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Magdalena Seidl-Philipp
Finanzielle Interessen: Ja
Erklärung zu nicht-finanziellen
Interessen: Universitätsklinikum für
Dermatologie Innsbruck, Assistenzärz-
tin; ÖGDV

Nina Frischhut
Finanzielle Interessen: Lilly, Janssen
Erklärung zu nicht-finanziellen
Interessen: Universitätsklinikum Inns-
bruck, Fachärztin für Dermatologie

Nicole Höllweger
Finanzielle Interessen: Ja
Erklärung zu nicht-finanziellen
Interessen: ÖGDV; ÖGIT

Matthias Schmuth
Finanzielle Interessen: Nein
Erklärung zu nicht-finanziellen
Interessen: Vorstand und Präsident
ÖGDV; Trustee Skin Science Foundation

Van Anh Nguyen
Finanzielle Interessen: Nein
Erklärung zu nicht-finanziellen
Interessen: Universitätsklinik für Der-
matologie, Innsbruck, Tirol, Österreich,
Leitende Oberärztin; ÖGDV, DKG

Known and new facts on basal cell carcinoma

Summary

Basal cell carcinoma (BCC) is the most common malignant tumor in light-skinned people and amounts to about 75 % of all cases of skin cancer. Increasing incidence rates have been reported for decades all over the world. The main risk factors include UV radiation, male sex, light skin type, advanced age, long-term immunosuppression, a positive individual or family history, and certain genodermatoses. BCC metastasizes only rarely, and its mortality is low, but it is associated with significant morbidity. Genetic mutations especially in the hedgehog pathway play an important role in BCC pathogenesis. Non-invasive procedures such as optical coherence tomography or confocal laser scan microscopy are increasingly utilized for diagnostics in addition to visual inspection and dermatoscopy, but only in exceptional cases can histological confirmation of the diagnosis be dispensed with. Various clinical and histological subtypes have been defined. Differentiating between BCC with high and low risk of recurrence has a significant influence on the choice of treatment. Most BCC can be treated effectively and safely with standard surgery, or in selected cases with topical treatment. Locally advanced and metastasized BCC must be treated with radiation or systemic therapy. Radiation is also an option for older patients with contraindications for surgery. The hedgehog inhibitors vismodegib and sonidegib are currently approved for systemic therapy of BCC in Europe. Approval for the PD1 inhibitor cemiplimab as second-line therapy is expected in the near future.

Magdalena Seidl-Philipp, Nina Frischhut, Nicole Höllweger, Matthias Schmuth, Van Anh Nguyen

University Hospital for Dermatology, Venereology, and Allergology, Medical University Innsbruck, Austria

Section Editor
Prof. Dr. Trautinger, St. Pölten

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Introduction and definition

Basal cell carcinoma (BCC) is the most common malignant tumor in light-skinned people [1] and amounts to about 75 % of all cases of skin cancer [2]. Historically, BCC has also been called "basalioma", but use of this term is no longer recommended because it does not accurately reflect the potential aggressiveness of this tumor caused by its infiltrating and destructive growth [3, 4].

BCC is a slow-growing, locally infiltrating and destructive epithelial tumor with basaloid differentiation. It develops from stem cells within the hair follicle and/or the interfollicular dermis without a preceding precancerous lesion [3–6]. Areas exposed to UV radiation are the predilection sites, especially the head and neck, followed by the trunk and limbs [7]. Primary emergence on the mucous membranes, palms, or soles is unusual but has been reported in individual cases [7, 8].

Most BCC can be treated effectively and safely with standard surgery, or in selected cases with topical treatment [2–4].

The rates of metastasizing and mortality for BCC are very low [7, 9]. BCC can however result in significant morbidity – on the one hand caused by its frequent

appearance in cosmetically sensitive areas, and on the other hand caused by its locally infiltrating and destructive growth. If treated incorrectly or not at all, after several years the BCC may reach an advance stage that necessitates an interdisciplinary therapeutic concept [1–4, 10]. Apart from the disease burden, BCC also imposes significant costs on the healthcare system [1].

Epidemiology

Increasing incidence rates of BCC have been reported worldwide for decades. The prognosis for Europe is an increasing incidence rate of 5.5 % per year [1]. This increase is likely due to several factors such as more frequent histopathological confirmation of the diagnosis, more frequent inclusion in cancer registries, and an ageing population – but also increased sun exposure [11]. International comparisons are difficult because statistical records differ from country to country [1]. In many countries, including Austria, data on non-melanoma skin cancer (NMSC) are not published in the cancer statistics because of its high prevalence and low mortality [12]. In many cases data are only based on small, regional observational studies [1]. Exact documentation is further complicated by the fact that in patients with more than one BCC, only the first tumor is actually registered [13]. A crude incidence rate of >200 cases per 100,000 inhabitants in 2020 has been prognosticated for Germany [14].

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The highest incidence rates for BCC world-wide have been reported for Australia and New Zealand, with >1000 per 100,000 population. However, rates appear to be leveling off in this part of the world [1]. There appears to be an association between increasing incidence and decreasing degrees of latitude (equator = latitude 0), at least for people with light skin [1, 11]. This was convincingly shown for the United States, with a marked increase of the incidence rates from North to South [1, 11] and BCC rates of 770–1070 per 100,000 inhabitants in the Southern states [15]. The average lifetime risk for BCC in light-skinned people is estimated at 30 % [16].

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According to cancer statistics from 2014, the mean age of first diagnosis in BCC patients in Germany was 72 years, with 52 % of patients being male [9]. Mortality has been shown to actually be lower than in the general population [9]. This is attributed to the fact that suspect skin lesions in older people are more frequently investigated in otherwise healthy individuals [9].

Metastasizing is very rare; at about 0.028 to 0.55 % [7], although this may be under-reported since spread diagnostics are not always performed as a matter of course [3, 4]. Locally advanced BCC (laBCC) is defined as a subgroup of tumors where R0 resection is not consistently possible due to affection of vitally or functionally important structures [3, 4]. A study found that this was the case in 0.8 % of all BCC [17].

Pathogenesis and risk factors

BCC develop from a complex interaction between environmental factors and individual phenotype and genotype [11]. The main risk factors for BCC include UV exposure, male sex, light skin type (Fitzpatrick I and II), advanced age (> 60 years), long-term immunosuppression, a positive family or individual history, as well as genodermatoses such as nevoid basal cell carcinoma syndrome (NBCCS) or xeroderma pigmentosum [2–4].

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UV radiation is the most important external risk factor, with intermittent high exposure (sunburns) during childhood and adolescence as well as tanning beds the most dangerous features [11]. It has also been shown that outdoor workers with

high occupational UV exposure have a significantly higher risk of BCC than people with low or moderate occupational UV exposure [18, 19]. Based on these data, it has been proposed that BCC be classified as an occupational disease in Germany. Less frequent external risk factors include chronic exposure to arsenic, as well as ionizing radiation [11]. Basal cell carcinomas may also develop in scars or chronic ulcers [3, 4]. The significance of immunosuppression can be deducted from the fact that BCC risk in organ transplant recipients is six times higher than in the normal population [20]. A meta-analysis showed that about one-third of patients who had one BCC will develop another [21].

Genetic mutations are an important factor in the pathogenesis of BCC. In fact, BCC is among the tumors with the highest burden of mutations [22, 23]. A large part of these mutations is induced by ultraviolet rays [22–24]. At the molecular level, this is in most cases triggered by abnormal activation of the hedgehog signaling pathway [24], which is important for organogenesis, maintenance of stem cells, and tissue regeneration [24].

Sporadic BCC show inactivating or activating mutations in *PTCH1* (about 90 %) and *SMO* (about 10 %), both of which are signal transducers in the hedgehog pathway [23]. Some BCC are associated with the NBCCS, a rare multisystem disease with autosomal dominant genetic transmission and an estimated prevalence of 1 : 56 000 [25]. This may also appear as a *de novo* mutation in up to 40 % of cases. In NBCCS, there is usually a germ line mutation in *PTCH1*, or more rarely in *PTCH2* or *SUFU* [26]. The main criteria for NBCCS, apart from multiple BCC at a young age, include mandibular cysts before age 20, palmar or plantar pitting, calcification of the falx cerebri, development of medulloblastoma, and a positive family history [3, 4].

Apart from the hedgehog pathway, other signaling pathways, tumor suppressors and proto-oncogenes such as *TP53* and the *RAS* proto-oncogene family may also be involved in the pathogenesis of BCC [23, 24]. A number of other genes (*MYCN*, *PPP6C*, *STK19, LATS1*, *ERBB2*, *PIK3CA*, *PTPN14*, *RB1, FBXW7*) have recently been identified [23].

> Genetic mutations are an important factor in the pathogenesis of BCC, which is among the tumors with the highest burden of mutations. A large part of these mutations is induced by ultraviolet rays. At the molecular level, this is in most cases triggered by abnormal activation of the hedgehog signaling pathway.

Classification

Various BCC subtypes with clinically and histologically distinct features have been identified. Typical clinical appearances include (ulcero-)nodular, superficial, sclerodermiform (Figure 1a–d) and pigmented subtypes [27]. The nodular subtype is the most common [27]. The histological subtype cannot be deducted purely from the clinical appearance [28].

There are various histological subtypes. All of them show nests of peripherally palisaded basaloid cells with hyperchromatic nuclei and scant cytoplasm [27] (Figure 2a, b). According to the current WHO definition, the following subtypes have a low risk of recurrence: superficial, nodular (Figure 2a, b), pigmented, infundibulocystic, fibroepithelial. The other subtypes, with a high risk of recurrence, are defined as aggressive: sclerosing/morphoeic, infiltrating, basosquamous, sarcomatoid, and micronodular [2, 27]. From a therapeutic point of view, the superficial, nodular, sclerodermiform, and infiltrating subtypes are particularly relevant [3, 4]. In many cases, several histological subtypes can be detected within one BCC [29].

On the other hand, a small portion of punch biopsies may not detect the underlying aggressive subtype [28, 29].

Apart from the clinical and histological classification, the current guidelines also divide BCCs according to their risk of recurrence, in subtypes with high or low risk of recurrence [2–4, 30]. The decisive criteria for this classification, apart from

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Figure 1 Selection of possible phenotypes of basal cell carcinoma (BCC): Exulcerated nodulocystic BCC with a morphoeic component (a), superficial BCC (b), nodulocystic BCC with a morphoeic component (c), nodular BCC.

histological subtype and perineural growth, are tumor location (see Table 1 for a definition of H zone, M zone, and L zone), combined with horizontal tumor diameter, tumor margins, and a positive history as to local recurrence or site of prior radiotherapy [3, 4, 30]. One risk factor is sufficient for categorizing a BCC as 'high risk of recurrence' [3, 4, 30]. The current German S2k guideline summarizes this complex categorization in a table. Our Table 1 reproduces this table, with small adaptations (Table 1). For the sake of completeness, we would like to add that the most current US guidelines from 2021 (available online) no longer use the terms H
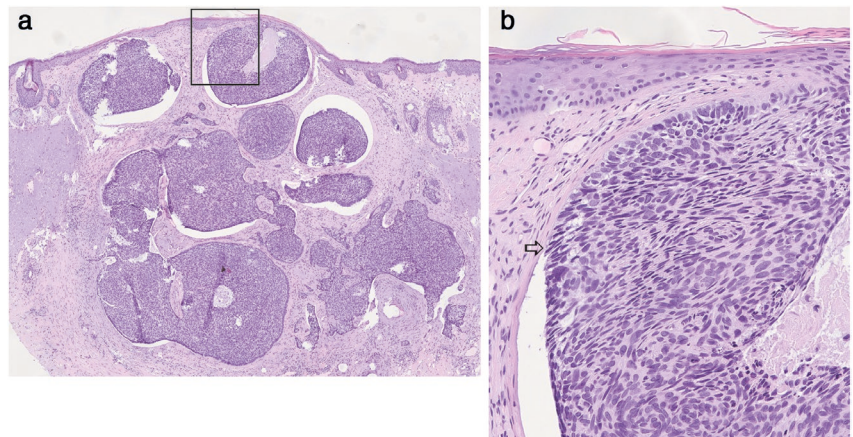

Figure 2 Histological overview showing a nodular BCC (nodulocystic variant) (a). Magnification of Figure 2: peripherally palisaded basaloid cells with hyperchromatic nuclei and scant cytoplasm (arrow) (b).

Table 1 BCC stratification depending on risk of recurrence; adapted from [3, 4, 27, 30].

	High risk of recurrence*	Low risk of recurrence
Horizontal tumor diameter and location	H zone** > 6 mm M zone** > 10 mm L zone** > 20 mm	H zone** < 6 mm M zone** < 10 mm L zone** < 20 mm
Margins	poorly-defined	Well-defined
Local recurrence	Yes	No
Histological subtype	– sclerosing/morphoeic – infiltrating – basosquamous – micronodular – sarcomatoid	– nodular – superficial – pigmented – infundibulocystic – fibroepithelial
site of prior radiotherapy	Yes	No
Perineural growth	Yes	No

*If one of these factors is present, the tumor is considered "high risk of recurrence".

**H zone = Location with high risk of recurrence: center of the face (periorbital, eyelids, eyebrows, nose, angle of the jaw, temples, ears, pre- and postauricular), genital region, hands, feet.

M zone = Location with moderate risk of recurrence: Cheeks, forehead, chin, lower lip, capillitium, neck, pretibial.

L zone = Location with low risk of recurrence: torso, limbs.

zone, M zone, and L zone. Only the trunk and limbs are still classified as low-risk if the BCC is smaller than 2 cm [31].

Stratification according to risk of recurrence is essential for deciding on the optimum treatment. A therapeutic algorithm is offered in the current German S2k guideline and can be found in our Figure 3, with minor adaptations (Figure 3).

Moreover, the European Association of Dermato-Oncology (EADO) has proposed a categorization into *easy to treat* (> 95 % of all BCC) and *difficult to treat* [2]. *Difficult to treat* comprises all laBCC, as well as other BCC that encounter difficulties during treatment due to one or more of the following features: functional or esthetic impairment after surgery because of the size or location of the tumor, poorly-defined tumor margins, previous multiple recurrences, previous irradiation, lack of consent, or comorbidities [2]. At the time of writing of this article, the new classification had not yet been published [2].

TNM classification is not commonly used for BCC due to its locally destructive growth and lack of metastasizing [3, 4].

Diagnostics

Suspected clinical diagnosis of BCC can be achieved through visual inspection if characteristic features are present (Figure 1a–d) [2–4]. The diagnosis must be confirmed histologically via (excision) biopsy [2–4, 32].

Exceptions where histological confirmation may conceivably be waived include superficial and small nodular BCC (< 1 cm in diameter) in low-risk locations (L zone) that have been conclusively identified by clinical or non-invasive means, especially if topical treatment is planned [2].

Apart from information on tumor thickness and tumor margins, the histological report should also state the histological subtype since this is essential for
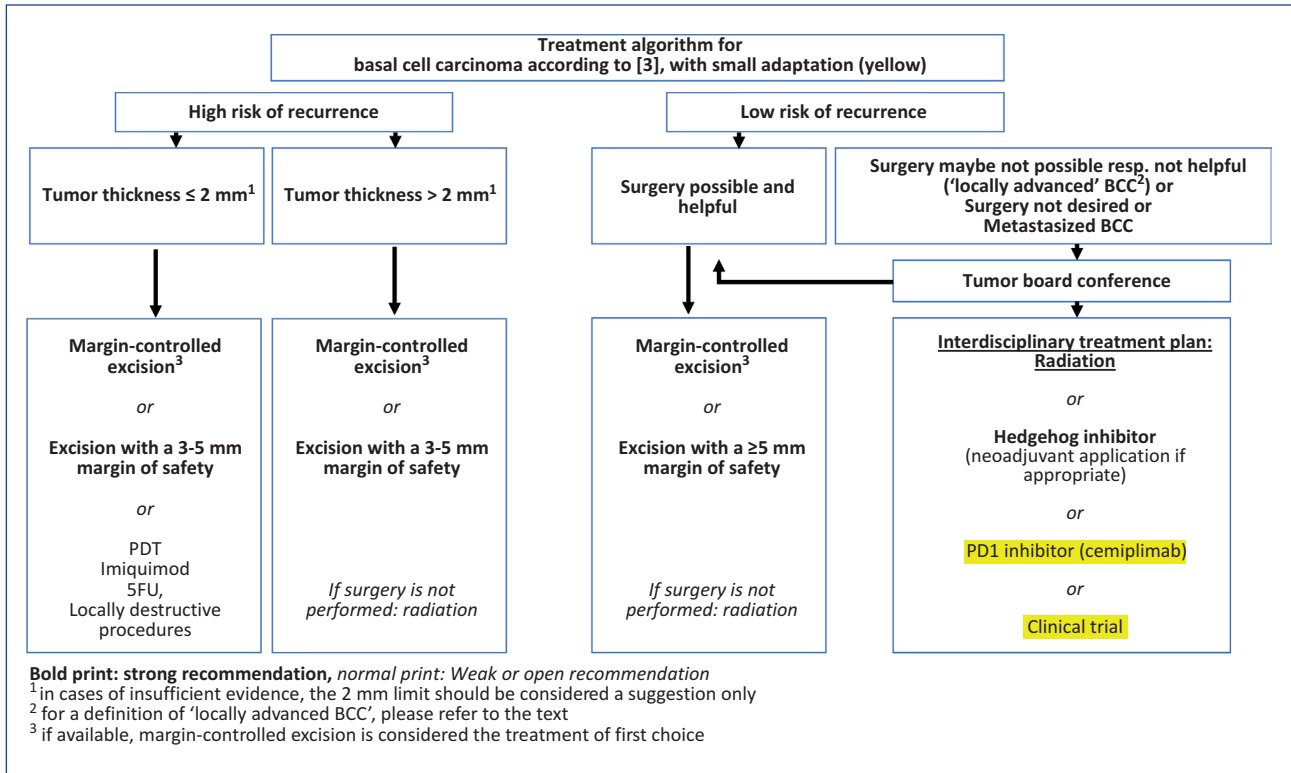
Suspected clinical diagnosis of BCC can be achieved through visual inspection if characteristic features are present. The diagnosis must be confirmed histologically via (excision) biopsy.

Treatment algorithm for basal cell carcinoma according to [3], with small adaptation (yellow)

High risk of recurrence

Low risk of recurrence

Tumor thickness ≤ 2 mm[1]	**Tumor thickness > 2 mm**[1]	**Surgery possible and helpful**	**Surgery maybe not possible resp. not helpful ('locally advanced' BCC**[2]**) or Surgery not desired or Metastasized BCC**

Tumor board conference

Margin-controlled excision[3] *or* **Excision with a 3-5 mm margin of safety** *or* PDT Imiquimod 5FU, Locally destructive procedures	**Margin-controlled excision**[3] *or* **Excision with a 3-5 mm margin of safety** *If surgery is not performed: radiation*	**Margin-controlled excision**[3] *or* **Excision with a ≥5 mm margin of safety** *If surgery is not performed: radiation*	Interdisciplinary treatment plan: **Radiation** *or* **Hedgehog inhibitor** (neoadjuvant application if appropriate) *or* PD1 inhibitor (cemiplimab) *or* Clinical trial

Bold print: strong recommendation, *normal print: Weak or open recommendation*
[1] in cases of insufficient evidence, the 2 mm limit should be considered a suggestion only
[2] for a definition of 'locally advanced BCC', please refer to the text
[3] if available, margin-controlled excision is considered the treatment of first choice

Figure 3 BCC treatment algorithm according to the German S2k guidelines, with minor adaptation.

> Dermatoscopy is especially helpful in differentiating BCC from melanoma, cutaneous squamous cell carcinoma, or benign skin tumors.

the subsequent therapeutic management [3, 4]. As mentioned before, aggressive subtypes cannot always be detected via punch biopsy [28, 29].

Non-invasive diagnostic procedures can support the clinical examination of BCC [3, 4]. These include dermatoscopy, optic coherence tomography (OCT), and confocal laser scan microscopy (CLSM) [3, 4]. OCT and CLSM however require special equipment and expertise.

Dermatoscopy is especially helpful in differentiating BCC from melanoma, cutaneous squamous cell carcinoma, or benign skin tumors [2–4, 33, 34].

A recent meta-analysis found that dermatoscopy achieved a pooled sensitivity of 91 % and specificity of 95 % in diagnosing BCC [35]. Both sensitivity and specificity were higher in pigmented as compared with non-pigmented BCC [35]. It has also been shown that dermatoscopy is helpful in differentiating superficial BCC from other histological subtypes, which may influence treatment decisions [36].

OCT is a non-invasive optical diagnostic procedure. It can visualize the microscopic structures of the skin up to a depth of one millimeter *in vivo*, within just a few seconds. The lateral resolution is less than 7.5 μm [37]. A recent meta-analysis of BCC diagnostics showed that conventional OCT has a higher sensitivity and specificity as compared with visual inspection plus dermatoscopy, so it may be helpful in case of clinically challenging lesions [38]. Tumor thickness can be measured up to a depth of one millimeter [39]. OCT is also able to diagnose histological subtypes with moderate accuracy [40], and improves the preoperative examination of the lateral tumor margins when used in addition to clinical inspection and dermatoscopy [39, 41].

CLSM is a non-invasive optical diagnostic procedure that can visualize the cellular structures of the skin down to the papillary dermis *in vivo*, within a few minutes. Due to its high resolution, the procedure is also called "optical biopsy". Low penetration (250 µm at most) is its limiting factor [42]. A recent meta-analysis, albeit with limited data, suggests that CLSM may help to avoid diagnostic biopsies when used for lesions that have been clinically determined with a high degree of probability to be BCC [43].

Both OCT and CLSM can be used to detect residual tumor tissue after biopsies as well as recurrent tumors [44–46] and to evaluate the response after non-invasive treatments [47–49].

Further developments that may play a role in the future are *ex-vivo* CLSM for investigating tumor margins after microscopically controlled surgery as a faster alternative to histological examination of frozen or paraffin-embedded slices [50, 51], and the combined use of OCT and CLSM [52, 53].

In cases of laBCC, or suspected metastasizing and perineural growth, further diagnostic procedures such as tomographic techniques (computer aided tomography, magnetic resonance tomography) are recommended [3, 4]. In addition, a clinical examination of the entire integument should be performed upon diagnosis of a BCC due to the increased risk of further epithelial skin tumors [3, 4].

Treatment

As mentioned above, an algorithm for the treatment of BCC has been published in the current German S2k guideline [3, 4]. This is mainly based on the categorization of high or low risk of recurrence. In cases with a low risk of recurrence, tumor thickness is another criterion for differentiation, while in cases with a high risk of recurrence, operability is a decisive factor (Figure 3) [3, 4].

Surgical treatment

Provided that surgery is a viable option, complete surgical removal of the BCC with all histologically abnormal cells and all subclinical extensions, and with a result that is functionally and esthetically satisfactory, is the treatment of first choice [3, 4].

A recent meta-analysis on interventions in BCC confirmed that surgical removal is associated with the lowest rates of recurrence [54]. Recurrence rates of 2–8 % after five years are stated in the literature [2].

There are basically two different procedures used for surgery: conventional excision with risk-adapted margin of safety and random histological examination of the resection margins (conventional histology), and microscopically controlled surgery (MCS) with step-wise, tissue-sparing operation techniques and systematic examination of the resection margins [3, 4, 55]. The term "MCS" comprises various techniques such as Mohs surgery, Munich method, or 3D histology such as the Tübinger Torte technique [55].

MCS methods are recommended particularly for high-risk BCC, recurrent BCC, and BCC in critical anatomical locations where tissue-sparing surgery is important [2–4, 55]. A prospective, randomized and controlled study comparing the frequency of recurrence after conventional excision versus MCS in primary facial high-risk BCC and recurrent facial BCC concluded after a ten-year observation period that MCS was superior to conventional excision both in primary BCC (4.4 % vs. 12.2 % recurrences) and in recurrent BCC (3.9 % vs. 13.5 % recurrences). However, statistical significance was found only for recurrent BCC [56]. It has also been shown that tissue-sparing surgery in MCS leads to better cosmetic results in
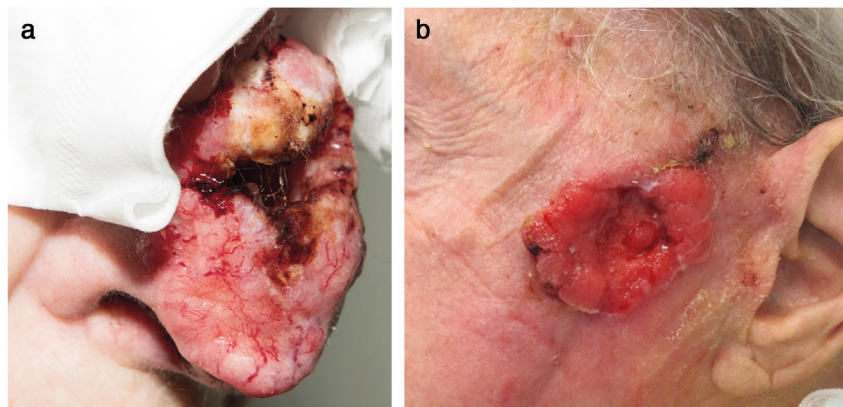
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Figure 4 Clinical presentations of locally advanced BCC (a, b).

many cases [57]. However, MCS is only available in specialized centers; it is more expensive and requires more staff [57–59].

Conventional excision and histology is widely employed [54]. Since excision margins are investigated only randomly [3, 4], R0 resection may in some cases be erroneously assumed [60]. Recommendations on safety margins depend on the risk of recurrence and show some variation in different guidelines [2–4]. The current German S2k guideline recommends a safety margin of 3–5 mm for BCC with a low risk of recurrence, and ≥ 5 mm for BCC with a high risk of recurrence [3, 4]. In cases of small, solid BCC, a safety margin of 2–3 mm may possibly be justified [61]. The risk of recurrence for solid BCC < 2 cm, removed with conventional excision and a safety margin of 3 mm, is less than 3 % [58].

According to the literature, incomplete excision (R1 resection) occurs in 4.7–24 % of cases [2]. This is influenced by surgical experience, tumor location, histological subtype, and excision of multiple lesions in one session [2]. Re-excision is recommended as the treatment of first choice [2–4]. Especially in BCC with a high risk of recurrence, MCS is recommended for this repeat procedure [2–4]. In BCC with a low risk of recurrence, non-surgical procedures may also be considered after R1 resection, albeit with tight clinical monitoring [3, 4]. Locally advanced basal cell carcinomas (laBCC) where R0 resection does not appear feasible (Figure 4) should be presented to an interdisciplinary tumor board to assess operability [3, 4].

Topical treatment

Basal cell carcinomas with a low risk of recurrence and a tumor depth of ≤ 2 mm may alternatively be treated with topical procedures. However, in comparison to surgery this recommendation is understated.

According to the current German S2k guideline, BCC with a low risk of recurrence and a tumor depth of ≤ 2 mm may alternatively be treated with topical procedures. However, in comparison to surgery this recommendation is understated [3, 4] (Figure 3).

Topical treatments mainly include topical medications (imiquimod, 5-Fluorouracil [5-FU]), photodynamic therapy (PDT), cryosurgery, and laser treatment [3, 4].

Topical medications

Imiquimod is an immune response modifier and has been approved for treating superficial BCC of < 2 cm diameter in immunocompetent adults [62]. In this indication, a 5 % cream is applied once a day on five days per week for a total of six weeks [63]. Imiquimod may be a useful alternative to surgery in superficial BCC,

especially in low-risk locations [3, 4]. The main side effect is local inflammation, and in more uncommon also flu-like symptoms [62, 63]. In a randomized controlled study that compared the efficacy of imiquimod to surgery in low-risk BCC (superficial and nodular), imiquimod was markedly inferior to surgery after three and five years of follow-up, with recurrence-free rates of 84 % and 83 % (surgery 99 % and 98 %) [64].

The database for treating nodular BCC is limited, and imiquimod is not approved for this indication in Europe [2]. In the abovementioned study, imiquimod achieved recurrence-free rates of 82 % and 81 % after three and five years when used for nodular BCC [64]. The European guideline states that imiquimod may possibly be effective for primary nodular low-risk BCC [2].

Topical use of the antimetabolite 5-FU, also called "topical chemotherapy", has been approved for superficial BCC if surgery and radiation have remained ineffective or were not feasible. In this indication, a 5 % cream is applied twice a day for a period of four weeks. Local inflammation has been reported as a common side effect [65]. A randomized controlled study compared the efficacy of topical 5-FU with imiquimod and MAL-PDT (one cycle with two treatments) in superficial BCC. After three and five years of follow-up, 5-FU was less effective than imiquimod but non-inferior to PDT [66].

Topical hedgehog inhibitors (HHI) are also being studied for treating BCC. In a Phase II study, topical use of the HHI patidegib prevented or attenuated the onset of BCC in patients with BCC syndrome. Class-specific and treatment-limiting side effects such as hair loss, loss of taste, and muscle cramps were not reported [67]. A Phase III study has recently been completed but the results have not yet been published (NCT03703310) [68].

Photodynamic therapy (PDT)

Conventional PDT – both with topical application of 5-aminolevulinic acid nano-emulsion (ALA-PDT with Ameluz®) and with methylaminolevulinate cream (MAL-PDT with Metvix®), and subsequent irradiation with red light – is approved in Europe for treating superficial and thin nodular (<2 mm) BCC. Like imiquimod and 5-FU, it should preferably be utilized only if surgery is contraindicated [2–4, 69]. PDT is also an option for patients with NBCCS [69]. Basal cell carcinomas located in the facial H zone, as well as rare or aggressive histological subtypes and pigmented BCC, should, however, not be treated with PDT [69].

In the indication of BCC one PDT cycle includes two illuminations which are scheduled one week apart. Response is evaluated after three months, and in cases of partial healing a second cycle is usually performed [70]. This is a very safe treatment which is generally well tolerated. The irradiation itself is often painful. Erythema and crusts will develop after the treatment session, and the erythema may persist for several weeks.

The efficacy of MAL-PDT in low-risk BCC has been evaluated in a large number of studies, with healing rates of 82–97 % for superficial BCC and 33–91 % for nodular BCC [71–76]. Long-term studies found a recurrence rate of 22 % after five years for superficial BCC and an estimated continued response of 76 % for nodular BCC [75, 76]. It should be stressed again that PDT is only recommended for thin nodular BCC < 2 mm [2–4]. This was not respected in all available studies [3, 4]. In addition, it is very important to remove any crusts from nodular BCC before PDT [3, 4, 69].

A Phase III study compared the efficacy of ALA-PDT with 5-aminolevulinic acid nano-emulsion (Ameluz®) with that of MAL-PDT (with Metvix®) in patients

with low-risk BCC [77]. Ameluz® was non-inferior to Metvix® with a total healing rate of 93 % versus 92 % [77]. Recurrence rates after twelve months were comparable in both groups with < 10 % [77]. Based on this study, the approval of Ameluz® was expanded in 2017 to include low-risk BCC [78].

Various other studies used ALA in other formulations [2]. Since non-standardized formulations were administered in many cases, direct comparisons are not possible [69].

A recently performed meta-analysis confirmed the efficacy of PDT in low-risk BCC, however surgical excision is more effective in sustained clearance and reducing recurrence [70]. When PDT is limited to one treatment cycle with two illuminations, also imiquimod is more effective [66, 69, 70]. However, PDT is associated with better cosmetic results and fewer severe side effects [70]. Studies investigating combination therapies with laser and subsequent PDT, or PDT plus imiquimod, showed a tendency towards better responses, or respectively lower recurrence rates, in the combination groups. However, most of the studies were small and the results were not statistically significant, so there is a need for more data [70, 79].

Daylight PDT does not play a role in the treatment of BCC since data and efficacy are limited and it is not approved for this indication [2, 69, 70].

Locally destructive procedures

Cryosurgery may be performed as a treatment of second choice in small superficial BCC, if there are contraindications against surgery or other topical procedures [3, 4]. The guidelines state explicitly that this only applies to extrafacial lesions (on the trunk or limbs) [2–4].

The database on local destruction of BCC with ablative (CO_2, Er:YAG) and non-ablative lasers (pulsed dye lasers, Nd: YAG,) is limited [2, 80, 81]. The data on efficacy and cosmetic results are quite promising especially for the 1064 nm Nd: YAG laser in low-risk BCC [80, 81].

The combined use of ablative fractionated lasers plus MAL-PDT, 5-FU, or imiquimod (ablative fractional laser [AFL]-assisted drug delivery) in low-risk BCC has also been investigated. Early results are promising for 5-FU but the database is still quite limited [82].

Curettage and electrodissection may also be performed as a treatment of second choice in small low-risk BCC on the trunk and limbs. However, there is no international consensus on the best procedure [2].

Cases of patients with high recurrence risk in whom surgery does not appear feasible or possible in a safe manner, or patients who refuse surgery, or patients with metastasized BCC (mBCC), should be discussed in an interdisciplinary tumor board so operability can be evaluated or the indication for radiation therapy or systemic treatment determined [3, 4] (Figure 3).

Radiation therapy

Indications for radiation therapy include laBCC where R0 resection is impossible due to affection of vital or functionally important structures, as well as tumors where resection would result in mutilation due to their size and location [2–4]. Radiation is also indicated if the patient's age and comorbidities argue against surgery, or if the patient refuses surgery [2–4]. Incomplete resection (R1, R2) where re-excision may be difficult, or perineural growth may also constitute an indication for radiation therapy to improve local tumor control [3, 4]. Prospective, randomized data on this topic are lacking, however [2–4, 83]. Different irradiation modes

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(usually electrons, photons, orthovolt therapy) and irradiation doses (usually total doses of 45–70 Gray), administered in a fractionated or hypofractionated regimen, may be chosen depending on the size, thickness, and location of the tumor and also depending on tumor status (primary tumor, R1 resection or R2 resection) [83]. Recurrence rates after radiation therapy are comparable to those after conventional excision or Mohs surgery [84].

Radiation therapy is generally well tolerated. Acute radiodermatitis may develop in the short term but will usually resolve within a few weeks [83]. However, due to possible long-term trophic skin damage and the small risk of secondary malignoma, radiation therapy should only be performed in the elderly [2–4, 83]. The presence of disorders with increased radiation sensitivity, such as NBCCS, xeroderma pigmentosum, speak against implementation of radiation therapy [3, 4].

Epidermal radioisotope therapy with rhenium-188 (Rhenium-SCT® [Skin Cancer Therapy]) is a new concept. This is a type of brachytherapy for treating NMSC up to a thickness of 3 mm. Rhenium-188 – a high-energy radioisotope emitting beta rays – is bound in a liquid acrylic matrix and applied to the lesion. The target dose of 50 Gray is reached after 45–180 minutes [85, 86]. A retrospective study with 55 lesions (32 of which were BCC) showed complete response after only one session in all cases. There were no recurrences three and twelve months later [86]. The treatment is administered by nuclear medicine specialists and has been reported to be safe, effective, fast, and painless [86].

Systemic treatment

In Europe, hedgehog inhibitors (HHI) are currently the only drug class approved for systemic therapy of BCC [87]. The PD1 inhibitor cemiplimab was recently approved in the US as a second-line treatment for patients with advanced BCC previously treated with a HHI or for whom a HHI is not appropriate. An accordant decision by the European Medicines Agency is expected for mid-2021 [88].

Before the era of targeted molecular therapies and checkpoint inhibitors, platinum-based chemotherapy was the method of choice for systemic treatment of metastasized BCC. However the data are based on case reports without long-term responses [89].

Hedgehog inhibitors

Both vismodegib and sonidegib are specific inhibitors of the oncogenic protein SMO, a signal transducer within the hedgehog pathway [87].

Vismodegib was the first available HHI and is approved for systemic treatment of mBCC and also laBCC if surgery or radiation therapy are not feasible. HHI are also indicated for patients with NBCCS and multiple BCC [2]. The approved dose is 150 mg once a day [90]. Approval was based on the ERIVANCE study which showed remission rates of 49 % for mBCC and 60 % for laBCC after 39 months of follow-up, with a median duration of response of 15 months (mBCC) and 26 months (laBCC) [91, 92]. The results of the ERIVANCE study have been confirmed in another international multicenter study (STEVIE), with response rates of 69 % for laBCC and 37 % for mBCC, with an average duration of response of 23, and 14 months, respectively [92, 93].

The second HHI, sonidegib, is approved for the treatment of laBCC if surgery or radiation therapy is not feasible. The approved dose is 200 mg once a day [94]. The drug has been available in Germany since 2017 and in Austria since 2020. Approval is based on the BOLT study. Its final analysis after 42 months of

There are no direct comparisons between the two HHIs, and the pivotal studies had different designs. However, the efficacy of sonidegib and vismodegib for laBCC is considered similar, and the side effect profile comparable.

follow-up showed a response rate of 56 % for laBCC and 8 % for mBCC, with an average duration of response of 26, respectively 24, months [92, 95].

There are no direct comparisons between the two HHIs, and the pivotal studies had different designs [87, 92]. However, the efficacy of sonidegib and vismodegib for laBCC is considered similar, and the side effect profile comparable [87].

Typical side effects such as muscle cramps, increase of CK (creatine kinase), taste disorders, weight loss, and hair loss have been reported for a majority of patients, but are usually mild (grade I and II) [87]. However, about 30 % of patients discontinued treatment due to side effects [2, 93, 95]. Recommendations for managing side effects include short-term 'drug holidays' lasting 2–4 weeks, as well as dose reductions (for example an every-other-day intake) [90, 94, 96–98]. A study in patients with multiple BCC, including those with NBCCS, showed that intermittent application of vismodegib (alternating between 12 weeks of treatment and 8 weeks of treatment-free intervals) was associated with less severe treatment-induced side effects as compared with continuous treatment, but that efficacy was sustained (MIKIE) [99]. Continuous treatment over a period of 36 months was only tolerated by 17 % of patients with NBCCS [100].

Case reports on patients with laBCC and mBCC who initially responded to HHI but subsequently developed secondary resistance, showed that combination therapy with vismodegib or sonidegib and pulsed itraconazol, a triazole antifungal drug with proven efficacy as a HHI [101], resulted in acceptable efficacy and safety [102, 103].

Neoadjuvant administration of vismodegib and sonidegib for laBCC is currently being studied in several Phase II trials (NCT03035188, NCT02667574, NCT03534947) [68]. The goal is to shrink the tumor before surgery to allow smaller resections with better functional/esthetic results. The preliminary results of the VISMONEO study show that 80 % of those cases that were inoperable before the study, or cases where excision would have resulted in severe functional or esthetic impairment, became operable after neoadjuvant treatment. 49 % of those patients achieved a histologically confirmed complete response [104].

Immune checkpoint inhibitors

In patients who display primary or secondary resistance to HHI, or cannot tolerate this type of drugs, immune checkpoint inhibitors have increasingly been administered in the last few years. This class of drugs is particularly suited for tumors with a high burden of mutation [105]. First data on the efficacy of cemiplimab, nivolumab, and pembrolizumab have been published in case reports and case series since 2016 [106].

The PD1 antibody cemiplimab (350 mg intravenously every three weeks) is currently being investigated in a Phase II study in patients with laBCC or mBCC who had previously shown disease progression on HHI, or merely achieved stable disease after nine months of treatment, or did not tolerate HHI therapy (NCT03132636). Preliminary data on laBCC show a response rate of 31 %; continued response after twelve months is estimated at 85 % [107]. The safety profile was comparable to other PD1 antibodies, and PD-L1 expression did not influence treatment efficacy [107]. Cemiplimab therefore constitutes a viable therapeutic option in the second or third-line treatment of laBCC [107].

Cemiplimab constitutes a viable therapeutic option in the second or third-line treatment of laBCC.

Based on these data, in February 2021 the US health authority FDA approved cemiplimab for laBCC patients after previous HHI treatment, or for whom HHI are not appropriate [108]. The FDA also approved cemiplimab as a second-line treatment for mBCC. In an interim analysis, cemiplimab showed a response rate of

Table 2 Recommended follow-up schedule according to the German S2k guidelines [3, 4].

Isolated, surgically treated BCC with low risk of recurrence	Multiple BCC, high risk of recurrence, laBCC, mBCC, syndrome
↓	↓
Follow-up after 6 months (check for local recurrence), once-yearly follow-up thereafter	Follow-up every 3 months. If neither recurrence nor a new BCC have appeared after two years, switch to once-yearly follow-up

21 % in this indication [88, 108]. As stated above, a decision by EMA is expected within this year [88].

There are also positive data from a small 'proof of concept' study with pembrolizumab [109]. The study showed that a combination of pembrolizumab and vismodegib was not superior to pembrolizumab monotherapy [109].

More study results are to be expected. A Phase II study with nivolumab monotherapy or a combination of nivolumab and ipilimumab is currently being conducted in patients with non-resectable laBCC or mBCC who have already been treated with other systemic drugs (NCT03521830). Another recently initiated Phase II study is investigating cemiplimab in combination with pulsed sonidegib (NCT04679480) [68]. There have been recent case reports on nivolumab or pembrolizumab as a first-line treatment in laBCC, with complete or partial responses, respectively [110]. However, due to possible severe immune-mediated side effects, further studies are required to ascertain if the use of PD1 inhibitors as first-line options for systemic treatment in advanced BCC can be justified [110]. A Phase I study with neoadjuvant pembrolizumab for locoregionally advanced but resectable BCC is currently being conducted (NCT04323202) [68].

Follow-up and prevention

Due to the likelihood of local recurrence and the increased risk of secondary BCC, or cutaneous squamous cell carcinoma, or melanoma, it is recommended that patients after treatment of BCC should receive regular follow-up examinations.

Due to the likelihood of local recurrence and the increased risk of secondary BCC, or cutaneous squamous cell carcinoma, or melanoma, it is recommended that patients after treatment of BCC should receive regular follow-up examinations [2–4].

The current German S2k guideline recommends a standardized and risk-stratified follow-up procedure (Table 2).

In the prevention of skin cancer, primary prevention is differentiated from secondary prevention. Primary prevention basically consists of avoiding excessive UV exposure, while secondary prevention is aimed at early detection of skin cancer lesions and prevention of progressive disease. Skin cancer screenings and regular self-inspection of the skin are important tools for secondary prevention [111]. There is also a recommendation that patients who previously had BCC should take nicotinamide supplements for secondary prevention [3, 4]. Due to the overall complexity of the issue, reference is made here to the German S3 guideline 'Prevention of skin cancer' [111].

Conflict of interest

M. Seidl-Philipp: Conference subsidies from MSD and Sanofi. N. Frischhut: Conference subsidies froa MSD und Lilly. N. Höllweger: Conference subsidies from BMS and MSD. M. Schmuth: no conflict of interest. V. A. Nguyen: Remunerations, consultation fees, or conference subsidies from BMS, MSD, Roche, Sanofi.

Correspondence to

Dr. med. Magdalena Seidl-Philipp
University Hospital for Dermatology, Venereology, and Allergology
Innsbruck

Anichstrasse 35
6020 Innsbruck, Austria

E-Mail: magdalena.philipp@
i-med.ac.at

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[CME Questions/Lernerfolgskontrolle]

1. Welche Aussage ist richtig?
a) Der Begriff Basaliom sollte gegenüber dem Begriff BZK bevorzugt verwendet werden, da es sich um einen semimalignen Tumor handelt.
b) Bei circa 50 % aller Hautkrebsfälle handelt es sich um BZK.
c) Eine primäre Manifestation eines BZK an Schleimhäuten, Handflächen oder Fußsohlen ist ungewöhnlich.
d) Basalzellkarzinome können nicht metastasieren.
e) Da BZK in der Regel unkompliziert exzidiert werden können, verursacht deren Behandlung im Gesundheitssystem keine wesentlichen Kosten.

2. Welche Aussage ist richtig?
a) Die höchsten Inzidenzraten von BZK werden in Skandinavien berichtet.
b) Für Deutschland wurde für 2020 eine rohe Inzidenz von > 500 pro 100 000 Einwohner vorausgesagt.
c) Patienten mit BZK haben im Vergleich zur Allgemeinbevölkerung eine erhöhte Mortalität.
d) In der Pathogenese des BZK spielt insbesondere die kumulative UV-Exposition eine große Rolle.
e) Beim lokal fortgeschrittenen BZK kann eine R0-Resektion aufgrund der Mitbeteiligung von vital oder funktionell wichtigen Strukturen nicht sicher erzielt werden.

3. Welcher Risikofaktor spielt beim BZK keine Rolle?
a) fortgeschrittenes Alter
b) heller Hauttyp
c) Ernährungsgewohnheiten
d) chronische Immunsuppression
e) Genodermatosen wie das BZK-Syndrom oder Xeroderma pigmentosum

4. Welche Aussage ist richtig?
a) Genetische Mutationen spielen in der Pathogenese des BZK eine untergeordnete Rolle.

b) Auf molekularer Ebene liegt in den meisten Fällen eine Downregulation des Hedgehog-Signalwegs vor.
c) Gene des Hedgehog-Signalwegs, die in der Pathogenese von BZK involviert sind, sind *PTCH1, PTCH2, SMO* und *SUFU*.
d) Die Hedgehog-Inhibitoren Vismodegib und Sonidegib sind spezifische Inhibitoren des onkogenen Proteins PTCH1.
e) Ein Hauptkriterium des BZK-Syndroms ist das Auftreten eines Katarakts vor dem 30. Lebensjahr.

5. Welche Aussage ist richtig?
a) Gemäß WHO Klassifikation 2018 werden histologisch vier verschiedene Subtypen (superfiziell, nodulär, sklerodermiform und infiltrativ) unterschieden.
b) In einem BZK wird stets ein histologischer Subtyp nachgewiesen.
c) Bei allen histologischen Unterformen liegen Nester von basaloiden Zellen mit hyperchromatischem Kern und schmalem Zytoplasma in granulomatöser Anordnung vor.
d) In den aktuellen deutschen Leitlinien werden BZK nach Rezidivrisiko stratifiziert.
e) Die TNM Klassifikation spielt beim BZK eine wichtige Rolle.

6. Bei der Stratifizierung der BZK nach Rezidivrisiko spielt folgender Parameter keine Rolle:
a) Tumorlokalisation
b) Tumordurchmesser
c) Alter des Patienten
d) Vorliegen eines Lokalrezidivs
e) Histologischer Subtyp

7. Welche Aussage zur Diagnostik von BZK ist richtig?
a) Bei allen BZK, die klinisch beziehungsweise mit nichtinvasiven Methoden

eindeutig als BZK identifiziert werden, ist eine histologische Sicherung der Diagnose nicht erforderlich.
b) Die Dermatoskopie von nichtpigmentierten BZK erreicht im Vergleich zu pigmentierten BZK eine höhere Sensitivität und Spezifität.
c) Mittels optischer Kohärenztomographie kann die Tumordicke bis zu 3 mm bestimmt werden.
d) Die konfokale Laserscanmikroskopie wird aufgrund der sehr hohen Auflösung auch als optische Biopsie bezeichnet.
e) Eine weitere Diagnostik mittels Schnittbildgebung wird beim lfBZK nicht empfohlen.

8. Welche Aussage ist falsch?
a) Die operative Entfernung von BZK ist die Therapie mit der geringsten Rezidivrate.
b) Die mikroskopisch kontrollierte Chirurgie wird insbesondere bei Hoch-Risiko-BZK, Rezidiv-BZK und bei BZK an kritischen anatomischen Lokalisationen empfohlen.
c) Im Falle einer konventionellen Exzision wird bei Hoch-Risiko-BZK ein Sicherheitsabstand von ≥ 5 mm empfohlen.
d) Im Falle einer R1-Resektion muss unabhängig vom Rezidivrisiko eine Nachresektion durchgeführt werden.
e) BZK, bei denen eine R0 nicht sicher erzielt werden kann (lfBZK), sollen in einem interdisziplinären Tumorboard vorgestellt werden, um die Operabilität zu prüfen.

9. Welche Aussage ist richtig?
a) Bei Niedrig-Risiko-BZK besteht in der Leitlinie eine gleichwertige Empfehlung für operative und topische Verfahren.
b) Imiquimod kommt insbesondere bei großen superfiziellen BZK (Durchmesser bis 5 cm) in Niedrig-Risiko-Lokalisationen als Alternative zur Operation in Frage.

c) Die konventionelle photodynamische Therapie (PDT) ist für die Behandlung von superfiziellen und dünnen (Tumordicke < 2 mm) nodulären BZK zugelassen.

d) Bei multiplen superfiziellen BZK wird der Einsatz von Tageslicht-PDT aufgrund der geringeren Schmerzen im Vergleich zur konventionellen PDT empfohlen.

e) Die Kryotherapie ist insbesondere bei dünnen nodulären BZK (Tumordicke < 2 mm) im Kopf-Hals-Bereich eine effektive und schnelle Behandlungsmethode.

10. **Welche Aussage ist richtig?**

a) Die Effektivität von Vismodegib und Sonidegib beim lfBZK sowie deren Nebenwirkungsprofil wird als ähnlich erachtet.

b) Typische Nebenwirkungen der Hedgehog-Inhibitoren (HHI) wie akneiformes Exanthem und Fieber treten bei einem Großteil der Patienten auf.

c) Bei Auftreten von Nebenwirkungen unter HHI-Therapie können intermittierende Therapiepausen aufgrund des möglichen Wirkungsverlustes nicht empfohlen werden.

d) Der PD1-Antikörper Cemiplimab ist den HHI in der Wirkung klar überlegen und wird in den USA als Erstlinientherapie eingesetzt.

e) Patienten, bei denen ein BZK mit einem hohen Rezidivrisiko behandelt wurde, sollen in den ersten beiden Jahren nach Therapie alle sechs Monate nachkontrolliert werden.Lösungen:

Liebe Leserinnen und Leser, der Einsendeschluss an die DDA für diese Ausgabe ist der 30. September 2021.
Die richtige Lösung zum Thema „Primär kutane T-Zell-Lymphome im Kindes- und Jugendalter" in Heft 4 (April 2021) ist: (1a, 2c, 3d, 4d, 5e, 6a, 7c, 8a, 9b, 10d).

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