NON-MELANOMA SKIN CANCERS: PERSPECTIVES OF EARLY DIAGNOSIS AND THERAPY

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ABSTRACT

Non-melanoma skin cancers (NMSC) belong to the group of most frequent malignant cancers among Caucasian race. Similar to other cancer types, NMSC progression is an outcome of environmental factors and genetic background. The predominating risk factor for NMSC is the prolonged exposure to ultraviolet (UV) light. The origin place for non-melanoma skin cancers is the epidermis. There are two main types: basal cell carcinoma (BSC) and squamous cell carcinoma (SCC). Basal cell carcinoma origins from the basal layer of epidermis. BCC progresses relatively slowly but exerts a substantial damaging impact on adjacent tissues. SCC, in contrast to basal cell carcinoma, metastasise more frequently, typically to local lymph nodes. The observed rise of NMSC incidence in recent years prompts to move forward to a more effective prophylactic approach and comprehensive treatment. Ultimately, the actual diagnosis of all subtypes of NMSCs is based on the result of a histopathological examination of an excised skin fragment. The therapeutic process depends on several features that account for the clinical image of the lesion: the primary focus, the presence of metastases to the local lymph nodes and to distant parts of the body. Photodynamic diagnosis (PDD) and photodynamic therapy (PDT) are promising, non-invasive methods which may be helpful in early diagnosis and treatment of superficially growing NMSCs.

BACKGROUND

Non-melanoma skin cancers (NMSC) belong to the group of most frequent malignant cancers among Caucasian race [1]. Similar to other cancer types, NMSC progression is an outcome of environmental factors and genetic background [2]. The predominating risk factor for NMSC is the prolonged exposure to ultraviolet (UV) light, particularly that of type B (UVB). Another significant etiological factor is light skin phenotype (commonly referred to as phenotypes I-III). Despite the expanding awareness of the harmfulness of UV radiation (UVR), the number of patients suffering from NMSC is on a steady rise [3]. There is a positive correlation between the NMSC incidence and the geographical latitude – it is substantially higher in the equatorial zone [4].

SKIN CANCERS

Skin cancers can be classified into two groups based on their origin: melanoma and NMSC. Melanoma is a highly metastatic cancer that arises from neuroectodermal melanocytes. In contrast to melanoma, NMSC are of epithelial origin, do not contain any pigment (melanin) and are thus colourless [5].

NON-MELANOMA SKIN CANCERS

The origin place for non-melanoma skin cancers is the epidermis. There are two main types: basal cell carcinoma (BSC) and squamous cell carcinoma (SCC) [6].

Basal cell carcinoma origins from the basal layer of epidermis. BCC progresses relatively slowly but exerts a substantial damaging impact on adjacent tissues. It is malignant only locally as the long-distance metastases are described in the literature as individual cases (<0.1%).

BCC accounts for 70-80% of all diagnosed non-melanoma skin cancers. The average age for the first diagnosis of NMSC is 60 years, but the incidence has been reported to be increasing in the younger groups of patients. Typically, a professional dermatologic help is sought by patients when a slowly growing lesion, bleeding upon mechanical disturbance, appears [7].

Clinical classification of basal cell carcinoma is based primarily on its morphological features and includes the following subtypes: superficial (*BCC superficiale*), nodulous (*BCC nodosum*), ulcerating (*BCC exulcerans, ulcus rodens*), cystic (*BCC cysticum*), pigmented (*BCC pigmentosum*) and morphoeic or sclerosing (*BCC morpheiforme*) [8].

BCC lesions localise predominantly within the facial skin (upper-middle part) that has been damaged by prolonged exposure to light radiation. Superficial subtypes usually localise on the truncal areas of skin [9].

Squamous cell carcinoma is a malignant cancer that originates from the stratum spinosum of epidermis. SCC, in contrast to basal cell carcinoma, metastasise more frequently, typically to local lymph nodes in 2.5-50% of reported cases [10]. Immunocompromised patients are at the upmost risk of SCC, thus SCC has 60-100 times higher incidence in post-transplantation patients who are receiving immunosuppressive drugs as compared with healthy population [11].

There are two subtypes of squamous cell carcinoma based on the morphological features of the lesion: *SCC exulcerans* and *SCC vegetans*. Progression and invasiveness of SCC are dependent on the localisation of the tumour and its malignancy. Squamous cell carcinoma most typically localises on the edge of skin and mucosa – on lower lip, auricular (high metastatic potential), areas adjacent to nostrils and reproductive organs.

Squamous cell carcinoma arises from the areas of skin damaged by UVR, at the spots of chronic inflammation, irritation (mechanical or chemical) or at the sites of actinic keratosis (AK). SCC that emerges *de novo* is characterised with a higher malignancy than that of AK origin [12].

ACTINIC KERATOSIS

In the context of the most recent molecular and genetic studies, AK is considered as squamous cell carcinoma *in situ*. Emergence of AK is induced by prolonged exposure to ultraviolet radiation, UVB in particular. Lesions occur typically in the areas exposed to sunlight, i.e. the skin of face, head, auricular and upper limbs. These lesions take a form of erythema spots, most frequently with superficial hyperkeratosis. Statistically, around 20% of untreated AK develop into metastatic squamous cell carcinoma [13].

The recommended method of AK treatment is a therapy of both clinically evident keratosis together with broader areas of sunlight damaged skin, the so-called field cancerisation. These areas appear as unaffected epithelium but are actually fields of photocancerisation. Within such fields, there are keratinocytes that harbour genetic alterations predisposing for skin cancer development. They can potentially give rise to AK, and to SCC as a consequence [14].

The consideration of field cancerisations in patient's treatment delivers preventive and therapeutic outcomes. It leads to the remission of the already emerged AK lesions and prevents the formation of potential new changes with cancer promotion included.

DIAGNOSIS OF NON-MELANOMA SKIN CANCERS

The diagnosis of typical forms of NMSC can be conducted based on the morphological features of the lesion. The majority of NMSCs (excluding superficial BCC) localise at the field of UVR damage. However, an examination of the whole skin is necessary as the disease might occur in multiple lesion spots.

The most frequent form of basal cell carcinoma, nodulous BCC, appears as a convex nodule surrounded by a pearly edge. Pigmented BCC can be recognised as a form of nodulous BCC with accommodation of melanin. Superficial BCC has a particularly chronic progression and localises in the shallow layers of truncal skin. Lesions are usually numerous, flat and well defined by a slightly protruding edge. *BCC exulcerans* exhibits an ulcerating focus surrounded by a rigid and infiltrated edge. This subtype can damage the adjacent tissues deeply, affecting muscles and bones (*ulcus rodens*). Lesions of

BCC morpheiforme subtype have a porcelain-like appearance and typically do not break apart. *BCC cysticum* takes a form of petit, transparent nodules located usually on eyelids. Dermoscopy might be a helpful tool in the diagnosis of certain types of BCC, such as pigmented BCC [15].

Squamous cell carcinoma typically appears with an infiltrated base and often with protruding, flipped edges but are devoid of pearly-like edge observed in BCC.

Upon examination of a patient diagnosed with cancer, it is recommended to always assess local lymph nodes of the head and neck. If the lesions are advanced, it is recommended to prescribe scans, i.e. abdominal USG, chest radiograph, to exclude long-distance metastases.

Ultimately, the actual diagnosis of all subtypes of NMSCs is based on the result of a histopathological examination of an excised skin fragment. In addition to diagnosis, tumour biopsy allows practitioners to assess the lesion in accordance to TNM classification (tumour, nodes, metastasis) [16].

PHOTODYNAMIC DIAGNOSIS

Photodynamic diagnosis (PDD) is a tool that allows for an early diagnosis of cancer and the assessment of the margins of the lesion. This method is based on the fluorescence of locally administered compound that sensitizes the skin against light, the so-called photosensitizer. Due to the fact that the photosensitizer accumulates selectively in cancerous cells, PDD enables the visualisation of pathological foci.

The mechanisms of PDD is based on the co-operation of two components:

1. the photosensitizer, a pigment that selectively accumulated in atypical tissue and sensitizes it against light,
2. the source of light of a specific wavelength [17].

The most frequently used photosensitizers are porphyrin compounds. In order to induce fluorescence, it is necessary to shine a light of a wavelength corresponding with the peak absorption of the photosensitizer. In the case of protoporphyrin IX (PpIX), a compound that arises from a precursor – aminolevulinic acid, the required wavelength is ca. 408 nm. PpIX becomes excited and upon return to its base energy state it emits red fluorescent light within the pathologically altered tissue that it accumulated in [18].

The 'shining tumour' image is usually visible by a naked eye. To further analyse the emission spectrum, it is possible to capture it as an image and then process it digitally.

Photodynamic method does not exclude the necessity to conduct histopathological examination but it facilities the determination of the biopsy site. It thus provides a kind of "optical biopsy" [19]. Such approach allows for the visualisation of the tumour together with the margin of dysplastic cells surrounding it. The latter are the main reason of cancer reappearance after imprecise surgical excision.

THERAPY OF NMSCs

The therapeutic process depends on several features that account for the clinical image of the lesion: the primary focus (dimensions, depth of invasion), the presence of metastases to the local lymph nodes and to distant parts of the body [20].

In order to absolutely eradicate an NMSCs lesion, it is crucial to use the most efficient therapy and at the same time, take necessary measures to ensure positive aesthetical effect as the lesions concern predominantly easily visible areas of patient's skin. Surgical measures oftentimes lead to deforming scars, and thus are not welcome by the patients [21]. That is why, provided that prophylactic examinations are conducted properly, a preferred way of treatment is a local operation, especially if the lesion is superficial or unlikely to metastasize. In a case of cancer reappearance or failure to eradicate it in the first attempt, a surgical operation is recommended (given that a margin of 4-6 mm is possible). If a radical surgical operation is not possible, it is necessary to apply radiotherapy [22].

Local ways of NMSC treatment include cryotherapy and photodynamic therapy (PDT), as well as pharmacological methods: 5-fluoruracyl and imiquimod [23].

Cryotherapy is a simple, cheap and quick method that can be applied to erase individual, non-invasive foci of NMSC. There are, however, unwelcome side effects: pain, the risk of pigmentation and peeling of the adjacent skin [24].

5-fluoruracil (5-FU) is a chemotherapeutic designed for a local administration that inhibits DNA synthesis and alters RNA function. The main disadvantage of 5-FU is the long treatment time and certain side effects: itching, erythema, pain and secondary infections and depigmentation.

Imiquimod is a immunomodulatory compound that affects immune response by stimulating monocytes and macrophages. Its anti-cancer effect is based on the enhanced cell-mediated immunity through the stimulation of immunocompetent cells and the release of pro-inflammatory cytokines. The most frequently observed side effects of imiquimod are excessive immune response of the skin [25].

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) enables a selective destruction of pathologically altered cells without the risk of damaging healthy tissues. The mechanism of action of photodynamic therapy requires presence of three components: a photosensitizer that localizes in pathologically altered tissue, a light source of specific wavelength that activates the photosensitizer and oxygen molecules dissolved within the tissue. The photosensitizer, administered locally, accumulates selectively in cancerous cells. The reason behind this phenomenon lies in the property of the photosensitizer – it tends to be retained by cells of pathologically high metabolic rate and proliferating in an uncontrollable manner, such as cancerous cells. Due to the radiation of light of specific wavelength adjusted to the absorptive properties of the photosensitizer, the latter becomes activated and passes the energy acquired from light to

surrounding molecules. This photodynamic reaction results in excitation of oxygen molecules and thus production of free radicals (*ROS – reactive oxygen species*) that lead to the cell death [26].

Among all ways of NMSCs treatment, PDT is reported as a non-invasive, selective and effective method [27].

Numerous clinical studies confirm the efficacy of PDT in basal cell carcinoma treatment, particularly the superficial and nodulous subtype of relatively small dimensions. Rhodes *et al.* observed a complete response of nodulous basal cell carcinoma after PDT, almost as high as surgical excision (91% and 98% in 3 months after treatment, respectively), however, the first yielded outstanding cosmetic results in comparison to the latter [28]. In the study of Peng *et al.* the application of ALA-PDT resulted in the treatment of 87% of lesions of superficial BCC subtype and 53% in the case of nodulous subtype [29]. Cosgarea *et al.* reported a similar therapeutic response in case of PDT treatment and surgical operation of the lesions (95.83% and 95.65%, respectively) [30].

Considering the limitations of light penetration into the tissues and bioavailability of photosensitizers, photodynamic therapy is not recommended as a monotherapy for deeply infiltrating squamous cell carcinomas. Early surgical operation is recommended to prevent the spread of SCC to local lymph nodes. It is noteworthy, however, that PDT is an effective method for the treatment of *in situ* SCC (carcinoma *in situ*, ca *in situ*) [31].

Photodynamic therapy plays an important role in the treatment of lesions of actinic keratosis, especially that of milder hyperkeratosis. In the study conducted by Piacquadio *et al.* out of 243 patients diagnosed with numerous multiple lesions, PDT yielded therapeutic effects in 77% of the examined group – already after the first light exposure [32]. It is worth to mention that PDT results in much better aesthetical effects than cryotherapy that is routinely practiced in the treatment of AK (taking into account comparable therapy outcomes).

CONCLUSIONS

Non-melanoma skin cancers are a challenge of modern oncological dermatology, both in terms of diagnosis and therapy. The observed rise of NMSC incidence in recent years prompts to move forward to a more effective prophylactic approach and comprehensive treatment. Photodynamic method, that encompasses both diagnostic and therapeutic tools, plays an important role in the treatment of non-melanoma skin cancers. Its selectivity and non-invasiveness makes it a preferred method for the treatment of easily visible areas of the body. Its aesthetical effectiveness makes it an anticipated therapy for patients who would otherwise have to face an invasive surgical operation followed by tissue damage, scars and no guarantee of absolute eradication of the cancerous cells.

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ABBREVIATIONS

5-FU – 5-fluoruracil
AK – actinic keratosis
BSC – basal cell carcinoma
NMSC – non-melanoma skin cancers
PDD – photodynamic diagnosis
PDT – photodynamic therapy
PpIX – protoporphyrin IX
SCC – squamous cell carcinoma
UVR – UV radiation

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