



# Standard of care in treating periocular basal cell carcinoma: a narrative review of the recommendations from the German S2k guidelines

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**Background and Objective:** The German S2K guideline offers an in-depth review of basal cell carcinoma (BCC). This review aimed to briefly summarize the German S2K guidelines of diagnostic and therapeutic strategies in BCC with special focus on periocular BCCs.

**Methods:** A summary was created based on the German S2K guidelines and additional English and German literature searched on PubMed published after 2010.

**Key Content and Findings:** The review summarizes the state-of-the-art care for BCC in Germany and focus on aspects for periocular BCC and therefore give recommendations to handle these tumors.

**Conclusions:** BCCs pose the most common malignant skin growth. Risk factors such as intensified UV radiation exposure, recurrent sunburns and activation of the sonic hedgehog pathway are well established variables. Although alternative treatment options in more complicated or neoadjuvant settings have become more available, complete surgical removal still remains the gold standard for periocular BCCs. Treatment of periocular BCCs follow the same principles, but often state a therapeutic problem as anatomical integrity of the eyelid and adnexa are crucial for the eye and visual function. A combination of systemic treatment and neoadjuvant or adjuvant approaches before or after surgery are promising options for a successful outcome which can further improve the standard treatment for locally advanced BCCs. Surgical removal of BCCs often followed by anatomical reconstruction still remains as the first line therapy of choice. Alternative therapy approaches for periocular BCC are available and have become more prevalent. However, these are only indicated when microscopically controlled excision with subsequent oculoplastic reconstruction is not possible. The discussion of each case within a tumor board is compulsory, and also in line with national guidelines.

**Keywords:** Basal cell carcinoma (BCC); periocular; German S2 guidelines; diagnosis and treatment; prevention

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## Introduction & methods

Objective of this narrative review was to summarize the current German S2k guidelines on basal cell carcinoma (BCC) with focus on the periocular region. The German S2K guideline offers an in-depth review of BCC (1,2). The following summary is based on the German S2K guideline and additional sources to create a brief overview of clinical characteristics and diagnostics as well as therapeutic options of BCC with special focus on periorbital BCC. Selection of additional sources was based on references cited in the German S2K guidelines as well as on PubMed search results which were retrieved using the term “basal cell carcinoma AND/OR ocular AND/OR treatment” within the last 10 years. While mainly focusing on well-established therapeutic options an overview of alternative treatments is further displayed by Erikson *et al.* (3).

*Table 1* summarizes our search strategy. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://fomm.amegroups.com/article/view/10.21037/fomm-21-27/rc>).

## Results and discussion

### *Epidemiology and clinical features*

BCCs are the most common type of malignant growth in Europe. The median age of diagnosis in Germany is currently 73 (male) and 71 (female) years, with a higher frequency of development by males. (<https://edoc.rki.de/handle/176904/3270>). Risk factors for developing BCCs include gender, genetic dispositions and previous history of BCC (4). Sixty percent of BCC affect the head and neck area including periocular BCC, which is due to increased exposure to sunlight (4,5). Exposure to UV light, especially repetitive high exposure peaks and sunburns with chronic exposure are major risk factors (4). UV light induces a cascade of cytokines, vasoactive and neuroactive mediators in the skin which all together lead to an inflammatory response and therefore causes sunburns. Ultimately, it induces the formation of radicals and activation of apoptotic pathways, thus altering and damaging DNS directly (6). Pathophysiology of BCC development also involves activation of the sonic-hedgehog pathway caused by either deactivation of a tumour suppressor gene called inhibitor patched (PTCH) or direct upregulation of replication ultimately resulting in apoptosis resistance of keratinocytes in both cases (7). Clinical features include e.g., slow growing, painless skin nodule with a waxy appearance and

small blood vessels running over it, as well as trichiasis, loss of eyelashes and malposition of the eyelids. BCCs indicate a range of histological subtypes, e.g., superficial BCC, infiltrative BCC and most commonly nodular BCC (8). Ulcerations may also be present as well. As a matter of fact, ulcero-nodular forms account for up to 80% of all BCCs (9). Although only a small fraction of BCCs metastasize either into regional lymph nodes or surrounding connective tissue and bones, the locally destructive growth can cause fulminant damage (10). Less than 5% of periorbital BCCs develop intraorbital metastases (11). BCCs of the ocular adnexa represent a challenge for treatment and subsequent reconstruction since anatomical integrity of structures such as eyelids or the tear system are essential for a proper function of the visual system. Surgical approaches without eye removal might therefore be limited by BCC growth adjacent to the orb or the orbital cavity. Early detection and treatment are therefore necessary.

### *Diagnostic strategies and risk assessment*

Most BCCs are diagnosed by clinical features and non-invasive dermatoscopy (12) with periorbital BCC showing the same clinical features as BCC of other regions. Typical findings include reddish papules or nodules with a characteristic pearly, shiny edge, and small arborizing telangiectasias (*Figure 1*) (13). Periorbital BCCs are typically diagnosed and treated by excisional, micrographic histopathological controlled biopsy. Excision with a defined safe margin can also be performed in cases of very small cases of BCCs. Early detection is essential for acquiring an appropriate treatment. As an untreated disease progresses limitation of eye globe motility and globe displacement may occur—therefore raising the suspicion of intraorbital growth and affection of bone (14). In any case of suspected periorbital or even intraorbital infiltration further imaging modalities (e.g., CT, MRI) are necessary to assess local growth dimensions and to rule out adjacent bone infiltration. Histology aggressive type of BCC, especially after biopsy, are then validated indicators for possible periorbital infiltration. A full body inspection is essential in any new case of BCCs with further diagnostic imaging being recommend in pronounced, aggressive and multiple occurrences of BCCs. BCCs rarely metastasizes. The most frequent locations of metastasis are the bones, lungs, liver, and regional lymph nodes. However, staging for far distant metastasis is only recommended in cases with clinical signs for those events

**Table 1** The search strategy summary

Items	Specification
Date of search	January 2021
Databases and other sources searched	PubMed
Search terms used	basal cell carcinoma AND/OR ocular AND/OR treatment
Timeframe	Since 2010
Inclusion and exclusion criteria	Exclusion: language other than English or German
Selection process	None



**Figure 1** Different forms of BCC. (A) Ulcerating basal cell carcinoma of the lower eyelid: Local destructive growth with loss of cilia and tenuous telangiectasia can be observed. (B) Nodular BCC with partial central necrosis. (C) Ulcerating BCC: typical clinical finding with beaded edge, ulceration and telangiectasia (all images are provided from the Department of Ophthalmology, University of Lübeck, Lübeck, Germany). BCC, basal cell carcinoma.

within the German S2K guideline (15). Facial BCCs, especially those affecting the nose, ears and eyelids show a higher rate of local recurrence. In general, localization, maximum tumor diameter, local recurrence, previous treatments with radiation with local recurrence (radioderm) as well as histological subtype determine the risk of recurrence (16,17) (*Table 2*). A multidisciplinary team must collaborate in planning management of orbital invasion, aggressive types of BCC or systemic proliferation (18).

## Therapy

### *Surgical resection*

Surgical removal with histological control (R0 resection) in healthy individuals is currently the therapy of choice as it represents as the most effective and definite therapy (1-3). Depending on the risk of recurrence (*Table 2*) surgery can be performed either with systematic margin control (microscopically controlled surgery), tumor-adapted safety margin and conventional histology or in cases of

superficial variants by horizontal excision (shave excision) with conventional histology. For BCCs with a low risk of recurrence, a safety margin of 3 to 5 mm should be determined in cases of conventional excisions without histology. For BCCs with a high risk of recurrence and recurrent tumors, a microscopically controlled excision should be performed. Otherwise, a safety margin of >5 mm should be determined for conventional excisions without histology. Incompletely excised BCCs should be re-excised as a first-line therapy (S2K). For incompletely excised BCCs with a low risk of recurrence non-surgical, procedures may also be offered (*Figure 2*). These parameters do not necessarily apply for BCC of the eyelid, since anatomical and functional features may prevent a set safety margin excision. Surgical treatment of BCCs should therefore imply an excision of tissue as much as necessary but also as little as possible to guarantee functionality (19). Following surgical removal, a variety of different surgical approaches are used to close eyelid defects that include Tenzel's oculoplasty, Cutler-Beard-oculoplasty or Hughes oculoplasty (*Figure 3*). Principles of reconstruction include

**Table 2** Classification of recurrence risk levels [original source; modified (1,2)]

	High risk of recurrence*	Low risk of recurrence
Horizontal tumor diameter and localization	H-zone $\geq 6$ mm	H-zone $< 6$ mm
Limitations	Poorly defined	Well defined
Local recurrence	Yes	No
Histological subtype	Sclerodermiform	Superficial
	Infiltrative	Nodular
	Metatypical	Adenoid
	Micronodular	Cystic
		Trabecular
Tumor on radioderm	Yes	No
Perineural growth	Yes	No

\*, The presence of one of these factors leads to classification in this category. H zone: “central” face—eyelids, eyebrows, periorbital, nose, upper lip, jaw angle region, pre- and postauricular, ears, temples, genitals, hands, feet (1,2).

anatomical correct recovery of the eyelid structures. Some cases, especially those with widespread intraorbital growth, do not allow R0-resection and therefore leaves the surgeon no other choice than to perform a total exenteration (including removal of all orbital tissue, including the periorbital, posterior to the orbital rim). In these cases, the eyelids may be preserved in tumors placed posteriorly within the orbit and even some arising in periocular skin. Most anteriorly placed tumors however require removal of all anterior orbital tissue and periorbital together with the eyelids, yet the posterior orbital tissues may be preserved (18). In inoperable cases of BCCs such as in multimorbid patients, extensive tumour growth including osseous infiltration or with failures to subsequent reconstructions as well as following the patient's wish not to perform surgery due to aesthetic impairment alternative treatment options are available.

### Radiotherapy

In locally advanced BCC, in which a local *in sano* resection cannot be achieved due to extension, location, age or comorbidity of the patient, the indication for radiotherapy should be considered after interdisciplinary consultation (S2K). Side effects of radiotherapy, especially further development of radiation-induced secondary malignancies, are low (20). Depending on the treatment method, level of energy and beam planning, radiation damages may occur in the surrounding tissue such as acute reddening

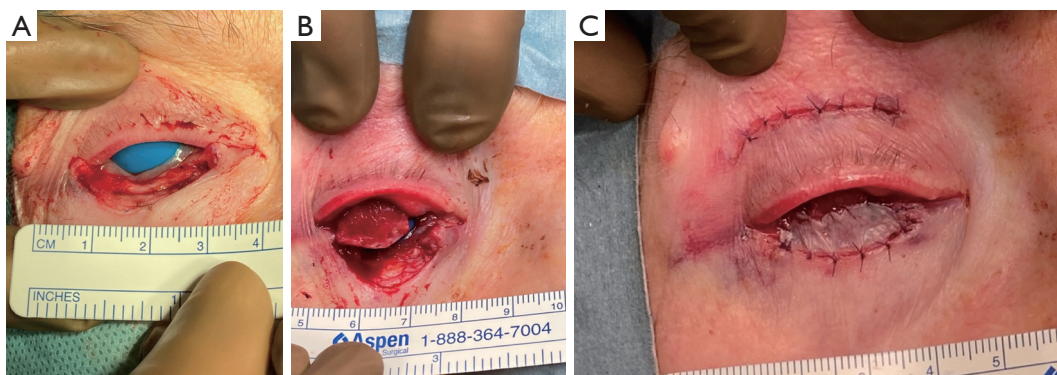
and swelling of the treated area, formation of cataract and secondary tumour induction. According to the German S2K guideline, radiotherapy should not be used in patients  $< 40$  years old or patient who suffer from systemic collagenosis (increased toxicity) because of its inferiority to surgical approaches and side effects. Also, both high energetic as well as brachytherapy and low energetic treatments option offer similar outcomes according to the German S2K guideline. On the other hand, the authors admire the possibility of precise radiation planning and the usage of radiation methods like brachytherapy, low energy protons or orthovoltage techniques which represents an excellent treatment option to treat BCC with good tumour control rates and rare side effects. Radiotherapy can be used as a single treatment form as well as in combination with previous R1 surgical resection (21,22).

### Topical therapy

Indications for topical therapy of BCC include low risk BCC as well as treatment in elderly multimorbid patients. Advantages include the application at home, protection of the surrounding tissue and good aesthetic results due to the avoidance of scarring (23). In addition, topical therapy options are important in case of multiple (superficial) BCCs. Treatment options are Imiquimod (TLR agonist) or 5-Fluorouracil (5-FU). Possible side effects are local inflammatory reactions e.g., swelling, scaling blistering and pain. Studies have shown a higher efficiency in Imiquimod in

BCC treatment strategy						
Low-risk BCC					High-risk BCC	
Superficial		Nodular		Intermediate risk BCC	Surgery possible:	Surgery not possible:
First-line treatment:	Surgery (3–4 mm), Imiquimod, PDT, Laser, curettage, cryosurgery	First-line treatment:	Surgery (3–4 mm), curettage	First-line treatment:	2-step surgery	Radiotherapy, chemotherapy, targeted therapy
		Second-line treatment:		Surgery (>4 mm), 2-step surgery		
		Cryosurgery, PDT, Imiquimod		Second-line treatment (if surgery not possible, 4 mm)		
				Radiotherapy		
				Third-line treatment		
				Cryotherapy, PDT, Imiquimod		

**Figure 2** BCC Treatment strategy according to the German S2k guidelines, modified (1,2). BCC, basal cell carcinoma; PDT, photodynamic therapy.



**Figure 3** Reconstruction after BCC resection with Hughes Plasty. (A) Extensive lower eyelid damage after resection of BCC. (B) Creation of upper tarsal flap. (C) Closed lower eyelid defect with free skin craft from upper eyelid in Hughes tarsoconjunctival flap (all images are provided from the Department of Ophthalmology, University of Lübeck, Lübeck, Germany). BCC, basal cell carcinoma.

comparison to photodynamic therapy (PDT) or 5-FU (24). Nevertheless, these options are not frequently used in the periocular region (22).

**PDT**

PDT relies on topical application of 5-aminolaevulinic

acid (5-ALA) and methyl-aminolaevulinic (MAL) and subsequent red-light exposition. Although PDT is an alternative treatment for superficial BCC, its use is limited for deeper infiltrating lesions. Also in comparison to primary surgery the recurrence rates are worse (S2K). Especially PDT-associated pain limits the advantages of good aesthetic results and the possibility of therapy in

immunosuppressed patients (25). Also, this therapy is not commonly used for the periocular region (22).

### **Cryosurgery**

Cryosurgery offers a stand-alone therapy option for small superficial BCCs of the body or extremities and can be used after incomplete surgical resection. Recurrence rates are higher than in radiotherapy (26).

### **Laser**

In cases of isolated low risk BCC ablative or non-ablative laser therapy might be considered. They offer reasonable aesthetic outcomes but are limited in cases of deeper subclinical growth on the other hand (22).

### **Hedgehog inhibitors**

An essential step in the pathogenesis of BCCs is activation which has been detected in 90% of all BCCs (27). According to the German S2K guidelines, Erikson *et al.* discussed that in cases of locally advanced, inoperable, or metastatic BCC or as a neoadjuvant treatment option, a therapy with hedgehog inhibitors should be discussed in an interdisciplinary tumour board. In addition, the possibility of inclusion in a clinical trial should be considered. Therapy adherence of approved hedgehog inhibitor for BCC like Vismodegib and Sonidegib is often limited by side effects including hair loss, muscle spasms, diarrhoea, fatigue and weight loss (22,28).

### **Prevention**

For general measures, we kindly refer to the German S3 guideline “Prevention of skin cancer” (29). Appropriate protective measures against solar UV radiation is particularly important for persons with increased risk for skin cancer development and includes avoidance of strong solar radiation exposure, wearing appropriate clothing and the usage of sunscreens (22). Drugs such as Nicotinamide (Vitamin b3), Retinoids or COX2 inhibitors have been investigated as a preventive option. With Nicotinamide being recommended for the tertiary prevention of BCC, especially in patients with a history of BCC, they are not recommended as primary or secondary prevention for prophylactic use as well as Retinoids or COX2 inhibitors (1,2,28).

### **Follow up**

At first, regular check-ups should be pursued by an ophthalmologist with an interval of every 3 to 6 months depending on the type of therapy. Special attention should be paid on the functions of eyelids and tear duct system (22). As soon as the diagnosis of BCC is made, a dermatological evaluation should be performed to exclude secondary cancer (1,2). Further regular dermatological consultations should be initiated once BCC has been treated in order to prevent local or systemic recurrence as well (1,2).

### **Summary**

BCCs pose the most common malignant skin growth. Risk factors such as intensified UV radiation exposure, recurrent sunburns and activation of the sonic hedgehog pathway are well established variables. Although alternative treatment options in more complicated or neoadjuvant settings have become more available, complete surgical removal still remains the gold standard for periocular BCCs. Treatment of periorbital BCCs follows the same principles but often state a therapeutic problem as anatomical integrity of the eyelid and adnexa are crucial for the eye and visual function. A combination of systemic treatment and neoadjuvant or adjuvant approaches before or after surgery are promising options for a successful outcome which can further improve the standard treatment for locally advanced BCCs.

The discussion of each case within a tumor board is compulsory and also in line with national guidelines.

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