Interdisciplinary Management of Skin Cancer

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ABSTRACT

The interdisciplinary treatment of skin cancer in the head and neck area requires close collaboration between different specialist disciplines. The most common non-melanoma tumor entities are cutaneous squamous cell carcinoma and basal cell carcinoma as well as their precursor lesions. One of the less common tumors is Merkel cell carcinoma, which also occurs primarily in light-exposed areas and, in contrast to squamous and basal cell carcinoma, is more likely to metastasize. Due to the low tendency of basal cell carcinoma as well as cutaneous squamous cell carcinoma to metastasize, a cure can often be achieved by surgery. If the tumor growth exceeds certain levels it may require collaboration between dermatology and otorhinolaryngology. The primary goal of this interdisciplinary collaboration is to achieve a functional, cosmetically and aesthetically acceptable result in addition to adequate tumor treatment. Depending on the stage of the tumor and the clinical course, a case may be discussed in an interdisciplinary tumor board in order to determine a personalised, appropriate and adequate treatment concept for each patient, including prevention, therapy and follow-up.

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Contents

ABBREVIATIONS

AFX	Atypical fibroxanthoma
BCC	basal cell carcinoma
DTT	difficult to treat
EGFRi	epidermal growth factor inhibitor
5-FU	Fluorouracil
HHI	Hedgehog pathway inhibitor
HIV	Human Immunodeficiency Virus
HPV	high risk human papilloma virus
laBCC	locally advanced basal cell carcinoma
LN	lymph node
mSCC	metastasized squamous cell carcinoma
PDS	Pleomorphic dermal sarcoma
PDT	photodynamic therapy
PD-1	programmed cell death protein 1
RT	radiotherapy
SCC	squamous cell carcinoma
cSCC	cutaneous squamous cell carcinoma

1. Introduction

The interdisciplinary cooperation of different medical specialties in patients with skin cancer is of particular relevance to ensure the best possible and stage-appropriate treatment of patients.

In the interdisciplinary decision-making process, ideally in the tumor board, the disciplines of oncology, surgery, and radiotherapy should be involved in addition to representatives of dermatology in drawing up the therapy recommendation for the care of skin cancer patients. Depending on the localization of the tumor, other specialist departments may also be involved. In the case of tumor localizations in the head and neck area, cooperation with experts experienced in tumors in the field of ear, nose and throat (ENT) medicine is of particular importance.

In this review, skin tumors, which occur preferentially or among others in the head and neck region are discussed and therefore require close cooperation with ENT specialist.

1.1 Types of skin cancer

With an area of 1.8 m², the skin is the largest organ of the human body. It protects the body from heat, light, injuries and infections. Other functions are the regulation of body temperature through sweating, as well as the formation of vitamin D and storage of fat.

Microscopically, the skin can be divided into three layers. The epidermis is composed of a multilayered keratinizing squamous epithelium. The outermost layer contains dead horny cells. Below this is the germinal layer, which is composed of the basal layer and the spinous layer. In the basal cell layer are the stem cells, from which keratinocytes arise that keratinize and lose their nucleus on their way through the spinous layer. Furthermore, melanocytes are found in the basal layer of the epidermis.

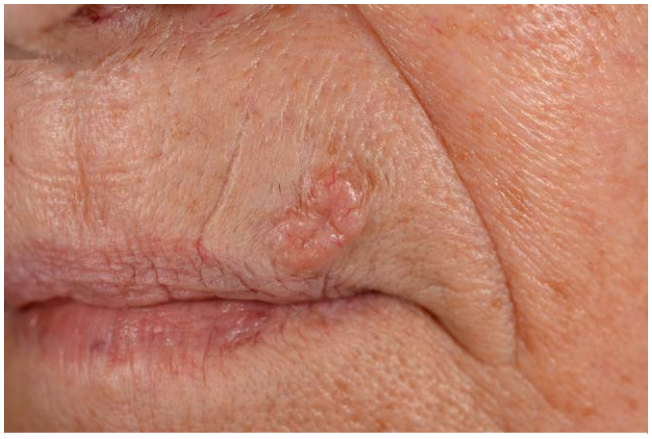
Below the epidermis lies the dermis, also called the corneum. It is a connective tissue rich in collagen fibers. Blood and lymph vessels are located here, as well as hair follicles, nerve fibers, sebaceous and sweat glands. Together, the dermis and epidermis form the cutis.

The subcutis is located below the cutis. It consists of loose connective and fatty tissue and serves as cold protection and energy storage.

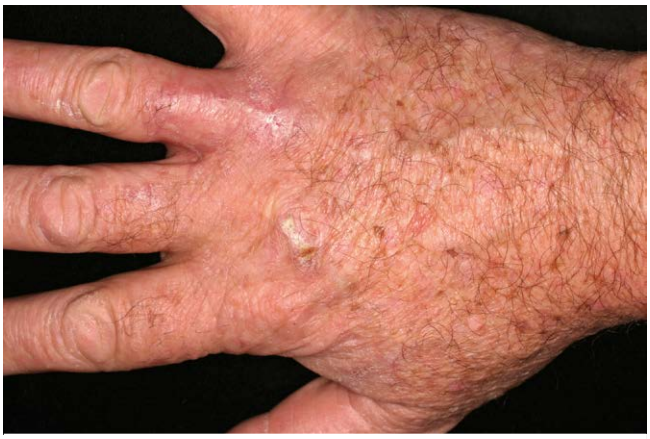
Various tumors can arise from the different cells of the skin. Basal cell carcinoma and squamous cell carcinoma are the most common tumor entities of epithelial origin. Malignant melanoma can develop from melanocytes. Less common skin tumors include, for example, Merkel cell carcinoma, sebaceous gland carcinoma, or sweat gland carcinoma [1]. Epithelial tumors also often occur concurrently or with only a slight time lag. The term of field cancerization describes the presence of precancerous and invasive tumors over a large area at several sites of a body area. In addition to field cancerization of the skin, field cancerization has also been described in the mucous membranes of the head and neck (oral cavity, oropharynx, larynx), as well as in the lungs, vulva, esophagus, cervix, colon, and bladder [2].

Basal cell carcinoma (BCC) is the most common malignant non-melanoma skin tumor [3]. Originating from the stem cells of hair follicles and interfollicular epidermis, basal cell carcinomas grow slowly to infiltrate and destruct, but metastasize very rarely. Basal cell carcinomas do not primarily occur on the mucous membranes, palms or soles [4, 5].

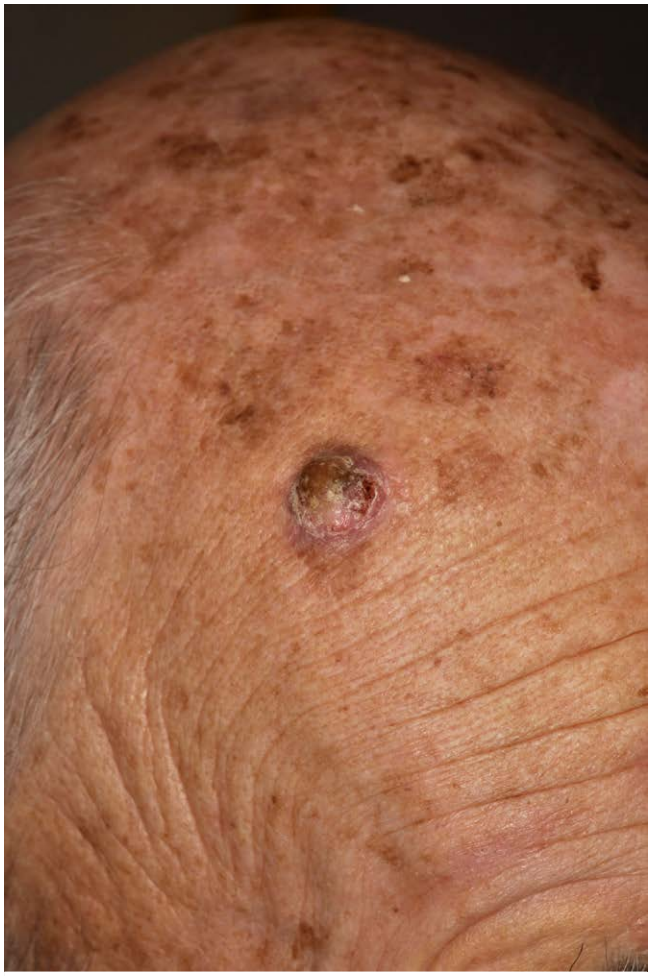
Clinically, a skin-colored to reddish node, plaque, or ulceration is seen. Classic nodular basal cell carcinomas are characterized by a bead-like rim and telangiectasia, with occasional central ulceration (▶ **Fig. 1**). Other subtypes include superficial basal cell carcinoma, sclerodermiform basal cell carcinoma, pigmented basal cell carcinoma, ulcerated basal cell carcinoma, and destructive basal



▶ **Fig. 1** Nodular basal cell carcinoma. Clinically, a skin-colored node with a pearl cord-like rim and telangiectasia is seen.



▶ **Fig. 3** Actinic keratosis of the hand. A rough brownish scaly plaque is seen.



▶ **Fig. 2** Squamous cell carcinoma of the forehead. A crusty dermal node is present, which may occasionally bleed.

cell carcinoma. The ulcero-nodular forms are the most common (60-80 % of cases).

Cutaneous squamous cell carcinomas (cSCC) are the second most frequent non-melanoma skin tumors with a percentage of 25 % after basal cell carcinoma with approximately 75 %. Similar to basal cell carcinomas, cutaneous squamous cell carcinomas rarely metastasize [6]. In addition to cutaneous forms, squamous cell carcinomas also occur on mucous membranes. Cutaneous squamous cell carcinomas usually, but not necessarily, develop from intraepidermal proliferation of atypical keratinocytes [7].

Clinically, squamous cell carcinomas of the skin present as a skin-colored to red, crusty, often eroded, dermal nodes or ulcerations, which occasionally bleed (▶ **Fig. 2**). In the oral mucosa, squamous cell carcinomas present as a rough leukoplakia or an ulcerated node.

Actinic keratosis (AK) is an obligate precancerous condition, which is classified as a precursor of squamous cell carcinoma. It is a malignant proliferation of keratinocytes [7]. Morphologically, actinic keratosis presents as rough, red or brownish desquamation. Wart-like growths may also occur (▶ **Fig. 3**). Progression of actinic keratosis to cutaneous squamous cell carcinoma is estimated to occur in 10 % of cases [8].

Bowen's disease is an intraepidermal carcinoma in situ. It can progress to invasive squamous cell carcinoma similar to actinic keratosis [9].

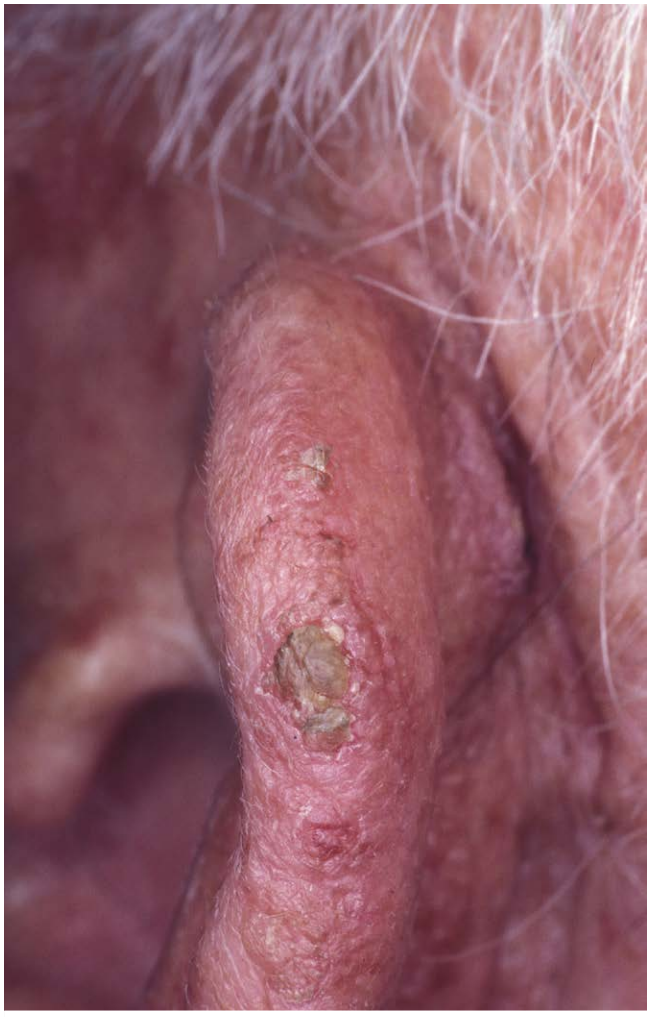
Clinically, Bowen's disease presents as a sharply demarcated, non-pigmented, reddish, partially scaling plaque and is characterized by slow growth [9] (▶ **Fig. 4**).

Merkel cell carcinoma (MCC) or cutaneous neuroendocrine carcinoma of the skin is a very rare but aggressive skin tumor [10]. It got its name from the similarity to the morphology to Merkel cells, which act as mechanoreceptors of the skin [11].

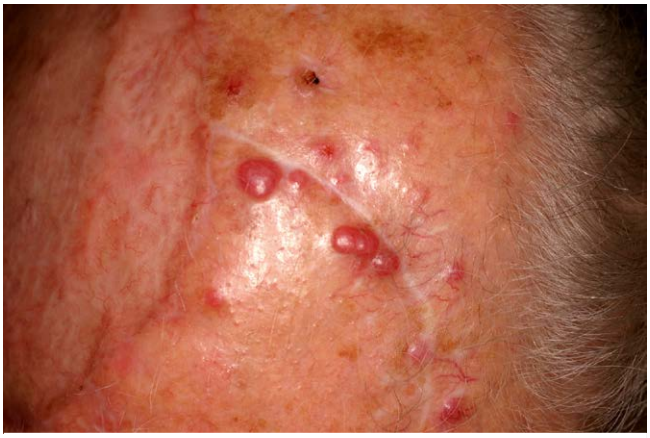
Merkel cell carcinomas occur in half of the cases in the head and neck region and in about 30 % in the distal extremities [11]. They arise from daughter cells of epidermal stem cells. Furthermore, an association between Merkel cell polyomavirus and Merkel cell carcinoma is suspected, as the virus can be detected within the tumor tissue in approximately 80 % of Merkel cell carcinomas [12, 13].

Clinically, Merkel cell carcinomas present as a painless, bluish or reddish nodes and are characterized by rapid growth. Occasionally, ulceration or induration can be seen as well (▶ **Fig. 5**).

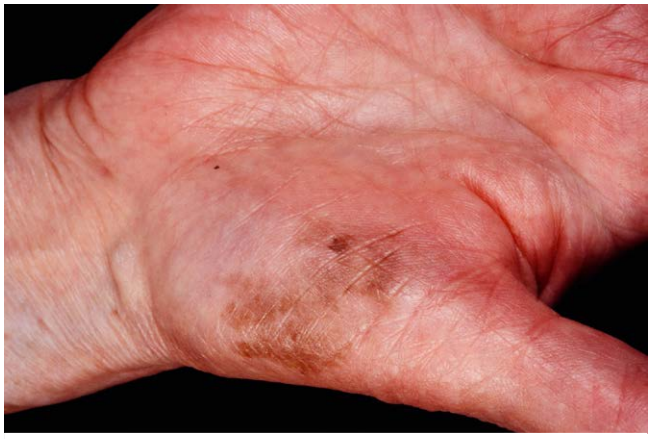
As the tumor disease progresses, both basal cell carcinomas and squamous cell carcinomas can grow in a locally destructive and ul-



▶ **Fig. 4** Bowen's disease of the ear. A sharply demarcated, non-pigmented plaque appears. Bowen's disease is characterized by slow growth.



▶ **Fig. 5** Merkel cell carcinoma at the capillitium. Painless reddish nodes, which are characterized by rapid growth.



▶ **Fig. 6** Lentigo maligna of the hand. Clinically, a pigmented, patchy, asymmetric macula is seen.

cerative manner. Merkel cell carcinomas show this behavior less frequently.

Malignant melanomas are aggressive skin tumors that originate in the melanocytes of the skin. They are characterized by early invasive growth and a tendency to lymphogenic and hematogenic metastatic spread.

Since melanocytes develop from the ectoderm, melanomas can occur not only on the skin but also on the mucous membranes, choroid, and substantia nigra [10].

Lentigo maligna as melanoma in situ or **lentigo maligna melanoma** is a subtype of malignant melanoma, which occurs primarily on actinically damaged skin in light-exposed areas, especially in the head and neck region [14]. Clinically, lentigo maligna appears as an inhomogeneous, brown to black pigmented, blurred macula (▶ **Fig. 6**). It usually affects older patients because, unlike other subtypes of malignant melanoma, lentigo maligna is etiologically associated primarily with chronic, cumulative UV exposure [15]. Lentigo maligna is confined to the epidermis and is therefore, by definition, a melanoma in situ. It exhibits overall slow and initially mainly radial and horizontal growth, but may progress to invasive growth and lentigo maligna melanoma over the long-term [14, 16]. Therefore, in case of clinical suspicion or histopathological confirmation of lentigo maligna or lentigo maligna melanoma, complete histological margin-proven excision is indicated [17].

For the sake of completeness, **atypical fibroxanthoma** (AFX) and **pleomorphic dermal sarcoma** (PDS) will also be mentioned here. The two cutaneous neoplasms are very rare and are now considered to be a spectrum of one entity, the differentiation of which is made histopathologically [18]. Here, atypical fibroxanthoma is confined exclusively to the dermis, whereas pleomorphic dermal sarcoma invades deeper layers and can often aggressively infiltrate into the subcutis, skeletal muscles, and fascial structures. Therefore, adequate depth needs to be ensured when obtaining a specimen biopsy. The peak age at first diagnosis is between 70-80 years of age and, as with other skin tumors, men are significantly more commonly affected than women [19]. Clinically, the skin changes are typically found in the chronically light-exposed areas, such as the face and capillitium, with both skin changes usually appearing as skin- to flesh-colored, partly indurated and frequently ulcerated

nodules. In contrast to atypical fibroxanthoma, pleomorphic dermal sarcoma presents with indistinct borders and aggressive infiltrative growth. After histopathologic confirmation, complete excision of the cutaneous neoplasia should be attempted. In case of locally advanced findings and questionable R0 operability or suspicion of metastasis in pleomorphic dermal sarcoma, further imaging is also indicated preoperatively, followed by determination of the further procedure in an interdisciplinary tumor board [18].

1.2 Epidemiology and etiology

Skin cancer is one of the most common types of cancer worldwide. Among the different types of skin cancer, basal cell carcinomas are the most common. Squamous cell carcinomas are the second most common skin tumors [3].

The incidence of **basal cell carcinoma** in Germany is 200 per 100,000 inhabitants per year with an increasing trend. The mean age of onset is 73 years in men and 71 years in women. Men are more frequently affected than women [20].

Basal cell carcinomas occur primarily in the head and neck region (approximately 60 %), but also in the trunk and extremities (approximately 40 %). The distribution is comparable in both sexes [21, 22].

In the development of basal cell carcinoma, activation of the Sonic Hedgehog (SHH) signaling pathway is of particular importance. An uncontrolled activation of Smoothened (SMO), caused by a mutation in the inhibitor patched gene (PTCH), leads to a resistance in the apoptosis behavior of keratinocytes. Among the sporadic basal cell carcinomas, 10 % have an activating mutation in SMO and 90 % have an inactivating mutation of PTCH [23]. In addition, point mutations in p53 contribute to tumorigenesis [24].

The main risk factor for all epithelial skin tumors is intense UV exposure (of natural or artificial genesis). In addition to cumulative sun exposure over a long period of time (causative especially for the epithelial skin cancers), the risk is also increased by frequent sunburns, especially during childhood (especially for melanoma risk) [25–27]. Consequently, the use of tanning beds also poses an increased risk for the development of all skin tumors [28].

Furthermore, endogenous risk factors such as the male sex and a light skin type (skin type I and II according to Fitzpatrick) play an important role, but also other risk factors such as prolonged immunosuppression and/or ionizing radiation [23]. In immunosuppressed patients, the risk of basal cell carcinoma is increased by a factor of 4 to 7 [29].

Less frequently, certain genetic syndromes lead to the occurrence of skin cancer. In basal cell carcinoma syndrome, also known as Gorlin-Goltz syndrome, an autosomal dominant genodermatosis, multiple basal cell carcinomas occur among others. Basal cell carcinoma syndrome is caused by a germline mutation in PTCH1 [30]. Radiation therapies are contraindicated because they induce tumor growth.

Other rarer syndromes associated with an increased incidence of basal cell carcinoma include Dugois-Colomb-Berthon syndrome, Rombo syndrome, and linear unilateral basal cell carcinoma.

According to the Robert Koch Institute, approximately 29,300 men and 20,100 women were initially diagnosed with squamous cell carcinoma in Germany in 2014 [31].

Various factors come together in the development of cutaneous **squamous cell carcinomas**. Chronic UV exposure and associated DNA damage, e. g. due to mutations in the tumor suppressor gene p53 or activation of EGFR, FYN or the Ras oncogene H-Ras, play a central role [32]. Further, squamous cell carcinomas occur more frequently in immunosuppressed patients, e. g., after organ transplantation, with a more than 65-fold increased incidence [33]. The risk for the development of actinic keratoses is also shown to be increased in organ transplanted patients. These actinic keratoses are additionally characterized by aggressive growth behavior and earlier progression to squamous cell carcinoma [34]. Preventive measures including counseling and educating patients at the time of organ transplantation are recommended.

Moreover, exposure to chemical carcinogens, such as arsenic or polycyclic hydrogens, is associated with an increased risk of developing squamous cell carcinoma. For squamous cell carcinomas at primarily non-sun-exposed sites, there is an association with high-risk human papillomavirus (HPV). Similar to other skin tumors, immunosuppressed patients (organ transplantation, Human Immunodeficiency Virus (HIV) infection) have an increased risk of developing squamous cell carcinoma. These patients do not only show a higher metastasis rate of 5-8 %, but are also more prone to local recurrence (13 %) [34].

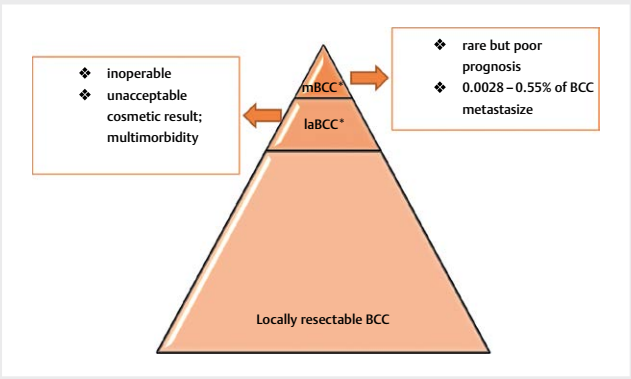
An increased incidence of squamous cell carcinoma and its precancerous lesions has been observed in some occupational groups, so that these can be recognized as occupational diseases under certain conditions. Skin cancer due to soot, crude kerosene, tar, anthracene, and pitch is considered one of the oldest recognized occupational diseases in Germany. The association between exposure to these substances and the development of malignant skin lesions has been recognized since 1925. Squamous cell carcinomas, carcinomas in situ, and basal cell carcinomas can occur even decades after exposure.

In occupations with increased sun exposure, such as activities in agriculture and forestry, horticulture, fishing and seafaring, construction and crafts (e. g. roofers, carpenters, builders, bricklayers, steel construction fitters), recognition of squamous cell carcinomas or multiple actinic keratoses of the skin caused by natural UV radiation can be requested as an occupational disease. In the case of several years of occupational activity in the field, a BG report should always be considered (BG = Berufsgenossenschaft, employers' liability insurance association).

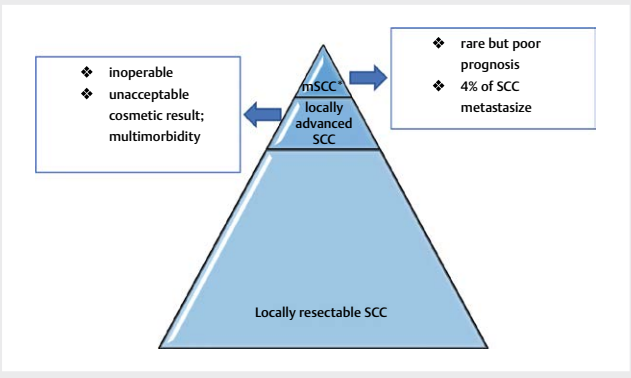
A reasonable suspicion exists only when cutaneous squamous cell carcinoma, Bowen's carcinoma or multiple precursors (AK or Bowen's disease) or field cancerization with an affected area > 4 cm^2 have been diagnosed at work-related exposed areas. In addition, a sufficiently long work-related exposure duration must be fulfilled [35].

Furthermore, depending on the dose, ionizing radiation can lead to the development of epithelial tumors, such as cutaneous squamous cell carcinoma and basal cell carcinomas, more rarely fibrosarcomas and angiosarcomas. This may affect, for example, occupational groups in the medical field or in materials testing. Radioactive materials may be a hazard to persons involved in the extraction, processing, use, or transport of these materials.

The latency period for the development of basal cell carcinomas is at least 20 years [36]. For squamous cell carcinomas, a latency period of approx. 20-30 years is given [37].



▶ **Fig. 7** Basal cell carcinoma – prognostic presentation. *BCC: basal cell carcinoma; mBCC: metastatic basal cell carcinoma; laBCC: locally advanced basal cell carcinoma.



▶ **Fig. 8** Squamous cell carcinoma – prognostic presentation. *mSCC: metastatic squamous cell carcinoma; SCC: squamous cell carcinoma.

Diseases caused by arsenic or its compounds play almost no role in today's dermatological practice, as exposure to these substances has become extremely unlikely due to improved occupational safety measures [38].

With a median age of diagnosis of 75 years, **Merkel cell carcinoma** occurs primarily in older age [13]. For Europe, the incidence is low and is estimated to be around 0.2-0.3/100,000/year, with men more commonly affected than women [39].

With regard to the development of Merkel cell carcinoma, the exact causes are not fully known yet. Presumably, a combination of different risk factors leads to the development of the tumor. In addition to UV radiation, weakened immune function such as iatrogenic, post organ transplantation, in the context of underlying hematological diseases or due to HIV infection, represent risk factors and are associated with a less favorable prognosis [10].

The association with Merkel cell polyomavirus has been known since 2008. Thus, up to 80 % of Merkel cell carcinomas in Europe have Merkel cell polyomavirus (MCPyV or MCV). Here, Merkel cell carcinomas that are MCPyV negative show a higher DNA mutational burden than MCPyV positive Merkel cell carcinomas as well as mutations in the TP53 gene. The extent to which MCPyV affects treatment response and prognosis is not known [12, 13].

Lentigo maligna melanoma accounts for 4-15 % of all melanomas and 10-26 % of melanomas in the head and neck region. Approximately 78 % of lentigo maligna melanomas occur on chronically sun-damaged skin in the head and neck region. The median age of onset is 66-72 years (approximately 10-15 years older than the other melanoma subtypes), and again, men are more commonly affected than women [40, 41].

Risk factors include older age with chronically sun-damaged skin and increased numbers of lentigines and actinic keratoses [42].

In particular, Whiteman et al. identified chronic sun exposure for the development of lentigo maligna. In addition, mutations in NF1, BRAF V600K, NRAS and KIT, as well as CCND1, MITF and TP53 may contribute to tumorigenesis [14, 43].

1.3 Prognosis

Basal cell carcinomas metastasize very rarely (0.0028 % to 0.55 % of cases) [2]. Metastasis is associated with increased mortality [48] (▶ **Fig. 7**).

In locally advanced basal cell carcinoma of the head, infiltration of the skull, dura, and brain may occur. The incidence of this is 0.3 % [49, 50].

In periorbital basal cell carcinoma, infiltration of the orbita is seen in 5 % of cases [44]. Risk factors are a localization of the primary tumor at the medial lid angle, recurrent situations, infiltrative growth, a sclerodermiform subtype, and perineural infiltration [45]. Perineural growth is described in 0.18 % to 3 % of cases [46].

Recurrences frequently occur in the face and head area. Therefore, a classification of risk zones has also been established for the facial area.

The nose, periorbital area, lips, jaw angle, temple, ears and periauricular areas, as well as genitals, hands and feet are classified in the "H zone", zone with high risk of recurrence. Cheek, forehead, capillitium, and neck are classified as "M zone" with moderate risk of recurrence. Trunk and extremities are assigned to the "L zone" with a low risk of recurrence [47].

Actinic keratoses are considered precancerous lesions of squamous cell carcinoma. Progression of actinic keratosis to cutaneous squamous cell carcinoma is estimated at a rate of approximately 10 % [8].

Cutaneous squamous cell carcinomas rarely metastasize. In a prospective study by Brantsch et al., a cohort of 615 patients showed a metastatic risk of 4 % [6] (▶ **Fig. 8**).

Increased tumor thickness, immunosuppression, and localization to the ear were identified as the most important prognostic factors. The risk of local recurrence seemed to be increased by greater tumor thickness, as well as by desmoplasia [6].

In the current AWMF guideline, in addition to the factors already mentioned above, horizontal tumor diameter (> 2 cm), histologic degree of differentiation (> grade 3), perineural growth, and affection of the lower lip are mentioned as additional sites besides the ear [38].

Recurrence of cutaneous squamous cell carcinoma is an indicator of poor prognosis. When multiple risk factors are also present, overall survival is significantly worse [48, 49].

While the 10-year relative survival rate is generally high (107 % in women and 106 % in men), it is significantly reduced in the presence of distant metastases. In stage IV, the median survival time is only 2 years [6].

Classification is analogous to malignant melanoma using the TNM classification, which takes into account horizontal tumor extension, lymph node status, and organ involvement. However, a prognostic value cannot be taken from the TNM classification. (▶ **Table 2, 3**).

The principle of field cancerization was first described by Slaughter et al. in 1953 [50]. They investigated the presence of histologically abnormal tissue in the vicinity of oral squamous cell carcinomas to explain the development of multiple primary tumors and recurrences. In addition to field cancerization of the skin, field cancerization has previously been described in the mucosa of the head and neck (oral cavity, oropharynx, larynx), as well as the lung, vulva, esophagus, cervix, colon, and bladder [51].

Recent molecular studies show that the formation of a field of genetically modified cells plays a significant role in the development of carcinomas. The development of a field cancerization starts with a stem cell that has genetic alterations and forms a field with a unit of clonally altered daughter cells. These fields can be identified based on a mutation in TP53. Additional genetic alterations create a "proliferating" field. The preneoplastic field gradually displaces the normal (mucous) skin, and one or more tumors or tumor precursor lesions develop. After surgery, these (subclinical) fields often remain and can thus lead to the development of further tumors, which are referred to as local recurrence or second primary tumor, depending on the localization and time interval [52].

Genetically, actinic keratoses show a similar mutation pattern as cutaneous squamous cell carcinomas. Whether this commonality results in a therapeutic consequence with regard to system therapy is currently being investigated in an ADO study on "FieldCancerization" by Gutzmer and colleagues (EudraCT-No. 2021-006372-17).

Merkel cell carcinomas have a tendency to lymphogenic metastasis, with approximately 30 % of patients showing lymph node metastases or cutaneous metastases at primary diagnosis. Recurrences of Merkel cell carcinoma are usually observed in the first 2 years after the initial diagnosis. When tumor progression occurs, locoregional metastases occur before distant metastases in most cases [53]. While distant metastases frequently involve the skin, soft tissues, bone, lung, and liver, cerebral branching is very rare [54].

The 5-year survival rate of Merkel cell carcinoma depends on the stage of the disease, it being 63-75 % in stage I and 35-60 % in stage II. In the presence of lymphogenic metastasis, the 5-year survival rate decreases to 27-40 % and further decreases to 13-18 % in the presence of distant metastases [55, 56].

In addition to the involvement of the sentinel lymph node, the number of affected organs in a metastatic situation is mentioned as a risk factor for a worse course. Furthermore, the localization of the primary tumor in the head and neck region, relevant immunosuppression, and male gender are considered unfavorable prognostic factors [57].

With regard to melanocytic tumors, **lentigo maligna** and **lentigo maligna melanoma** will be discussed here, focusing on the head and neck region. In general, there is a good prognosis for lentigo maligna. For invasive lentigo maligna melanoma, the prognosis is the same as for other invasive melanomas, depending on the tumor thickness [40].

Initially, lentigo maligna is limited to the uppermost layer of the skin, but can progress to invasive melanoma, although the exact percentage is unknown. It is assumed that the risk is between two and five percent [58].

2. Prevention

The generic term "prevention" encompasses targeted behavioral and situational measures that are intended to prevent the occurrence and spread of diseases and their health and socioeconomic effects. Behavioral prevention describes individual behavior and how it can influence personal health risks. Education, information and thus strengthening of the health competence of the individual is obligatory for this so that people are enabled to avoid potential risk factors in their personal lifestyle or to influence them positively. Ideally, behavioral prevention should be combined with situational prevention, which influences living, working and environmental conditions. The aim here is to improve the framework conditions for risk avoidance and health maintenance. Furthermore, it is divided into primordial, primary, secondary, tertiary and quaternary prevention. Primordial prevention precedes primary prevention and is intended to prevent the emergence of social risk factors. Primary prevention addresses healthy people and aims to prevent the new development of a (chronic) disease, thereby reducing the incidence or accidents. Secondary prevention is concerned with the early detection of a disease before symptoms or complaints have developed and aims to prevent or mitigate disease progression. Screening of supposedly healthy subjects plays an important role in this regard. In the context of tertiary prevention, the aim is to prevent the occurrence of complications and/or health sequelae/damage in people with the disease. Finally, quaternary prevention describes the avoidance of unnecessary medical measures, be it examinations, medication or prevention. It focuses on people who, from the physician's point of view, do not have a disease but feel ill. Here, the importance lies in the responsible decision of the physician to forego further diagnostics and therapy.

As a prerequisite for targeted prevention, it is indispensable to know the pathogenetic relationships of a disease and to be able to act preventively according to the development and stage of a disease. Regarding the prevention of skin cancer, there is a separate S3 guideline: "Prevention of skin cancer", the content of which is presented here only in abbreviated form for the sake of clarity, with the kind reference to the guideline for a more detailed presentation [59].

As the etiology and progression of the different types of skin cancer are described in detail elsewhere (see section 1.2), reference is made to the corresponding text passages.

UV exposure of the skin is the most significant factor for the development of skin cancer. In addition to intermittent sun exposure, cumulative and, in some cases, occupational UV exposure is also critical to its development. Therefore, effective sun protection is one of the primary core preventive measures in an individual's behavioral prevention. Avoiding the midday sun and staying in the shade whenever possible is recommended. Wearing long clothing is considered a physical sun protection measure, which is especially recommended for children and adolescents. If sun exposure cannot be avoided, sunscreens such as sunscreens with SPF > 50 + should be used to avoid sunburns [68]. In addition, the use of solariums should be avoided.

Furthermore, constitutional risk factors, such as skin type in non-melanoma skin cancer as well as skin type and the size of congenital nevi in malignant melanoma, have to be considered. Acqui-

red risk factors for non-melanoma skin cancer entities include actinic keratoses, a history of non-melanoma skin cancer, immunosuppression, and radiographic combination damage [59]. Acquired risk factors for the development of malignant melanoma include a history of melanoma, a positive family history for melanoma, number of acquired nevi, and clinically atypical nevi [59].

In the context of secondary prevention, regular self-examinations for changes in the skin, such as unusual pigmentation, changes in birthmarks and skin lesions, are recommended in the guideline "Prevention of skin cancer" based on consensus. As an evidence-based recommendation, a physician's full-body inspection is listed as a screening examination in the guideline. Skin cancer screening is part of the statutory cancer screening program in Germany, entitling statutorily insured persons over 35 years of age to participate every two years.

3. Diagnostics

In the diagnosis of epithelial tumors, clinical findings, in addition to histopathologic findings, are often seminal. Dermoscopy is an important tool for clinical diagnosis of basal cell carcinoma. In 2016, a study by Anhlide et al. showed that dermoscopy can be used to diagnose basal cell carcinoma with a sensitivity of 93.3 % and a specificity of 91.8 % [69].

To assess the risk of recurrence and the aggressiveness of basal cell carcinoma, size and location are important in addition to the histologic subtype.

The *European Association of Dermatooncology* (EADO) has proposed a definitive classification of basal cell carcinoma into four stages (▶ **Table 1**). This EADO staging system is the first staging system that takes into account the operability and specificities of basal cell carcinoma and covers the entire spectrum of basal cell carcinoma.

In practice, most basal cell carcinomas fall into stage I. They are easily treated with a low risk of recurrence.

EADO stage IIA includes basal cell carcinomas that are difficult to treat because of their location or the patient profile (poor general condition of the patient, comorbidities), whereas in stage IIB the number of basal cell carcinomas makes treatment difficult. Stage IIIA, IIIB, and IIIC includes large, destructive basal cell carcinomas in functionally critical locations. Metastatic basal cell carcinomas are classified as stage IV [60].

However, the histologic subtype can only be reliably determined by histologic examination [61, 62].

Not least for this reason, punch or excision biopsies are usually performed to confirm the diagnosis. Histopathologic findings should include information on vertical tumor diameter (tumor thickness), resection margins, and histologic subtype. Evidence of infiltrative narrow-cap, fibrosing/sclerosing, or perineural growth is of particular interest, as it provides important parameters for further treatment selection (surgical vs. non-surgical) [63].

Further cross-sectional imaging should be performed only in certain cases, such as suspected metastasis, infiltrative growth, or perineural growth [64].

If **actinic keratosis** is suspected, inspection and palpation are suitable for diagnosis. Clinical and histologic grading may differ in this regard [65]. Assessment of invasive growth cannot be confidently

▶ **Table 1** EADO classification of basal cell carcinoma.

	Risk	Stage		Characteristics	
Classic, but DTT	Easy to treat & low risk of recurrence	Classic BCC	I	Classic low-risk BCC	Recurrences only develop because of blind treatment or insufficient resection margins
			IIA	Classic BCC, but DTT	▪ Due to tumor and/or patient-related factors, the treatment is more complex then usually ▪ Good results and low recurrence rates can be expected with surgery even if it is technically complicated, provided that the patient is cooperative
Locally advanced BCC (laBCC)	Increasingly difficult treatment & increasing risk of recurrence		IIB	DTT-BCC (due to multiple classic BCC)	▪ Many classic BCC (>10) or multiple complex BCC (>5) occurring sporadically or in the context of basal cell carcinoma syndrome* *if at least one of the multiple BCC can be identified as II or IV, the patient is classified accordingly and not as IIB
		Locally advanced BCC	IIIA	laBCC in non-critical areas	▪ Large destructive tumors in uncritical or functionally relevant areas considered as curable, without expecting functional impairment
			IIIB	laBCC in critical areas	▪ Large destructive tumors in critical or functionally relevant areas considered as resectable, however, functional impairment or mutilation is unavoidable
			IIIC	Extremely advanced BCC	▪ Advanced and deeply invasive tumors that involve extracutaneous tissue and are responsible for extreme clinical situations ▪ Healing by surgery cannot be expected, independently from the tumor size
Metastatic situation		mBCC	IV		Distant metastasis

(DTT: difficult to treat; BCC: basal cell carcinoma; laBCC: locally advanced basal cell carcinoma)

▶ **Table 2** TNM classification of squamous cell carcinoma of the skin of the head and neck (8th edition, 2017).

T categories	
TX	Primary tumor cannot be assessed
T0	No hint to primary tumor
Tis	Carcinoma in situ
T1	Tumors of ≤ 2 cm max.
T2	Tumors of > 2 cm to < 4 cm max.
T3	Tumors of > 4 cm max. or superficial bone invasion/ perineural invation/deep invation*
T4a	Tumors with gross cortical bone/marrow invasion
T4b	Tumor with skull base or axial skeleton invasion including foraminal involvement and/or vertebral foramen involvement to the epidural space
N category	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastases identified
pN1	Metastases in a solitary ipsilateral lymph node of ≤ 3 cm (without extranodal spread)
pN2a	Metastases inn a solitary ipsilateral lymph node of ≤ 3 cm (with extranodal spread) or > 3 cm to ≤ 6 cm (without extranodal spread)
pN2b	Metastases in multiple ipsilateral lymph nodes of ≤ 6cm (without extranodal spread)
pN2c	Metastases in bilateral or contralateral lymph nodes of ≤ 6 cm (without extranodal spread)
pN3a	Metastases in one lymph node of > 6 cm (without extranodal spread)
pN3b	Metastases in one lymph node of > 3 cm (with extranodal spread) or in multiple ipsilateral, contralateral, or bilateral lymph nodes (with extranodal spread)
M category	
M0	No distant metastases
M1	Distant metastases

*"deep invasion": invasion beyong subcutaneous adipose tissue or > 6 mm Perineural invasion as criterion for T3: clinical or radiological involvement of identified nerves without involvement of the foramina/skull base. In multiple simultaneous tumors, the tumor with the highest T category is classified and the number of definable tumors is given in brackets; e. g. T2(4).

estimated [66]. Progression of actinic keratosis to cutaneous squamous cell carcinoma occurs in an estimated 10 % of cases [8].

Nevertheless, dermoscopy is a good and noninvasive initial methodology to differentiate actinic keratosis from other tumor entities [67]. Histologic confirmation is not necessary in all cases with typical clinical findings of actinic keratosis. In a clinical study, dermoscopy was shown to be similarly reliable in diagnosing actinic keratosis compared to the gold standard of histologic confirmation [68]. However, in cases of clinically inconclusive findings, biopsy or excision is still recommended, as well as in cases of suspected cutaneous squamous cell carcinoma.

Actinic keratosis is characterized both clinically and histologically by hyperplasia of atypical keratinocytes. Actinic keratoses can be classified histologically according to the extent of atypical keratinocytes throughout the epidermis [69].

In the differentiation of an actinic keratosis and invasive cutaneous squamous cell carcinoma, the detection of proliferation crossing the basal membrane is crucial. The transition from an actinic keratosis to a cutaneous squamous cell carcinoma can be described by a 3-stage classification, the "KIN I-III concept".

In keratinocytic intraepidermal neoplasia (KIN) I, atypical keratinocytes are seen in the lower third of the epidermis. This stage may progress to stage KIN II, in which atypical keratinocytes can be found in two-thirds of the epidermis. Finally, in stage KIN III, the entire epidermis is affected [7].

In premalignant or precancerous actinic keratoses, only KIN III is classified as in situ cutaneous squamous cell carcinoma [70]. Alternatively, the tumor can be directly excised completely [71].

If **cutaneous squamous cell carcinoma**s metastasize, about 80 % of the metastases occur as locoregional lymph node filiae or as satellite or in-transit metastases. Early detection of metastasis is of particular importance, as it often allows complete resection of the metastases.

Especially for head and neck cutaneous squamous cell carcinoma, lymph node sonography is an effective method to detect filiae [72]. In cutaneous squamous cell carcinomas with presence of risk factors (tumor thickness > 5mm, grade 3 differentiation, immunosuppressed patients) or suspicion of regional lymph node metastases, lymph node sonography should be performed obligatorily [38]. In case of sonographic suspicion of cervical or parotid metastasis, the diagnosis should be extended by a CT scan of the neck and thorax, an MRI of the parotid gland, and fine-needle cytology [72]. Also, further cross-sectional imaging should be performed in locally advanced squamous cell carcinoma to exclude distant metastases [73]. Various studies on HNSCC postulate the better sensitivity and specificity of FDG-PET/CT as a sectional imaging diagnostic of spread [38].

Since the clinical appearance of **Merkel cell carcinoma** can vary, the clinical diagnosis is difficult and should ultimately always be confirmed by means of fine-tissue diagnostics. Histopathologic findings should include tumor extension, growth pattern (nodular or infiltrative), lymphatic and vascular infiltration, and R-situation. Immunohistochemical staining (chromogranin A, synaptophysin, cytokeratin 120) is helpful for differentiation from metastases of other small cell carcinomas [74].

After histopathological diagnosis, lymphogenic and distant metastasis should be excluded, especially with regard to the prognostic value. Up to one third of patients show metastasis at the time of initial diagnosis, which is why the diagnosis of spread by lymph node sonography and further sectional imaging ideally by 18F-FDG PET/CT or PET/MRI are indicated [54, 75].

Because occult lymph node metastases are often present, a sentinel lymph node biopsy should be performed [76]. Staging is according to the 8th edition of the AJCC classification. (▶ **Table 4**).

When the presence of **lentigo maligna/lentigo maligna melanoma** is suspected, biopsy with histopathological examination of the tissue ensures the final diagnosis. In this regard, excisional biopsy with narrow margins is considered the gold standard for melanoma, as this allows sufficient assessment with regard to depth [77].

▶ **Table 3** Classification of squamous cell carcinoma of the skin (8th edition, 2017). (For the labial skin (excluding labial red), trunk, upper extremities and shoulders, lower extremities and hip, and scrotum).

T categories			
TX	Primary tumor cannot be assessed		
T0	No hint to primary tumor		
Tis	Carcinoma in situ		
T1	Tumors of ≤ 2 cm max.		
T2	Tumors of > 2 cm to < 4 cm max.		
T3	Tumors of > 4 cm max. or superficial bone invasion/perineural invation/deep invation*		
T4a	Tumors with gross cortical bone/marrow invasion		
T4b	Tumor with skull base or axial skeleton invasion including foraminal involvement and/or vertebral foramen involvement to the epidural space		
N category			
pNX	Regional lymph nodes cannot be assessed		
pN0	No regional lymph node metastases identified		
pN1	Metastases in a solitary ipsilateral lymph node of ≤ 3 cm (without extranodal spread)		
pN2a	Metastases inn a solitary ipsilateral lymph node of ≤ 3 cm (with extranodal spread) or > 3 cm to ≤ 6 cm (without extranodal spread)		
pN2b	Metastases in multiple ipsilateral lymph nodes of ≤ 6cm (without extranodal spread)		
pN2c	Metastases in bilateral or contralateral lymph nodes of ≤ 6 cm (without extranodal spread)		
pN3a	Metastases in one lymph node of > 6 cm (without extranodal spread)		
pN3b	Metastases in one lymph node of > 3 cm (with extranodal spread) or in multiple ipsilateral, contralateral, or bilateral lymph nodes (with extranodal spread)		
M category			
M0	No distant metastases		
M1	Distant metastases		
Staging			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1	M0
Stage IV	T1, T2, T3	N2, N3	M0
	T4	each N	M0
	each T	each N	M1

*"deep invasion": invasion beyong subcutaneous adipose tissue or > 6 mm Perineural invasion as criterion for T3: clinical or radiological involvement of identified nerves without involvement of the foramina/skull base. In multiple simultaneous tumors, the tumor with the highest T category is classified and the number of definable tumors is given in brackets; e. g. T2(4).

Histologically, lentiginous proliferation of basal atypical melanocytes is seen on sun-damaged skin [16], often extending well beyond the clinically apparent margin and then too frequently leading to incomplete resections, re-resections, and large defects. Tumor mapping should also be considered early in these cases.

4. Treatment of precancerous and primary lesions

4.1 Non-surgical treatment approaches

For the treatment of **low-risk basal cell carcinoma** as well as basal cell carcinoma in elderly multimorbid patients, a variety of non-surgical treatment approaches are available according to the guideline. Various preparations are approved for topical use in histologically confirmed or superficial basal cell carcinoma. An overview is provided in ▶ **Table 5**. Advantages of topical therapeutics are the possibility of home application, sparing of surrounding tissue, and good esthetic results. Disadvantages are the lack of histological control and the limited penetration depth, with the risk of residual tumor nests at depth.

According to the guideline, ablative as well as non-ablative lasers can also be used for low-risk basal cell carcinoma in the presence of contraindications to surgery or topical procedures. However, similar to cryosurgery, laser procedures are used in a limited

▶ **Table 4** Pathological/clinical classification (pTNM) of Merkel cell carcinoma.

Stage	Primary tumor	T	Regional lymph nodes	N	Distant metastases	M
0	In situ	Tis	Inconspicuous lymph nodes	N0	None	M0
I	≤2 cm max. tumor diameter	T1	Histopathologically inconspicuous lymph nodes	pN0	None	M0
IIA	>2 cm max. tumor diameter	T2-3	Histopathologically inconspicuous lymph nodes	pN0	None	M0
IIB	Infiltration of fascia/ muscles/ cartilage/ bones	T4	Histopathologically inconspicuous lymph nodes	pN0	None	M0
IIIA	Independent of the primary tumor	T1-4	Histopathologically proven lymph node metastasis, with previously clinically inconspicuous findings	N1sn N1a	None	M0
IIIA	Unknown primary	T0	Pathologically confirmed lymph node metastasis, with clinical suspicion	N1b	None	M0
IIIB	Independent of the primary tumor	T1-4	Pathologically confirmed lymph node metastasis with clinical suspicion or intransit metastasis	N1b-3	None	M0
IV	Independent of the primary tumor	T0-4	Independent of the lymph node stage	N0-3	Distant metastasis	M1

way due to the lack of histopathologic control. Thus, ongoing regular clinical follow-up after laser treatment is important, as subclinical extension of basal cell carcinomas tends to be deep rather than lateral [23].

According to the recommendation of the S2K guideline, the indication for radiotherapy should be considered after interdisciplinary consultation in cases of inoperability of locally advanced basal cell carcinoma due to extension and location, age or comorbidity of the patient or other contraindications against surgery [23]. Incomplete surgical excision of basal cell carcinoma (R1, R2) without the possibility of resection also indicates radiotherapy [86]. In a meta-analysis of 40 randomized and 5 non-randomized trials with variable follow-up, the recurrence rate after radiotherapy (3.5 %) was comparable to surgical excision (3.8 %) and micrographic surgery according to Mohs (3.8 %) [87].

With norm fractionation (5 x 2 Gy per week), at least 60 Gy should be applied according to the guideline recommendation, and up to 66 Gy for tumors larger than 2 cm in diameter. In older multimorbid patients, hypofractionated regimens can be offered.

Due to the risk of secondary malignancies, the indication for radiotherapy should also be based on the life expectancy of the patients, assuming a latency period until the development of a second tumor of at least 10 years [88]. Patients with an increased risk for the induction of a second tumor (age <40 years, genetic syndromes, such as Gorlin-Goltz syndrome and xeroderma pigmentosum) or collagenoses (lupus erythematosus, scleroderma), which are associated with a high probability for the occurrence of acute or late radiation reactions, should not receive radiotherapy for basal cell carcinoma [23].

Various therapeutic options are available for **actinic keratosis** in clinical practice. The choice of therapy should take into account age, comorbidities, immunosuppression, and patient preference [89].

In general, topically applied 5-Fluorouracil (5-FU) is shown to be an effective therapeutic option for patients with established or new-onset actinic keratoses. Topical application of diclofenac is another therapeutic option. Diclofenac is inferior to 5-FU but has the advantage of a milder side effect profile [90].

Tirbanibulin (KX2-391) is a dual small molecule inhibitor. It inhibits the protein tyrosine kinase Src, as well as tubulin polymerase [91]. Src is expressed at increased levels in actinic keratoses [7]. Tirbanibulin has been approved since July 2021 for topical use in non-hyperkeratotic, non-hypertrophic actinic keratoses of the face and scalp. Transient side effects with tirbanibulin are comparatively mild [92].

In two identically designed studies, 1 % tirbanibulin ointment applied once daily for 5 days showed to be superior to vehicle in the treatment of actinic keratosis at 2 months (NCT03285477 and NCT03285490). Transient local reactions and recurrence of lesions after 1 year were observed with treatment.

A total of 702 patients were randomized into the two studies. Complete remission occurred in 44 % of patients in the tirbanibulin group and in 5 % of patients in the vehicle group in study 1. In study 2, the percentages were 54 % and 13 %, respectively. At one year, the estimated percentage of patients with relapse was 47 %. These patients had previously shown complete remission.

Photodynamic therapy, cryosurgery, and laser surgery may also be used for actinic keratoses [7].

According to the guideline, a combination of field-directed and lesion-directed therapy may also be recommended. In immunocompetent patients, treatment can be offered for grade I-III actinic keratoses by cryosurgery, ablative laser procedure, or surgical removal by curettage, shallow ablation, or complete excision, for both single and multiple actinic keratoses. Surgical excision is preferred in immunosuppressed patients.

For grade I-II actinic keratoses, topically assisted procedures, such as the application of 5 % 5-fluorouracil cream, may be offered for single or multiple actinic keratoses. The formulation may also have application in field-directed treatment in the presence of field cancerization. A formulation containing 0.5 % 5-FU with 10 % sali-

▶ **Table 5** Topical therapy options for basal cell carcinoma.

Treatment procedure	Type of application/ intervention/ (dosage) intervals	Effect	Side effects and tolerance	Practicability	References
Imiquimod 5 % Creme (Aldara)	Toll-like-receptor-7-agonist 1 x daily on 5 days per week over 6 weeks in cases of lesions of less than 2 cm in diameter	Tumor absence between 43-100 % in superficial basal cell carcinomas, according to guideline	Local inflammation reaction with reddening, swelling, scaling, blistering, and pain	Easy application, at home	[78]
5-Fluorouracil (5-FU) 5 % Creme (Efudix)	Cytostatic/ antimetabolite 2 x per day over 4 weeks	Comparable effectivenes as MAL-PDT, but inferior to imiquimod	Local inflammation reaction with reddening, swelling, scaling, blistering, ulceration, and pain	Easy application, at home	[79–80]
Photodynamic therapy (PDT) with 5-ALA or MAL	ALA/MAL = photo-sensibilisator Application of ALA/MAL, acting time of 3-4 hours, then red light for 10-20 min, repeat after 4 weeks, if necessary	Response rate of 89-97 %, according to guideline	Painful erythema and edema as well as formation of erosions and crusts after application, healing usually after 2-6 weeks	Outpatient application, practice/ hospital	[81–83]
Cryosurgery	Local exposition to cold (liquid nitrogen) of the lesion for a few seconds (“whitening”)		Well tolerated	Easy to perform by physician, outpatient, practice/ hospital	[84–85]

cylic acid in solution can be used lesion-directed or field-directed in immunocompetent patients [7].

Alternatively, for grade I-II actinic keratoses, the use of diclofenac sodium 3 % in hyaluronic acid 2.5 % gel may be offered for single or multiple actinic keratoses in immunocompetent patients. In the case of field cancerization, diclofenac sodium 3 % in hyaluronic acid 2.5 % gel can be used for field-directed therapy. Diclofenac is inferior to 5-FU in efficacy but is characterized by a milder side effect profile [7].

A third topical option is 5 % imiquimod cream, which can be used for single or multiple actinic keratoses, as well as field carcinogenesis for immunocompetent patients. The formulation is also available in 3.75 % dosage and can be used in the previously mentioned patient group [7].

A recommendation for the use of colchicine, difluoromethylornithine, canola phenolic acid, topical nicotinamide or sunscreen filters cannot be given due to the lack of data. For birch cork and glucans, no benefit was achieved so that these active substances should not be used [7].

Various therapeutic modalities are also available for **Bowen’s disease**. Due to the lack of head-to-head studies, there is no direct comparison of the different treatment approaches. In summary, the AWMF guideline makes the following recommendations: For the removal of Bowen’s disease after histological confirmation, surgical removal as well as cryosurgery or ablative laser procedures can be applied.

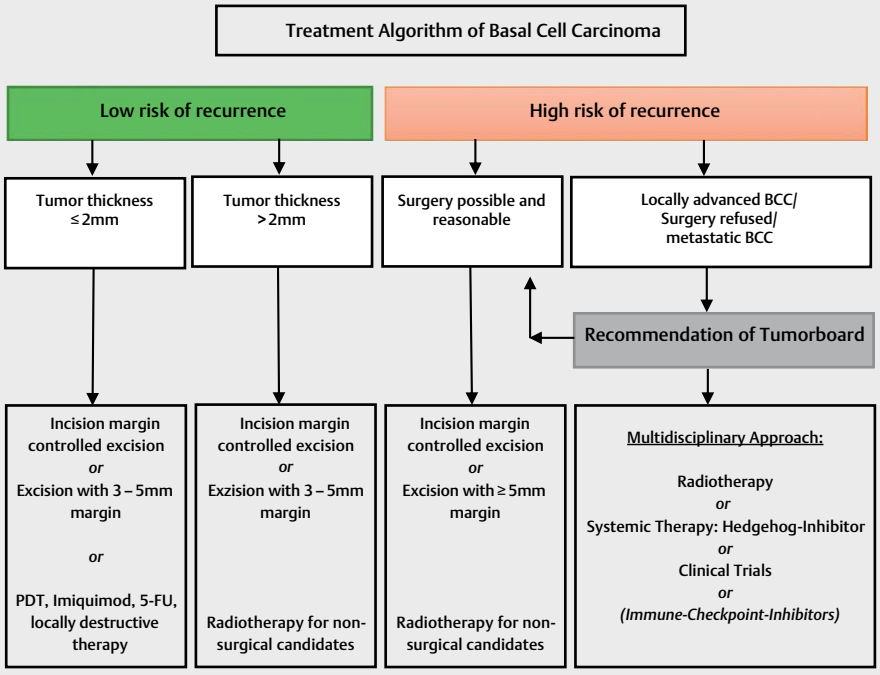
For topical therapy, 5 % 5-FU cream is suitable, as well as 5 % Imiquimod cream.

With photodynamic therapy (PDT), it should be noted that for the treatment of Bowen’s disease, 2 cycles of therapy within 4 weeks should be given.

Definitive radiotherapy may be used for unresectable **cutaneous squamous cell carcinoma** and when esthetically unacceptable results are anticipated [7]. Although prospective randomized trials comparing the efficacy of primary radiotherapy with other local therapy modalities are lacking, retrospective studies show high local tumor control after radiotherapy alone of 94 % at 5 years [93, 94]. While the radiation dose for small tumors should be between 60-70Gy, the recommended radiation dose for large tumors is 70Gy [93]. A combination of primary radiotherapy with simultaneous chemotherapy is currently not recommended due to the lack of studies in large patient collectives [7].

In the case of **field cancerization**, mapping biopsies can be helpful to assess the extent of the tumor area. Depending on the extent of the cancerization, the therapy concept should be determined in the tumor board. For example, it may be appropriate to use large-area procedures, such as photodynamic therapy, in addition to surgical therapy. In case of non-resectable findings, where tumor control cannot be achieved through surgery, radiotherapy or by large-area therapy, the use of a systemic therapy should be discussed.

For unresectable primary tumors of **Merkel cell carcinoma**, therapeutic radiotherapy can be performed with a total dose of 50-56Gy for subclinical tumors or a total dose > 56Gy for clinically detectable tumors. Results are available showing a local recurrence-free 5-year survival of 90 % and a disease-specific survival of 68 % for definitive radiotherapy, making definitive radiotherapy an ef-



▶ **Fig. 9** Treatment pathway of basal cell carcinoma [23]. BCC: basal cell carcinoma; SM: safety margin.

fective treatment option [104]. Good tumor control can also be achieved with primary therapeutic radiotherapy for unresectable locoregional metastases [95]. Other therapeutic options for locoregional tumor control may include electrochemotherapy (ECT), isolated limb perfusion, and intralesional application of T-VEC [10].

Definitive radiotherapy is also a valuable alternative for the treatment of **lentigo maligna melanomas** that cannot be surgically removed due to their size, tumor location, or patient comorbidities. In this context, a recurrence-free rate of up to 93 % can be achieved with irradiation of the primary region and a safety margin of 1 cm [96].

4.2 Surgical treatment approaches

Basal cell carcinoma

Over 95 % of **basal cell carcinomas** can be treated completely by excision. The surgical approach is superior to topical therapy. With complete histologically controlled excision, the 5-year recurrence rate is 2-8 % [97, 98].

Surgical treatment can be conventional excision or microscopically controlled tissue-sparing surgery. In conventional excision, the safety margin should be adapted to the risk of recurrence. In this case, a safety margin of 3-5 mm is recommended for a tumor thickness of > 2 mm. For a tumor thickness of > 5 mm, the safety margin should be > 5 mm [99].

For basal cell carcinomas with a high risk of recurrence, the safety margin to the adipose tissue can be up to 15 mm. For tumors in the nose, ears, and scalp, the safety margin may extend to the underlying fascia, perichondrium, or periosteum [100].

For basal cell carcinoma with subsequent postoperative R1 situation, a post-excision should be performed [101].

In conventional surgery, the histopathological assessment of the margins is performed postoperatively, so that initially no primary wound closure is recommended, at best linear wound closure. Only after a histopathologically confirmed R0 situation should extensive defect closure by means of flap be performed [102].

Micrographic controlled surgery either following the 3D histology or "Tübinger Torte" commonly used in Germany [103] or the Mohs surgery (MMS) preferred in North America allows a complete assessment of the margins [104]. Furthermore, microscopically controlled surgery represents a tissue-sparing technique with lower recurrence rates compared with conventional surgery [105]. Microscopically controlled surgery is recommended for complex tumors with a high risk of recurrence and those at cosmetically sensitive sites [102].

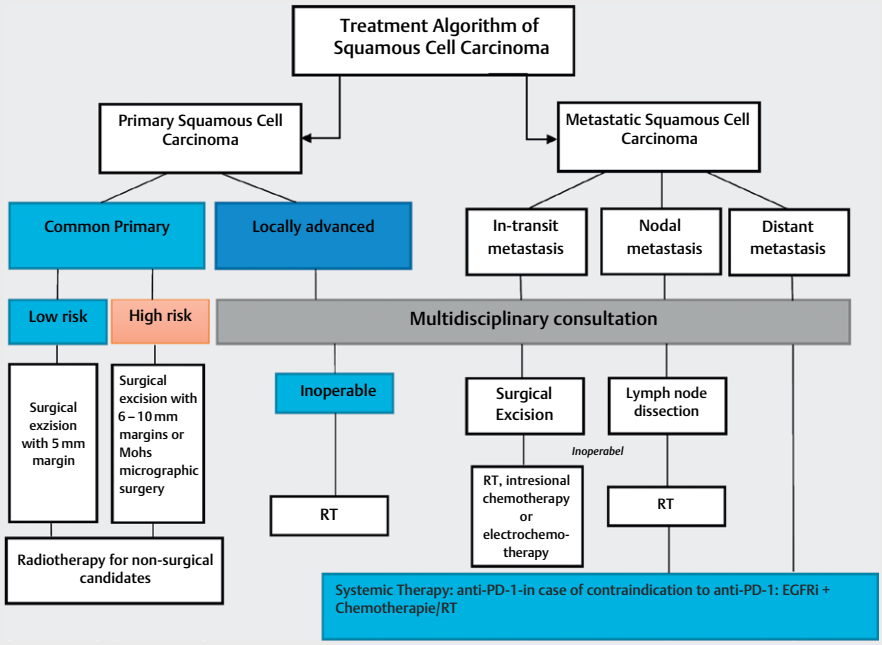
Smaller and superficial basal cell carcinomas with a low risk of recurrence can alternatively be removed by means of flat excision [106]. An overview of the therapy recommendations is provided in ▶ **Fig. 9**.

Squamous cell carcinoma

Undoubtedly, surgical excision of **cutaneous squamous cell carcinomas** is the treatment of choice [48]. The risk factors for local recurrence or locoregional metastasis are important for surgical planning, because high-risk squamous cell carcinoma should be treated differently than low-risk squamous cell carcinoma.

To date, the strongest prognostic factors for local recurrence or metastasis include tumor thickness of 6 mm or greater, desmoplasia, and perineural invasion [38].

According to the German guideline for actinic keratoses and squamous cell carcinomas of the skin, curettage with a 7 mm ring



▶ **Fig. 10** Treatment pathway of squamous cell carcinoma [38]. RT: Radiotherapie; SA: Sicherheitsabstand; EGFRi: epidermal growth factor inhibitor; PD-1: programmed cell death; RT: Radiotherapy; SM: safety margin; EGFRi: epidermal growth factor inhibitor; PD-1: programmed cell death.

curette or shave excision is suitable for the treatment of small tumors with a diameter of < 10 mm [38].

For larger tumors, the excision depth should be 6 mm. A sufficiently deep excision allows assessment of tumor thickness and differentiation and on this basis, the presence of risk criteria can be evaluated [38].

If complete excision can be easily achieved, reprocessing of the incision margins should be performed on the frozen section or kerosene section to assess whether R0 resection could be achieved.

If the procedure of a "wide local excision", WLE (excision with wide resection margin) is applied, the current European guideline recommends a safety margin of 5 mm for low-risk squamous cell carcinomas and 6-10 mm for high-risk squamous cell carcinomas [107].

Due to the usually large defects caused by WLE, microscopically controlled surgery with gapless three-dimensional incision margin control can be done in tumors in the head and neck region, since microscopically controlled surgery results in a significantly smaller defect. In depth, excision down to the subcutaneous fat tissue and resection of the galea aponeurotica, if necessary, are recommended [107].

In the case of large tumors or difficult-to-operate localization, it is advisable to close the defect only after tumor-free incision margins have been demonstrated.

In the presence of risk factors for local or locoregional recurrence, postoperative radiotherapy should be provided according to the guideline. Risk factors include R1 or R2 resection without the option of post-resection, narrow resection margin (< 2 mm in the absence of the option of post-resection), recurrent tumor, maximum tumor size (> 2 cm), maximum depth of penetration (> 4 mm), infiltration of adipose tissue, PNI, and extensive lymphogenic involvement (> 1 affected lymph node, capsular rupture), and intraparotid lymph node involvement [7]. In two meta-analyses, each with 20 trials and 2605 and 3534 patients, respectively, adjuvant radiotherapy was associated with significant improvement in overall survival, disease-free survival, and recurrence [108] or overall survival alone [109].

To date, there is no clear evidence of improved prognosis with postoperative platinum-based radiochemotherapy compared with radiotherapy alone [38]. For example, the randomized phase III TROG 05.01 trial, which evaluated 310 patients with resected high-risk cutaneous squamous cell carcinoma of the head and neck region, failed to demonstrate an advantage of adjuvant radiochemotherapy with carboplatin over adjuvant radiotherapy alone in terms of local control or overall survival [110]. Based on these data, adjuvant chemotherapy is not recommended outside of clinical trials [38]. In cases of local recurrence of squamous cell carcinoma, a multidisciplinary approach is required. It is always recommended to discuss such a case in an interdisciplinary tumor board. When possible, surgical excision using micrographically controlled surgery should be used [38]. In the presence of R1 or R2 resection and tumor that cannot be further resected, adjuvant radiotherapy should be used. If inoperability is determined in the interdisciplinary tumor board, primary radiotherapy is also the first-line therapy. If additional radiation reserve is lacking, the indication for electrochemotherapy or systemic therapy should be considered. ▶ **Fig. 10** provides a schematic overview of the therapeutic approaches.

Merkel cell carcinoma

In primary **Merkel cell carcinoma tumors** without evidence of metastasis to organs, complete excision is the standard of care and should be preferred to an excisional biopsy. A safety margin of 1

cm is recommended in stage I, and 2 cm in stage II, in order to remove microscopic satellite metastases as well [10]. In the head and neck region, compliance with the recommended safety margin often cannot be maintained due to the anatomical localization with attention to functional structures. In these cases, excision by microscopically controlled surgery may be considered.

The indication for postoperative radiotherapy of the tumor region is given regardless of the safety margin in order to reduce the risk of recurrence, and therefore postoperative wound conditions should allow early initiation of radiation [111]. Surgical excision is also the first choice in the presence of local recurrence. In Merkel cell carcinoma, due to the aggressive tumor biology, the frequent indication for sentinel node biopsy, and the implementation of adjuvant therapies, the procedure should always be determined by an interdisciplinary tumor board at initial diagnosis [10].

Lentigo maligna and lentigo maligna melanoma

If **lentigo maligna** is clinically suspected, complete resection with complete histologic margin control should be performed. Often the melanocytic cells are detectable in the apparently healthy tissue, which leads to frequent resections and large defect fields.

Consequently, in the face and other difficult-to-excise locations, microscopically controlled surgery is an option to spare the surrounding tissue in these cosmetically sensitive areas and to ensure complete excision. Good results are achieved with low recurrence rates of 0.5-5 % [112, 113].

4.3 Lip

Cheilitis actinica

The lips, in particular the lower lip, is one of the most sun-exposed skin areas of the body and is very susceptible to acute or chronic light damage due to the lack of pigmentation. In the context of tumor diseases, the focus here will be placed on cheilitis actinica chronica, which can develop after years of light exposure and is a form of actinic keratosis on the red of the lip. In most cases, it is already a spinocellular carcinoma in situ. Clinically, cheilitis actinica usually presents as an areal, partly atrophic, partly erosive or even scaly skin change affecting the entire lower lip. In terms of clinical morphology, it thus resembles a field carcinoma, as it can occur on the other parts of the body. According to recent reviews, if cheilitis actinica persists for a longer period of time, it can turn into an invasive carcinoma in 10-30 %, with approximately 90 % of squamous cell carcinomas in the area of the labial red arising from cheilitis actinica [114, 115]. Not least because of this, the indication for treatment of cheilitis actinica should be made taking into account other risk factors such as patient age and general condition, immunosuppression, comorbidities and patient preferences.

Treatment options include ablative procedures such as surgical intervention, laser therapy, cryosurgery and chemical peeling, as well as drug-assisted procedures like topical application of active substances and photodynamic therapy. Depending on the severity, vermilionectomy or lip-shave are recommended surgical measures for extensive manifestation; alternatively, ablative laser procedures (CO_2, Er:YAG) can be offered. The advantage of surgical therapy is that a histopathological evaluation of the complete excidate can be performed afterwards. Intraoperative bleeding is much less frequent with laser therapy due to the thermally induced coagulation, but histopathological examination is no longer possible after complete vaporization. However, compared with vermilionectomy, laser ablation also showed a lower risk for the occurrence of postoperative complications with comparable effectiveness [114]. With regard to cryosurgery, no conclusive statements can be made to date due to the current data situation. Likewise, there is no clear proof of benefit for chemical peeling. For topical therapy, treatment with diclofenac sodium 3 % gel can be recommended based on the review by Lai et al. Here, rates of complete clinical response up to 45.2 % are described as well as a recurrence rate of 6.5 % [115]. For the agents of 5-FU and imiquimod, the data situation is insufficient, so no recommendations can be made. Alternatively, photodynamic therapy may be pursued [38].

While the 7th edition of the TNM classification assigned squamous cell carcinomas of the labial red to oral cavity carcinomas, carcinomas of the labial red are assigned to skin carcinomas in the current 8th edition, due to exposure to ultraviolet light. Despite this reclassification, the labial red has unique characteristics as a transition zone between the skin and oral cavity. Therefore, a separate S2k guideline on lip carcinomas is currently in preparation. For lip carcinoma, contact of the lip with the cigarette or pipe is considered a major risk factor, regardless of the total amount of tobacco use [116]. The labial red is thin, highly vascularized, and directly overlies the orbicularis muscle. Due to the low fat barrier, squamous cell carcinomas of the labial red can reach the lymphovascular space of the muscle more quickly and therefore have a greater metastatic potential than squamous cell carcinomas in the skin area of the lip. This is confirmed by retrospective studies. In a collective of 303 patients with squamous cell carcinomas of the lip, Wang et al. demonstrated that the risk of nodal metastasis was 5-fold higher for squamous cell carcinomas of the lip than for those in the skin area of the lip, which have a similar risk of lymph node metastasis as squamous cell carcinomas of the skin in general (1.5 %) [117]. This shows constant lymphatic drainage to the submental, submandibular, and high cervical lymph nodes (levels Ia, Ib, and IIa) for the lower lip, which should be removed if neck dissection is indicated [118].

Surgical excision is the standard treatment for basal cell carcinoma and squamous cell carcinoma of the lip. Due to the relevance for speech and mastication, a functionally and esthetically satisfactory reconstruction with sufficient oral width should be aimed for even in the case of extensive postoperative defects. A wide variety of near and distant flap techniques are available for this purpose. The localization of squamous cell carcinoma to the lip is considered a risk factor for metastasis and poorer disease-specific survival. Nevertheless, the benefit of elective neck dissection has not been proven for lip carcinomas with cN0 neck [119].

4.4 Lymph node surgery of the head and neck

Squamous cell carcinoma

In the head and neck region, most localizations show variable lymphatic drainage, which may also include the contralateral neck lymph node regions if the tumor is located close to the midline. Only in a few localizations, such as the lip, lymphatic drainage is relatively reliably predictable. Variable lymphatic drainage complicates the possibilities of sentinel lymph node biopsy in the head and

neck region because multiple sentinel lymph nodes are often present there.

In sentinel lymph node biopsy, a radioactive tracer or dye is infiltrated peritumorally so that lymphatic drainage and the first draining lymph node, known as the sentinel lymph node, can be visualized. It is then surgically removed and examined histopathologically. In squamous cell carcinomas, the sensitivity of SLNB is 79 % and the specificity is 100 %, so the technique is classified as reliable [129]. The rate of intraoperative as well as postoperative complications is 3-5 % and includes the development of lymphedema, infection, hematoma, seroma, cutaneous lymphatic fistula, and suture dehiscence [59]. Because there is insufficient data on the prognostic and therapeutic value of sentinel lymph node biopsy in squamous cell carcinoma, there is no general recommendation for the procedure according to the AWMF guideline [38].

Elective (prophylactic) lymph node dissection in cN0 neck should not be performed because the benefit in terms of disease-specific and overall survival has not been proven [120, 121]. For example, a retrospective analysis of 1,111 patients, of whom 173 underwent elective neck dissection and 938 were clinically controlled, failed to show any differences between the groups in terms of 5-year disease-specific survival (73 vs. 75 %) [122]. Therapeutic neck dissection should be performed for clinically or pathologically manifest neck lymph node metastases according to guideline recommendations [38, 71]. The study situation is insufficient for an evidence-based decision on the extent (level, radicality) of the necessary therapeutic neck dissection in cN + /pN + neck [7]. While the AWMF guideline recommends excision of the affected and adjacent levels in the presence of lymph node metastases [38], the European guideline recommends therapeutic lymph node dissection of all 5 cervical lymph node levels in the presence of clinically or histologically confirmed neck lymph node metastases [71].

The consensus is that lymph node dissection should preserve the functionally important structures (selective-functional dissection). Only in cases of extensive metastasis is radical dissection recommended for squamous cell carcinoma [123, 124].

The presence of parotid lymph node metastases is associated with a poor prognosis. In particular, there is a poor prognosis in cases of infiltration of the facial nerve and a size of the parotid metastasis > 6 cm [125]. In cases of parotid metastases, parotidectomy (preferably with preservation of the facial nerve) is recommended. In retrospective studies, radiotherapy alone is inferior to surgical therapy in terms of lateral parotidectomy, neck dissection, and adjuvant radiotherapy with regard to the disease-specific survival [125]. In a systematic review with meta-analysis, Rotman et al. analyzed the prevalence of occult cervical metastases in patients with parotid lymph node metastases of cutaneous squamous cell carcinoma. Here, the analysis of 17 studies with 874 patients showed an occult cervical metastatic spread of 22.5 % [126]. Based on this study, the European cutaneous squamous cell carcinoma guideline recommends providing elective neck dissection to patients with parotid metastases [127]. Depending on tumor-specific and patient-specific factors, the extent of neck dissection should be discussed in the tumor board [127].

Therapeutic neck dissection is only indicated for squamous cell carcinomas of the skin in the head and neck region if the patient is operable with the intention of an R0 resection and an overall surgical concept seems possible and reasonable. If operability is not given due to the general condition of the patient or tumor-specific factors, a non-surgical overall concept should be determined in the interdisciplinary tumor board.

Merkel cell carcinoma

Merkel cell carcinomas often show lymphogenic metastasis already at initial diagnosis. Thus, even with clinically bland lymph node status, micrometastases were detected in 30 % of patients [128, 129]. In patients who show no evidence of metastasis clinically and in the imaging, a sentinel lymph node biopsy should be provided, also with regard to the prognostic value, since occult lymph node metastases may often be present [76]. In a study by Iyer et al, the risk of lymphogenic spread of Merkel cell carcinoma was shown to increase with larger tumor diameter [130].

Considering the frequency of nodal metastasis in the head and neck region and the difficulty in identifying the sentinel lymph node due to variable lymphatic drainage pathways as well as a high rate of false-negative histopathological findings, a functional neck dissection can be considered in cN0 neck [131]. In cN + neck, neck dissection should be performed with curative intent [10]. The number of affected lymph nodes and the ratio of positive to examined lymph nodes, the so-called lymph node ratio, are associated with the 5-year survival rate in patients with Merkel cell carcinoma [132].

5. Systemic treatment of advanced disease

5.1 Interdisciplinary tumor boards

Therapeutic options, particularly for patients with advanced and metastatic skin cancer, have increased significantly in recent years. The further development of surgical procedures, optimization of radiotherapeutic precision therapies, and improvement in the understanding of tumor biology with the development of new systemic therapeutics, such as hedgehog and checkpoint inhibitors, have led to a broad diversification of treatment options and make it difficult even for specialized oncologists to have a complete overview of the development and to use the sometimes extremely expensive therapy options in a meaningful and coordinated manner. Due to these innovations and thus also increase in the complexity of the therapy of advanced tumor stages, recurrences and metastatic tumors, the therapy decision should be made in a multidisciplinary manner for advanced and metastatic tumors and the treatment sequence should be jointly determined.

By discussing the patient's case in the interdisciplinary skin tumor board, the treatment recommendation for the patient is detached from the initially treating specialist discipline and the orientation towards clinical guidelines is improved [133]. In a systematic review on various tumor diseases, it was shown that the joint tumor board decision differs from treatment planning by individual physicians in up to 52 % of cases [134]. By bringing together the expertise of multiple disciplines, tumor boards are therefore an important form of quality management. The goal is to optimize the quality of outcomes and thus the prognosis of patients with skin cancer. In addition, the interdisciplinary tumor board facilitates the continuous exchange of knowledge between the different disciplines and has a teaching function for residents and students. In sum-

mary, decision-making in the form of interdisciplinary tumor boards is a cornerstone of modern cancer treatment to provide evidence-based and best-practice recommendations considering all tumor- and patient-specific factors. Interdisciplinary tumor boards are therefore called for in the Federal Government's National Cancer Plan as a standard of oncology care [135].

Regarding the therapy of basal cell carcinoma and cutaneous squamous cell carcinoma, the corresponding AWMF guidelines require interdisciplinary therapy determination in the context of tumor boards only for advanced and metastasized cases. Thus, the guideline on basal cell carcinoma states that patients with basal cell carcinoma with a high risk of recurrence, for whom surgery is apparently not possible or not advisable (locally advanced), not desired, or who already are in a metastatic condition, and especially before starting a systemic therapy, the therapy concept should be determined in the interdisciplinary tumor board [23]. The cutaneous squamous cell carcinoma guideline also states that advanced and metastatic cutaneous squamous cell carcinomas should be discussed in an interdisciplinary skin tumor board and that local and systemic therapy options should be carefully weighed in terms of benefit and risk. In particular, the indication for systemic therapy should be determined in the interdisciplinary tumor board. However, an internationally accepted definition of locally advanced disease does not yet exist [38]. Due to the aggressiveness of the tumor, the usually given indication for sentinel lymph node biopsy, the necessary evaluation of the indication of possible adjuvant therapies, as well as the complexity of the necessary diagnostics, the AWMF guideline Merkel cell carcinoma calls for the determination of the therapy concept by an interdisciplinary tumor board already at the time of initial diagnosis [10].

5.2 Adjuvant systemic therapy

Squamous cell carcinoma

Local recurrence or locoregional metastasis occurs in up to 50 % of patients with completely resected high-risk squamous cell carcinoma after adjuvant radiation [136].

Based on this, randomized clinical trials are currently investigating the benefit of adjuvant systemic therapy.

A phase 3 double-blind randomized clinical trial is evaluating the efficacy of adjuvant immunotherapy with pembrolizumab compared with placebo in patients with high-risk squamous cell carcinoma (KEYNOTE-630, NCT03833167). A second study is evaluating the efficacy of adjuvant immunotherapy with cemiplimab compared with placebo (NCT03969004). Inclusion in both studies requires criteria for the presence of high-risk squamous cell carcinoma, which include nodal involvement, tumor extension, perineural invasion, in-transit metastases, and recurrence.

Merkel cell carcinoma

Merkel cell carcinoma is radiosensitive, which is why radiotherapy can be used in all tumor stages [137]. In the adjuvant setting, the data on adjuvant radiotherapy is controversial. The German guideline recommends that after R0 resection, adjuvant radiation of the tumor bed should be given in single doses of 2Gy, up to a total dose of 50Gy [10].

Patients may benefit from postoperative radiotherapy, particularly for small tumors in the head and neck region. In a study by Takagishi et al., local recurrence occurred in 26 % of patients without postoperative radiotherapy. In the group of patients with postoperative radiotherapy, no recurrences occurred [138].

Systemic therapy is usually given only in stage IV, when distant metastases are present.

Interim data from the ADMEC-O study by Becker et al. on adjuvant immunotherapy with nivolumab in patients with completely resected Merkel cell carcinoma demonstrated a higher progression-free survival during the observation period of 24.3 months [139].

5.3 Neoadjuvant systemic therapy

Squamous cell carcinoma

Regarding neoadjuvant systemic therapy in squamous cell carcinoma, there is now evidence for the efficacy of the PD-1 inhibitor cemiplimab. In a pilot study with 20 participants with resectable stage III-IV recurrence in the head and neck region, the efficacy of two cycles of cemiplimab applied neoadjuvantly (2 cycles with 350 mg, each, Q3W) was investigated.

Eighty-five percent (17/20) of patients demonstrated a pathologic response (≤ 50 % viable tumor cells), with 55 % achieving a pathologic complete response, 20 % achieving a significant pathologic response (≤ 10 % viable tumor cells), and 10 % of patients achieving a pathologic partial response (> 10 % and ≤ 50 % viable tumor cells). Patients with complete remission did not receive scheduled radiotherapy after surgery. Patients who did not have a pathologic response experienced either disease progression and death (5 %) or recurrence (10 %) despite surgery and adjuvant radio(chemo) therapy. After a median follow-up of 34.5 months (range: 7.7-42.7), no recurrence occurred in any of the patients who achieved a pathologic response [140]. Based on the initial results of this pilot study, a multicenter, non-randomized phase 2 trial was conducted to evaluate cemiplimab as neoadjuvant therapy (350 mg, every 3 weeks, up to 4 doses) in patients with stage II, III, or IV (M0) resectable squamous cell carcinoma of the skin. Of 79 patients, 40 patients (51 %) showed a pathologic complete response and 10 patients (13 %) showed a clear pathologic response (< 10 % live tumor cells). Adverse events of any grade were observed in 69 patients (87 %) [141].

Merkel cell carcinoma

In 2020, the results of the CheckMate 358 study, an open-label phase I/II trial of neoadjuvant systemic therapy with nivolumab in patients with resectable Merkel cell carcinoma, were published. 358 patients received 240 mg of nivolumab intravenously on days 1 and 15. Surgery followed on day 29, and tumor regression was assessed radiographically and microscopically. It was found that nivolumab, administered approximately four weeks prior to surgery, was generally well tolerated and resulted in a histologically complete response, as well as radiographic tumor regression, in approximately 50 % of treated patients [142].

Patients are currently being recruited for a phase 2 clinical trial of neoadjuvant immunotherapy with pembrolizumab in resectable stage I-III Merkel cell carcinoma (NCT04975152), as well as a phase 2 clinical trial of neoadjuvant therapy with pembrolizumab and lenvatinib in non-resectable stage II-IV Merkel cell carcinoma (NCT04869137). A third study is evaluating neoadjuvant mono-

therapy with cemiplimab in patients with initial diagnosis of stage I-II Merkel cell carcinoma or recurrence (NCT049751529).

5.4 Locally advanced and/or metastasized tumors

Basal cell carcinoma

In 2012, the two Hedgehog pathway inhibitors (HHI) vismodegib and sonidegib, which inhibit the Smoothened molecule, were approved by the FDA and EMA for locally advanced and metastatic basal cell carcinoma, respectively. Vismodegib showed a remission rate of 48 % for locally advanced basal cell carcinoma and 33 % for metastatic basal cell carcinoma in the pivotal study, with remission durations of 9.5 and 7.6 months, respectively. Therapy-associated side effects included muscle spasms, hair loss, fatigue, and weight loss, which led to discontinuation of therapy in 30 % of patients [143].

Sonidegib showed a 36 % remission rate in the pivotal study from 2017 (BOLT). The most recent update of the BOLT trial showed a remission rate of 56 % and a median duration of response of 26.1 months in the pivotal review trial for locally advanced basal cell carcinoma, and a response rate of 7.7 % with a duration of response of 24.0 months for metastatic basal cell carcinoma, with a similar side effect profile to vismodegib [144, 145].

Since June 2021, cemiplimab has been approved for the treatment of patients with locally advanced or metastatic basal cell carcinoma who have experienced disease progression on a hedgehog pathway inhibitor or who are intolerant to an HHI. This was based on the results of a multicenter phase II study in which 84 patients were treated with cemiplimab (350mg, Q3W). Reasons for discontinuation of prior HHI therapy were disease progression (71 %), intolerance to prior HHI therapy (38 %), or stable disease after nine months of HHI therapy (8 %). The response rate was 31 % (95 % CI 21-42 %) after a median follow-up of 15 months, with complete remission in 6 % and partial remission in 25 % of patients. Treatment-related adverse events and serious treatment-related adverse events of grade 3-4 occurred in 48 % of patients [146]. Interim long-term follow-up data published over a period of up to 40 months showed a median progression-free survival of 16.5 months [147].

Currently, combination therapies of HHIs and PD-1 inhibitors, intralesional therapies, and new drugs, such as relatlimab, are being studied for basal cell carcinoma.

Squamous cell carcinoma

For patients with locally advanced or metastatic squamous cell carcinoma, given the very high mutational burden, first-line therapy should include PD-1 immune checkpoint blockade. Response rates up to 41-50 % with a median duration of response of 8.1-22.4 months have been reported in trials with cemiplimab and pembrolizumab [145–147]. Since 2019, cemiplimab has been approved by the EMA and FDA as monotherapy for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are ineligible for curative surgery or curative radiotherapy. After promising results in a phase I study showing a 50 % response to cemiplimab [146], the results were confirmed in the non-randomized, phase II EMPOWER-cSCC-1 study. In this study, 193 patients with advanced cutaneous squamous cell carcinoma who were not suitable for curative surgery or radiation were treated with either cemiplimab 3 mg/kg body weight every 2 weeks or a fixed dose of 350 mg every 3 weeks. At a median follow-up of 15.7 months, the response rate in all patients was 46.1 %, with a complete response in 16.1 % of patients. The disease control rate was 72.5 %. Of all patients with an objective response, 87.8 % showed a sustained response 12 months after the initial response, although the median duration of response was not reached. The estimated median disease-free survival was 18.4 months for all patients. The safety profile was consistent with other studies of the same agent [148]. The results of this study led to the approval of cemiplimab for the treatment of cutaneous squamous cell carcinoma. The dose of 350 mg every 3 weeks (Q3W), administered as an intravenous infusion over a 30-minute period, is now established.

Pembrolizumab was initially approved by the FDA for recurrent or metastatic squamous cell carcinoma of the skin that is not curable by surgery or radiation. This indication was later expanded to include locally advanced tumors. Pembrolizumab has not yet been approved in Europe for squamous cell carcinoma of the skin (as of 09/2023). Approval in the U.S. was based on the non-randomized phase II KEYNOTE-629 trial, in which 159 patients with locally advanced or recurrent/metastatic squamous cell carcinoma of the skin received 200 mg of pembrolizumab every 3 weeks for up to 35 cycles. In the cohort with recurrent/metastatic tumors (105 patients), the objective response rate was 35.2 %, with 10.5 % showing complete remission. In the cohort with locally advanced tumors (54 patients), the response rate was 50.0 %, including 16.7 % with complete response. Median response duration was not achieved in any cohort. Treatment-related grade 3-5 adverse events occurred in 11.9 % of patients [149].

If progression occurs with immunotherapy, inclusion in a clinical trial should be considered. Otherwise, chemotherapy or EGFR-targeted therapy should be taken into account [38, 150]. Therapy protocols are often based on the treatment of oral cavity carcinoma [59].

Even if polychemotherapies and combined radiochemotherapies show a higher response, they are also associated with an increased side effect profile [59].

Merkel cell carcinoma

In the metastatic or locally advanced situation of Merkel cell carcinoma, in which the tumor cannot be treated by surgery or controlled by radiotherapy, the recommendation is immunotherapy with PD-1/PD-L1 blockade, since both viral and UV-associated Merkel cell carcinomas have high immunogenicity [10]. FDA and EMA approval currently exists only for avelumab in metastatic Merkel cell carcinoma. In patients who progress on immune checkpoint blockade with avelumab, case series describe a response to combination therapy with ipilimumab and nivolumab [151]. Another treatment approach is treatment with oncolytic viruses (T-VEC) as monotherapy or in combination with immunotherapy.

Second-line therapy or contraindications to immunotherapy may include chemotherapy with anthracyclines, antimetabolites, cyclophosphamide, etoposide, or platinum-containing cytostatics, although Merkel cell carcinoma tends to rapidly develop resistance to chemotherapeutic agents [152].

6. Conclusion and outlook

In summary, surgical excision represents the gold standard in therapy for most operable non-melanoma skin tumors. Depending on tumor location and tumor extension, collaboration with different surgical departments is necessary to ensure adequate treatment with a satisfactory functional and aesthetic outcome. Alone or together with radiotherapy, this is considered a potentially curative treatment. The interdisciplinary tumor conference is always the best place to determine the optimal treatment (sequence) for the patient.

Since the head and neck region is one of the localizations in which skin tumors preferentially occur, especially with regard to the pathogenesis of epithelial tumors, close cooperation between otorhinolaryngology and dermatology and, if necessary, radiotherapy is of particular importance. Considering the increasing incidence of non-melanoma skin tumors, some patients require repeated collaborative treatment.

In the case of advanced or metastasized diseases, the development of a therapy concept within the framework of an interdisciplinary tumor board is recommended. Various systemic treatment approaches are available.

The common goal is to take care of the individual patient with regard to comorbidities, stage of disease and treatment wishes. After a treatment concept has been worked out, it makes sense in more complex cases to link the patient to a skin tumor center to enable interdisciplinary care and follow-up.

Conflicts of Interest

Dres. Eisenburger, Leven and Rudolph declare no conflicts of interest. Prof. Schadendorf declares to have various conflicts of interest: Anaveon, Advisory Board, Personal AstraZeneca, Expert Testimony, Personal BioAlta, Expert Testimony, Personal BioNTech, Advisory Board, Personal BMS, Invited Speaker, Personal BMS, Advisory Board, Personal CureVac, Advisory Board, Personal Daiichi Sanyko, Expert Testimony, Personal Erasca, Advisory Board, Personal Formycon, Expert Testimony, Personal Immatics, Advisory Board, Personal Immunocore, Advisory Board, Personal InFlarX, Expert Testimony, Personal Merck Serono, Invited Speaker, Personal MSD, Invited Speaker, Personal MSD, Advisory Board, Personal Neracare, Advisory Board, Personal Neracare, Invited Speaker, Personal Novartis, Advisory Board, Personal NoviGenix, Advisory Board, Personal PamGene, Expert Testimony, Personal Pfizer, Advisory Board, Personal Philogen, Advisory Board, Personal Pierre Fabre, Advisory Board, Personal Replimune, Advisory Board, Personal Sanofi, Invited Speaker, Personal Sanofi/Regeneron, Advisory Board, Personal Seagen, Expert Testimony, Personal SunPharma, Advisory Board, Personal SunPharma, Invited Speaker, Personal Ultimovacs, Advisory Board, Personal BMS, Coordinating PI, Institutional, No financial interest BMS, Steering Committee Member, Personal, Financial interest BMS, Research Grant, Institutional, Financial interest MSD, Coordinating PI, Institutional, No financial interest MSD, Research Grant, Institutional, Financial interest MSD, Steering Committee Member, Personal, Financial interest Novartis, Coordinating PI, Institutional, No financial interest Novartis, Steering Committee Member, Personal, No financial interest Philogen, Local PI, Institutional, No financial interest Pierre Fabre, Coordinating PI, Institutional, No financial interest Sanofi, Local PI, Institutional, No financial interest Non-Financial Interests EORTC-MG, Member of Board of Directors European Melanoma Registry (EuMelaReg), Leadership Role, Founding member and SC chair

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References

[1] Die Haut – Anatomie und Funktion | DKG. (o.D.). https://www.krebsgesellschaft.de/onko-internetportal/basis-informationen-krebs/krebsarten/hautkrebs/der-aufbau-der-haut.html

[2] Braakhuis BJM, Tabor MP, Kummer JA et al. A genetic explanation of Slaughter's concept of field cancerization: evidence and clinical implications. Cancer Res 2003; 63: 1727–1730

[3] Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. British Journal of Dermatology 2012; 166: 1069–1080. DOI: 10.1111/j.1365-2133.2012.10830.x

[4] Rubin AI, Chen EH, Ratner D. Basal-Cell Carcinoma. New England Journal of Medicine 2005; 353: 2262–2269. DOI: 10.1056/NEJMra044151

[5] Peterson SC, Eberl M, Vagnozzi AN et al. Basal Cell Carcinoma Preferentially Arises from Stem Cells within Hair Follicle and Mechanosensory Niches. Cell Stem Cell 2015; 16: 400–412. DOI: 10.1016/j.stem.2015.02.006

[6] Brantsch KD, Meisner C, Schönfisch B et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. Lancet Oncol 2008; 9: 713–720. DOI: 10.1016/S1470-2045(08)70178-5

[7] Heppt MV, Leiter U, Steeb T et al. S3-Leitlinie „Aktinische Keratose und Plattenepithelkarzinom der Haut" – Kurzfassung, Teil 1: Diagnostik, Interventionen bei aktinischen Keratosen, Versorgungsstrukturen und Qualitätsindikatoren. JDDG: Journal der Deutschen Dermatologischen Gesellschaft 2020; 18: 275–294. DOI: 10.1111/ddg.14048_g

[8] Glogau RG. The risk of progression to invasive disease. J Am Acad Dermatol 2000; 42: S23–S24. DOI: 10.1067/mjd.2000.103339

[9] Palaniappan V, Karthikeyan K. Bowen's disease. Indian Dermatol Online J 2022; 13: 177. DOI: 10.4103/idoj.idoj_257_21

[10] Becker JC, Beer AJ, DeTemple VK et al. S2k-Leitlinie – Merkelzellkarzinom – Update 2022. J Dtsch Dermatol Ges 2023; 21: 305–317. DOI: 10.1111/ddg.14930_g

[11] Becker JC, Stang A, DeCaprio JA et al. Merkel cell carcinoma. Nat Rev Dis Primers 2017; 3: 17077. DOI: 10.1038/nrdp.2017.77

[12] Feng H, Shuda M, Chang Y et al. Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science 2008; 319: 1096–1100. DOI: 10.1126/science.1152586

[13] Schrama D, Peitsch WK, Zapatka M et al. Merkel Cell Polyomavirus Status Is Not Associated with Clinical Course of Merkel Cell Carcinoma. Journal of Investigative Dermatology 2011; 131: 1631–1638. DOI: 10.1038/jid.2011.115

[14] DeWane ME, Kelsey A, Oliviero M et al. Melanoma on chronically sun-damaged skin: Lentigo maligna and desmoplastic melanoma. J Am Acad Dermatol 2019; 81: 823–833. DOI: 10.1016/j.jaad.2019.03.066

[15] Kallini JR, Jain SK, Khachemoune A. Lentigo Maligna: Review of Salient Characteristics and Management. Am J Clin Dermatol 2013; 14: 473–480. DOI: 10.1007/s40257-013-0044-6

[16] De Luca EV, Perino F, Di Stefani A et al. Lentigo maligna: diagnosis and treatment. Giornale Italiano di Dermatologia e Venereologia 2020; 155:. DOI: 10.23736/S0392-0488.18.06003-0

[17] Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Diagnostik, Therapie und Nachsorge des Melanoms, Langversion 3.3, 2020, AWMF Registernummer: 032/024OL, http://www.leitlinienprogramm[1]onkologie.de/leitlinien/melanom/ (abgerufen am: 30.08.2023).

[18] Helbig D, Ziemer M, Dippel E et al. S1-Leitlinie Atypisches Fibroxanthom (AFX) und pleomorphes dermales Sarkom (PDS). JDDG: Journal der Deutschen Dermatologischen Gesellschaft 2022; 20: 235–245. DOI: 10.1111/ddg.14700_g

[19] Persa OD, Loquai C, Wobser M et al. Extended surgical safety margins and ulceration are associated with an improved prognosis in pleomorphic dermal sarcomas. Journal of the European Academy of Dermatology and Venereology 2019; 33: 1577–1580. DOI: 10.1111/jdv.15493

[20] , Krebs in Deutschland für 2013/2014. 11. Ausgabe. Robert Koch-Institut (Hrsg) und die Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. (Hrsg). Berlin, 2017 (DOI: 10.17886/rkipubl-2017-007).

[21] Asgari MM, Moffet HH, Ray GT et al. Trends in Basal Cell Carcinoma Incidence and Identification of High-Risk Subgroups, 1998-2012. JAMA Dermatol 2015; 151: 976. DOI: 10.1001/jamadermatol.2015.1188

[22] Schäfer I, Reusch M, Siebert J et al. Health care characteristics of basal cell carcinoma in Germany: the role of insurance status and socio-demographic factors. JDDG: Journal der Deutschen Dermatologischen Gesellschaft 2014; 12: 803–811. DOI: 10.1111/ddg.12415

[23] Lang BM, Balermpas P, Bauer A et al. S2k-Leitlinie Basalzellkarzinom der Haut – Teil 2: Therapie, Prävention und Nachsorge. J Dtsch Dermatol Ges 2019; 17: 214–231. DOI: 10.1111/ddg.13755_g

[24] Ling G, Ahmadian A, Persson Å et al. PATCHED and p53 gene alterations in sporadic and hereditary basal cell cancer. Oncogene 2001; 20: 7770–7778. DOI: 10.1038/sj.onc.1204946

[25] Kricker A, Armstrong BK, English DR et al. Does intermittent sun exposure cause basal cell carcinoma? a case-control study in Western Australia. Int J Cancer 1995; 60: 489–494. DOI: 10.1002/ijc.2910600411

[26] Kricker A, Weber M, Sitas F et al. Early Life UV and Risk of Basal and Squamous Cell Carcinoma in New South Wales, Australia. Photochem Photobiol 2017; 93: 1483–1491. DOI: 10.1111/php.12807

[27] Rosso S, Zanetti R, Martinez C et al. The multicentre south European study „Helios". II: Different sun exposure patterns in the aetiology of basal cell and squamous cell carcinomas of the skin. Br J Cancer 1996; 73: 1447–1454. DOI: 10.1038/bjc.1996.275

[28] Wehner MR, Shive ML, Chren M-M et al. Indoor tanning and non-melanoma skin cancer: systematic review and meta-analysis. BMJ 2012; 345: e5909–e5909. DOI: 10.1136/bmj.e5909

[29] Penn I. Cancers in Renal Transplant Recipients. Adv Ren Replace Ther 2000; 7: 147–156. DOI: 10.1053/rr.2000.5269

[30] Gambini D, Passoni E, Nazzaro G et al. Basal Cell Carcinoma and Hedgehog Pathway Inhibitors: Focus on Immune Response. Front Med (Lausanne) 2022; 9: 893063. DOI: 10.3389/fmed.2022.893063

[31] Togsverd-Bo K, Lei U, Erlendsson AM et al. Combination of ablative fractional laser and daylight-mediated photodynamic therapy for actinic keratosis in organ transplant recipients – a randomized controlled trial. British Journal of Dermatology 2015; 172: 467–474. DOI: 10.1111/bjd.13222

[32] Lewis KG, Weinstock MA. Trends in nonmelanoma skin cancer mortality rates in the United States, 1969 through 2000. J Invest Dermatol 2007; 127: 2323–2327. DOI: 10.1038/sj.jid.5700897

[33] Euvrard S, Kanitakis J, Claudy A. Skin Cancers after Organ Transplantation. New England Journal of Medicine 2003; 348: 1681–1691. DOI: 10.1056/NEJMra022137

[34] Ulrich C, Schmook T, Nindl I et al. Cutaneous precancers in organ transplant recipients: an old enemy in a new surrounding. British Journal of Dermatology 2003; 149: 40–42. DOI: 10.1046/j.0366-077X.2003.05633.x

[35] https://www.krebsinformationsdienst.de/aktuelles/2023/weisser-hautkrebs-berufskrankheit.php

[36] Lichter MD. Therapeutic Ionizing Radiation and the Incidence of Basal Cell Carcinoma and Squamous Cell Carcinoma. Arch Dermatol 2000; 136: 1007. DOI: 10.1001/archderm.136.8.1007

[37] Sugita K, Yamamoto O, Suenaga Y. Seven Cases of Radiation-Induced Cutaneous Squamous Cell Carcinoma. J UOEH 2000; 22: 259–267. DOI: 10.7888/juoeh.22.259

[38] Leiter U, Heppt MV, Steeb T et al. S3-Leitlinie „Aktinische Keratose und Plattenepithelkarzinom der Haut" – Kurzfassung, Teil 2: Epidemiologie, chirurgische und systemische Therapie des Plattenepithelkarzinoms, Nachsorge, Prävention und Berufskrankheit. JDDG: Journal der Deutschen Dermatologischen Gesellschaft 2020; 18: 400–413. DOI: 10.1111/ddg.14072_g

[39] Stang A, Becker JC, Nghiem P et al. The association between geographic location and incidence of Merkel cell carcinoma in comparison to melanoma: An international assessment. Eur J Cancer 2018; 94: 47–60. DOI: 10.1016/j.ejca.2018.02.003

[40] Cohen LM. Lentigo maligna and lentigo maligna melanoma. J Am Acad Dermatol 1995; 33: 923–936. DOI: 10.1016/0190-9622(95)90282-1

[41] Fröhlich SM, Cazzaniga S, Kaufmann LS et al. A Retrospective Cohort Study on Patients with Lentigo Maligna Melanoma. Dermatology 2019; 235: 340–345. DOI: 10.1159/000499689

[42] Connolly KL, Nehal KS, Busam KJ. Lentigo maligna and lentigo maligna melanoma: contemporary issues in diagnosis and management. Melanoma Manag 2015; 2: 171–178. DOI: 10.2217/mmt.15.3

[43] Whiteman DC, Watt P, Purdie DM et al. Melanocytic Nevi, Solar Keratoses, and Divergent Pathways to Cutaneous Melanoma. JNCI Journal of the National Cancer Institute 2003; 95: 806–812. DOI: 10.1093/jnci/95.11.806

[44] Howard GR, Nerad JA, Carter KD et al. Clinical Characteristics Associated With Orbital Invasion of Cutaneous Basal Cell and Squamous Cell Tumors of the Eyelid. Am J Ophthalmol 1992; 113: 123–133. DOI: 10.1016/S0002-9394(14)71523-5

[45] Leibovitch I, Mcnab A, Sullivan T. Et Al. Orbital Invasion by Periocular Basal Cell Carcinoma. Ophthalmology 2005; 112: 717–723. DOI: 10.1016/j.ophtha.2004.11.036

[46] Niazi ZBM, Lamberty BGH. Perineural infiltration in basal cell carcinomas. Br J Plast Surg 1993; 46: 156–157. DOI: 10.1016/0007-1226(93)90150-A

[47] Dubin N, Kopf AW. Multivariate risk score for recurrence of cutaneous basal cell carcinomas. Arch Dermatol 1983; 119: 373–377

[48] Sun L, Chin R-I, Gastman B et al. Association of Disease Recurrence With Survival Outcomes in Patients With Cutaneous Squamous Cell Carcinoma of the Head and Neck Treated With Multimodality Therapy. JAMA Dermatol 2019; 155: 442. DOI: 10.1001/jamadermatol.2018.5453

[49] Eigentler TK, Leiter U, Häfner H-M et al. Survival of Patients with Cutaneous Squamous Cell Carcinoma: Results of a Prospective Cohort Study. Journal of Investigative Dermatology 2017; 137: 2309–2315. DOI: 10.1016/j.jid.2017.06.025

[50] Slaughter DP, Southwick HW, Smejkal W. "Field cancerization" in oral stratified squamous epithelium. Clinical implications of multicentric origin. Cancer 1953; 6: 963–968. DOI: 10.1002/1097-0142(195309)6:5<963::AID-CNCR2820060515>3.0.CO;2-Q

[51] Braakhuis BJM, Tabor MP, Kummer JA et al. A genetic explanation of Slaughter's concept of field cancerization: evidence and clinical implications. Cancer Res 2003; 63: 1727–1730

[52] Braakhuis BJM, Tabor MP, Kummer JA et al. A genetic explanation of Slaughter's concept of field cancerization: evidence and clinical implications. Cancer Res 2003; 63: 1727–1730

[53] Andruska N, Mahapatra L, Brenneman RJ et al. Reduced Wide Local Excision Margins are Associated with Increased Risk of Relapse and Death from Merkel Cell Carcinoma. Ann Surg Oncol 2021; 28: 3312–3319. DOI: 10.1245/s10434-020-09145-7

[54] Song Y, Azari FS, Tang R et al. Patterns of Metastasis in Merkel Cell Carcinoma. Ann Surg Oncol 2021; 28: 519–529. DOI: 10.1245/s10434-020-08587-3

[55] Farley CR, Perez MC, Soelling SJ et al. Merkel Cell Carcinoma Outcomes: Does AJCC8 Underestimate Survival? Ann Surg Oncol 2020; 27: 1978–1985. DOI: 10.1245/s10434-019-08187-w

[56] Schadendorf D, Lebbé C, zur Hausen A et al. Merkel cell carcinoma: Epidemiology, prognosis, therapy and unmet medical needs. Eur J Cancer 2017; 71: 53–69. DOI: 10.1016/j.ejca.2016.10.022

[57] Harms KL, Healy MA, Nghiem P et al. Analysis of Prognostic Factors from 9387 Merkel Cell Carcinoma Cases Forms the Basis for the New 8th Edition AJCC Staging System. Ann Surg Oncol 2016; 23: 3564–3571. DOI: 10.1245/s10434-016-5266-4

[58] Requena C, Manrique E, Nagore E. El lentigo maligno: actualización y claves en el diagnóstico y el tratamiento. Actas Dermosifiliogr 2023; 114: 413–424. DOI: 10.1016/j.ad.2023.02.019

[59] Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Prävention von Hautkrebs, Langversion 2.1, 2021, AWMF Registernummer: 032/052OL, https://www.leitlinienprogramm[1]onkologie.de/leitlinien/hautkrebs-praevention/ (abgerufen am: 29.07.2023))

[60] Grob JJ, Gaudy-Marqueste C, Guminski A et al. Position statement on classification of basal cell carcinomas. Part 2: EADO proposal for new operational staging system adapted to basal cell carcinomas. Journal of the European Academy of Dermatology and Venereology 2021; 35: 2149–2153. DOI: 10.1111/jdv.17467

[61] Christensen E, Mjønes P, Grimstad Ø et al. Diagnostic Accuracy in Subtyping Basal Cell Carcinoma by Clinical Diagnosis Compared with Punch Biopsy. Acta Dermato Venereologica 2014 0. DOI: 10.2340/00015555-2448

[62] Roozeboom M, Kreukels H, Nelemans P et al. Subtyping Basal Cell Carcinoma by Clinical Diagnosis Versus Punch Biopsy. Acta Dermato Venereologica 2015; 95: 996–998. DOI: 10.2340/00015555-2113

[63] Armstrong LTD, Magnusson MR, Guppy MPB. Risk factors for recurrence of facial basal cell carcinoma after surgical excision: A follow-up analysis. Journal of Plastic, Reconstructive & Aesthetic Surgery 2017; 70: 1738–1745. DOI: 10.1016/j.bjps.2017.04.006

[64] Humphreys TR, Shah K, Wysong A et al. The role of imaging in the management of patients with nonmelanoma skin cancer. J Am Acad Dermatol 2017; 76: 591–607. DOI: 10.1016/j.jaad.2015.10.009

[65] Schmitz L, Kahl P, Majores M et al. Actinic keratosis: correlation between clinical and histological classification systems. Journal of the European Academy of Dermatology and Venereology 2016; 30: 1303–1307. DOI: 10.1111/jdv.13626

[66] Wheller L, Soyer HP. Clinical Features of Actinic Keratoses and Early Squamous Cell Carcinoma. 2015; 58–63

[67] Akay BN, Kocyigit P, Heper AO et al. Dermatoscopy of flat pigmented facial lesions: diagnostic challenge between pigmented actinic keratosis and lentigo maligna. British Journal of Dermatology 2010; 163: 1212–1217. DOI: 10.1111/j.1365-2133.2010.10025.x

[68] Huerta-Brogeras M, Olmos O, Borbujo J et al. Validation of Dermoscopy as a Real-time Noninvasive Diagnostic Imaging Technique for Actinic Keratosis. Arch Dermatol 2012; 148: 1159. DOI: 10.1001/archdermatol.2012.1060

[69] Schmitz L, Gupta G, Stücker M et al. Evaluation of two histological classifications for actinic keratoses – <scp>PRO</scp>classification scored highest inter-rater reliability. Journal of the European Academy of Dermatology and Venereology 2019; 33: 1092–1097. DOI: 10.1111/jdv.15580

[70] Fernández-Figueras MT, Carrato C, Sáenz X et al. Actinic keratosis with atypical basal cells (AK I) is the most common lesion associated with invasive squamous cell carcinoma of the skin. Journal of the European Academy of Dermatology and Venereology 2015; 29: 991–997. DOI: 10.1111/jdv.12848

[71] Stratigos A, Garbe C, Lebbe C et al. Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline. Eur J Cancer 2015; 51: 1989–2007. DOI: 10.1016/j.ejca.2015.06.110

[72] de Bree R, Takes RP, Castelijns JA et al. Advances in diagnostic modalities to detect occult lymph node metastases in head and neck squamous cell carcinoma. Head Neck 2015; 37: 1829–1839. DOI: 10.1002/hed.23814

[73] Liao L-J, Lo W-C, Hsu W-L et al. Detection of cervical lymph node metastasis in head and neck cancer patients with clinically N0 neck—a meta-analysis comparing different imaging modalities. BMC Cancer 2012; 12: 236. DOI: 10.1186/1471-2407-12-236

[74] Walsh NM, Cerroni L. Merkel cell carcinoma: A review. J Cutan Pathol 2021; 48: 411–421. DOI: 10.1111/cup.13910

[75] Singh N, Alexander NA, Lachance K et al. Clinical benefit of baseline imaging in Merkel cell carcinoma: Analysis of 584 patients. J Am Acad Dermatol 2021; 84: 330–339. DOI: 10.1016/j.jaad.2020.07.065

[76] Jenkins LN, Howle JR, Veness MJ. Sentinel lymph node biopsy in clinically node-negative Merkel cell carcinoma: the Westmead Hospital experience. ANZ J Surg 2019; 89: 520–523. DOI: 10.1111/ans.15228

[77] Swetter SM, Tsao H, Bichakjian CK et al. Guidelines of care for the management of primary cutaneous melanoma. J Am Acad Dermatol 2019; 80: 208–250. DOI: 10.1016/j.jaad.2018.08.055

[78] Geisse J, Caro I, Lindholm J et al. Imiquimod 5 % cream for the treatment of superficial basal cell carcinoma: results from two phase III, randomized, vehicle-controlled studies. J Am Acad Dermatol 2004; 50: 722–733. DOI: 10.1016/j.jaad.2003.11.066

[79] Roozeboom MH, Arits AHMM, Mosterd K et al. Three-Year Follow-Up Results of Photodynamic Therapy vs. Imiquimod vs. Fluorouracil for Treatment of Superficial Basal Cell Carcinoma: A Single-Blind, Noninferiority, Randomized Controlled Trial. Journal of Investigative Dermatology 2016; 136: 1568–1574. DOI: 10.1016/j.jid.2016.03.043

[80] Arits AH, Mosterd K, Essers BA et al. Photodynamic therapy versus topical imiquimod versus topical fluorouracil for treatment of superficial basal-cell carcinoma: a single blind, non-inferiority, randomised controlled trial. Lancet Oncol 2013; 14: 647–654. DOI: 10.1016/S1470-2045(13)70143-8

[81] Peng Q, Warloe T, Berg K et al. 5-Aminolevulinic acid-based photodynamic therapy. Cancer 1997; 79: 2282–2308. DOI: 10.1002/(SICI)1097-0142(19970615)79:12<2282::AID-CNCR2>3.0.CO;2-O

[82] Basset-Seguin N, Ibbotson SH, Emtestam L et al. Topical methyl aminolaevulinate photodynamic therapy versus cryotherapy for superficial basal cell carcinoma: a 5 year randomized trial. Eur J Dermatol 2008; 18: 547–553. DOI: 10.1684/ejd.2008.0472

[83] Szeimies R, Ibbotson S, Murrell D et al. A clinical study comparing methyl aminolevulinate photodynamic therapy and surgery in small superficial basal cell carcinoma (8-20 mm), with a 12-month follow-up. Journal of the European Academy of Dermatology and Venereology 2008; 22: 1302–1311. DOI: 10.1111/j.1468-3083.2008.02803.x

[84] Kuflik EG. Cryosurgery for Skin Cancer: 30-Year Experience and Cure Rates. Dermatologic Surgery 2004; 30: 297–300. DOI: 10.1111/j.1524-4725.2004.30090.x

[85] Har-Shai Y, Sommer A, Gil T et al. Intralesional cryosurgery for the treatment of basal cell carcinoma of the lower extremities in elderly subjects: a feasibility study. Int J Dermatol 2016; 55: 342–350. DOI: 10.1111/ijd.13168

[86] Berking C, Hauschild A, Kölbl O et al. Basal cell carcinoma-treatments for the commonest skin cancer. Dtsch Arztebl Int 2014; 111: 389–395. DOI: 10.3238/arztebl.2014.0389

[87] Drucker AM, Adam GP, Rofeberg V et al. Treatments of Primary Basal Cell Carcinoma of the Skin. Ann Intern Med 2018; 169: 456–466. DOI: 10.7326/M18-0678

[88] McKeown SR, Hatfield P, Prestwich RJ et al. Radiotherapy for benign disease; assessing the risk of radiation-induced cancer following exposure to intermediate dose radiation. Br J Radiol 2015; 88: 20150405. DOI: 10.1259/bjr.20150405

[89] Dirschka T, Gupta G, Micali G et al. Real-world approach to actinic keratosis management: practical treatment algorithm for office-based dermatology. Journal of Dermatological Treatment 2017; 28: 431–442. DOI: 10.1080/09546634.2016.1254328

[90] Arcuri D, Ramchatesingh B, Lagacé F et al. Pharmacological Agents Used in the Prevention and Treatment of Actinic Keratosis: A Review. Int J Mol Sci 2023; 24: 4989. DOI: 10.3390/ijms24054989

[91] Smolinski MP, Bu Y, Clements J et al. Discovery of Novel Dual Mechanism of Action Src Signaling and Tubulin Polymerization Inhibitors (KX2-391 and KX2-361). J Med Chem 2018; 61: 4704–4719. DOI: 10.1021/acs.jmedchem.8b00164

[92] Blauvelt A, Kempers S, Lain E et al. Phase 3 Trials of Tirbanibulin Ointment for Actinic Keratosis. New England Journal of Medicine 2021; 384: 512–520. DOI: 10.1056/NEJMoa2024040

[93] Mendenhall WM, Amdur RJ, Hinerman RW et al. Skin Cancer of the Head and Neck With Perineural Invasion. Am J Clin Oncol 2007; 30: 93–96. DOI: 10.1097/01.coc.0000251224.16075.60

[94] Lansbury L, Bath-Hextall F, Perkins W et al. Interventions for non-metastatic squamous cell carcinoma of the skin: systematic review and pooled analysis of observational studies. BMJ 2013; 347: f6153–f6153. DOI: 10.1136/bmj.f6153

[95] Fang LC, Lemos B, Douglas J et al. Radiation monotherapy as regional treatment for lymph node-positive Merkel cell carcinoma. Cancer 2010; 116: 1783–1790. DOI: 10.1002/cncr.24919

[96] Farshad A, Burg G, Panizzon R et al. A retrospective study of 150 patients with lentigo maligna and lentigo maligna melanoma and the efficacy of radiotherapy using Grenz or soft X-rays. British Journal of Dermatology 2002; 146: 1042–1046. DOI: 10.1046/j.1365-2133.2002.04750.x

[97] Trakatelli M, Morton C, Nagore E et al. Update of the European guidelines for basal cell carcinoma management. European Journal of Dermatology 2014; 24: 312–329. DOI: 10.1684/ejd.2014.2271

[98] Kauvar ANB, Cronin T, Roenigk R et al. Consensus for Nonmelanoma Skin Cancer Treatment. Dermatologic Surgery 2015; 41: 550–571. DOI: 10.1097/DSS.0000000000000296

[99] Gulleth Y, Goldberg N, Silverman RP et al. What Is the Best Surgical Margin for a Basal Cell Carcinoma: A Meta-Analysis of the Literature. Plast Reconstr Surg 2010; 126: 1222–1231. DOI: 10.1097/PRS.0b013e3181ea450d

[100] Nahhas AF, Scarbrough CA, Trotter S. A Review of the Global Guidelines on Surgical Margins for Nonmelanoma Skin Cancers. J Clin Aesthet Dermatol 2017; 10: 37–46

[101] Wolf DJ, Zitelli JA. Surgical margins for basal cell carcinoma. Arch Dermatol 1987; 123: 340–344

[102] Bichakjian CK, Olencki T, Aasi SZ et al. Basal Cell Skin Cancer, Version 1.2016, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network 2016; 14: 574–597. DOI: 10.6004/jnccn.2016.0065

[103] Möhrle M. Von der „mikroskopisch kontrollierten Chirurgie" zur „3D-Histologie" – eine Erfolgsgeschichte. Aktuelle Derm 2009; 35: 283–286. DOI: 10.1055/s-0029-1214845

[104] Chen OM, Kim K, Steele C et al. Advances in Management and Therapeutics of Cutaneous Basal Cell Carcinoma. Cancers (Basel) 2022; 14: 3720. DOI: 10.3390/cancers14153720

[105] Rowe DE, Carroll RJ, Day CL. Mohs Surgery Is the Treatment of Choice for Recurrent (Previously Treated) Basal Cell Carcinoma. J Dermatol Surg Oncol 1989; 15: 424–431. DOI: 10.1111/j.1524-4725.1989.tb03249.x

[106] Abramson AK, Krasny MJ, Goldman GD. Tangential Shave Removal of Basal Cell Carcinoma. Dermatologic Surgery 2013; 39: 387–392. DOI: 10.1111/dsu.12106

[107] Stratigos AJ, Garbe C, Dessinioti C et al. European interdisciplinary guideline on invasive squamous cell carcinoma of the skin: Part 1. epidemiology, diagnostics and prevention. Eur J Cancer 2020; 128: 60–82. DOI: 10.1016/j.ejca.2020.01.007

[108] Zhang J, Wang Y, Wijaya WA et al. Efficacy and prognostic factors of adjuvant radiotherapy for cutaneous squamous cell carcinoma: A systematic review and meta-analysis. Journal of the European Academy of Dermatology and Venereology 2021; 35: 1777–1787. DOI: 10.1111/jdv.17330

[109] Sahovaler A, Krishnan RJ, Yeh DH et al. Outcomes of Cutaneous Squamous Cell Carcinoma in the Head and Neck Region With Regional Lymph Node Metastasis. JAMA Otolaryngology–Head & Neck Surgery 2019; 145: 352. DOI: 10.1001/jamaoto.2018.4515

[110] Porceddu SV, Bressel M, Poulsen MG et al. Postoperative Concurrent Chemoradiotherapy Versus Postoperative Radiotherapy in High-Risk Cutaneous Squamous Cell Carcinoma of the Head and Neck: The Randomized Phase III TROG 05.01 Trial. Journal of Clinical Oncology 2018; 36: 1275–1283. DOI: 10.1200/JCO.2017.77.0941

[111] Han AY, Patel PB, Anderson M et al. Adjuvant radiation therapy improves patient survival in early-stage merkel cell carcinoma: A 15-year single-institution study. Laryngoscope 2018; 128: 1862–1866. DOI: 10.1002/lary.27031

[112] Hazan C, Dusza SW, Delgado R et al. Staged excision for lentigo maligna and lentigo maligna melanoma: A retrospective analysis of 117 cases. J Am Acad Dermatol 2008; 58: 142–148. DOI: 10.1016/j.jaad.2007.09.023

[113] Iznardo H, Garcia-Melendo C, Yélamos O. Lentigo Maligna: Clinical Presentation and Appropriate Management . . Clin Cosmet Investig Dermatol 2020; Volume 13: 837–855. DOI: 10.2147/CCID.S224738

[114] Robinson JK. Actinic Cheilitis: A Prospective Study Comparing Four Treatment Methods. Archives of Otolaryngology – Head and Neck Surgery 1989; 115: 848–852. DOI: 10.1001/archotol.1989.01860310086029

[115] Lai M, Pampena R, Cornacchia L et al. Treatments of actinic cheilitis: A systematic review of the literature. J Am Acad Dermatol 2020; 83: 876–887. DOI: 10.1016/j.jaad.2019.07.106

[116] Perea-Milla López E, Miñarro-del Moral RM, Martínez-García C et al. Lifestyles, environmental and phenotypic factors associated with lip cancer: a case–control study in southern Spain. Br J Cancer 2003; 88: 1702–1707. DOI: 10.1038/sj.bjc.6600975

[117] Wang DM, Kraft S, Rohani P et al. Association of Nodal Metastasis and Mortality With Vermilion vs Cutaneous Lip Location in Cutaneous Squamous Cell Carcinoma of the Lip. JAMA Dermatol 2018; 154: 701. DOI: 10.1001/jamadermatol.2018.0792

[118] Gooris PJJ, Vermey A, de Visscher JGAM et al. Supraomohyoid neck dissection in the management of cervical lymph node metastases of squamous cell carcinoma of the lower lip. Head Neck 2002; 24: 678–683. DOI: 10.1002/hed.10079

[119] Bhandari K, Wang D, Li S et al. Primary cN0 lip squamous cell carcinoma and elective neck dissection: Systematic review and meta-analysis. Head Neck 2015; 37: 1392–1400. DOI: 10.1002/hed.23772

[120] Newlands C, Currie R, Memon A et al. Non-melanoma skin cancer: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol 2016; 130: S125–S132. DOI: 10.1017/S0022215116000554

[121] Martinez J-C, Cook JL. High-Risk Cutaneous Squamous Cell Carcinoma without Palpable Lymphadenopathy: Is There a Therapeutic Role for Elective Neck Dissection? Dermatologic Surgery 2007; 33: 410–420. DOI: 10.1111/j.1524-4725.2007.33087.x

[122] Amit M, Liu C, Mansour J et al. Elective neck dissection versus observation in patients with head and neck cutaneous squamous cell carcinoma. Cancer 2021; 127: 4413–4420. DOI: 10.1002/cncr.33773

[123] Peiffer N, Kutz JW, Myers LL et al. Patterns of Regional Metastasis in Advanced Stage Cutaneous Squamous Cell Carcinoma of the Auricle. Otolaryngology–Head and Neck Surgery 2011; 144: 36–42. DOI: 10.1177/0194599810390908

[124] Ferlito A, Rinaldo A, Silver CE et al. Elective and therapeutic selective neck dissection. Oral Oncol 2006; 42: 13–24. DOI: 10.1016/j.oraloncology.2005.03.009

[125] Audet N, Palme CE, Gullane PJ et al. Cutaneous metastatic squamous cell carcinoma to the parotid gland: analysis and outcome. Head Neck 2004; 26: 727–732. DOI: 10.1002/hed.20048

[126] Rotman A, Kerr SJ, Giddings CEB. Elective neck dissection in metastatic cutaneous squamous cell carcinoma to the parotid gland: A systematic review and meta-analysis. Head Neck 2019; 41: 1131–1139. DOI: 10.1002/hed.25561

[127] Han A, Ratner D. What is the role of adjuvant radiotherapy in the treatment of cutaneous squamous cell carcinoma with perineural invasion? Cancer 2007; 109: 1053–1059. DOI: 10.1002/cncr.22509

[128] Gunaratne DA, Howle JR, Veness MJ. Sentinel lymph node biopsy in Merkel cell carcinoma: a 15-year institutional experience and statistical analysis of 721 reported cases. British Journal of Dermatology 2016; 174: 273–281. DOI: 10.1111/bjd.14240

[129] Stokes JB, Graw KS, Dengel LT et al. Patients With Merkel Cell Carcinoma Tumors ≤ 1.0 cm in Diameter Are Unlikely to Harbor Regional Lymph Node Metastasis. Journal of Clinical Oncology 2009; 27: 3772–3777. DOI: 10.1200/JCO.2008.20.8272

[130] Iyer JG, Storer BE, Paulson KG et al. Relationships among primary tumor size, number of involved nodes, and survival for 8044 cases of Merkel cell carcinoma. J Am Acad Dermatol 2014; 70: 637–643. DOI: 10.1016/j.jaad.2013.11.031

[131] Timmer FCA, Klop WMC, Relyveld GN et al. Merkel cell carcinoma of the head and neck: emphasizing the risk of undertreatment. European Archives of Oto-Rhino-Laryngology 2016; 273: 1243–1251. DOI: 10.1007/s00405-015-3558-0

[132] Cheraghlou S, Agogo GO, Girardi M. Evaluation of Lymph Node Ratio Association With Long-term Patient Survival After Surgery for Node-Positive Merkel Cell Carcinoma. JAMA Dermatol 2019; 155: 803–811. DOI: 10.1001/jamadermatol.2019.0267

[133] Hong NJL, Wright FC, Gagliardi AR et al. Examining the potential relationship between multidisciplinary cancer care and patient survival: An international literature review. J Surg Oncol 2010; 102: 125–134. DOI: 10.1002/jso.21589

[134] Lamb BW, Brown KF, Nagpal K et al. Quality of Care Management Decisions by Multidisciplinary Cancer Teams: A Systematic Review. Ann Surg Oncol 2011; 18: 2116–2125. DOI: 10.1245/s10434-011-1675-6

[135] Bundesministerium für Gesundheit. Broschüre: Nationaler Krebsplan – Handlungsfelder, Ziele und Umsetzungsempfehlungen. Berlin 2012

[136] Ascierto PA, Schadendorf D. Update in the treatment of non-melanoma skin cancers: the use of PD-1 inhibitors in basal cell carcinoma and cutaneous squamous-cell carcinoma. J Immunother Cancer 2022; 10: e005082. DOI: 10.1136/jitc-2022-005082

[137] Harrington C, Kwan W. Radiotherapy and Conservative Surgery in the Locoregional Management of Merkel Cell Carcinoma: The British Columbia Cancer Agency Experience. Ann Surg Oncol 2016; 23: 573–578. DOI: 10.1245/s10434-015-4812-9

[138] Takagishi SR, Marx TE, Lewis C et al. Postoperative radiation therapy is associated with a reduced risk of local recurrence among low risk Merkel cell carcinomas of the head and neck. Adv Radiat Oncol 2016; 1: 244–251. DOI: 10.1016/j.adro.2016.10.003

[139] Becker JC, Ugurel S, Leiter U et al. Adjuvant immunotherapy with nivolumab versus observation in completely resected Merkel cell carcinoma (ADMEC-O): disease-free survival results from a randomised, open-label, phase 2 trial. The Lancet 2023. DOI: 10.1016/S0140-6736(23)00769-9

[140] Ferrarotto R, Nagarajan P, Maronge JM et al. Outcomes of Treatment With Neoadjuvant Cemiplimab for Patients With Advanced, Resectable Cutaneous Squamous Cell Carcinoma of the Head and Neck. JAMA Otolaryngology–Head & Neck Surgery 2023. DOI: 10.1001/jamaoto.2023.1729

[141] Gross ND, Miller DM, Khushalani NI et al. Neoadjuvant Cemiplimab for Stage II to IV Cutaneous Squamous-Cell Carcinoma. New England Journal of Medicine 2022; 387: 1557–1568. DOI: 10.1056/NEJMoa2209813

[142] Topalian SL, Bhatia S, Amin A et al. Neoadjuvant Nivolumab for Patients With Resectable Merkel Cell Carcinoma in the CheckMate 358 Trial. Journal of Clinical Oncology 2020; 38: 2476–2487. DOI: 10.1200/JCO.20.00201

[143] Sekulic A, Migden MR, Oro AE et al. Efficacy and Safety of Vismodegib in Advanced Basal-Cell Carcinoma. New England Journal of Medicine 2012; 366: 2171–2179. DOI: 10.1056/NEJMoa1113713

[144] Migden MR, Guminski A, Gutzmer R et al. Treatment with two different doses of sonidegib in patients with locally advanced or metastatic basal cell carcinoma (BOLT): a multicentre, randomised, double-blind phase 2 trial. Lancet Oncol 2015; 16: 716–728. DOI: 10.1016/S1470-2045(15)70100-2

[145] Lear JT, Migden MR, Lewis KD et al. Long-term efficacy and safety of sonidegib in patients with locally advanced and metastatic basal cell carcinoma: 30-month analysis of the randomized phase 2 BOLT study. Journal of the European Academy of Dermatology and Venereology 2018; 32: 372–381. DOI: 10.1111/jdv.14542

[146] Stratigos AJ, Sekulic A, Peris K et al. Cemiplimab in locally advanced basal cell carcinoma after hedgehog inhibitor therapy: an open-label, multi-centre, single-arm, phase 2 trial. Lancet Oncol 2021; 22: 848–857. DOI: 10.1016/S1470-2045(21)00126-1

[147] Stratigos AJ, Sekulic A, Peris K et al. Cemiplimab in locally advanced basal cell carcinoma after hedgehog inhibitor therapy: an open-label, multi-centre, single-arm, phase 2 trial. Lancet Oncol 2021; 22: 848–857. DOI: 10.1016/S1470-2045(21)00126-1

[148] Rischin D, Khushalani NI, Schmults CD et al. Integrated analysis of a phase 2 study of cemiplimab in advanced cutaneous squamous cell carcinoma: extended follow-up of outcomes and quality of life analysis. J Immunother Cancer 2021; 9: e002757. DOI: 10.1136/jitc-2021-002757

[149] Hughes BGM, Munoz-Couselo E, Mortier L et al. Pembrolizumab for locally advanced and recurrent/metastatic cutaneous squamous cell carcinoma (KEYNOTE-629 study): an open-label, nonrandomized, multicenter, phase II trial. Ann Oncol 2021; 32: 1276–1285. DOI: 10.1016/j.annonc.2021.07.008

[150] Hitt R, Irigoyen A, Cortes-Funes H et al. Phase II study of the combination of cetuximab and weekly paclitaxel in the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of head and neck. Annals of Oncology 2012; 23: 1016–1022. DOI: 10.1093/annonc/mdr367

[151] Glutsch V, Kneitz H, Gesierich A et al. Activity of ipilimumab plus nivolumab in avelumab-refractory Merkel cell carcinoma. Cancer Immunology, Immunotherapy 2021; 70: 2087–2093. DOI: 10.1007/s00262-020-02832-0

[152] Nghiem P, Kaufman HL, Bharmal M et al. Systematic literature review of efficacy, safety and tolerability outcomes of chemotherapy regimens in patients with metastatic Merkel cell carcinoma. Future Oncology 2017; 13: 1263–1279. DOI: 10.2217/fon-2017-0072