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Update of the European guidelines for basal cell carcinoma management*

Developed by the Guideline Subcommittee of the European Dermatology Forum

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Background European guidelines for the management of basal cell carcinoma (BCC) prepared by the former BCC subcommittee of the Guidelines Committee of the European Dermatology Forum (EDF) were published in 2006. *Objectives* To present updated guidelines that include consensual expert definitions on various BCC types, prognosis and risk factors for BCC as well as review recommendations for diagnosis and treatment reflecting current published evidence. *Methods* These guidelines (S1 type) were prepared by the new BCC subgroup of the European Dermatology Forum (EDF)'s Guidelines Committee through extensive literature review (up to 2012) and expert experience; they were extensively discussed within the EDF subcommittee and approved by peer reviewers of the EDF. *Results* BCC is a common tumour with an incidence rising worldwide. Three major clinical types of BCC are recognized: nodular, superficial and morpheaform. Four histological subtypes are defined: superficial, nodular, infiltrative and morpheaform. On the basis of the risk of relapse, three prognosis groups have been identified: high, intermediate and low risk. According to these classifications and evidence-based evaluation of the therapeutic strategies available, a decision tree is proposed for the management of BCCs. *Conclusions.* The guidelines offer a useful tool that will help dermatologists to select the most appropriate treatment for individual patients.

Basal Cell Carcinoma (BCC) is the most common malignancy in the fair skinned population. It accounts for around 80% of all non-melanoma skin cancers (NMSC) [4]. It is a slow growing tumour, which rarely metastasizes but can cause substantial morbidity due to its location on the face, its tendency to relapse, its multiplicity and the potential to invade and destroy local tissues. BCCs are a heterogeneous group of tumours ranging from superficial to deeply-invasive tumours than can be life-threatening. The present guidelines aim at updating the current definition and classification of BCC and selection of the most appropriate treatment for individual patients.

Incidence/prevalence

BCC incidence is difficult to estimate as NMSC are usually not included in cancer registries [5]. Additionally, there are marked geographical variations in the incidence of NMSC [5]. In France, in the Haut-Rhin area, the cancer registry standardised incidence was estimated at 75.4/100,000 inhabitants in men and 60.5/100,000 inhabitants in women [6]. In South Wales (UK), the corresponding numbers are 128/105 male/female/100,000 inhabitants. In Girona, Spain, a recent study reported an age-adjusted incidence of 44.6 per 100,000 inhabitants [7]. In the US, age standardized yearly rates have been estimated at up to 407/100,000 inhabitants in men and 212/100,000 inhabitants in women [8]. In Australia an incidence of as high as 2% per year has been reported in some regions [4].

* **Disclaimer**
This update of the BCC EDF guidelines is based on the initial EDF guidelines published in 2006 [1], the French guidelines and the British Association of Dermatologists' guidelines published in 2006 [2] and 2008 [3]. It presents consensual expert definitions on various BCC types, prognosis and risk factors for BCC and treatment options reflecting current published evidence. These guidelines (S1 type), were prepared by the BCC subgroup of the European Dermatology Forum (EDF)'s guidelines committee. The members of the BCC subgroup who co-authored this update were chosen among expert leaders in oncodermatology throughout Europe. Literature analysis was based on Pubmed searches and papers were graded on the basis of supporting evidence according to Telfer NR [3].

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The incidence of BCC continues to increase worldwide. A recent paper from Denmark reported an increase in age-adjusted incidence of BCC from 27.1 to 96.6 cases/100,000 inhabitants in women and from 34.2 to 91.2 cases/100,000 inhabitants for men between 1978 and 2007 [9]. Additionally, age incidence rates in the Netherlands were shown to increase approximately three fold (from 40 to 148/100,000 in males and from 34 to 141/100,000 in females between 1973 and 2008) [10]. In a study from Spain, for both sexes, age-adjusted incidence increased from 48.5 (1994-1995) to 60.5 (2004-05) [7].

A study of population-based incidence of first and multiple BCC in 4 European regions (Finland, Malta, Southeast Netherlands and Scotland) reported that age incidence of first BCC was estimated to vary between 77 and 158 per 100,000 person years [11]. This work showed that considering only the number of first BCC underestimates the total number of BCC in a given year. This study suggested that the incidence of the first BCC should be multiplied by 1.3 for an estimate of the total numbers of patients diagnosed with a BCC in a given year.

Risk factors

The most significant aetiologic factor for skin carcinoma is exposure to sunlight (UV). While squamous cell carcinomas appear strongly related to cumulative sun exposure, the link between sun-exposure and risk of BCC is more complex. Sun exposure in childhood and recreational sun exposure seem to be critical in the development of BCC in adult life [12-14]. In 1996, Rosso *et al.* [15] reported that the risk of developing a BCC exhibited a 2-fold increase of risk for lower exposure (8,000-10,000 cumulated hours in a lifetime) but with a plateau and a slight decrease of risk for the highest exposures (100,000 cumulated hours or more). However, a recent case control study suggested that sun exposure is associated with both BCC and SCC risk regardless of the pattern in which the exposure was received (i.e. intermittent *vs* continuous) [16].

Furthermore, in a systematic review and meta-analysis Bauer *et al.* [17] recently reported that outdoor workers are at a significantly increased risk for BCC and this risk should be taken into account for effective prevention strategies.

Phenotypical factors including fair skin, red or blond hair, light eye colour that influence sensitivity to UV are also independent risk factors [4]. Additionally, radiation, arsenic, psoralen and UVA exposure can participate in BCC development [4]. Immunosuppression, such as that observed in organ transplant recipients (OTR), also increases the risk of NMSC. Although the risk is much higher for squamous-cell carcinoma (SCC), with a 1:4 BCC/SCC ratio, the risk of development of BCC in OTR is also estimated to be increased by 10 [18-21].

Genetic factors also predispose to BCC. This is highlighted by the development of multiple BCC in Gorlin's/naevoid basal cell carcinoma syndrome (NBCCS) patients, who have a germline mutation in the PATCH1 gene, which encodes for the patched protein involved in the patch sonic hedgehog pathway controlling embryonic development and is downregulated in most normal adult tissues. However, the patch sonic hedgehog pathway seems to play a limited role in adult homeostasis [22, 23]. Loss of the second allele of PATCH in BCC tumours in Gorlin's patients is thought to occur according to the two-hit hypothesis of Knudson [24]. However, some other mechanisms of inactivation, including haplo-insufficiency or dominant negative effect, have also been reported [25]. Almost all sporadic tumours are thought to be driven by activation of the sonic hedgehog pathway, through inactivating mutation of PATCH1 or activating mutations of smo or HH [26, 27]. Other genetic diseases can predispose to the formation of BCC [28]. Among them the most well-known is xeroderma pigmentosum, which is due to germline mutation in DNA repair genes. These patients develop multiple tumours, including BCC but also melanoma and SCC, and often at an early age. Other more common genetic traits may predispose to NMSC including gene polymorphisms in the DNA repair gene, Melanocortin 1 receptor (MC1R) gene, or even the patch gene, among others [29-35].

Socioeconomic status and BCC

A recent paper from Denmark has suggested that high socioeconomic status, measured by both education and disposable income, was strongly associated with a higher risk of BCC, which was not the case for SCC [36]. This finding most probably reflects different patterns of sun-exposure related to the socio-economic status.

Cell of origin and molecular pathway of transformation

The cell of origin for BCC is still not clearly known. Whereas it was long thought to arise from the hair follicle bulge stem cell [37], a recent paper claimed that BCC stem cells were located in the interfollicular epidermis and in the infundibulum, and not in the hair bulge [38]. It can be hypothesized that different stem cell compartments can be targeted, according to the carcinogenic agent involved.

Diagnosis

French guidelines are the only ones that have defined different clinical and histological subtypes of BCC. According to the French working group, BCCs should be divided into three clinical and four histological subtypes. Clinical subtypes include nodular, superficial and morpheaform. Nodular BCC presents as a papule or a nodule with overlying telangiectasias. The superficial type presents as a flat, scaly, erythematous, well-demarcated patch or plaque. The morpheaform type appears as an indurated, scar-like whitish plaque with indistinct borders. Pigmentation or ulceration can be observed in all these forms. The fibroepithelial tumour of Pinkus is considered by some authors to be a rare anatomic and clinical form of BCC [2]. The four histological variants that are recognized are: nodular, superficial, infiltrating and morpheaform. Two additional histological forms have also been identified:

– Metatypical BCC: This is defined as a BCC that includes squamous carcinomatous differentiation. Classifying this lesion as a histological subtype of BCC or as a transitional form with SCC remains controversial.
– Mixed or composite carcinoma: This is defined as a combination of a BCC with a SCC, each component being histologically clearly distinguishable.

Aggressive histological subtypes include infiltrating (or micronodular), morpheaform and the rarer metatypical basosquamous forms. Perineural invasion also seems to be a histological sign of aggressiveness [39].
The diagnosis of BCC is suspected clinically but is usually confirmed by histology (except for small typical lesions where an excisional biopsy can be performed). The biopsy confirms the diagnosis and can help to define the pathological subtype. However, appreciation of the histological subtype is more reliably made upon examination of the whole tumour. A combination of histological subtypes may be present, in which case the subtype of the least favourable component is the one to be adopted. In a review of 1039 consecutive cases of BCC, Sexton *et al.* [40] found that 38.6% are mixed, 21% are nodular, 17.4% superficial and 14.5 % micronodular.
Variations exist in histological subtypes by body site [41]. A large cohort study (n: 13,457) in which only three different histological subtypes (superficial, nodular and morpheaform) were considered, found that superficial lesions are more frequent in men on the trunk, whereas nodular and morpheaform lesions are more frequent on the face and in women.

Dermoscopy

Dermoscopy may be useful for the clinical diagnosis both of pigmented and non-pigmented BCC. A retrospective study of 609 BCC demonstrated that these lesions show a large spectrum of global and local dermoscopic features [42]. Expert observers provided an accurate (sensitivity: 97%) and reliable (K: 87%) dermoscopic diagnosis of BCC, although significant differences in specificity (p: 0.0002) and positive predictive value (p: 0.0004) were found. Classic BCC patterns include arborizing telangiectasias, blue/grey ovoid nests, ulceration, multiple blue/grey globules, leaf-like areas and spoke-wheel areas. Non-classic BCC patterns include fine superficial telangiectasias, multiple small erosions, concentric structures and multiple in-focus blue/grey dots. Arborizing telangiectasias, leaf-like areas and large blue/grey ovoid nests represent the most reliable and robust diagnostic dermoscopy parameters.

Emerging techniques in digital imaging diagnostics

Over the past decade, novel non-invasive diagnostic techniques, including *in-vivo* reflectance confocal microscopy (RCM), multiphoton microscopy (MPT) and optical coherence tomography (OCT), have become available for the *in-vivo* diagnosis of skin tumours at near-histological resolution. Of these techniques, RCM has shown high diagnostic accuracy for the diagnosis of BCC, with a sensitivity of 100% and a specificity of 88.5% in a large multicentre study [43]. Although MPT and OCT also show good histomorphological correlation of BCC features, the diagnostic accuracy of these techniques still needs to be determined in larger studies [44, 45].

Evolution

Most primary BCC can easily be treated by surgery or, for superficial subtypes, by non-surgical methods. Recurrent BCC need to be treated with wider margins, up to 15 mm. The risk of recurrence increases with tumour size, poorly-defined margins, aggressive histological subtype and previous recurrences. Additionally, some tumours can destroy adjacent structures (muscle, bone, cartilage etc). This local destruction is often due to lack of treatment of the tumour for many years, but in rare cases, some tumours can also be rapidly destructive. These BCCs are called locally advanced BCC. Imaging (RMN or scanner) may be necessary for evaluation of advanced tumours. When multiple local recurrences make surgery and/or radiotherapy not feasible, or when invasion of extra-cutaneous structures occurs, an interdisciplinary approach is recommended to manage these patients. Metastasis very rarely occurs, with an incidence ranging from 0.0028 to 0.55% of cases. Metastasis is most often observed in the regional lymph nodes, followed by the lungs and liver. The prognosis of metastatic BCC is very poor, with a mean survival ranging from 8 months to 3.6 years [46].

Definition of prognostic groups

The prognostic groups of BCC are defined according to the likelihood of cure, which depends on several factors. These prognostic groups help to select the treatment options.

Prognostic factors

– ***Tumour size*** (increasing size confers higher risk of recurrence).
– ***Tumour location*** (high-risk zones include the nose, periorificial areas of the head and neck, intermediate-risk zones are the forehead, cheek, chin, scalp and neck, and low-risk zones are the trunk and limbs).
– ***Definition of clinical margins*** (poorly-defined lesions are at higher risk).
– ***Histological subtype*** (aggressive forms: morpheaform, infiltrating and metatypical form) or histological features of aggression: perineural invasion.
– ***Failure of previous treatment*** (recurrent lesions are at higher risk).
– ***The role of immunosuppression*** as a prognosis factor is not clear.

According to these prognostic factors, guidelines have proposed the concept of low- and high-risk tumours [1-3].

Table 1. Prognostic groups of BCC (according to Dandurand *et al.* –[2]).

Classification of BCC according to risk for recurrence		
Low risk	**Intermediate risk**	**High risk**
Superficial primary BCC	**Superficial recurrent BCC**	**Clinical forms:** *Morpheaform or ill-defined*
Nodular primary BCC when : *<1 cm in intermediate risk area* *<2 cm in low risk area*	**Nodular primary BCC when :** *<1 cm in high risk area* *>1 cm in intermediate risk area* *>2 cm in low risk area*	**Nodular primary BCC when:** *>1 cm in high risk area*
Pinkus tumor BCC		**Histological forms:** *Aggressive* **Recurrent forms** (apart from superficial BCC)

This classification is based on data from large retrospective studies that have defined prognostic factors involved in the risk of recurrence. However this classification has not been validated in prospective studies. High-risk BCC are tumours harbouring or 'that present with' one or more poor prognostic factors. Low-risk tumours are superficial BCC (sBCC), Pinkus tumour and small nodular BCC on intermediate- or low-risk zones. French guidelines have defined a third group: intermediate prognosis group, to separate recurrent sBCC from other recurrent BCC, and some nodular BCC according to size and location, whose risk of recurrence seems lower [2] (*table 1*).

Treatment options

Surgical excision

Surgical removal of the tumour with a variable margin of clinically-uninvolved surrounding skin is the standard treatment of BCC to which other techniques should be compared [47]. This procedure allows the histologic assessment of the whole tumour and of the surgical margins.

The width of surgical margins is variable; it depends on some tumour characteristics and the local anatomy, which influence the degree of subclinical extension of the tumour [48-51]. The tumour size is crucial and a BCC with a diameter less than 2 cm would need a minimum margin of 4 mm to totally eradicate the tumour in more than 95% of cases [52]. However, the margins are also different for the different types of BCC and also depend on whether the tumour is primary or recurrent or incompletely excised, and on the presence or absence of perineural invasion [53, 54]. For example, a high-risk primary BCC of 2 cm would need a safety margin of at least 13 mm for relative certainty of removal of the tumour in 95% of cases [55]. In all cases, particularly for lesions on the head, the deep margins should reach the fascia, perichondrium or the periosteum, wherever appropriate. Particularly in nodular and sBCC, the use of curettage prior to excision of primary BCC may increase the cure rate by defining more precisely the true limits of the lesion [56]. Examination of excision margins can be performed using different techniques. The most common technique is by using postoperative vertical (bread-loaf) sections obtained from formalin-fixed, paraffin-embedded tissue [52]. The main limitation of this technique is that less than 1% of the tissue margins are examined and thus no certainty about completeness of excision can be obtained in cases where no tumour cells are found on the section margins [57]. This is especially important in those tumour types displaying an irregular lateral and deep infiltration growth pattern, i.e. infiltrative or morpheaform BCC. It is advisable to mark the excised tumour with a suture or tissue dyes for subsequent orientation. Before closure of the defect, particularly in cases with complex reconstruction, information about completeness of excision is mandatory. A recent meta-analysis searched for the best surgical margins for BCC through reading 89 articles referring to 16,066 lesions. Recurrence rates for 5, 4, 3 and 2 mm surgical margins were 0.39, 1.62, 2.56, and 3.96%, respectively. The authors concluded that for lesions of 2 cm or smaller, non-morpheaform, a 3 mm surgical margin was sufficient to obtain 95% cure rates. In addition, they showed that a positive margin had an average recurrence rate of 27% [58]. Surgical excision is very effective for primary BCC treatment. Recurrence rates vary from less than 2% to 8% at 5 years after surgery [59-61]. Remarkably, one-third of the recurrences appear in the first year, 50% of the recurrences occur between the second and the fifth year of follow-up; up to 18% of recurrent BCC may present even later [61, 62]. Cure rates for recurrent BCC are inferior to those of primary lesions, with figures of 11.6 to 17.4% for re-recurrence at 5 years [61, 63, 64]. Very few randomised trials are available for surgery. Neuman *et al.* [64] compared a group of patients treated by surgical excision with a group of patients treated by Mohs surgery. Their results showed a significantly lower recurrence rate at 5 years for recurrent BCC treated with Mohs surgery (2.4%) compared to surgical excision (12.1%); whereas the difference is not significant for primary BCC (2.1 and 4.1% respectively).

Evidence level (3)

Surgical excision is a good treatment for primary BCC (Strength of recommendation: A, quality of evidence I)

Incompletely excised BCC

Incomplete excision, where one or more surgical margins are involved with tumour, has been reported in 4.7 to 24%

of excisions, influenced by surgical experience, anatomical site, histological subtype of tumour and the excision of multiple lesions during one procedure [65, 66]. Besides, these percentages might be underestimated because of the histopathological analysis procedure itself. This reflects the extent of subclinical tumour spread that is not completely predictable by the above-discussed features. Recurrence after surgery of incompletely-excised BCC is not as high as might be expected; it ranges from 26 to 41% after 2 to 5 years of follow-up, and the maximum number of tumour recurrences has been detected in series with a predominance of morpheaform BCC [67-69]. An absence of residual tumour has been observed in the surgical specimens in half of BCCs after re-excision due to positive surgical margins [70, 71]. However, the risk of further recurrences among tumours that have recurred once is over 50%, especially when both lateral and deep margins are involved [70, 72]; besides, the treatment of lesions in some areas, e.g. the face, can be difficult and regrettably there is no single characteristic that defines which cases will have no remaining tumour cells and thus be candidates for clinical surveillance [73]. Some incompletely-excised lesions may present with a more aggressive histological subtype when the lesion recurs [74]. Therefore, data support re-treatment of the tumour, particularly when it involves the midface or other risk sites. Special attention should be paid to lesions with surgical defects repaired with skin flaps or grafts, those with a deep surgical margin involved and those of aggressive histological subtypes [75]. Mohs micrographic surgery should be considered in the latter situations [76]; however, clinical follow-up could also be considered for non-aggressive, small lesions on the trunk.
Lesions with surgical margins that are extremely close to the tumour should be managed as incompletely excised.

Evidence level (3)

Tumours which have been incompletely excised, especially high-risk BCC and lesions incompletely excised at the deep margin, are at high risk of recurrence and should be re-excised (Strength of recommendation A, quality of evidence II-i)

Micrographic surgery

Mohs micrographic surgery, most commonly known as Mohs surgery (MS), is a specialized surgical procedure that examines the margins using intraoperative frozen sections. With MS, serial sections are excised with precise mapping of the operation field so that the whole undersurface and outer edges of the tumour can be examined microscopically. This technique allows the surgeon to take additional stages only from those areas with persistent foci of tumour and thus it spares as much uninvolved skin as possible [77]. The procedure begins with a precise drawing of the tumour, followed by careful assessment and marking of the clinical borders. The tumour is then often debulked with a curette or scalpel. Then the curetted wound, including a small margin of epidermal layer, is excised at an angle of 45°. The specimen is cut into small parts and the cutting edges are coloured to allow correct orientation of the removed tissue. After careful flattening by pressure, horizontal sections are obtained, including the whole resection margin (both the deeper and epidermal layers). This surgical technique results in extremely high cure rates, including in high-risk lesions, with maximal preservation of uninvolved tissues [78]. As disadvantages, MS is time-consuming and needs special laboratory processing and microscopic examination.
According to several retrospective studies, the overall cure rates for BCC treated with MS range from 97-99% for primary tumours and 93-98% for recurrences, after 3 to 5 years of follow-up [62, 63, 79-83]. Some studies based on large series with BCC on specific locations (such as the ear or the eyelid) that have been treated with MS surgery, have shown similar cure rates [84, 85]. Two prospective studies from Australia reported a 5-year cure rate of 100% and 92.2% for primary and recurrent tumours, respectively, on the periocular region [86] and 98.6% for primary and 96% for recurrent BCC on the head and neck [87].
MS has been prospectively compared with surgical excision for the treatment of BCC of the face in a series of 408 primary and 204 recurrent BCCs [64]. The authors concluded that MS might be considered cost-effective for recurrent, but not for primary BCCs, since the difference in recurrence rates was not statistically significant for primary tumours. However, due to the design of the study and the fact that some patients moved from one arm to the other, a clear selection bias was present and there were much more aggressive tumours in the group of patients treated with MS than in the group treated with surgical excision. According to some authors, MS is cost-effective compared to surgical excision [88]. In addition, other authors have also shown that MS does not generate significantly higher costs than conventional surgery at least in selected patients with high-risk facial BCCs [89].

Evidence level (3)

Mohs micrographic surgery is a good treatment for high-risk BCC and for high-risk recurrent BCC (Strength of recommendation : A, quality of evidence I)

Curettage and electrodesiccation/cautery

This technique consists of the curettage of the tumour using curettes of several sizes in order to minimize removal of surrounding tissue. The curettage is applied firmly and used in multiple directions over the tumour and immediate adjacent skin. The wound is desiccated (coagulated), with the electrode making direct contact with the tissue. The entire process may be repeated one or two more times depending on the lesion characteristics. However, there is no consensus on the best protocol.
This technique is particularly useful in friable tumours that are not embedded in a fibrous stroma [90]. Therefore, it might be considered in nodular or superficial BCC but not in the aggressive subtypes of BCC, such as morpheaform, infiltrating, micronodular and recurrent tumours, which are usually not friable.

Residual tumour can be found if wounds created after curettage and electrodesiccation are immediately re-excised, and they are much more frequently found on head and neck (47%) than the trunk or limbs (8.3%) [91].
Overall 5-year recurrence rates for primary tumours treated with this technique vary from 3.3% in low-risk sites to 18.8% in high-risk ones [62, 92]. The rates are higher for recurrent BCCs, with figures of 60% [63]. However, these high rates might be due to the size and characteristics of the BCCs treated during the period evaluated in the studies; much lower rates are expected in carefully-selected tumours [93, 94].

Evidence level (3)

Curettage and cautery is a good treatment for low-risk BCC (Strength of recommendation: A, Quality of evidence II-iii)

Cryosurgery

The basic concept of cryosurgery is based on the induction of selective necrosis by using cryogenic materials. Each freeze/thaw cycle leads to changes in tissue texture or even to destruction. Prior to the freezing cycles, the tumour can be curetted carefully to diminish its mass. Liquid nitrogen is applied to the clinically apparent lesion. It uses the effects of extreme cold (tissue temperatures of -50 to -60 °C) to achieve deep destruction of the tumour and surrounding tissues. No single standard technique exists. Both open and closed spray techniques, with either single or multiple freeze/thaw cycles) have been proposed. The main disadvantage is the lack of histological control for the completeness of treatment.
Double freeze/thaw cycles are generally recommended for the treatment of facial BCC, although superficial lesions on the trunk may require only a single treatment cycle. Wounds usually heal with good cosmetic results, although two cycles of 20 seconds freeze and 60 seconds thaw are associated with significantly worse cosmetic outcome than standard surgical excision for superficial and nodular BCCs of the head and neck [95]. Recurrence rates vary greatly (8-40%), but in selected lesions and in expert hands, they may be as low as 1% [96-99].

Evidence level (3)

Cryosurgery is a good treatment for low-risk BCC (Strength of recommendation: A, Quality of evidence II-ii)

Laser

Carbon dioxide (CO_2) laser ablation is an infrequently used treatment for BCC. This procedure provides a bloodless field, minimal postoperative pain and good postoperative appearance without scar formation. Therefore, it may be considered when a bleeding diathesis is present, as bleeding is unusual when this laser is used. However, the main disadvantage of this technique is the great variability in reported recurrence rates [100].

Evidence level (3)

Carbon dioxide laser ablation may be effective in the treatment for low-risk BCC (Strength of recommendation: C, Quality of evidence III)

Medical treatments

Medical treatments can be indicated for low-risk BCC. Their main advantages are good cosmetic outcomes, preservation of surrounding tissue and potential for home application.

5-fluorouracil

Although 5-fluorouracil (5-FU) has been widely used on actinic keratosis and *in situ* SCC, there are only a few studies investigating its use in BCC. In the first one [101], the cream was applied twice daily for 11 weeks with 90% clearance observed 3 weeks after treatment but no clinical follow-up was provided. However, a recent, single-blinded, non-inferiority, randomised, controlled trial from the Netherlands compared the use of 5-FU (twice daily for 4 weeks) with imiquimod cream (once daily, five times a week for 6 weeks) and photodynamic therapy (PDT) (two sessions with an interval of 1 week) also in sBCC [102]. This study demonstrated that topical 5-FU is non-inferior to PDT in a direct head-to-head comparison and therefore it can be considered as a therapeutic option for this type of BCC.

Evidence level (3)

5-Fluorouracil appears effective for the treatment of superficial BCC (Strength of Recommendation A, Quality of Evidence I)

Imiquimod

The major biological effects of imiquimod or (1-2methylpropyl)-1 H-imidazo (4,5c) quinolin-4amine) are mediated through agonistic activity towards toll-like receptors (TLR) 7 and 8 and consecutively, activation of Nuclear Factor kappa B (NFkB). The result of this activity is the induction of pro-inflammatory cytokines, chemokines and other mediators, leading to activation of antigen-presenting cells and other components of innate immunity and, finally, the mounting of a profound T helper (Th1)-weighted antitumoural cellular immune response. Moreover, independently of TLR-7 and TLR-8, imiquimod appears to interfere with adenosine receptor signalling pathways and also induces apoptosis of tumour cells at higher concentration [103]. Imiquimod may also exert tumour suppression function via induction of Notch signalling [104].
The side-effects of imiquimod are mainly local site reactions, including erosion, ulceration and induration, as well

as itching, burning or pain, affecting from 58 to 92% trial participants [105]. A positive correlation was shown between the severity of local site reaction and clinical response rate [106]. In the 2007 Cochrane review [107], all studies (except one, [109]) were judged to be of medium quality. It was also reported that, in a pooled analysis of 5 studies, testing higher and lower dosing regimens for BCC (not only sBCC), there was a 50% reduction in the risk of early treatment failure with the more frequent dosing regimen than the less frequent. Many different treatment regimens were used but clinical utility as a topical treatment for treating sBCC has been established when used 5 or 7 times per week for six weeks [108, 109]. 5 times per week for 6 to 12 weeks is now currently approved in the EU and the USA for the treatment of sBCC <2 cm in diameter on the neck, the trunk and the extremities (excluding the hands and feet) in immunocompetent adults. The following text mostly refers to this treatment regimen.

Concerning sBCC, pooled results collecting prospective, retrospective and case studies using SORT recommendation taxonomy showed that, in class A studies, within a group of 515 patients treated at least daily and for six to 12 weeks, 81% of patients were histologically tumour-free at six or 12 weeks [110]. These studies did not include tumours in high-risk locations (within 1 cm of the hairline, eyes, nose, mouth or ear, or tumours in the anogenital, hand, foot regions) or tumours >2 cm^2 [111].

Studies including 5-year follow-up showed similar results: 5-year follow-up results were available in one study that included 182 patients and showed that the estimated probability of overall treatment success was 77.9% after once daily application five days per week for six weeks. When most patients had completed the 12-week visit with a histological evaluation, the probability of overall treatment success reached 80.9% [103]. Most recurrences occurred early, indicating that careful follow up is warranted during the first year of treatment. Another 5-year follow-up study showed an 80.9% overall estimate of treatment success at 60 months, but recurrent tumours were observed during the first 24 months of follow-up [112].

Concerning nodular BCC, the larger study included 167 patients treated with multiple regimens. Tumours within 1 cm of the hairline, eyes, nose, mouth and ear were also excluded and tumour size ranged from 0.5 to 1.5 cm^2 total area. This study reported 76% histological clearance at six weeks when applying imiquimod daily for 12 weeks and 42% histological clearance at 8 weeks when applying the drug twice daily three days per week for 10 weeks.

One study, also including infiltrative BCC treated with imiquimod, showed 5-year clearance rates of 63 and 56%, depending on the regimen used [113, 114].

The main conclusion from these initial studies was that imiquimod can be a first-line treatment of superficial (but of neither nodular nor infiltrative) BCC not located in high-risk locations.

The more recent literature also proposes the use of imiquimod for specific body sites (the face and specifically the eyelids) in combination with other non-surgical treatments such as photodynamic therapy and cryosurgery, or for locally recurring lesions, even for larger lesions in combination with other therapies or even MS, and finally in specific clinical settings, such as in immunosuppressed patients.

Interestingly, a comparative cost-effectiveness study of surgery and imiquimod 5% cream showed that the latter is a cost-effective alternative to excision surgery in patients with sBCC [115].

Evidence level (3)

Topical Imiquimod appears effective in the treatment of primary small superficial BCC (Strength of recommendation A, Quality of evidence I); it may have a role in the treatment of primary nodular BCC (Strength of recommendation C, Quality of evidence I)

Photodynamic therapy

Photodynamic therapy (PDT) is licensed for the treatment of some BCC in many European countries. Many studies used 5-aminolaevulinic acid (ALA) as the prodrug, applied under occlusion for 4-6 hours, but more recent studies use its lipophilic methylester, methyl-aminolaevulinate (MAL), with a licensed protocol for 3 hour incubation between application and illumination by red light (75 J/cm^2 570-670 nm or equivalent dose of narrowband red light) and repeat treatment after 7 days. Various light sources can be used, although practitioners now typically use narrowband red LED sources, to maximize the depth of action by targeting the 630/635nm peak of protoporphyrin IX and hence to promote the photodynamic reaction.

MAL-PDT cleared 92-97% of sBCC in two pivotal multicentre randomized comparison studies, with recurrence rates of 9% in each study at one year [116, 117]. PDT was as effective as cryotherapy with equivalent 5-year recurrence rates of 22% and 20% respectively, despite a possible suboptimal PDT protocol with a single initial treatment followed by two further sessions at 3 months. Cosmetic outcome was superior following PDT. In the 1-year comparison study of PDT (two treatments seven days apart, repeated at three months if required) with surgery, no lesions recurred with surgery but cosmetic outcome was again superior with PDT [117]. A weighted initial clearance rate of 87% was reported for sBCC treated by ALA-PDT in a review of 12 studies [118]. No statistically-significant difference in response was observed when ALA-PDT was compared with cryotherapy for both superficial and nodular BCC, although healing times were shorter and cosmesis superior with PDT [119]. Clearance at three months of 91% of primary nodular BCC following MAL-PDT using the currently approved protocol has an estimated 5-year sustained lesion clearance response rate of 76% [120, 121]. PDT was inferior to surgery when recurrence rates were compared (91% *vs* 98% initial clearance, 14% and 4% 5-year recurrence). Histologically-confirmed response rates were observed in two randomized studies of MAL-PDT for nodular BCC, using the standard protocol. Treatment site excisions (at six months for responders) revealed an overall clearance rate of 73%, most effectively for facial lesions, where 89% achieved complete histological response [122]. In a follow-up study of 53 BCCs <3.5 mm thick treated by ALA-PDT using the penetration enhancer dimethylsulfoxide, 81% of sites remained tumour-free at 72 months [123].

Nodular subtype and location on the limbs were predictors of failure in a large multicentre series of BCC treated by MAL-PDT, with an 82% clearance rate for sBCC but only 33% of nodular lesions clearing following standard protocol [124].

Gentle removal of overlying crusts/scales is commonly performed for sBCC. Some have observed reduced efficacy if lesions are not debrided prior to PDT. Lesion preparation is probably more important when treating nodular BCC with recommended practice to gently remove overlying crust with a curette/scalpel in a manner insufficient to cause pain and thus not requiring local anaesthesia. A small comparative study found no difference in efficacy between ALA and MAL-PDT. Residual tumour was more often observed in nodular BCC that had not been debulked [125].

Discontinuous illumination using two light fractions of 20 J/cm^2, then 80 J/cm^2 four and six hours after application, has improved the responsiveness of sBCC to ALA-PDT compared with single illumination (97% *vs* 89% clearance rate 12 months after therapy), but is dependent on protocol, with a low initial dose important [126]. In a further study with an average follow-up of two years, the same dose schedule achieved complete lesion clearance of 97% sBCC and 80% of nodular BCC [127]. An alternative fractionation protocol of two doses of 75 J/cm^2 at four and five hours was associated with an initial 94% clearance rate for nodular BCC, but with a cumulative failure rate of 30% by three years [128]. This response difference with fractionated light has yet to be replicated with MAL-PDT.

PDT has been used to treat patients with Gorlin syndrome/NBCCS, with a large cohort of 33 patients treated by topical or systemic PDT, depending on whether lesions were less or greater than 2 mm in thickness as assessed by ultrasonography [129]. A recent short report found that MAL-PDT for NBCCS improves patient satisfaction and reduces the need for surgical procedures [130].

Topical PDT has been used to treat BCC in immunosuppressed patients with ALA-PDT clearing 30/32 facial tumours (including 21 BCC) in 5 OTR after one to three treatments [131]. PDT has also been assessed for its ability to prevent/delay new cancer development in OTR. A single treatment of MAL-PDT delayed (9.6 *vs* 6.8 months for control sites) the development of new lesions (BCC, actinic keratosis, keratoacanthoma, SCC or warts) in an open intrapatient randomised study of 27 renal OTR with 2-10 skin lesions in two contralateral 5 cm areas [132]. By 12 months, 62% of treated areas were free from new lesions compared to only 35% in control areas, with no new BCC or SCC observed during this follow-up time.

Pain/burning sensation is often experienced during PDT; it usually develops within minutes of commencing light exposure and is more likely when large lesions and fields are treated, with treatments to the face and scalp more likely to be painful [133]. Pain may be less in BCC compared with actinic keratosis, although this may be due to the area of treatment. Greater pain has been observed with increasing lesion size [133, 134]. Most patients tolerate PDT without anaesthesia but a variety of methods of pain relief can be provided, including lesional injected anaesthesia and nerve blockade. Topical anaesthetics have shown no benefit but a simple cold-air fan can reduce discomfort. Using a device to blow air at a temperature of -35 °C reduced pain duration and severity in a study of ALA-PDT for Bowen's disease and BCC [135]. Modifying the method of delivery of PDT can reduce pain, with low intensity ambulatory light less painful than delivering PDT using conventional light sources [136]. PDT is otherwise well tolerated, although localised erythema and oedema are common, with erosion, crust formation and healing over 2–6 weeks, and treatment sites can remain light-sensitive for up to 48 hours. The cost of topical PDT depends on several variables but a detailed analysis of cost per full responder calculated that MAL-PDT was better value for money in BCC compared with excision over five years (to allow time for recurrences) [137]. In a real-life practice study, total cost of care per patient was 318€ for nodular BCC and 298€ for sBCC, consistent with the predicted cost-effectiveness in the above model [138].

Topical PDT is most appropriate for primary superficial and thin nodular BCC in patients with large or multiple lesions and those in sites of high cosmetic importance, although responsiveness is influenced by tumour thickness [139].

Evidence level (3)

PDT appears effective for the treatment of superficial BCC (Strength of Recommendation A, Quality of Evidence I) and for the treatment of nodular BCC (Strength of Recommendation B, Quality of Evidence I)

Radiotherapy

Radiotherapy (RT) is an efficient treatment modality in terms of local control of many clinicopathological forms of BCC. It requires prior histological confirmation of the diagnosis. It uses low-energy X-ray (particularly suitable for treating BCC), brachytherapy (for curved surfaces) or high-energy radiotherapy (photons or electrons) which penetrates deeper tissues, depending on the clinical presentation. However, given the superiority of surgery to control BCC and the fact that surgery is always more complicated on irradiated tissues, a multidisciplinary approach is recommended before starting RT to treat BCC.

Careful patient selection can result in very high cure rates; in a series of 412 BCCs treated with RT, 5-year cure rates of 90.3% were achieved [140]. In a prospective trial, where 93 patients with BCC were randomized to receive either cryosurgery or radiation therapy, the 2-year cure rate for the RT group was 96% [141]. Two reviews of all studies published since 1945 and 1947 showed overall 5-year cure rates of 90.2% and 91.3% respectively, following RT for primary BCC [142, 143]. RT can be used to treat even BCC overlying bone and cartilage, although it is probably less suitable for the treatment of large tumours in critical sites, as very large BCC are often both resistant and require radiation doses that closely approach tissue tolerance. However, the only study comparing surgery and RT showed that surgery should always be preferred for BCC of the face measuring <4 cm in diameter, as long-term follow-up shows recurrence rates of 0.7% for surgery and 7.25 % for RT [144]. RT is also not indicated for BCCs on areas subject to repeated trauma, such as the extremities or trunk, and for young patients, as the late-onset changes of cutaneous atrophy and telangiectasias may result in a cosmetic result

inferior to that achieved with surgery [145, 146]. It can also be difficult to use RT to re-treat BCCs that have recurred following RT. Modern fractionated dose therapy has many advantages but requires multiple visits. Late-onset fibrosis may cause problems such as epiphora and ectropion following treatment of lower eyelid and inner canthal lesions, where cataract formation is also a recognized risk, although this can be minimized by the use of protective contact lenses [147]. In the elderly, infirm patient, single-fraction regimens are still used, as the long-term cosmetic result of treatment is less of a concern. There is some evidence suggesting that BCCs recurring following RT may behave in a particularly aggressive fashion, although this may simply reflect the fact that these lesions were of an aggressive, high-risk type from the very beginning [148, 149]. A recent retrospective study on 148 patients (64 women/84 men; mean age, 69 years) with 175 BCC of different subtypes (103 nodular, 25 superficial and 47 sclerosing) treated with RT, found an overall 5-year recurrence rate of 15.8% (8.2% for nodular, 26.1% for superficial and 27.7% for sclerosing BCC). 86.4% of all recurrences occurred within three years following treatment. The authors concluded that sclerosing BCC was a risk factor for recurrence after RT. In contrast, excellent results were achieved for patients with predominantly nodular BCC [150]. A recent long-term analysis of the efficacy of a hypofractionated schedule for electron-beam therapy has shown for BCC (n: 332) an actuarial 3-year local recurrence-free rate of 97.6% for tumours treated with 54 Gy and 96.9% for those treated with 44 Gy. In view of the similar efficacy and patient's convenience of the hypofractionated schedule, the authors suggested that 44 Gy in 10 fractions could be regarded as the radiation schedule of choice [151]. RT has short-, medium- and long-term side effects (tissue necrosis, radiodermatitis, pigmentation) that can progress over time. Additionally, surgery is difficult for the treatment of BCC recurring after RT; besides, RT has long-term carcinogenic properties that can favour the development of secondary carcinomas. Accordingly, RT is contra-indicated in genetic syndromes predisposing to skin cancers such as the Nevoid Basal-cell carcinoma syndrome and Xeroderma Pigmentosum, and is not recommended: a) as first-line treatment if excision surgery is possible, b) in patients aged under 60 years, c) for morpheaform BCC, and d) on the ears, hands, feet, legs and genitalia.

RT (with minimum safety margins of 5-10 mm applied to the irradiated volume depending on tumour prognosis) should be reserved for cases where surgery is not possible because of contra-indications or patient's refusal). In these circumstances, the best indications are: a) BCC with incomplete excision, b) recurrent BCC, c) nodular BCC of the head and neck < 2 cm, and d) BCC invading bones or cartilage.

In BCC with perineural invasion, surgery and adjuvant radiotherapy (median dose 55 Gy) has provided a high local control rate (97%) [152].

Evidence level (3)

Radiotherapy is a good treatment for some primary BCC and for recurrent BCC (with the exception of recurrence following previous RT) (Strength of recommendation A, Quality of evidence I)

Chemotherapy

Chemotherapy has been used both for the management of uncontrolled local disease and for patients with metastatic BCC. Metastatic BCC is an extremely rare but rapidly fatal condition with a median survival time of only 8 months [153, 154]. No standard therapy for metastatic BCC or even for cases of locally advanced tumours exists. Due to the absence of randomized trials or even large case series, treatment is guided by anecdotal evidence or the availability of clinical trials. Published data suggest that platinum-based therapy can induce responses in metastatic BCC and should be considered first for such patients if treatment is warranted [155-157]. However, there are issues to be considered when deciding to begin therapy in these patients. Patients with BCC are often elderly and present significant comorbidities. Treatment with cisplatin requires adequate kidney function and is associated with important bone-marrow toxicity [157]. The duration of responses after platinum-based therapy varies; in the absence of randomized trials, the survival benefit and effect on quality-of-life of this treatment regimen is unclear, so before chemotherapy initiation all data should be taken into account.

Evidence level (3)

Presently no level of evidence supports the use of chemotherapy in the treatment of advanced BCC (Strength of recommendation: C, Quality of evidence IV)

Targeted therapies

In recent years, novel tumor-specific and pathogenesis-based molecules have been developed and are currently under investigation for the treatment of BCC [158]. They include several compounds that can be categorized into three groups: natural products (e.g. cyclopamine and its derivatives), synthetic Hh-signaling antagonists (e.g. GDC-0449 or vismodegib) and Hh-signaling modulators (e.g. vitamin D3 and tazarotene).

The Hedgehog (Hh) signaling pathway, which has a crucial role during morphogenesis and organogenesis, is a driver element in the pathogenesis of BCC. Indeed, inactivation of PTCH releases the inhibition of SMO allowing a cascade of downstream events such as transcription of Gli proteins and Hh target gene expression. Mutations of the PTCH1 gene are common in BCC of patients with Nevoid Basal-Cell Carcinoma syndrome (NBCCS) and in sporadic BCCs. Activation of the sonic hedgehog pathway is a driver element in the development of BCC. More rarely, activating mutations of SMO have been detected in sporadic BCC.

The first SMO antagonist discovered is cyclopamine, a naturally-occurring steroid alkaloid derived from the plant *Veratrum californicum,* California corn lily. It was initially observed that sheep eating lily plants containing cyclopamine during pregnancy gave birth to offspring with severe developmental defects such as holoprosencephaly and cyclopia.

In phase I clinical trials, patients affected by locally-advanced BCC (laBCC) and metastatic BCCs (mBCC) were treated with 150-270 mg/day of a synthetic SMO inhibitor (GDC-0449 or vismodegib) for a median of 10

months. The overall response rate was 60% in laBCC and 50% in mBCC [159, 160]. In a subsequent phase II trial that included 104 patients treated with vismodegib 150 mg once daily for a median of 7.6 months, the response rate was 42.9% in laBCC and 30.3% in mBCC [161]. In both phase I and II trials, the mean duration of clinical response was eight months. Notably, a significant decrease of the size of existing BCCs and reduction of newly developed BCCs were described in a double blind phase II trial on 41 patients with NBCCS treated with vismodegib for at least eight months [162]. Regression of palmoplantar pits and jaw odontogenic keratocysts was also observed in patients with NBCCS [162, 163]. The most common side effects were muscle spasms, dysgeusia, hair loss and fatigue.

Long-term use of vismodegib is limited by these side effects; indeed, almost half of NBCCS patients discontinue the drug because of them. Clinical studies are being developed to check if intermittent doses (on and off treatment protocols) can improve tolerance without reducing efficacy. The initial phase I study tested several doses and the lowest one (150mg/day) was retained for further studies. As far as we know, lower doses have not yet been tested. The mechanism of recurrence of BCC after treatment discontinuation as well as drug resistance is being studied. Vismodegib is currently licensed in the USA for the treatment of advanced BCC in adult patients and has received from European Medicines Agency a conditional marketing authorization for the treatment of symptomatic mBCC or laBCC inappropriate for surgery or RT.

Additional inhibitors of the Hh pathway that are being investigated in phase I/II clinical trials include systemic BMS-833923 (XL139) and topical LED225 in patients with NBCCS and in laBCC and mBCC (NCI clinical trial database).

Evidence level (3)

Anti-smo agents are effective against locally advanced or metastatic BCC (Strength of recommendation A, Quality of evidence II-i)

Future therapies

Ingenol mebutate

Ingenol mebutate (PEP005) is a diterpene ester extracted and purified from the plant *Euphorbia peplus*. It has been successfully used as a topical treatment for actinic keratosis [164]. The results of a phase I/II study showed that ingenol mebutate gel 0.05% applied to nodular and sBCC once daily for three consecutive days achieved 82% complete clinical response rate at one month and histological clearance in 57% of cases [160]. In another recent phase IIa trial, complete histological clearance was achieved in 38% and 63% of patients with sBCC treated with ingenol mebutate gel 0.05% for two consecutive days or at days 1 and 8, respectively [163]. Side-effects consisted of mild-to-moderate erythema, that may extend beyond the application site and may persist for some months, flaking/scaling, pain on treatment site, and headache [165, 166].

Evidence level (3)

Presently no recommendation can be made for ingenol mebutate gel 0.05% for the treatment of BCC.

Topical retinoids

Systemic retinoids have been used as chemopreventive agents in patients with BCC with rather controversial results and high recurrence rates observed after treatment discontinuation. One phase II study assessing tazarotene 0.1% gel, a topical receptor-selective retinoid, applied once daily for 12-24 months to BCCs located on the chest and back, is currently ongoing [http://clinicaltrials.gov].

Evidence level (3)

Presently no recommendation can be made for topical retinoids for the treatment of BCC.

Follow-up

There is no official consensus on either the frequency or total duration of follow-up of patients that have developed a primary BCC. However, long-term surveillance of patients having presented a BCC is advisable, especially for patients with high-risk and recurrent BCC, as is patient education regarding sun-protection measures and self-examination.

It has become clearer that such a practice is important as a patient who has been treated for a BCC is both at risk for the appearance of new primary lesions as well as for treatment failure and the appearance of local recurrence.

Concerning the appearance of new lesions, the NCCN 2011 guidelines state that 30-50% of NMSC patients will develop another NMSC within 5 years [167], that these patients are also at an increased risk of developing cutaneous melanoma [168], and suggest complete skin examination every 6-12 months for life.

The possibility of developing additional BCC after the appearance of a first tumour has been studied by several authors. McLoone *et al.* [169] found that patients diagnosed with BCC had an 11.6% risk of developing a new BCC in the first year and a 6.3% risk in the second year following treatment. Kiiski *et al.* [167] have recently shown that the 3-year cumulative risk of a subsequent BCC after a first tumour was around 44%. A review and meta-analysis of seven studies [171] assessing the risk of developing a second BCC reported that the 3-year cumulative risk ranged from 33% to 70% (mean 44%), representing an approximately 10-fold increase over the rate expected in a control population. The highest rates (60-70%) came from studies including large populations of patients with at least two (sometimes more) previous BCCs, suggesting that as the number of BCCs increases, so does the risk of developing more tumours. By contrast, patients with only their index BCC who remain disease-free for three years appear to have a decreased on-going risk of further BCC. There was no general agreement on particular factors that might confer a higher risk of subsequent BCC. Several other authors

have tried to identify specific factors associated with an increased risk of developing further BCC. Van Iersel *et al.* [172] identified a possible higher risk in older patients, those with multiple BCC at first presentation and those with an index tumour >1 cm in size. Others reported that the risk of subsequent BCC is greater if the age is above 60 years at presentation, the initial occurrence is on the trunk, is of superficial subtype and with male sex [173].
The risk of local recurrence of a treated BCC is an individual risk, based upon the tumour characteristics and the treatment used. Recurrence rates are higher in lesions that have already recurred in the past. As BCCs are slowly-growing tumours, recurrent disease may take up to 5 years to present clinically, with up to 18% of recurrent BCC presenting even later, making a long-term follow-up appear necessary for high-risk tumours [174]. This need is also confirmed by a review study showing that for primary (previously untreated) BCCs treated by a variety of modalities, less than one-third of all recurrences occurred in the first year following treatment, 50% appeared within 2 years, and 66% within 3 years [175].

It seems reasonable to have at least one follow-up visit for all BCC patients, to counsel them for sun-protection measures, to explain the risk of developing new lesions and to stress the importance of self-monitoring.
Ideally all patients presenting with BCC should be offered a lifelong follow-up yearly. However, as such a scenario is unfeasible for some public health systems, follow-up every 6-12 months for 3-5 years (if not lifelong) should be proposed to:
- patients who are at high-risk for recurrences
- those who have already been treated for recurrent BCC (increased risk of further recurrence following all types of treatment)
- those with a history of multiple BCC (significantly increased risk of further BCC)

In case of **metastatic** BCC, follow-up should be practised by a **multidisciplinar**y team at a frequency dictated by each individual case.

Prevention

The use of sunscreens to prevent the development of BCC is still a matter of debate, as controversial data have been reported so far [176, 177]. A recent systematic review [170] showed that, although regular sunscreen use may prevent SCC, it is unclear whether it can prevent BCC. Indeed, some studies showed no effect of sunscreen use on BCC prevention. In a case-control Italian study [178], the frequent use of sunscreens entailed a non-significant protective effect (OR 0.6, 95% CI 0.3-1.4) and a recent Brazilian case-control study carried out in subjects aged 18-80 years found no effect of sunscreen or protective clothing use on BCC risk [179]. Finally, two cohort studies did not show a decrease in SCC or BCC risk with sunscreen use after adjusting for skin phenotype and sun-exposure [180, 181]. In contrast, a protective effect of sunscreen use on BCC prevention has been suggested by several case-control and cohort studies, and in clinical trials.
Recent clinical trials [182-184] showed that individuals randomly-assigned to regular sunscreen use had a decreased risk for SCC after eight years of follow-up (RR 0.65, CI, 0.45–0.94) but no statistically-significant decreased risk for BCC. Notably, at eight years, a substantial proportion of participants had only passive follow-up with pathology records. Two additional case-control studies suggested a protective effect of sunscreen for BCC, although both used crude measures of sunscreen use and neither study adjusted for sun-exposure [185, 186].
A trend toward a lower risk of subsequent BCC was found in sunscreen users enrolled in an Australian randomized trial [187]. Gordon *et al.* [188] demonstrated that the use of sunscreens in Australia was a good strategy to prevent skin cancer and to lower costs associated with skin cancer management; moreover, it has been reported that patients with a history of BCC had fewer subsequent BCCs if they protected themselves from UV exposure [189].
A recent study on potential risk factors for sporadic BCC in a subset of young adults (19 to 40 years) showed that sunscreen use had a protective effect. The influence of sun-protective measures taken by parents during patients' childhood on BCC development was also evaluated and a protective effect was found, supporting that sun-protection during childhood prevents skin carcinogenesis [190]. The regular use of sunscreens may prevent the development of further BCCs in OTR [191]. Finally, sunburn avoidance has been shown to decrease the incidence of sporadic BCC [192].

Evidence level (3)

The use of sunscreens may protect from the development of subsequent BCC, but currently insufficient evidence supports the use of sunscreens in BCC prevention.

Conclusion

This review aims to present updated guidelines that include consensual expert definitions on various BCC types, prognosis and risk factors for BCC as well as recommendations for treatment reflecting current published evidence. The prognostic groups of BCC first presented by the French National Guidelines were defined according to the likelihood of cure and are based on data from large retrospective studies that have revealed prognostic factors involved in the risk of recurrence. Though this classification has not been validated in prospective studies, the experts participating in the BCC EDF guidelines subcommittee, after extensive discussions and review of the current literature, agreed unanimously to present them as such in order to help guide the choice of treatment. *Figure 1* shows a treatment algorithm with options according to the risk of recurrence of the tumour and *table 2* summarizes the treatment recommendations for primary, recurrent or incompletely-excised BCC, as well as for locally advanced and metastatic BCCn according to the existing evidence. We hope these tools

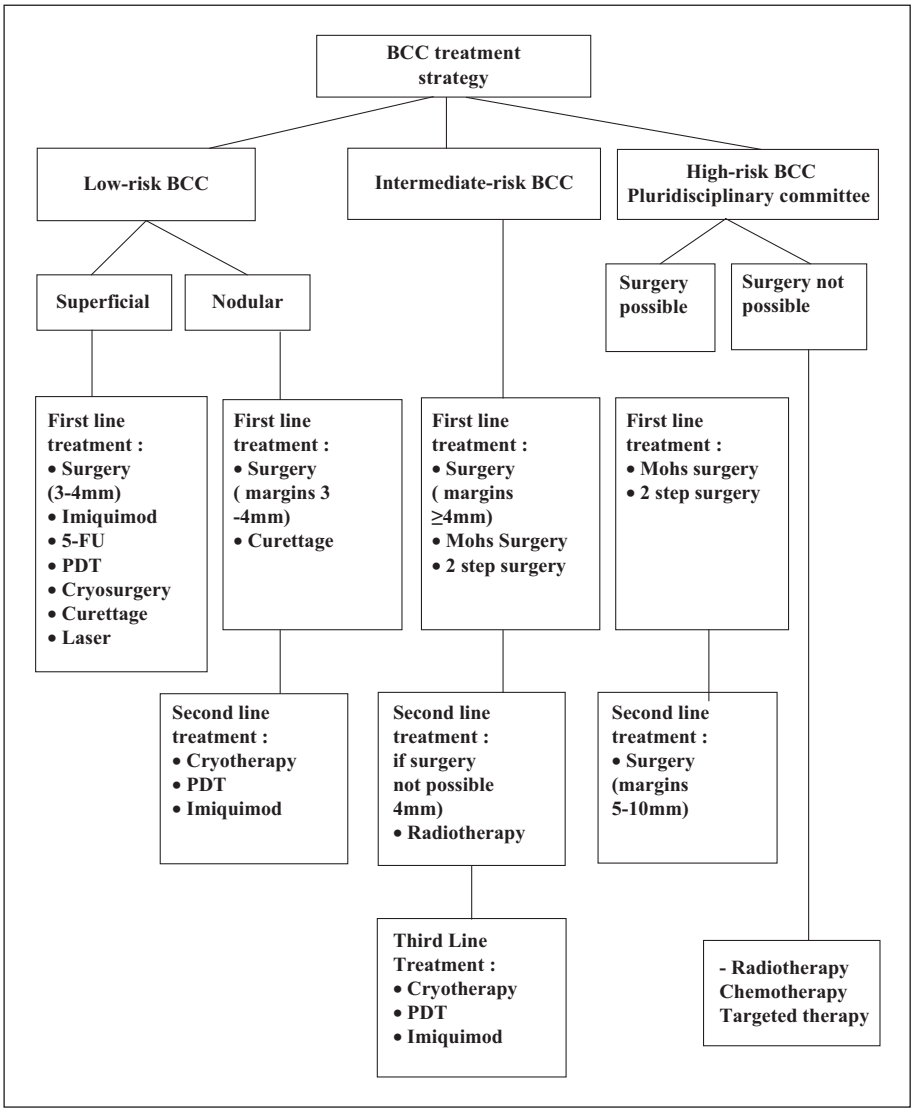

Figure 1. BCC treatment strategy.

Table 2. Therapeutic recommendations according to existing evidence

SUMMARY OF THERAPEUTIC RECOMMENDATIONS FOR BCC
A. PRIMARY BCC:
1. Surgery *- Surgical excision is a good treatment for primary BCC (Strength of recommendation: A, Quality of evidence I)* *- Mohs micrographic surgery is a good treatment for high-risk BCC (Strength of recommendation: A, Quality of evidence I)*
2. Ablative Treatments I. *Curettage and cautery (C/C)* *- C/C is a good treatment for low-risk BCC (Strength of recommendation: A, quality of evidence II-iii)* II. *Cryosurgery* *- Cryosurgery is a good treatment for low-risk BCC (Strength of recommendation: A, Quality of evidence II-ii)* III. *Carbon dioxide (CO2) laser ablation* *- CO_2 laser ablation may be effective in the treatment of low-risk BCC (Strength of recommendation: C, Quality of evidence III)*
3. Topical Medical Treatments I. *5-FU:* *- 5-Fluorouracil appears effective for the treatment of superficial BCC (Strength of Recommendation A, Quality of evidence I)* II. *Imiquimod:* *- Topical Imiquimod appears effective in the treatment of primary small superficial BCC (Strength of recommendation A, Quality of evidence I)* *- Topical imiquimod may have a role in the treatment of primary nodular BCC (Strength of recommendation C, Quality of evidence I)* III. *Ingenol Mebutate:* *- Presently no recommendation can be made for ingenol mebutate gel 0.05% for the treatment of BCC* IV. *Topical Retinoids:* *- Presently no recommendation can be made for topical retinoids for the treatment of BCC*
4. Photodynamic Therapy (PDT) *- PDT appears effective for the treatment of superficial BCC (Strength of Recommendation A, Quality of evidence I)* *- PDT appears effective for the treatment of nodular BCC (Strength of Recommendation B, Quality of evidence I)*
5. Radiotherapy *- Radiotherapy is a good treatment for certain primary BCC (Strength of recommendation A, Quality of evidence I)*
B. INCOMPLETELY EXCISED OR RECURRENT BCC:
1. Surgery *- Tumours which have been incompletely excised, especially high-risk BCC and lesions incompletely excised at the deep margin are at high risk of recurrence and should be re-excised (Strength of recommendation A, Quality of evidence II-i)* *- Mohs micrographic surgery is a good treatment for high-risk recurrent BCC (Strength of recommendation: A, Quality of evidence I)*
2. Radiotherapy *- Radiotherapy is a good treatment for recurrent BCC except if recurrence has followed previous RT (Strength of recommendation A, Quality of evidence I)*
C. LOCALLY ADVANCED OR METASTATIC BCC:
1. Chemotherapy *- Presently no level of evidence supports the use of chemotherapy in the treatment of advanced BCC (Strength of recommendation: C, Quality of evidence IV)*
2. Targeted Therapy *- Anti-smo agents are effective against locally-advanced or metastatic BCC (Strength of recommendation A, Quality of evidence II-i)*

will help clinicians with decision taking for BCC management, pending large prospective studies that will shed more light into BCC prognosis and response to different treatments. ■

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