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Periocular basal cell carcinoma of the eyelids – review

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Introduction. Basal cell carcinoma is the most common tumour of the eyelids and periocular region throughout the world. BCC represents 90 % of malignant tumours of the eyelids, predominantly in the male population. The incidence is higher in age over 60. Over 50% of BCC of the periocular region initially occur on the lower lid and inner angle.

Research objectives. Literature review of the epidemiology, aetiopathogenesis, clinical attributes, diagnostics, treatment histopathology, recurrence, prognostic factors, and management of BCC.

Core of work. Standardised incidence of diagnosis C44 in the period 1997–2012 in Slovakia ranged from 35.05 to 73.9 cases per 100,000 inhabitants. The histopathological examination is essential. The first consideration for treatment of periocular BCC is radical surgical excision using Mohs micrographic technique. We can consider the apoptotic index, the expression of Bcl-2, as an unexplained prognostic factor of BCC recurrence.

Conclusion. Increased attention must be given to periocular malignant tumours. Functional and aesthetic outcome in patients is important after clear excisions and reconstruction should be carefully considered. Radical exenteration is considered in the case of orbital invasion of high-risk aggressive BCC.

Introduction. Non-melanoma skin tumours (NMSC) are the most widespread malignancies in the Caucasian population, with 18–20-times higher incidence than malignant melanoma and representing 5–10% of all skin tumours. [1]. The most common skin cancer is the basal cell carcinoma (BCC). Over 75% percent of BCC occur in the head and neck region. At about 20% of BBC appear in periocular region. The age of BCC is typically in patients over 60 years. [2, 3]. It arises from pluripotent cells localised in the stratum basale of the epidermis and in the area of the outer hair sheath. Squamous cell carcinoma (SCC) is a much less common but more aggressive tumour than BCC, with eventual metastases into regional lymph nodes. [4]. Orbital invasion is uncommon with a reported incidence about 2%. [5]. BCC of the eyelids has a high risk of recurrence, especially in infiltrative types. They can invade the orbit region and lead to the probability of radical exenteration. The orbital invasion of BCC is in 2–4% and the risk factors include large size of the primary tumour also multiple recurrences, infiltrative histological subtype, perineural spread, the medial canthus and inner angle localization and patient's age over seventy. In less than 1% of basal cell carcinomas perineural invasion is present. [6, 7]. The primary treatment modality for BCC is surgical resection. [8-10].

Core of work

Epidemiology

Nowadays it is impossible to collect the data from cancer registries that would analyse BCC worldwide. We analysed data of 68,516 patients with dg.C44. in the period 1997–2012. The standardised incidence ranged from 35.05 to 73.9 cases per 100,000 inhabitants. The development of the incidence of clinical stages of malignant skin tumours in the period from 2000–2012, regardless of age. Standardised mortality ranged from 0.2 to 0.9 cases per 100,000 population. Specific data on the diagnosis of C44.1 (Malignant tumour of the skin of the eyelid, including the canthus – the third position of the C44 reporting code) cannot be obtained (NCR 2022). The first data on the detected disease are in the age category of 10–14-year-olds. The incidence then gradually increases up to the maximum in the age category of 70–74-year-olds. Age-specific incidence (or mortality) is the number of cases per 100,000 patients in a given age category and shows a rising tendency for the monitored diagnosis (Fig. 1).

Approximately 40% of patients who have had one BCC will develop another lesion within five years, although the probability of developing a subsequent BCC following the first BCC is significantly less than after a next BCC (12.8% versus 33.9% percent in first year; 20% versus 51.8% in 2 year interval and 34.6% versus 75% in 5 year interval). [11].

The aetiology is linked mainly to exposure to UV radiation in people with pale skin. This fact is founded on extensive studies conducted in Europe, Australia and
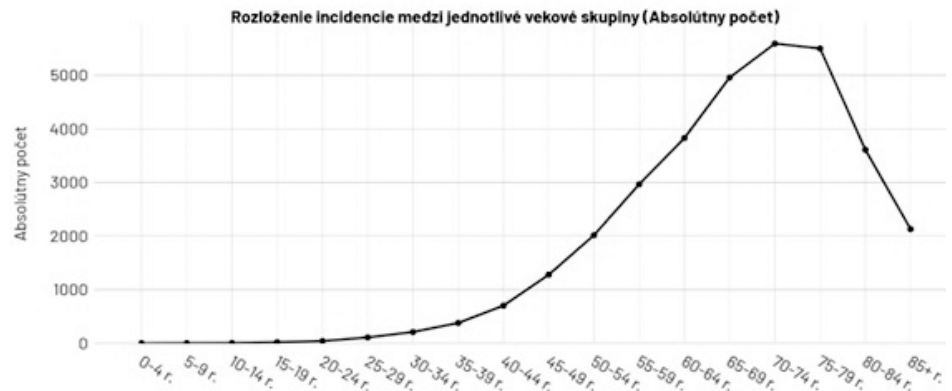
Fig. 1. Malignant tumours of the skin of the eyelid - age structure of patients in the period 1997–2012 (NCR SR).

North America. [1, 12 - 14]. UV radiation produces DNA damage (formation of cyclobutane pyrimidine dimers), gene mutations, immunosuppression, oxidative stress and inflammatory responses, all of which have an important role in photoaging of the skin and skin cancer. In addition to this, UV radiation creates mutations to p53 tumor suppressor genes; these are genes which are involved in DNA repair or the apoptosis of cells that have lots of DNA damage. Therefore, if p53 genes are mutated, they will no longer be able to aid in the DNA repair process; as a result, there is "dysregulation of apoptosis, expansion of mutated keratinocytes, and initiation of skin cancer." UVA radiation has an important role in the carcinogenesis of stem cells of the skin. UVB radiation induces DNA damage, which causes inflammatory responses and tumorigenesis. [15]. In skin carcinogenesis the mutations play a significant role by activating hedgehog intercellular signaling pathway genes. Patched Ptch-1 mutations promote the development of eyelid BCC. [16, 17]. Viral oncoprotein E6 from beta HPV has the ability to bind to the p53 protein and inactivate it, which results in limiting the induction of apoptosis of cells damaged by UV radiation through the reduction of the pro-apoptotic protein

Bcl-2. Oncoprotein E7 interferes with p16, and these mechanisms lead to an accumulation of mutations and oncogenic transformation of keratinocytes, which are more sensitive to UV-induced carcinogenesis. [18].

Risk factors of multiple BCC are important; the high-risk patients have to be followed up for recurrence or development of new lesions and they have to examine their skin regularly. [19].

There are many factors as risk factors of multiple BCC development. In several studies, a demonstrable dependence between sex, age and the incidence of BCC can be seen. This occurs most often in patients in the sixth to eighth decade of life, with a median age of 62 years (46% were at least 65 years old). A moderate predominance occurs in the male population; i.e. 61% is male. The relationship of the sex of patients to the risk of BCC recurrence is still controversial. In Silverman's studies, no relationship between sex and tumour recurrences was evident. [19 - 24]. Important are severe actinic damage [25], history of previous radiotherapy [26], increased numbers of identi-

fied tumours already present [26 - 28], tumour size over 1 cm [29], lesions on trunk [30-32], positive family history of other skin tumours [33] low DNA repair capacity [34] detected tumour necrosis factor (TNF), microsatellite polymorphism [35], PTCH gene polymorphism [36] and glutathione S-transferase and cytochrome P450 polymorphism [23, 37].

Classification

For determining the stage of advancement of a tumour, the TNM "staging" classification is used, as well as determining the histopathological degree of "grading" differentiation. Grading is based mainly on the cytological characteristics of the tumour, whereby we distinguish 4 grades: differentiated (G1), moderately differentiated (G2), poorly differentiated (G3) and anaplastic (G4). The classification and stages of basal cell carcinoma in the eyelid region are shown in Fig.2.

Clinical features

More than 50% of the BCCs appear on the lower eyelid, 30% on the medial canthus, 15% on the upper lid and 5% on the lateral canthus. [4]. The clinical manifestations of BCC are diverse. It is most often expressed as erythema, induration, a palpable lesion, recurrent bleeding, or a cystic nodule (Fig. 3, 4, 5 – see cover page 3). Patients are often without symptoms and without subjective problems [38]. BCC with orbital invasion occur more frequently in the medial canthus (average 60%) compared to the lower eyelid (average 30%), upper eyelid (average 6%) or lateral canthus (average 14%). [39 - 48].

Nodular BCC (50–80%) is the most common type of BCC. It manifests as a slowly growing greyish-white, shiny papule to skin-coloured nodule with a thinned epidermis and telangiectasias. Cystic BCC is often a multilobular lesion made up of transparent nodules with telangiectasias. Both are considered to be low-risk forms of BCC. Superficial BCC (10–30%) (multicentric basal cell carcinoma) are easily infiltrated brown-red lesions, with fine peeling or scabs on the surface; the epidermis in the extent of the tumour lesion has an atrophic appearance. Among the high-risk subtypes of basal cell carcinoma is sclerodermiform BCC (6–10%) – morphea-like basal cell carcinoma. It can grow deep into the dermis and spread perineurally. This type of basal cell carcinoma rarely ul-
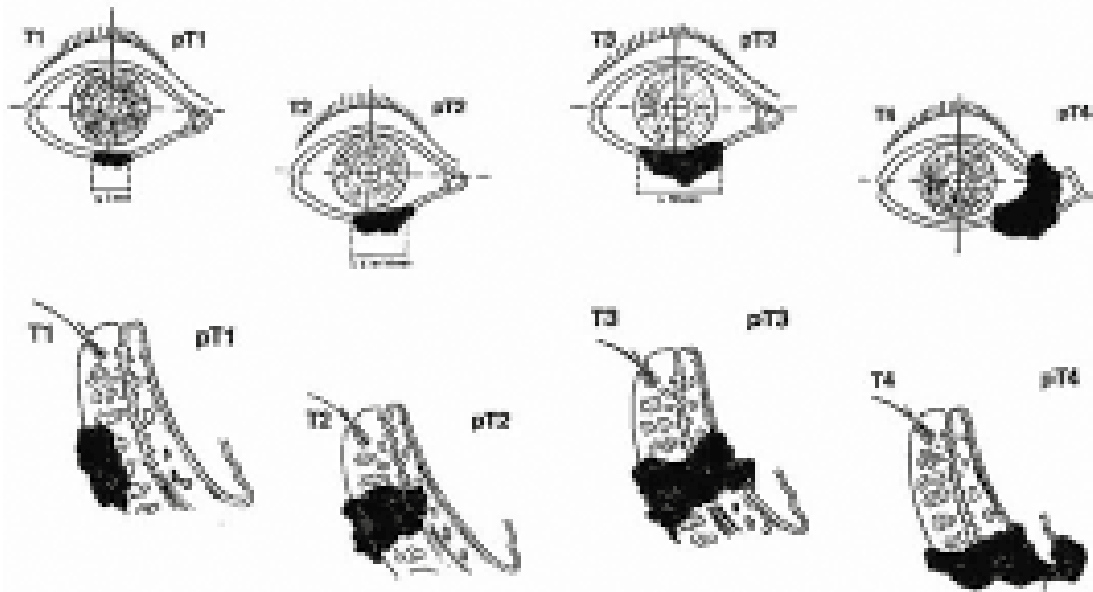
Fig. 2. TNM classification of basal cell carcinoma of the eyelids.

cerates. Infiltrative BCC (5% of cases) is a locally destructive aggressive subtype with a higher risk of local recurrence, and Micronodular BCC (14–15%) is an aggressive and locally destructive subtype with subclinical spread and a higher risk of recurrence. Basal squamous cell carcinoma (so-called metatypical carcinoma) is a tumour that includes mixed regions with typical basaloid differentiation and regions approaching squamous cell carcinoma. [18, 43, 44] An aggressive, infiltrative type of BCC showed a high expression of an apoptotic gene Bcl-2 and moderate levels of proliferation associated markers - proliferating cell nuclear antigen. [44]. It was found that telomere length was shortened and gene expression correlated with cell proliferation (Bcl-2, Ki-67) was increased in BCC [45].

Treatment of periocular BCC

The primary treatment modality for BCC is surgical resection [44]. With respect to the tumour's location, tissue-sparing methods are often used, which increase the risk of recurrence [45 - 48]. Margin control is necessary to achieve clear resection margins to reduce the risk of local recurrence. The recurrence rate after primary surgery is 1%–5% per year [49, 50].

Mohs micrographic surgery has been regarded as the best method of removing BCC with minimal recurrence rate, it is expensive and time consuming and not recommended usually for orbital infiltration due to difficulties by obtaining orientation of specimens from orbital soft tissue. The incidence of recurrence in patients treated without using Mohs micrographic surgery or "en-face" frozen sections intraoperatively ranged from 1.8 to 39%, and the proportion of recurrence increased with longer follow-up of patients. [51-53].

A multidisciplinary team must collaborate in planning management of BCC with orbital invasion (Fig. 6 – see cover page 3). In many patients orbital exenteration is the approach selected after the failure of previous therapeutic modalities. Given that recurrence after exenteration can be as high as 50–75%, it is very important not to underestimate the timely management of these lesions. Complications can include fistula formations into sinuses, to the nasolacrimal duct, tissue necrosis, chronically exposed bone, cerebrospinal fluid leak, pain or secondary infections. The time interval after exenteration for healing with granulation can occasionally far exceed the usual 3–4 months. Cosmetic defects after exenteration are covered by individual epithesis.

Other treatment modalities

Vismodegib is an available, orally administered specific inhibitor of the Hedgehog pathway with a small molecule. The signalisation of the Hedgehog pathway through the transmembrane protein Smoothened leads to activation and nuclear localisation of Glioma-Associated Oncogene (GLI) transcription factors and the inducing of the Hedgehog target genes. Vismodegib has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for patients with locally advanced and metastatic basal cell carcinoma that cannot be managed with surgery or radiotherapy. The approved oral dose of vismodegib is 150 mg/day. [54–56]. Vismodegib can be used to treat basal cell nevus syndrome (Gorlin syndrome) in patients not amenable to surgery with multiple cutaneous lesions of the periocular region and head. [54–56]. The results of a pilot phase 2 clinical trial (ERIVANCE) in 104 patients with locally advanced BCC (laBCC) and metastatic BCC (mBCC) showed a response rate of 48% (laBCC) and 33% (mBCC), respectively, and median duration of response of 9.5 and 7.6 months. Median survival for patients with mBCC was 33.4 months. In laBCC, it is possible to discuss neoadjuvant treatment with an Hh inhibitor with the intention of shrinking the

lesions, but there is no randomised data to demonstrate a favourable outcome. In a series of 15 patients treated with vismodegib for 3–6 months before surgery, only 1 patient relapsed after 22 months. [61].

Vismodegib in cream form or per os therapy is generally well tolerated. Side effects like alopecia, muscle spasms, fatigue, nausea, decreased appetite, weight loss, dyssomnia, or diarrhoea are sometimes the reasons to give up the therapy with vismodegib. Necessity of additional long term studies is required to estimate the risks factors to establish the treatment criteria for periocular BCC. [62].

Local pharmacological treatment, including the immunomodulator imiquimod and 5% 5-Fluoruracil, is less successful and is not yet widely used in localisation near the edge of the eyelid or the outer or inner corner. The principle of PDT (photodynamic therapy) is the accumulation of a photosensitizer: δ-aminolevulinic acid (ALA) or its methyl ester (MAL, Metvix® creme). PDT is the method of choice in patients with non-aggressive low risk BCC, for example, the superficial or nodular type not exceeding 2 mm in thickness, when surgery is not possible or is contraindicated. [18]. Usually the cream is applied once per day, five times per week at least 8 to 16 weeks depending on the tumour stage. In a study with 19 patients they evaluated the efficacy of topical immunotherapy for the treatment of BCC and the histological clearance rate was about 90% after 3 months and 84% at 40 months. The 3-year interval of histological clearance rate was 100% for lesions up to 10 mm [62]. Garcia-Martin et al compared the efficacy, cosmetic results and tolerance of Imiquimod and radiotherapy. In the Imiquimod cream group all patients had complete clinical clearance at 24 months of follow-up. In the radiotherapy group patients received treatment 2 or3 times per week for 5 weeks with a dose of 300 cGy per session (total administered dose was 4,000–7,000 cGy). Aesthetic and functional results were superior in the Imiquimod group, but radiotherapy was better tolerated. [63].

Curettage and electrocoagulation, cryotherapy and laser ablation are methods suitable for small, non-risky basal cell tumours that are not localised on the face and do not have a multifocal character. In the past, chemotherapy was also applied in the treatment of BCC, but unsuccessfully. [64].

With basal cell carcinomas significantly advanced locally, after incomplete excision, in lesions with a high risk of local recurrence or an unacceptable expected cosmetic effect, in elderly patients or with repeatedly recurring lesions, definitive radiotherapy is a suitable solution. [65]. Today there are several types of radiotherapy for BCC: external radiotherapy and also interstitial brachytherapy. About 25% of patients undergo radiation therapy alone for invasive orbital BCC. [66]. Brachytherapy has a theoretical advantage compared to surgery in that it enables the covering of larger areas of the skin with a high dose (macroscopic disease, microscopic disease, safety margin) without the need for irreversible damage to the surrounding tissues. It can be done by means of the interstitial route (the surgical introduction of brachytherapy applicators directly into the tumour tissue by puncture) or superficially. Surface brachytherapy is done by using standard applicators (e.g. Leipzig Applicator, Brock Applicator, Nucletron BV, Netherlands) or custom-made emulsions. Standard applicators are characterised by ease of use and good treatment reproducibility, but they cannot be used for irregular lesions and in a "curved" irregular terrain such as the periocular area. [67].

The side effects after external radiotherapy but also brachytherapy can be dry eye, secondary cataract, ectropion, cicatrisation of the lacrimal duct, secondary neovascular glaucoma, radiation retinopathy and maculopathy, radiation optic neuropathy which can lead to blindness.

The recurrence of basal cell carcinoma

Data on the recurrence after surgical treatment of basal cell carcinoma depend on the localization, size, infiltration, histological type, previous treatment options the surgical technique used. The risk of recurrence of BCC after surgery is estimated at 5%–15%. The most recurrences appear on the lower eye lid and in the medial canthus and in infiltrative types. Aggressive histological forms of BCC are associated with a higher risk of recurrence. Lesions with perineural invasion are usually regarded as more aggressive and are associated with higher rates of recurrences. [68].

One of important prognostic factors can be Ki-67, assay of Ki-67 expression is simple and repeatable and is recommended for evaluation of proliferative activity of malignant tumours. In most cases of BCC the values of the Ki-67 index are higher in recurrenced tumours than in primary BCC. [69, 70].

We can include the apoptotic index as an unexplained prognostic factor of BCC recurrence. In the work of Staibano et al. 60 BCCs were evaluated, 30 of which were BCC1 (non-aggressive type) and 30 BCC2 (aggressive type). BCC1 showed a lower apoptotic index (AI) than BCC2, with the AI of BCC1 from 2.03 – 10.45% (mean value: 5.98%) and the AI of BCC2 from 21.91 – 43.82% (mean value: 39.82%). It is assumed that low AI in BCC1 could indicate a good prognosis. High expression of the Bcl-2 protein is recorded in indolent, slow-growing BCC, while low expression of Bcl-2 occurs in highly aggressive types of BCC [71].

Conclusions

In the scope of onco-ophthalmology, increased attention must be paid to the issue of malignant periocular tumours. Despite a relatively small percentage of invasive diseases today, advanced stages may still occur. Early diagnosis, multidisciplinary cooperation, lifelong dispensary of the patient with early detection of recurrences are all important. Multidisciplinary cooperation and cooperation of the patient in the area of cancer tumours is essential, as it improves the early diagnosis, treatment and survival of patients.

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Abbreviations: *BCC – Basal cell carcinoma; SCC – Squamous cell carcinoma; NMSC – Non-melanoma skin cancer; NCR – National Cancer Registry; GLI – Glioma-Associated Oncogene; FDA – Food and Drug Administration; EMA – European Medicines Agency.*