

# Periocular basal cell carcinoma - clinical perspectives

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## Abstract

Basal cell carcinoma (BCC) as a non-melanoma skin cancer type is the most common malignant tumor throughout the world. The incidence is higher in age over 60. The intense of exposure to ultraviolet radiation is one of the known risk factors. Over 50% of BCC of the periocular region initially occur on the lower lid and inner angle. Literature review of treatment options for basal cell carcinoma, which consist of surgery, or combined techniques plus vismodegib, radiotherapy and imiquimod. The first consideration for treatment of periocular BCC is radical surgical excision using Mohs micrographic technique. Functional and esthetic outcome in patients are 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

The incidence of all skin malignancies is slowly increasing worldwide, especially the non-melanoma skin cancer types (NMSC). The relative incidence of periocular tumors varies with geographical area and racial group. 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 BCC appear in periocular region.<sup>1,2</sup> Orbital invasion is uncommon with a reported incidence about 2%.<sup>3</sup> The age of BCC emergence is typically in patients over 60 years. BCC of the eyelids has a high risk of recurrence, especially in infiltrative types. Late diagnosis of BCC can lead to functional and cosmetic defects. Any periocular

skin malignancy 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 tumor 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 carcinoma perineural invasion is present.<sup>4,5</sup>

Early diagnosis and exact surgery promise better treatment outcome functionality and better cosmetic outcome, but in some cases also other treatment options are necessary to be combined with surgery.<sup>6-8</sup>

The new last 8<sup>th</sup> edition of American Joint Committee on Cancer (TNM system) allows more objective and consistent designation of the T category.<sup>9</sup>

## Epidemiology

Nowadays it is impossible to collect the data from cancer registries that would analyze BCC worldwide. Due to data of the American Cancer society in 2012, 5.4 million cases of NMSC were diagnosed in 3.3 million people. In 8 patients from 10 histopathologically BCC was verified. A population-based study estimated that 3.5 million patients with NMSC were treated in the United States in 2006.<sup>10</sup> In the United States estimated an age-adjusted prevalence and incidence of BCC was 226 to 343 per 100,000 persons per year, respectively.<sup>11</sup> Due to other incidence-based mathematical model support approximately 13 million non-Hispanic patients in the United States in 2007 may have had a personal history of NMSC. Today a high prevalence of NMSC not only in the United States is present.<sup>12</sup>

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).<sup>13</sup>

One of the most important risk factors of BCC is the intermittent intense exposure to ultraviolet (UV) radiation; other risk factors include long-term sun abuse, family history of other skin cancers, immunosuppressive status, previous irradiation or exposure to toxic substances. Short-wavelength UVB radiation (290-320 nm) plays a more important role than long-wavelength UVA radiation (320-400 nm). UVB radiation damages not only DNA and its repair system, but changes the immune system resulting in progressive genetic alterations which are responsible of neoplasm formation. Mutations induced by UV in the TP53 tumor-suppressor gene have been verified in about 50% of BCC lesions. In skin carcinogenesis the mutations play a significant role by activating hedgehog intercellular signaling pathway genes. Patched Ptc-1 mutations promote the development of eyelid BCC.<sup>14,15</sup>

Risk factors of multiple BCC are important; the high-risk patients have to be followed up for recurrence or development of

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new lesions and they have to examine their skin regularly.<sup>16</sup>

There are many factors as risk factors of multiple BCC development mentioned in different previous studies. Important are age,<sup>17,18</sup> male sex,<sup>19</sup> pale white skin, blue or green iris color, blond or red hair (skin phototype I, II),<sup>19,20</sup> frequent sun exposure and sunburn,<sup>21,22</sup> severe actinic damage,<sup>20</sup> history of previous radiotherapy,<sup>23</sup> increased numbers of identified tumors already present,<sup>24-26</sup> tumor size over 1 cm,<sup>17</sup> lesions on trunk,<sup>27-29</sup> positive family history of other skin tumors,<sup>22</sup> low DNA repair capacity,<sup>30</sup> detected tumor necrosis factor (TNF), microsatellite polymorphism,<sup>19,31</sup> *PTCH* gene polymorphism,<sup>32</sup> and glutathione S-transferase and cytochrome P450 polymorphism.<sup>19,33</sup>

In Europe the high incidence of developed stage of BCC size are associated with a low socioeconomic status, patients who live under socio-economic deprivation are more likely to get BCC. Small BCC (stage T1) are usually easily managed with a good prognosis and cosmetic result.<sup>34</sup>

### Periocular localization, clinical examination

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.<sup>2</sup> Risk factors such as chemical or physical irritation (e.g. of tears) may do more harm to the lower eyelid. 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%).<sup>2,35-38</sup>

BCC is characterized by pink color but in advanced stages it can have ulceration or bleeding. In a large series of orbital invasion visible or palpable mass was found in all the patients. Mass fixation to orbital bone (35%), limitation of ocular motility (30%) and globe displacement (18%) are serious signs of orbital infiltration. Other important signs are immobile eyelids, tearing secondary to canalicular or sac BCC infiltration and ptosis.<sup>2,5</sup>

Instead of examination in the daylight and slit lamp examination other imaging methods in patients with orbital invasion are necessary. Computed tomography with bone windows can be used for visualizing bony destruction and magnetic resonance imaging is a better option for visualizing soft tissue changes and rare perineural invasion.<sup>2</sup>

Diagnostic performance of optical coherence tomography (OCT) does not depend on the lesion's anatomical location. Diagnostic performance for lesions with mediocre image quality is still better than by clinical and dermoscopic examination. Good OCT image quality is correlated with improved diagnostic performance.<sup>39</sup>

High-frequency ultrasound (HFUS) is a new non-invasive technique that allows visualizing skin lesions *in vivo* to obtain size, shape, and tumor volume. *Ex vivo* HFUS could increase surgeon confidence on complete tumor excision by visualizing the tumor and surgical margins.<sup>40</sup> To avoid unfounded surgical excisions or excisional biopsies a new noninvasive imaging technique, *in vivo* reflectance confocal microscopy, is available. In a study of Cinotti *et al.* was found that this method had a high sensitivity (100%) and specificity (70%) for eyelid margin tumors and has a great advance to examine both the skin and the conjunctiva of the eyelid.<sup>41</sup>

BCC arises from basal cells of the epidermis and clinical symptoms can be variable as mentioned below, but the final diagnosis must always be verified by pathological examination. Biopsy (excisional biopsy) is not necessary for all BCC lesions just a simple (even partial) shave biopsy is adequate to establish diagnosis, different from melanoma when depth of invasion is needed for staging. The basic histological types of BCC are superficial, infil-

trating and nodular tumors, and those with adnexal differentiation. The most common types of BCC which tend to be less aggressive are nodular and superficial types. The infiltrating subtypes of BCC are more aggressive but rare, morpheaform types do have a higher rate of residual positive margins after excision, as well as a higher risk of recurrence. In cases with orbital invasion most aggressive subtypes are found (80%).<sup>2,5,6</sup>

Typical clinical manifestation is a single lesion with ulceration, or central scarring and keratosis, with possibility of deep infiltration of BCC, but the presence of inflammation with or without the ulceration increases the possibility to be transformed into more aggressive phenotype.<sup>37</sup> Large, recurrent tumors and incompletely excised tumors are factors inducing more aggressive histological types of BCC.<sup>14</sup> 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.<sup>42</sup> It was found that telomere length was shortened and gene expression correlated with cell proliferation (*Bcl-2*, *Ki-67*) was increased in BCC.<sup>43</sup>

### Treatment of periocular basal cell carcinoma - surgery

Surgery is the first line treatment of the BCC, including wide surgical excision and Mohs micrographic surgery with frozen section margin control.<sup>44,45</sup> Margin control is necessary to achieve clear resection margins in order to reduce the risk of local recurrence. Treatment needs to be individualized due to general status of patient, tumor stage and histological characteristics (Figure 1). Depending on the stage, localization and pathological variety of the BCC a cure rate of about 95% is achieved after treatment. The recurrence rate after primary surgery is 1%-5% per year.<sup>4,6,46,47</sup>

After surgery there it is necessary a good interdisciplinary cooperation between ophthalmologist and pathologist. The integrity of the eyelids and its function is important for protecting and preserving the function of the eye globe. The shape of the tumor, the distance from the eyelid margin and its diameter are important to choose the best surgical technique. Reconstruction with a skin flap based on the tumor size in the eyelid is necessary to preserve eyelid function and cosmetic result. Skin flap is only one of so many different factors and techniques that eyelid reconstruction entails, and over simplifies the process of reconstruction. The aim of surgery is to excise the lesion with clear margins 3 mm around the tumor and reestablish eyelid function. The localization of the tumor on the eyelid margin makes surgical reconstruction more difficult. The smaller the size of the tumor (stage T1), the simpler the surgical reconstruction and better functional and cosmetic results can be achieved. The UK National Multidisciplinary Guidelines recommend that non-infiltrative BCC lesions 2 cm should be excised with a margin of 4-5 mm. Margins closer to the tumor (2-3 mm) may be taken in case of limited reconstructive options.<sup>46</sup>

In a randomized study compared Mohs micrographic surgery to radiotherapy local failure rate was 1% in group of patients treated with surgery and 7.5% in group treated with radiotherapy. Patients after surgery considered their cosmetic outcome as *good* or *better* (surgery 87%, radiotherapy 69%).<sup>48-50</sup>

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 risk of false-negative

results with standard frozen section techniques is higher. Therefore, paraffin section histology remains the choice of margin control for BCCs with orbital invasion.<sup>2,4</sup> In prospective studies in patients with periocular BCC managed by Mohs micrograft surgery using fresh-frozen tissue sections was a recurrence rate of 0% in 5 year interval for primary tumors and 7.8% for recurrent tumors. This is the treatment of choice for periocular BCC, Mohs for periocular BCC followed by reconstruction has definitely not lost popularity and is the standard of care in many places.<sup>44,45</sup> But due to second intention healing, it has lost popularity because of the long healing process and potential functional alteration of important anatomical structures if certain wound healing factors are not carefully taken into consideration.<sup>51</sup>

Mohs surgery is often undertaken in specialized centers and hence may not be accessible (*e.g.* often long travel is required), is not suitable for patients who require sedation/general anesthesia as it needs several passes often in one day but that in conjunction of an ophthalmologist with an oculoplastic surgeon a reconstruction can take place. In some studies the rate of tissue sparing of 46% can be reached by using it for primary infiltrative growth pattern BCC.<sup>52</sup>

Ho *et al.* in their one of the largest series of BCC excisions with the non-Mohs rapid paraffin technique performed the reconstruction few days after the histology results were available. Only when the margins were clear, plastic reconstruction was performed. In condition the margins were involved, further excision was performed using frozen section or paraffin examination until a negative margin was obtained.<sup>36</sup>

Monitoring of surgical margins with frozen sections during the operation or later paraffin sections is necessary. The surgeon should repair the surgical defect after obtaining tumor negative margins. Conway *et al.* evaluated the recurrence of primary BCC infiltrating the eyelid margins after resection with and without intraoperative frozen section control. There was no tumor recurrence in group with control.<sup>53,54</sup>

When unmonitored perioperative excision is performed aggressive histological subtypes of BCC are more likely to be incompletely excised. Exenteration of the orbit is considered only in cases of extensive orbital invasion. It may be combined with adjunctive radiotherapy when margins are not clear or in high-risk aggressive infiltrative types of tumors.<sup>8</sup> Madge *et al.* in their study of patients with orbital invasion by inner angle canthal BCC treated with non-exenterating surgery found final margins were clear in 18 of 20 patients. After 3 years interval, in only one patient the BCC was relapsed. Due to their results *conservative* (non-exenterating) surgery with margin control in this highly selected group of patients can have good results in BCC recurrence.<sup>3</sup>

A multidisciplinary team must collaborate in planning management of BCC with orbital invasion (Figure 1). Shields *et al.* in their study in patients indicated for exenteration reported in 4 of the 9 skin tumors allowed some eyelid sparing.<sup>6</sup> Ben *et al.* in group of patients with exenterations reported complications in 23.5%.<sup>7</sup> 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 individualized epithesis (Figure 2). [The photographic documentation is published with the consent of the patients.]



**Figure 1.** Patient with large periocular basal cell carcinoma on his right side. According to patients history tumor started to develop 3 years before from a small lesion in the lower eyelid. Later without any treatment. The first visit of this patient at Dept. of Ophthalmology, Faculty of Medicine, Comenius University.



**Figure 2.** Patient after biorbital exenteration of the orbit due to basal cell carcinoma - left, individualized epithesis of the same patient - right (Dept. of Ophthalmology, Faculty of Medicine, Comenius University).

## Other treatment modalities - vismodegib, imiquimod

Primary treatment of BCC is surgery but there is no effective therapy for locally advanced or infiltrative BCC.

In last decades a hedgehog pathway inhibitor vismodegib was invented as an adjuvant therapy or in certain cases as a prior medical treatment for periocular and orbital BCC.<sup>55-57</sup>

In pathogenesis of BCC but also basal cell nevus syndrome alterations in hedgehog signaling are involved. The hedgehog signal transduction pathway plays an important role in cell proliferation. Alterations in hedgehog signaling may transform an intraepithelial neoplasia into the invasive cell carcinoma.<sup>14</sup> Indication is for advanced stage of BCC where no effective surgery is possible or failed or radiotherapy is not sufficient. It is used in patients when radical surgery leads to visual acuity loss, double vision or loss of the whole eye globe or orbital structures (exenteration). 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.<sup>58-61</sup> Vismodegib reduces the size of tumors while it represses the hedgehog pathway by directly inhibiting the G protein-coupled receptor protein.<sup>62,63</sup>

Kahana *et al.* published the first histopathological description of the effects of vismodegib treatment. After 5 months interval of treatment, the surgical specimen failed to show nuclear immunoreactivity for the proliferation marker Ki-67 and residual squamous cells exhibited degenerative cytologic features.<sup>64</sup>

Many studies confirmed that vismodegib is effective in BCC patients, but the long-term results after finishing treatment are still unknown. Demirci *et al.* in four patients with orbital BCC present vismodegib as the only treatment. In their results it was described a partial response after 7 months - a mean tumor reduction (over 80%). In 2 patients taking vismodegib as adjuvant therapy complete remission in 7 months interval was present and no evidence of clinical recurrence in 15 months was present. In 2 two patients with extensive infiltration after 14 months of oral treatment a complete clinical remission was present.<sup>65</sup>

In study of Gill *et al.* in 7 patients with extensive periocular or orbital BCC treated with vismodegib in 11 weeks interval in 7 patients were demonstrated recurrent tumors previously excised with controlled margins by frozen sections or Mohs microsurgery. The mean follow-up duration of this study was 7 months. One (14%) patient showed disease progression.<sup>60</sup> In a case report of advanced recurrent periocular BCC the periorbital tumor regressed after vismodegib therapy in 3 months, but recurred after 9 months and patient was finally treated with orbital exenteration. The reason was the resistance to vismodegib.<sup>61</sup>

Vismodegib in cream form or per os therapy is generally well tolerated. Side effects like alopecia, muscle spasms, fatigue, nausea, decreased appetite, weight loss, dysosmia, or diarrhea 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.<sup>66</sup>

In elderly skin cancer patient should be ideally implemented also a geriatric assessment in clinical therapy decision. Current clinical practice guidelines for BCC and non melanoma skin cancer only partially address geriatric aspects of cancer care, such as limited life-expectancy, geriatric comorbidities and but also treatment compliance.<sup>67</sup>

Topical immunotherapy - imiquimod - may be an alternative treatment for patients with periocular BCC when the surgery is not

possible to be performed. Imiquimod is an immune modulator which induces apoptosis in tumor cells and stimulates innate and adaptive immunity. Large number of studies reported the use of imiquimod in a 5% cream form for nodular skin BCC. Usually the cream is applied once per day, five times per week at least 8 to 16 weeks depending on the tumor 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.<sup>61</sup> In another study of 15 patients remission was observed in all patients after 3 months of imiquimod treatment and clinical remission at 24 months.<sup>68</sup> In a study of ten patients with BCC lesions, 80% showed clinical and histological progress and remained asymptomatic for 12 months.<sup>69</sup> 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 or 3 times per week for 5 weeks with a dose of 300 cGy per session (total administered dose was 4000-7000 cGy). Esthetic and functional results were superior in the imiquimod group, but radiotherapy was better tolerated.<sup>62</sup> In the study of 24 patients the recurrence rate of periocular nodular BCC following treatment with imiquimod was low. The 3-year histological clearance rate was 100% (8/8) for lesions less than 1 cm and 81.8% (9/11) for lesions more than 1 cm, but significant neoadjuvant effects in larger lesion were observed.<sup>70</sup> Vismodegib frequently needs to be undertaken in a specialist center so access for patient is not always easy, because patients with advanced disease are often elderly and this can limit their option.

## Adjunctive radiotherapy possibilities

As an adjunctive therapy to high-risk aggressive BCC with perineural invasion radiotherapy is used or, it can be applied to residual inoperable tumors. It can be indicated to patients with comorbidities with high risk of surgery. National organization guidelines have established that standard therapy of BCC is complete surgical removal and radiation therapy is an option only for inoperable tumors. In certain patients it can be the only treatment modality when the post-operative defect would be cosmetically disfiguring and comorbidity is present. Irradiation therapy after histological sample should be considered as the multidisciplinary management. Today there are several types of radiotherapy for BCC: external radiotherapy and also interstitial brachytherapy. Very few studies have been conducted to define the optimum treatment in terms of recurrence rate, cosmetic outcome and side-effects. In most of studies, the overall local control rate was between 80-100% and over 90% of patients reported good or excellent cosmetic outcome. About 25% of patients undergo radiation therapy alone for invasive orbital BCC.<sup>71</sup> In case report of a 73-year-old man with recurrent BCC in the inner canthus extending to the orbit treated with CyberKnife stereotactic body radiation therapy the patient enjoyed rapid tumor regression, with complete remission after 6 months without toxicity.<sup>72</sup> Brachytherapy HDR Ir<sup>192</sup> can be used also in patients with BCC.<sup>73</sup>

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

## Risk factors of recurrence and prevention

The risk of recurrence of BCC after surgery is estimated at 5%-15%. The rate of recurrence depends on the localization, size, infiltration, histological type and previous treatment options. 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. In a 5-year review of periocular BCC, none of the patients with primary nodular BCC suffered recurrences, but the recurrence rate of infiltrative BCC reached up to 4%. Lesions with perineural invasion are usually regarded as more aggressive and are associated with higher rates of recurrences.<sup>35,36,74</sup>

Recurrence rate has been reported as 1%, but 3% for more aggressive forms of BCC. The recurrence rate of periorbital BCC after exenteration may be lower than after local excision or radiotherapy alone.<sup>2,4</sup> Patients with mixed, infiltrative, morpheaform, micronodular, or any recurrent BCC should be followed up for at least 5 years interval after therapy. Patients with primary nodular BCC may be discharged after one 6-month follow-up once complete excision with clear margins was confirmed. But all patients are advised to be monitored for new lesions not only in the periocular, head and neck region, but elsewhere. The monitoring schedule does vary in many centers - whilst there is some logic to histological severity and the intensity and frequency of monitoring should include specific factors (not least their preference) that would come into play with the schedule and personalize the follow-up.<sup>75</sup> 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 tumors. In most cases of BCC the values of the Ki-67 index are higher in recurrence tumors than in primary BCC.<sup>76,77</sup> The mechanism of BCC should be further studied in order to discover additional treatment options for patients unable to undergo surgery. Avoiding extensive sun exposure can reduce the incidence of head and neck and also periocular skin cancers. Long term randomized studies with longer follow-up are required to better understand treatment outcome in patients with BCC treated with different modalities. The results of adjunctive radiotherapy, vismodegib and imiquimod also require further studies to evaluate and compare their long-term effects. Additional long term studies are required to estimate the risks factors to establish the treatment criteria for periocular BCC, because infiltrative types leading to orbital invasion may be associated even though rarely, but death. Orbital invasion may often be clinically silent, clinicians need to be alert to the possibility in high-risk tumors and consider appropriate imaging, because exenteration of the orbit is mutilating procedure, leading to cosmetic defects and wide social and psychological problems. In the large defects only relatively satisfying cosmetic result can be achieved with an individualized facial prosthesis.<sup>7</sup>

## Literature search

A web-based literature search using databases such as PubMed, Scopus, Embase, Google Scholar and Directory of Open Access Journals (DOAJ) was carried out. The keywords like basal cell carcinoma, eyelid, periocular were used to search the databases. The search was limited to articles published in English language. A total of 9 490 articles were screened, and 55 articles were included in the review.

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