European Dermatology Forum

Guideline on the Treatment of Basal Cell Carcinoma

Developed by the Guideline Subcommittee of the
European Dermatology Forum

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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 Dermatologist guidelines published in 2006 (2) and 2008 (3). These guidelines (S1 type) have been prepared by the BCC subgroup of the European Dermatology Forum (EDF)'s guidelines committee. It presents consensual expert definitions on various BCC types, prognosis and risk factors for BCC and treatment options reflecting current published evidence.

Introduction

Basal Cell Carcinoma (BCC) is the most common malignancy in the fair skin 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 possibility that it can invade and destroy local tissues. BCCs are a heterogenous group of tumours ranging from superficial to deeply invasive tumours than can be life threatening.

These guidelines aim at updating 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. Additionally there are marked geographical variations in incidence for NMSC. 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 (5). In South Wales, UK, the equivalent numbers are 128/105 male/female/100,000 inhabitants. In Girona, Spain, a recent study reported an age-adjusted incidence for BCC of 44.6 per 100,000 inhabitants (6). In the US age standardized yearly rates have been estimated at up to 407 BCC/100,000 inhabitants in men and 212 cases per 100,000 inhabitants in women (7). In Australia an incidence of as high as 2% per year has been reported in certain regions (4).

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(8). Additionally age incidence rates in the Netherlands was shown to increase approximately 3 fold from 40 to 148 per 100,000 in males and from 34 to 141 in females between 1973 and 2008 (9). In a study from Spain, for both sex age-adjusted incidence increased from 48.5 (1994-1995) to 60.5 (2004-05)(6).

A recent estimate of population-based incidence of first and multiple BCC in 4 European regions (Finland, Malta, Southeast Netherlands and Scotland) has been performed. Age incidence of first BCC was estimated to vary between 77 and 158 per 100,000 person years(10). This work showed that considering only the number of first BCC underestimates the total number of BCC in a given year. These authors have suggested that incidence of first

BCC should be multiplied by a factor 1.3 for an estimate of total numbers of patients diagnosed with a BCC in a given year.

Risk factors

The most significant aetiologic factor is sun exposure to UV. However the link between sun exposure and risk of BCC is complex. Sun exposure in childhood and recreational sun exposure seems to be critical in the development of BCC in adult life (11,12,13). In 1996, Rosso et al 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) (14). Intermittent exposure both occupational and recreational are thought to be responsible of BCC development. Furthermore, in a systematic review and meta-analysis Bauer et al have recently reported that outdoor workers are at significant increased risk for BCC (15) 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 response 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 patients (OTR) also increases the risk of NMSC. Although the risk is much more increased for squamous cell carcinoma(SCC), with a ratio 1BCC/4SCC, the risk of development of BCC in OTR is also estimated to be increased by 10 (16-17). The cumulative risk of developing additional NMSC in these patients is 70% and is even more pronounced in heart transplant/ liver transplant/ renal transplant (18, 19).

Genetics factors also predispose to BCC. This is illustrated by the development of multiple BCC in Gorlin's/ naevoid basal cell carcinoma syndrome (NBCCS) patients who have a germline mutation in the Patch 1 gene that encodes for the patched protein implicated in the patch sonic hedgehog pathway controlling embryonic development and cell proliferation in post natal life (20). Loss of the second allele of patch in BCC tumour of Gorlin's patients is considered to occur due to the two hit hypothesis of Knudson (21). However some other mechanisms of inactivation including haplo insufficiency or dominant negative effect have also been reported (22). In sporadic tumours more than 70% have alteration of the pathway (23). Other genetic diseases can predispose to the formation of BCC (24). 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 (25- 31)

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(32). 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 totally clear. Whereas it was long thought to arise from the hair follicle bulge stem cell (33), a recent paper has stated instead that BCC stem cells were located in the interfollicular epidermis and in the infundibulum but not in the hair bulge (34). 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 3 clinical and 4 histological subtypes. Clinical subtypes include nodular, superficial, and morpheaform. Nodular BCC presents as a papule or a nodule with overlying telangiectasia. 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 fibroepithelioma of Pinkus is considered by some authors to be a rare anatomical and clinical form of BCC (2).
The 4 histological variants that are recognized are: nodular, superficial, infiltrating and morpheaform .
Two other specific 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 squamous cell carcinoma remains controversial.
- Mixed or composite carcinoma: This is defined as a combination of a BCC with a squamous cell carcinoma, each component being histologically clearly distinguishable.

Aggressive histological subtypes are: infiltrating, morpheaform and more rare metatypic basosquamous forms. Perineural infiltration seems also to be a histological sign of aggressiveness (35).

BCC diagnosis is suspected clinically but is usually confirmed by histology (except for small typical lesions were an excision biopsy can be performed).

The biopsy confirms the diagnosis and can help to define the clinical subtype. However the appreciation of the histological subtype will always been more accurate on examination of the entire 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* found that 38.6 % are mixed, 21% are nodular, 17.4% superficial and 14.5 % micronodular (36).

There is variation in histological subtype by body site (37) A large cohort study (N= 13,457) in which only 3 different histological subtypes (superficial, nodular and morpheaform) were considered, has shown 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 (38) of 609 BCC demonstrated that these lesions show a large spectrum of global and local dermoscopic features. Expert observers provided an accurate (sensitivity: 97%) and reliable (K: 87%) dermoscopic diagnosis of BCC, although significant differences in specificity (P = .0002) and positive predictive value (P = .0004) were found. Classic BCC patterns include arborizing telangiectasias, blue/gray ovoid nests, ulceration, multiple blue/gray globules, leaf-like areas, and spoke-wheel areas. Nonclassic BCC patterns are fine superficial telangiectasia, multiple small erosions, concentric structures and multiple in-focus blue/gray dots. Arborizing telangiectasia, leaf like areas, and large blue/gray ovoid nests represent the most reliable and robust diagnostic dermoscopy parameters. In selected cases naked eye and dermoscopy, due to its high sensitivity, might be enough to start a non-surgical therapy.

Emerging techniques in digital imaging diagnostics

In the past decade, novel non-invasive diagnostic techniques including in-vivo reflectance confocal microscopy (RCM), multiphoton microscopy (MPT) und optical coherence

tomography (OCT) have become available for the in-vivo diagnosis of skin tumours at near histological resolution. Of these techniques, reflectance confocal microscopy (RCM) has shown high diagnostic accuracy for the diagnosis of basal cell carcinoma, with a sensitivity of 100% and a specificity of 88.5% in a large multicenter study (39). Although MPT and OCT also show good histomorphological correlation of BCC features, the diagnostic accuracy of these techniques still need to be determined in larger studies (40,41).

Evolution

Most primary BCC can be easily treated by surgical or non-surgical methods for certain subtypes. Recurrent BCC need to be treated more aggressively. Risk of recurrence increases with tumour size, poorly defined margins, aggressive histological subtype and previous recurrences. Additionally certain tumours can be locally more aggressive and 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. Both recurrent (except sBCC) and locally advanced BCC need to be discussed in multidisciplinary committee. Imaging (RMN or scanner) may be necessary for evaluation of advanced tumours. Metastasis very rarely occurs with incidence ranging from 0.0028 to 0.55% of cases. Most often metastasis is observed in the regional lymph nodes followed by lung and liver. The prognosis for metastasis is very poor with mean survival ranging from 8 months to 3.6 years (42).

Definition of prognostic groups

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

<u>Prognostic factors</u>:

-Tumour size (increasing size confers higher risk of recurrence)

-Tumour location (High risk zones are the nose, periorificial areas of the head and neck, intermediate risk zones are the forehead, cheek, chin, scalp and neck, and the low risk zones are the trunk and limbs)

-Definition of clinical margin (poorly defined lesions are at higher risk)

- ***Histological subtype*** (aggressive forms: morpheaform, infiltrating and metatypical form) or histological feature of aggression: perineural involvement.

- ***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). High risk BCC are tumours harbouring or 'that present with' one or more poor prognostic factors. Low risk tumours are superficial BCC, 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 superficial BCC from other recurrent BCC, and some nodular BCC according to size and location which risk of recurrences seems lower (2) (table2).

Table 1

Poor prognosis	Intermediate prognosis	Good prognosis
- clinical forms: morpheaform or ill-defined	- superficial recurrent BCC	- superficial primary BCC
	-Nodular BCC	- pinkus tumor BCC
- histological forms: aggressive	< 1 cm in high risk area	- nodular primary BCC :
- recurrent forms (apart from superficial BCC)	> 1 cm in intermediate risk area	< 1 cm in intermediate risk area
- nodular BCC >1 cm in high risk zone	> 2 cm in low risk area	< 2 cm in low risk area

(From Dandurand et al, European Journal of Dermatology. Volume 16, Number 4, 394-40),

Treatment

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 (43). This procedure allows the histologic assessment of the whole tumour and of the surgical margins.

The width of surgical margins is variable and relies on some tumour characteristics and the local anatomy that influence the degree of subclinical extension of the tumour (44-47). 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 (48). 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 (49-50). Therefore, for example, 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 (51). In all cases, particularly for lesions on the head, the deep margins should reach the fascia, perichondrium or the periosteum, where appropriate. For superficial BCC, or in BCC lesions located in areas with thicker skin, the deep margins may be less deep. Particularly in nodular and superficial BCC, 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 (52).

Examination of excision margins can be done using different techniques. The most common technique is by using postoperative vertical (bread-loaf) sections obtained from formalin-fixed, paraffin-embedded tissue(48). 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 drawn in cases where no tumour cells are found on the section margins (53). This is especially important in those tumour types displaying pattern of growth with irregular lateral and deep infiltration, i.e. infiltrative or sclerodermiform. 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.

Surgical excision is very effective for primary BCC treatment. Recurrence rates vary from less than 2% to 8% at 5 years after the surgery (54-56). It is remarkable that 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 and that up to 18% of recurrent BCC may present even later(56-57). 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 (56,58-59).

Evidence level:

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

<u>Incompletely excised BCC</u>

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 and

histological subtype of tumour, and the excision of multiple lesions during one procedure (60-61). Besides, these percentages might be underestimated because of the histopathological analysis procedure itself. It reflects the extent of subclinical tumour spread that is not completely predictable by the above discussed features. Recurrence after the surgery of incompletely excised BCC is not as high as it might be expected ranging 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 (62-63,64). An absence of residual tumour has been observed in the surgical specimens in half of BCCs after re-excision due to positive surgical margins (65,66). However, the risk of further recurrences among tumour that have recurred once is over 50%, especially when both lateral and deep margins are involved,(65,67). Besides, 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(68). Some incompletely excised lesions may demonstrate a more aggressive histological subtype when the lesion recurs(69). Therefore, data supports re-treatment of the tumour, particularly when it involves the midface or other compromised sites and special attention should be paid to lesions with surgical defects repaired with skin flaps or grafts, and those with the deep surgical margin involved and aggressive histological subtypes (70). Mohs surgery should be considered in the latter situations (71). 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:

- 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, is a specialized surgical procedure that examines the margins using intraoperative frozen sections. With Mohs surgery 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 (72).

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 45º. 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 deeper and epidermal layer). This surgical technique results in extremely high cure rates, including high-risk lesions, with maximal preservation of uninvolved tissues (73). As disadvantages, Mohs surgery is time consuming and needs special laboratory processing and microscopic examination.

According to several retrospective studies, overall cure rates for BCC treated with Mohs surgery range between 97 to 99% for primary tumours and 93 to 98% for recurrences, after 3 to 5 year of follow-up (57,58,74-78). Some studies based on large series with BCCs on specific locations like the ear or the eyelid that have been treated with Mohs surgery have shown similar cure rates(79,80). 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 (81) and 98.6% for primary and 96% for recurrent BCC on the head and neck(82).

Mohs surgery has been prospectively compared with surgical excision for the treatment of BCCs of the face in a series of 408 primary BCCs and 204 recurrent BCCs (59). The authors stated that Mohs surgery might be considered cost-effective for recurrent BCCs 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 Mohs surgery than in the group treated with surgical excision. According to some authors, Mohs surgery is cost-effective compared to surgical excision (83). In addition, other authors have also shown that Mohs surgery does not generate significantly higher costs than conventional surgery at least in selected patients with high-risk facial BCCs (84).

Evidence level:

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

-Mohs micrographic surgery is a good treatment 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 in several sizes 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 about what is the best protocol.

This technique is particularly useful in friable tumours that do not tend to be embedded in fibrous stroma (85). 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 electrodessication are immediately re-excised, and they are much more frequently found on head and neck (47%) than the trunk or limbs (8.3%)(86).

An 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 sites (57,87). Rates are higher for recurrent BCCs with figures of 60% (58). However, these high rates might be due to the size and characteristics of the BCCs treated during the period evaluated in the studies and much lower rates are expected in carefully selected tumours (88-89).

Evidence level:

-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 change 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 -60ºC) to achieve deep destruction of the tumour and surrounding tissues. There is no one single standard technique. Either open and closed spray techniques with either single or multiple cycles of freezing (freeze/thaw cycles) have been described. The main disadvantage is the lack of histological control for the completeness of clearance of the treatment.

Double freeze/thaw cycles are generally recommended for the treatment of facial BCC, although superficial lesions on the trunk might require only a single treatment cycle. Wounds usually heal with good cosmetic result although two cycles of 20 seconds freeze and 60 seconds thaw are associated with significantly worse cosmetic outcome than standard surgical excision for head and neck superficial and nodular BCCs (90).

Recurrence rates are very variable, ranged between 8 to 40%, but in selected lesions and in expert hands recurrence rates may be as low as 1% (91-94).

Evidence Level:

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

Laser

Carbon dioxide (CO2) laser ablation is an infrequently used form of treatment for BCC. This procedure provides a bloodless field, minimal postoperative pain, and good postoperative appearance without scar formation. Therefore, it might 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 variance in reported recurrence rates (95).

Evidence Level:

-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 treatment can be indicated for low risk BCC. The main advantages of medical treatment for BCC are good cosmetic outcome, preservation of surrounding tissue and potential for home application of certain treatments.

5-Fluorouracil

Although 5-fluorouracil has been widely used on actinic keratosis and in situ squamous carcinoma, only one recent study was performed with this compound for the treatment of superficial BCC (96). The therapy cream was applied twice daily for 11 weeks with 90% clearance observed 3 weeks after treatment but no clinical follow up was provided.

Evidence Level:

-5Fluorouracil may be a therapeutic option for superficial BCC but there is insufficient evidence to support its current use (Strength of recommendation: C, quality of evidence IV)

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 proinflammatory cytokines, chemokines and other mediators leading to activation of antigen presenting cells and other components of innate immunity and, eventually, the mounting of a profound T Helper (Th1) weighted antitumoural cellular immune response. Moreover, independent 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 (97). Imiquimod may also exert tumour suppression function via induction of Notch signalling (98).

The side effects from use 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 (99). An association was shown between severity of local site reaction and clinical response rate. The greater the reaction, the better is the response (100). In the 2007 Cochrane review (101), all studies except the study undertaken by Sterry et al were judged to be of medium quality. It was also related 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 the clinical utility as a topical treatment for treating superficial BCC (sBCC) lesions has been established when used 5x per week or 7x per week for 6 weeks (102-103). The 5x per week from 6 to 12 weeks is now currently approved in the EU and the USA for treatment of sBCC less than 2 cm in diameter on the neck, the trunk and the extremities (excluding hands and feet) in immunocompetent adults. The following text is mostly referring 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 6 weeks to 12 weeks, 81% of patients were histologically free of disease at 6 or 12 weeks (104). These studies did not include tumours in high risk

location (within 1 cm of the hairline, eyes, nose, mouth or ear, or tumours in the anogenital, hand, foot regions) and tumours bigger than 2 cm² were also excluded (105).

Studies including five-year follow-up were quite similar in their results: Five year follow up results were available in one study that included 182 patients and showed that the estimate probability of overall treatment success was 77.9% after once a day application 5 days per week for 6 weeks. But when most patients had completed the 12 weeks visit with a histological evaluation, the respective probability of overall treatment success was 80.9% (97). They noted that most of the recurrences occurred early, indicating that careful follow up is warranted during the first year of treatment. Another 5 year follow up study showed a 80.9% overall estimate of treatment success at 60 months but the recurrent tumours were observed during the first 24 months of follow up(106).

Concerning the 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 cm² total area. This study reported 76% histological clearance at 6 weeks when applying imiquimod daily for 12 weeks and 42 % histological clearance at 8 weeks when applying twice daily 3 days per week for 10 weeks.

One study including also infiltrative BCC treated with imiquimod showed 5 years clearance rates of 63 and 56% depending on the regimens used (107-108).

The main conclusion from these initial studies were, that imiquimod can be a first line treatment of sBCC not located in high risk location and if it is not for nodular or infiltrative basal cell carcinoma .

The more recent literature also proposes the use of imiquimod in specific body location (the face and more specifically the eyelids) , in combination with other non surgical therapy such as photodynamic therapy, cryosurgery, or local recurrence lesions, even larger lesions in combination with other therapies or even Mohs surgery, and finally in specific clinical situation such as immunosuppressed patients.

Interestingly, the cost effectiveness of treatment option between surgery and imiquimod 5% cream was studied by a Spanish group and showed that imiquimod cream is a cost effective alternative to excision surgery in patient with sBCC(109).

Evidence Level :

-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)

Photodynamic Therapy

Photodynamic therapy (PDT) is licensed for the treatment of certain basal call carcinomas in many European countries. Many studies utilized 5-aminolaevulinic acid (ALA) as the prodrug, applied under occlusion for 4-6 hours, but more recent studies use its lipophilic methyl ester, methyl aminolaevulinate (MAL), with a licensed protocol for 3 hour incubation between application and illumination by red light (75 J/cm2 570-670 nm or equivalent dose of narrowband red light) and repeat treatment at 7 days. Various light sources can be used but practitioners now typically use narrow-band red LED sources, to maximize depth of action by targeting the 630/635nm peak of Protoporphyrin IX and hence 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 (110-111). PDT was as effective as cryotherapy with equivalent 5 year recurrence rates of 22% and 20% respectively despite a possible sub-optimal PDT protocol with a single initial treatment followed by two further sessions at 3 months. Cosmetic outcome was superior following PDT. In the one year comparison study of PDT (2 treatments 7 days apart, repeated at 3 months if required) with surgery, no lesions recurred with surgery, but cosmetic outcome was again superior with PDT (111). A weighted initial clearance rate of 87% was reported for superficial BCC treated by ALA-PDT in a review of 12 studies (112). 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 (113). Clearance at 3 months of 91% of primary nodular BCC following MAL-PDT using the currently approved protocol has an estimated sustained lesion clearance response rate of 76% at 5 years (114-115). PDT was inferior to surgery when recurrence rates are compared (91% vs. 98% initial clearance, 14% and 4% recurrence at 5 years). Histologically confirmed response rates were observed in two randomized studies of MAL-PDT for nBCC, using the standard protocol. Treatment site excisions (at 6 months for responders) revealed an overall clearance rate of 73%, most effective for facial lesions where 89% achieved complete histological response (116). In a follow-up study of 53 BCCs less than 3.5mm thick treated by ALA-PDT using the penetration enhancer dimethylsulfoxide, 81% of sites remained disease free at 72 months (117).

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 (118).

Gentle removal of overlying crust and scale is commonly performed for superficial BCC and some practitioners have observed reduced efficacy if lesions are not debrided prior to PDT. Lesion preparation is probably more important when treating nBCC 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. In a small comparison study of ALA and MAL PDT, there was no difference in efficacy between the photosensitizing agents and residual nodular BCC was more often observed in lesions that were not debulked (119).

Discontinuous illumination using two light fractions of 20 J/cm^2 then 80 J/cm^2 four and six hours after application has improved responsiveness of sBCC to ALA-PDT compared with single illumination (97% vs. 89% clearance rate 12 months after therapy) , but is dependant on protocol with a low initial dose important (120). In a further study with an average follow-up of 2 years, the same dose schedule achieved complete lesion clearance of 97% for sBCC, but 80% for nBCC (121). An alternative fractionation protocol of two doses of 75 J/cm^2 at 4 and 5 hours was associated with an initial 94% clearance rate for nBCC, but with a cumulative failure rate of 30% by 3 years (122). This difference in response has with fractionated light has yet to be replicated with MAL-PDT.

PDT has been used to treat patients with Gorlin / NBCCS, with a large cohort of 33 patients treated by topical or systemic PDT depending on whether lesions were less than/greater than 2 mm in thickness when assessed by ultrasound (123). A recent short report observed that MAL-PDT for NBCCS improves patient satisfaction and reduces the need for surgical procedures (124).

Topical PDT has been used to treat BCC in immuno-suppressed patients with ALA-PDT clearing 30/32 facial tumours (including 21 BCC) in 5 OTR patients after 1-3 treatments (125). PDT also has been assessed for its ability to prevent/delay new cancer development in organ transplant recipients. A single treatment of MAL-PDT delayed (9.6 vs. 6.8 months for control site) the development of new lesions (BCC, AK, keratoacanthoma, SCC or warts) in an open intra-patient randomised study of 27 renal OTR with 2-10 skin lesions in two contralateral 5cm areas (126). 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, usually developing within minutes of commencing light exposure, and is more likely where large lesions and fields are treated, with treatments to the face and scalp more likely to be associated with pain (127). Pain may be less when BCC are treated compared with AK, although this may reflect area of treatment and greater pain has been observed with increasing lesion size (127-128). 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 a lack of benefit, but simple cold air fan can reduce discomfort and using a device to blow air at a temperature of -35ºC, reduced pain duration and severity in a study of ALA-PDT for Bowen's disease and BCC (129). Modifying the method of delivery of PDT can reduce pain with low intensity ambulatory light less painful than delivering PDT using conventional light sources (130).

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 will depend on many 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 5 years (to allow time for recurrences) (131). In a real-life practice study, total cost of care per patient was 318 euro for nBCC and 298 euro for sBCC consistent with the predicted cost-effectiveness in the above model (132).

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 (133).

Evidence Level:

-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)

Radiotherapy

Radiotherapy (RT) is an efficient form of treatment, in terms of local control of many clinical and histological forms of BCC. It requires prior histological confirmation of the diagnosis. It

may use low energy X-ray (which is particularly suitable for treating BCC), brachytherapy (for curved surfaces), or high-energy radiotherapy (photons or electrons) that 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 (134). 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% (135). A review of all studies published since 1947 suggested an overall 5-year cure rate of 91.3% following RT for primary BCC and a review of all studies published since 1945 suggested an overall 5-year cure rate of 90.2% following RT for recurrent BCC (136-137). Radiotherapy can be used to treat many types of BCC, even those overlying bone and cartilage, although it is probably less suitable for the treatment of large tumours in critical sites, as very large BCC masses are often both resistant and require radiation doses that closely approach tissue tolerance. However, in the only comparative study between surgery and RT, it has been shown that surgery should always be preferred for BCC of the face measuring < 4 cm in diameter as long term follow up shows a recurrence rate of 0.7% for surgery and 7.25 % for RT (138). Radiotherapy 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 following surgery (139,140). 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 to a specialist centre. 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 (141). 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 suggestion that BCCs recurring following RT may behave in a particularly aggressive and infiltrative fashion, although this may simply reflect that these lesions were of an aggressive, high-risk type from the very beginning (142,143). A recent paper reported a retrospective study of 175 BCCs in 148 patients (64 female patients and 84 male patients; mean age, 69 years) who were treated with radiotherapy for different BCC subtypes. According to their histologic patterns, BCCs were classified as nodular (n = 103), superficial (n = 25), and sclerosing (n = 47). The estimated 5-year recurrence rate for all patients with BCC was

15.8%: 8.2% for patients with the nodular subtype, 26.1% for patients with the superficial subtype, and 27.7% for patients with the sclerosing subtype. 86.4% of all recurrences occurred within 3 years after treatment. The authors conclude that the sclerosing subtype of BCC was a risk factor for recurrence after radiotherapy. In contrast, excellent results were achieved for patients with predominant nodular subtype (144). A recent long term analysis of efficacy of hypofractionnated schedule for electron beam therapy has shown for BCC (N=332) an actuarial 3 year local recurrence free rates of 97.6% for tumours treated with 54 Gy and 96.9% for 44Gy. In view of a similar efficacy and patient's convenience of the hypofractionated schedule, authors suggest that 44 Gy in 10 fractions could be regarded as the radiation schedule of choice (145). RT has short medium and long term side effects: tissue necrosis, radiodermatitis, pigmentation. These side effects can progress over time. Additionally, surgery is difficult in the situation of recurrence of an irradiated tumour and radiotherapy has long term carcinogenic properties that can favour the development of a secondary carcinoma.

According to this, Radiotherapy is contraindicated or not recommended in the following cases:

- – It is contraindicated in genetic syndromes predisposing to skin cancers such as basal cell naevus syndrome and xeroderma pigmentosum.
- – It is not recommended as first-line treatment if excision surgery is possible.
- – It is not recommended:
    - – in subjects aged under 60 years,
    - – as treatment for morpheaform BCC,
    - – on areas such as ears, hands, feet, legs or genital organs.

Radiotherapy (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 (contraindication to surgery, surgical problems, patient's refusal). In these circumstances, the best indications are:

- – BCC with incomplete excision
- – recurrent BCC
- – nodular BCC of the head and neck, under 2 cm
- – BCC with invasion of bone or cartilage.

In BCC with perineural invasion, surgery and adjuvant radiotherapy (median dose 55Gy) has been shown to provide a high local control rate (97 %) (146).

Evidence Level:

-Radiotherapy is a good treatment for certain primary BCC(Strength of recommendation A, Quality of evidence I)

- Radiotherapy is a good treatment 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 and rapidly fatal condition with a survival time that varies widely, but presents a median of only 8 months (147-148). There is no standard therapy for metastatic BCC or even for cases of locally advanced tumours. Due to the absence of randomized trials and even large case series, treatment is guided by anecdotal evidence or availability of clinical trials. Published data (149-152) suggest that platinum-based therapy is effective in inducing responses in metastatic BCC and should be considered in first for patients with metastatic BCC, if treatment is warranted. However there are issues to be considered when making a decision to begin therapy in these patients. Patients with BCC are often elderly and present significant comorbidities. Treatment with cisplatin requires adequate kidney function and has been associated with important bone marrow toxicity (151). The duration of response reported after platinum-based therapy varies and 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 elements should be taken into account.

Evidence level:

- If chemotherapy may be a therapeutic option for advanced BCC, actually no level of evidence support the use chemotherapy in the treatment of advanced BCC.(Strength of recommendation: C, quality of evidence IV)

Future therapies

Targeted therapy

In recent years, novel tumor-specific and pathogenesis-based molecules have been developed and are currently under investigation for treatment of BCC. Such targeted treatments include a high number of 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).

Hedgehog (Hh) signaling pathway, which has a crucial role during morphogenesis and organogenesis, has shown to be mutated in several tumors including BCC, medulloblastoma, leukemia, gastrointestinal, pancreatic, liver, ovarian, breast, lung and prostate cancer. Indeed, activated 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 PTCH1 gene represent so far the most common genetic alteration found in BCC lesions of patients with Nevoid Basal Cell Carcinoma (NBCCS) syndrome and in sporadic BCCs.

The first SMO antagonist discovered for the treatment and chemoprevention of BCC is cyclopamine, a naturally occurring steroid alkaloid derived from a plant (Veratrum californicum corny 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, i.e. development of one-eyed animals. In recently reported phase I and II studies, a dramatic overall response rate (ORR) was observed in inoperable, locally advanced BCCs (ORR: 43-50%; CR: 21%) and in metastatic BCCs (ORR: 30-60%) treated with 150-270mg/day of a synthetic SMO inhibitor (GDC-0449 or vismodegib) for a median of 10 months (153-155). Notably, in patients with NBCCS syndrome, regression of BCCs and odontogenic keratocysts of the jaw was also observed (156-157). Median duration of response after vismodegib treatment was 8.8 months. Side effects included fatigue, dysgeusia, hair loss and muscle spam. The mechanism of recurrence of BCC after treatment discontinuation as well as drug resistance is currently the objective of research studies. Vismodegib is currently licensed in the USA for treatment of advanced basal cell carcinoma in adult patients.

Additional agents that inhibit Hh pathway are being investigated in phase I/II clinical trials including systemic BMS-833923 (XL139) and topical LED225 in patients with NBCCS and in locally advanced and metastatic BCC (NCI clinical trial database).

Evidence level:

-Anti-smo agents have been shown to have potential interest for the treatment of advanced or metastatic BCC (Strength of recommendation A, quality of evidence II-i)

Ingenol mebutate

Ingenol mebutate (PEP005) is a diterpene ester extracted and purified from the plant Euphorbia peplus, that has been successfully used as a topical treatment for AKs (158). The results of one phase I/II study suggest that ingenol mebutate gel 0.05% applied to nodular and superficial BCC lesions once daily for 3 consecutive days provided 82% complete clinical response rate at 1 month, and histological clearance in 57% of cases (159). In another recent phase IIa trial, complete histological clearance was observed in 38% and 63% of patients with superficial BCCs treated with ingenol mebutate gel 0.05% for 2 consecutive days or at day 1 and 8, respectively.(157). 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 (159-160).

Evidence level:

At the present time 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 rate 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:

At the present time 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 presented with a primary BCC. However, long term surveillance of patients having presented with 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 that has been treated for a BCC is both at risk from the appearance of new primary lesions as well as for failure of the treatment and the appearance of local recurrence.

Concerning the appearance of new lesions, NCCN 2011 guidelines state that 30-50% of non-melanoma skin cancer (NMSC) patients will develop another NMSC within 5 years (161), that these patients are also at an increased risk of developing cutaneous melanoma (162) and suggest complete skin examination every 6-12 months for life.

The possibility of having additional BCC after the appearance of a first has been studied by several authors. McLoone *et al* found that patients who are diagnosed with BCC had a 11.6% risk of developing a new BCC in the first year and a 6.3% in the second year following treatment (163). Kiiski *et al* have recently demonstrated that the 3 year cumulative risk of a subsequent BCC after a first BCC was around 44% (161). A review and meta-analysis of seven studies (165) 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 comparable general population. The highest rates (60-70%) came from studies including large populations of patients with at least two (sometimes more than two) previous BCCs, suggesting that as the number of BCC lesions increases, so does the risk of developing more. In contrast, patients with only their index BCC who remain disease free for 3 years appear to have a decreased ongoing risk of further BCC. There was no general agreement on particular risk factors that might confer a higher risk of subsequent BCC. Several other authors have tried to identify specific risk factors associated with an increased risk of developing further BCC. Van Iersel *et al.* (166) 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 report that the risk of subsequent BCC is greater if age above 60 years at presentation, initial occurrence on trunk, superficial subtype and male sex (167).

The risk of local recurrence of a treated BCC is an individual risk, based upon the tumour characteristics and the treatment used. Recurrent rates are higher in lesions that have already recurred in the past. As BCC 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 (168). The need for a long term follow up 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% appear within 2 years, and 66% within 3 years (169).

Taking into account all of the above 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 having a new lesion appear and to stress the importance of self monitoring.
Ideally all patients presenting with a BCC should be offered a life long follow up every year. 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 at least be proposed to patients who present with high risk for recurrent lesions, for those who have already been treated for recurrent disease (increased risk of further recurrence following all types of treatment) and 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 multidisciplinary team at a frequency dictated by each individual case.

Prevention

The use of sunscreen to prevent development of BCC is still a matter of debate since controversial data have been reported so far (170-171). A recent systematic review (164) showed that although regular sunscreen use may prevent SCC, it is unclear whether it can prevent BCC. Indeed, few studies showed no effect of sunscreen use on BCC prevention. In a case control study carried out by an Italian group (172), the frequent use of sunscreens showed a tendency to have 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 (173). 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 (174-175).

In contrast, a protective effect of sunscreen use on BCC prevention has been supported in several case-control and cohort studies, and in clinical trials.

Recent clinical trials (176-178) demonstrated that individuals randomly assigned to regular sunscreen use had a decreased risk for SCC after 8 years of follow-up (RR, 0.65 [CI, 0.45–0.94]) but no statistically significant decrease in risk was seen for BCC. Notably, at 8 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 (179-180) .

A trend toward a lower risk of subsequent BCC lesions has been shown in sunscreen users enrolled in an Australian randomized trial (181). Gordon *et al.* 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(182). Moreover, it has been also reported that patients with a history of BCC had fewer subsequent BCCs if they had protected themselves from UV exposure (183).

A recent study on potential risk factors for sporadic BCC in a subset of young (19 to 40 years) adults showed that sunscreen use had a protective effect. The influence of sun protective measures by parents during patients' childhoods on BCC development was also evaluated and a protective effect was found, supporting that sun protection during childhood prevents skin carcinogenesis (184). The regular use of sunscreens may prevent the development of further BCCs in organ transplant patients(185). Finally, sunburn avoidance has been shown to decrease the incidence of sporadic BCC(186).

Evidence level:

-Use of sunscreens may protect for the development of subsequent BCC but currently insufficient evidence support the use sunscreens in the prevention of BCC.

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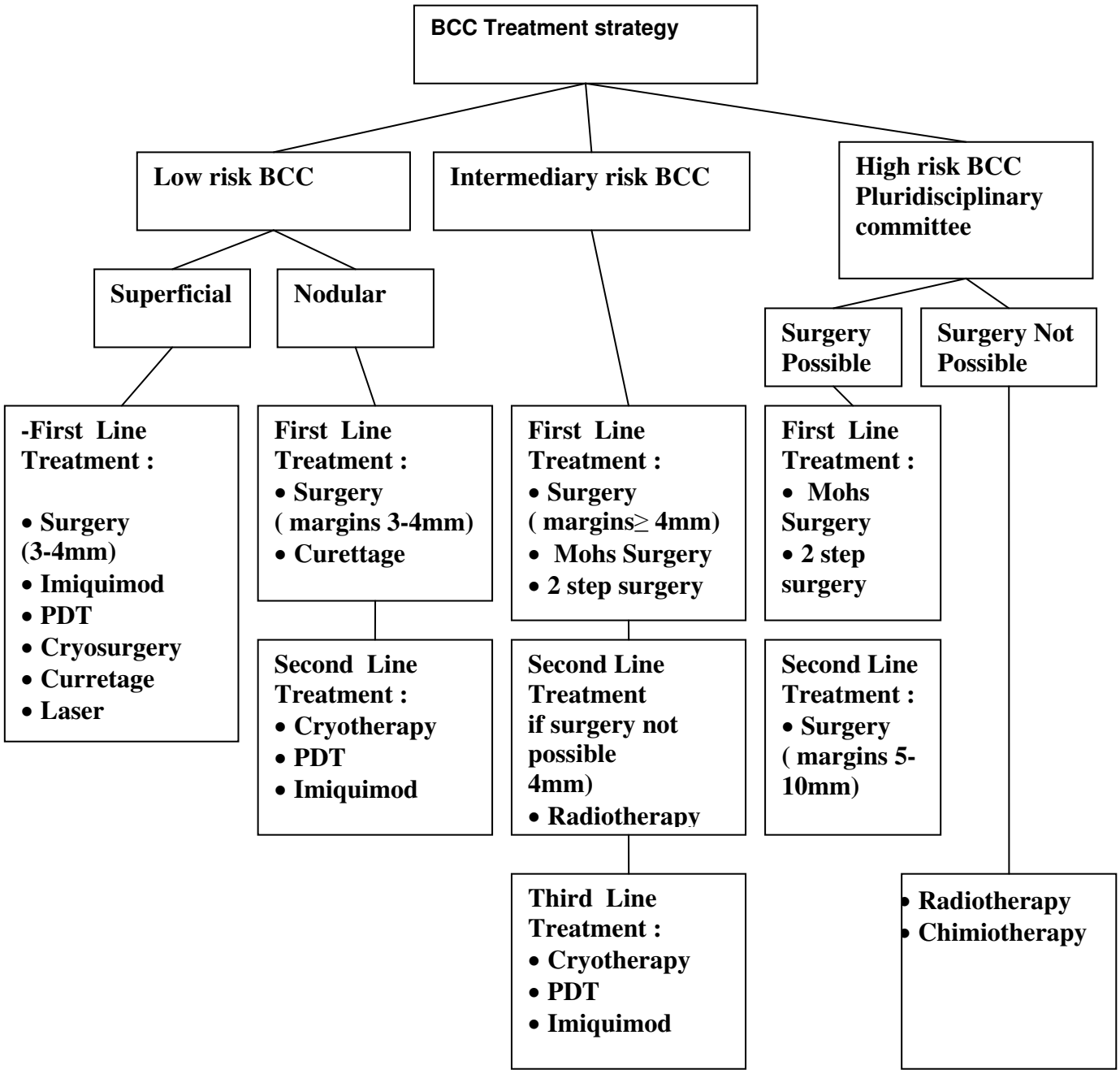
Table 1: Prognosis groups for BCC.

Table 2: Grading of studies (according to Telfer NR et al.(3))

Strength of recommendations
A There is good evidence to support the use of the procedure
B There is fair evidence to support the use of the procedure
C There is poor evidence to support the use of the procedure
D There is fair evidence to support the rejection of the use of the procedure
E There is good evidence to support the rejection of the use of the procedure
Quality of evidence
I Evidence obtained from at least one properly designed, randomized control trial
II-i Evidence obtained from well-designed controlled trials without randomization
II-ii Evidence obtained from well-designed cohort or case-control analytic studies, Preferably from more than one centre or research group
II-iii Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the introduction of penicillin treatment in the 1940s) could be regarded as this type of evidence
III Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees
IV Evidence inadequate owing to problems of methodology (e.g. sample size, or length or comprehensiveness of follow-up or conflicts of evidence)

Fig 1: BCC treatment strategy

Fig 1: BCC treatment strategy



Conflicts of interests

The Work Under Consideration for Publication					
		Basset-seguin	**Colin Morton**	**Nagore**	**Ulrich**
1	Grant	no	no	no	no
2	Consulting fee or honorarium	no	no	no	no
3	Support for travel to meetings for the study or other purposes	no	no	no	no
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no	no	no	no
5	Payment for writing or reviewing the manuscript	no	no	no	no
6	Provision of writing assistance, medicines, equipment, or administrative support	no	no	no	no
7	Other	no	no	no	no

* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	Yes (Roche Meda, Leo	Yes (Leo, Almirrall)	no	Almirall,Galderma
2	Consultancy	Yes (Roche Meda, Leo)	no	no	Spirig, Almirall, Galderma
3	Employment		no	no	no
4	Expert testimony		no	no	no
5	Grants/grants pending		no	no	no
6	Payment for lectures including service on speakers bureaus	Yes (Roche leo)	Yes (Leo, Galderma)	Yes (Meda)	no
7	Payment for manuscript preparation	no	no	no	no
8	Patents (planned, pending or issued)	no	no	no	no
9	Royalties	no	no	no	no
10	Payment for development of educational presentations	no	no	no	no
11	Stock/stock options	no	no	no	no
12	Travel/accommodations/meeting expenses unrelated to activities listed**	Yes (Roche, BMS, Galderma)	Yes (Leo, Galderma)	Yes (Roche,Galderma,Meda)	no
13	Other (err on the	no	no	no	no

	side of full disclosure)				

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	no	no	no	no

Conflicts of interests

The Work Under Consideration for Publication					
		Trakatelli Myrto	**Ketty Peris**	**Del Marmol**	**Name**
1	Grant	no	no	no	
2	Consulting fee or honorarium	no	no	no	
3	Support for travel to meetings for the study or other purposes	no	no	no	
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no	no	no	
5	Payment for writing or reviewing the manuscript	no	no	no	
6	Provision of writing assistance, medicines, equipment, or administrative support	no	no	no	
7	Other				

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Relevant financial activities outside the submitted work					
1	Board membership	no	Yes (Roche, Meda, LEO, Galderma)	Yes (Roche, Abbott, Léo)	
2	Consultancy	no	Yes (Roche, Meda, LEO)	no	
3	Employment	no	no	no	
4	Expert testimony	no	no	no	
5	Grants/grants pending	no	no	no	
6	Payment for lectures including service on speakers bureaus	Yes (Meda)	Yes (Roche)	Yes (Roche)	
7	Payment for manuscript preparation	no	no	no	
8	Patents (planned, pending or issued)	no	no	no	
9	Royalties	no	no	no	
10	Payment for development of educational presentations	no	no	no	
11	Stock/stock options	no	no	no	
12	Travel/accommodations/meeting expenses unrelated	Yes (Janssen-Cilag, Meda, Uriage)	Yes (Roche, LEO)		

	to activities listed**				
13	Other (err on the side of full disclosure)	no	No	no	

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	no	no	no	