

Analysis of Tumour Related Data and Clinical Features o Eyelid Carcinomas

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ABSTRACT: Almost 10% of worldwide skin cancers are located at the eyelid level. In European countries, malign eyelid tumours are mostly represented by basal and squamous cell carcinomas, and usually affect elderly patients. In order to study the clinical features of eyelid tumours, and potential correlations between tumour parameters, we have enrolled a cohort of 98 subjects from a south-western region of Romania. Our study confirmed the majority of results from other European studies, as basal cell carcinoma was the most frequent malign form, being diagnosed for more than 85% of patients with declared prolonged sun exposure; tumours were mostly located on the superior eyelid, especially for males, and may present slow progression rates. We have identified significant correlations only between the tumour stage and symptoms' duration, and also between the tumour stage and smoking habit, for females.

KEYWORDS: Eyelid tumour, basal cell carcinoma, squamous cell carcinoma, skin cancer.

Introduction

The eyelid is a small organ, yet it accounts for almost 10% of all skin cancers around the world [1].

It is characterized by a very thin skin, divided in several layers: subcutaneous tissue, striated muscle, tarsus, and conjunctiva.

Lesions develop in the periocular area and initially generate aesthetic and physical discomfort.

Based on their progression rate, lesions may just change the normal appearance of the eye or, when the tumour size is large enough, may eventually induce a functional impact on the patient's vision.

Thus an early diagnosis and treatment is essential regarding the development of this condition.

The lower eyelid seems to be significantly more affected than the upper lid, since between 50% and 70% of neoplasms occur at this level [2].

Medial and lateral canthus are also possible locations, but are characterized by a lower prevalence.

There are sometimes significant differences between the prevalence of cases or tumours' location in the world, and this is due to the geographic localization of regions around the globe, which is in fact related to a different incidence angle of sun rays.

Persons living in the equatorial region or at high altitudes tend to have a higher risk of developing skin tumours.

Ultraviolet (UV) radiation exposure is identified as the most important factor in the development of skin carcinomas.

Radiation penetrates the skin (UVA more than UVB), induces the formation of carcinogenic components, produces DNA damage, local immune suppression, all leading to a proper context for skin tumours.

Other risk factors for eyelid neoplasms are the presence of precancerous lesions, like actinic keratosis, a fair skin type, advanced age and, recently, gender has become a potential risk factor, after several studies indicated that males are more susceptible compared to women, who seem to be protected by estrogen-induced mechanisms at skin level.

The most common forms of eyelid carcinomas in European regions are: basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).

Other forms are also encountered: sebaceous cell carcinoma, Merkel cell carcinoma, or melanoma, but are less frequent.

The aim of this study is to determine the prevalence of eyelid neoplasms in a group of patients from a south-western region in Romania, defining also potential correlations between clinical and non-clinical parameters.

Material and Methods

We have performed a research study upon a lot of 98 patients admitted between 2016 and 2019 in the Ophthalmology Clinic of the Emergency Hospital Craiova, all of them presenting a form of eyelid carcinoma.

The Ethic Committee of the Medicine and Pharmacy University of Craiova gave us the approval needed to complete our study. Also, each patient included in the study lot provided an informed consent regarding treatment and subsequent data analysis.

For all patients, we have compiled digital records composed by sociodemographic and clinical variables, dichotomized when possible. We have recorder information regarding age, sex, residency, tumour type and stage (according to TNM grading system), duration of symptoms based on the initial manifestations, location, extension, treatment, and recidive. Regarding the general health context, we have analyzed the following variables: prolonged sun exposure, precancerous lesions, previous neoplasms (no matter their location), smoking status, skin type I or II, diabetes mellitus, arterial hypertension, scleroderma, systemic lupus erythematosus (SLE), acute articular rheumatism, actinic keratosis, cutaneous infections (viral/bacterial), HIV, radiotherapy in antecedents.

We have used Microsoft Excel to centralize all digital records and apply statistical techniques and procedures. Descriptive statistical analysis was carried out upon the set of digital records, and it was completed by Student's t-tests for independent variables, and Chi-square test for group distributions ($p < 0.05$ is statistically significant).

Results

The present study was performed between 2016 and 2019, on a group of 98 patients, all diagnosed with a form of eye neoplasm. All patients were admitted in the Ophthalmology Clinic from the Emergency County Hospital Craiova.

The study lot had an almost equal distribution of sexes, with 51 males (52.04%) and 47 females (47.96%). Patients included in our study had ages comprised between 39 and 91 years old, mean value 67.4 ± 12.5 years (66.02 ± 11.2 for females, 68.67 ± 13.61 for males), thus covering an important age interval. There is no significant age difference between sexes ($p > 0.05$). To ease the subsequent analysis, the lot was divided into age decades, starting from 30-39 years old. We obtained thus 6 decades, up to 90-99 years old (Figure 1a). To be consistent with the patients' real age, we named the decades from 3 to 9, instead of 1 to 6.

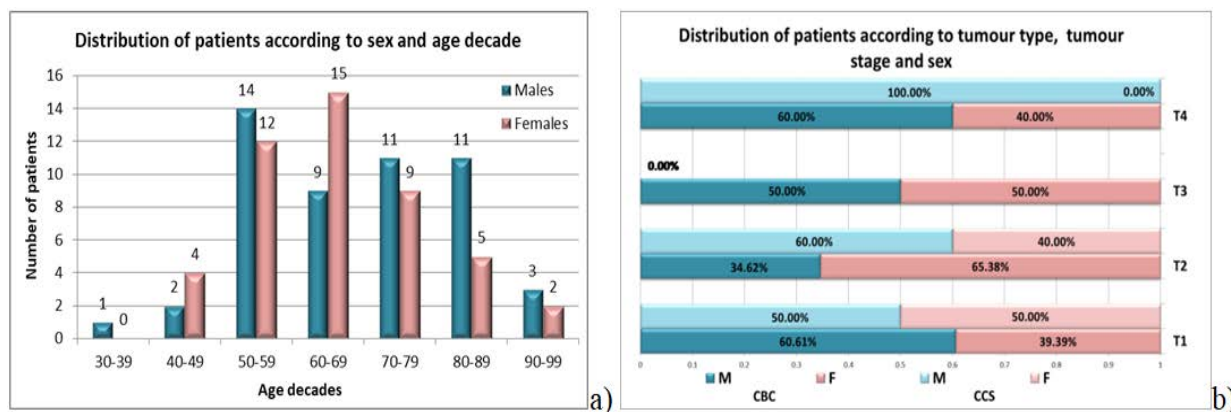


Figure 1. Distribution of patients according to: a) age decades; b) tumour type, stage and sex.

Our study lot was composed mainly of patients with middle to high ages.

Decades 5, 6 and 7 have each almost a quarter of the entire group, while decades 3, 4 and 9 represent the rest.

Concerning the residence area, most patients were from the rural environment (64 patients, representing 65.31%), 28 females and 36 males. The patients with urban residence are divided as following: 19 females and 15 males.

Two types of neoplasms were identified within our study lot: 87.76% (86 patients) had BCC, while 12.24% (12 patients) had SCC. All 4 tumour stages (from T1 to T4) were identified (Figure 1b).

Almost two thirds of patients with BCC (59 patients) had T1 and T2 tumours, while only 5.81% had T4 tumours. One quarter of patients with SCC had stage T4 tumours at the moment of the inclusion in our group, and one third had T1 tumours. No patient with SCC was diagnosed

with stage T3. Regarding the sex division, patients' distribution is rather equal.

As Figure 1b indicates, a maximum for women is only seen in BCC stage T2, with 65.38%, compared to only 34.62% for men. For all other combinations, women tend to have percentages smaller than men do, or at most equal. There is no significant difference between the ages of patients grouped according to their tumour stages ($p>0.05$).

All patients had a unilateral neoplasm, extended on the orbit for 8 patients (8.16% from the entire study lot). All 8 patients with orbit extensions had T4 stage tumours (88.00% being from rural areas). Lesions were mainly located on the inferior eyelid (52 patients, representing

53.06%), but also on the superior eyelid (32 patients, representing 32.65%), medial canthus (9 patients, representing 9.18%) and lateral canthus for 5 patients (5.10%). Women mostly present neoplasms located on the inferior eyelid, while men tend to dominate the other categories (Figure 2a).

As Figure 2b indicates, patients with carcinomas located in the medial canthus are exclusively from rural areas. Patients with rural residence also tend to dominate the superior eyelid category, and especially the higher tumour stages. Patients from urban areas have mostly neoplasms located at the inferior eyelid, or lateral canthus (100% for T3 stage).

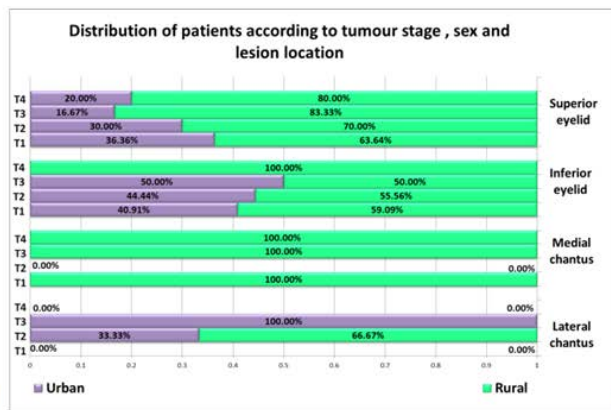
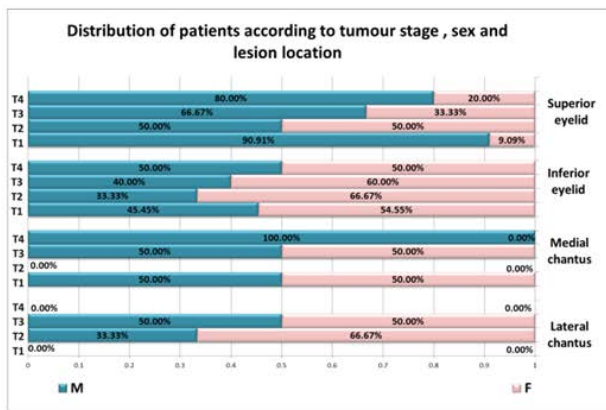


Figure 2. Distribution of patients according to tumour type, stage and: a) sex; b) residency.

Based on patients' symptoms duration before seeking medical treatment, the study group was divided in 3 categories: less than 1 year (42.86%), 1-5 years (37.76%) and 5-10 years (19.39%). The average age for the third group is 72.73 ± 11.71 years, compared with the other two categories, with a mean age of around 66 years. Men have a maximum of presence for T4 tumours with symptoms present for more than a year (100%), followed by T1 tumours with symptoms' duration less than a year (62.5% from this category), and T3 tumours lasting for

more than a year, with 54.55%. Women outnumber men for all other categories, as indicated in Figure 3a.

Less than half of the patients (25 males, 17 females) sought treatment within the first year from the first manifestations of symptoms, presenting only tumours in stages T1 and T2. They globally represent 44.11% from patients living in urban areas, and 42.18% from patients from rural areas. T1 category is dominated by rural patients, while T2 exhibits an equal distribution (Figure 3b).

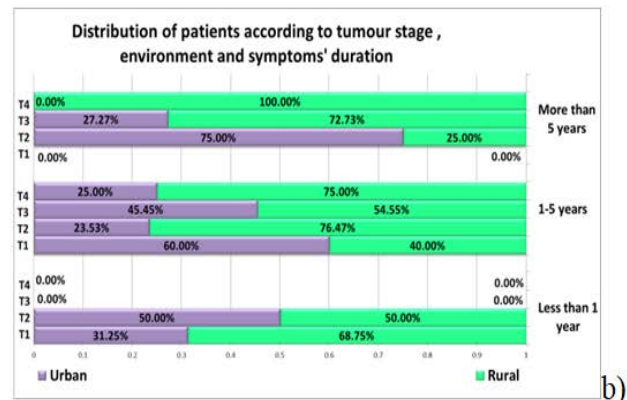
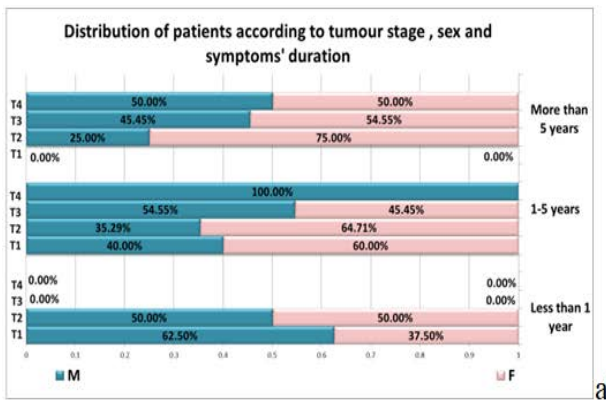


Figure 3. Distribution of patients according to tumour stage, symptoms' duration and: a) sex; b) residency.

Patients who waited longer than 1 year had tumours of all stages, mainly T2 and T3. They represent around one third from the entire study lot, divided as following: 38.24% from subgroup living in urban area, and 37.50% from subgroup living in rural areas. In fact, this subgroup is dominated by patients with rural residency (more than 3 quarters from T2 and T4 stages). Women are more numerous for T1 and T2 stages, and represent less than half for T3 category.

Patients who came to the doctor after more than 5 years of symptoms' manifestation represent almost 20% of the entire study lot, and were diagnosed with tumours of stages T2, T3 and T4. Even with slow progression rates, their tumours have evolved beyond the T1 level in more than 5 years of symptoms' presence. This category is dominated by women from rural areas.

Figure 4 emphasizes the distribution of patients according to their location, tumour stage and symptoms' duration. Except for lateral

canthus, T1 tumours located in all other locations determined the patients to seek medical treatment as soon as possible, more than 75% being diagnosed within the first year.

All 5 patients with tumours located in the lateral canthus came to the doctor after more than 1 year of symptoms, having tumours of stages T2 and T3. Only 33.33% of patients with tumours in the medial canthus came after less than 1 year; 44.44% came after 1 year and 22.22% after 5 years. Patients with tumours at the superior eyelid came sooner to the doctor, 50% presenting in the first year (mostly from rural area, rather than urban). Similarly, only 44.23% patients with lesions located at the inferior eyelid level came in the first year, while 17.31% came after 5 years. Tumours present for more than 1 year were mostly diagnosed with stages T2 and T3, while those present for more than 5 years are associated with stages T3 and T4. There is a significant correlation between the tumour stage and symptoms' duration ($p < 0.01$).

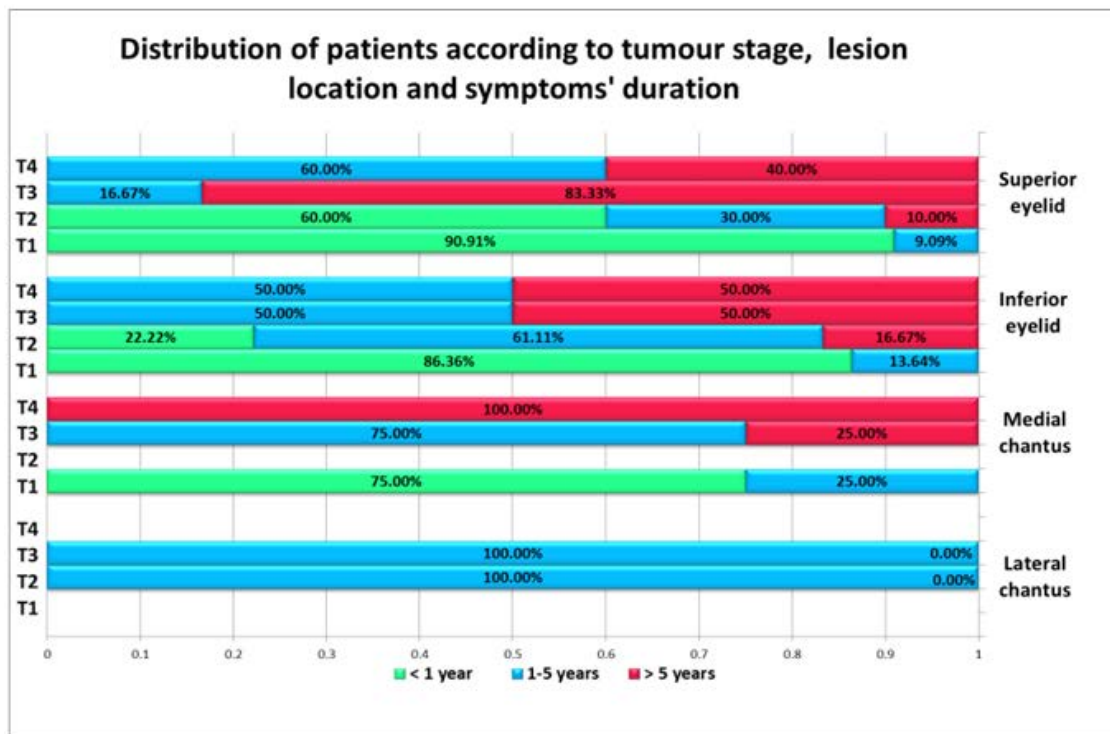


Figure 4. Distribution of patients according to tumour stage, sex and lesion location.

All patients underwent surgical excision of the tumour, for some patients being followed by chemotherapy (7 patients, 7.14%), radiotherapy (1 patient, 1.02%) or both (2 patients, 2.04%). Patients who underwent chemotherapy had tumours in stages T4 (7 patients, symptoms older than 1 year) or T1 (2 patients with symptoms manifested for less than 1 year, both

males from rural environment, but with declared prolonged sun exposure and neoplasm recidive). The patient with recommended radiotherapy was 91 years old, a male from rural environment, with T4 stage CSS.

From the entire study lot, only 4 patients had recidive (4.08%), 3 males and 1 female. All patients had BCC in stages T1, T2 or T4 (all

from rural areas, two males were smokers), with extensive sun exposure in antecedents.

A confirmed important key factor in the development of eyelid carcinomas is sunlight. From our study lot, 80 patients (representing 81.63%) have declared previous extensive sun exposure. The other 18 patients were mostly from urban areas, with ages comprised in decades 5 to 9, diagnosed both with BCC and SCC, with tumours with stages T1, T2 and T3 located only at eyelids levels (no medial or lateral canthus involved). Eight patients with declared sun exposure (representing 8.16%) had precancerous lesions in antecedents, and three quarters of them came to the doctor after more than 5 years of symptoms presence, being diagnosed with T3 and T4 stage tumours. Eleven patients had previous forms of neoplasms, with various locations, in antecedents; 5 patients were diagnosed in the first year of symptoms manifestations, mostly males, with T1 and T2 tumours, the others with T2, T3 and T4 tumours.

The presence of comorbidities like diabetes mellitus, arterial hypertension, scleroderma,

SLE, acute articular rheumatism, cutaneous infections (viral/bacterial), actinic keratosis, HIV, does not seem to be associated with the tumour type, stage or location, at the moment of the initial diagnostic ($p>0.05$).

A significant part of our study lot, 45.92% of all patients, is represented by active smokers. Table 1 summarizes tumour related data, divided according to smoking status. For several parameters, notable differences are encountered: more men are smokers, compared to women; mean age for non-smokers is smaller; smokers are mostly males from rural areas; almost half of smokers were diagnosed within the first year of symptoms, compared to non-smokers where category 1-5 years is significant. The distribution of patients regarding the symptoms' duration is similar for males, smokers and non-smokers; for females, we have identified a significant correlation between the smoking status and the symptoms' duration at the moment of diagnosis ($p<0.01$).

Table 1. Distribution of patients, divided as non-smokers and smokers.

		Smoking status			
		Non-smokers		Smokers	
		Males	Females	Males	Females
Mean age (years)		23	30	28	17
Mean age (years)		67.43	64.2	69.67	69.23
Environment	Urban	7 (30.43%)	13 (43.33%)	8 (28.57%)	6 (35.29%)
	Rural	16 (69.57%)	17 (56.67%)	20 (71.43%)	11 (64.71%)
Tumour stage	T1	10 (43.48%)	10 (33.33%)	12 (42.86%)	5 (29.41%)
	T2	4 (17.39%)	13 (43.33%)	8 (28.57%)	6 (35.29%)
	T3	6 (26.09%)	6 (20.00%)	5 (17.86%)	5 (29.41%)
	T4	3 (13.04%)	1 (3.33%)	3 (10.71%)	1 (5.88%)
Localization	Lateral canthus	0 (0.00%)	3 (10.00%)	2 (7.14%)	0 (0.00%)
	Medial canthus	3 (13.04%)	2 (6.67%)	2 (7.14%)	2 (11.76%)
	Inferior eyelid	8 (34.78%)	20 (66.67%)	13 (46.43%)	11 (64.71%)
	Superior eyelid	12 (52.17%)	5 (16.67%)	11 (39.29%)	4 (23.53%)
Symptoms' duration	< 1 year	10 (43.48%)	10 (33.33%)	15 (53.57%)	7 (41.18%)
	1-5 years	9 (39.13%)	16 (53.33%)	9 (32.14%)	3 (17.65%)
	5-10 years	4 (17.39%)	4 (13.33%)	4 (14.29%)	7 (41.18%)

Discussions

Eyelid tumours represent a rather common diagnostic for elderly patients with ophthalmologic affections, in both benign and malign forms. Our study was focused on two of the most encountered skin carcinomas: BCC and SCC. The study lot comprised 98 patients, with an almost equal sex distribution, all diagnosed

with one of the previously mentioned eyelid tumour forms.

Male-to-female ratio for BCC and SCC seems to be a debatable issue. For BCC, we have an equal distribution; however, there are authors that report results consistent with our own, others indicate that BCC is more commonly encountered in males compared to females (almost twice as much) [3,4,5], or, in reverse, report a female preponderance for all types of

eyelid tumours [6]. An *in vivo* study performed on mice indicated that gender is a key factor in the development of BCC, since the skin is known to be strongly estrogen-responsive, still further study is necessary to determine the relation of this parameter with the other factors involved in this complex process [7,8].

In our study, males represent two thirds of patients with SCC. In a recent paper, Mancuso et al. studied the female resistance to induced SCC (on mice), proving that estrogens have a protective effect in case of SCC, compared to BCC [9], which would explain this difference.

The mean age of our patients (at the moment of the initial diagnosis) is consistent with the results reported by other authors [3-5,10], confirming that mostly patients above 60 years are prone to develop eyelid malignant tumours. Kaliki et al. [6] reported a lower mean age for patients with SCC, compared to patients with BCC (5 years difference), but we have not found any significant mean age difference between the two forms, for our patients. There is however a difference on sexes, as both for BCC and SCC, the mean age of women is lower than that of men.

More than 85% of our patients were diagnosed with BCC, and the rest with SCC. Our results are confirmed by other studies performed in American and European countries, indicating that BCC is the most common form of eyelid neoplasms, followed by SCC [10-15].

Domingo et al. reported an incidence of 17.1% for SCC [16], while Asproutis et al., in their retrospective study related to eyelid tumours in Ioannina, Greece, report only 7% [3].

On the other hand, studies performed on patients from Asian countries report a third position for SCC and, sometimes, a second position for BCC, being outclassed by sebaceous gland carcinomas [17-20].

In our study, the most common location of neoplasms was the lower eyelid, accounting for more than half of our patients. Given the fact that this area is characterized by an increased exposure to sunlight compared to the upper eyelid, medial and lateral canthus, the results are clear and confirmed by similar studies. The less frequent location amongst our patients was the lateral canthus, with only 5.1% of all study lot. The incidence of neoplasms at medial canthus level is situated around 10-15%, both for our study and similar research [3,5,9,15].

However, the analysis for each neoplasm form indicates slightly different results. BCC is encountered at the lower eyelid for more than

55% patients, as other authors have indicated [3,5,6,21].

Similar results are valid for medial and lateral canthus. Less than 20% of women were diagnosed with upper lid neoplasms, compared to men where the percentage is more than 45%. Women use makeup, especially on the upper lid, which probably has a protective role against sunlight. According to Silverman et al., SCC is most commonly diagnosed at lower eyelid level and medial canthus [1], but in our study however, 50% of patients had SCC located at the upper eyelid level, more than patients with lower eyelid neoplasms. Further study is required from this point of view, since the number of patients with SCC from our lot was rather small. Eyelid neoplasms were usually strictly located within a single region. However, 8.16% of patients had their orbit affected by the extension of their initial lesions. All these patients had T4 stage tumours, mostly males from rural environment, and presented symptoms for more than 1 year. The majority of patients had ages from decades 7, 8 and 9, which could explain why they delayed so much the moment of diagnosis.

Regarding the time difference between the first symptoms' manifestations and the moment when patients actually come to see a doctor, we have divided our study lot in 3 groups: patients who came in the first year, patients who waited between 1 and 5 years, and those who waited more than 5 years. A person usually comes to a doctor when symptoms either reach an unbearable level, or generate concerns related to the physical aspect. As expected, the first category (less than 1 year) is the largest, since most patients are usually preoccupied with their health status and are conscious of the need to seek medical treatment as soon as possible. Women are more concerned and aware of their symptoms, thus they tend to present earlier to the doctor. We must also take into account the fact that women may worry more regarding a potential changed aspect of their eyelids, since they are more preoccupied with their general aesthetic aspect. Also, since the majority of women use makeup, they pay attention to their eyelids almost every day, so even the smallest change is rapidly discovered. Older men usually tend to ignore their physical appearance, and do not seem to be disturbed by aesthetic changes. They were most likely motivated either by a concern regarding their general health, or by a feeling of discomfort generated by their lesions.

Patients from the second category (1-5 years) are middle aged (mostly decades 5 and 6), and more than 66% live in rural areas.

The third category, patients waiting more than 5 years, is the smallest, with less than 20% of the study lot. The average age of these patients is around 72 years old. So those two subgroups are mostly comprised by elderly patients with rural residency. The delay in their diagnostic moment may be explained by various arguments: access to a specialist is more difficult compared to urban areas, the average income is lower, and they tend to ignore the discomfort induced by their lesions. Still, this does not necessarily mean that those patients are less concerned of their health, as it is known that BCC, for example, is characterized by a slow progression rate, which could create the impression of a less severe lesion [5].

More than 85% of patients with precancerous lesions are included in these two categories, especially the last one. Those patients were aware of the presence of their lesions, but failed to monitor them correctly, in order to rapidly evaluate all changes towards a worse diagnostic.

As a general trend, the tendency of our study lot indicates that the percentage of women with higher stages is decreasing, while it seems to increase for men. Therefore, men tend to wait longer before seeking medical treatment.

For all patients included in our study lot, we have analyzed a series of clinical parameters, in search of potential correlations with the neoplasm presence and characteristics. We have found significant correlations only with symptoms' duration and smoking status, for females only. All other clinical parameters do not seem to exert a significant influence on tumour outcome.

Smoking status is an important factor in carcinogenesis and tumour progression and several studies have analyzed its association with particular types of skin neoplasms. It appears that active and former smokers have a higher risk of developing SCC, compared to BCC [22,23].

We have also noticed that smokers tend to present tumours in higher stages than non-smokers, for the same duration of symptoms' presence before the initial diagnosis. So this would indicate a more aggressive progression of tumours in their case, compared to non-smokers, which could be explained by the presence of numerous chemical components in smoke with proved impact on cell cycle, cell apoptosis mechanism or oncogenes deregulation [24,25].

Conclusions

Our study regarding the prevalence and characteristics of eyelid neoplasms within a study lot indicated that BCC is the most common form of skin carcinoma, located mostly at the inferior eyelid level.

Both BCC and SCC affect elderly patients, usually above 65 years old, from rural areas, with extensive sun exposure declared in antecedents.

These results are in agreement with findings from similar research conducted for patients in other regions, with different life conditions.

Conflict of interests

None to declare.

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