



European Dermatology Forum

Update of the Guideline on Basal Cell Carcinoma

Developed by the Guideline Subcommittee "Basal Cell Carcinoma" 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 where 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 be 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) and 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.

Prognostic factors:

-*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)

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 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 curretted 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 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 electrodesiccation 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 -60°C) 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 cell 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/cm² then 80 J/cm² 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/cm² 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 -35°C, 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 hypofractionated 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 spasm. 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.

References

- 1 Sterry W: European Dermatology Forum Guideline Committee. Guidelines: the management of basal cell carcinoma. *Eur J Dermatol.* 2006 Sep-Oct;16(5):467-75.
- 2 Dandurand M, Petit T, Martel P, Guillot B; ANAES. Management of basal cell carcinoma in adults Clinical practice guidelines. *Eur J Dermatol.* 2006 Jul-Aug;16(4):394-401.
- 3 Telfer NR, Colver GB, Morton CA; British Association of Dermatologists. Guidelines for the management of basal cell carcinoma. *Br J Dermatol.* 2008 Jul;159(1):35-48.
- 4 Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. *N Engl J Med.* 2005 Nov 24;353(21):2262-9..
- 5 Halna JM, Grandadam M, Bueni A. Epidemiologic study of skin cancers from french population (1988-1996). Report of cancer registration of "Haut Rhin" area. *Nouv Dermatol* 2000;19(1):48-55.
- 6 Vilar-Coromina N, Miró-Queralt J, Cano-Bautista A, Vilardell-Gil L, Torres Babié P, Marcos-Gragera R *Med Clin (Barc).* Non-melanoma skin cancer: incidence time trends analysis in Girona, Spain, 1994-2007. 2011 Jul 9;137(4):145-51.
- 7 Miller DL, Weinstock MA. Nonmelanoma skin cancer in the United States: incidence. *J Am Acad Dermatol.* 1994 May;30(5 Pt 1):774-8.
- 8 Birch-Johansen F, Jensen A, Mortensen L, Olesen AB, Kjær SK. Trends in the incidence of non melanoma skin cancer in Denmark 1978-2007: Rapid incidence increase among young Danish women. *Int J Cancer.* 2010 Nov 1;127(9):2190-8.
- 9 Flohil SC, de Vries E, Neumann HA, Coebergh JW, Nijsten T. Incidence, prevalence and future trends of primary basal cell carcinoma in the Netherlands. *Acta Derm Venereol.* 2011 Jan;91(1):24-30.
- 10 de Vries E, Micallef R., Brewster DH., Gibbs JH., Flohil SC, Saksela O, Sankila R, Forrest AD, Trakatelli M., Coebergh JW, Proby C.M, ;EPIDERM group Population-based estimates of the occurrence of multiple vs first primary basal cell carcinomas in 4 European regions *Arch Dermatol,* 2012 Mar;148(3):347-54.

11 Gallagher RP, Hill GB, Bajdik CD, Fincham S, Coldman AJ, McLean DI, Threlfall WJ. Sunlight exposure, pigmentary factors, and risk of nonmelanocytic skin cancer. I. Basal cell carcinoma. *Arch Dermatol*. 1995 Feb;131(2):157-63.

12 Armstrong BK, Kricger A. The epidemiology of UV induced skin cancer. *J Photochem Photobiol B*. 2001 Oct;63(1-3):8-18.

13 Kricger A, Armstrong BK, English DR, Heenan PJ. Does intermittent sun exposure cause basal cell carcinoma? a case-control study in Western Australia. *Int J Cancer*. 1995 Feb 8;60(4):489-94.

14 Rosso S, Zanetti R, Martinez C, Tormo MJ, Schraub S, Sancho-Garnier H, Franceschi S, Gafà L, Perea E, Navarro C, Laurent R, Schrameck C, Talamini R, Tumino R, Wechsler J. The multicentre south European study 'Helios'. II: Different sun exposure patterns in the aetiology of basal cell and squamous cell carcinomas of the skin. *Br J Cancer*. 1996 Jun;73(11):1447-54.

15 Bauer A, Diepgen TL, Schmitt J. Is occupational solar ultraviolet irradiation a relevant risk factor for basal cell carcinoma? A systematic review and meta-analysis of the epidemiological literature. *Br J Dermatol*. 2011 Sep;165(3):612-25.

16 Berg D, Otley CC. Skin cancer in organ transplant recipients: epidemiology, pathogenesis and management. *J Am Acad Dermatol* 2002;47:1-17.

17 Jensen P, Hansen S, Møller B *et al*. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. *J Am Acad Dermatol*. 1999 Feb;40(2 Pt 1):177-86.

18 Wisgerhof HC, Edelbroek JR, de Fijter JW *et al*. Subsequent squamous- and basal-cell carcinomas in kidney-transplant recipients after the first skin cancer: cumulative incidence and risk factors. *Transplantation* 2010;89(10):1231-8.

19 Euvrard S, Kanitakis J, Decullier E *et al*. Subsequent skin cancers in kidney and heart transplant recipients after the first squamous cell carcinoma. *Transplantation* 2006;81(8):1093-100.

- 20 Johnson RL, Rothman AL, Xie J, Goodrich LV, Bare JW, Bonifas JM, Quinn AG, Myers RM, Cox DR, Epstein EH Jr, Scott MP. Human homolog of patched, a candidate gene for the basal cell nevus syndrome. *Science*. 1996 Jun 14;272(5268):1668-71.
- 21 Knudson AG Jr. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci U S A*. 1971 Apr;68(4):820-3.
- 22 Pan S, Dong Q, Sun LS, Li TJ. Mechanisms of inactivation of PTCH1 gene in nevoid basal cell carcinoma syndrome: modification of the two-hit hypothesis. *Clin Cancer Res*. 2010 Jan 15;16(2):442-50.
- 23 Boukamp P. Non-melanoma skin cancer: what drives tumor development and progression? *Carcinogenesis*. 2005 Oct;26(10):1657-67.
- 24 Castori M, Morrone A, Kanitakis J, Grammatico P. Genetic skin diseases predisposing to basal cell carcinoma. *Eur J Dermatol*. 2012 May-Jun;22(3):299-309.
- 25 Liboutet M, Portela M, Delestaing G, Vilmer C, Dupin N, Gorin I, Saiag P, Lebbé C, Kerob D, Dubertret L, Grandchamp B, Basset-Seguin N, Soufir N. MC1R and PTCH gene polymorphism in French patients with basal cell carcinomas. *J Invest Dermatol*. 2006 Jul;126(7):1510-7.
26. Stacey SN, Sulem P, Masson G, Gudjonsson SA, Thorleifsson G, Jakobsdottir M, Sigurdsson A, Gudbjartsson DF, Sigurgeirsson B, Benediktsdottir KR, Thorisdottir K, Ragnarsson R, Scherer D, Hemminki K, Rudnai P, Gurzau E, Koppova K, Botella-Estrada R, Soriano V, Juberias P, Saez B, Gilaberte Y, Fuentelsaz V, Corredera C, Grasa M, Höiom V, Lindblom A, Bonenkamp JJ, van Rossum MM, Aben KK, de Vries E, Santinami M, Di Mauro MG, Maurichi A, Wendt J, Hochleitner P, Pehamberger H, Gudmundsson J, Magnusdottir DN, Gretarsdottir S, Holm H, Steinthorsdottir V, Frigge ML, Blondal T, Saemundsdottir J, Bjarnason H, Kristjansson K, Bjornsdottir G, Okamoto I, Rivoltini L, Rodolfo M, Kiemenev LA, Hansson J, Nagore E, Mayordomo JI, Kumar R, Karagas MR, Nelson HH, Gulcher JR, Rafnar T, Thorsteinsdottir U, Olafsson JH, Kong A, Stefansson K. New common variants affecting susceptibility to basal cell carcinoma. *Nat Genet*. 2009 Aug;41(8):909-14. Epub 2009 Jul 5. PubMed PMID: 19578363;

27. Rizzato C, Scherer D, Rudnai P, Gurzau E, Koppova K, Hemminki K, Canzian F, Kumar R, Campa D. POMC and TP53 genetic variability and risk of basal cell carcinoma of skin: Interaction between host and genetic factors. *J Dermatol Sci*. 2011 Jul;63(1):47-54. Epub 2011 Apr 1. PubMed PMID: 21536413.
28. Rizzato C, Canzian F, Rudnai P, Gurzau E, Stein A, Koppova K, Hemminki K, Kumar R, Campa D. Interaction between functional polymorphic variants in cytokine genes, established risk factors and susceptibility to basal cell carcinoma of skin. *Carcinogenesis*. 2011 Dec;32(12):1849-54. Epub 2011 Aug 30. PubMed PMID: 21880580.
29. Stacey SN, Gudbjartsson DF, Sulem P, Bergthorsson JT, Kumar R, Thorleifsson G, Sigurdsson A, Jakobsdottir M, Sigurgeirsson B, Benediktsdottir KR, Thorisdottir K, Ragnarsson R, Scherer D, Rudnai P, Gurzau E, Koppova K, Höiom V, Botella-Estrada R, Soriano V, Juberías P, Grasa M, Carapeto FJ, Tabuenca P, Gilaberte Y, Gudmundsson J, Thorlacius S, Helgason A, Thorlacius T, Jonasdottir A, Blondal T, Gudjonsson SA, Jonsson GF, Saemundsdottir J, Kristjansson K, Bjornsdottir G, Sveinsdottir SG, Mouy M, Geller F, Nagore E, Mayordomo JI, Hansson J, Rafnar T, Kong A, Olafsson JH, Thorsteinsdottir U, Stefansson K. Common variants on 1p36 and 1q42 are associated with cutaneous basal cell carcinoma but not with melanoma or pigmentation traits. *Nat Genet*. 2008 Nov;40(11):1313-8. Epub 2008 Oct 12. PubMed PMID: 18849993.
30. Gudbjartsson DF, Sulem P, Stacey SN, Goldstein AM, Rafnar T, Sigurgeirsson B, Benediktsdottir KR, Thorisdottir K, Ragnarsson R, Sveinsdottir SG, Magnusson V, Lindblom A, Kostulas K, Botella-Estrada R, Soriano V, Juberías P, Grasa M, Saez B, Andres R, Scherer D, Rudnai P, Gurzau E, Koppova K, Kiemeny LA, Jakobsdottir M, Steinberg S, Helgason A, Gretarsdottir S, Tucker MA, Mayordomo JI, Nagore E, Kumar R, Hansson J, Olafsson JH, Gulcher J, Kong A, Thorsteinsdottir U, Stefansson K. ASIP and TYR pigmentation variants associate with cutaneous melanoma and basal cell carcinoma. *Nat Genet*. 2008 Jul;40(7):886-91. Epub 2008 May 18. Erratum in: *Nat Genet*. 2008 Aug;40(8):1029. PubMed PMID: 18488027.

31. Scherer D, Bermejo JL, Rudnai P, Gurzau E, Koppova K, Hemminki K, Kumar R. MC1R variants associated susceptibility to basal cell carcinoma of skin: interaction with host factors and XRCC3 polymorphism. *Int J Cancer*. 2008 Apr 15;122(8):1787-93. PubMed PMID: 18067130.
32. Steding-Jessen M, Birch-Johansen F, Jensen A, Schüz J, Kjær SK, Dalton SO. Socioeconomic status and non-melanoma skin cancer: a nationwide cohort study of incidence and survival in Denmark. *Cancer Epidemiol*. 2010 Dec;34(6):689-95.
33. Wang GY, Wang J, Mancianti ML, Epstein EH Jr. Basal cell carcinomas arise from hair follicle stem cells in Ptch1(+/-) mice. *Cancer Cell*. 2011 Jan 18;19(1):114-24.
34. Youssef KK, Van Keymeulen A, Lapouge G, Beck B, Michaux C, Achouri Y, Sotiropoulou PA, Blanpain C. Identification of the cell lineage at the origin of basal cell carcinoma. *Nat Cell Biol*. 2010 Mar;12(3):299-305.
35. Ratner D, Lowe L, Johnson TM, Fader DJ. Perineural spread of basal cell carcinomas treated with Mohs micrographic surgery. *Cancer*. 2000 Apr 1;88(7):1605-13. perineural inv
36. Sexton M, Jones DB, Maloney ME. Histologic pattern analysis of basal cell carcinoma. Study of a series of 1039 consecutive neoplasms. *J Am Acad Dermatol*. 1990 Dec;23(6 Pt 1):1118-26.
37. Scrivener Y, Grosshans E, Cribier B. Variations of basal cell carcinomas according to gender, age, location and histopathological subtype. *Br J Dermatol*. 2002 Jul;147(1):41-7.
38. Altamura D, Menzies SW, Argenziano G, Zalaudek I, Soyer HP, Sera F, et al. Dermoscopy of basal cell carcinoma: Morphologic variability of global and local features and accuracy of diagnosis. *J Am Acad Dermatol*. 2010; 62: 67-75.
39. Guitera P, Menzies SW, Longo C, Cesinaro AM, Scolyer RA, Pellacani G. In vivo confocal microscopy for diagnosis of melanoma and Basal cell carcinoma using a two-step method: analysis of 710 consecutive clinically equivocal cases. *J Invest Dermatol*. 2012 Oct;132(10):2386-94.

40. Seidenari S, Arginelli F, Bassoli S, Cautela J, Cesinaro AM, Guanti M, Guardoli D, Magnoni C, Manfredini M, Ponti G, König K. Diagnosis of BCC by multiphoton laser tomography. *Skin Res Technol*. 2012 Jul 8. doi: 10.1111/j.1600-0846.2012.00643.x. [Epub ahead of print]
41. Mogensen M, Joergensen TM, Nürnberg BM, Morsy HA, Thomsen JB, Thrane L, Jemec GB. Assessment of optical coherence tomography imaging in the diagnosis of non-melanoma skin cancer and benign lesions versus normal skin: observer-blinded evaluation by dermatologists and pathologists. *Dermatol Surg*. 2009 Jun;35(6):965-72.
42. Walling HW, Fosko SW, Geraminejad PA, Whitaker DC, Arpey CJ. Aggressive basal cell carcinoma: presentation, pathogenesis, and management. *Cancer Metastasis Rev*. 2004 Aug-Dec;23(3-4):389-402. Review.
43. Bath-Hextall F, Bong J, Perkins W, Williams H. Interventions for basal cell carcinoma of the skin: systematic review. *BMJ*. 2004 sep 25;329(7468):705.
44. Breuninger H, Dietz K. Prediction of subclinical tumor infiltration in basal cell carcinoma. *J Dermatol Surg Oncol*. 1991 jul;17(7):574-8.
45. Batra RS, Kelley LC. Predictors of extensive subclinical spread in nonmelanoma skin cancer treated with Mohs micrographic surgery. *Arch Dermatol*. 2002 ago;138(8):1043-51.
46. Ratner D, Bagiella E. The efficacy of curettage in delineating margins of basal cell carcinoma before Mohs micrographic surgery. *Dermatol Surg*. 2003 sep;29(9):899-903.
47. Ro KW, Seo SH, Son SW, Kim I-H. Subclinical infiltration of Basal cell carcinoma in asian patients: assessment after mohs micrographic surgery. *Ann Dermatol*. 2011 ago;23(3):276-81.
48. Wolf DJ, Zitelli JA. Surgical margins for basal cell carcinoma. *Arch Dermatol*. 1987 mar;123(3):340-4.

49. Leibovitch I, Huilgol SC, Selva D, Richards S, Paver R. Basal cell carcinoma treated with Mohs surgery in Australia III. Perineural invasion. *J. Am. Acad. Dermatol.* 2005 sep;53(3):458–63.
50. Feasel AM, Brown TJ, Bogle MA, Tschen JA, Nelson BR. Perineural invasion of cutaneous malignancies. *Dermatol Surg.* 2001 jun;27(6):531–42.
51. Kuijpers DIM, Thissen MRTM, Neumann MHA. Basal cell carcinoma: treatment options and prognosis, a scientific approach to a common malignancy. *Am J Clin Dermatol.* 2002;3(4):247–59.
52. Chiller K, Passaro D, McCalmont T, Vin-Christian K. Efficacy of curettage before excision in clearing surgical margins of nonmelanoma skin cancer. *Arch Dermatol.* 2000 nov;136(11):1327–32.
53. Abide JM, Nahai F, Bennett RG. The meaning of surgical margins. *Plast. Reconstr. Surg.* 1984 mar;73(3):492–7.
54. Walker P, Hill D. Surgical treatment of basal cell carcinomas using standard postoperative histological assessment. *Australas. J. Dermatol.* 2006 feb;47(1):1–12.
55. Griffiths RW, Suvarna SK, Stone J. Do basal cell carcinomas recur after complete conventional surgical excision? *Br J Plast Surg.* 2005 sep;58(6):795–805.
56. Silverman MK, Kopf AW, Bart RS, Grin CM, Levenstein MS. Recurrence rates of treated basal cell carcinomas. Part 3: Surgical excision. *J Dermatol Surg Oncol.* 1992 jun;18(6):471–6.
57. Rowe DE, Carroll RJ, Day CL Jr. Long-term recurrence rates in previously untreated (primary) basal cell carcinoma: implications for patient follow-up. *J Dermatol Surg Oncol.* 1989 mar;15(3):315–28.
58. Rowe DE, Carroll RJ, Day CL Jr. Mohs surgery is the treatment of choice for recurrent (previously treated) basal cell carcinoma. *J Dermatol Surg Oncol.* 1989 abr;15(4):424–31.
59. Mosterd K, Krekels GAM, Nieman FH, Ostertag JU, Essers BAB, Dirksen CD, et al. Surgical excision versus Mohs' micrographic surgery for primary and recurrent basal-cell

carcinoma of the face: a prospective randomised controlled trial with 5-years' follow-up. *Lancet Oncol.* 2008 dic;9(12):1149–56.

60. Kumar P, Orton CI, McWilliam LJ, Watson S. Incidence of incomplete excision in surgically treated basal cell carcinoma: a retrospective clinical audit. *Br J Plast Surg.* 2000 oct;53(7):563–6.

61. Dieu T, Macleod AM. Incomplete excision of basal cell carcinomas: a retrospective audit. *ANZ J Surg.* 2002 mar;72(3):219–21.

62. Nagore E, Grau C, Molinero J, Fortea JM. Positive margins in basal cell carcinoma: relationship to clinical features and recurrence risk. A retrospective study of 248 patients. *J Eur Acad Dermatol Venereol.* 2003 mar;17(2):167–70.

63. De Silva SP, Dellon AL. Recurrence rate of positive margin basal cell carcinoma: results of a five-year prospective study. *J Surg Oncol.* 1985 ene;28(1):72–4.

64. Park AJ, Strick M, Watson JD. Basal cell carcinomas: do they need to be followed up? *J R Coll Surg Edinb.* 1994 abr;39(2):109–11.

65. Sei JF. [Excision limits and reoperation in cutaneous carcinoma]. *Ann Dermatol Venereol.* 1997;124(5):421–6.

66. Wilson AW, Howsam G, Santhanam V, Macpherson D, Grant J, Pratt CA, et al. Surgical management of incompletely excised basal cell carcinomas of the head and neck. *Br J Oral Maxillofac Surg.* 2004 ago;42(4):311–4.

67. Menn H, Robins P, Kopf AW, Bart RS. The recurrent basal cell epithelioma. A study of 100 cases of recurrent, re-treated basal cell epitheliomas. *Arch Dermatol.* 1971 jun;103(6):628–31.

68. Angulo J, Serra-Guillén C, Traves V, Botella-Estrada R, Sanmartín O, Llombart B, et al. [Mohs micrographic surgery for repeat excision of basal cell carcinomas on the head with positive margins]. *Actas Dermosifiliogr.* 2011 dic;102(10):797–804.

69. Boulinguez S, Grison-Tabone C, Lamant L, Valmary S, Viraben R, Bonnetblanc JM, et al. Histological evolution of recurrent basal cell carcinoma and therapeutic implications for incompletely excised lesions. *Br. J. Dermatol.* 2004 sep;151(3):623–6.

70. Robinson JK, Fisher SG. Recurrent basal cell carcinoma after incomplete resection. *Arch Dermatol.* 2000 nov;136(11):1318–24.
71. Bielely HC, Kirsner RS, Reyes BA, Garland LD. The use of Mohs micrographic surgery for determination of residual tumor in incompletely excised basal cell carcinoma. *J. Am. Acad. Dermatol.* 1992 may;26(5 Pt 1):754–6.
72. Swanson NA. Mohs surgery. Technique, indications, applications, and the future. *Arch Dermatol.* 1983 sep;119(9):761–73.
73. Williford PM, Feldman SR. Surgery for basal-cell carcinoma of the face. *Lancet.* 2004 nov 13;364(9447):1732–3.
74. Emmett AJ. Surgical analysis and biological behaviour of 2277 basal cell carcinomas. *Aust N Z J Surg.* 1990 nov;60(11):855–63.
75. Miller PK, Roenigk RK, Brodland DG, Randle HW. Cutaneous micrographic surgery: Mohs procedure. *Mayo Clin. Proc.* 1992 oct;67(10):971–80.
76. Swanson NA. Mohs surgery. Technique, indications, applications, and the future. *Arch Dermatol.* 1983 sep;119(9):761–73.
77. Smeets NWJ, Kuijpers DIM, Nelemans P, Ostertag JU, Verhaegh MEJM, Krekels GAM, et al. Mohs' micrographic surgery for treatment of basal cell carcinoma of the face--results of a retrospective study and review of the literature. *Br. J. Dermatol.* 2004 jul;151(1):141–7.
78. Paoli J, Daryoni S, Wennberg A-M, Mölne L, Gillstedt M, Miocic M, et al. 5-year recurrence rates of Mohs micrographic surgery for aggressive and recurrent facial basal cell carcinoma. *Acta Derm. Venereol.* 2011 oct;91(6):689–93.
79. Mohs F, Larson P, Iriondo M. Micrographic surgery for the microscopically controlled excision of carcinoma of the external ear. *J. Am. Acad. Dermatol.* 1988 oct;19(4):729–37.
80. Mohs FE. Micrographic surgery for the microscopically controlled excision of eyelid cancers. *Arch. Ophthalmol.* 1986 jun;104(6):901–9.

81. Malhotra R, Huilgol SC, Huynh NT, Selva D. The Australian Mohs database, part II: periocular basal cell carcinoma outcome at 5-year follow-up. *Ophthalmology*. 2004 abr;111(4):631–6.
82. Leibovitch I, Huilgol SC, Selva D, Richards S, Paver R. Basal cell carcinoma treated with Mohs surgery in Australia II. Outcome at 5-year follow-up. *J. Am. Acad. Dermatol*. 2005 sep;53(3):452–7.
83. Cook J, Zitelli JA. Mohs micrographic surgery: a cost analysis. *J. Am. Acad. Dermatol*. 1998 nov;39(5 Pt 1):698–703.
84. Blázquez-Sánchez N, de Troya-Martín M, Frieyro-EliceGUI M, Fúnez-Liébana R, Martín-Márquez L, Rivas-Ruiz F. [Cost analysis of Mohs micrographic surgery in high-risk facial basal cell carcinoma]. *Actas Dermosifiliogr*. 2010 sep;101(7):622–8.
85. Spiller WF, Spiller RF. Treatment of basal cell epithelioma by curettage and electrodesiccation. *J. Am. Acad. Dermatol*. 1984 nov;11(5 Pt 1):808–14.
86. Suhge d'Aubermont PC, Bennett RG. Failure of curettage and electrodesiccation for removal of basal cell carcinoma. *Arch Dermatol*. 1984 nov;120(11):1456–60.
87. Kopf AW, Bart RS, Schragger D, Lazar M, Popkin GL. Curettage-electrodesiccation treatment of basal cell carcinomas. *Arch Dermatol*. 1977 abr;113(4):439–43.
88. Chren M-M, Torres JS, Stuart SE, Bertenthal D, Labrador RJ, Boscardin WJ. Recurrence after treatment of nonmelanoma skin cancer: a prospective cohort study. *Arch Dermatol*. 2011 may;147(5):540–6.
89. Barlow JO, Zalla MJ, Kyle A, DiCaudo DJ, Lim KK, Yiannias JA. Treatment of basal cell carcinoma with curettage alone. *J. Am. Acad. Dermatol*. 2006 jun;54(6):1039–45.
90. Thissen MR, Nieman FH, Ideler AH, Berretty PJ, Neumann HA. Cosmetic results of cryosurgery versus surgical excision for primary uncomplicated basal cell carcinomas of the head and neck. *Dermatol Surg*. 2000 ago;26(8):759–64.
91. Kuflik EG. Cryosurgery for skin cancer: 30-year experience and cure rates. *Dermatol Surg*. 2004 feb;30(2 Pt 2):297–300.

92. Hall VL, Leppard BJ, McGill J, Kessler ME, White JE, Goodwin P. Treatment of basal-cell carcinoma: comparison of radiotherapy and cryotherapy. *Clin Radiol.* 1986 ene;37(1):33–4.
93. Jaramillo-Ayerbe F. Cryosurgery in difficult to treat basal cell carcinoma. *Int. J. Dermatol.* 2000 mar;39(3):223–9.
94. Tuppurainen K. Cryotherapy for eyelid and periocular basal cell carcinomas: outcome in 166 cases over an 8-year period. *Graefes Arch. Clin. Exp. Ophthalmol.* 1995 abr;233(4):205–8.
95. Nouri K, Chang A, Trent JT, Jiménez GP. Ultrapulse CO₂ used for the successful treatment of basal cell carcinomas found in patients with basal cell nevus syndrome. *Dermatol Surg.* 2002 Mar;28(3):287-90.
96. Gross K, Kircik L, Kricorian G 5% fluorouracil cream for the treatment of small superficial basal cell carcinoma : efficacy, cosmetic outcome, and patient satisfaction *Dermatol surg* 2007(4) :433-440.
97. Schon MP and Schon M: Imiquimod : mode of action.. *Br J Derm* 2007 :157 (suppl 2) :8-13.
98. Wuest M, Dummer R, Urosevic M Induction of the members of Notch pathway in superficial basal cell carcinomas treated with imiquimod. *Arch Derm Res* :2007:299 : 493-498.
99. Schulze HJ , Cribier B, Requena L et aln Imiquimod 5% cream for the treatment of superficial basal cell carcinoma : results from a randomized vehicle-controlled study .*Br J Dermatol* 2005 :152(5) :939-947.
100. Gollnick H, Barona CG, Frank RG et al Recurrence rate of superficial basal cell carcinoma following successful treatment with imiquimod 5% cream : conclusion of a 5 year long term follow up study in Europe *Eur J Derm* 2008 : 18(6) : 677-682.

101. Bath-Hextall FJ, Perkins W, Bong J, Williams HC Interventions for basal cell carcinoma of the skin. *Cochrane data Syst Rev* :CD003412.Review, 2007.
102. Geisse J, Caro I, Lindholm J, Golitz I, Stampone P, Owens M .Imiquimod 5% cream for the treatment of superficial basal cell carcinoma : results from two phase III randomized vehicle controlled studies .*J Am Acad Dermatol* 2004 :50(5) : 722-733.
103. Sterry W, Ruzicka T, Herrera E, et al, Imiquimod cream 5% cream for the treatment of superficial and nodular basal cell carcinoma : randomized studies comparing low frequency dosing with and without occlusion. *Br J Derm* 2002 :147 :1227-36
104. Ebell MH, Siwek J, Weiss BD Strength of recommendation taxonomy (SORT) : A patient centered approach to grading evidence in medical literature. *Am Fam Physician* 2004 :69(3) :548-556.
105. Love E, Bernhard J, Bordeaux J Topical imiquimod or fluouracil therapy for basal and squamous cell carcinoma-systematic review.*Arch Derm* , 2009, 145 : (12) :1431-1438.
106. Quikck C, Gebauer K, De'Ambrosis B, Slacke H, Meng T Sustained clearance of superficial basal cell carcinomas treated with imiquimod cream 5% : results of a prospective 5-year Study.*Cutis* 2010 :85 :318-324.
107. Vidal D , Matias–Gulu X, Alomar A A open study of the efficacy and mechanism of action of topical imiquimod in basal carcinoma .*Clin Exp Derm* 2004, 29 (5) :518-525.
108. Vidal D, Matias –Gulu X Alomar A : Forty basal cell carcinoma treated with topical imiquimod : outcome 5 years follow up . *Arch Derm* 2007 : 143(2) :266-268.
109. Vanalocha F, Dauden E, Badia X, Guillen C, Conejo Mir J, Sainz de los Terreros M, Hamel L,Llorens M Cost-effectiveness of treatment of superficial basal cell carcinoma: surgical excision vs. imiquimod 5% cream.*Br J Dermatol*. 2007 Apr;156(4):769-71.

110. Basset-Seguin N, Ibbotson SH, Emtestam L, Tarstedt M, Morton C, Maroti M, *et al.* Topical methyl aminolaevulinate photodynamic therapy versus cryotherapy for superficial basal cell carcinoma: a 5 year randomized trial. *Eur J Dermatol* 2008; 18: 547-53.
111. Szeimies RM, Ibbotson S, Murrell DF, Rubel D, Frambach Y, de Berker D, Dummer R, Kerrouche N, Villemagne H. A clinical study comparing methyl aminolevulinate photodynamic therapy and surgery in small superficial basal cell carcinoma (8-20 mm), with a 12-month follow-up. *JEADV*. 2008 22: 1302-11.
112. Peng Q, Warloe T, Berg K *et al.* 5-Aminolevulinic acid-based photodynamic therapy. Clinical research and future challenges. *Cancer* 1997; 79: 2282-308.
113. Wang I, Bendsoe N, Klinteberg CA *et al.* Photodynamic therapy vs. cryosurgery of basal cell carcinomas: results of a phase III clinical trial. *Br J Dermatol* 2001; 144: 832-40.
114. Rhodes LE, de Rie M, Enstrom Y *et al.* Photodynamic therapy using topical methyl aminolevulinate vs surgery for nodular basal cell carcinoma: results of a multicenter randomized prospective trial. *Arch Dermatol* 2004; 140: 17-23.
115. Rhodes LE, de Rie MA, Leifsdottir R *et al.* Five-year follow-up of a randomized prospective trial of topical methyl aminolevulinate-photodynamic therapy versus surgery for nodular basal cell carcinoma. *Arch Dermatol*, 2007; 143: 1131-6.
116. Foley P, Freeman M, Menter A, *et al.* Photodynamic therapy with methyl aminolevulinate for primary nodular basal cell carcinoma: results of two randomized studies *Int J Dermatol* 2009; 48: 1236-45.
117. Christensen, E., Skogvoll, E., Viset, T., Warloe, T. and Sundstrøm, S. Photodynamic therapy with 5-aminolaevulinic acid, dimethylsulfoxide and curettage in basal cell carcinoma: a 6-year clinical and histological follow-up. *JEADV*, 2009; 23: 58–66.

118. Fantini, F., Greco, A., Del Giovane, C., Cesinaro, A., Venturini, M., Zane, C., Surrenti, T., Peris, K. and Calzavara-Pinton, P. Photodynamic therapy for basal cell carcinoma: clinical and pathological determinants of response. *JEADV*, 2011; 25: 896–901.
119. Kuijpers D, Thissen MR, Thissen CA, Neumann MH. Similar effectiveness of methyl aminolevulinate and 5-aminolevulinate in topical photodynamic therapy for nodular basal cell carcinoma. *J Drugs Dermatol* 2006; 5: 642-5.
120. de Haas ER, Kruijt B, Sterenborg HJ et al. Fractionated illumination significantly improves the response of superficial basal cell carcinoma to aminolevulinic acid photodynamic therapy. *J Invest Dermatol* 2006; 126: 2679-86.
121. de Haas ER, de Vijlder HC, Sterenborg HJ et al. Fractionated aminolevulinic acid-photodynamic therapy provides additional evidence for the use of PDT for non-melanoma skin cancer. *J Eur Acad Dermatol Venereol* 2008; 22: 426-30.
122. Mosterd K, Thissen MRTM, Nelemans P, et al. Fractionated 5-aminolaevulinic acid-photodynamic therapy vs. surgical excision in the treatment of nodular basal cell carcinoma: results of a randomized controlled trial *Br J Dermatol* 2008; 159: 864-70.
123. Loncaster J, Swindell R, Slevin F, et al. Efficacy of photodynamic therapy as a treatment for Gorlin Syndrome-related basal cell carcinomas. *Clinical Oncology* 2009; 21: 502-8.
124. Pauwels, C., Mazereeuw-Hautier, J., Basset-Seguin, N., Livideanu, C., Viraben, R., Paul, C. and Meyer, N. Topical methyl aminolevulinate photodynamic therapy for management of basal cell carcinomas in patients with basal cell nevus syndrome improves patient's satisfaction and reduces the need for surgical procedures. *JEADV* 2011; 25: 861–864.
125. Schleier P, Hyckel P, Berndt A et al. Photodynamic therapy of virus-associated epithelial tumours of the face in organ transplant recipients. *J Cancer Res Clin Oncol* 2004; 130: 279-284.

126. Wulf HC, Pavel S, Stender I, Bakker-Wensveen CAHB. Topical photodynamic therapy for prevention of new skin lesions in renal transplant recipients *Acta Derm Venereol* 2006; 86: 25-28.
127. Ibbotson SI. Adverse effects of topical photodynamic therapy *Photoderm Photoimmunol Photomedicine* 2011; 27: 116-30.
128. Grapengiesser S, Ericson M, Gudmundsson F et al. Pain caused by photodynamic therapy of skin cancer. *Clin Exp Dermatol* 2002; 27: 493-7.
129. Pagliaro J, Elliott T, Bulsara M et al. Cold air analgesia in photodynamic therapy of basal cell carcinomas and Bowen's disease: an effective addition to treatment: a pilot study. *Dermatol Surg* 2004; 30: 63-6.
130. . Attili SK, Lesar A, McNeill A et al. An open pilot study of ambulatory photodynamic therapy using a wearable low-irradiance organic light-emitting diode light source in the treatment of nonmelanoma skin cancer. *Br J Dermatol* 2009; 161: 170-3.
131. Caekelbergh K, Annemans L, Lambert J, Roelands R. Economic evaluation of methyl aminolevulinate photodynamic therapy in the management of actinic keratoses and basal cell carcinoma. *Br J Dermatol* 2006; 155: 784-90.
132. Annemans L, Roelandts R, Boonen H, et al. Real-life practice study of the clinical outcome and cost-effectiveness of photodynamic therapy using methyl aminolevulinate (MAL-PDT) in the management of actinic keratosis and basal cell carcinoma. *Eur J Dermatol* 2008; 18: 539-46.
133. Morton CA, MacKie RM, Whitehurst C *et al.* Photodynamic therapy for basal cell carcinoma: effect of tumour thickness and duration of photosensitizer application on response. *Arch Dermatol* 1998; 134: 248-9.
134. Dubin N, Kopf AW. Multivariate risk score for recurrence of cutaneous basal cell carcinomas. *Arch Dermatol*. 1983 May; 119(5):373-7.

135. Hall VL, Leppard BJ, McGill J, Kessler ME, White JE, Goodwin P. Treatment of basal-cell carcinoma: comparison of radiotherapy and cryotherapy. *Clin Radiol*. 1986 Jan;37(1):33-4.
136. Rowe DE, Carroll RJ, Day CL Jr. Long-term recurrence rates in previously untreated (primary) basal cell carcinoma: implications for patient follow-up. *J Dermatol Surg Oncol*. 1989 Mar;15(3):315-28.
137. Rowe DE, Carroll RJ, Day CL Jr. Mohs surgery is the treatment of choice for recurrent (previously treated) basal cell carcinoma. *J Dermatol Surg Oncol*. 1989 Apr;15(4):424-31.
138. Avril MF, Auperin A, Margulis A, Gerbaulet A, Duvillard P, Benhamou E, Guillaume JC, Chalon R, Petit JY, Sancho-Garnier H, Prade M, Bouzy J, Chassagne D. Basal cell carcinoma of the face: surgery or radiotherapy? Results of a randomized study. *Br J Cancer*. 1997;76(1):100-6.
139. Silverman MK, Kopf AW, Gladstein AH, Bart RS, Grin CM, Levenstein MJ. Recurrence rates of treated basal cell carcinomas. Part 4: X-ray therapy. *J Dermatol Surg Oncol*. 1992 Jul;18(7):549-54.
140. Cooper JS. Radiation therapy for cancers of the skin. *Dermatol Clin*. 1991 Oct;9(4):683-7. Review
141. Orton CI. The treatment of basal cell carcinoma by radiotherapy. *Clin Oncol*. 1978 Dec;4(4):317-22.
142. Smith SP, Foley EH, Grande DJ. Use of Mohs micrographic surgery to establish quantitative proof of heightened tumor spread in basal cell carcinoma recurrent following radiotherapy. *J Dermatol Surg Oncol*. 1990 Nov;16(11):1012-6
143. Smith SP, Grande DJ. Basal cell carcinoma recurring after radiotherapy: a unique, difficult treatment subclass of recurrent basal cell carcinoma. *J Dermatol Surg Oncol*. 1991 Jan;17(1):26-30.
144. Zagrodnik B, Kempf W, Seifert B, Müller B, Burg G, Urosevic M, Dummer R. Superficial radiotherapy for patients with basal cell carcinoma: recurrence rates, histologic subtypes, and expression of p53 and Bcl-2. *Cancer*. 2003 Dec 15;98(12):2708-14.

145. van Hezewijk M, Creutzberg CL, Putter H, Chin A, Schneider I, Hoogeveen M, Willemze R, Marijnen CA. Efficacy of a hypofractionated schedule in electron beam radiotherapy for epithelial skin cancer: Analysis of 434 cases. *Radiother Oncol*. 2010 May;95(2):245-9.
146. Jackson JE, Dickie GJ, Wiltshire KL, Keller J, Tripcony L, Poulsen MG, Hughes M, Allison RW, Martin JM. Radiotherapy for perineural invasion in cutaneous head and neck carcinomas: toward a risk-adapted treatment approach. *Head Neck*. 2009 May;31(5):604-10
147. Wadhera A, Fazio M, Bricca G, Stanton O. Metastatic basal cell carcinoma: a case report and literature review. How accurate is our incidence data? *Dermatol Online J* 2006;12(5):7.
148. Raszewski RL, Guyuron B. Long-term survival following nodal metastases from basal cell carcinoma. *Ann Plast Surg* 1990; 24:170-5.
149. Guthrie TH Jr, Porubsky ES, Luxenberg M. Net al Cisplatin-based chemotherapy in advanced basal and squamous cell carcinomas of the skin: results in 28 patients including 13 patients receiving multimodality therapy. *J Clin Oncol* 1990; 8: 342-6.
150. K. Moeholt, H. Aagaard, P. Pfeiffer, O. Hansen . Platinum-based cytotoxic therapy in basal cell carcinoma – a review of the literature. *Acta Oncol*, 35 1996, pp. 677–682.
151. Carneiro BA, Watkin WG, Mehta UK, et al.: Metastatic basal cell carcinoma: complete response to chemotherapy and associated pure red cell aplasia. *Cancer Invest* 2006; Jun-Jul. 24 (4): 396-400.
152. Apar Kishor Ganti, Anne Kessinger . Systemic therapy for disseminated basal cell carcinoma: An uncommon manifestation of a common cancer *Cancer Treatment Reviews*, Volume 37, Issue 6, Pages 440-443.
153. Von Hoff DD, LoRusso PM, Rudin CM, Reddy JC, Yauch RL, Tibes R, Weiss GJ, Borad MJ, Hann CL, Brahmer JR, Mackey HM, Lum BL, Darbonne WC, Marsters JC Jr, de Sauvage FJ, Low JA. Inhibition of the hedgehog pathway in advanced basal-cell carcinoma. *N Engl J Med*. 2009 Sep 17;361(12):1164-72.

154. LoRusso PM, Rudin CM, Reddy JC, Tibes R, Weiss GJ, Borad MJ, Hann CL, Brahmer JR, Chang I, Darbonne WC, Graham RA, Zerivitz KL, Low JA, Von Hoff DD. Phase I trial of hedgehog pathway inhibitor vismodegib (GDC-0449) in patients with refractory, locally advanced or metastatic solid tumors. *Clin Cancer Res*. 2011 Apr 15;17(8):2502-11.
155. Sekulic A, Migden MR, Oro AE, Dirix L, Lewis KD, Hainsworth JD, Solomon JA, Yoo S, Arron ST, Friedlander PA, Marmur E, Rudin CM, Chang AL, Low JA, Mackey HM, Yauch RL, Graham RA, Reddy JC, Hauschild A. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Engl J Med*. 2012 Jun 7;366(23):2171-9.
156. Goldberg LH, Landau JM, Moody MN, Kazakevich N, Holzer AM, Myers A. Resolution of odontogenic keratocysts of the jaw in basal cell nevus syndrome with GDC-0449. *Arch Dermatol*. 2011 Jul;147(7):839-41.
157. Tang JY, Mackay-Wiggan JM, Aszterbaum M, Yauch RL, Lindgren J, Chang K, Coppola C, Chanana AM, Marji J, Bickers DR, Epstein EH Jr. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. *N Engl J Med*. 2012 Jun 7;366(23):2180-8.
158. Anderson L, Schmieder GJ, Werschler WP, Tschen EH, Ling MR, Stough DB, Katsamas J. Randomized, double-blind, double-dummy, vehicle-controlled study of ingenol mebutate gel 0.025% and 0.05% for actinic keratosis. *J Am Acad Dermatol*. 2009 Jun;60(6):934-43.
159. Ramsay JR, Suhrbier A, Aylward JH, Ogbourne S, Cozzi SJ, Poulsen MG, Baumann KC, Welburn P, Redlich GL, Parsons PG. The sap from *Euphorbia peplus* is effective against human nonmelanoma skin cancers. *Br J Dermatol*. 2011 Mar;164(3):633-6.
160. Siller G, Rosen R, Freeman M, Welburn P, Katsamas J, Ogbourne SM. PEP005 (ingenol mebutate) gel for the topical treatment of superficial basal cell carcinoma: results of a randomized phase IIa trial. *Australas J Dermatol*. 2010 May;51(2):99-105.
161. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Basal Cell and Squamous Cell Skin Cancers. 2011;v.1: Accessed June 3 2011. Available at http://www.nccn.org/professionals/physician_gls/pdf/nmsc.pdf.

162. Chen J, Ruczinski I, Jorgensen TJ et al. Nonmelanoma skin cancer and risk for subsequent malignancy. *J Natl Cancer Inst.* 2008 Sep 3;100(17):1215-22.
163. Mc Loone NM, Tolland J, Walsh M, et al. Follow-up of basal cell carcinomas: an audit of current practice. *J Eur Acad Dermatol Venereol.* Jul 2006;20(6):698-701.
164. Kiiski V; de Vries E ,;. Flohil,SC; Bijl,MJ ; Hofman, A; Stricker,BH; Nijsten, T . Risk Factors for Single and Multiple Basal Cell Carcinomas *Arch Dermatol.* 2010;146(8):848-855.
165. Marcil I, Stern RS. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. *Arch Dermatol* 2000; 136:1524–30.
166. van Iersel CA, van de Velden HV, Kusters CD et al. Prognostic factors for a subsequent basal cell carcinoma: implications for follow up. *Br J Dermatol* 2005; 153:1078–80
167. Lovatt TJ, Lear JT, Bastrilles J, Wong C, Griffiths CE, Samarasinghe V, Roebuck J, Ramachandran S, Smith AG, Jones PW, Fryer AA, Strange RC. Associations between ultraviolet radiation, basal cell carcinoma site and histology, host characteristics, and rate of development of further tumors. *J Am Acad Dermatol.* 2005 Mar;52(3 Pt 1):468-73.
168. Silverman MK, Kopf AW, Grin CM et al. Recurrence rates of treated basal cell carcinomas. Part 2: curettage-electrodesiccation. *J Dermatol Surg Oncol* 1991; 17:720–6.
169. Rowe DE, Carroll RJ, Day CL Long-term recurrence rates in previously untreated(primary) basal cell carcinoma: implications for patient follow-up. *J Dermatol Surg Oncol* 1989; 15: 315-28.
170. Lin JS, Eder M, Weinmann S, Zuber SP, Beil TL, Plaut D, et al. *Behavioral Counseling to Prevent Skin Cancer: Systematic Evidence Review to Update the 2003 U.S. Preventive Services Task Force Recommendation: 2011, Rockville MD.*
171. Kutting B, Drexler H: UV-induced skin cancer at workplace and evidence-based prevention. *Int Arch Occup Environ Health* 2010; 83:843-54.

172. Corona R, Dogliotti E, D'Errico M, Sera F, Iavarone I, Baliva G, *et al.* Risk factors for basal cell carcinoma in a Mediterranean population: role of recreational sun exposure early in life. *Arch Dermatol* 2001; 137:1162-8.
173. Gon A, Minelli L : Risk factors for basal cell carcinoma in a southern Brazilian population: a case-control study. *Int J Dermatol* 2011; 50:1286-90.
174. Grodstein F, Speizer FE, Hunter DJ A prospective study of incident squamous cell carcinoma of the skin in the nurses' health study. *J Natl Cancer Inst* 1995; 87:1061-6.
175. Hunter DJ, Colditz GA, Stampfer MJ, Rosner B, Willett WC, Speizer FE Risk factors for basal cell carcinoma in a prospective cohort of women. *Ann Epidemiol* 1990;1:13-23.
176. Green A, Battistutta D, Hart V, Leslie D, Marks G, Williams G, *et al.* The Nambour Skin Cancer and Actinic Eye Disease Prevention Trial: design and baseline characteristics of participants. *Control Clin Trials* 1994; 15:512-22.
177. Green A, Williams G, Neale R, Hart V, Leslie D, Parsons P, *et al.* Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. *Lancet* 1999; 354:723-9.
178. van der Pols JC, Williams GM, Pandeya N, Logan V, Green AC Prolonged prevention of squamous cell carcinoma of the skin by regular sunscreen use. *Cancer Epidemiol Biomarkers Prev* 2006; 15:2546-8.
179. Kricke A, Armstrong BK, English DR, Heenan PJ Pigmentary and cutaneous risk factors for non-melanocytic skin cancer--a case-control study. *Int J Cancer* 1991;48:650-62.
180. Rosso S, Joris F, Zanetti R Risk of basal and squamous cell carcinomas of the skin in Sion, Switzerland: a case-control study. *Tumori* 1999; 85:435-42.
181. Pandeya N, Purdie DM, Green A, Williams G Repeated occurrence of basal cell carcinoma of the skin and multifaailure survival analysis: follow-up data from Nambour Skin Cancer Prevention Trial. *Am J Epidemiol* 2005; 161:748-54

182. Gordon LG, Scuffham PA, van der Pols JC, McBride P, Williams GM, Green AC Regular sunscreen use is a cost-effective approach to skin cancer prevention in subtropical settings. *J Invest Dermatol* 2009; 129:2766-71.
183. Robinson JK, Rademaker AW Relative importance of prior basal cell carcinomas, continuing sun exposure, and circulating T lymphocytes on the development of basal cell carcinoma. *J Invest Dermatol* 1992; 99:227-31.
184. Bakos RM, Kriz M, Muhlstadt M, Kunte C, Ruzicka T, Berking C Risk factors for early-onset basal cell carcinoma in a German institution. *Eur J Dermatol* 2011; 21:705-9.
185. Ulrich C, Jurgensen JS, Degen A, Hackethal M, Ulrich M, Patel MJ, *et al.* Prevention of non-melanoma skin cancer in organ transplant patients by regular use of a sunscreen: a 24 months, prospective, case-control study. *Br J Dermatol* 2009; 161 Suppl 3:78-84.
186. Walther U, Kron M, Sander S, Sebastian G, Sander R, Peter RU, *et al.* Risk and protective factors for sporadic basal cell carcinoma: results of a two-centre case-control study in southern Germany. Clinical actinic elastosis may be a protective factor. *Br J Dermatol*(2004; 151:170-8.

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

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