



Original Research

Diagnosis and treatment of basal cell carcinoma: European consensus—based interdisciplinary guidelines



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Immunotherapy

Abstract Basal cell carcinoma (BCC) is the most common malignant tumour in white populations. Multidisciplinary experts from the European Dermatology Forum, the European Association of Dermato-Oncology and the European Organization of Research and Treatment of Cancer collaborated to develop recommendations on diagnosis and treatment of BCC. A new classification into ‘easy-to-treat (common) BCC and ‘difficult-to-treat’ BCC is proposed. Diagnosis is based on clinicodermatologic features for ‘easy-to-treat’ BCCs. Histopathological confirmation is mandatory in ambiguous lesions and in BCCs located in high-risk areas. The first-line treatment of ‘easy-to-treat’ BCC is complete surgery. Microscopically controlled surgery shall be offered for high-risk BCC, recurrent BCC and BCC in critical anatomical sites. Topical therapies (5% imiquimod, 5% fluorouracil) and destructive approaches (curettage, electrocautery, cryotherapy, laser ablation) should be considered in patients with low-risk superficial BCC. Photodynamic therapy is an effective treatment for superficial BCC and thin nodular BCC. The therapy for a ‘difficult-to-treat’ BCC should preferentially be discussed by a multidisciplinary tumour board. Hedgehog inhibitors, vismodegib or sonidegib, should be offered to patients with locally advanced and metastatic BCCs. Immunotherapy with anti-programmed cell death 1 (PD-1) antibodies is a promising therapeutic option, currently being investigated in clinical trials. Radiotherapy represents a valid alternative to surgery for BCC on the face, especially in elderly patients. In patients with naevoid basal cell carcinoma syndrome (NBCCS), close surveillance and regular skin examinations are required to diagnose and treat BCCs at early stage. Long-term follow-up is recommended in patients with high-risk BCC subtypes, high-risk sites, multiple BCCs and NBCCS.

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1. Information about these guidelines

1.1. Societies in charge

These guidelines were developed on behalf of the European Dermatology Forum (EDF), as decided at the EDF meeting in January 2017. The European Association of Dermato-Oncology (EADO) coordinated the authors’ contributions within its Guideline Program in Oncology (GPO). The responsible editor is Jean Jacques Grob (senior author), and the coordinator of the guideline is Ketty Peris (first author). To guarantee the interdisciplinary character of these guidelines, they were developed in cooperation with the European Organization for Research and Treatment of Cancer (EORTC). Twenty-four experts from 11 countries, all of whom

were delegates of national and/or international medical societies, collaborated in the development of these guidelines.

1.2. Financing

The authors did this work on a voluntary basis and did not receive any honorarium or reimbursements. Guidelines development group members had no competing interests.

1.3. Disclaimer

Medicine is subject to a continuous development process. This entails that all statements, especially with regard to diagnostic and therapeutic procedures, can only

reflect scientific knowledge current at the time of printing of these guidelines. Utmost care was applied with respect to stated therapeutic recommendations and the selection as well as dosage of drugs. Nevertheless, users are prompted to use package inserts and expert information by the manufacturers as backup and, in case of doubt, consult a specialist. Pursuant to public interest, questionable discrepancies shall be communicated to the GPO editors. The user himself/herself remains responsible for all diagnostic and therapeutic applications, medications and doses. Registered trademarks (protected product names) are not specified in these guidelines. From the absence of respective indications, it may thus not be inferred that product names are unprotected.

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1.4. Scope and purpose

These guidelines have been written to assist clinicians in treating patients with basal cell carcinoma (BCC). The article was initiated mainly because of advances in the medical treatment of patients with BCC, which justify a newer approach of classification and multidisciplinary therapeutic strategies. The use of these guidelines in clinical routine should improve patient care.

1.4.1. Target population

The present guidelines contain recommendations with regard to the diagnosis, therapy and follow-up of patients with BCC, addressing in detail all aspects of BCC management, from the common types of tumours to those which are ‘advanced’ or ‘difficult to treat’.

1.4.2. Objectives and formulation of questions

The guidelines are produced primarily for those clinicians who are providing the care to patients with BCC. A new classification system is proposed based on ‘real-life’ scenarios of complex cases rather than a simple ‘stepwise’ prognostic model such as tumour-node-metastasis, which is less easily applicable to BCC. Particular emphasis is given on the evolving field of systemic therapy for advanced BCC, e.g. targeted therapy and immunotherapy. Prevention issues are also briefly addressed. Formulation of questions has been made relevant to clinicians in their general practice context.

1.4.3. Audience and period of validity

This set of guidelines will assist healthcare providers in managing their patients according to the current standards of care and evidence-based medicine. It is not intended to replace national guidelines accepted in their original country. These guidelines reflect the best published data available at the time the report was prepared. Caution should be exercised in interpreting the data; the results of future studies may modify the conclusions or recommendations in this report. In addition, it may be necessary to deviate from these guidelines for individual patients or under special circumstances. Just as adherence to the guidelines may not constitute defence against a claim of negligence, deviation from them should not necessarily be deemed negligent. These guidelines will require updating every three years (Expire date: 04/2022), but advances in medical sciences may demand an earlier update.

1.5. Principles of methodology

These guidelines are based on the updated EDF guidelines [1], the German S2k guidelines [2], the French guidelines [3] and the British Association of Dermatologists’ guidelines [4] for the management of BCC.

De novo literature search was conducted by the authors by Medline search. All diagnostic and treatment recommendations, summarised at the end of each section in special tables, are graded based on evidence-based data or provided as expert consensus wherever adequate evidence is not available. The methodology of these updated guidelines was based on the standards of the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument. The levels of evidence are graded according to the Oxford classification (Table 1). The degree of recommendation is also classified (Table 2). A structured consensus process was used to discuss and agree upon recommendations. The meeting was held on October, 11 2018 in Paris, France.

2. Introduction

2.1. Etiopathogenesis

2.1.1. What is the histogenesis of BCC?

BCC is a skin carcinoma derived from epidermal cells. Different hypotheses have been formulated on the cell of origin of BCC. Most BCCs seem to arise from stem cells of the hair follicle [5,6], whereas some authors contend that BCC stem cells are located in the interfollicular epidermis and infundibulum and not in the hair bulge [7]. It has been suggested that depending on the carcinogenic agent involved, different stem cell compartments may be targeted and subsequently give rise to BCC. It is noteworthy that BCC cell lines have not been easily developed, suggesting that their isolation and

Table 1
Oxford levels of evidence Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence.

Question	Step 1 (Level 1 ^a)	Step 2 (Level 2 ^a)	Step 3 (Level 3 ^a)	Step 4 (Level 4 ^a)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances ^b	Local non-random sample ^b	Case series ^b	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross-sectional studies with consistently applied reference standard and blinding	Individual cross-sectional studies with consistently applied reference standard and blinding	Non-consecutive studies or studies without consistently applied reference standards ^b	Case-control studies, or poor or non-independent reference standard ^b	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomised trial ^a	Case series or case-control studies, or poor-quality prognostic cohort study ^b	n/a
Does this intervention help? (Treatment benefits)	Systematic review of randomised trials or <i>n</i> -of-1 trials	Randomised trial or observational study with dramatic effect	Non-randomised controlled cohort/follow-up study ^b	Case series, case-control studies or historically controlled studies ^b	Mechanism-based reasoning
What are the <i>common</i> harms? (Treatment harms)	Systematic review of randomised trials, systematic review of nested case-control studies, <i>n</i> -of-1 trial with the patient you are raising the question about or observational study with dramatic effect	Individual randomised trial or (exceptionally) observational study with dramatic effect	Non-randomised controlled cohort/follow-up study (postmarketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms, the duration of follow-up must be sufficient.) ^b	Case series, case-control or historically controlled studies ^b	Mechanism-based reasoning
What are the <i>rare</i> harms? (Treatment harms)	Systematic review of randomised trials or <i>n</i> -of-1 trial	Randomised trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomised trials	Randomised trial	Non-randomised controlled cohort/follow-up study ^b	Case series, case-control or historically controlled studies ^b	Mechanism-based reasoning

^a Level may be graded down on the basis of study quality, imprecision and indirectness (study PICO does not match questions PICO) because of inconsistency between studies or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size. PICO, P (Patient, Population, or Problem), I (Intervention), C (Comparison), O (Outcome).

^b As always, a systematic review is generally better than an individual study.

Table 2
Grades of recommendation.

Grade of recommendation	Description	Syntax
A	Strong recommendation	shall
B	Recommendation	should
0	Recommendation pending	may/can

proliferation require unidentified environmental or cellular factors.

2.1.2. What do we know about the aetiology and the genetics of BCC?

The main carcinogenic factor is ultraviolet light (UV), which explains why most tumours are located on sun-exposed sites. Indeed, BCC is one of the most highly mutated human tumours (65 mutations/megabases) [8,9]

and harbours a large percentage of UV-induced mutations (C:T or CC:TT transitions at dipyrimidine sites) [10]. At the genetic level, the main driver is activation of the Hedgehog (Hh) pathway with inactivating mutations of *PTCH1* identified in 90% of sporadic BCCs and activating mutations of *SMO* in approximately 10% (Fig. 1). Alterations of the Hh pathway are also found in other Hh-dependent tumours such as medulloblastoma and neuroblastoma [11]. All these tumours develop in patients with naevoid basal cell carcinoma syndrome (NBCCS; *syn* Gorlin syndrome), a rare genetic disorder predisposing them to multiple BCCs, due to germline mutations in *PTCH1* and, less frequently, in *PTCH2*, *SMO* and *SUFU* (see section 7). Very few BCCs have no mutations in the Hh pathway. Other driver mutations have also been found in cancer-related genes such as *MYCN*, *PPP6C*, *STK19*, *LATS1*, *ERBB2*, *PIK23C*, *N-*

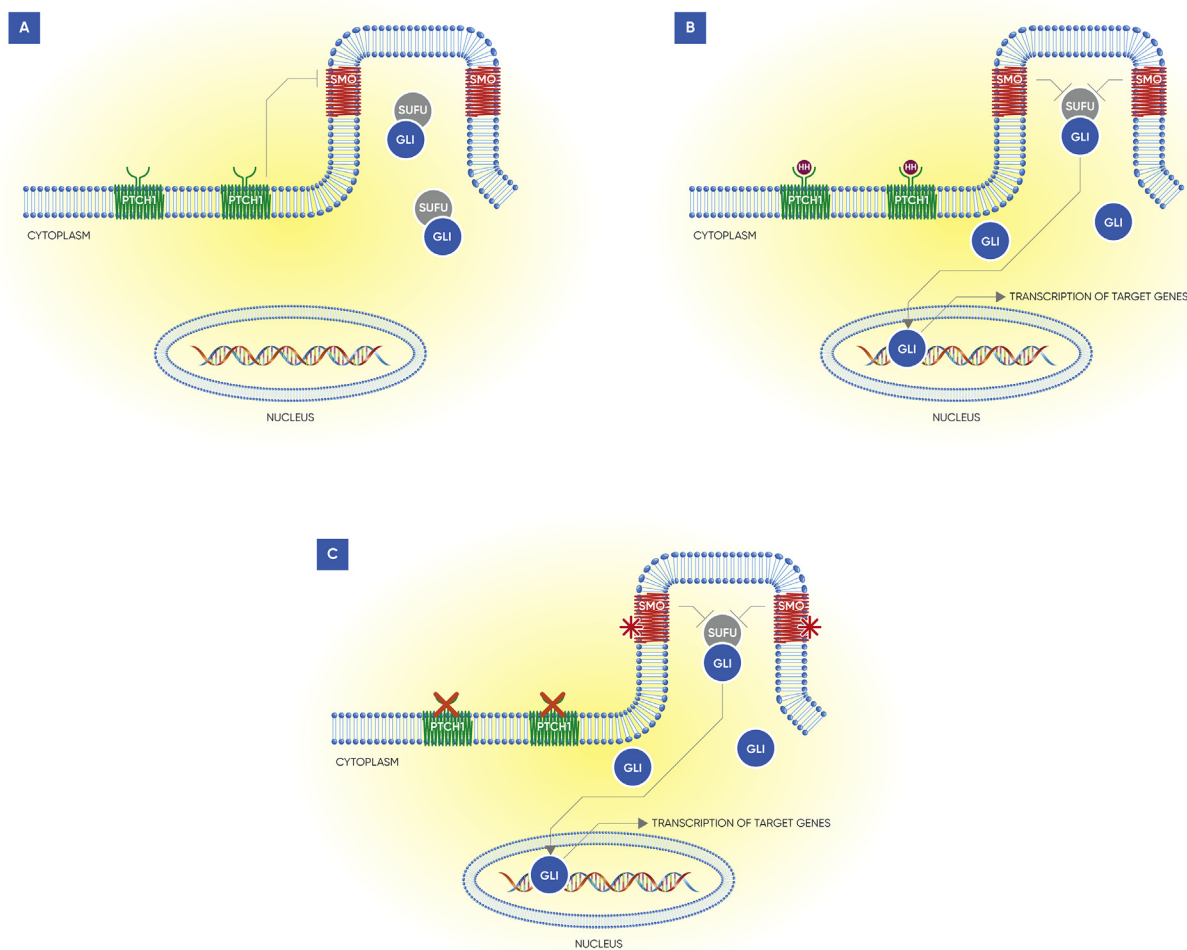


Fig. 1. Overview of the physiologic and oncogenic Hedgehog pathway. A) In the absence of Hh ligand, PTCH1 receptor constitutively inhibits SMO, blocking the Hh signal transduction. B) If Hh ligand binds to PTCH1, SMO de-represses. Activated SMO inhibits the binding of SUFU to GLI, which is then able to enter the nucleus leading to the expression of the target genes involved in the cell survival and proliferation. C) Loss of function of PTCH1 (red cross) or activating mutations of SMO (black star) induce the oncogenic signalling activation in the absence of Hh ligands. Hh; Hedgehog; PTCH1; Patched Homologue 1; SMO; Smoothened; SUFU; suppressor of fused; GLI; glioma-associated oncogene.

RAS, *K-RAS* and *H-RAS*, as well as loss of function of *PTPN14*, *RBI* and *FBXW7*. Mutations in the P53 gene are also frequently observed [10]. However, to date, no genetic profile has been associated with a specific histopathological subtype.

Other genetic diseases can predispose patients to the formation of BCC. Among them, the most well-known is xeroderma pigmentosum which is due to germline mutations in DNA repair genes [12]. These patients develop multiple tumours, including BCC, and also melanoma and squamous cell carcinoma (SCC), often at an early age. BCC is also observed in Bazex-Dupr -Christol syndrome, a cancer-prone genodermatosis with an X-linked, dominant inheritance pattern. Recently, mutations in the *ACTRT1* gene and its enhancer leading to activation of the Hh pathway have been demonstrated in families affected by this syndrome [13].

2.2. Epidemiology

BCC accounts for 75% of all skin cancers and is the most common malignant tumour in white populations. The average lifetime risk for white-skinned individuals to develop BCC is approximately 30% [14]. Rates of BCC have been reported to be increasing in many countries around the world as a result of the increasing longevity of the general population and sun exposure behaviours.

2.2.1. How is the incidence of BCC developing in Europe?

The epidemiology of BCC is difficult to describe accurately because routine recording of BCC is often not performed by cancer registries because of the large number of cases. In addition, not all BCC cases are sent for histopathologic diagnosis and there are large regional variations in reported incidence rates of BCC. These differences may be due to geographic location (latitude) of the study populations, study periods and methods for registering BCC [14]. As most cancer registries record only the first histologically confirmed BCC per patient, the true incidence of BCC may be significantly underestimated [15].

The highest incidence of BCC has been reported in Australia, followed by the US and Europe [16,17]. Among European countries, an average incidence rate of 76.21/100,000 person-years has been reported in England in the period 2000–2006 [18]. A crude annual incidence rate of BCC varying from 89 to 163.8/100,000 was reported in two Scottish studies (1995–1997) [19,20]. In the Netherlands (1973–2009), the age-standardised incidence rates increased approximately fourfold for men and women to 165 and 157 per 100,000 person-years, respectively [21]. The Trentino Skin Cancer Registry in Italy (1993–1998) reported an incidence rate of 88 per 100,000 persons [22]. The German cancer registry data (1998–2010) showed a 2.4-fold increase of BCC [23]. Mortality rates of BCC are overall low. The 5-

year absolute survival in German patients with BCC was 87.1%, and survival was on average 3–6% higher than the survival of the general population, 5 and 10 years after diagnosis [24].

Advanced BCC includes locally advanced BCC (laBCC), with direct tumour spread and occasionally extensive tissue destruction, and metastatic BCC (mBCC) [25]. A retrospective cohort US study reported that laBCC was uncommon and accounted for 0.8% of all BCC cases (age-adjusted incidence rate: 1.83 per 100,000 persons, which projected to 4399 cases in the US population). Rates for laBCC and mBCC were higher for patients older than 65 years and for males [26]. Another US study reported higher rates: An age-adjusted rate of 10 per 1,000,000 persons was noted for laBCC [27]. mBCCs with histologically confirmed BCC metastases are extremely rare, with an estimated incidence of 0.0028%–0.55% [28,29]. However, there is a risk of underreporting because even in patients with large primary BCC tumours, typically no staging examinations were performed in the past [30]. A systemic review of 100 published mBCC cases reported that 50% had regional metastases and 50% had distant metastases. Patients with distant metastases were younger (mean age: 58.0 years) than patients with regional metastases (66.3 years). Shortened survival was reported in patients with mBCC and distant metastases (median survival: 24 months) than in patients with regional metastases (median survival: 87 months) [30].

2.2.2. What do we know about risk factors?

BCC most frequently occurs in adults, especially in the elderly population, although it is frequently seen lately in adults younger than 50 years. BCC is more common in men than in women, with a male-to-female ratio of approximately 2:1 [31]. Women younger than 40 years have been found to outnumber men in this age group [32,33]. This may be attributed to changes in women's clothing and sun exposure behaviours. Major risk factors for BCC include UV radiation exposure, fair pigmented characteristics (fair skin colour, red hair), older age, genodermatoses, a family history of BCC and immunosuppression. Organ transplant recipients represent a group of patients for special consideration. Population-based studies reported a sixfold to 16-fold increased risk for post-transplant BCC, with a higher risk in kidney recipients [34,35]. However, as the major risk for organ transplant recipients is SCC, the ratio BCC/SCC in these patients is inverted.

2.3. Classification

The natural history of a BCC is usually that of a slow-growing skin cancer starting from a tiny, hardly visible papule, growing usually for years without any aggressiveness into a nodule or a plaque, sometimes ulcerated, leaving time to be diagnosed and managed correctly.



Fig. 2. Clinical BCC subtypes. A) Nodular, B) superficial, C) morphoeic and D) ulcerated (ulcus rodens) BCC.

A few forms of common BCC, such as superficial, nodular, morphoeic, ulcerated (ulcus rodens), are clinically recognised (Fig. 2). However, common BCCs are highly polymorphic and sometimes difficult to classify into one of these standard subtypes. However, BCCs should not be mistakenly regarded in general as ‘indolent cancers’, a reputation which they deserve only when they are treated early and adequately.

Destructive growth and invasion of surrounding tissues usually occur while the rate of metastasis is very low. If BCC lesions are not treated for years, or in case of multiple relapses after surgery or ablative procedures, they become progressively ‘locally advanced’. ‘Advanced BCC’ is a vague term that was introduced when patients who were not candidates for surgery and radiotherapy were sought for studies with targeted Hh inhibitors. Although not clearly defined, the word ‘advanced’ usually implies that (1) there has been a long history without treatment or with repeated failures of treatments and recurrences, (2) there is extensive tissue destruction in the surrounding anatomical area and (3) it has become difficult or impossible to cure the tumour through standard surgery (unresectable) or through radiotherapy.

We consider a more pragmatic and operational classification for BCC is into ‘easy-to-treat’ BCC, which includes the most ‘common BCC’, and ‘difficult-to-treat’ BCC (submitted). More than 95% of BCCs are easy to treat through standard surgery or a range of alternative blind treatments at least during the initial months or years after diagnosis. Difficult-to-treat BCCs include ‘all locally advanced BCCs’ and also common BCCs which,

for any reason, pose specific management problems. These reasons may be (1) the technical difficulty of maintaining function and aesthetics due to the size or location (eyes, nose, lips and ears) of the tumour; (2) the poorly defined borders often associated with morphoeic subtype or prior recurrence; (3) multiple prior recurrences on the face (often requiring much larger excision); (4) prior radiotherapy; (5) patient’s reluctance to accept the consequences of surgery and (6) patient’s comorbidities interfering with surgery.

The most severe forms of BCC are quite heterogeneous. In an effort to classify ‘difficult-to-treat’ BCC (DTT-BCC) into different categories relevant to practice, the EADO group designed a study based on the clustering of real cases by international experts from various specialities with a mathematical modelling of the results (submitted). A 5-group classification was generated which basically describes 5 different practical situation patterns, namely, common BCC but difficult to treat for any reason linked to the tumour or the patient, BCC difficult to treat because of the number of BCC, locally advanced BCC out of critical areas, locally advanced DTT-BCC in critical areas and extremely advanced DTT-BCC. Based on these results, an EADO classification of all BCC is under revision. In addition, similar to all other solid tumours, a staging system is needed for BCC, but tumour-node-metastasis does not fit the natural evolution of this tumour, which does not follow the 3-step process, i.e. tumour, nodal involvement and distant metastases. Progression-free survival or overall survival curves are not meaningful for these tumours, which are not measurable by Response Evaluation

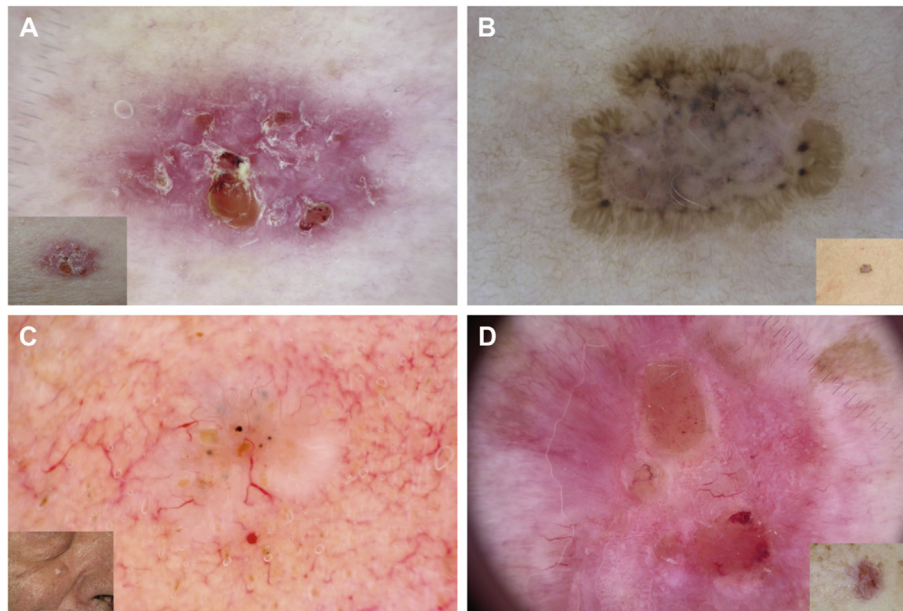


Fig. 3. Dermatoscopic criteria and clinical images (inset) of different BCC subtypes. A) Superficial BCC: multiple erosions and scales on a pink homogenous area; B) Pigmented superficial BCC: radial lines connected to a common base (leaf-like areas), radial lines converging to a central dot or clod (spoke-wheel areas) and blue-grey clods; C) Nodular BCC: branching vessels, bluish-grey clods and white areas; D) Infiltrating BCC: branching and linear vessels providing a stellate appearance and central ulceration.

Criteria in Solid Tumours (RECIST) criteria, and can destroy large anatomic areas without affecting survival.

2.3.1. How do we define high-risk BCC for recurrence?

BCC can also be classified according to the risk of recurrences into high risk and low risk. All difficult-to-treat BCCs are at high risk of recurrence mainly because of difficulty in the management that often leads to compromise with regard to ideal treatment and recommended safety margins of excision. Most easy-to-treat BCCs are at low risk of recurrence. However, some apparently easy-to-treat BCCs may still be at risk of recurrences such as those located on the H area of the face affecting the invasion of the tumour, those with aggressive histological characteristics (perineural and/or perivascular involvement) and those in immunosuppressed patients. All BCCs managed by ablative procedures without histopathological control instead of surgical excision are at high risk of recurrence. It must however be mentioned that not all recurrences have the same implications. A recurrence of an invasive BCC on eyelids, nose, lips and ears significantly increases the risk of deleterious consequences, while a recurrence of a superficial BCC (sBCC) on the back will be easily managed.

2.4. Diagnosis

2.4.1. When is clinical or dermatoscopic diagnosis of BCC sufficient?

In a systematic review of studies comparing test performance of naked eye examination and dermatoscopy,

sensitivity improved from 66.9% to 85% and specificity, from 97.2% to 98.2% [36]. The pooled sensitivity and specificity of dermatoscopy for the diagnosis of BCC were 91.2% and 95%, respectively. The sensitivity and specificity of dermatoscopy were higher for pigmented than non-pigmented BCC. Sensitivity increased when dermatoscopy was performed by experts and when the diagnosis was based on in-person dermatoscopy as opposed to dermatoscopic photographs. The main value of dermatoscopy is in the diagnostic differentiation of BCC from melanoma, SCC including Bowen's disease and benign tumours.

In addition to clinical diagnosis, dermatoscopy has also been found to be a useful tool in the preoperative prediction of the BCC subtype and in the non-invasive assessment of tumour response to topical treatments [37,38]. However, the evidence of the studies is limited and in equivocal lesions, the BCC subtype has to be assessed histopathologically [39].

Dermatoscopic criteria for BCC are absence of brown reticular lines (pigment network), branching and linear vessels (arborising and superficial telangiectasias), multiple erosions, ulceration, bluish-grey clods of variable size (ovoid nests and globules and focused dots), radial lines connected to a common base (leaf-like areas), radial lines converging to a central dot or clod (spoke-wheel areas) and clods within a clod (concentric structure) (Fig. 3) [40]. Multiple erosions are associated with sBCC [38,41], whereas white structureless zones (scar-like areas) with fine linear vessels are predictors of aggressive subtypes (morphoeic and infiltrative BCCs).

Diagnosis by clinical examination confirmed on dermatoscopy without histopathological examination is acceptable for the small nodular subtype on typical locations such as the head/neck or trunk, for multiple BCCs in NBCCS and for the superficial subtype located on the trunk and extremities.

The nodular subtype of BCC (nBCC) presents clinically as a reddish to skin-coloured, sometimes translucent papule, nodule or plaque. It is most commonly located on the head/neck area. The most striking dermatoscopic features are branching, focused vessels (arborising vessels, consisting of focused, bright red large stem vessels with multiple finer ramifications) [42]. In cases of partially pigmented tumours, bluish-grey clods of variable size are also commonly observed. Importantly, the presence of bluish-grey clods and branching linear vessels are negative predictors for the diagnosis of sBCC [38].

sBCC presents as a scaly erythematous patch or plaque that usually is well demarcated and is typically located on the trunk and lower extremities. Dermatoscopically, it exhibits white to pinkish-red structureless areas and, if any, small focused linear vessels mainly at the border. In addition, sBCC typically shows multiple small erosions. In pigmented variants, the presence of radial lines connected to a common base (leaf-like areas), radial lines converging to a central dot or clod (spoke-wheel areas) and clods within a clod (concentric structure) facilitate the diagnosis. Using polarised dermatoscopy, the presence of short white lines (chrysalis structures) represents an additional clue for the diagnosis of sBCC.

Another non-invasive skin-imaging tool that has been shown to be of high diagnostic value is reflectance confocal microscopy, which however is not so widely used and often only accessible in specialised skin cancer centres [43]. In clinically challenging lesions, initial data suggest that optical coherence tomography may have a role for the diagnosis of BCC. In a meta-analysis, it was shown that optical coherence tomography improves the sensitivity and specificity when compared with visual inspection plus dermatoscopy [44].

2.4.2. When is histopathological examination of BCC mandatory?

Histopathological examination is always mandatory in the case of ambiguous lesions and in any ulcerated or large tumour for which the diagnosis is uncertain. Furthermore, high-risk BCCs require histopathological diagnosis to assess the surgical margins. In case of low-risk subtypes, non-invasive imaging techniques may be sufficient to confirm the diagnosis, especially when the tumour is scheduled for topical or destructive treatments.

A prior incisional biopsy can be regarded an option before proceeding with complex surgery or systemic treatment in high-risk BCC and is indicated to confirm recurrences after surgery or destructive or topical treatments in low-risk subtypes.

Histopathology	Evidence-based recommendation
Grade of recommendation B	Histopathological confirmation is mandatory in ambiguous lesions, in large tumours and in BCCs located in high-risk areas
Level of evidence 3	De novo literature search [39] Strength of consensus: 100%

BCC, basal cell carcinoma.

2.4.3. Which histopathological subtypes should be reported?

Histological subtypes of BCC stratified by the risk of recurrence described in the current WHO classification [45] are as follows: (1) lower risk: nodular, superficial, pigmented, infundibulocystic (a variant of BCC with adnexal differentiation), fibroepithelial; 2) higher risk: basosquamous carcinoma, sclerosing/morphoeic, infiltrating, BCC with sarcomatoid differentiation, micronodular. Mixed forms of these subtypes are frequently found as well as collision tumours with SCC. Differential diagnosis with SCC can be difficult: immunohistological markers such as the Ber-EP4 antibody (marker for BCC) and the epithelial membrane antigen (marker for SCC) are very helpful here. This applies in particular

Clinical diagnosis	Evidence-based recommendation
Grade of recommendation A	Histological diagnosis may not be required in superficial and small nodular (<1 cm) BCCs in low-risk areas, if clearly diagnosed clinically and/or with non-invasive techniques
Level of evidence 1	De novo literature search [36] Strength of consensus: 100%
Non-invasive diagnosis	Evidence-based recommendation
Grade of recommendation B	Aided non-invasive diagnosis with dermatoscopy, reflectance confocal microscopy and/or optical coherence tomography can improve the diagnostic accuracy in difficult-to-recognise BCCs
Level of evidence 1	De novo literature search [36,43,44] Strength of consensus: 100%

BCC, basal cell carcinoma.

to the assessment of excision margins in micrographic surgery and the differentiation between benign follicular hyperplasia and parts of BCCs.

The histopathological report should also include if excision is complete with free lateral and deep margins and prognostic features such as perineural invasion and lymphatic/vascular invasion.

3. Management of common (easy-to-treat) bcc

3.1. Primary therapy

Most primary BCCs can be easily treated by surgery or by non-surgical methods for certain subtypes. BCCs with high risk of recurrence need to be treated more aggressively. Risk of recurrences increases with tumour size, poorly defined margins, aggressive histological subtype or previous recurrences. Certain tumours can be locally advanced with destruction of adjacent tissues or difficult to treat for other reasons which might need discussion regarding appropriate therapy in a multidisciplinary board.

3.1.1. Which BCC should be excised?

Surgical excision is a very effective treatment for primary BCC treatment, with recurrence rates varying from less than 2%–8% at 5 years after surgery (reviewed in the study by Trakatelli *et al.* [1]). Scalpel excision is performed using either a standard (2D) excision with safety margins or a microscopically controlled stepwise procedure (3D excision).

Alternatively, surgical removal by destructive (blind) treatments and non-surgical modalities including topical treatments or photodynamic therapy (PDT), either alone or combined, may be used for low-risk BCCs when surgery is contraindicated or impractical (see sections 3.2, 3.3, 3.4, 3.5).

Surgery	Evidence-based recommendation
Grade of recommendation A	Surgical removal is highly effective to treat BCC and allows histological confirmation
Level of evidence 3	Guideline adaption [1] Strength of consensus: 100%

BCC, basal cell carcinoma.

3.1.2. Which BCC should not be treated by topical or destructive (blind) treatments?

Histological examination of damaged tissue is not possible using topical or destructive treatment techniques. Moreover, deeper parts of tumours might not be reached because of methodology-inherent penetration limits (e.g. PDT) or only with an inappropriate risk of tissue scarring (e.g. deep cryotherapy). As a rule, blind techniques should be avoided in BCCs, in which a deeper

tissue invasion cannot be ruled out and in those at increased risk for subclinical spread or local recurrence. However, radiotherapy can be considered in patients when surgery is not expected to give optimal results, including tumours with deep tissue invasion, provided modern imaging procedures can define the tumour area.

Avoidance of topical or destructive treatments	Consensus-based statement
GCP	Topical or destructive (blind) treatments shall be avoided in BCCs at risk of recurrences (see sections 3.2, 3.3, 3.4, 3.5) Strength of consensus: 100%

BCC, basal cell carcinoma; GCP, good clinical practice.

3.1.3. Safety margins in standard excision with 2D histology

The purpose of surgical therapy is to eliminate both the clinically apparent tumour and its microscopic extension into normal-appearing skin. Standard removal of BCC therefore includes the circumferential excision of all visible tumour borders together with an adequate adjacent safety margin of clinically uninvolved tissue. Histological assessment of the excised tumour bed is routinely performed in a cross-sectional fashion with the examination of vertical sample cuts (bread loaf sections for 2D histology) obtained from formalin-fixed, paraffin-embedded tissue.

3.1.3.1. How should margins be assessed? The preoperative decision about the adequate width of a chosen safety margin surrounding the tumour depends on individual parameters predicting its risk for incomplete excision and/or local recurrence. To more precisely define the preoperative tumour borders particularly in ill-defined non-pigmented lesions, the use of dermatoscopy may be helpful, although the limited number of studies on this matter do not demonstrate any statistical difference between dermatoscopy and visual inspection for the most accurate appreciation of the margins (reviewed in the study by Que [46]). In addition, reflectance confocal microscopy has been recently reported to reveal BCC foci even beyond dermatoscopically defined margins, and their potential role for routine use in preoperative assessment of BCC tumour borders has to be further evaluated [47].

3.1.3.2. Can we define an optimal safety margin? Recommendations on safety margins in BCC standard excision vary according to the risk profile of each tumour. Current guidelines suggest a range of peripheral margins between 2 mm and 5 mm in low-risk tumours and between 5 mm and 15 mm in high-risk lesions [48,49]. In addition to other factors (e.g. primary or recurrent lesion, presence or absence of perineural invasion), the tumour size is crucial in predicting the risk of subclinical extension: while a BCC with a

diameter less than 2 cm would need a minimum peripheral margin of 4 mm to totally eradicate the tumour in more than 95% of cases [50], a tumour of 2 cm and additional high-risk features would instead require a safety margin of at least 13 mm to achieve the same relative certainty of complete removal [51]. In clinically well-defined pigmented BCCs, narrower margins of 2–3 mm have been shown to yield a removal rate of 99% [52]. Small margins (2–3 mm) may also be considered in sites where reconstructive options are limited and subsequent reconstruction is intended in a setting of micrographic (3D) surgery [48].

Guidelines addressing the deep margins recommend an excision down to the level of the fat and in cases involving the head, down to the level of the fascia, perichondrium or periosteum [49].

Surgical margins Low-risk BCC	Consensus-based statement
GCP	In low-risk BCCs, a safety margin of 3–4 mm is recommended for standard excisions with 2D histology Strength of consensus: 100%
Surgical margins High-risk BCC	Consensus-based statement
GCP	In high-risk BCCs, in which micrographic surgery is not accessible, a variable safety margin of 5–15 mm should be chosen based on individual tumour characteristics Strength of consensus: 100%

BCC, basal cell carcinoma.

3.1.3.3. Should we re-excise if clinically intended optimal margins are not met? Clinical and histological margins do not necessarily correspond. This might be because of not only tumour infiltration that is not clinically visible within the area of surrounding safety margins but also shrinkage of excised tissue after fixation for histopathological examination. Although shrinkage is less in aged and elastotic skin, a percentage shrinkage of 17–20% in length and about 10% in width can be expected [53,54]. Nevertheless, there are currently no data supporting the need for re-excision in the event of a complete excision with histologically narrow margins.

Re-excision after narrow margins	Consensus-based statement
GCP	If histologically free margins are reported, re-excision may not be required Strength of consensus: 100%

3.1.4. Excision using 3D histology

Microscopically controlled surgery (3D histology with different possible approaches of examining vertical and/

or horizontal planes) best enables complete examination of surgical margins. It represents a safe and proven method to confirm thorough resection of infiltrating tumours, especially at problematic sites, while preserving the adjacent tissue. This provides aesthetic results that are superior or equivalent to non-surgical and less-safe procedures [55]. It is both an efficient and cost-effective procedure providing highest cure rates [56].

In a prospective randomised trial comparing standard 2D excision with micrographic 3D surgery, the 10-year cumulative probability of recurrence for primary BCC was 12.2% after standard excision and 4.4% after micrographic surgery ($p = 0.100$). For recurrent BCCs, cumulative 10-year recurrence probability was 13.5% and 3.9% for 2D and 3D excision, respectively ($p = 0.023$) [57]. Apart from a higher risk of incomplete excision with an increased likelihood of recurrence, standard 2D excision and reconstruction might result in more invasive or cosmetically less desirable reconstruction [58].

3.1.4.1. Which BCC requires surgery with 3D histology? Primary BCCs associated with a higher risk of local recurrence or subclinical extension and those in cosmetically or functionally sensitive locations (e.g. periocular region) or exhibiting destructive growth patterns are candidates for a stepwise surgery with 3D histology (if technically available) [55,59,60]. In addition, recurrent tumours should undergo microscopically controlled surgery because their cure rates are inferior to those of primary lesions with a reported re-recurrence rate between 11.6% and 17.4% (reviewed in the study by Trakatelli *et al.* [1]). In addition to aggressive histology, recurrence is a predictor of extensive subclinical spread [61].

Surgery with 3D histology	Evidence-based recommendation
Grade of recommendation A	Microscopically controlled surgery (3D) shall be offered in high-risk BCC, in recurrent BCC and in BCC in critical anatomical sites
Level of evidence 3	De novo literature search [57,58,60,61] Strength of consensus: 100%

BCC, basal cell carcinoma.

3.1.5. Procedure in the event of incomplete excision

Incomplete excision, where one or more surgical margins still contain neoplastic cells, has been reported in 4.7–24% of excisions and is influenced by surgical experience, anatomical site, histological subtype of tumour and the excision of multiple lesions during one procedure [1,62–64]. It reflects the extent of subclinical tumour spread that is not completely predictable by the aforementioned features. Recurrence after surgery of incompletely excised BCC is not as high as it might be

expected, ranging from 26% to 41% after 2–5 years of follow-up, and the maximum number of tumour recurrences has been detected in BCC series with a predominance of the morphoeic type [62]. An absence of residual tumour in the surgical specimen can be observed in about half of BCCs after re-excision because of positive surgical margins. However, the risk of further recurrences among tumours that have already recurred once is more than 50%, especially when both lateral and deep margins are involved [64]. Moreover, the treatment of lesions in certain areas, e.g. the face, can be difficult, and unfortunately, there is no single characteristic that defines which cases will have no remaining tumour cells and thus be candidates for clinical surveillance [65]. Some incompletely excised lesions may demonstrate a more aggressive histological subtype when the lesion recurs [66]. Therefore, re-treatment is suggested in aggressive tumours prone to high recurrence rates (e.g. micronodular or multifocal tumours) or those in which the deep surgical margins are involved, particularly when they are located in the mid-face or other complicated sites [62]. Mohs surgery should be considered in the latter situations. Lesions with surgical margins that are tangential or extremely close to the tumour should be managed as incompletely excised. Radiotherapy should be considered in patients with a high risk of not having a complete resection with surgery. Finally, clinical follow-up could also be considered for non-aggressive, small lesions on the trunk.

3.1.5.1. How should we re-excise in the event of incomplete excision? In the event of an incomplete excision, microscopically controlled (3D) re-excision should be considered, if the incompletely excised BCC exhibits high-risk features of recurrence (aggressive histological subtypes, deep surgical margin involved). In a setting of microscopically controlled (3D) surgery, re-excision in the presence of a positive margin is part of the stepwise procedure.

Re-excision after incomplete excision	Evidence-based recommendation
Grade of recommendation A	BCC lesions that have been incompletely excised, especially high-risk BCCs, and those incompletely removed at the deep margin, shall be re-excised
Level of evidence 3	De novo literature search [62–64] Strength of consensus: 100%

BCC, basal cell carcinoma.

3.2. Topical therapies

3.2.1. When should we consider topical therapies?

Topical therapies should be considered in selected patients with low-risk sBCC and in patients declining

surgical intervention or if surgery is contraindicated because of patient-related factors (age, comorbidities, medications, logistic difficulties).

3.2.1.1. Imiquimod. Imiquimod is an immune response modifier currently approved in Europe and the USA for the treatment of small sBCCs in immunocompetent adults, applied 5 times per week for 6 weeks. A non-inferiority, randomised controlled trial (RCT) compared 5% 5-fluorouracil (5-FU) (twice daily for 4 weeks) with imiquimod 5% cream (once daily, five times a week for 6 weeks) and methyl aminolevulinate photodynamic therapy (MAL-PDT) (two sessions with an interval of 1 week) in patients with sBCC followed up for 5 years [67–69]. The overall estimate of treatment success at 1 year was 72.8% for MAL-PDT, 83.4% for imiquimod and 80.1% for 5% 5-FU, supporting that topical 5-FU was non-inferior and imiquimod was superior to MAL-PDT for treatment of sBCC [67]. Tumour thickness and adnexal extension of sBCC appeared not to predict treatment failure [70]. Five years after treatment, the probability of tumour-free survival was 70.0% for 5% 5-FU, 62.7% for MAL-PDT and 80.5% for imiquimod, confirming that 5% imiquimod is superior to both MAL-PDT and 5% 5-FU in the treatment of patients with primary sBCC [69]. The efficacy of imiquimod 5% cream versus surgical excision was assessed in patients with low-risk BCC with a successful response in 84% and in 98% of the patients ($p < 0.0001$), respectively [71]. The 5-year follow-up data of this trial were comparable with the 3-year data, reporting maintenance of the clinical benefit in 82.5% of imiquimod-treated patients versus 97.7% of the surgery group ($p < 0.001$) [72]. Limited evidence is available on the efficacy of imiquimod for BCC of the nodular type. Clearance rates varied between 42% and 81%, depending on the regimen used in the different studies [72]. A few case reports and case series have described the effectiveness of imiquimod for the treatment of nBCC of the eyelid [73].

Imiquimod represents a clinically useful alternative to surgery in the treatment of low-risk, single or multiple sBCC. Combination therapies with curettage or cryotherapy have been reported, but they need to be further investigated and might be discussed on an individual basis for nBCC (see section 3.5).

5% Imiquimod sBCC	Evidence-based recommendation
Grade of recommendation A	Topical 5% imiquimod is effective in the treatment of primary sBCC
Level of evidence 2	De novo literature search [68,69] Strength of consensus: 100%

5% Imiquimod nBCC	Evidence-based recommendation
Grade of recommendation	Topical 5% imiquimod may have a role in the treatment of primary low-risk nBCC

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5% Imiquimod nBCC	Evidence-based recommendation
B	
Level of evidence 2	De novo literature search [71,72] Strength of consensus: 100%

nBCC, nodular subtype of basal cell carcinoma; sBCC, superficial basal cell carcinoma.

3.2.1.2. *5-Fluorouracil.* The 5% formulation of the anti-metabolite 5-FU is approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of sBCC with 2 applications daily for 2–4 weeks. Few studies evaluated the efficacy of 5% 5-FU in sBCC with no long-term follow-up data [74]. As described previously, a recent RCT comparing 5% 5-FU with imiquimod 5% cream and MAL-PDT in sBCC demonstrated that topical 5-FU is inferior to imiquimod and non-inferior to MAL-PDT in the treatment of sBCC after 3 years [68] and 5 years of follow-up [69].

5% 5-Fluorouracil	Evidence-based recommendation
Grade of recommendation A	Topical 5% 5-FU is an effective treatment for sBCC
Level of evidence 2	De novo literature search [68,69] Strength of consensus: 100%

5-FU, 5-fluorouracil; sBCC, superficial basal cell carcinoma.

3.3. Destructive therapies

Destructive therapies with curettage, electrocautery (electrodesiccation), cryotherapy and laser ablation are therapeutic options for small, low-risk non-facial BCC and for multiple small BCCs. Curettage allows histopathological assessment, which is not possible with cryotherapy or laser ablation because of tissue destruction.

3.3.1. When should we consider destructive therapies?

Curettage and electrodesiccation are recommended treatment options for low-risk primary BCCs although there is no international consensus regarding the optimal protocol. Efficacy is highly dependent on operator skills, tumour characteristics and anatomical location [75]. The overall reported 5-year recurrence rates vary from 3% to 20%, with lower recurrence rates for low-risk sites such as trunk and extremities. High recurrence rates are reported for facial and recurrent BCC and for BCCs on terminal hair-bearing skin [75,76].

Cryotherapy is a treatment option for low-risk BCC [77], for small or multiple BCC on extra-facial areas. Cryotherapy is applied directly to the BCC and differs from cryosurgery, which refers to intralesional treatment, guided by an inserted temperature probe. Lack of histological control is a disadvantage of cryotherapy

because of tissue destruction. RCTs comparing cryotherapy with several other treatment modalities (PDT, surgery, radiotherapy) have reported recurrence rates for cryotherapy ranging between 6% at 1 year and 39% after 2 years of follow-up [77,78]. Complete remission with carbon dioxide (CO₂) laser ablation of limb and trunk sBCCs was similar to that with cryotherapy but significantly lower than surgery 3 months after treatment [79].

Curettage plus electrodesiccation and cryotherapy	Evidence-based recommendation
Grade of recommendation B	Curettage plus electrodesiccation and cryotherapy may be alternative treatments for small, low-risk BCC on the trunk and extremities
Level of evidence 3	De novo literature search [79] Strength of consensus: 100%

BCC, basal cell carcinoma.

CO₂ and erbium yttrium aluminium garnet (Er:YAG) lasers ablate tissue through the vapourisation of tissue water, either in full ablative or fractional mode [80,81]. Tissue interaction and efficacy rates depend on operator settings, and there are no standard operational procedures. A few studies have evaluated the efficacy of laser ablation for the treatment of BCC, mainly as pretreatment before PDT [79,82,83].

Laser ablation	Evidence-based recommendation
Grade of recommendation B	Laser ablation is not recommended for treatment of BCC
Level of evidence 4	De novo literature search [79–81,83] Strength of consensus: 100%

BCC, basal cell carcinoma.

3.4. Photodynamic therapy

3.4.1. When should we consider PDT?

PDT with 5-aminolevulinic acid (ALA) or its methyl ester (methyl-5-amino-4-oxopentanoate, MAL) should be considered in patients with non-aggressive, low-risk BCC, i.e. small superficial and nodular types, not exceeding 2 mm tumour thickness, where surgery is not suitable or contraindicated because of patient-related limitations (age and comorbidities, medications, logistic difficulties) [84]. PDT is also a good treatment choice for recurrent small and large sBCC. Less common histologic variants of BCC, morpheic, pigmented and micronodular types, as well as areas with higher risk of tumour survival and deep penetration (facial ‘H’-zone), should not be treated with PDT.

MAL, the methyl ester of 5-ALA, and ALA nano-emulsion formulation are currently approved in Europe for the treatment of low-risk superficial and nodular BCCs.

MAL-PDT achieved initial clearance rates of 92–97% for sBCC, with recurrence rates of 9% at 1 year and 22% at 5 years [78,85]. For nBCC treated by MAL-PDT, 91% were clinically clear at 3 months, with a sustained lesion clearance response rate of 76% after 5 years of follow-up [86]. MAL-PDT was equivalent to surgery (92% vs. 99% initial clearance, 9% and 0% recurrences at 1 year) for sBCC but inferior to excision for nBCC when recurrence rates are compared (14% and 4% recurrences at 5 years) [85,86]. Cosmetic outcome, however, was superior after PDT compared with surgery. Clearance rates were equivalent when MAL-PDT was compared with cryotherapy for the treatment of sBCC, with overall clearance identical at 76% of lesions initially treated after 5 years, but with superior cosmesis after PDT [78].

PDT using the ALA nanoemulsion gel was compared with MAL in the treatment of non-aggressive BCC. Of the ALA-treated patients, 93.4% were complete responders compared with 91.8% in the MAL group, establishing non-inferiority ($p < 0.0001$) [87]. Other formulations of ALA have also been widely used in treating BCC, with a weighted initial clearance rate of 87% noted for sBCC treated by ALA-PDT in a review of 12 studies, compared with 53% for nodular lesions [88]. Fractionated ALA-PDT produced a superior response of sBCC versus single PDT (88% vs. 75% respectively) 5 years after treatment [89]. In another study, fractionated ALA-PDT was equivalent to surgery in initially clearing nBCCs but with a 31% failure rate over a median of 5 years after PDT, compared with only 2% after surgery [90]. A 10-year clinical and histological follow-up of 60 BCCs, originally less than 3.5 mm thick, and treated by one or two sessions of ALA-PDT using the penetration enhancer dimethylsulfoxide and with prior lesion curettage, reported 75% of treated sites remained disease free at 120 months [91].

A cohort of 33 patients with Gorlin syndrome was treated by topical PDT with an overall local control rate at 12 months of 56.3% [92].

PDT with MAL or ALA Evidence-based recommendation

Grade of recommendation A Level of evidence 1	5-ALA or MAL in combination with red light is an effective treatment for superficial and thin nodular BCC De novo literature search [84,88] Strength of consensus: 75%
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5-ALA, 5-aminolevulinic acid; BCC, basal cell carcinoma; MAL, methyl-5-amino-4-oxopentanoate; PDT, photodynamic therapy.

3.5. Combined therapies

Combination of therapies is based on the principle that their mechanisms of action are complementary or

synergistic. Combined therapies can be considered for treating BCC lesions in selected patients, in whom surgical outcomes may be either too disfiguring or with low expected curative rate.

3.5.1. When should we consider combined therapies?

Combined therapies can be considered in patients not suitable for standard treatment although in off-label situations.

CO₂, Er:YAG, diode lasers or partial surgical debulking before PDT have shown cure rates of 92.9–98.9% in nBCC, which is higher than what was reported for each method separately with mild side-effects such as hypopigmentation [93].

The reduction of the tumour burden of nBCC with curettage before medical treatment with imiquimod is also very effective when imiquimod is applied to nBCC [94,95]. A histological clearance of 94% of cases was demonstrated in a series of 34 lesions [94], and a clearance rate of 96% at an average of 36 months of follow-up was shown in 101 tumours [95].

The combination of PDT with imiquimod has also been reported in small case series or case reports [96]. The administration of a 6-week regimen of imiquimod after 2 sessions of PDT increased the cure rate from 60% to 75% when compared with PDT alone followed by placebo in recurrent cases [97].

Cryotherapy before the immediate administration of imiquimod provided a complete clinical response rate of 83% in tumours not responding to previous monotherapy with imiquimod [98], while cryotherapy between the 2nd and 5th week of imiquimod treatment achieved an efficacy of 95% in a prospective single-arm trial including 119 primary nBCCs [99].

Neoadjuvant treatment with imiquimod before Mohs surgery showed a significant reduction of the size of the tumour and resulted in a smaller surgical defect than the vehicle group [100]. However, the possibility of imiquimod treatment producing discontinuous tumour nests, which can reduce the accuracy of margin evaluation during Mohs surgery, should be considered [101].

Finally, PDT or imiquimod might be used to treat the superficial component of large BCCs once the gross tumour mass has been excised by Mohs surgery [102].

No specific combination of treatments can be currently recommended because of lack of formal evidence.

4. Management of ‘difficult-to-treat’ BCC

4.1. Surgical therapy

4.1.1. When should we still consider surgery for difficult-to-treat BCC?

Surgery can be considered as a primary therapeutic option, as a palliative option and also following a

neoadjuvant approach attempting to reduce the extent of the surgical procedure. The appropriate management should be carefully planned in a skin cancer multidisciplinary board wherein the potential strategies on surgical excision, reconstruction, tissue preservation, indications for prosthesis and radiotherapy are discussed. Appropriate imaging to determine the extent of the tumour is indicated when perineural involvement or bone invasion is suspected [48,103].

Surgery of difficult-to-treat BCC	Consensus-based recommendation
GCP	Decision on the potential suitability, indication and technique in difficult-to-treat BCC shall be made in a multidisciplinary team Strength of consensus: 100%

BCC, basal cell carcinoma.

4.2. Medical therapy

The decision whether a BCC is resectable or treatable with radiotherapy and/or medical therapy should preferably be discussed by a multidisciplinary tumour board. There are two systemic medications, vismodegib and sonidegib, with a documented efficacy in laBCC and mBCCs.

4.2.1. Hedgehog inhibition

4.2.1.1. What are the indications for Hedgehog inhibition? Vismodegib and sonidegib are specific inhibitors of an oncogenic protein named Smoothened approved by the FDA and EMA, and both are both indicated for the treatment of patients with laBCC who are not good candidates for surgery or radiotherapy, while vismodegib is also approved for mBCC [30,104]. The approved oral dose is 150 mg/day for vismodegib and 200 mg/day for sonidegib.

Vismodegib was the first approved Hh inhibitor. A phase 2 pivotal clinical trial (ERIVANCE) in 104 patients with laBCC and mBCC showed initially a response rate of 48% (laBCC) and 33% (mBCC) and a median response duration of 9.5 and 7.6 months, respectively [105]. An update on ERIVANCE after 39 months of follow-up showed a response rate of 60.3% for laBCC and 48.5% for mBCC. Twenty of 60 patients with laBCC showed a complete response. Of note, in patients with mBCC, there were no complete but only partial responses. The median response duration in the updated study results was 14.8 months (mBCC) and 26.2 months (laBCC). The median survival for patients with mBCC was 33.4 months and has not been reached for the patients with laBCC [105]. The results of the pivotal trial (ERIVANCE) have been confirmed by a global safety study SafeTy Events in Vismodegib

(STEVIE) [106]. A STEVIE update revealed a response rate of 68.5% for laBCCs and 36.9% for mBCCs after a median follow-up of 17.9 months.

Another approved drug, which has been subsequently introduced to the market in many countries, is sonidegib. The pivotal clinical trial Basal Cell Carcinoma Outcomes with LDE225 Treatment (BOLT) was a prospective randomised double blinded trial of a 200 mg dose compared with an 800 mg dose once daily; the FDA and EMA approved the 200 mg dose based on the risk/benefit ratio. The response rate assessed in the initial study, which had very stringent modified RECIST criteria, was 36% [25]. In a 12-month analysis of the BOLT trial, the response rate for the 200 mg group improved to 57.6% for laBCC and 7.7% for mBCC [107]. The last BOLT update published after a median follow-up of 30 months [108] reported a response rate of 56.1% (central review) and 71.2% (response evaluation by investigator). The corresponding response rates for mBCCs were 7.7% and 23.1%. The median duration of responses was 26.1 months (laBCC) and 24.0 months (mBCC). The median survival has not been reached in the two groups. However, the 2-year survival rate was 93.2% (laBCC) and 69.3% (mBCC).

Multiple BCCs in patients with NBCCS should be considered as laBCCs and treated accordingly. They have been included as small subgroups in the pivotal clinical trials on vismodegib (ERIVANCE) and sonidegib (BOLT).

In laBCCs, a neoadjuvant treatment with an Hh inhibitor with the intention to shrink lesions can be discussed, but there are no randomised data to prove its beneficial outcome. In a series of 15 patients treated with vismodegib for 3–6 months before surgery, only 1 patient recurred after 22 months [109,110].

Radiotherapy could be used in complicated cases in combination with vismodegib [111] and may be indicated after surgery when perineural invasion is present [112].

4.2.1.2. How to manage the adverse events from Hh inhibitors?

During treatment with Hh inhibitors, there were several class-specific adverse events such as muscle spasms, taste alterations, hair loss, fatigue and weight loss. These adverse events appear in the majority of patients and lead to treatment discontinuation in approximately 30% of all patients [25,105–108,113]. No treatment-related deaths have been reported in clinical trials with Hh inhibitors.

Different preventive and management strategies related to address the side-effects of Hh inhibitors have been proposed to improve patients' quality of life and clinical benefit [114].

Because therapy with Hh inhibitors is associated with a number of low-grade toxicities that can cause significant discomfort during long-term treatment and because there are no consistent strategies to ameliorate them, drug holidays may be introduced [108].

Two alternative schemes with less-intense adverse events have been tested in a randomised trial of vismodegib (MIKIE) trial, showing equal efficacy but a lower rate of high-grade adverse events for a schedule with a 3-month induction phase followed by a drug holiday compared with continuous treatment with vismodegib [115]. Thus, individual modifications of the treatment scheme may lead to better quality of life during the treatment.

More recently, dose reduction has been considered an alternative in the management of drug toxicities from Hh inhibitors [116].

Hedgehog inhibitors Evidence-based recommendation

Grade of recommendation **B** Hh inhibitors should be offered to patients with locally advanced or metastatic BCCs

Level of evidence **3** De novo literature search [104]
Strength of consensus: 100%

BCC, basal cell carcinoma.

4.2.2. Chemotherapy

4.2.2.1. *Is there a place for chemotherapy in difficult-to-treat BCC?* The use of systemic chemotherapy for mBCC has been addressed only in case reports and case series [117]. Most patients with widespread metastases receive platinum-based chemotherapies. These patients are typically treated similar to patients with metastatic SCC. The response rate is not higher than 20–30%, but occasionally response rates up to 60% are reported. However, in almost all of the successfully treated cases, the response duration was no longer than 2–3 months [30].

Chemotherapy might be considered for laBCC and mBCC as second- or third-line treatment in patients who are not responsive or have progressed after Hh inhibitors, often in combination with radiotherapy. However, if currently ongoing studies on therapy with PD1-immune checkpoint inhibitors show significant activity in BCC, chemotherapy might remain as a last-line treatment.

Chemotherapy Consensus-based recommendation

GCP The use of chemotherapy in the treatment of BCC can be discussed if Hh inhibitors are contraindicated and no clinical trials are available
Strength of consensus: 100%

BCC, basal cell carcinoma.

4.2.3. Immunotherapy

4.2.3.1. *Is there already a place for immunotherapy in difficult-to-treat BCC?* It is well known that BCCs are carrying a high mutational load induced by the total carcinogen

UV light. According to the current knowledge on the relationship of mutational load and response to immune checkpoint inhibitors, BCCs could be considered as ideal candidates for a response to immunotherapies. There are anecdotal reports about responses to anti-PD-1 agents such as nivolumab or pembrolizumab in treatment-naïve and treatment-refractory patients with laBCC and mBCCs [118,119]. Of interest, also patients who received Hh inhibitors and failed to respond have subsequently been treated successfully with immune checkpoint inhibitors. However, data from clinical trials are so far lacking.

The efficacy of nivolumab, alone or in combination with ipilimumab, and of cemiplimab (REGN2810), a PD-1 antibody recently approved for locally advanced and metastatic cSCC, is currently being investigated in patients with laBCC and mBCC in two independent phase 2 clinical trials (<https://clinicaltrials.gov>). In addition, in a proof-of-principle study, pembrolizumab was shown to be active against advanced BCCs and the response rate of the pembrolizumab plus vismodegib group was not superior to the monotherapy group [120].

5. Radiotherapy of BCC

During recent decades, radiotherapy has been reported as a valid alternative to surgery. The risk of developing a radiotherapy-induced secondary skin cancer is negligible using required radiation doses to treat cutaneous carcinomas. In contrast, a high risk exists in patients treated with lower doses for benign cutaneous conditions [121,122].

5.1. When should we consider radiotherapy?

Radiotherapy may be considered as a primary treatment in patients who are not candidates for surgery (e.g. locally advanced disease, comorbidities or decline surgery) or in cases when curative surgery is not possible or could be disfiguring or burdened by poor aesthetic outcome [123,124], including BCCs located on the face (i.e. eyelid, nose, lip) or large lesions on the ear, forehead or scalp [125,126]. A recent systematic review and network meta-analysis on primary BCC, analysing and comparing 40 randomised trials and 5 non-randomised studies with variable follow-up, reported an estimated recurrence rate of 3.5% after radiotherapy, fully comparable with surgery (3.8%) and Mohs surgery (3.8%) [123].

Different radiotherapy techniques have been developed to date: External beam radiotherapy (orthovoltage X-rays, electron and megavoltage photon treatment) remains the most used treatment modality. However, interstitial interventional radiotherapy (or interstitial brachytherapy) and contact radiotherapy (superficial

brachytherapy and electronic brachytherapy) represent alternative treatment strategies.

The choice between external beam radiotherapy and brachytherapy has to consider many factors: size, location, infiltration depth, team expertise and institutional resources [124]. Results of brachytherapy are similar to those obtained with external beam radiotherapy with the advantage of the steep dose fall off allowing the surrounding tissue to be spared [124,127,128]. Furthermore, the use of intensity modulated brachytherapy (stepping source technique) allows optimisation and individualisation of the dose distribution, especially when the implant configuration is difficult because of anatomical reasons [128].

Total prescribed dose and fractionation should reflect the differences in radiobiological effectiveness between different radiation modalities. Advanced lesions may be treated with megavoltage to doses between 60 and 70 Gy, using 2 Gy fractions, while equivalent radiobiological doses such as 45 Gy in 10 fractions or 51 Gy in 17 fractions represent equi-effective treatment schedules by orthovoltage for smaller lesions. Higher doses per fraction lead to higher rates of late toxicity. Therefore, accelerated fractionation schedules should be reserved for elderly, frail patients or when cosmetic outcome is of less importance. Prescribed dose must encompass all visible tumours plus an appropriate variable margin (clinical target volume), sparing as much as possible of the surrounding healthy structures [124]. Irrespective of treatment intent (definitive, adjuvant, palliative), dosimetric and technical considerations should be surveyed by a certified medical physicist.

Radiotherapy is an overall safe procedure, although it can be associated with complications such as an acute, often erosive, radiation-induced dermatitis and chronic onset of depigmentation and telangiectasias. We suggest it is devoted to elderly people because the potential risk of very-long-term trophic disorders is not well addressed.

The main indications for radiotherapy are either inoperable tumours or when the tumour board considers the certainty of disfigurement is not balanced by a certainty of clear margins. Although it has not been evaluated as an adjuvant therapy, radiotherapy may be also considered after incomplete resection with microscopic (R1) or macroscopic (R2) residual tumour, when the tumour board does not consider follow-up or a new resection as the best option.

Radiotherapy	Consensus-based recommendation
Grade of recommendation A	In BCC on the face including periorbital regions and other anatomical regions, radiotherapy is an alternative to surgery in elderly patients and in patients who are not candidates for surgery
Level of evidence 1	De novo literature search [123] Strength of consensus: 100%

BCC, basal cell carcinoma.

6. Follow-up

Follow-up should be performed in patients with BCC because of risk of local recurrence (treatment failure), subsequent BCC development (metachronous BCCs) and increased risk of development of other skin cancers (SCC and melanoma) [1,29,48].

6.1. Which follow-up schedule for which patient?

There is no evidence that intensive follow-up results in better outcomes (burden of disease, cosmetic results) in patients with low-risk BCC [4,129,130]. However, a recent study showed that patients with BCC need to receive all the relevant information tailored to their situation, and therefore, it seems reasonable to provide one follow-up visit for all patients with BCC to discuss their diagnosis and treatment, to counsel them about sun protection measures and to stress the importance of self-monitoring for possible local recurrence and new skin cancers [131]. Risk of tumour recurrence depends on the nature of the primary tumour and the treatment used. For most primary BCCs treated according to guidelines, this risk is low. However, recurrence rates are higher for recurrent BCC and increase even more in case of multiple recurrences [29,132]. Patients with recurrent lesions should therefore be counselled accordingly and should be advised to come back for clinical evaluations if they notice any changes at the site of previous surgery. Long-term follow-up is not feasible because recurrent disease may take up to 5 years to be clinically visible and for 18% of recurrences, this might be even longer [75].

Most metachronous BCCs occur within the first 3 years after diagnosis, but the risk remains elevated over time [133,134]. A meta-analysis observed a pooled mean 5-year cumulative risk of a subsequent (metachronous) BCC of 36%, comparable with another observational study [129,134].

When primary BCCs are found in large numbers and the age of onset is below 30 years, the patient should be screened for potential NBCCS (see section 7). These patients are also at increased risk of other tumours.

In conclusion, there seem to be two groups of patients that would require a more rigorous and long-term follow-up: (1) patients who are at high risk for recurrent lesions, such as those who have already been treated for recurrent BCC (increased risk of further recurrence after all types of treatment) and (2) patients with a history of multiple BCC (significantly increased risk of further BCC). These patients should benefit from a closer follow-up every 6–12 month for 3–5 years (if not lifelong).

In case of difficult-to-treat BCC or mBCC, follow-up should be practiced by a multidisciplinary team at a frequency dictated by each individual case.

Follow-up	Consensus-based statement
GCP	Follow-up is recommended in patients with BCC in 3, 6 or 12 monthly intervals according to the risk category Strength of consensus: 100%

BCC, basal cell carcinoma.

7. Diagnosis and management of patients with naevoid basal cell carcinoma syndrome

NBCCS is a rare, autosomal dominant familial cancer syndrome with a high degree of penetrance and variable expression. Its prevalence is estimated at 1 per 40,000–60,000 persons. NBCCS is caused by mutations in the *PTCH1* gene, with *de novo* mutations occurring in about 20%–30% of patients, and more rarely by mutations in *SMO*, *SUFU* and *PTCH2* [135].

7.1. How is NBCCS defined?

The diagnosis of NBCCS is established in a proband with the following findings [136]:

- Two major diagnostic criteria and one minor diagnostic criterion or one major and three minor diagnostic criteria
- Identification of a heterozygous germline *PTCH1* or *SUFU* pathogenic variant on molecular genetic testing. This finding establishes the diagnosis if clinical features are inconclusive.

Major criteria: multiple BCCs (>5 in a lifetime) or a BCC before 30 years of age, lamellar (sheet-like) calcification of the falx, jaw keratocyst, palmar/plantar pits (≥ 2), first-degree relative with NBCCS.

Minor criteria: childhood medulloblastoma, lymphoenteric or pleural cysts, macrocephaly (occipitofrontal circumference >97th centile), cleft lip/palate, vertebral/rib anomalies observed on chest x-ray and/or spinal x-ray, preaxial or postaxial polydactyly, ovarian/cardiac fibromas, ocular anomalies.

Genetic testing for *PTCH1* is suggested for the following situations: (1) to confirm the diagnosis in patients lacking sufficient clinical diagnostic criteria; (2) predictive testing for patients at risk with an affected family member but not meeting clinical criteria; (3) prenatal testing if there is a known familial mutation.

Diagnosis – NBCCS	Consensus-based statement
GCP	The diagnosis of NBCCS is based on clinical criteria. Genetic testing for germline mutations in the Hh pathway can be offered in selected cases Strength of consensus: 100%

NBCCS, naevoid basal cell carcinoma syndrome.

7.2. How do we manage BCCs in patients with NBCCS?

A multidisciplinary approach is required to manage patients with NBCCS. Close surveillance and regular skin examinations carried out by a dermatologist trained in skin cancer detection and dermatoscopy are required to diagnose and treat BCCs at early stage.

Depending on BCC location, number and size and surgical and medical treatment approaches used for sporadic BCC can be considered [137]. Radiotherapy is not recommended because of the carcinogenic effect of x-rays resulting in the formation of new BCCs. In patients who are not candidate for surgery or for other treatment options because of a high tumour burden or difficult-to-treat BCC, systemic treatment with an Hh inhibitor is suggested.

Management of patients with NBCCS	Consensus-based statement
GCP	Treatment of patients with NBCCS requires a multidisciplinary approach. In selected patients, treatment with Hh inhibitors may be considered Strength of consensus: 100%

NBCCS, naevoid basal cell carcinoma syndrome.

7.3. Which follow-up schedule should be used for patients with naevoid basal cell carcinoma syndrome?

Although onset of BCCs may occur during childhood, the average age of first BCC development occurs around the 2nd decade of life. Skin examination should be carried out every 4–6 months. Besides regular skin examination, a number of additional imaging investigations are recommended for associated extra-cutaneous abnormalities [138]. In particular, a study suggests that childhood brain magnetic resonance imaging surveillance for the risk of medulloblastoma is justified in *SUFU*-related, but not *PTCH1*-related, Gorlin syndrome [139].

Follow-up of patients with NBCCS	Consensus-based statement
GCP	Follow-up is recommended in patients with NBCCS. However, skin examination should be scheduled on an individual basis. Strength of consensus: 100%

NBCCS, naevoid basal cell carcinoma syndrome.

8. Information for patients

When diagnosing BCC, it is important to explain to patients that these tumours are only locally invasive and

will not have any detrimental effects on survival unless in rare high-risk or advanced cases. Even though most tumours are growing slowly, the potential consequences of foregoing treatment should be explained. There may be a need to discuss surgery-associated morbidity as the psychological impact of disfiguring surgery cannot be underestimated. The patient should always be offered choices when treating BCC, where appropriate. This is especially relevant when different referral pathways lead patients to either surgical or dermatological services because the availability of different treatment modalities may differ between specialities. In elderly patients, the choice of curettage and cautery for BCC (when appropriate) needs to be discussed as this can also avoid more invasive surgical treatments with grafts and flaps. Patients who have had radiotherapy are also at an increased risk of BCC on the irradiated site, and these patients cannot be treated with radiotherapy again, so it is important to check for previous radiotherapy in the field in the past medical history.

Advice about sun protection should be given, and vitamin D levels may need to be checked if advocating significant reduction in sun exposure, especially in those with the fairest skin where vitamin D deficiency is more common. Potential vitamin D deficiency in these patients may affect many other aspects of health such as autoimmune diseases, cancer and psychiatric disorders [140]. Immunosuppressed patients with BCC should be followed up in dedicated clinics because these patients are at high risk of SCC as well.

Patients with BCC should be informed that they should remain vigilant and keep an eye for potential recurrences and new primaries. The risk of developing a second BCC is 10 times the risk of the general population [141]. If patients present with multiple primaries at the onset, they should be warned that their risk of relapse is higher. Truncal BCCs, especially of the superficial types, often have multiple new primaries in the first 5 years after the original diagnosis [4,142].

There are patients who may need long-term follow-up as discussed previously, and these are likely to be those with high-risk tumours, high-risk sites, multiple BCCs and NBCCS. Patients with NBCCS should be reassured because these patients often become highly anxious about having multiple skin cancers. Although they present with a large number of tumours from a young age, the BCC tumours themselves are not a major issue and usually not aggressive in NBCCS. When proposing systemic treatment with Hh pathway inhibitors in NBCCS, patients should be made aware of the side-effects and the clinician should weigh carefully the advantages and disadvantages of such treatments on a case-by-case basis. Most patients with NBCCS treated with Hh inhibitors do not stay on the drug for more than 6 months because significant side-effects are common (especially muscle cramps) and may be severe [137]. These agents are therefore unlikely to be the answer for

long-term management, and intermittent dosing should be openly discussed with patients. The use of non-surgical options is especially important in NBCCS families and need to be considered as much as possible and discussed at every visit with the patient. In suspected NBCCS cases, there is also a need to discuss potential genetic testing looking for mutations in the *PTCH1* gene. NBCCS families have a small increased risk of other rare cancers, so it is important that the family is aware of this, as any unusual symptoms in the future need to be taken seriously with earlier detection of cancers [143]. Patients with NBCCS are also at increased risk of vitamin D deficiency, and supplementation may be necessary [144].

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