. Basal cell carcinoma of the right lower eyelid and lateral canthus. Published with the patient's permission.

Five essential types of eyelid malignancies exist: basal cell carcinoma, squamous cell carcinoma, sebaceous carcinoma, melanoma, and Merkel cell carcinoma. Rarer malignancies include sweat gland carcinomas, but these will not be discussed in this review. Basal cell carcinoma is the most common eyelid malignancy (approximately 90%).[3] It is associated with fair skin (Fitzpatrick I, II, and III) and a history of sun exposure or radiation treatment. This is a slow-growing lesion and rarely metastasizes. Patients usually describe a slowly growing lesion that may periodically bleed. It is most commonly found on the lower eyelid and medial canthus. On examination, the lesion often has pearly, irregular borders with telangiectasias and central ulceration (**Figure 1**). The lesion is destructive, and the architecture of the eyelid margin is often altered, with associated eyelash loss. The pathologist categorizes the specimen as either nodular or morpheaform. Nodular lesions are usually confined to the clinically visible margins of the lesion, whereas morpheaform lesions extend beyond these boundaries. Treatment of basal cell carcinoma comprises complete excision. This can be performed with delayed closure after the pathologist evaluates the margins, frozen-section evaluation, or Mohs surgery. Each of these excision options has advantages and disadvantages.

Basal cell nevus syndrome is a condition in which patients are predisposed to developing basal cell carcinomas at a young age. This is an autosomal dominant condition secondary to mutations in the patched 1 (*PTCH1*) gene.[4] Treatment was traditionally repeated excision of basal cell carcinomas which, by definition, led to substandard results. Patients are now often treated with an agent that inhibits the hedgehog signaling pathway (vismodegib or sonidegib).[5] These agents have also shown promise in patients who have advanced basal cell carcinomas that are not amenable to excision without disfiguring surgery.[6]

Squamous cell carcinoma is the second most common eyelid malignancy, constituting about 5% of cases. The history and risk factors for developing squamous cell carcinomas are very similar to basal cell carcinoma. Precursor lesions to squamous cell carcinomas include actinic keratoses and keratoacanthomas. On examination, a squamous cell carcinoma can be difficult to distinguish from a basal cell carcinoma;

however, these lesions tend to produce more keratin and are often crusty in appearance. Squamous cell carcinomas are more worrisome compared to basal cell carcinoma due to the potential to spread along the nerves (perineural spread) or the lymph nodes. Treatment is very similar to basal cell carcinoma in that complete excision is preferred. For extensive lesions that have spread into the orbit or the lymph nodes, the use of programmed cell death protein 1 (PD-1) inhibitors has shown significant success.[7] Before immunotherapy, if a patient had perineural spread, exenteration was performed and the patient was treated with radiation. Many fewer exenterations are now being performed since the advent of immunotherapy.

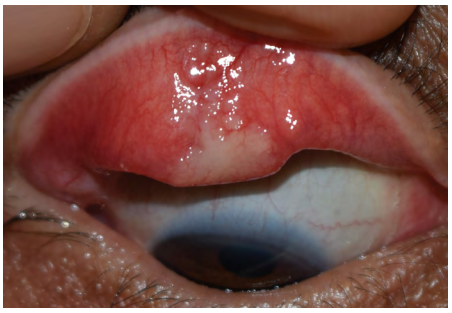


Figure 2. Sebaceous carcinoma of the right upper eyelid. Everting the lid in the examination of eyelid lesions is always important. Published with the patient's permission.

Sebaceous carcinoma is a rare malignancy with a predilection to the eyelid. This is a tumor that originates from the sebaceous glands, most commonly the meibomian glands. It occurs more commonly in patients over 70 years old and usually involves the upper eyelid. It can be a very difficult malignancy to diagnose, and patients commonly have the lesion for some time before they are diagnosed.[8] Additionally, it does not necessarily have a characteristic appearance and has been called a "masquerader" in that patients are often diagnosed initially with a recurrent chalazion or chronic unilateral blepharitis. The lesion often has areas of yellow deposits corresponding to the sebaceous nature of the lesion (**Figure 2**). In older patients who have a recurrent chalazion, biopsying the lesion and alerting the pathologist to the possibility of a sebaceous carcinoma is always recommended. If the suspicion is high, a full-thickness wedge biopsy should be performed. Sebaceous carcinomas are "bad actors" and can metastasize to the lymph nodes and distant sites. Additionally, they can have intraepithelial (pagetoid) spread in the conjunctiva. In treating sebaceous carcinoma, after confirming the diagnosis, complete excision is performed, and the extent of the disease is determined. Complete excision is performed with wide local excision of the eyelid, with delayed closure after the pathologist has confirmed free margins. Map biopsies of the conjunctiva are also performed to determine any pagetoid spread.[9] Adjuvant therapy is often performed with cryotherapy or mitomycin C if the margins are close or evidence exists of pagetoid spread. Sentinel lymph node evaluation is recommended by some if the lesion is greater than 10 mm in its greatest dimension.[10] Muir–Torre syndrome is an autosomal dominant condition in which patients can develop sebaceous carcinomas early in life.[11] This condition is also associated with gastrointestinal carcinomas.

Melanoma is a relatively uncommon tumor of the eyelid. Similar to other parts of the body, melanocytic lesions can be difficult to determine if they have malignant characteristics. The "ABCs" are useful in evaluating melanocytic lesions: A is for asymmetry, B is for border, and C is for color. If the lesion is asymmetrical, has irregular borders, or has color variegation, a biopsy should be performed. Sun exposure and fair skin are the main risk factors for melanoma. Malignant melanoma is a potentially fatal diagnosis, and early detection can be life-saving. The pathologist should comment on the Breslow thickness of the lesion, the number of mitotic figures, and whether any ulceration is present because these characteristics affect prognosis and treatment.[12] Sentinel lymph node biopsy may be performed depending on the thickness of the lesion. Lentigo maligna is a precursor lesion to melanoma and is treated with surgery and/or topical imiquimod.[13] The treatment for melanoma is complete excision, comprising wide local excision with delayed closure. Patients should be evaluated by a medical oncologist for metastatic disease. Fortunately, survival is better now for metastatic melanoma due to the use of immunotherapy in its treatment.[14]

Figure 3. Merkel cell carcinoma of the right upper eyelid. Published with the patient's permission.

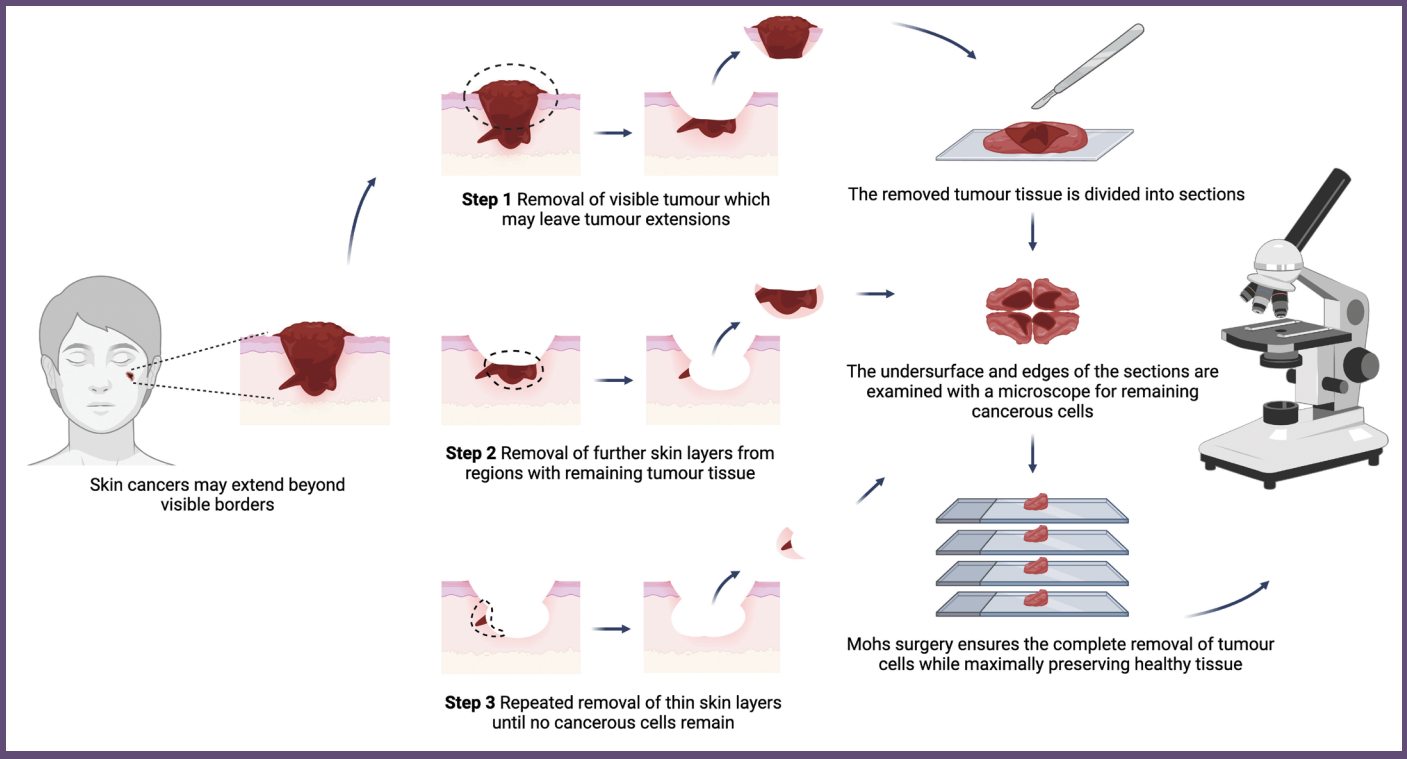
Merkel cell carcinoma is a malignancy of the mechanoreceptors in the skin. This is a lesion of older patients (over 80 years) and, as opposed to the previous four malignant lesions, it is a fast-growing lesion over weeks to months. Merkel cell carcinoma has a high risk of metastasis.[15] The lesion starts as a painless, red-purple lesion that enlarges relatively quickly (**Figure 3**). Similar to melanoma, treatment is by wide local excision with delayed reconstruction. Due to the high risk of metastasis, sentinel lymph node evaluation is performed in almost all patients, with evaluation by a medical oncologist.

In evaluating patients with eyelid lesions, determining whether the lesion is possibly malignant is crucial. Some are obviously benign, but even in lesions that are thought to be benign, oculoplastic surgeons are wrong about 2–4% of the time.[16,17] The threshold for biopsy should be relatively low so that a malignancy is not missed, or the patient should be reevaluated or given instructions on how to watch the lesion for any change or malignant characteristics. Ideally, with the advancement of imaging, non-invasive techniques will help with the diagnosis of these lesions. Fortunately, when lesions are caught early, complete excision is usually curative. Complete excision can be performed with a variety of methods, all with the goal of attaining clear tumor margins. Mohs surgery, when appropriate, confirms margin control while preserving healthy skin. For permanent-section or frozen-section analysis, margins are drawn around the visible portion of the tumor with excision and histological analysis. Basal cell carcinomas and squamous cell carcinomas are usually drawn with 3-mm margins, whereas sebaceous carcinoma, Merkel cell carcinoma, and melanoma are drawn with 5-mm or greater margins. However, these margins may be wider in lesions that are more aggressive or show intraepithelial spread (sebaceous carcinoma) or a morpheaform subtype (basal cell carcinoma).[12] With further development of molecularly targeted agents and immunotherapy, many patients with advanced disease can be treated medically to save them from disfiguring surgery.[18]

Conflict of interest
none

Box 1. What is Mohs surgery?

- Mohs surgery was developed by Frederic E. Mohs in 1938.
- The surgery is performed by subspecialist dermatologists.
- The tumor is mapped and excised.
- Frozen-section histology is used to evaluate the margins while the patient waits.
- Each excision represents a "stage."
- Surgical excision is completed when the entire tumor excision is attained and margins are clear.
- The surgery results in the highest success rate for tumor excision with the narrowest of margins, thus conserving healthy tissue, which is particularly important for the eyelids.
- The technique is most commonly used for basal cell and squamous cell carcinomas, although success has also been described with sebaceous carcinoma and melanoma.



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Key points:

- Malignant eyelid neoplasms are destructive and alter the normal architecture of the eyelid.
- The only 100% certain method to diagnose an eyelid lesion is histological analysis.
- Basal cell carcinoma is the most common lesion and rarely metastasizes.
- Squamous cell carcinoma may invade the orbit through perineural invasion.
- Sebaceous carcinoma may masquerade as a recurrent chalazion or chronic unilateral conjunctivitis.
- Melanoma and Merkel cell carcinoma have a high risk of metastasis.

Will medical therapy replace surgical excision of eyelid malignancies?

Think of the surgeon 150 years ago who was amputating limbs for infection. If you told the surgeon that they would be able to give a pill someday that would replace amputation and kill the infection, allowing the patient to keep their limb, they would not believe you. We are currently in the same situation with malignancies. We treat malignancies the same way that the surgeon 150 years ago treated infection. With the advent of molecularly targeted agents, consisting of monoclonal antibodies and small molecule inhibitors, we are at the cusp of treating malignancies with medicine rather than surgery.

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