S2k Guidelines for Cutaneous Basal Cell Carcinoma – Part 1: Epidemiology, Genetics and Diagnosis

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S2k Guidelines 032-021 "Basal Cell Carcinoma" (Update 2017/18)

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Summary

Basal cell carcinoma is the most common malignant tumor among fair-skinned individuals, and its incidence has been rising steadily in the past decades. In order to maintain the highest quality of patient care possible, the German S2k guidelines were updated following a systematic literature search and with the participation of all professional societies and associations involved in the management of the disease. Part 1 highlights new developments in genetics in particular as well as aspects regarding epidemiology, diagnosis, and histology.

Preamble

This preamble to the revised and extended S2k guidelines for Basal Cell Carcinoma is intended to define the disease-related terminology. Compared to the last version of the guidelines, we sought to corroborate each statement with corresponding evidence (systematic literature search), even though the present guidelines were developed only at the S2k level (according to the AWMF classification).

Although the historic term "basalioma" is still widely used among German physicians, it will no longer be used herein. Instead, it is replaced by the histopathologically correct term "basal cell carcinoma". This step is meant to underline the potential aggressiveness of the tumor and to adopt the terminology used in the international literature.

Other changes include the term "nodular basal cell carcinoma" instead of "solid basal cell carcinoma" and "superficial basal cell carcinoma" instead of "basal cell carcinoma of the trunk", given that the latter occurs not only – as the German term suggests – on the trunk but also in other sites, especially on the extremities.

"Locally advanced" basal cell carcinomas comprise a subgroup of tumors that require an interdisciplinary therapeutic concept due to their extent and in particular because of their destructive infiltrative growth. The hallmark of these tumors is that

– following clinical diagnosis, primary excision for diagnostic confirmation, unsuccessful re-excision, and obtaining interdisciplinary expertise (tumor board) – R0 resection cannot be definitively achieved due to factors such as involvement of vital or functionally important structures.

Given the risk of confusion with Goltz-Gorlin syndrome (focal dermal hypoplasia), the term "basal cell carcinoma syndrome" is used instead of the historic designation "Gorlin-Goltz syndrome" or "basal cell nevus syndrome".

Moreover, it should be noted that the authors of the present guidelines chose to subsume a patient's request not to undergo surgery after the informed consent discussion (informed decision making) under the term "contraindication for surgery".

In the present guidelines, the strength of consensus was determined based on the following degrees of agreement:
– *Strong consensus:* > 95 % of eligible voters
– *Consensus:* > 75–95 % of eligible voters
– *Majority agreement:* > 50–75 % of eligible voters

Statements with a strength of consensus of less than 50 % were not included in the guidelines or were revised.

1 Epidemiology, clinical presentation, genetics

Statements (strong consensus)

- Cutaneous basal cell carcinoma is the most common malignant tumor in Central Europe. Clinically, the tumor is characterized by infiltrative and destructive local growth, whereas metastasis is uncommon.
- In Germany, the incidence is at least 200 new cases per 100,000 population per year.
- Basal cell carcinomas arise *de novo*.
- Risk factors are UV exposure as well as genetic predisposition (skin type, gender, syndromes).
- The same patient may experience multiple primary tumors over the course of years or decades.

Basal cell carcinoma (BCC) is the most common malignant tumor in Central Europe [1]. Characterized by destructive local growth, it is an epithelial neoplasm with basaloid differentiation that arises from stem cells within the hair follicle and the interfollicular epidermis [2]. Clinically, it presents as skin-colored, erythematous, or brownish-red nodules, plaques (superficial basal cell carcinoma [sBCC]), or ulcers – depending on the site and disease stage. Classic nodular basal cell carcinoma (nBCC) presents as a shiny, pearly nodule with prominent margins laced with telangiectasias; there may be central ulceration. The following subtypes can be distinguished based on their different clinical appearance: nodular BCC, superficial BCC, sclerosing BCC, pigmented BCC, ulcerated BCC (ulcus rodens, historic term), destructive BCC (ulcus terebrans, historic term). Ulceronodular subtypes account for 60–80 % of all BCC cases [3].

The incidence of BCC has steadily increased in recent years. In Germany, it is currently reported to be approximately 200/100,000 population per year [4–6]. That number is likely to be significantly higher, given that most cancer registries only record the first occurrence of BCC and multiple tumors are not represented. The incidence has been predicted to continue to increase in the decades to come [7]. For ethnic groups from Central and Northern Europe, the life-time prevalence has been estimated to more than 10 % [8]. Based on data from cancer registries, the mean age of disease onset is currently 73 (men) and 71 (women), respectively, in Germany. While both genders are affected, the disease occurs slightly more often in men [4]. BCCs typically exhibit a locally infiltrative and destructive growth type. Metastasis formation is very rare (estimated incidence 0.0028–0.55 %) [9]. Basal cell carcinomas account for more than 80 % of all epithelial skin tumors and occur most commonly on head and neck, followed by trunk and extremities [6, 10, 11]. Basal cell carcinomas can only develop in skin areas with hair follicles; consequently, primary manifestation cannot occur on mucous membranes or palms and soles.

Activation of the sonic hedgehog (SHH) signaling pathway plays a key role in the development of BCCs. A mutation in the inhibitor *patched* (PTCH) of SHH causes uncontrolled activation of *smoothened* (SMO) rendering keratinocytes resistant to apoptosis. Ten percent of sporadic BCCs exhibit an activating mutation in SMO, while 90 % are caused by an inactivating mutation in PTCH. The latter is also responsible for BCCs associated with syndromes such as basal cell carcinoma syndrome and xeroderma pigmentosum [9]. In addition, (UV-triggered) point mutations in *p53* have been reported to be involved in the development of BCCs [12]. However, a 2016 study also revealed the large variety of genetic mutations in BCCs. Although 85 % of examined BCCs (n = 293) showed mutations in the SHH signaling pathway (*PTCH1* [73 %], *SMO* [20 %], *SUFU* [8 %]) and 61 % in *TP53*, 85 % of the BCCs had additional mutations in other cancer-associated genes (*MYCN* [30 %], *PPP6C* [15 %], *STK19* [10 %], *LATS1* [8 %], *ERBB2* [4 %], *PIK3CA* [2 %], *NRAS/KRAS/HRAS* [2 %], *PTPN14* [23 %], *RB1* [8 %], *FBXW7* [5 %]). While the relevance of these mutations needs to be further investigated, they might play a future role in the treatment of locally advanced basal cell carcinoma (laBCC) or metastatic basal cell carcinoma (mBCC) [13].

Intensive UV exposure is regarded as major risk factor for the development of BCCs, in particular, apart from chronic exposure, intermitting high exposure peaks (sunburns, especially in childhood) [14–16]. Consequently, the use of tanning beds carries a high risk [17]. Compared to the general population, patients with very high occupational UV exposure have

a significantly higher risk of developing BCCs (OR 1.43; 95 % CI 1.23–1.66) [18, 19]. Overall, however, this correlation is – compared to squamous cell carcinoma – less pronounced and consistent [19, 20]. Currently however, the legal prerequesites for recognition of BCCs as an occupational disease due to chronic solar UV exposure (BK5103) are not fulfilled in Germany [21]. Further risk factors include: male gender, skin type I and II according to Fitzpatrick (individuals with genetically determined low skin pigmentation), BCC in personal history, chronic exposure to arsenic, exposure to ionizing radiation, long-lasting immunosuppression, and genetic syndromes (basal cell carcinoma syndrome, xeroderma pigmentosum). Scars and chronic ulcerations are especially important for development of BCCs in non-chronically UV-exposed areas.

Regarding risk factors and prevention of BCC, we also refer to the contents of the S3 Guideline "Prevention of Skin Cancer".

2 Genodermatoses with increased incidence of basal cell carcinoma

Recommendation (strong consensus)

- In case of multiple BCCs occurring before the age of 20, a diagnostic workup shall be performed to rule out a genetic syndrome.

2.1 Basal cell carcinoma syndrome (Gorlin-Goltz syndrome, basal cell nevus syndrome)

Basal cell carcinoma syndrome is a multisystem disorder with autosomal dominant inheritance characterized by multiple BCCs occurring early in life. Additional findings include malformations that affect the skeletal system, the central nervous system, the genitourinary system, and the heart. Apart from multiple BCCs, the disorder clinically presents with odontogenic keratocysts, rib abnormalities and calcification of the falx cerebri. Other notable signs consist of macrocephaly with a protruding jaw, broad nasal bridge, and frontal bossing. Childhood medulloblastoma occurs in 5–10 % of the patients. The diagnosis requires that either one major criterion be present in conjunction with genetic confirmation; or two major criteria; or one major and two minor criteria (Table 1). The prevalence is reported to be approximately 1 : 56,000. Both life expectancy and quality of life are reduced [22]. The disorder is caused by a mutation in the *PTCH1* gene (9q22.3), which encodes the Patched receptor. Spontaneous mutations are common; the family history is negative in almost one-half of the cases [23–25]. Inhibitors of the hedgehog signaling pathway are novel therapeutic options for these patients. In case of a positive family history or findings suggestive of basal cell carcinoma syndrome, regular skin cancer screening and adequate sun protection should be initiated early in life, even if the diagnosis has not been confirmed. It should also be noted that exposure of affected patients to ionizing radiation should be minimized as much as possible; if in doubt, it is preferable to use MRI [26].

2.2 Bazex-Dupré-Christol syndrome

Bazex-Dupré-Christol syndrome is a very rare syndrome with X-linked dominant inheritance. Apart from early development of BCCs, it is characterized by the following clinical features: generalized hypotrichosis, alopecia, atrophoderma vermiculatum (dorsa of the hands and feet), and hypohidrosis. The prevalence is less than 1 : 1,000,000. A 2017 study showed mutations in the *ACTRT1* gene to be responsible for the aberrant activation of the hedgehog signaling pathway [27].

2.3 Rombo syndrome

Rombo syndrome is a very rare autosomal dominant syndrome. In addition to the development of BCCs, it presents with acrocyanosis, keratosis pilaris, atrophoderma vermiculatum, hypotrichosis as well as hypohidrosis. Notably, the onset of the disease is before the age 10. The prevalence is less than 1 : 1,000,000. It is difficult to distinguish the disorder from Bazex-Dupré-Christol syndrome [28].

Table 1 Major and minor criteria for the diagnosis of basal cell carcinoma syndrome [26].

Major criteria	Minor criteria
▸ First BCC before the age of 20 or excessive number of BCCs	▸ Rib abnormalities
▸ Odontogenic keratocysts before the age of 20	▸ Other specific skeletal malformations or radiological abnormalities
▸ Palmar or plantar pitting	▸ Macrocephaly
▸ Calcification of the falx cerebri	▸ Cleft palate or cleft lip
▸ Medulloblastoma (usually desmoplastic)	▸ Cardiac or ovarian fibromas
▸ First-degree relative with basal cell carcinoma syndrome	▸ Lymphomesenteric cysts
	▸ Ocular anomalies (strabismus, hypertelorism, congenital cataract, glaucoma, coloboma)

Other rare syndromes include Dugois-Colomb-Berthon syndrome and linear (unilateral) basal cell carcinoma. Moreover, all types of albinism, T-cell immunodeficiency as well as xeroderma pigmentosum (types B/C/E/F/G/V) are associated with a higher incidence of BCC and require close follow-up and the use of preventive measures.

3 Diagnosis

3.1 Clinical diagnosis

Statement (strong consensus)

- Inspection of the patient without additional tools is suitable for making a suspected clinical diagnosis.

Recommendation (strong consensus)

- Following the diagnosis of BCC, a total body skin examination shall be performed or recommended.

BCC is marked by great clinical heterogeneity. Typical features of ulceronodular lesions in particular consist of a pearly sheen, telangiectasias, raised margins, central ulceration, and a cystic appearance. Superficial BCC is usually characterized by erythematous, frequently multiple macules or plaques with central erosion (and bleeding), whereas sclerosing BCC has a whitish, atrophic appearance. The clinical presentation alone does not allow for definitive conclusions to be drawn with respect to the histological subtype [29, 30].

Factors that are crucial for assessing the risk of recurrence or aggressive growth include the histological subtype as well as clinical parameters such as size, location, margins (ill-defined vs. well-circumscribed) and aspects of the patient's history (recurrence, history of radiation therapy at the tumor site). Accordingly, this information must be collected and included in the risk assessment.

The presence of a BCC generally increases the risk of developing other epithelial malignancies. While this is true for sun-exposed skin of the head and neck region and the upper extremities in particular, it also applies – albeit to a lesser extent – to skin not exposed to the sun. A total body skin examination is therefore recommended. In the diagnostic workup of BCC, such an exam involves complete inspection of the skin including the scalp.

3.2 Non-invasive diagnostic procedures

3.2.1 Dermoscopic diagnosis

Statement (strong consensus)

- Dermoscopy may contribute to improving the reliability of the clinical diagnosis of BCC.

Several studies have investigated to what extent dermoscopy is able to predict the histological subtype prior to surgery. In a prospective, non-comparative study with more than 3,500 BCCs, the sensitivity and specificity of dermoscopy for detecting any type of BCC were 93.3 % and 91.8 %, respectively. Moreover, rigorous use of dermoscopy significantly improved the diagnostic accuracy for the superficial subtype [31]. However, studies investigating the usefulness of dermoscopy in differentiating aggressive from non-aggressive subtypes revealed a lack of discriminatory power: while aggressive tumors more commonly showed multiple blue-gray globules, arborizing vessels, and concentric structures, non-aggressive variants only exhibited blue-gray nests [32]. There is evidence that rigorous use of dermoscopy facilitates early detection of small BCCs [33]. In addition to distinguishing various BCC subtypes, the crucial role of dermoscopy is based on its ability to facilitate the diagnostic differentiation from melanoma (amelanotic melanoma in particular), Bowen's disease, and squamous cell carcinoma [34].

3.2.2 Confocal laser microscopy

Statement (strong consensus)

- Confocal laser microscopy may be useful in the diagnosis of BCC.

There are numerous studies on the significance of confocal laser microscopy in the non-invasive diagnosis of BCCs. Criteria typical for BCCs have been described (in particular, cone-shaped epithelial cell clusters with peripheral palisading and a dark rim, dark silhouettes). Confocal laser microscopy enables non-invasive diagnosis of BCCs; due to the low penetration, however, it is not possible to measure tumor thickness. Kadouch et al. showed that laser microscopy and biopsy had similar sensitivity for detecting BCCs (100 % vs. 94 %); however, biopsies were more specific (79 % vs. 38 %). Specificity was markedly increased when the assessment was performed by physicians experienced in this method (75 %) [35, 36].

3.2.3 Optical coherence tomography

Statements (strong consensus)

- Optical coherence tomography may be useful in the diagnosis of BCC.
- Confocal laser microscopy and optical coherence tomography may be useful in assessing the effect of topical therapies for BCC.

With BCC, optical coherence tomography reveals typical changes – such as ovoid, homogeneous tumor cell nests and a dark rim – that vary depending on the subtype. In a study with 164 patients and 235 lesions, Ulrich et al. showed

that the use of optical coherence tomography increased the diagnostic accuracy compared to clinical and dermoscopic diagnosis. While optical coherence tomography resulted in equal sensitivity, specificity was increased from 29 % to 75 % [37]. Basal cell carcinoma differs from actinic keratosis both morphologically and using objective parameters such as epidermal thickness and signal intensity of the dermis [38]. Optical coherence tomography is suitable for measuring the thickness of BCCs up to a thickness of approximately 1 mm. The lateral margins can be visualized to assess the extent of a given lesion preoperatively. The various BCC subtypes show differences in morphology [39–42].

There are numerous studies that have used confocal laser microscopy and optical coherence tomography to visualize and quantify the therapeutic effects of topical therapies for BCC as well as to monitor clinical recovery and detect recurrences [43–46].

3.2.4 High-frequency ultrasound

High-frequency ultrasound may be useful for determining the lateral and deep margins of BCC preoperatively [47].

3.3 Cross-sectional imaging

Only in certain cases of BCC further imaging such as CT or MRI scans are indicated. This includes laBCC as well as lesions where there is clinical suspicion of perineural growth or metastasis [48].

3.3.1 Locally advanced basal cell carcinoma (laBCC)

Recommendation (strong consensus)

- If there is clinical suspicion of osseous infiltration, computed tomography and/or contrast-enhanced magnetic resonance imaging shall be performed to assess the extent of intraosseous tumor spread.

Locally advanced BCC can infiltrate the skull, dura, and brain through continuous growth. The incidence of intracranial invasion has been reported to be 0.3 % [49, 50]. If clinical examination shows a fixed tumor mass above a soft area with a palpable osseous rim, infiltration of the skull must be suspected and further imaging studies are indicated. While computed tomography (CT) allows for detailed, high-resolution visualization of bone destruction, especially with respect to cortical bone, it is only of limited value for the detection of intraosseous tumor spread in cancellous bone or bone marrow [51]. Compared to CT, magnetic resonance imaging (MRI) is inferior when it comes to assessing cortical bone; it is, however, clearly superior with respect to visualizing soft tissue and thus the method of choice for assessing both intraosseous and intracranial spread. Here, fat-suppressed T2-weighted and contrast-enhanced T1-weighted sequences allow for differentiation between tumor and fatty bone marrow and thus facilitate detailed visualization of tumor spread in the medullary cavity of the infiltrated bone [52].

3.3.2 Periorbital basal cell carcinoma

Recommendation (strong consensus)

- If orbital invasion is clinically suspected, computed tomography of the orbit shall be performed to assess bone destruction, and contrast-enhanced magnetic resonance imaging of the orbit to assess intraorbital tumor spread.

Orbital invasion occurs in less than 5 % of periocular BCCs. It is caused by continuous growth into the orbit by advanced BCCs or perineural growth of tumors with perineural infiltration [53]. Clinical findings suggestive of orbital invasion are a fixed periorbital tumor or limited ocular motility. Other factors associated with an increased risk of orbital invasion include a primary tumor at the medial canthus, multiple recurrences, infiltrative or sclerosing BCC, and perineural infiltration [54]. Given the good soft-tissue contrast associated with MRI, it provides detailed visualization of intraorbital structures. It thus helps assess whether there is intraconal tumor spread with potential infiltration of the bulbus oculi, optical nerve, or ocular muscles.

3.3.3 Perineural growth

The prevalence of perineural invasion by BCCs reported in the literature varies from 0.18 % to 3 % [55–58]. Prospective studies suggest that the higher percentages tend to be correct and that they significantly contribute to subclinical spread and an increased risk of recurrence [59, 60]. Moreover, perineural spread is more common in BCCs that show deep invasion. In advanced lesions, MRI is the most sensitive imaging method for the detection of perineural invasion prior to surgery or radiation therapy [61]. In general, however, the extent of perineural spread is significantly underestimated, given that detection using imaging methods requires a certain tumor size, whereas it is usually impossible to detect small clusters or thin layers of perineural tumor cells by imaging studies [62]. If perineural growth is suspected, MRI with fat-saturated, high-resolution, contrast-enhanced T1-weighted sequences is the method of choice.

3.3.4 Metastatic basal cell carcinoma

Recommendation (strong consensus)

- If metastasis is clinically suspected, cross-sectional imaging studies shall be performed, and the primary histology shall be reevaluated.

Metastatic BCC is rare and occurs in 0.0028 % to 0.55 % of all cases [9]. Metastasis is, however, associated with high mortality, with a mean survival time of 87 months for isolated lymphatic spread and 24 months for hematogenous spread [63]. Muscles, bones, lungs, and lymph nodes are primarily affected.

On 18F-FDG-PET/CT, primary tumors and metastases of BCC are usually detectable as hypermetabolic masses. However, given the low glucose metabolism of slowly growing BCCs, such tumors often can only be detected morphologically by CT but not metabolically by PET [64]. In patients with mBCC with initially increased glucose metabolism on PET/CT, a decrease in glucose uptake (SUV_{max}) on vismodegib therapy indicates a favorable prognosis and is therefore useful in assessing the response to treatment [65].

3.3.5 Basal cell carcinoma syndrome

Recommendation (strong consensus)

- If basal cell carcinoma syndrome is suspected, imaging studies to rule out additional malignancies and to detect associated abnormalities should be done using magnetic resonance imaging in order to prevent radiation-induced neoplasms.

Basal cell carcinoma syndrome is an autosomal dominant disorder characterized by the occurrence of multiple BCCs early in life. Other frequent findings include odontogenic keratocysts, palmar and plantar dyskeratoses as well as skeletal anomalies. Apart from other neoplasms, children often develop desmoplastic medulloblastoma. Establishing the diagnosis requires a total body skin examination, MRI of the skull, echocardiography, X-ray of the spine, dental panoramic imaging, and – in women – a gynecological (pelvic) ultrasound [66]. On the one hand, imaging studies are required in these patients to rule out additional malignancies and to detect associated findings, such as skeletal anomalies, to confirm the presence of a syndrome. On the other hand, exposure to radiation must be avoided as affected patients have an increased sensitivity to ionizing radiation with respect to the induction of malignant tumors, in particular additional BCCs [67–69].

4 Histology

Recommendation (strong consensus)

- The diagnosis of BCC shall be confirmed by histological examination of the excised specimen following a biopsy and/or therapeutic excision, depending on the size of the tumor and the therapeutic approach. Exceptions may be made for multiple superficial tumors or in case of basal cell carcinoma syndrome.

Statement (strong consensus)

- Subclinical spread can be assessed with sufficient certainty only histologically; this applies to the sclerosing subtype in particular, which is histologically characterized by fibrosis.
- The highest accuracy for histological detection of subclinical spread is achieved by microscopically controlled surgery.

Recommendation (strong consensus)

- During tissue processing, the potential inhomogeneity of tumors should be taken into account. If necessary, serial sections should be examined.

Statement (strong consensus)

- The histopathological diagnosis is performed on routine H&E-stained sections; only in rare, specific situations are special stains or immunohistology useful.

Recommendation (strong consensus)

- Apart from the diagnosis, the dermatopathology report shall include the following information:
  - vertical tumor diameter (tumor thickness)
  - information about the excision margins
- Moreover, the report should contain – if applicable – information about the histological subtype, in particular if there is evidence of infiltrative growth (narrow strands) and/or fibrosing/sclerosing or perineural growth.

In everyday clinical practice, the diagnostic workup usually includes punch or excisional biopsies both to confirm the diagnosis and to determine the tumor characteristics the subsequent therapeutic approach in each individual case is based upon. The diagnosis of tumors with a superficial (multicentric) growth pattern in particular frequently requires that serial sections through the entire punch specimen be examined. Moreover, serial sections increase the accuracy with respect to both subclassification and assessment of the depth of invasion [70]. However, given the inhomogeneities in tumor architecture, subtype classification using punch biopsies is frequently not sufficiently reliable [71]. The highest accuracy for histological detection of subclinical spread is achieved by microscopically controlled surgery [72, 73]. Similar problems are encountered when measuring the vertical tumor diameter (tumor thickness), which is considered an important parameter in terms of the therapeutic approach chosen (surgical vs. non-surgical). In general, the dermatopathology report shall contain information on the vertical tumor diameter; in analogy to melanoma and squamous cell carcinoma, it is measured from the granular layer down to the deepest tumor margins. If the tumor extends down to the deep margin of the biopsy, the

tumor thickness shall be reported as minimal tumor thickness. For shave excisions, too, the tumor thickness should be reported along with the surgical method used.

Horizontal tumor spread is measured clinically; it is frequently neither useful nor feasible to do such measurements on fixed tissue. The distance of tumor cells from the lateral and deep margins of the specimen is not measured for partial excisions or biopsies; moreover, such measurement is unnecessary if the excision margins are processed and examined separately, and it is even misleading when dealing with tumors with a multicentric growth pattern. Instead of the histological tumor diameter, the presence of tumor strands (depending on the growth pattern) that extend close to the excision margins as well as their exact location should be specified in the histopathological report. In general, any dermatopathology report referring to the excision of a tumor shall include information about the completeness of its removal based on the surgical method chosen; this requires close communication between surgeon and pathologist.

The "cell of origin" of BCC has not been conclusively characterized. Apart from basal cells of the interfollicular epidermis, primitive hair follicle cells have also been implicated as they share many common morphological and histochemical features [2]. Some authors therefore use the term "trichoblastic carcinoma". BCC is characterized by great morphological variability, both clinically and histologically. Thus, a given tumor may exhibit various types of differentiation, especially in relation to adnexal structures (e. g. follicular, sebocytic, adenoid/glandular).

In terms of treatment considerations, the growth pattern of a given tumor is of much greater clinical relevance than the cellular differentiation pattern [74]. Tumors characterized by infiltrative growth (narrow strands) and/or fibrosing/sclerosing as well as perineural growth often exhibit subclinical spread and also have a greater tendency for recurrence than well-circumscribed lesions. The dermatopathology report should therefore include information relating to these characteristics. Increased melanin pigmentation and a cystic growth pattern are no relevant prognostic factors. Subtype classification should be based on WHO guidelines [3]. In this context, it is of key importance for subsequent treatment planning to distinguish between nodular, superficial, infiltrative, and sclerosing. Other subtypes according to the aforementioned classification include micronodular, fibroepithelial (Pinkus tumor), basosquamous or metatypical (there is controversy as to whether this is a distinct entity), keratotic, cystic, infundibulocystic, adenoid, and pigmented subtypes as well as BCC with adnexal differentiation. It is, however, frequently impossible to unequivocally determine the subtype as the criteria classically associated with a given subtype may be present to varying degrees; in many cases, there is also a combination of various morphological criteria.

The histological diagnosis is made on H&E-stained sections; special stains and immunohistology are rarely required. In analogy to squamous cell carcinoma, tumors can be classified using the TNM classification (UICC). However, in everyday clinical practice this is not useful, given that the T classification is too nonspecific and that lymph node (N) and distant metastases (M) are rarely found. In patients with BCC, it is therefore not required to provide information on the TNM status.

Conflict of interest

Please refer to the guideline report for a complete list of the conflicts of interest and information on how they were dealt with during the development of these guidelines. The report is available on the AWMF website (registry number 032-021).

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