NON-MELANOMA SKIN CANCERS OF THE EYELIDS AND INNER CANTHUS – BASAL CELL CARCINOMA

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SUMMARY

Aim: Non-melanoma skin cancer cases in the European population are increasing. Basal cell carcinoma (BCC) is the most common non-melanoma skin cancer of the eyelids and in the inner corner of the eyelid. Due to the latest statistics compiled and published in 2008 in the Slovak Republic (SR) there were registered 5,173 cases of non-melanoma skin cancer (C44 according to ICD-10) in both sexes together (of which women accounted for 51.2 %). The proportion of non-melanoma skin cancer accounted for 17.2 % (16.3 % of men and 18 % of women) of the total number of all reported cancer cases (n = 30,144). The aim of this study is to evaluate the number of clinical relapses in a group of patients.

Material: Retrospectively analyzed data from the medical records of patients with newly detected basal cell carcinoma in period between Jan. 1 2008 to Dec. 31 2013 who underwent surgery and outpatient follow-up at the Department of Ophthalmology and the University Hospital in Bratislava.

Methods: The incidence of relapse was evaluated up to date Dec. 31 2014. We followed the following parameters: location and tumor size, TNM classification, histopathological degree of differentiation, the edges of excised tissue and evaluated recurrence rate separately for each parameter. Statistics were analyzed by chi2 test, which was found to be significant for $P < 0.05$. The results of continuous parameters were expressed as arithmetic mean ± standard deviation.

Results: At the Department of Ophthalmology Faculty of Medicine and UNB, Ruzinov Hospital, in Bratislava, in the period 2008 - 2013 were treated 219 basal cell carcinomas in 217 patients and basal cell carcinoma was histologically confirmed. Basal cell carcinomas were divided into groups according to the stage: G1 (n = 139), G 1-2 (n = 41) and G 2 (n = 39). Localization was more frequent on left side (n = 112) compared to the right one (n = 107). We recorded significantly lower incidence (n = 5) in the area - angulus externus, prevalent occurrence was in the inner area - angulus internus (n = 65). The incidence in the lower eyelid (palpebra inferior) was recorded more frequently (n = 127) as in the upper eyelid (palpebra superior) - (n = 24). During these six years period we have seen 11 recurrences (5.02 %). Exenteration of the orbit was indicated in 5 cases (2.7 %).

Conclusion: When monitoring patients with newly detected eyelid basal cell carcinoma, operated at the Department of Ophthalmology Faculty of Medicine and UNB in period 2008-2013, incidence of recurrence was recorded in 11 cases, accounting for 5.02 %, which is about one percentage point lower share than in the previous reporting period from period 2005 -2007 from the same Department. The occurrence of relapses corresponds to those in the literature. None of the clinical parameters statistically did affect significantly the incidence of relapses.

Key words: eyelid basal cell carcinoma, non-melanoma skin cancer, tumors eyelashes

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INTRODUCTION

Non-melanoma skin cancers represent the most frequently occurring malignant tumours in both sexes, with increasing incidence worldwide. As many as 70 – 80 % of these tumours are basal cell carcinomas (BCC), which have a good prognosis and low mortality rate, leading to an expression of an entire topographic group of tumours from the oncological-epidemiological statistics, and on the other hand this fact is a probable cause of the highly suspected under-reporting of the total number of pathologies [7].

Epidemiological situation in the Slovak Republic

In the last statistically processed and published year of 2008, there were 5173 non-melanoma skin cancers (C44 according to ICD-10) registered in the Slovak Republic (SR) in both sexes together (of whom women represented 51.2%). Of the total number of all reported malignant tumours (n = 30144) that year, they thus accounted for a proportion of 17.2% (specifically 16.3% in men and 18% in women). However, current data on the representation of histological types and topographic sub-localisations of non-melanoma skin cancers is not available [23].

The last detailed published data is available from our portal on the incidence of malignant tumours in the Slovak Republic for the period 1999 - 2003 (3). During this time period a total of 19091 non-melanoma skin cancers (in both sexes together) were registered in the SR,

of which basal cell carcinomas constituted 14484 cases (on average 75.9%, ranging from 70.8% in 2003 to 86.2% in 2002) and squamous cell carcinomas 2062 cases (average 10.8%), with the remainder comprising other and unspecified malignant tumours of the skin. The proportion of all the histological types of non-melanoma skin cancers localised on the eyelids (C44.1 according to ICD-10) was 1328 cases (7%) [20].

Of the total number of basal cell carcinomas registered in the SR during the period 1999 – 2003 for both sexes (n = 14484), 8.4% of cases (n = 1215) occurred on the eyelids, without any significant differences between the sexes. Of this number, 46.2% of cases (n = 561) occurred on the left side of the face and 48.7% (n = 592) on the right side, with the remainder constituting bilateral and unspecified findings. The age range of the patients with reported basal cell carcinomas in the period from 1999-2003 was from 24-94 years (median 68 years, 25% - 75% quantile 57-75 years) [20].

If we overlooked developmental changes, and upon application of the mean values obtained in the period 1999 – 2003, the estimate of the proportion of basal cell carcinomas in the Slovak Republic in the last statistically processed year of 2008 would represent approximately 3926 cases in both sexes together, of which 275 are localised on the eyelids [20].

Non-melanoma skin cancers (NMSC)

Risk factors for the occurrence of NMSC are considered to include cumulative doses of ultraviolet radiation, more advanced age, skin phototype – in particular fairer phototypes (phototypes I and II), inability to repair damaged DNA, loss of control over the growth of keratinocytes, immunological condition (organ transplant), work with ionising radiation or tar. Mutations occur in the area of the nucleus and of mitochondrial DNA. Keratinocytes with mutations of gene p53 have blocked apoptosis, advantaged growth and a higher risk of further mutations and transformations. Exposure to UV radiation also causes indirect damage to DNA – generation of free oxygen radicals (oxidation stress), UV radiation causes local immune suppression, meaning that abnormal cells cannot be detected and removed by the immune system. The group of non-melanoma skin cancers is composed predominantly of basal cell carcinomas (BCC) and squamous cell carcinomas (SCC).

Basal cell carcinomas of the eyelids

Basal cell carcinoma is most frequently malignant on the eyelids. It occurs most commonly on the lower eyelid and in the medial canthus. It appears very often in the sixth, seventh and eighth decade of life, although in 10% of cases it may also occur between the ages of 20 and 40 years. The etiology is linked mainly with exposure to sunlight in people with a fair complexion. This concept is based on extensive studies incorporating Europe, Australia and North America. However, basal cell carcinoma also occurs in eastern Japan, Korea and India. These studies have not recorded any predilection in terms of sex.

Although basal cell carcinoma has various clinical manifestations, the physical characteristics and patterns of behaviour of these tumours may be in correlation with their diverse histological results. The most common type is a tumescent, firm, nodular tumour, which frequently appears with teleangiectasias. Basal cell carcinoma in the initial stage does not cause the patient any discomfort, and precisely for this reason patients frequently leave this tumour unnoticed until it begins to grow to larger dimensions. Histologically, the nodular type of basal cell carcinoma grows in networks with peripheral palisading. The nodular type has a tendency to be the least aggressive, and only rarely spreads subcutaneously, which is not clinically visible. A typical basal cell carcinoma has morphological features which make this tumour easily distinguishable by an experienced doctor. It has a number of diverse clinical manifestations, which correspond with the given histological subtype of basal cell carcinoma. Most frequently manifested as an iridescent papula or node with teleangiectasias, and sometimes with central ulceration, this type is known as nodular basal cell carcinoma (fig. 1, 2, 3). Histopathologically, basal cell carcinoma may be manifested in a number of variants. A bordered nodular ulcerated lesion usually indicates conspicuous lobes or a network of well differentiated basal cells, which are separated by ligament tissue. The cancer cells typically manifest parallel alignment on the perimeter of each lobe, forming “peripheral palisading”. The stroma is usually shrunken around the lobe, and forms a characteristic fissure (fig. 4, 5, 6) Histopathologically, basal cell carcinoma is divided into the following groups: multicentric, sclerodermiform, fibroepithelial, keratinising, metatypical and intraepidermal. We differentiate 4 fundamental degrees of grading: G1 – G4.

Basal cell carcinoma usually occurs in middle aged and older patients, particularly in individuals with a fair complexion. Basal cell carcinoma may grow more rapidly in children and younger individuals. Although basal cell carcinoma does not usually metastasise, such spread has been recorded. Age, fair skin, exposure to solar radiation, exposure to arsenic, scars, previous exposure to radiation and immune suppression are considered factors which may predetermine the development of basal cell carcinoma of the eyelids. Cigarette smoking is also a predisposing factor, although only in women and not in men. Chronic inflammatory changes or trauma may also contribute to the occurrence of BCC. In the case of genetic disorders, it is common in patients with xeroderma pigmentosum and nevoid basal cell carcinoma syndrome (Gorlin-Goltz syndrome). In differential diagnostics, a quantity of lesions of the eyelids and inner canthus may imitate basal cell carcinoma, their clinical features are frequently similar in their initial stages and may be easily mistaken. Keratoacanthoma has a more rapid onset and progression, it is necessary to differentiate pigmented basal cell carcinomas from melanocytic nevi, melanoma and seborrhoeic keratosis [8, 10, 11, 12, 13].

Fig. 1a, b Typical localisation of basal cell carcinoma in area of inner canthus – condition before excision and plastic surgery (4/2015)

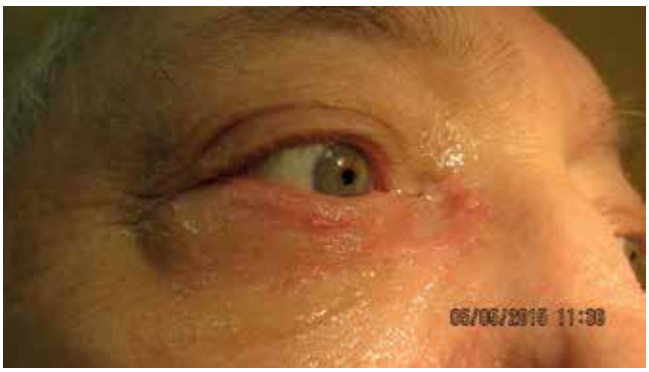

Fig. 2 Patient 2 weeks after excision and plastic surgery for basal cell carcinoma of inner canthus (5/2015)

Fig. 3 Patient 3 weeks after excision and plastic surgery for basal cell carcinoma of inner canthus (5/2015)

MATERIAL AND METHOD

A retrospective study was conducted at the Department of Ophthalmology, Faculty of Medicine of Comenius University in Bratislava, on patients with basal cell carcinoma of the eyelids in the period of 2008 – 2013. We recorded 219 cases of BCC in 217 patients who were treated surgically and in whom basal cell carcinoma was histopathologically confirmed.

RESULTS

At the Department of Ophthalmology at the Faculty of Medicine of Comenius University in Bratislava, in a retrospective study conducted in the period 2008 – 2013, we recorded 219 cases of BCC in 217 patients (136 women and 81 men; average age of women 69.3 years, average age of men 70.6 years). In 2013 we recorded two patients who had 2

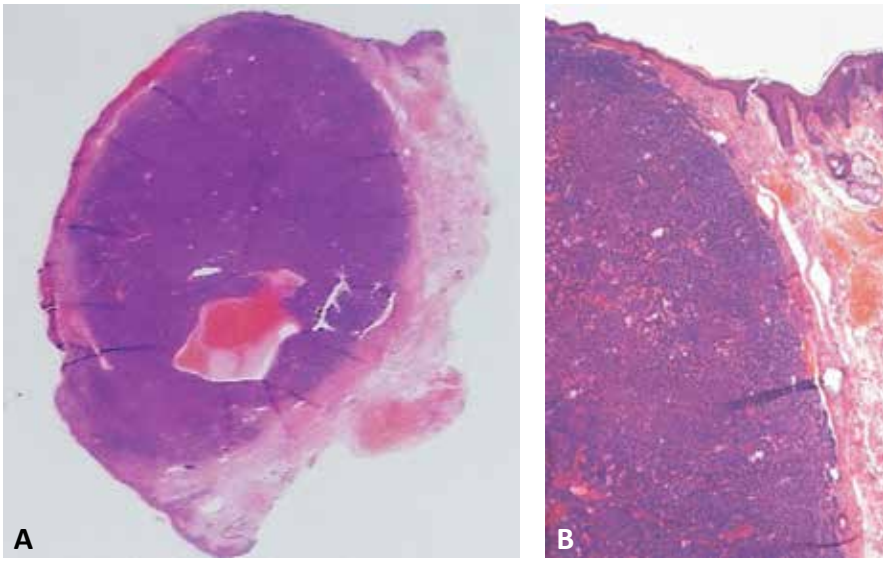

Fig. 4a, b Nodular basal cell carcinoma of eyelids G 1, well bordered. Hematoxylin and eosin (HE), A: histotopogram of tissue section, B: 200x

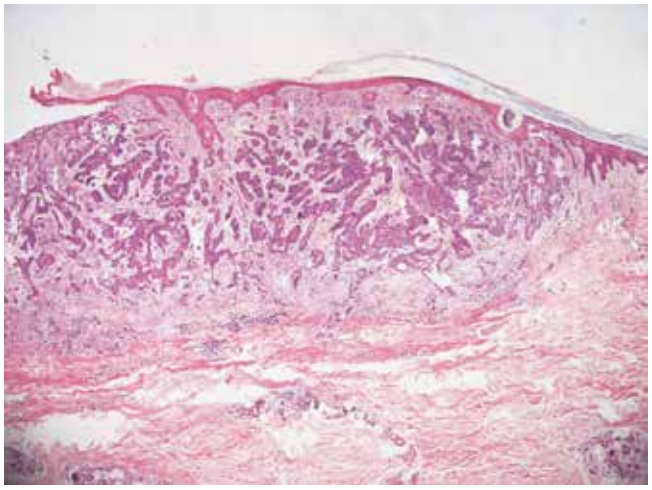

Fig. 5 Basal cell carcinoma G 2, with infiltrative growth, spreading beneath intact epidermis. HE 200x

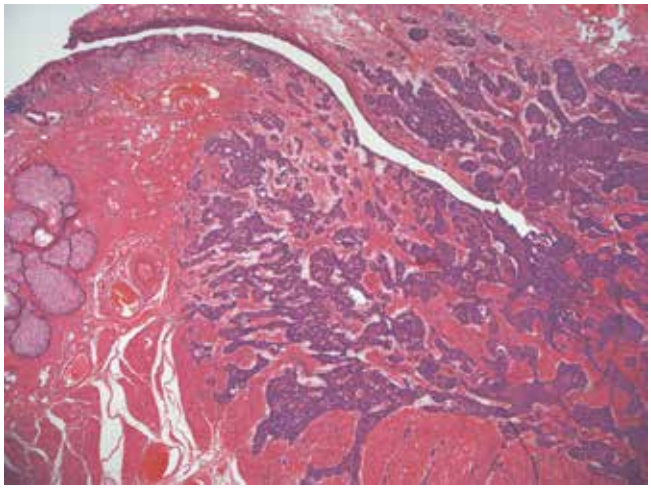

Fig. 6 Nodular basal cell carcinoma of eyelids with deep infiltration of soft tissues and orbit (above right). HE 100x

incidences of BCC simultaneously.

According to the histological finding, BCCs were divided into groups according to stage: G1 (n = 139), G 1-2 (n = 41) and G 2 (n = 39). Localisation was more frequent on the left side (n = 112) in comparison with incidence on the right side (n = 107).

According to localisation of the finding, BCCs were divided into groups according to localisation within the areas of the canthi (outer and inner), and localisation within the area of the eyelids (on upper and lower eyelid).

Within the area of the canthi, incidence predominated in the inner canthus - angulus internus (n = 64). In the outer canthus - angulus externus we recorded a markedly lower incidence (n = 5).

On the lower eyelid (palpebra inferior) we recorded a markedly higher incidence (n = 126) than on the upper eyelid (palpebra superior) - (n = 24). During the course of these 6 years we recorded 11 recurrences (5.02 %). Exenteration of the orbit was indicated in 5 cases (2.7 %).

The main overviews are presented in tables 1, 2 and 3 and by graphs 1 to 8.

DISKUSIA

Basal cell carcinoma is a locally invasive cancer of epithelial origin, which was first described in 1827. In the last two years, surgical treatment has been replaced in certain indicated cases (impossibility of surgical treatment) by peroral therapy – Vismodegib (Erivedge), which however is not yet available in our conditions.

Vismodegib is a perorally available Hedgehog pathway inhibitor with small molecule. Signalling of the Hedgehog pathway via the transmembrane protein Smoothened (SMO) leads to the activation and nuclear localisation of transcription factors of the glioma-associated oncogene (GLI) and induction of the Hedgehog target genes. Several of these genes are engaged in proliferation, survival and differentiation. Vismodegib binds to and inhibits the SMO protein, thus preventing transduction of the Hedgehog signal [1, 3, 4, 5].

The pivotal clinical trial was ERIVANCE BCC (SHH4476g), an international, multicentric, 2-cohort single-arm trial. Metastatic BCC was defined as BCC which had spread beyond the skin also to other parts of the body, including the lymph nodes, lungs, bones and/or internal organs. Patients with laBCC had skin lesions which were not suitable for surgical intervention (inoperable, several times recurring, in which curative resection was not considered probable or in which a surgical procedure could result in pronounced deformity or morbidity), and in whom radiotherapy was unsuccessful or contraindicated as unsuitable. Before inclusion in the study, the diagnosis of BCC was confirmed histologically. Patients with Gorlin-Goltz syndrome who had at least one aBCC lesion and met the inclusion criteria were qualified to take part in the trial. The patients were treated with peroral daily doses of 150 mg Erivedge.

The median age of the population with evaluable effectiveness was 62 years (46% were aged at least 65 years), 61% of male sex and 100% with pale complexion. In the mBCC group, 97% of patients had undergone previous treatment, including a surgical procedure (97 %), radiotherapy (58 %) and systemic therapy (30 %). In the laBCC group (n = 63), 94 % of patients had undergone previous treatment, including a surgical procedure (89 %), radiotherapy (27 %) and systemic/local therapy (11 %). The median duration of treatment was 12.9 months (range 0.7 to 47.8 months).

The primary final indicator was Objective Response Rate (ORR) evaluated by an independent review facility (IRF). Objective response was defined as a complete or partial response, determined at two consecutive evaluations with an interval of at least 4 weeks. In the mBCC group, the response of the tumour was evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.0. In the laBCC group, the response of the tumour was evaluated on the basis of visual assessment of the external tumour and ulcerati-

Table 1 Overview of patients with basal cell carcinoma of the eyelids and canthi at the Department of Ophthalmology at the Faculty of Medicine of Comenius University and University Hospital in Bratislava in the period 2008-2013

	2008	2009	2010	2011	2012	2013
Women	17	23	20	20	29	27
Men	7	5	16	15	13	25
Mean age of women	73.3	70.1	65.9	70.3	68.6	67.6
Mean age of men	69.1	71.4	67.6	71.5	73.4	70.8
Sin	8	14	17	19	24	30
Dx	16	14	19	16	18	24
Recurrence	2	2	1	1	3	2

Table 2 Overview of localisation of BCC of eyelids and canthi at the Department of Ophthalmology at the Faculty of Medicine of Comenius University in Bratislava in the period 2008-2013

	2008	2009 [No (%)]	2010 [No (%)]	2011 [No (%)]	2012 [No (%)]	2013 [No (%)]	Spolu [No (%)]
[No (%)]	2009	6 (2,73)	9 (4,10)	10 (4,56)	18 (8,21)	15 (6,84)	64 (29,22)
[No (%)]	2010	0 (0)	0 (0)	1 (0,45)	1 (0,45)	2 (0,91)	5 (2,28)
[No (%)]	2011	21 (9,58)	22 (10,04)	20 (9,13)	18 (8,21)	29 (13,24)	126 (57,53)
[No (%)]	2012	1 (0,45)	5 (2,28)	4 (1,82)	5 (2,28)	8 (3,65)	24 (10,95)

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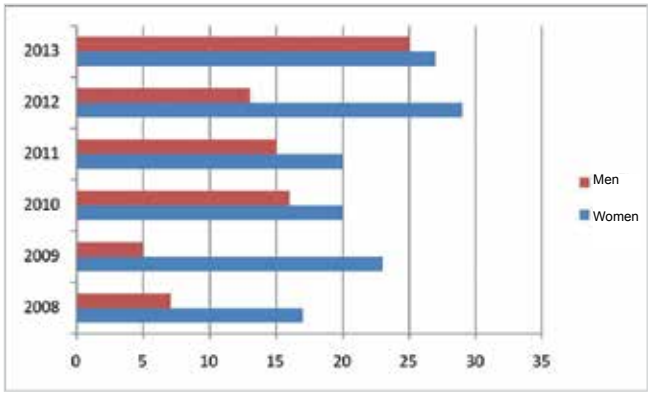
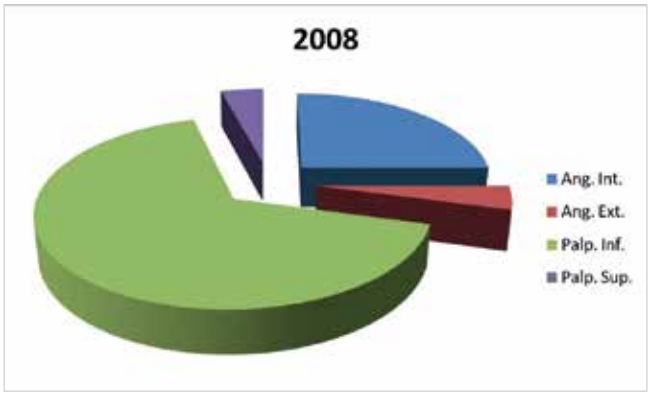
Table 3 Overview of stages of BCC of eyelids and canthi at the Department of Ophthalmology at the Faculty of Medicine of Comenius University in Bratislava in the period 2008-2013

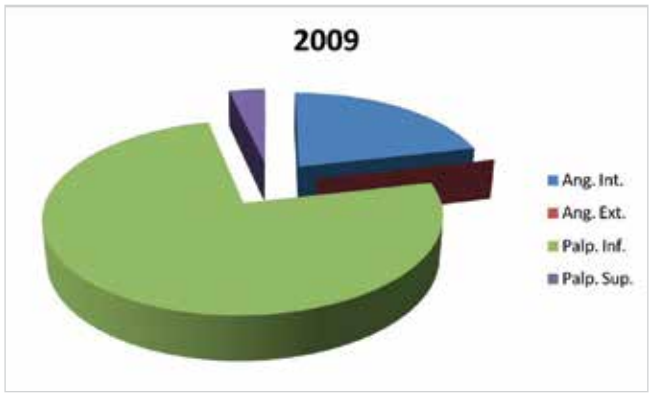
	2008	2009	2010	2011	2012	2013
stage G 1	16	18	29	24	22	32
stage G 1-2	6	7	2	5	10	10
stage G 2	2	3	5	6	10	12



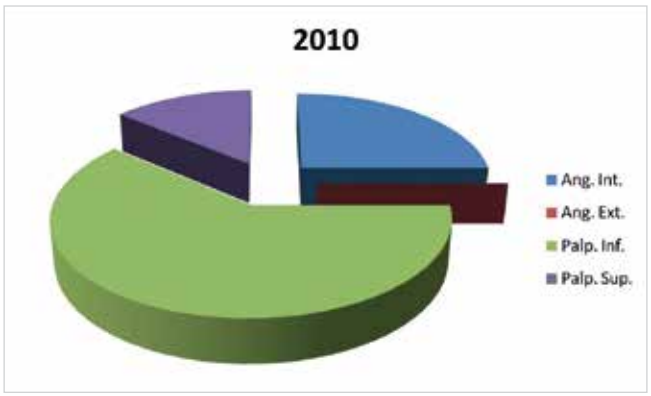
Graph 1 Overview of patients with basal cell carcinoma – men/women at the Department of Ophthalmology at the Faculty of Medicine of Comenius University in Bratislava in the period 2008-2013.
Throughout the entire observation period of 2008 – 2013 we recorded a higher incidence in women than in men, in every observed calendar year of the given period.



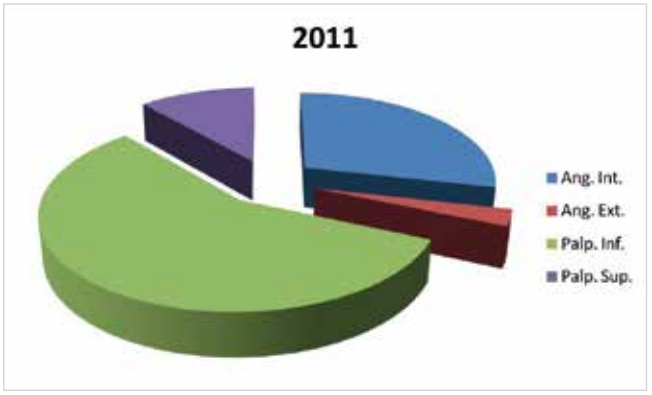
Graph 2 Overview of localisation in patients with basal cell carcinoma at the Department of Ophthalmology at the Faculty of Medicine of Comenius University in Bratislava in 2008.
In the observation period of 2008 – 2013, in 2008 we recorded the highest incidence of cases on the lower eyelid.



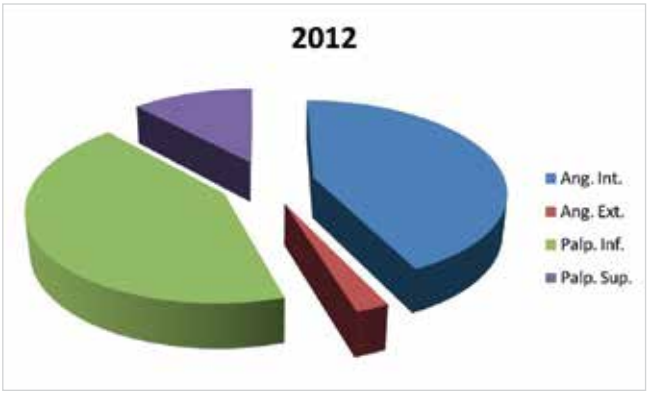
Graph 3 Overview of localisation in patients with basal cell carcinoma at the Department of Ophthalmology at the Faculty of Medicine of Comenius University in Bratislava in 2009.
In the observation period of 2008 – 2013, in 2009 we recorded the highest incidence of cases on the lower eyelid.



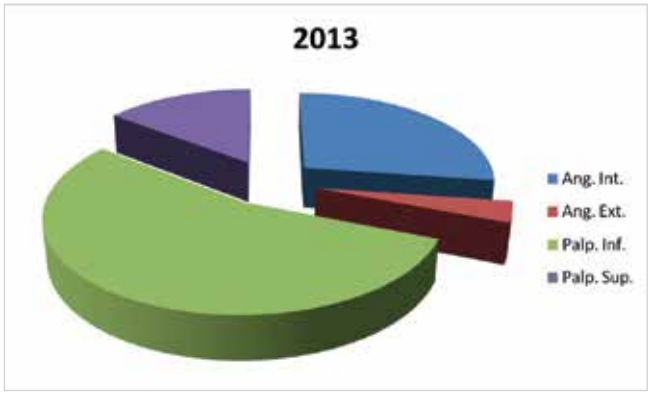
Graph 4 Overview of localisation in patients with basal cell carcinoma at the Department of Ophthalmology at the Faculty of Medicine of Comenius University in Bratislava in 2010.
In the observation period of 2008 – 2013, in 2010 we recorded the highest incidence of cases on the lower eyelid.



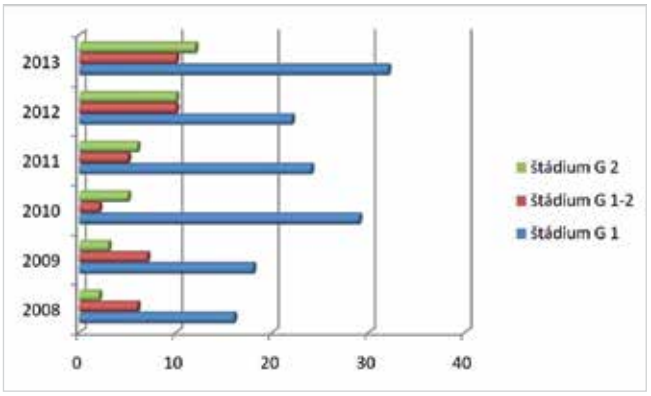
Graph 5 Overview of localisation in patients with basal cell carcinoma at the Department of Ophthalmology at the Faculty of Medicine of Comenius University in Bratislava in 2011.
In the observation period of 2008 – 2013, in 2011 we recorded the highest incidence of cases on the lower eyelid.



Graph 6 Overview of localisation in patients with basal cell carcinoma at the Department of Ophthalmology at the Faculty of Medicine of Comenius University in Bratislava in 2012.
In the observation period of 2008 – 2013, in 2012 we recorded the highest incidence of cases on the lower eyelid and inner canthus.



Graph 7 Overview of localisation in patients with basal cell carcinoma at the Department of Ophthalmology at the Faculty of Medicine of Comenius University in Bratislava in 2013.
In the observation period of 2008 – 2013, in 2013 we recorded the highest incidence of cases on the lower eyelid.



Graph 8 Overview of stages of basal cell carcinomas at the Department of Ophthalmology at the Faculty of Medicine of Comenius University in Bratislava in the period 2008-2013.
In the observation period of 2008 - 2013 we recorded a higher incidence of stage G 1 in every year.

on, imaging of the tumour (where appropriate) and biopsy of the tumour. In the laBCC group, the patient was considered responsive if they met at least one of the following criteria and did not have progression:

(1) reduction of size of lesion by ≥ 30 % [sum of longest diameters (SLD)] from baseline value in target lesions using radiography;

(2) reduction of SLD by ≥ 30 % from baseline value in external visible dimension of target lesions;

(3) complete regression of ulceration in all target lesions [1, 3, 4, 5].

Conventional therapy of tumours of the eyelids and canthi depends to a large extent on the character, size and localisation of the tumour. A surgical solution is the best option of therapy for the pathology in question [2]. In our study the highest proportion of BCC was in the G1 stage, more in the female sex with more frequent localisation on the lower eyelid, and overall occurred more on the left side of the face. The average age at which the pathology afflicted our patients was rounded up to 70 years, otherwise most frequent in the sixth or seventh decade of life. During a retrospective study over 6 years we recorded an increase; for example in a comparison between 2008 and 2013 the incidence doubled. This may be caused by the increased rate of identification in recent years, by surgical solution and histological confirmation due to a larger interest on the part of patients, but also because basal cell carcinoma has a rising tendency generally [18].

Recurrences after excision are caused by multiple factors. The most common is failure to abide by the recommendations for radical excision of basal cell carcinoma 0.3-1 cm from the clinically visible edges of the tumour. In addition to insufficiently radical procedure, a further supporting factor of incomplete excision is that basal cell carcinoma may spread subclinically as far as several centimetres from the clinically identifiable tumour. Locally infiltrated growth of basal cell carcinoma is characterised by an asymmetrical, frequently highly inconspicuous subclinical margin in a horizontal direction, which may reach more than several centimetres from the macroscopic boundaries of the tumour.

Wilson et al. in their study on 3795 basal cell carcinomas determined incomplete excision in 6.2% of cases [26].

The following localisations were demonstrated to be significant risk factors of incomplete excision: medial ocular canthi, lower eyelid and nasolabial fold, as well as simultaneous excision of a number of basal cell carcinomas. In the case of the first risk factor, the endeavour to attain a good cosmetic effect is of determining significance, in the case of the second factor it is impossible to find any reason other than haste on the part of the surgeon. In advanced stages it is necessary to proceed to a mutilating procedure – exenteration of the orbit, which means a serious psycho-social problem for the patient [14, 15].

Data on recurrences following surgical treatment of basal cell carcinomas differ depending on the used surgical technique. In the studies known to us, published during the course of the last 10 years, the incidence of recurrences in patients treated without the use of Mohs micrographic surgery or “en-face” frozen sections perioperatively was within a range from 1.8 % to 39 %, upon longer observation of patients the proportion of recurrences increased. Within the framework of possible causes, we can consider the lesser degree of attention paid by this section of the Slovak population concerning the incidence of what from a layperson's perspective appear to be merely “cosmetic” lesions on the face [16, 17, 19, 21, 24].

The factors influencing the incidence of recurrences have not yet been entirely clarified. Within the area of the eyelids, the inner canthus is considered problematic due to impaired excision of the lesion caused by the surrounding vulnerable anatomical structures. The histological cleanliness of the edges of the excised tissue, as well as co-operation between the pathologist and the surgeon, is considered a significant factor in the incidence of recurrences. In our cohort of observed patients there were recurrences of tumours with histologically clean edges, thus the edges and the base were loose, which could be explained also by the time interval between the operation and the evaluation of the excised tissue in the sense of the more difficult orientation for the pathologist within the excised tissue. An endeavour to improve co-operation and communication between the surgeon and the pathologist resides in sending photographic documentation of tumours before excision, sketches, as well as a demarcation of the edges and orientation of patterns, e.g. by suture.

The incidence of recurrences in the academic literature is on the level of 6.0 % [6, 9, 22]. Data on recurrences following surgical treatment of basal cell carcinoma differs depending on the used surgical technique or localisation of the tumour. In the cohort of patients at the Department of Ophthalmology at the Faculty of Medicine of Comenius University in Bratislava in the period 2005-2007 (3 years), recurrence was recorded in 4 cases, which represented 6.0% of the cohort of patients [25]. In our present observed cohort from the same centre from the period 2008 - 2013 (6 years) we recorded a slightly lower value, in which the percentage of recurrences was only 5.02 %. This fact may indicate that thanks to gradually progressing experience in the area of BCC, more attention is paid to significant risk factors of incomplete excision during the surgical procedure, of which in the final result the patient is the beneficiary.

CONCLUSION

Within the framework of ophthalmic oncology, the issue of basal cell carcinomas requires increased attention, because an untreated tumour may, upon overgrowth into the orbit, lead to loss of the visual organ, in which treatment and reconstruction surgery of the advanced stages represents a serious aesthetic intervention.

LITERATURE

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