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Updates on eyelid cancers

Kristina Joana Schoelles*, Claudia Auw-Haedrich

Eye Center, Medical Center - University of Freiburg, Freiburg, Germany

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ABSTRACT

In this review, we aim to provide an overview of the five most common malignant eyelid tumors with current treatment recommendations based on international guidelines. Particular attention is paid to the clinicopathological correlation and the update with regard to adequate treatment. Newer systemic therapies enrich the existing treatment options, of which complete tumor excision remains the most important therapeutic measure.

Introduction

Malignant eyelid tumors are a serious medical condition that requires prompt diagnosis and appropriate treatment. These tumors can arise from various cell types within the eyelid, including the epidermis, skin adnexa, and connective tissue. They pose a significant threat to both the visual function and overall health of the affected individuals. Early detection and intervention are crucial in improving the prognosis and minimizing the potential complications associated with these tumors, which account for approx. 5–10 % of all skin malignancies. The incidence is 15.7 cases per 100,000 inhabitants per year in the USA, in Singapore an incidence of 5.1 cases per 100,000 inhabitants per year is reported.[1]

In this article, we will provide an overview of the five most common malignant eyelid tumors, including their different types, diagnostic methods, and available treatment options. Understanding the characteristics, risk factors, and clinical presentation of these tumors is essential for healthcare professionals and patients alike. By delving into the intricacies of diagnosis and treatment, we aim to empower readers with the knowledge necessary to identify and manage malignant eyelid tumors effectively. An update on systemic therapies for the respective entities is provided in Table 1 containing an overview with relevant information on indication, dosage and most important side effects.

Basal cell carcinoma

Clinical appearance

Basal cell carcinoma (BCC) is the most common malignant tumor in humans in central Europe and, at approx. 90 %, is the most common entity of malignant eyelid tumors.[1]

It occurs mainly on the lower eyelid, grows slowly locally invasive and destructive, but metastasizes extremely rarely (0.0028 % to 0.55 %). Invasion into the orbit is possible, particularly in cases of localization in the medial canthus or with perineural infiltration (less than 5 % of periocular basal cell carcinomas).[2]

Risk factors are chronic or intense UV exposure, light skin type, male sex or genetically based syndromes like nevoid basal cell carcinoma syndrome or xeroderma pigmentosum.[2]

Clinically, various subtypes occur with different recurrence rates. The lower risk types include nodular, superficial, pigmented, infundibulocystic and fibroepithelial basal cell carcinoma, while the higher risk types include basosquamous, sclerosing/morphoeic, infiltrating basal cell carcinoma, basal cell carcinoma with sarcomatoid differentiation and micronodular basal cell carcinoma.[3] Nodular basal cell carcinoma is the most common variant. A typical basal cell carcinoma presents as a pearly, firm, telangiectatic nodule with a shiny surface with or without central retraction and ulceration (Fig. 1). It may also present as a scaly or indurated plaque or as a scar-like tumor.[3]

Histopathology

Basal cell carcinoma develops from basal cells of the interfollicular epidermis or hair follicle, which proliferate in depth. They are morphologically variable, but in most cases contain nests with peripheral palisading basaloid cells with hyperchromatic nuclei and scant cytoplasm.[3] A retraction space occurs typically between tumor islands and stroma, which was considered a fixation artifact characteristic for basal cell carcinoma (Fig. 2). Nevertheless Mentzel et al. found the same retraction space of BCC in ex vivo confocal laser scanning microscopy (CLSM), which allows direct microscopic examination of fresh tissue. They showed similar patterns obtained by CLSM in comparison to

* Correspondence to: Eye Center, Medical Center - University of Freiburg, Killianstraße 5, D-79106 Freiburg, Germany.
E-mail address: kristina.schoelles@uniklinik-freiburg.de (K.J. Schoelles).

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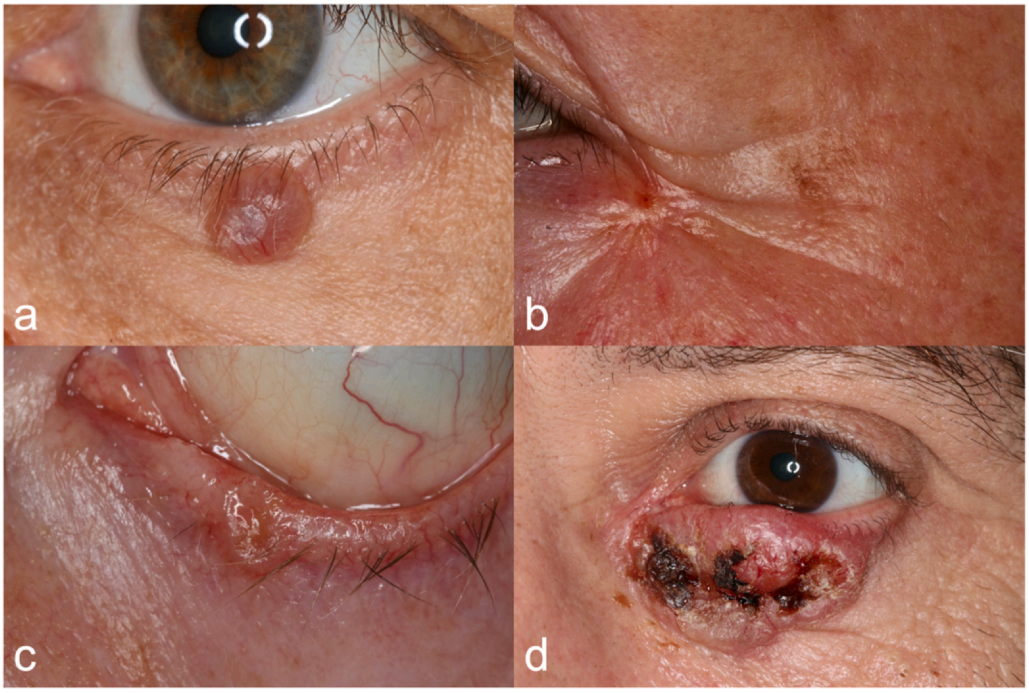

Fig. 1. Basal cell carcinoma (BCC). a Nodular BCC with apparent telangiectasia and shiny surface. b Sclerosing recurrent BCC with firm tumor without obvious margin and central retraction below and lateral the temporal canthus, hardly distinguishable from scar tissue. c Nodular BCC with central ulceration and notable madarosis. d Advanced, locally destructive nodular BCC extending from the lateral lower eyelid into the medial corner of the eyelid, obliterating the inferior lacrimal punctum. The tumor is firm, ulcerated at its lower part with crusts covering the ulcer.

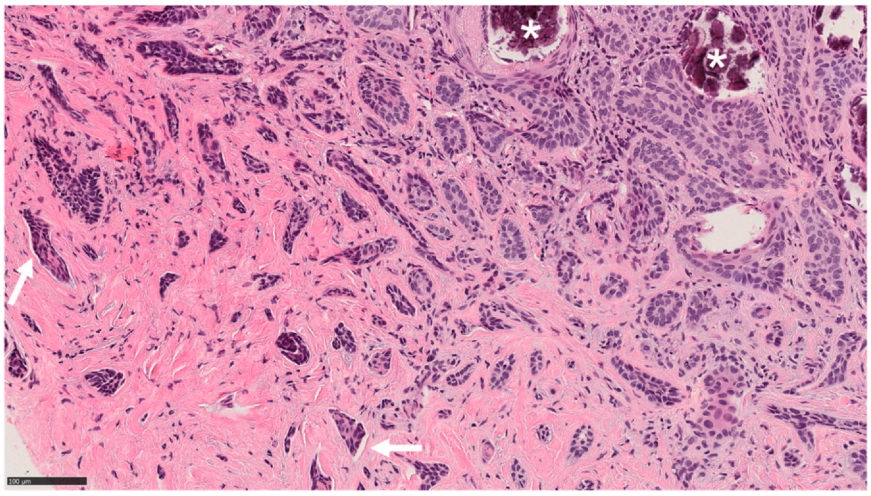

Fig. 2. Histopathology of BCC. Sclerosing basal cell carcinoma with diffusely distributed tumor islands with palisading pattern at the periphery, retraction space (arrows), calcification (asterisks) and abundant fibrous stroma between the tumor islands. Same case asFig. 1b. Hematoxylin Eosin, magnification bar = 100 μm.

histological patterns of HE-stained sections of paraffin-embedded BCC of the same tissue. There is evidence that hyaluronidase digests hyaluronic acid between tumor islands and adjacent stroma, leaving the clefts in between.[4] The tumor pattern depends on the basal cell carcinoma type with variations of size, shape and localization of tumor lobules and the amount of fibrous stroma surrounding the tumor lobules. Necrosis and cornification might be present. Immunohistochemistry shows positivity of BerEP4 and negativity for EMA, whereas the opposite is usually the case for squamous cell carcinoma. Vertical tumor thickness should be indicated, as it might be relevant as for decision of further treatment.[3]

Staging

If a basal cell carcinoma is diagnosed, a full body skin examination is recommended. In locally advanced basal cell carcinomas with clinically suspected perineural growth, infiltration into the orbit or bone CT should be performed to assess bony destruction and/or MRI to evaluate periocular or intraorbital tumor extension.[2] Systemic staging is recommended only in larger tumors as the incidence of metastatic basal cell carcinoma is less than 0.03 %. The reported incidence of basal cell carcinoma with metastases is 1.9 % for tumors larger than 3 cm, of 45 cases described in the literature the mean diameter of the primary tumor was 8.7 cm.[5]

Staging follows the eighth edition of the AJCC guidelines (American Joint Committee on Cancer).[6] For the first three tumor entities mentioned in this article classification of primary tumor (T) is based on Table 2.

Update on therapy

The histologically margin-controlled complete excision in healthy tissue represents the first line therapy. A clinical safety margin of 3 mm in low risk BCC such as nodular basal cell carcinoma and at least 5 mm in the high risk BCC such as the sclerodermiform or micronodular type should be ensured.[7]

Table 1
Clinical trials on systemic therapies relevant for malignant eyelid tumors. For complete information please read careful through the prescribing information for each listed medicament.

Cancer entity	trial number	mechanism of action	drug	dose and frequency	warnings and side effects	indication
Basal cell carcinoma	NCT00833417	hedgehog pathway inhibitor (HHI)	vismodegib	150 mg orally once daily, until disease progression or until unacceptable toxicity	embryo-fetal toxicity, blood donation should be avoided, cutaneous or musculoskeletal adverse reactions, muscle spasms, alopecia, dys-/ageusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, arthralgias, vomiting	metastatic or locally advanced basal cell carcinoma, that has recurred following surgery, or in case surgery or radiation is not possible
	NCT01327053	hedgehog pathway inhibitor (HHI)	sonidegib	200 mg orally once daily, taken on an empty stomach until disease progression or intolerable toxicity	embryo-fetal toxicity, musculoskeletal adverse reactions (serum creatine kinase and creatinine levels should be checked), muscle spasms, alopecia, dysgeusia, fatigue, nausea, musculoskeletal pain, diarrhea, decreased weight, decreased appetite, myalgia, abdominal pain, headache, pain, vomiting, and pruritus	locally advanced basal cell carcinoma, that has recurred following surgery or radiation therapy, or in case surgery or radiation is not possible
	NCT03132636	PD-1 inhibitor	cemiplimab	350 mg intravenously over 30 min every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months	embryo-fetal toxicity, immune-mediated adverse reactions, fatigue, musculoskeletal pain, rash, diarrhea, and anemia	metastatic basal cell carcinoma previously treated with a HHI or for whom a HHI is not appropriate
Squamous cell carcinoma	NCT02383212, NCT02760498	PD-1 inhibitor	cemiplimab	350 mg intravenously over 30 min every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months	embryo-fetal toxicity, immune-mediated adverse reactions, fatigue, musculoskeletal pain, rash, diarrhea, and anemia	metastatic or locally advanced cutaneous squamous cell carcinoma
	NCT03284424	PD-1 inhibitor	pembrolizumab	200 mg intravenously 30-minute infusion every 3 weeks or 400 mg every 6 weeks, until disease progression, unacceptable toxicity, or up to 24 months	embryo-fetal toxicity, immune-mediated adverse reactions (pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, skin reactions), fatigue, musculoskeletal pain,decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain.	recurrent or metastatic cutaneous squamous cell carcinoma or locally advanced cutaneous SCC that is not curable by surgery or radiation
Malignant melanoma (selection, see all approved drugs e.g. at www.cancer.gov)	NCT00006249	immunomodulation	interferon alfa-2b	induction: 20 million IU/m2 as an intravenous infusion, over 20 min, 5 consecutive days per week, for 4 weeks; maintenance: 10 million IU/m2 as a subcutaneous injection three times per week for 48 weeks	can cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders; contraindicated with autoimmune hepatitis and decompensated liver disease; "flu-like" symptoms	malignant melanoma, adjuvant after surgery with high risk of recurrent cancer
	NCT01866319, NCT01704287, NCT02362594	PD-1 inhibitor	pembrolizumab	200 mg intravenously 30-minute infusion every 3 weeks or 400 mg every 6 weeks, until disease progression or unacceptable toxicity (adjuvant: or for up to 12 months without recurrence)	embryo-fetal toxicity, immune-mediated adverse reactions (pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, skin reactions), fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain	unresectable or metastatic melanoma, adjuvant treatment with Stage IIB, IIC, or III following complete resection

(*continued on next page*)

Table 1 (*continued*)

Cancer entity	trial number	mechanism of action	drug	dose and frequency	warnings and side effects	indication
NCT0172174, NCT01721772, NCT01844505, NCT0409925, NCT0238890	PD-1 inhibitor	nivolumab	≥ 40 kg body weight: 240 mg intravenously 30-minute infusion, every 2 weeks or 480 mg every 4 weeks, until disease progression/ recurrence or unacceptable toxicity (adjuvant: up to one year)	embryo-fetal toxicity, immune-mediated adverse reactions (pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, skin reactions), fatigue, diarrhea, nausea, musculoskeletal pain, rash, pruritus, cough, upper respiratoy tract infection, peripheral edema	unresectable or metastatic melanoma (+/- ipilimumab), adjuvant after complete resection ≥ stage IIB	
NCT00405587	BRAF kinase inhibitor	vemurafenib	960 mg (four 240 mg tablets) orally every 12 h with or without a meal, until disease progression or unacceptable toxicity	new primary (cutaneous) malignancies, serious hypersensitivity reactions, severe dermatologic reactions, including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis, QT prolongation, hepatotoxicity, photosensitivity, ocular uveitis, embryo-fetal toxicity, radiation sensitization and radiation recall, renal failure, Dupuytren's contracture and plantar fascial fibromatosis, rthralgia, rash, alopecia, fatigue, nausea, pruritus, and skin papilloma	unresectable or metastatic melanoma with BRAF V600E mutation	
NCT01909453	BRAF- and MEK-inhibitor combination	encorafenib and binimetinib	encorafenib 450 mg orally once daily and binimetinib 45 mg orally twice daily, until disease progression or unacceptable toxicity	encorafenib: new primary malignancies, hemorrhage, uveitis,QT prolongation, embryo-fetal toxicity; binimetinib: cardiomyopathy, venous thromboembolism, ocular toxicities, interstitial lung disease, hepatotoxicity, rhabdomyolysis, hemorrhage, embryo-fetal toxicity; combination: fatigue, nausea, diarrhea, vomiting, abdominal pain, and arthralgia	unresectable or metastatic melanoma with a BRAF V600E or V600K mutation	
NCT0009465, NCT00636168	CTLA-4 inhibitor	ipilimumab	3 mg/kg every 3 weeks intravenously90-minute infusion up to a maximum of 4 doses; adjuvant: 10 mg/ kg every 3 weeks up to a maximum of 4 doses, followed by 10 mg/kg every 12 weeks for up to 3 years	embryo-fetal toxicity, immune-mediated adverse reaction, fatigue, diarrhea, pruritus, rash, and colitis	unresectable or metastatic melanoma, adjuvant with involvement of regional lymph nodes (>1 mm) after complete resection (including total lymphadenectomy)	

(*continued on next page*)

Table 1 (*continued*)

Cancer entity	trial number	mechanism of action	drug	dose and frequency	warnings and side effects	indication
Merkel cell carcinoma	NCT02267603	PD-1 inhibitor	pembrolizumab	200 mg intravenously 30-minute infusion every 3 weeks or 400 mg every 6 weeks, until disease progression, unacceptable toxicity, or up to 24 months	embryo-fetal toxicity, immune-mediated adverse reactions (pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, skin reactions), fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain	recurrent locally advancedor metastatic Merkel cell carcinoma
	NCT02155647	PD-L1 inhibitor	avelumab	800 mg intravenously 60-minute infusion every 2 weeks, until disease progression or unacceptable toxicity	embryo-fetal toxicity, immune-mediated pneumonitis, hepatitis, colitis, endocrinopathies, nephritis, cardiovascular events, embryo-fetal toxicity, fatigue, musculoskeletal pain, diarrhea, nausea, infusion-related reaction, rash, decreased appetite, and peripheral edema	metastatic Merkel cell carcinoma
	NCT03599713	PD-1 inhibitor	retifanlimab	500 mg intravenously 30-minute infusion every 4 weeks, until disease progression, unacceptable toxicity, or up to 24 months	embryo-fetal toxicity, immune-mediated adverse reactions (pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, skin reactions), fatigue, musculoskeletal pain, pruritus, diarrhea, rash, pyrexia, and nausea	metastatic or recurrent locally advanced Merkel cell carcinoma

Imiquimod 5 % or 5-fluorouracil 5 % cream can be used as topical therapies, particularly for superficial basal cell carcinoma with contraindications to surgery.[8,9] Exuberant local inflammatory reaction may occur. For superficial basal cell carcinoma, various studies have shown a tumor-free rate of 43 % to 100 % after imiquimod application, and a rate of 90 % for 5-fluorouracil.[10] Nevertheless, the superiority of a surgical approach was demonstrated in a comparative study between surgery and topical imiquimod, where surgery achieved a tumor-free rate of 97.7 % after 5 years, compared to 82.5 % in the imiquimod group.[11] Photodynamic therapy with 5-ALA (5-aminolevulinic acid) or MAL (methyl aminolevulinate) is also a treatment option for superficial basal cell carcinoma with contraindications to surgery.[7,12] In general topical therapies are suitable only for basal cell carcinoma with a depth of less than 1 mm. Cryocoagulation and laser surgery remain as secondary treatment options which unfortunately are associated with an unclear margin situation of the tumor surrounding tissue.[7] We do not prefer these options in our daily practice as they can lead to scarring reactions that are barely distinguishable from a tumor recurrence and might cause lid malposition.

In the case of locally advanced tumors, where excision in healthy tissue is not possible due to the extent, location, age or comorbidity of the patient, the treatment concept should be determined on an interdisciplinary basis. Radiotherapy could be offered, but not for patients with syndromes and autoimmune diseases that are associated with increased radiosensitivity.[7] In multiple studies, clinical control rates of 92 – 99 % for smaller and 70 – 90 % for high-risk basal cell carcinomas were compiled for different radiotherapy modalities (follow-up time between 4 months and 10 years).[7] However, a randomized study (n = 347) comparing surgery and radiotherapy, including untreated nodular (45 % vs. 43 %), ulcerating (30 % vs. 29 %), superficial and pagetoid (21 % vs. 23 %) as well as sclerosing (4 % vs. 5 %) basal cell carcinomas of the face, showed a significant superiority of surgery regarding local control with 99.3 % versus 92.5 % after 4 years.[13] In patients with high-risk basal cell carcinoma adjuvant radiation has been recommended, but no randomized controlled study has yet proven its benefit.[14]

Activation of the Sonic Hedgehog signaling pathway plays a central role in the development of basal cell carcinoma.[2] In the case of locally advanced or metastatic basal cell carcinoma, where surgery or radiotherapy are not possible, treatment with an oral hedgehog inhibitor like vismodegib and sonidegib should be discussed in an interdisciplinary tumor board (both approved by the U.S. Food and Drug Administration, FDA, and the European Medicines Agency, EMA), see alsoTable 1.[7,15] Current data show a remission rate with vismodegib of 68.5 % for locally advanced and 36.9 % for metastatic basal cell carcinoma.[16] The median survival was 33.4 months in the metastatic cohort.[15] The duration of treatment is long-term, can be interrupted for up to 4 weeks and should be evaluated individually. Muscle spasms, hair loss, fatigue or weight loss are common side effects which lead to discontinuation of treatment in 30 % of patients.[7] Although not yet approved by the FDA for this application, neoadjuvant therapy with a hedgehog inhibitor may be discussed for locally advanced BCC. The VISORB Trial could show that primary or more commonly neoadjuvant vismodegib treatment for 3–6 months prior surgery preserves globe and visual function in patients with orbital and extensive periocular basal bell carcinoma.[17]

If the hedgehog inhibitors are ineffective, the PD-1 inhibitor cemiplimab is approved as a second-line therapy for adults with locally advanced or metastatic basal cell carcinoma (PD-1 = programmed-cell-death-protein 1), see alsoTable 1. The response rate is 31 % with 6 % complete response. The most common side effects reported are hypertension and colitis (5 % of patients each). It is administered intravenously at 3-week intervals up to 93 weeks or until tumor progression or unacceptable toxicity occur.[18]

As secondary prevention especially in patients with a history of basal cell carcinoma, it could be shown that the daily intake of nicotinamide 500 mg twice a day can reduce the risk of developing basal cell carcinoma by 20 %.[19]

Table 2
Definition of primary tumor (T) for basal cell carcinoma (BCC), squamous cell carcinoma (SCC), sebaceous carcinoma (SC).[6]

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 10 mm in greatest dimension
T1a	Tumor does not invade the tarsal plate or eyelid margin
T1b	Tumor invades the tarsal plate or eyelid margin
T1c	Tumor involves full thickness of the eyelid
T2	Tumor > 10 mm but ≤ 20 mm in greatest dimension
T2a	Tumor does not invade the tarsal plate or eyelid margin
T2b	Tumor invades the tarsal plate or eyelid margin
T2c	Tumor involves full thickness of the eyelid
T3	Tumor > 20 mm but ≤ 30 mm in greatest dimension
T3a	Tumor does not invade the tarsal plate or eyelid margin
T3b	Tumor invades the tarsal plate or eyelid margin
T3c	Tumor involves full thickness of the eyelid
T4	Any eyelid tumor that invades adjacent ocular, orbital, or facial structures
T4a	Tumor invades ocular or intraorbital structures
T4b	Tumor invades (or erodes through) the bony walls of the orbit or extends to the paranasal sinuses or invades the lacrimal sac/ nasolacrimal duct or brain

Follow-up

After R0 resection and in case of lower-risk basal cell carcinoma a 6-month local control is recommended for follow-up, otherwise 3-monthly controls should be performed in the first 2 years, after which annual checks are sufficient.[7]

Squamous cell carcinoma

Clinical appearance

Squamous cell carcinoma (SCC) occurs less frequently compared to basal cell carcinoma and represents the second most common group of malignant eyelid tumors at approx. 3 – 13 %.[1] Squamous cell carcinoma also occurs preferentially on the lower eyelid and medial canthus, men are more often affected than women (up to three times), most probably due to higher UV-associated skin damage. It metastasizes to the regional lymph nodes in up to 24 % and can lead to distant metastases in up to 6 % (most commonly lung, followed by bone, CNS and liver), the mortality rate is less than 1 %.[1,3,20] In facial and periorbital squamous cell carcinoma perineural invasion is reported in 8–14 % of cases with possible involvement of trigeminal or facial nerve producing pain or paraesthesias, or invasion of the orbit.[21–23]

It can develop de novo or from precancerous conditions such as actinic keratosis or Bowen's disease. In addition to chronic sun exposure and light-colored skin, risk factors include HPV infection, chronic immunosuppression particularly after organ transplantation or exposure to chemical carcinogens such as polycyclic aromatic hydrocarbons or arsenic.[3,20]

Squamous cell carcinomas and their precursors are characterized by a roughened hyperkeratotic irregular or erythematous surface (Fig. 3). In contrast to basal cell carcinomas, telangiectasias are usually absent. Early stages may resemble chronic blepharitis. Invasive and rapid growth results in a hyperkeratotic nodule with possible ulceration, such as in the well-differentiated crater-shaped keratoacanthoma, a variant of squamous cell carcinoma with a central keratin plug.[3]

Histopathology

Squamous cell carcinoma arises from the epidermal keratinocytes with various degrees of differentiation that resemble the cytology of squamous cells of the epidermal stratum spinosum.[3] Characteristic invasive growth into the dermis might be combined with in situ precursor lesions.

The precursor lesion, actinic keratosis, is characterized by focal parakeratosis, atypia of the basal cell layer, nuclei with irregularity in size, hyperchromasia, and pleomorphism. The keratinocytic dysplasia may extend into the upper layers of the epidermis. If the dysplasia is seen in full-thickness of the epidermis the lesion is classified as squamous cell carcinoma in situ (Bowen disease).[3]

In squamous cell carcinoma atypical epithelial cells with invasion of the dermis are the hallmark for the diagnosis.[24] Differentiation varies from well to poorly differentiated, with the well-differentiated tumors having a better prognosis regarding recurrence rate, metastasis and survival.[3,6] Unusual types as clear cell SCC occur occasionally (Fig. 4).

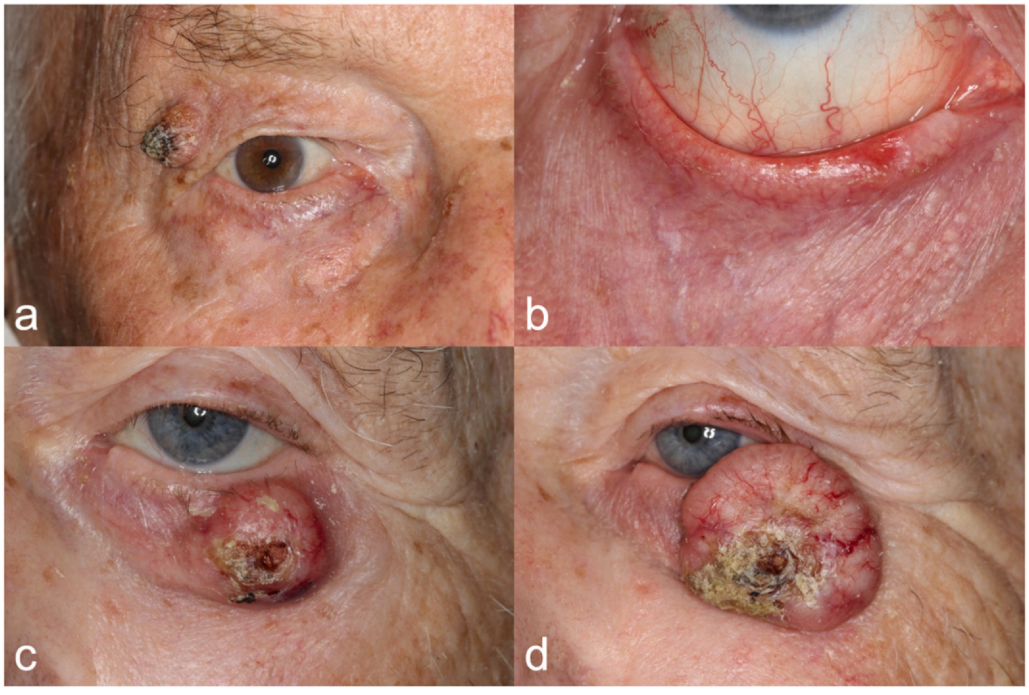

Fig. 3. Squamous cell carcinoma (SCC). a Prominent nodular SCC with central keratinization on the lateral upper eyelid. b The initially suspected inflammatory change similar to chronic blepharitis on the medial lower eyelid showed no improvement after anti-inflammatory local therapy. Histologically, SCC was confirmed. c Clear cell SCC on the lateral lower eyelid, which had been present for 5 years with further enlargement since 2 weeks. In this case, rather atypical telangiectasias can be seen on the nodular tumor with keratinization extending centrally. d Rapid tumor growth in the same patient shown in c only 4 weeks later with almost doubling of the tumor mass.

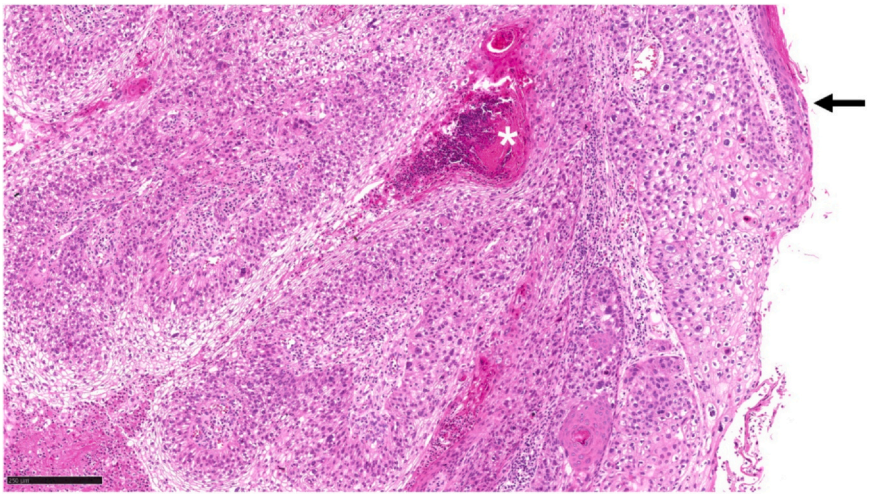

Fig. 4. Histopathology of SCC. Clear cell squamous cell carcinoma of the lower eyelid (same case asFig. 2c and d, area of the upper edge of the ulcer). Tumor cells with clear, but also eosinophilic cytoplasm with basophilic, pleomorphic nuclei. Keratin (asterisk), epidermal margin at the ulcer edge also containing atypical tumor cells (arrow). Hematoxylin eosin, magnification bar = 250 μm.

Usually immunohistochemistry is not required, but might be helpful for poorly differentiated or histological atypical lesions. Typically, positive markers for cutaneous squamous cell carcinoma are p63, p40, EMA, CK5/6, MNF116, and high-molecular-weight 34βE12. In contrast to basal cell carcinoma BerEp4 is negative.[3]

Staging

For staging of the primary tumor seeTable 2. Once a squamous cell carcinoma has been (clinically) diagnosed, the entire skin should be examined. If locoregional metastases are suspected or risk factors are present, lymph node sonography is recommended preferably prior surgery to avoid a false positive lymph node assessment due to postoperative inflammation. If positive lymph nodes were diagnosed or distant metastases are suspected, a sectional image diagnosis should be carried out using CT, MRI or FDG-PET/CT.[20]

Sentinel lymph node biopsy or prophylactic lymphadenectomy are not routinely recommended. If lymph node metastasis is clinically manifest regional lymphadenectomy should be performed.[20]

Update on therapy

In the case of precancerous lesions, the indication for treatment should be based on the clinical picture (single lesion or field cancerization), risk factors, comorbidities, life expectancy and the patient's wishes.[20] Surgical excision, cryosurgery, chemical peels, ablative or non-ablative laser procedures, topical drug-based procedures such as diclofenac sodium 3 % gel, 5-fluorouracil 4 % (esp. for face indication) or 5 % cream, imiquimod 3,75 % or 5 % cream or tirbanibulin 1 % ointment,[25] photodynamic therapy, or combinations of those can be offered in case of actinic keratosis.[20] Among the topical procedures, the longest experience has been with imiquimod 5 % cream which achieved a complete healing rate of 63 %.[26,27] It should be applied three times a week for four weeks and left for 8 hours onto the skin at a time. After a four-week treatment-free period the healing should be assessed. If lesions are still present, treatment should be continued for another four weeks. The most common side effects are local skin reactions such as itching, burning, erythema and crusting. Eye contact must be avoided with all topical medications, so their application is limited up to the lash line. Surgical excision is recommended for eyelid margin involvement.

In squamous cell carcinoma, histologically excisional margin-controlled excision in healthy tissue is the gold standard. The current European guideline recommends a clinical safety margin of 5 mm for low-risk squamous cell carcinoma and 6–10 mm for high-risk squamous cell carcinoma.[28] Micrographically controlled surgery, such as Mohs surgery, allows significantly smaller defects, which is beneficial for the facial region.[29]

After R0 resection with micrographically controlled surgery, most publications state recurrence rates between 2–8 %.[20]

Clinical risk factors for recurrence and distant metastasis are local recurrence, tumor diameter > 2 cm (> 2 – ≤3 cm categorizes as T3),[6] immunosuppression, evidence of perineural invasion and no displaceability from the subsurface. Histological risk factors are > 6 mm depth of invasion, desmoplasia, perineural invasion, extension into subcutis and poor differentiation (G3).[20]

If excision in healthy tissue is not possible or with inoperable patients, radiotherapy should be considered.[20] Retrospective data show high local tumor control: After primary radiotherapy a local recurrence rate of 6 % at 5 years up to 12 % at 15 years is reported. Depending on initial tumor size in the same cohort local recurrence rates are described between 1.7 % for T1 tumors after 15 years up to 25 % for T3 tumors after 10 years.[30]

Adjuvant radiotherapy should be performed in case of R1 or R2 resection, extensive or intraparotid lymph node involvement, or if perineural sheath infiltration is present.[20,31] Regarding perineural invasion, the likelihood of cure is related to the presence of symptoms and the radiographic extent of the tumor. It could be shown that patients with clinical perineural invasion, such as cranial nerve deficits, only have a local control rate of about 50–55 % compared to those with incidental, asymptomatic perineural invasion with a local control rate of 80–90 %.[30,32]

In the case of distant metastases or advanced disease that cannot be controlled by radiotherapy or surgical means, the indication for systemic therapy should be evaluated interdisciplinary.[20] Immunotherapy with a PD-1 inhibitor should be offered as first-line therapy for such patients, see alsoTable 1. For distant metastases, the PD-1 inhibitor cemiplimab shows a response rate up to 49 % with fatigue and diarrhea as most common side effects.[33,34] In case of contraindications or non-response to PD-1 inhibitors, EGFR-targeted therapy or chemotherapy should be offered.[20] It must be borne in mind that these systemic therapies carry a high potential for side effects, which may force the patients to discontinue medication after some time. This is particularly important when a decision has to be made between exenteration and medium-term systemic therapy. Nevertheless, series have been published in which virtually no side effects were reported by the patients included and who showed an excellent response to treatment with cemiplimab.[35]

Follow-up

In the first 2 years, 6-monthly local checks are recommended including the inspection of the entire skin and inspection and palpation of

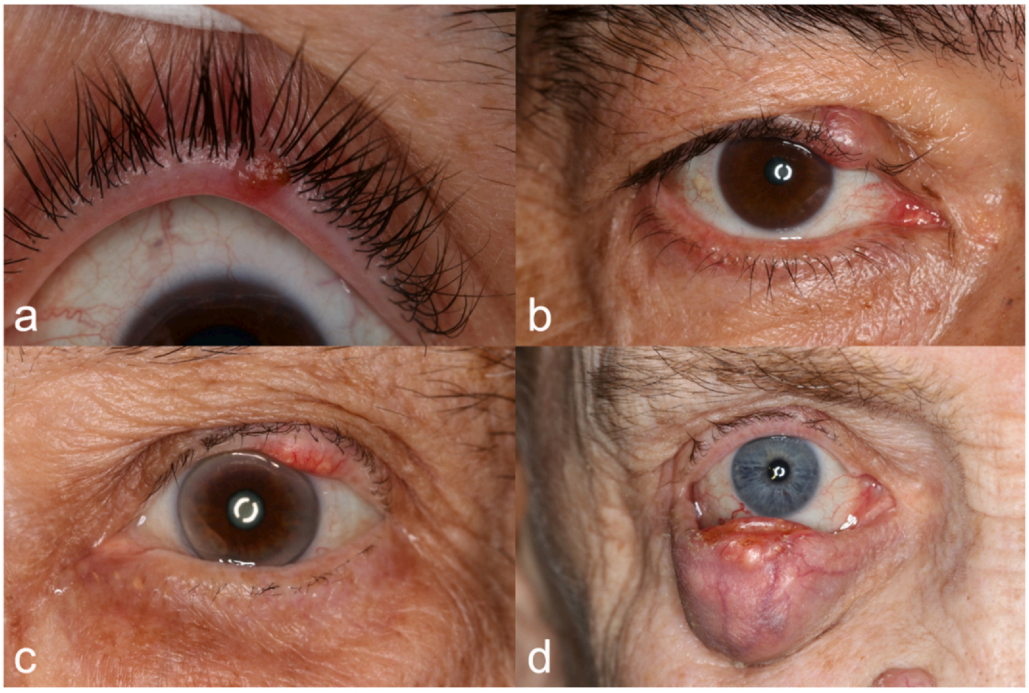

Fig. 5. Sebaceous carcinoma (SC). a A small reddish SC with tiny central ulceration, displacement of the eyelashes and progression in size over the last few months can be seen in the middle of the upper eyelid margin. b Chalazion on the medial upper eyelid was suspected for a year with no improvement following conservative therapy and surgical chalazion removal was performed. The histological examination revealed a SC, followed by extensive resection. c A yellowish-reddish shimmering lesion at the edge of the upper eyelid that had been present for 10 years and had already been excised twice elsewhere on suspicion of hordeolum and chalazion without histological examination. After a third recurrence with increase in size, another excision was performed, which revealed a SC histologically. d Extensive SC of the entire lower eyelid with 2 years growth, which was also excised elsewhere in suspicion of hordeolum without histological diagnostics. One year after the wide local excision, no lymph node metastases were present.

the excision site, the in-transit route and the regional lymph nodes, then annual checks to year 5. For high-risk tumors, local checks are recommended every 3 months for 2 years, then up to year 5 every 6 months and up to year 10 annual checks. Ultrasound of the lymph nodes can also be done at low risk, but must be performed at high-risk tumors up to 3-monthly intervals in the first 2 years and up to 6-monthly intervals to years 5. Regular checks for distant metastases should be performed in the high-risk group up to twice a year in the first 3 years.[20,28]

Sebaceous carcinoma

Clinical appearance

Periocular sebaceous carcinoma (SC) is with 0.6 % to 10.2 % of all malignant eyelid tumors a very rare, slow-growing tumor that affects women more frequently (63.3 %) and appears at a mean age of 67.7 years.[1,36] Asia-Pacific islanders (56.1 %) and Caucasians (42.1 %) are the most affected ethnic groups. The upper eyelid with its highest density of sebaceous glands throughout the whole body is most frequently affected.[37]

Periocular sebaceous carcinoma metastasizes to the regional lymph nodes in up to 23 % of cases - at diagnosis, regional lymph node metastases are present in at least 10–20 % of cases.[6,38] It is one of the most lethal eyelid tumors with an overall mortality rate of up to 33 %.[6] Perineural growth is rare but possible, distant metastasis are uncommon.[36]

Clinically, sebaceous carcinoma present typically as painless tan-pink or yellowish nodular lesions (Fig. 5). It can measure several centimeters in greatest dimension and can ulcerate.[3] Sebaceous gland carcinoma can easily be confused with chronic blepharitis or therapy-resistant chalazion, so that the diagnosis might be delayed by an average of 1.7 years.[36] Unilateral chronic blepharitis or atypical chalazion, not only in patients over 60 years should lead to eyelid biopsy of the suspicious area.[39] Previous immunosuppression or radiotherapy are risk factors for the development of sebaceous carcinoma.[36,40]

Histopathology

Sebaceous carcinoma usually arises from the tarsal Meibomian glands, less frequently from the cutaneous Zeis glands demonstrating sebocytic differentiation.[3,41] Histopathologically, cell lobules with pale, foamy, lipid-containing cytoplasm and large, polymorphous and hyperchromatic nuclei can be recognized (Figs. 6 and 7).

Pagetoid growth refers to the spread in the epithelium of the eyelids and/or conjunctiva and occurs in approximately 24 % of periocular SC, which is at higher risk for metastasis.[36]

To confirm the diagnosis, an immunohistochemical profile is recommended. In periocular sebaceous carcinoma, the markers EMA, adipophilin, BRST1 and CAM5.2 are mostly positive, BerEP4 usually negative, but rarely positive.[36] There is little evidence that a high ALDH1 or androgen receptor index predicts a higher rate of metastasis or recurrence.[36]

Staging

Staging follows the eighth edition of the AJCC guidelines (American Joint Committee on Cancer, seeTable 2), in which T2 tumors are defined as 10–20 mm in greatest dimension with a) no invasion, b) invasion of the tarsal plate or eyelid margin and c) full thickness involvement of the eyelid. T4 includes tumors that invade the ocular, intraocular or facial structures.[6] Esmaeli et al. found that T category of T2b or worse (Tumor > 10 mm, but not > 20 mm, in greatest dimension; or, involves full thickness eyelid) correlated with regional lymph node metastases. Disease-specific survival was poorer among patients with T category of T3a or worse (Tumor > 20 mm in greatest dimension; or, any tumor that invades adjacent ocular or orbital structures; any T with perineural tumor invasion).[42]

If the diagnosis is confirmed, a full body examination and regional lymph node status should be performed. In addition, bulbar motility, proptosis and pupillary reaction should be checked to rule out orbital involvement.[36]

There is no evidence for the need of systematic screening regarding Muir-Torre syndrome for periocular in contrast to extraocular sebaceous carcinoma below the neck region.[36]

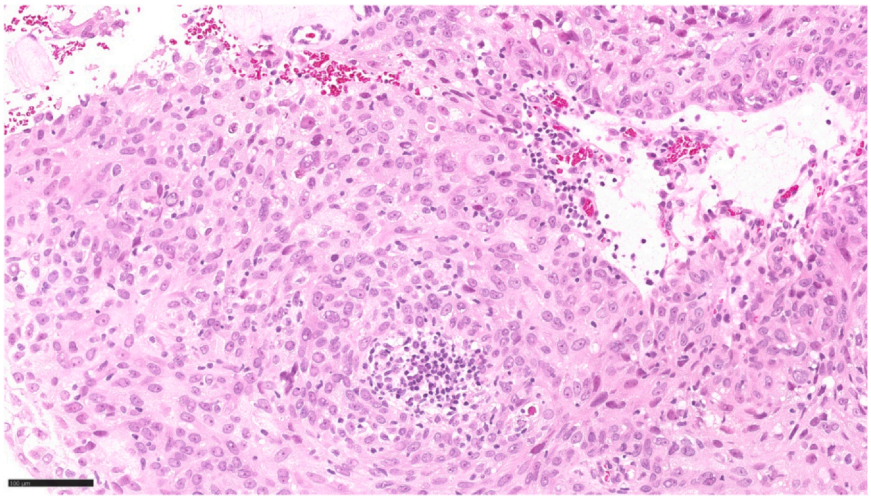

Fig. 6. Histopathology of SC, HE. Histology of a case with suspicion of a chalazion (same case asFig. 5b) showing tumor cells with foamy cytoplasm and large, polymorphous nuclei of a sebaceous gland carcinoma. Hematoxylin Eosin, magnification bar = 100 μm.

With periocular sebaceous carcinoma stage T2c or higher sentinel lymph node biopsy with or without imaging can be considered. If lymph node metastases are present, lymph node dissection and / or adjuvant radiotherapy are recommended. Also staging should be extended to evaluate distant metastases with CT or PET-CT, in case of orbital involvement MRI should be performed.[36]

Update on therapy

Histologically controlled excision in healthy tissue with full margin assessment such as CCPDMA (complete circumferential peripheral and deep margin assessment) = 3D-histology (paraffin sections) or Mohs micrographic surgery (frozen sections) is first-line treatment.[43] In extraocular sebaceous carcinoma complete peripheral margin clearance would be expected with mean margins of 5.4 mm.[36] Despite R0 resection with full margin assessment as in Mohs micrographic surgery, the 5-year recurrence rate is 7 %.[38] In the case of pagetoid growth, conjunctival mapping is recommended to determine the extension to the conjunctiva. Adjuvant therapy with topical mitomycin or cryotherapy can be used in case of focally positive conjunctival margins, or local conjunctival recurrence.[36]

If surgical resection is not possible or there is extensive orbital involvement, radiotherapy may be considered, but is probably inferior to exenteration. Adjuvant radiotherapy can also be considered in case of perineural invasion.[36] For neoadjuvant treatment only retrospective case studies or series are available. In a series of 8 patients undergoing platinum-based neoadjuvant systemic chemotherapy the mean percentage reduction of tumor diameter was 71 %, which may lead to a less extensive surgery.[44] In this series recurrence rate after 44.5 months was 50 %. In another current case report a patient with bilateral periocular sebaceous carcinomas with microsatellite instability was treated with neoadjuvant PD-1 inhibitor pembrolizumab, which is approved by the FDA for microsatellite instability-high or mismatch repair deficient cancer, resulting in a reduced tumor burden to less than 1/3 of the original size leading to a smaller defect after Mohs surgery and a better reconstructive outcome.[45]

There are no systemic treatment regimens established for distant metastases. Conventional chemotherapy based on anthracycline or platinum is possible, immunotherapy with PD-1 inhibitors[46] or targeted therapies can be considered after multidisciplinary consultation.[36] In future, next-generation sequencing may lead to individual therapy options.

Follow-up

In the first three years, semi-annual local and lymph node checks are recommended, thereafter annual checks. Depending on disease stage additional annual controls for distant metastases should be performed.[36]

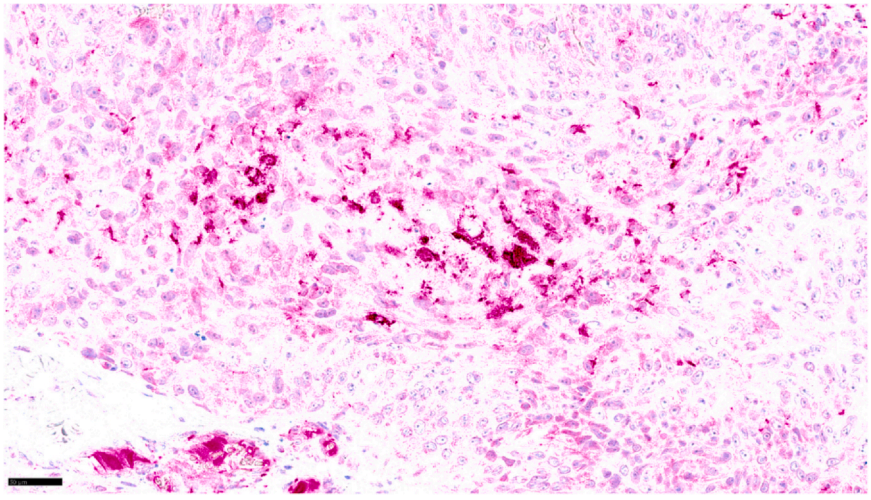

Fig. 7. Histopathology of SC, immunohistochemistry. Tumor cells of the same case asFigs. 5b and6 showing inhomogenous, granular cytoplasmic positivity for adipophilin. Magnification bar = 50 μm.

Eyelid melanoma

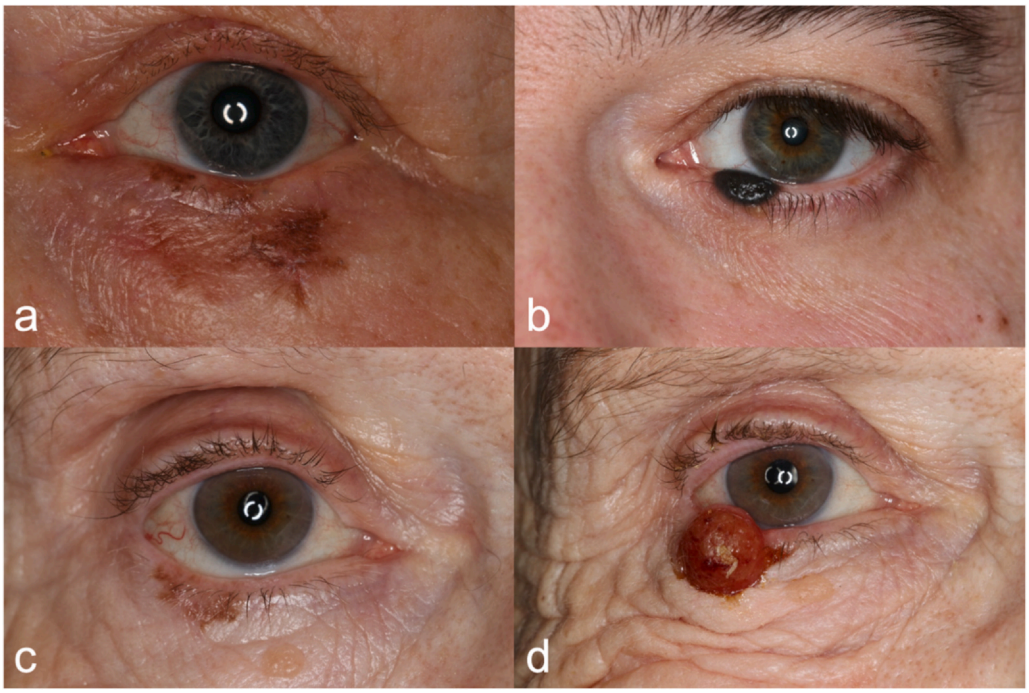

Fig. 8. Eyelid melanoma. a Lentigo maligna melanoma with irregular pigmentation and borders at the lower eyelid skin and the eyelid margin in a 57-year-old patient. b 47-year-old patient with malignant melanoma on the medial lower eyelid with nearly black pigmentation, which formed de novo one year before and had progressed in size since then. c Lentigo maligna was suspected on the lateral lower eyelid. As the pigmentation had not changed for years, the 74-year-old female patient refused to have a tissue sample taken, so it was initially only observed. d 3 years later, there was a drastic change of the finding in the same patient of c with a now prominent vascularized and irregularly pigmented malignant melanoma confirmed histologically after wide local excision.

Clinical appearance

Eyelid melanoma is rare and accounts for less than 1 % of all eyelid malignancies.[1] It metastasizes to the regional lymph nodes in up to 11 % of cases and forms distant metastases in 7 %,[47] mainly in the lungs, liver, brain or bones.[48] The mortality rate is high at 25 %.[49] Pain occurs in case of rare perineural growth.[50] With regard to histological types considering 11 studies included in a review by Mancera et al. superficial spreading melanoma is the most frequently diagnosed (35 %), followed by Lentigo maligna melanoma (31 %), nodular melanoma (19 %) and other melanoma types (16 %).[51]

Superficial spreading melanoma and lentigo maligna melanoma occur in chronically sun-exposed skin, more often in men. Usually, they present as slowly growing pigmented maculae fulfilling the ABCDE criteria for clinical diagnosis of melanoma: asymmetry, border irregularity, color variegation, diameter enlargement, and evolution (history of change).[3]

Nodular melanomas appear as nodular tumors with a broad spectrum of pigmentation, ranging from very dark to amelanotic variants, which can lead to diagnostic difficulties (Fig. 8). In the superficial spreading form, an irregularly defined and pigmented plaque is visible, ranging from tan to nearly black.[3]

Histopathology

In lentigo maligna melanoma, mostly single cytologically atypical melanocytes proliferate in the basal layer of the epidermis forming coalescing nests. It is characterized by a lentiginous in situ component, called lentigo maligna, and actinic elastosis. In contrast to superficial spreading melanoma lentigo maligna melanoma often shows a more indefinite border with epidermal thinning and loss of rete ridges.[3]

Superficial spreading melanoma is dermal invasive but has cytological features similar to those of the intraepidermal tumor cells displaying a pagetoid growth pattern. The atypical melanocytes present large nuclei with prominent nucleoli, irregularly clumped or dense

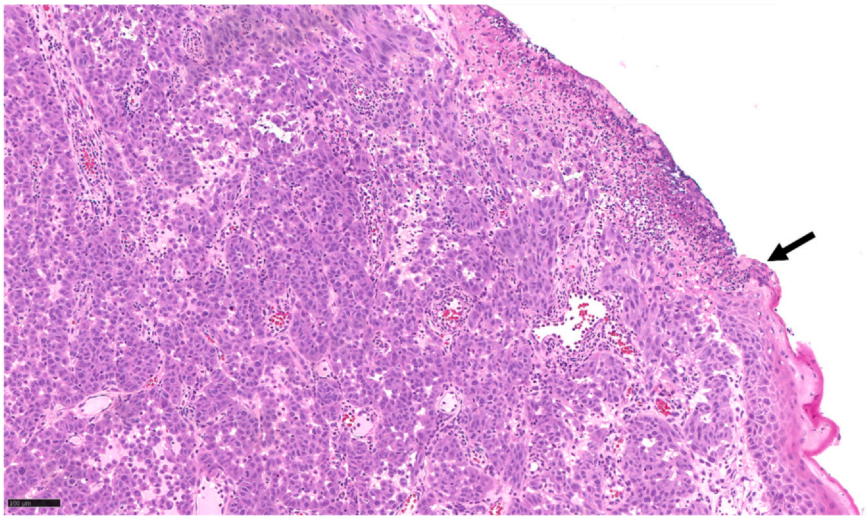

Fig. 9. Histopathology of malignant melanoma, HE. Malignant melanoma with ulceration, in the lower right area an epidermal segment, the transition is marked by an arrow (same case as inFig. 8d). The dysplastic tumor cells are diffusely and trabecularly arranged and show hyperchromatic nuclei. Hematoxylin Eosin, magnification bar = 100 µm.

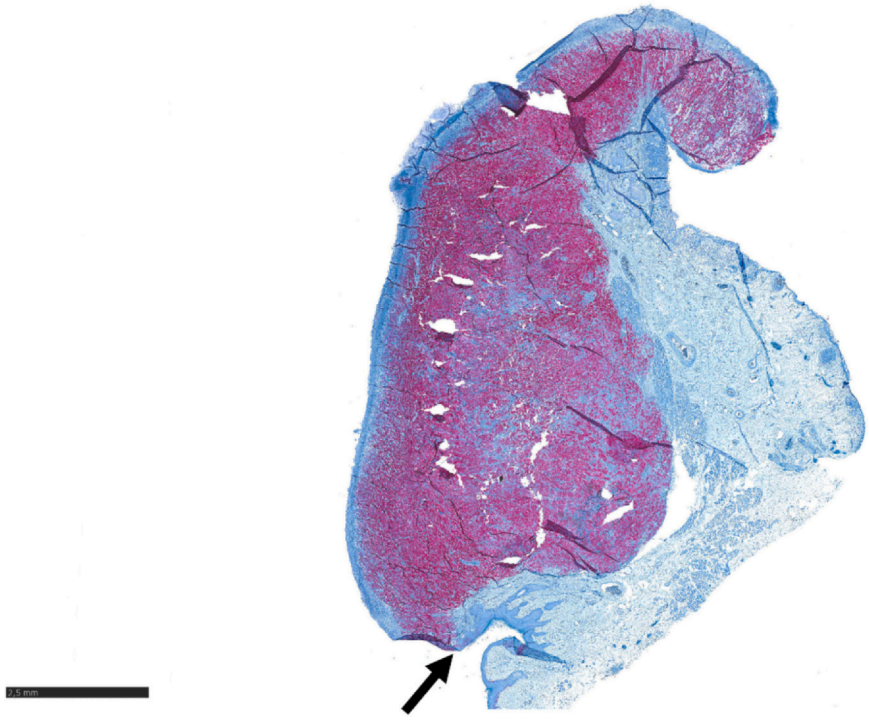

Fig. 10. Histopathology of malignant melanoma, immunohistochemistry. Tumor cells stained positive with antibodies against Melan A with negative epidermis in the lower corner and also negative superficial ulceration above the edge (arrow) of the epidermal segment (same case asFigs. 8d and9). Magnification bar = 2.5 mm.

Table 3
Definition of primary tumor (T) for melanoma.[6]

T Category	Thickness	Ulceration status	Pathological stage group
TX: primary tumor thickness cannot be assessed (e.g., diagnosis by curettage)	Not applicable	Not applicable	
T0: no evidence of primary tumor (e.g., unknown primary or completely regressed melanoma)	Not applicable	Not applicable	
Tis (melanoma in situ)	Not applicable	Not applicable	0
T1	≤ 1.0 mm	Unknown or unspecified	
T1a	< 0.8 mm	Without ulceration	IA
T1b	< 0.8 mm	With ulceration	IA
	0.8-1.0 mm	With or without ulceration	
T2	> 1.0-2.0 mm	Unknown or unspecified	
T2a	> 1.0-2.0 mm	Without ulceration	IB
T2b	> 1.0-2.0 mm	With ulceration	IIA
T3	> 2.0-4.0 mm	Unknown or unspecified	
T3a	> 2.0-4.0 mm	Without ulceration	IIA
T3b	> 2.0-4.0 mm	With ulceration	IIB
T4	> 4.0 mm	Unknown or unspecified	
T4a	> 4.0 mm	Without ulceration	IIB
T4b	> 4.0 mm	With ulceration	IIC

chromatin, and eosinophilic or bright cytoplasm.[3]

In nodular melanomas, large clusters of atypical melanocytes are visible in the dermis (Fig. 9) with possible epidermal ulceration. Usually, the melanoma cells are epitheloid, tumor cytology can be uniform or vary, forming a clonal pattern. Differentiation from other entities is particularly important in amelanotic variants of malignant melanoma. The immunohistochemical staining of Melan-A (Fig. 10), HMB45 antigen, tyrosinase, S100 protein, and SOX10, as well as the absence of keratinocyte-derived cells with negativity for cytokeratin AE1/AE3 and lymphoid cells (CD3) usually helps to establish the diagnosis of a melanocytic malignancy.[3] Recently, PRAME was added to the list of antibodies that can contribute to the diagnosis of skin melanomas with nodular nevi rather staining negative and melanomas rather positive.[52]

Histopathologic diagnosis of malignant melanoma should be based on the current AJCC classification. The tumor thickness according to Breslow is the most important prognostic factor in the primary stages of melanoma (measured from the top of the stratum granulosum to the deepest tumor cell in the dermis or subcutis). In addition, the presence of ulceration should also be indicated.[6,48]

From stage IIIA (one detected lymph node), testing for specific mutations should be carried out, as specific inhibitors are therapeutically available when BRAF, NRAS and c-kit mutations are detected.[48] The most frequently mutated oncogene in malignant melanomas is BRAF, which is detectable in around 50 % of primary melanomas.[53]

Staging

If a malignant melanoma is suspected or diagnosed, the entire skin including the adjacent visible mucous membranes should be inspected and the draining lymph nodes should be palpated or scanned.[48]

Staging follows the eighth edition of the AJCC guidelines (American Joint Committee on Cancer) with the definitions of TNM.[6] Classification

of primary tumor (T) is listed in Table 3 with the according pathological stage groups up to stage IIC. Stages IIIA-D include lymph node involvement (N1–3c), stage IV includes distant metastasis (M1).

As of tumor stage IB (< 0.8 mm thickness with ulceration or 0.8 – 1.0 mm thickness), locoregional lymph node ultrasonography should be performed in patients with a primary diagnosis of malignant melanoma. A sentinel lymph node biopsy is recommended from a tumor thickness of 1.0 mm, in the presence of risk factors such as ulceration, increased mitotic rate or patient age < 40 years even with thinner primary tumors. From stage IIC (> 4 mm with ulceration), additional staging using brain MRI, cross-sectional imaging of the entire body like PET/CT is recommended as well as the examination of the tumor markers S100B and LDH.[6,48]

Update on therapy

Wide local excision with margins of at least 5 mm is the gold standard to treat clinically highly suspicious eyelid melanoma. Also in case of a suspected or diagnosed lentigo maligna, a complete excision should be performed in order to prevent progressive growth and thus the transition to an invasive malignant melanoma.[48]

In special anatomical localizations such as the face with the eyelid area, reduced safety margins can be accepted when using 3D-histology (micrographically controlled surgery) without increased local recurrence or reduced overall survival.[48] Nevertheless, the choice of safety margin depends on the tumor thickness according to Breslow: If the tumor thickness is less than 1 mm, a safety margin of at least 3 mm is recommended; if the thickness is greater than 1 mm, a safety margin of 5 mm should be maintained. For melanomas ≥ 2 mm, wider margins of excision should be considered.[47,54]

If an R0 situation cannot be achieved by surgical measures, following wound healing radiotherapy should be added to achieve local control.[48]

If lymph node metastases of malignant melanoma are present, lymph node dissection and, if necessary, adjuvant radiotherapy are recommended. Distant metastases can also be treated with radiotherapy; depending on their location, surgical resection may also be an option.[48]

Depending on the stage of the tumor, patients can be offered various adjuvant drug therapies, see alsoTable 1:

Patients with tumor stage AJCC IIB/C (> 2.0 to > 4.0 mm with ulceration) should be offered adjuvant interferon therapy. For patients with tumor stage III A-D (lymph node positive) and IV (distant metastasis positive) adjuvant therapy with checkpoint inhibitors as anti-PD1 antibodies are an option.[48] In terms of recurrence-free survival, a risk reduction of 43 % was achieved with pembrolizumab (compared to placebo) and of 35 % with nivolumab (compared to ipilimumab).[55,56] Despite the potential risk of life-threatening and permanent side effects, the benefits of the therapy seem to outweigh the risks.

Patients with tumor stage III A-D (lymph node positive) and BRAF-V600-mutation should be offered adjuvant therapy with BRAF and MEK inhibitors (BRAF = v-raf murine sarcoma viral oncogene homolog B; MEK = mitogen-activated protein kinase kinase).[57,58] A risk reduction of 53 % of recurrences and 43 % of melanoma-related death was demonstrated with combination therapy.[57] A recent study stated a median progression free survival of 14.9 months with combination therapy of encorafenib and binimetinib compared to 7.3 months with BRAF inhibitor vemurafenib monotherapy.[59] In 66–70 % of patients grade 3 or 4 adverse events occurred such as gastrointestinal disorders, eye disorders, pyrexia, decreased left ventricular ejection fraction and increased gamma-glutamyl transferase.[59] With vemurafenib ocular toxicity was described in 22 % of patients including uveitis, conjunctivitis and dry eyes.[60] In stage IV (any stage with distant metastases) BRAF/MEK-inhibitor combinations with PD1-inhibitors with or without CTLA-4 inhibitor are options (CTLA-4 = cytotoxic T-lymphocyte-associated protein 4). If these drugs are ineffective, chemotherapy remains another therapeutic option.[48]

Follow-up

3 to 6-monthly local checks are recommended for 3 years, which can be extended slightly up to year 10. However, an annual full-body examination should be carried out for the rest of the patient's life. From stage IB, additional lymph node checks and control of serum S100B are recommended every 3 to 6 months until year 5, and from stage IIC, further PET-CT scan should be performed every 6 months in the first 3 years.[48]

Merkel cell carcinoma

Clinical appearance

Merkel cell carcinoma (MCC) occurs very rarely, accounting for less than 1 % of all malignant eyelid tumors.[1] Men are affected more often than women. It is usually localized at the upper eyelid, fast-growing and highly malignant.[61,62] In 2/3 of cases it metastasizes to the regional lymph nodes, in 1/3 of cases distant metastases occur (usually in skin, bone, liver, lungs and brain).[1,63] Metastases already exist at the time of diagnosis in up to 1/3 of cases. The 5-year overall survival is reported to be 50–60 %, with a more advanced stage being associated with a poorer prognosis.[63] Most of the patients are older than 70 years. Only 4 % are younger than 50 years and have a higher risk of other malignancies due to germline variants in genes associated with cancer predisposition, which requires genetic testing and counseling.[64] Increased UV exposure, immunodeficiency, and clonal integration of the Merkel cell polyomavirus (MCPyV) are cited as risk factors.[3]

Clinically, a reddish-purple, well-defined nodule with intact skin with a usually shiny surface is typically seen (Fig. 11). Merkel cell carcinoma grows very quickly and painlessly. Ulceration or telangiectasia are relatively rare, satellite metastases are more common.[63] Rarely MCC conceal a chalazion, which underlines the histological diagnosis of an excised atypical chalazion.[65]

Histopathology

From a histopathological point of view, Merkel cell carcinoma exhibits both epithelial and neuroendocrine differentiation.[63] It belongs to the "small blue round cell tumors" with a round cell nucleus with nuclear moulding and fine, bubble-shaped chromatin (so-called salt-and-pepper pattern), high nucleocytoplasm ratio and little cytoplasm (Fig. 12). Tumor cells almost always infiltrate the dermis and subcutaneous tissue, often with lymphatic and vascular invasion, which is associated with a poorer prognosis.[63] The diagnosis can be confirmed by immunohistochemical detection of cytokeratin 20 (CK 20), which is

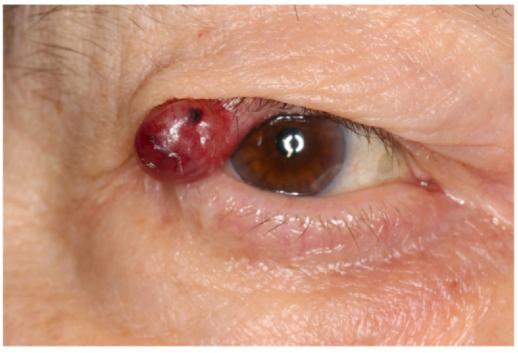

Fig. 11. Merkel cell carcinoma (MCC). MCC on the temporal upper eyelid existing for three months with noticeably progression in size. A reddish-purple globular, firm, non-movable tumor with smooth surface can be seen.

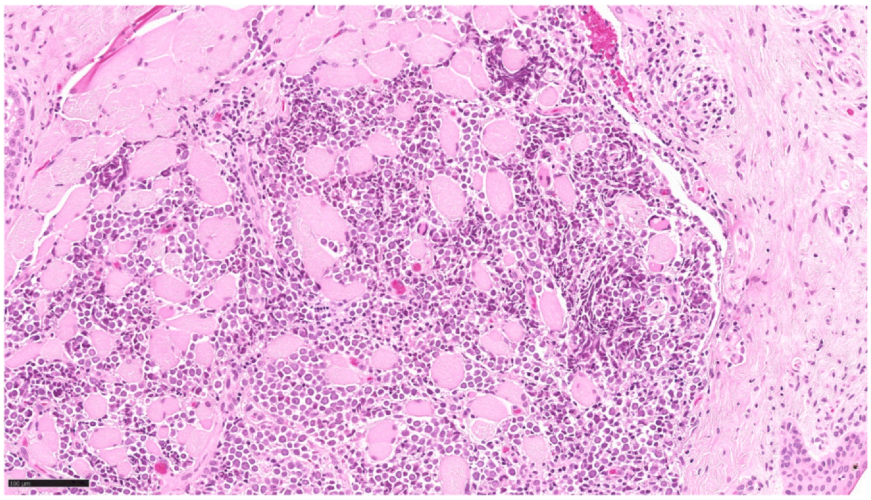

Fig. 12. Histopathology of MCC. Diffuse infiltrating Merkel cell carcinoma consisting of multiple round cells with large basophilic nuclei infiltrating the orbicularis muscle. A small epidermis segment at the right lower corner. Same case asFig. 11. Hematoxylin Eosin, magnification bar = 100 µm.

Table 4
Definition of primary tumor (T) for Merkel cell carcinoma (MCC).[6]

T Category	T Criteria
TX	Primary tumor cannot be assessed (e.g., curetted)
T0	No evidence of primary tumor
Tis	*In situ* primary tumor
T1	Maximum clinical tumor diameter ≤ 2 cm
T2	Maximum clinical tumor diameter > 2 cm but ≤ 5 cm
T3	Maximum clinical tumor diameter > 5 cm
T4	Primary tumor invades fascia, muscle, cartilage, or bone

typically found in the neuroendocrine granules, as well as the absence of thyroid transcription factor 1 (TTF-1). Other positive markers can be pancytokeratin, Chromogranin A, neuron-specific enolase (NSE), synaptophysin, INSM1 or N-CAM (CD56).[66,67]

Staging

In addition to inspecting the tumor itself, the initial examination should also include inspection of the entire skin and palpation of the regional skin and lymph node sites. Imaging of the draining lymph nodes via ultrasound and cross-sectional imaging to exclude distant metastases should also be performed by using 18F-FDG-PET/CT or alternatively, CT thorax/abdomen and brain MRI.[63]

Staging follows the eighth edition of the AJCC guidelines (American Joint Committee on Cancer), see Table 4.[6]

Update on therapy

Wide local excision with a large safety margin in healthy tissue represents the gold standard. In the eyelid region, a safety margin of at least 5 mm is a recommended compromise – in contrast to other areas of the body, where a safety distance of 1–2 cm should be maintained.[61,63] Due to the high frequency of lymphogenic metastasis, a sentinel lymph node biopsy should be performed even in the case of a clinical and imaging N0/M0 situation.[63]

Since local recurrences occur with a quite high rate, e.g. in 26 % of low-risk cases located in head and neck, the excision area should be treated with adjuvant radiotherapy.[63,68]

If lymphogenic metastasis is present (positive sentinel lymph node biopsy), lymph node dissection or radiotherapy of the locoregional lymph nodes is recommended.[63]

In the case of distant metastasis or locally advanced disease that cannot be controlled by surgical or radiotherapeutic interventions, the indication for systemic therapy should be examined. Immunotherapy using PD-1/PD-L1 blockade appears to be superior to chemotherapy in terms of survival, duration of response and toxicity.[63] The PD-1 inhibitor pembrolizumab, which has been approved for recurrent locally advanced or metastatic Merkel cell carcinoma, showed a response rate of 58 %, a median progression-free survival of 16.8 months and a 3-year progression-free survival of 39.1 %, see alsoTable 1.[69,70] The checkpoint inhibitor avelumab, a human monoclonal immunoglobulin G1 (IgG1) antibody directed against programmed cell death-ligand 1 (PD-L1), has been approved for the treatment of metastatic Merkel cell carcinoma. A response rate of approximately 30 – 40 % could be shown.[63]

Follow-up

3-monthly local checks for the first 2 years, then 6-monthly checks for another 3 years, including lymph node palpation and sonography are recommended. In case of lymphatic metastasis or unclear lymph node status, additional PET/CT imaging for distant metastases at least once or twice a year should be performed.[63,71]

Summary

Wide local excision remains the primary therapeutic gold standard of various eyelid malignancies with safety margins depending upon malignancy grade of each tumor type. Margins of at least 5 mm should be maintained in case of potentially metastasizing tumors with even larger margins — if possible, in highly malignant tumor types such as Merkel cell carcinoma or malignant melanoma. Conventional chemotherapy has been replaced and/or substituted by immune checkpoint inhibitors providing effective antitumoral impact in patients with advanced eyelid malignancies caring metastases. The spectrum of side effects differs from that of conventional chemotherapy. This has to be kept in mind and if affecting the eye and its adnexa should be communicated with treating oncologists to provide optimal care of these patients.

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Declaration of Competing Interest

The authors have no relevant financial or non-financial interests to disclose.

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Kristina Joana Schoelles, Doctor of Medicine (MD), FEBO. Lid- and plastic surgery, member of laboratory for ophthalmic pathology (Prof. Auw-Haedrich). Eye Center, Medical Center - University of Freiburg, Freiburg, Germany