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Review

Basal cell carcinoma: review of etiopathogenesis, diagnosis and management

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Abstract. Basal cell carcinoma (BCC) is the most common form of skin cancer in white populations, with rising incidence even at early age, thus becoming a burden for health services and a concern for patients. Some risk factors are well-known such as ultraviolet radiation, fair skin type, arsenic exposure, ionizing radiation; but there are others like HPV that still need clarifying. Also, the role of vitamin D in the development of BCC is controversial. Despite the scientific effort and the high advances in fundamental research that identified the implication of p53 and Ptch1 mutation, the origin and signaling pathways involved in the development of this tumor are still not clarified. Presented as single or multiple lesions with several specific clinical aspects, the gold-standard regarding diagnosis continues to be the histopathologic examination. Therapeutic approach of BCC depends on localization, subtype and number of lesions, age of the patient and comorbidities. The best option in most cases is surgical excision with free margins (classical or Mohs' micrographic surgery) to avoid local recurrences, especially on the facial H zone; but cryotherapy, photodynamic therapy, imiquimod, 5-florouracil, electrodessication or electrochemotherapy can also be considered in selected cases. Although the use of sunscreen in secondary prevention of non-melanoma skin cancer would be a rational approach, conclusive evidence published by the last systematic review from Cochrane is lacking due to high inhomogeneity in the design of the available studies concerning this matter.

Key Words: basal cell carcinoma, pathogeny, risk factors, therapy

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Introduction

Non-melanoma skin cancers (NMSC) are represented mainly by basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). It also refers to other types of skin neoplasia like fibroepithelioma of Pinkus, dermatofibrosarcoma protuberans and Merkel cell carcinoma.

NMSC is estimated as one third of all cancers detected in the UK (Lomas et al 2012). Having a very high incidence, they are both an economic burden for health services, and a concern for patients as they can occur on visible areas such as head and neck. BCC is not considered to be fatal (Barton et al 2017). Though, if it is diagnosed late or treated incorrectly, it can destroy anatomical structures and it becomes a therapeutic challenge.

Its development is associated with intensive ultraviolet radiation exposure over time.

Incidence

Basal cell carcinoma is the most common form of skin cancer in white populations, although accurate registry data lack worldwide (Lomas et al 2012). Its incidence is reported to be rising in many countries (Canada, Australia, Spain, Belgium) (Rubió-Casadevall et al 2016; Callens et al 2016) either due to a better report or by increasing exposure to risk factors, such as ultraviolet radiation (UVR).

The incidence varies widely worldwide (1955-2007) for NMSC. From highest to lowest, basal cell carcinoma recorded > 1000 /100,000 person-years in Australia and < 1 in Africa, respectively. The average incidence rates in England were 76.21/100,000 person-years for BCC (Lomas et al 2012).

Europe's population consists mainly in lightly-pigmented individuals, types I-IV Fitzpatrick (over 95%). But data about BCC incidence in Eastern Europe are not reliable due to lack of NMSC registries (Trakatelli et al 2007).

In 1993-1995 the age-standardized incidence rate for BCC in Slovakia was 38.0 (Plesko et al 2000).

In 2011, there were 102,000 cases of NMSC registered in the UK, 75% of them being BCCs. There is also a regional variation in the incidence of BCC, between 0.24/100,000 person-years in London and 121.29/100,000 per person-years in South Wales (Griffin et al 2016).

In Belgium, the world age-standardized incidence rate for BCC increased from 36.9 in 2004 to 98.4/ 100 000 person years in 2012 for males and from 34.2 in 2004 to 102.0 in 2012 for females (Callens et al 2016).

In USA, in 2012, age-adjusted BCC incidence was 226.09/100,000 person (Bath-Hextall et al 2007).

Approximately 10% of patients with BCC have multiple tumors (Rubió-Casadevall et al 2016).

The high incidence among elderly population might be explained by increase of life-expectancy, the accumulation of cell mutations, combined with a poor education concerning sun damage. But research showed that the incidence of NMSC is rising in the young, especially among those aged 30–39 (Bath-Hextall et al 2007). Furthermore, under-recording is a known problem in the matter of NMSC, so surely the morbidity and the impact on health systems are much higher than proven in literature.

Pathogeny

So far, the carcinogenesis of BCC is not clear. Some molecular pathways and cellular progenitors have been identified, but they do not apply for all BCC diagnosed, and do not explain the phenotypic variations.

Molecular

In most cases, the development of BCC is due to a dysregulated signaling of Hedgehog (Hh) pathway towards excessive activation. In normal skin there are factors that can promote signaling, like Smoothened (SMO), and others that suppress it, Patched1 (Ptch1). The end active molecule in this pathway is Glioma-associated homologue (GLI), specifically GLI1. Thus, in BCC, aberrant activation of Hh pathway can be either due to inhibition of Ptch or supra-activation of Smo (Becker and zur Hausen 2014; Epstein 2008).

Hh signaling has been first identified in Drosophila melanogaster, but is of crucial importance to living organisms, so it was conserved throughout evolution. Sonic-Hedgehog ligand (SHH) is one of the most studied ligands in vertebrate pathogenesis. It binds to its receptor Ptch1 on the cell's primary cilia. Consequently, Ptch1 will de-repress SMO, leading to activation of GLI transcription factors (Becker and zur Hausen 2014). In vertebrates, there is another negative regulator of Hh, Suppressor of Fused (SUFU). Its suppression results in high activation of Hh. SUFU acts directly of GLI1 activity, not allowing it to penetrate the nucleus. SUFU is suppressed by SMO activation (Urman et al 2016).

It appears that 90% of human BCC are caused by loss of Ptch1 function (Epstein 2008). Other alterations can be gain-of-function mutations of SMO, GLI (Xie et al 1998) and p53 (Kasper et al 2012).

Gorlin syndrome, basal cell nevus syndrome, is characterized by the development of multiple BCC starting at an early age, and also other tumors like medulloblastoma. It is an autosomal dominant disease, caused by a loss-of-function mutation of Ptch1 gene.

Mutations of p53 tumor-suppressor gene have been identified in nearly 50% of sporadic BCC. Many of its mutations are transitions in dipyrimidine sequences, which are indicative of UVB exposure (Rubin et al 2005). In case of complete loss-of-function of p53, an upregulation of Hh pathway has been reported, through SMO activation in the interfollicular epidermis in mice (Kasper et al 2012).

Besides of Hh pathway itself, later studies have shown the implication of other secondary pathways which are crucial to BCC development.

One of them is Wnt pathway, which has a role in the normal development of hair follicles. Both human and mice BCC show increased levels of β-catenin, which is a critical mediator on the Wnt pathway. In mice, the suppression of Wnt though one of its known antagonists resulted in inhibition of hamartomas developing by Hh activation. Thus, active Wnt is also required for BCC to appear (Kasper et al 2012).

Another indispensable pathway is Inturned (INTU), which has ciliogenic functions during morphogenesis, including in the skin. It is also present in adult tissue. Its expression is elevated in human BCC, together with increased primary cilia formation and activation of Hh. Experimentally, INTU suppression prevented BCC formation in a SMO directed way, preventing cilia formation and Hh signaling. Also, in embryonic fibroblasts which normally respond to Hh activation, INTU disruption blocked SMO-induced Hh; but further GLI2 activation restored Hh function (Yang et al 2017).

Genomic analysis of BCC revealed that mutations are very frequent, probably the most frequent among cancers (65 mutations/Mb). 85% of the BCCs had mutations in TP53 (61%) and mostly in Hh pathway genes (73% in PTCH1, 20% in SMO, 8% in SUFU). Additionally, other oncogenes also presented mutations in more than 80% of the tumors, genes such as: MYCN, PPP6C, STK19, LATS1, ERBB2, PIK3CA, RAS, PTPN14, RB1 and FBXW7. N-Myc and Hippo-YAP pathways were activated in BCC, suggesting their implication in tumorigenesis. Moreover target genes of these pathways seem to be more active in vismodegib-resistant tumors (Bonilla et al 2016).

High risk of BCC is also observed in syndromes related to impaired DNA repairing and telomerase maintenance and others, such as Bazex-Dupré-Christol syndrome, Rombo syndrome, cartilage-hair hypoplasia, and xeroderma pigmentosum (Kasper et al 2012).

Cellular

For most types of neoplasia the cell of origin is yet unknown, but some general mechanisms have been established. One of them is the existence of cancer stem cells that allows tumor growth, and that seem to originate from normal tissue stem cells, and supported by the stroma. However, they are still rarely cited regarding solid tumors (Hanahan et al 2011).

Due to the fact that oncogenic pathways seem to have been identified for most cases of BCC, this allowed experimental tumorigenesis for a more detailed study. There are mouse models of BCC, either with Ptch1 deletion or with activation of Smo through M2 mutant expression (Xie et al 1998). They induce tumors that resemble human superficial BCC (Sánchez-Danés et al 2016).

The name "basal cell carcinoma" originates from its histological resemblance to the basal layer of the epidermis, not its origin.

As for the cells responsible for generating BCCs, there has been a great debate in the literature over the past few years whether stem cells of origin are located in the follicular or rather interfollicular epidermis, or both. Thus, studies have been carried out on mouse models (Sánchez et al 2016; Peterson et al 2015; Grachtchouk et al 2011).

Some studies demonstrated that in the hair follicle there are more stem cell populations that can induce tumors upon Ptch1 deletion (upper and lower hair follicle bulge and secondary hair germ, isthmus), whereas in the interfollicular epidermis only the touch dome epithelia was able to induce tumorigenesis. Touch dome is a mechano-sensory unit and its sensory denervation

blocked tumor formation. It is not excluded that Ptch1 can form tumors from interfollicular stem cells after extended latency. Activation of SmoM2 induce tumor in the interfollicular epidermis, but not from de hair follicle bulge (Peterson et al 2015). In mice, it appears that tumors originating from hair follicles, secondary to Ptch1 deletion, tend to be nodular, whereas the ones associated with the interfollicular epidermis and SmoM2 activation are superficial. The author suggests that there might be a connection between the cell of origin and the phenotype (Grachtchouk et al 2011).

One research assessed the impact of Hh signaling in different cell populations in inducing BCC formation. According to their results, stem cell are able to initiate tumor formation, but not progenitor cells. Stem cells are more dependent on p53- induced apoptosis. Both progenitor cells and stem cells p53 deficient were able to induce BCC, but tumors derived from stem cells were larger in size (Sánchez-Danés et al 2016).

Clinical aspects

Basal-cell carcinoma characteristically arises in body areas exposed to the sun and is most common on the head and neck (80% of cases), followed by the trunk (15% of cases) and arms and legs. Basal-cell carcinomas have also been reported in unusual sites, including the axillae, breasts, perianal area, genitalia, palms, and soles (Rubin et al 2005).

Unlike squamous cell carcinoma, BCC arises on previously normal skin, no premalignant lesion has been identified.

Initially, it can appear as a non-healing lesion, most commonly seen on the face.

Subtypes

Nodular BCC presents as a papule or nodule, with pearly aspect at the periphery, and telangiectasia on the surface.

Superficial BCC resembles a scaly patch or plaque. When examined closely, pearly papules or a fine line of hypopigmentation can be observed at the periphery.

Morpheaform (sclerodermiform, infiltrative) appears as an atrophic indurated, scar-like plaque, with ill-defined margins. Sometimes it can be elevated, with a keloid-like appearance (Burgdorf & Braun-Falco 2009).

Occasionally, it can have a polypoid or verrucous aspect.

All types can present ulceration followed by the formation of crusts. Ulcerations can have irregular margins, much like a rodent's gnaw, thus the name "ulcus rodens". If left untreated it can evolve into "ulcus terebrans", destroying soft tissue, cartilage, even bone.

Also pigmentation can occur (presence of melanin) which can be seen as brown, black or blue, depending on the depth of the melanin.

A special type, fibroepithelioma of Pinkus, a soft pink or skin-colored papule is considered as borderline between BCC and benign follicular tumors.

Naevoid BCC syndrome (Gorlin syndrome) is an autosomal dominantly inherited condition characterized by developmental abnormalities, the occurrence of multiple BCCs and other cancers. Mutations have been found on the patched gene located on chromosome 9, which appears to be crucial for proper embryonic development and for tumor suppression (Johnson et al 1996).

Diagnosis

The clinical aspect is in most cases typical (see in next section). However, there are cases when additional clues are necessary. The first tool in hand is dermoscopy. Of course, the final accurate diagnosis is made by histology (the biopsy is preferred at the periphery of the lesion)

Apart from leading to the diagnosis of the cutaneous tumor, dermoscopy can influence the treatment choice, in terms of histopathologic subtype, presence of pigmentation or ulceration (Russo et al 2016).

As a non-melanocytic lesion, BCCs do not present pigmented network.

For non-pigmented BCC, dermoscopic criteria include: arborizing vessels (or thin vessels with few ramifications), white-red areas, ulcerations or erosions, short white steaks. Fine telangiectasia and small erosions predict a superficial subtype whereas arborizing vessels and ulcerations predict a nodular subtype (Russo et al 2016).

Pigmented BCCs are characterized by blue-gray color, in terms of dots/globules/nests, maple-leaf areas, spoke-wheel or concentric structures. If blue-gray ovoid nests can be identified, the tumor will most probably be non-superficial. All the other structures are more commonly seen in superficial BCC (Russo et al 2016).

White/red structureless areas predict an infiltrative form of BCC. However, a whitish background suggest a sclerodermiform BCC, corresponding to its histologically high amount of underlying fibrosis (Russo et al 2016).

CT or MRI are not commonly used in the diagnosis of BCC. However, 2.5% of periorbital BCCs are associated with orbital invasion. In case of a primary tumor located on the orbital rim, especially if an infiltrative or morpheaform subtype is suspected, or if there is a decreased range of motion of the extraocular muscles, CT or MRI should be considered (Humphreys et al 2017).

By cutaneous ultrasound (high-frequency), one can assess the morphology of NMSC and also the extension of the primary tumor. BCC may present hyperechoic spots, and ultrasound could also be used to identify BCC subtypes. Three-dimensional reconstruction of NMSC using the ultrasound aspect can be performed. At this time, it is a promising technique but is not available in current clinical practice (MacFarlane et al 2017).

Optical coherence tomography is a new imaging technique used in dermatology. Concerning non-pigmented BCC it proved slightly increased sensitivity (not statistically relevant), but significantly increased specificity compared to clinical and dermoscopic assessment (Ulrich et al 2015).

The utility of PET CT is limited for slowly growing tumors, such as BCC (MacFarlane et al 2017).

Histological aspect

Regarding the histological aspect, in hematoxylin-eosin staining, BCC is characterized by a proliferation of basaloid cells (round or cubic cells, with a large nucleus, and basophilic cytoplasm), with a marginal palisadation of individual tumor nests. Mitosis are frequent. The tumor nests are surrounded by a fibrous stroma, usually with a thin cleft in between. No proliferations of melanocytes are present.

The subtypes include: nodular, superficial, infiltrative (micronodular), morpheaform (sclerosing), or mixed. Some rare

variants are basosquamous (metatypical), or composite carcinomas (Myrto Trakatelli et al 2017).
Nodular tumors present asymmetric tumor nests in the dermis, generally circumscribed. In superficial tumors, nests are observed along the dermo-epidermal junction, along with apparently normal skin in between. It is multifocal and progresses radially, laterally. Micronodular BCC presents tumor nests much smaller in size compared to nodular BCC. It also infiltrates the deep dermis and/or subcutis. Thin, branched islands of tumor cells surrounded by fibrous stroma can be seen in sclerosing forms. Infiltrative BCC is characterized by irregular tumor nests in shape and size, with sharp angulation at their peripheral contour. In fibroepithelioma, stroma is more prominent than the tumor cell strands. Basosquamous form (metatypical BCC) presents focal keratinization, similar to squamous cell carcinoma (Burgdorf & Braun-Falco 2009; Crowson 2006). Composite carcinomas present features of both SCC and BCC, clearly distinguishable (Trakatelli et al 2017).
Most BCCs are nodular and superficial, and both have a rather slow growth. On the contrary, micronodular, infiltrative, basosquamous subtypes are considered aggressive due to high recurrence rates (Trakatelli et al 2017).

Risk factors

There are many studies concerning risk factors associated with the development of BCC, the most convincing evidence being related to sun exposure (skin type, hair color, actinic keratosis, sunburn in childhood, outdoor occupation, high altitude, indoor tanning, vitamin D serum levels and photosensitizing drugs). Similarly, behavioral aspects can have the same bias (overweight, alcohol consumption, psychiatric disorders). Immunosuppression and impaired DNA repair mechanisms are also linked to increased BCC incidence. The relation with HPV infection is not yet well defined.

UVR

The waveband of terrestrial UVR is ~295 to 400nm), of which the majority is UVA (~78% UVA I 340 -400nm; ~17% UVA II 320 -340nm), with UVB (~295 -320nm) typically comprising less than 5% (Fajuyigbe & Young 2016).
UVR is absorbed by chromophores in the skin. DNA is one important chromophore (maximum of DNA and RNA absorption is about 260 nm, so UVB is causing most of the cellular lesions). Chromophores can have lesions of their own or determine the production of reactive oxygen species that damage adjacent molecular and cellular targets. The lesions that DNA can suffer can lead to: skin cancer, erythema (presence of sunburn cells – apoptotic keratinocytes), immunosuppression and photoageing (Anna et al 2007).
UVR induces the synthesis of matrix metalloproteinases (MMP), especially MMP – 1, which are associated with degradation of dermal structural proteins such as collagen (Dong et al 2008).
Many studies highlight the greater incidence of BCC, and skin cancer in general, in light-skin populations.
Protection against UV are extrinsic (ozone layer, antioxidant consumption, sunscreen, clothes) and intrinsic (stratum corneum, melanin pigment).
The ozone layer also partially impedes the transmission of UVB and, to a lesser extent, UVA. Thus any environmental insult that results in depletion of the ozone layer would be expected to increase the population risk of keratinocyte carcinomas.
There are some factors that influence the effective dose of UVR, even if the duration of the exposure is identical. These are latitude, altitude, and time of day. Consequently, those who live near the equator receive higher UVR doses due to greater proximity to the sun. Also, higher the altitude, higher the UVR dose. Solar UVR doses are greatest during the afternoon and in summer months (World Health Organization, 2015) (Small et al 2016). Persons who were born at higher altitude are more prone to develop multiple BCCs than single BCC (Hallaji et al 2011).
Outdoor workers are more likely to develop nodular BCC with no increased risk for superficial BCC. Truncal BCC was more common in indoor workers, which may suggest other etiological factors are involved in BCC such as genetic predisposition (Husein-Elahmed et al 2017).
Indoor tanning has been classified by the International Agency for Research on Cancer among the highest category of carcinogens, and a recommendation discouraging persons younger than 30 years old to use sunbeds has been published. Regarding the specific association with BCC there is weak evidence (Belbasis et al 2016).
Increased levels of serum vitamin D (25-OH cholecalciferol) seem to be associated with higher risk to develop a BCC (Caini et al 2014). It is known that inactive vitamin D (cholecalciferol) is synthetized in the skin under the effect of UVR. It is then activated in the liver and kidney. Serum levels of 25-OH cholecalciferol are used to indicate the status of vitamin D (Belbasis et al 2016). High levels of vitamin D are associated with high incidence of basal cell carcinoma and melanoma, but not of squamous cell carcinoma (van der Pols et al 2013). Dietary supplements of vitamin D, seem to reduce the incidence of melanoma in patients with NMSC (Reddy et al 2013). However, a recent meta-analysis showed slightly increased risk of BCC with high dietary or supplement intake of vitamin D (Park et al 2016).

Skin type

Skin color is traditionally defined by the Fitzpatrick skin type system since 1988 that categorizes individuals into six skin photo types (I -VI) based on self-reported tanning and sunburning susceptibility. It is defined genetically, involving over 17 genes (Fajuyigbe and Young 2016).
The World Health Organization (WHO) estimated that nearly 98% of all keratinocyte carcinoma cases occur in patients with sun-sensitive skin types (Fitzpatrick skin types I, II, III) (World Health Organization, 2006) (Small et al 2016).
Skin color influences the differential distribution of DNA damage in the epidermis. Melanin in the basal layer (especially in dark skin) has photoprotective effects. Patients with fair skin types have greater susceptibility to skin cancer due to DNA lesions in the basal layer, which contains proliferative stem cells (Fajuyigbe and Young 2016).
Also, a high risk of actinic damage and non-melanoma skin cancer was reported in African albinos, suggesting a protective role for melanin (Wright et al 2015).
However, patients with vitiligo seem to have a reduced incidence of skin neoplasms compared to the general population, despite the belief concerning the protective role of melanin. A possible explanation given by the authors is a decreased photodamage

and increased levels of wild-type p53 in keratinocytes found in their skin (Paradisi et al 2014).
Overall, there seem to be other factors than the quantity of melanin implicated in the development of BCC due to sun exposure, such as the type of melanin, the repair mechanisms and the antioxidant capacity (Fajuyigbe and Young 2016).
Actinic keratosis is a premalignant skin lesion induced by chronic exposure to UV light, which is known to be associated with SCC. There is recent evidence concerning the association of actinic keratosis, and hair color with risk of BCC. Hair color is also related to the Fitzpatrick skin type, confirming a skin photosensitivity (Belbasis et al 2016).

Alcohol consumption
There is some poor evidence regarding the intake of alcohol and the risk of developing a BCC, however it appears not to be dose-related. In US at least sunburns seem to be more frequent and severe in alcohol consumers. We may say that alcohol consumption is a marker for persons who are unaware of their health status, rendering them more susceptible to disease. This includes too much sun exposure, thus augmenting the risk of BCC. Most probably alcohol does not cause BCC (Reinau et al 2014).

Smoking
Although smoking is a well-known risk factor for cancer, it seems that it is not the case with BCC. Moreover, some authors implied that smoking might even decrease the risk of BCC. (Reinau et al 2014).

Body mass index (BMI)
Same as for smoking, overweight seems to be "protective" for BCC. The supposition is that overweight people have a much more sedentary way of life, spending less time outdoors, and using less revealing clothes, overall having less sun exposure. However, bodyweight itself does not influence the risk for developing a BCC (Reinau et al 2014).
A recent meta-analysis reveals a non-linear inverse correlation between BMI and the risk for non-melanoma skin cancer, both for BCC and squamous cell carcinoma. Also, women tend to be more protected than men. The correlation was maintained when corrected for sun exposure and outdoor activities. Thus, there is a hypothesis concerning the protective effect of estrogen and/or adipokine (leptine) in the development of skin neoplasms (Zhou et al 2016).

Comorbidities
The relation between BCC and other diseases appears to be significant in terms of iatrogenic or non-iatrogenic immunosuppression (rheumatoid arthritis, inflammatory bowel disease, organ transplantation, malignancies, seborrheic dermatitis) (Reinau et al 2014). This can be explained both by an impaired immune system and specific photosensitizing and oncogenic effects of certain immunosuppressive drugs. Non-melanoma skin cancers are more frequent in organ transplant recipients, thus, dermatological surveillance is part of post-transplant care (Mudigonda et al 2013).
Also, screening for skin cancer should be in mind for persons suffering from rheumatoid arthritis and inflammatory bowel disease. BCC is also associated with rosacea and melanoma, probably due to their common risk factor, the sun exposure (Reinau et al 2014).
Psoriasis is associated with a high risk of NMSC, especially SCC, but also BCC, whereas the risk of melanoma is not increased. This risk is highly correlated with psoralen-UVA treatment, being dose-dependent, but also with immunosuppressive therapies such as cyclosporine and possibly methotrexate (Pouplard et al 2013). Treatment with TNF-alpha inhibitors in patients with psoriasis increases the rate of SCC but not BCC (Asgari et al 2017). The relation between UVB-NB therapy and NMSC in psoriatic patients is not yet well known. However, it appears not to be a risk factor in retrospective studies (Archier et al 2012).
NMSC seemed to appear less frequently in patients with diabetes mellitus, schizophrenia and dementia. The explanation could be a bias concerning UVR (Reinau et al 2014).

Other cancers
A personal history of BCC may be an indicator for reduced DNA repair capacity and so, may predict the risk of subsequent cancer development (Linos et al 2017).
In a large cohort study, white patients with NMSC were more prone than healthy individuals to develop a second primary malignancy. Both men and women present high risk of melanoma. Women also have a slightly higher risk of breast and lung cancer (Song et al 2013).
A systematic review until February 2016 shows no increased risk of mortality in patients with a history of BCC (for non-melanoma cutaneous neoplasia, a high risk was observed for SCC). However, among patients with multiple neoplasia, the presence of either BCC or SCC was responsible for lower survival rates from second primary malignancies (Barton et al 2017).

HPV
Many studies have mentioned an association between non-melanoma cutaneous malignancies and the presence of HPV (lesional HPV DNA and seropositivity of cutaneous HPV). HPV seems not to have an involvement in carcinogenesis of BCC but rather of squamous cell carcinoma (Iannacone et al 2012). The mechanism is unclear, but HPV proliferation is strongly related to keratinocyte maturation, probably leading to a squamous differentiation. More studies are needed to elucidate this aspect (Ally et al 2013).

Arsenic
Arsenic is a known risk factor for NMSC. Besides occupational exposure, there is also the risk of contaminated food or water, which is a public health problem worldwide. High arsenic contamination has been reported in Africa, Asia, Eastern Europe and also USA. In a recent case-control study, it was shown that in patients with low-dose arsenic exposure (<5ug/L), patients suffering from NMSC have higher inorganic arsenic levels in their urine compared to the control group (Kim et al 2017).

Treatment

Management of BCC depends on a number of factors including the size, site and histological subtype of the tumor, comorbidities, previous treatment history, life expectancy and patient

preference. It is also important to consider whether the intention of treatment is curative or palliative.
Options include: surgical excision, electrodessication and curettage, cryosurgery, imiquimod, photodynamic therapy, 5-fluorouracil, radiation therapy, Hh inhibitors, combination therapy and observation (Wiznia & Federman 2016).
Due to local extension of the tumors, lesions occurring on the face, especially in the center area, should be treated as soon as possible to reduce adverse effects of the treatments, such as unaesthetic or dysfunctional scars. One should not disregard the fact that an amelanotic melanoma can mimic a BCC, emphasizing the importance of immediate treatment.
The treatment of choice for most cases of BCC is surgical excision with 4 mm margins, down to the subcutaneous fat. Facial nodular BCC <1cm can be excised with 2-3 mm margins with 13-24% risk of recurrence (Lewin & Carucci 2015).
If the tumor is recurrent or located in sites where tissue preservation is essential (facial H zone), either for functional or cosmetic reasons, the gold standard is Mohs' micrographic surgery (excisional surgery which allows three-dimensional evaluation of the tumor margins through frozen sections). It has the best margin control, but a very high cost and it consists in multiple stages of surgery (Lewin & Carucci 2015).
Electrodissecation and cryotherapy have no margin control and therefore high recurrence rates (Wiznia and Federman 2016).
Imiquimod, PDT and 5-FU have high costs, good cosmetic results, but no control of histologic clearance (Wiznia and Federman 2016).
Hh inhibitors (vismodegib and sonidegib) are approved by the FDA for metastatic BCC, locally advanced inoperable BCC or those recurred after surgery. They are costly and have some low severity side effects (e.g. dysgeusia and muscle cramps) (Sekulic et al 2012). An increased risk of non-response to vismodegib was reported for BCCs with CD56 and CXCR4 expression of tumor cells. The authors explain this by possible cross-talks between pathways. Since SMO is inactivated through vismodegib early in the hedgehog pathway, the presence of either CD56 or CXCR4 might induce a hedgehog activation along the way (Castillo et al 2016).
Laser treatment are also an option for biopsy-proven BCC. Vascular targeting (PDL and NdYAG) and ablative lasers (CO2) have the potential of good cosmetic outcome, reduced damage to collateral skin, lower bleeding, better scarring. They have been shown to have similar or higher recurrence rates than other approved therapies. Further studies are needed to optimize parameters (Soleymani et al 2017).
Electrochemotherapy that combines cytotoxic agents (bleomycin for BCC) with electric pulses to enhance penetration can be an option for multiple or large BCC who cannot undergo conventional therapy. One or two cycles of electrochemotherapy seems to be a good palliative treatment for these cases (Campana et al 2017).
In elderly patients observation can also be an option, but more aggressive tumor can be missed such as amelanotic melanoma or Merkel cell carcinoma (Wiznia & Federman 2016).

Nodular BCC
Treatment of choice is surgical excision with 4mm or more excision margins (Lear et al 2014). Dermoscopy can offer a more precise assessment of the tumor extension, therefore it can guide the estimation of excision margins to reduce recurrence rates (Russo et al 2016).
Topical treatment with photodynamic therapy using 5-aminolaevulinic acid can be used only in thin nodular BCC (<0.7mm) with similar efficacy as surgery but better cosmetic results (Cosgarea et al 2013). This procedure requires prior debulking (Roozeboom et al 2013).

Infiltrative / large tumors or sensitive sites
Mohs' micrographic surgery allows the best control for tumor-free margins, having the lowest recurrence rates (Lear et al 2014).

Superficial BCC
If clinical and dermoscopic features are highly suggestive for a superficial type of BCC, the clinician usually chooses non-surgical techniques, such as cryotherapy, 5-fluorouracil or imiquimod. Imiquimod is more likely chosen when small erosions or ulcereations are present on dermoscopy (Russo et al 2016).
PDT with methylaminolaevulinate seems to be inferior to imiquimod and similar to 5-FU although tumor-free survival at 1 year was 70-80% for all groups, with similar cosmetic outcomes (Lear et al 2014). Pigment can be detected through dermoscopy in about 30% of non-pigmented BCC, which restrict the use of PDT in such tumors (it will not be effective enough due to the competitive absorption of light by melanin) (Russo et al 2016).
Imiquimod is known to activate Th1 cells in vicinity of the tumors. A recent study shows that it has also a direct effect of Hh signaling in BCC through adenosine receptors (ADORA) (Wolff et al 2013).

Positive margins and no possibility of re-excision
Radiotherapy can be used for these patients, as an adjuvant therapy. Also it can be an option for patients who cannot undergo surgery due to comorbidities or other criteria. Cosmetic outcomes are not favorable and can worsen over time, and thus it is more suitable for elderly patients. The risk of recurrence is rather high (about 16% or 8% with brachytherapy) and 60% of patients develop new tumors (Lear et al 2014). Also acute toxicity has been reported in 25% to 91% of cases (Delishaj et al 2016).

Metastatic BCC
Although BCC is considered a non-metastatic skin cancer, there were 172 cases published in English between 1981 and 2011. Distant and regional metastasis were equally present. Patients who developed distant metastasis (mostly distant lymph nodes, lung, bone or bone marrow, liver) tended to be younger (58 years old) compared to the ones with regional metastasis (66 years old). The treatment used were chemotherapy and surgery. The mean survival interval was between 24 months (distant metastasis) and 84 months (regional metastasis) (McCusker et al 2014).
There is a supposition that metastatic BCC resistant to Hh-inhibitors (vismodegib) may respond to nivolumab (anti PD-L1 antibody) based on molecular pathology (PD-L1 amplification and high mutation rate of tumor cells). One case presented rapid regression in 4 months under nivolumab treatment (Ikeda et al 2016).

Prevention

Sun protection education

There is one review assessing the efficacy of solar protection in preventing non-melanoma skin cancer which included only one article which was suitable. It concerned sunscreens (daily vs. discretionary use) and it showed no significant effect in the development of either BCC or squamous cell carcinoma over 5 years follow-up. The authors conclude that more research should be carried out on this subject and that results may alter the current perspective (Sánchez et al 2016).

Chemoprevention

A review published in 2016 shows no clear association between the use of chemoprotective agents and decrease of incidence in BCC. Most studies focus on pre-malignant lesions such as actinic keratosis. Products like beta-carotene, polyphenols (either systemic or topical), statins, oral retinoids have no influence. However, topical use of tazarotene gel 0.1% daily for 12 weeks can decrease by 25% the size of the tumor before excision. A topical use of combined antioxidants (L-ascorbic acid (vitamin C), α-tocopherol (vitamin E) and ferulic acid or phloretin) reduce the thymine dimer formation, in addition to sunburn cell formation, and explession of matrix metalloproteinase-9 and p53, most of which are involved in the ethiopathogeny of BCC. Oral administration of difluoromethylornithine (a synthetic analog of the amino acid ornithine) over 4-5 years can reduce BCC incidence in organ-transplanted patients (Mounessa et al 2016).

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