Original Paper

Basal Cell Carcinoma and its Impact on Different Anatomical Regions

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ABSTRACT: Basal cell carcinoma (BCC) is the most common skin cancer. We conducted a retrospective study over a period of two years (2018-2019), on 214 patients from the Plastic Surgery clinic in order to identify the clinical and histopathological aspects of the disease: the case distribution according to sex, living environment, age, histopathological subtype, location. Results. The F/M ratio was of 1.03 in favour of women. The incidence was higher for patients from rural areas (55.14%). The most affected group age was between 70-80 years old, with 76 patients (35.51%). The most frequent histological type was nodular basal cell carcinoma (65.42%), followed by micronodular subtype (17.29%). We observed the association of basal cell carcinoma with a number of other conditions such as: high blood pressure (92 cases), diabetes (19 cases), chronic kidney disease (2 cases), liver disease (5 cases), epilepsy (2 cases). Correlating the histopathological subtype and the invasion of the edges of the surgical excision specimen, we noticed that edge invasion was present: in the case of nodular basal cell carcinoma (15.71%), micronodular subtype (43.24%), superficial subtype (50%), morpheaform subtype (40%). Dividing the cases by location, we highlighted the risk areas: nasal region (29.44%), cheek (10.75%), orbital region (13.55%), scalp (10.75%), auricular region (7.48%), forehead (8.41%), etc. Thus, 89.72% of cases were located on photo-exposed areas (head and neck). Patients from rural areas registered a higher number of cases both in photo-exposed and non-exposed areas.

KEYWORDS: *Basal cell carcinoma, histopathological subtype, location, risk areas.*

Introduction

Basal cell carcinoma is the most common cancer in humans with an overall incidence that is increasing worldwide significantly, by 3-10% each year, especially in young women [1].

While accounting for approximately 80% of all nonmelanoma skin cancers, its incidence is 20 times higher than that of melanoma, and four times higher than that of squamous cell carcinoma (SCC) [2].

Several statistical analyses of affected populations have shown that BCC is more frequent between men, rather than women, while black people are protected by melanin and melanosomal dispersion, thus being less affected [3].

There are a few factors that can explain the rise in incidence rates for BCC in the last few years, such as: frequent sunburns (especially in patients with skin phenotype I and II), ionizing radiation, arsenic, environmental and occupational factors, green or blue eyes, blonde or red hair [4].

BCC arises within photoexposed areas (especially in light skinned individuals) of the head (the eyelids represent a frequent site) and neck, but can occur anywhere on the body, rarely on the mucous membranes or palms and soles. However, it may be present even on regions where UV exposure cannot be incriminated, such as the axilla or pubic region [5-7].

Similar to melanoma and SCC, the pathogenesis of BCC involves cumulative and intermittent exposure to ultraviolet (UV) radiation, particularly the ultraviolet B spectrum (290-320nm).

There is a latency period between sun exposure and clinical onset of the skin cancer, so is more common in older individuals.

Both UV types, UVA and UVB, cause DNA damage and immune suppression leading to neoplasms.

UV-light-induced signature mutations in the p53 tumor suppressor have been found in about 50% of BCC cases [8-12].

Malignant activation of the sonic hedgehog (SHH) signaling pathway is well known as a key feature of BCC and therefore it became a therapeutic target for treatment.

The most common genes mutated in sporadic basal cell carcinoma are: PTCH1 (73%), SMO, SUFU [13].

Basal cell carcinoma (BCC) generally has an indolent course and is associated with an excellent prognosis after curettage and electrosurgery [14].

However, sometimes BCC grows aggressively, locally destructive, rarely giving

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distant metastases, causing significant morbidity or mortality [15,16].

The anatomic location may have a role in the development of a particular clinical subtype: nodular (the most common, representing approximately 60-80% of all BCCs), superficial, morpheaform, pigmented (endothelins may be involved in pigmentation process) and fibroepithelioma of Pinkus [17].

In order to understand spontaneous regression, to appreciate the biological behavior of these tumors or differentiate basal cell carcinoma from other skin cancers like squamous cell carcinoma, several immunohistochemical markers has been tested: replication initiation factors like MCM2, beta-catenin-a cytoplasmic protein that controls cell adhesion, COX-2-an important factor for tumor formation, angiogenesis and metastasis, cathepsin K-a cysteine protease, class III beta-tubulin which, according to previous studies, is not expressed in normal skin and squamous cell carcinoma, D2-40-a monoclonal antibody, matrix metalloproteinase-10, p53 and bcl-2-markers expression of apoptosis, Ki-67 and PCNA-markers of cell proliferation, E-cadherin-a calcium-dependent cell-cell adhesion molecule, Aquaporin-3-which has a role in cell proliferation, tumorigenesis, and cell migration, CD10-a zinc-dependent metallopeptidase, CXCR-4, P120 catenin, MMP-2 and MMP-9 [18-29].

Material and Method

A retrospective study was conducted over two years (2018-2019) which involved the identification and selection of a group of patients.

The study included patients from the Plastic Surgery clinic of the Emergency Clinical Hospital from Craiova.

The material was represented by surgical excision specimen that received the clinical diagnosis of skin tumor and the final histopathological diagnosis of basal cell carcinoma.

The study included 214 patients diagnosed with basal cell carcinoma.

For each case, several aspects were highlighted, such as personal data (age, sex), living environment, the existence of certain comorbidities that could have facilitated the development of a neoplasm, the location of the tumor, the histopathological subtype, and the tumoral invasion of the excision specimen.

The data were statistically processed, taking into account the following objectives: establishing the preferred locations of basal cell carcinoma in relation to exposure to UV radiation, establishing the distribution by area of origin, establishing a link between histopathological subtype and invasion of surgical excision margins.

Statistical analysis was performed using Microsoft Excel (Microsoft Corp., Redmond, WA, USA), and IBM SPSS Statistics 20.0 (IBM Corp., Armonk, NY, USA) for processing the data. Data was recorded using Microsoft Excel files.

After that, it was statistically analysed to find a relationship between histopathological and clinical parameters of the patients. MS Office was used to perform a descriptive analysis of the study group based on various parameters along with its graphic representation. The Chi square test was used to analyse the distributions from the interactions of different factors.

The values obtained in the end were analysed, interpreted, compared and represented graphically.

The study was approved by the local ethical committee. Written informed consent was obtained from all the patients.

Results

The 214 patients included in the study were divided by sex into 109 female patients (50.93%) and 105 male patients (49.07%). Thus, an approximately equal incidence is observed for both sexes, with a slight female predominance (Figure 1). The F/B ratio was 1.03.

The distribution by living environment showed a number of 96 patients from urban areas (44.86%) and 118 patients from rural areas (55.14%) (Figure2).

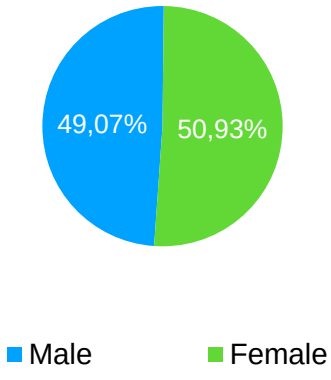

Figure 1. Distribution of patients by gender.

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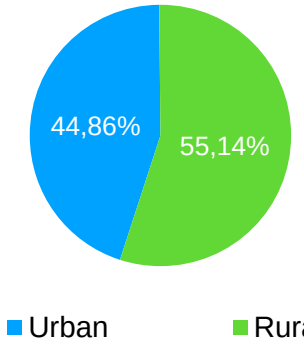

Figure 2. Distribution of patients by living environment.

The distribution by age groups revealed that in the age group <30 years there were no cases of basal cell carcinoma; there were 2 patients (0.93%) aged 30-39 years, 7 patients (3.27%) aged 40-49 years, 17 patients (7.94%) aged 50-59 years, 61 patients (28.5%) aged 60-69 years, 76 patients (35.51%) aged 70-79 years, 50 patients (23.36%) aged between 80-89 years and a single patient (0.47%) aged over 90 years.

There is an increase of the incidence with age, with a peak in the group of 70-80 years; the appearance of basal cell carcinoma at ages younger than 40-50 years was an exception (Figure 3).

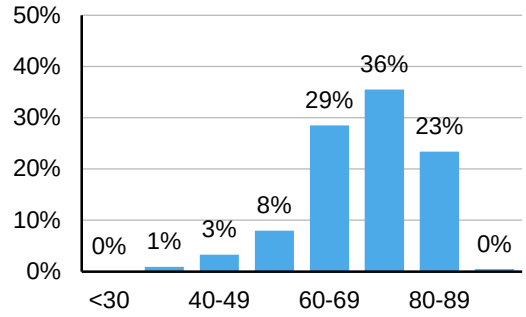

Figure 3. Distribution of patients by age.

The frequency of malignant invasion of the edges of the surgical excision specimens was analysed, registering 73 tumors that had one or more invaded edges (34%) and 141 tumors that did not show any invaded edge (66%). It could be noticed that the number of pieces with non-invaded edges was higher (Figure 4).

These data were obtained despite the fact that most tumors were considered high-risk due to the location, size and histopathological subtype. So it was performed an excision with 0,5-1cm clinical margins.

Several histopathological subtypes of basal cell carcinoma have been identified. The most common subtype was nodular, being present in 140 patients (65.42%). This was followed by the micronodular subtype, which recorded a number of 37 cases (17.29%) and the adenoid subtype which recorded a number of 25 cases (11.68%).

Other histopathological subtypes, such as morpheaform, superficial were highlighted at a number of 5 (2.34%) and 6, respectively (2.80%), while the basosquamous type only in one case (0.47%) (Figure 5).

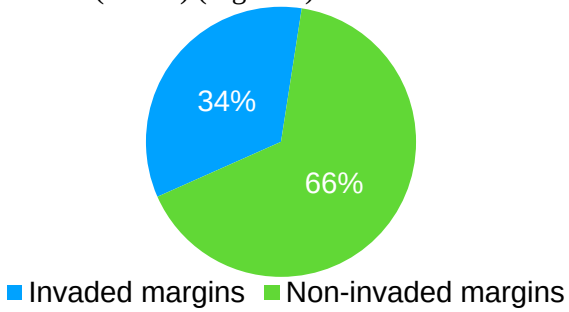

Figure. 4. Distribution of cases by margin invasion.

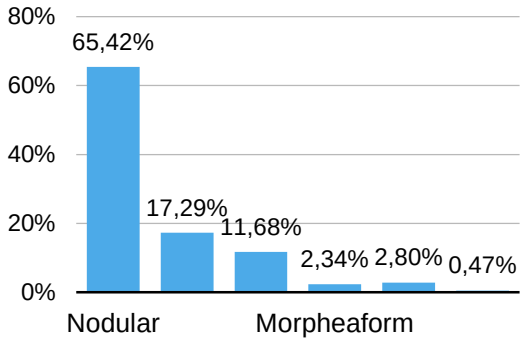

Figure 5. Distribution of cases by histopathological subtype.

The correlation between the histopathological subtype and the invasion of the edges of the surgical excision specimen revealed different values for each of the studied groups. Thus, in the case of nodular basal cell carcinoma, edge invasion was present in 22 cases (15.71%) while 118 cases had free margins (84.29%).

Similar values were obtained for the micronodular subtype, with 16 cases with invaded margins (43.42%) compared to 21 cases with non-invaded margins (56.76%).

In the case of the morpheaform subtype, approximately equal values were obtained regarding the number of cases with invaded edges compared to those with free edges, 2 (40%) and 3 (60%).

The superficial subtype was the only one that recorded equal values for the two variables. Regarding the adenoid subtype and the basosquamous subtype, the frequency of free margins was higher, totalling 21 cases (84%) and 1 case (100%) (Figure 6).

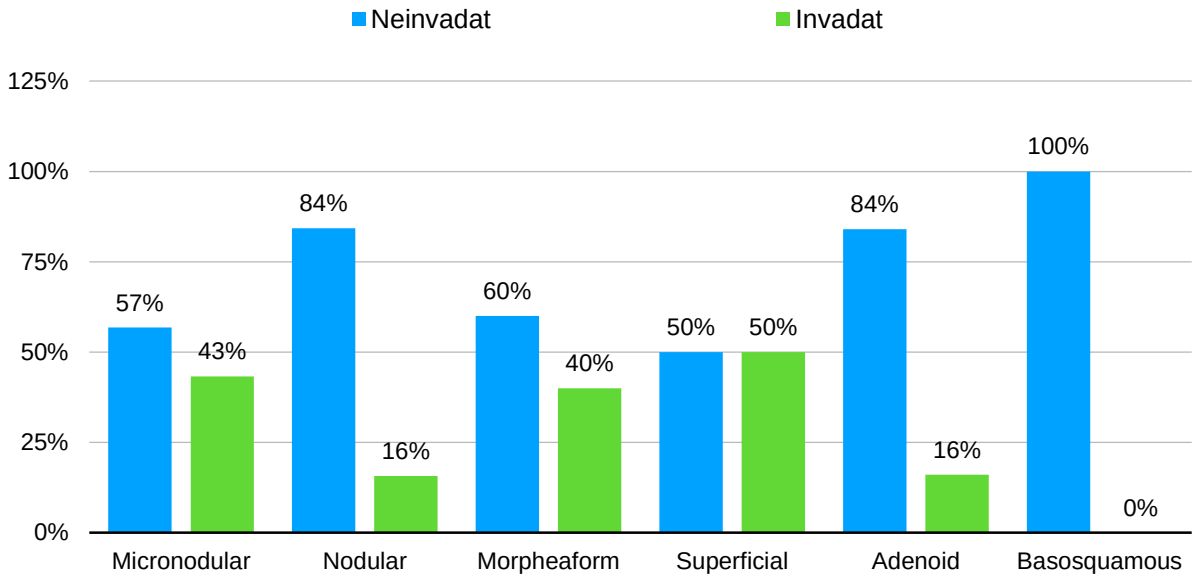

Figure 6. Correlation between histopathological subtype and margin invasion.

We distributed the group of patients according to the location of basal cell carcinoma in different topographic regions and highlighting the risk areas for the development of this malignancy. Thus, the following data were obtained: at the level of the nasal region-63 cases (29.44%), cheek-23 cases (10.75%), orbital region-29 cases (13.55%), scalp-23 cases (10.75%), auricular region-16 cases (7.48%), forehead-18 cases (8.41%). A smaller number of cases was obtained for other topographic areas as follows: lips-7 cases (3.27%), mandible-6 cases (2.80%), cervical region-7 cases (3.27%), trunk-14 cases (6.54%) and extremities-8 cases (3.74%) (Figure 7). We thus observed that the most common location of basal cell carcinoma is in the H area (56.54%). This area includes the central area of the face, orbital region, nose, auricular region, mandible, lips, hands and feet. Area H has an increased risk of recurrence, regardless of the size of the tumor. The next affected area is area M (33.18%). It is represented by the cheeks, forehead, scalp, neck, pretibia. The last area affected is area L (10.28%). This is represented by the trunk and extremities (excluding the hands, feet, nails, pretibia and ankles).

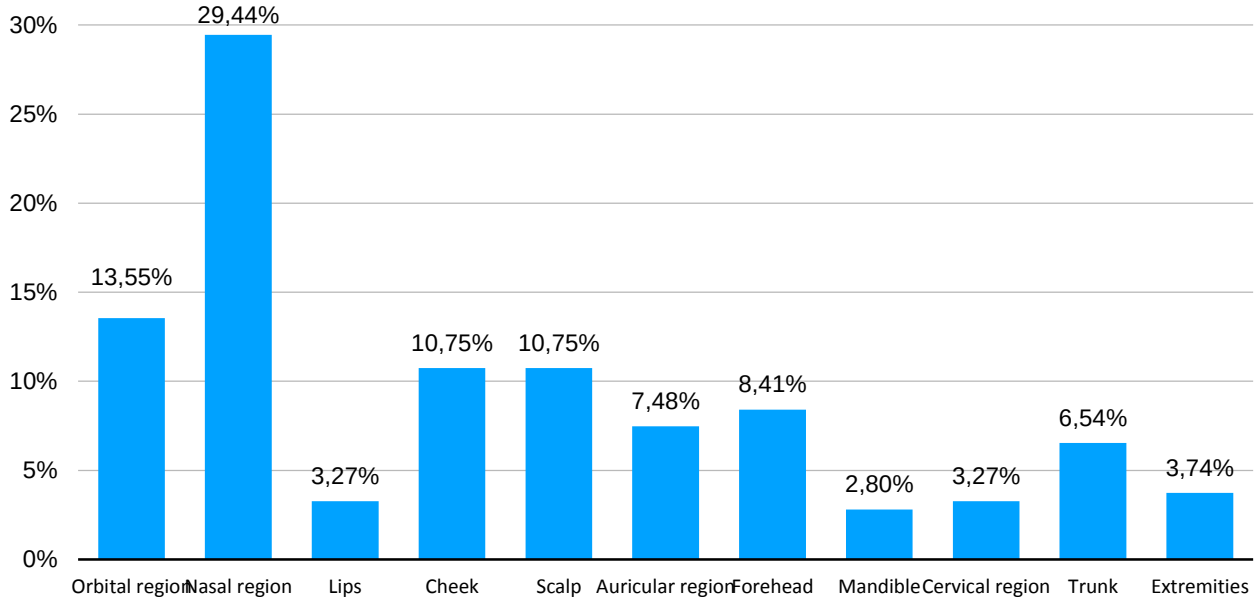

Figure 7. Distribution of cases by location.

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We highlighted the risk areas for the development of a skin carcinoma. These are represented by the photo-exposed areas, especially at the head and neck. At this level, 192 cases were identified (89.72%). Areas not exposed to UV radiation or intermittently exposed (trunk and extremities) recorded a number of 22 cases (10.28%) (Figure 8).

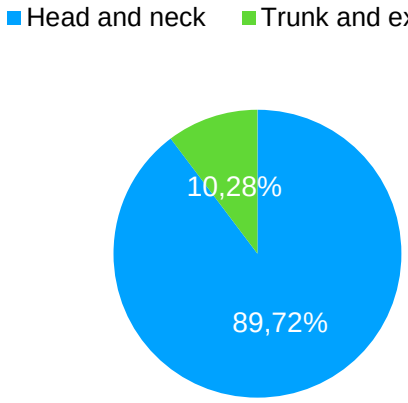

Figure 8. Distribution of cases by risk areas.

We analysed the frequent location of basal cell carcinoma and the living environment of patients and observed similar values for both control groups. Patients from urban areas have the following results: 87 cases (90.63%)-photo-exposed areas (head and neck) and 9 cases (9.37%)-intermittently exposed areas (trunk and extremities). Patients from rural areas obtained the following results: 105 cases (88.98%)-photo-exposed area and 13 cases (11.02%)-intermittent exposed area (Figure 9).

We observed the tropism of basal cell carcinoma, in both cases it was more common in areas frequently exposed to the sun.

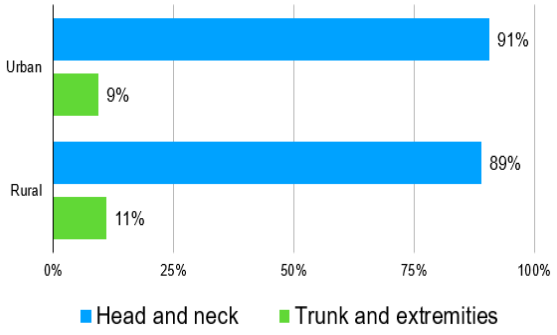

Figure 9. Correlation between location of the disease and living environment.

Among the patients included in the study, in addition to the diagnosis of basal cell carcinoma, a number of secondary conditions have been identified, some of which may facilitate the development of a tumor (Figure 10).

High blood pressure, the best known and most common risk factor, was the highest numerical secondary diagnosis in these patients, being present in 92 cases. Other heart conditions such as heart disease and atrial fibrillation were present in 6 and 8 cases, respectively. Diabetes has a fairly high frequency, being present in a number of 19 cases. A total of 5 patients were diagnosed with liver disease while chronic kidney disease was present in a total of 2 patients. Other secondary diagnoses such as asthma and epilepsy were present in 1 and 2 patients.

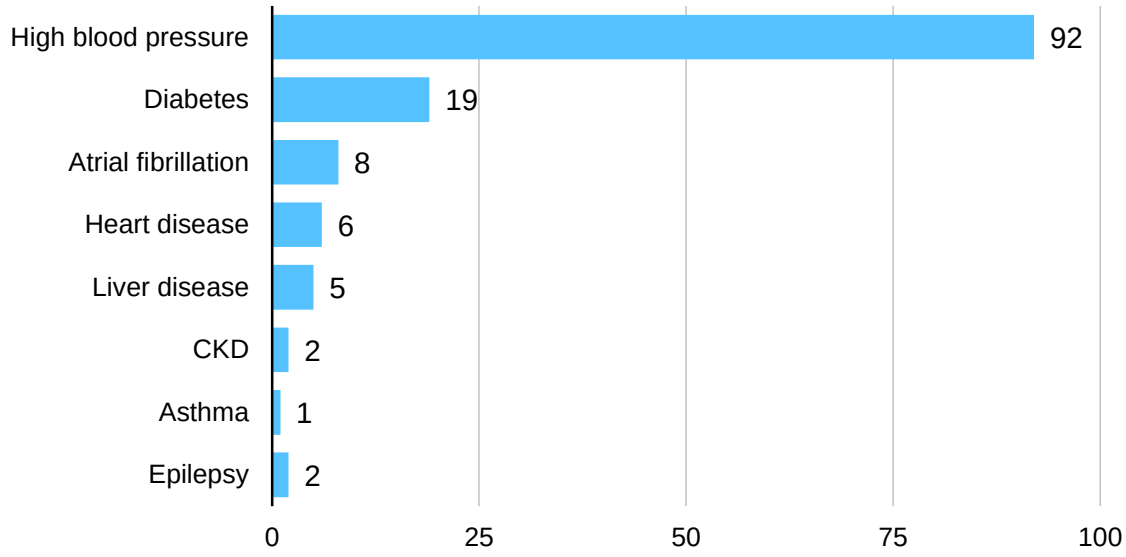

Figure 10. Distribution of patients by secondary diagnosis.

We analysed different relationships between the variables recorded in our study, creating contingency tables for each pair of variables and applying the Chi square test of independence. None of the results were under the maximum limit that shows statistical significance, $p<0.05$, but two of them were under the $p<0.1$ limit, which shows a statistical confidence of 90%, and 6 more were under the 0.2% limit, which shows a statistical confidence of 80% (Figure 11).

First variable	Second variable	Chi square p
Tumor type	Age group	0.303
Tumor type	Gender	0.505
Tumor type	Area of residence	**0.068**
Tumor type	Tumor location	**0.186**
Tumor type	Invasion of margins	**0.149**
Tumor type	Wound closure	**0.183**
Tumor type	Pigmented BCC	0.312
Tumor location	Age group	0.591
Tumor location	Gender	0.721
Tumor location	Area of residence	0.694
Pigmented BCC	Age group	**0.105**
Pigmented BCC	Gender	**0.162**
Pigmented BCC	Area of residence	**0.159**
Invasion of margins	Age group	0.994
Invasion of margins	Gender	**0.093**
Invasion of margins	Area of residence	0.612
Wound closure	Age group	0.973
Wound closure	Gender	0.519
Wound closure	Area of residence	0.699

Figure. 11. Table of performed correlations.

We correlated the area of residence of the patients with their tumor type and obtained the following results: for urban residents: nodular type-58 cases (60.42%), micronodular type-20 cases (20.83%), adenoid type-9 cases (9.38%), and other types-9 cases (9.38%); and for rural residents: nodular type-82 cases (69.49%), micronodular type-17 cases (14.41%), adenoid type-16 cases (13.56%), and other types-3 cases (2.54%) (Figure 12).

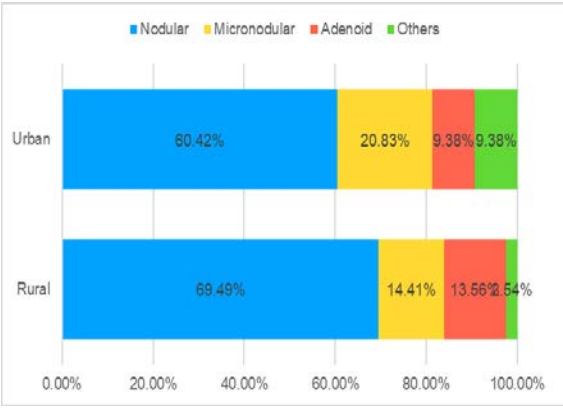

Figure 12. Correlation between tumor type and area of residence.

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Another relevant correlation was between margin invasion and gender, where we obtained the following results: for males-30 invaded margin cases (28.57%) and 75 (71.43%) non-invaded margin cases; and for females: 43 (39.45%) invaded margin cases and 66 (60.55%) non-invaded margin cases. (Figure 13)

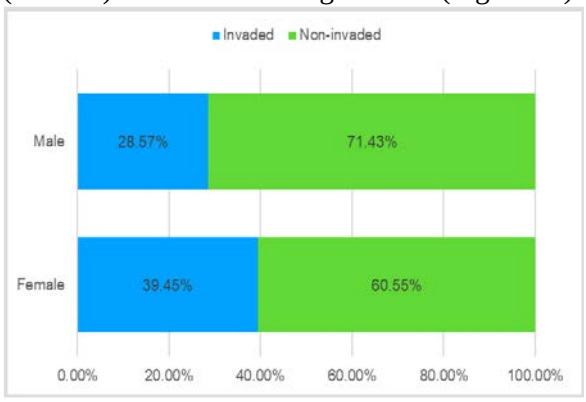

Figure 13. Correlation between margin invasion and gender.

Discussions

Other studies have shown a similar incidence of basal cell carcinoma between females and males but with a slightly increased frequency among men [30].

The higher incidence of basal cell carcinoma in rural areas can be explained by the increased frequency of professions involving prolonged and repeated exposure to UV radiation, a higher incidence of sunburn for this category and neglecting of the rules of photo-protection with SPF 50 lotions and clothing.

Data from the literature suggest that the occurrence of carcinoma is more common in old age, although recently there has been reported an increased number of patients diagnosed with basal cell carcinoma among the young population, under 40 years, especially among female patients [31].

Basal cell carcinoma shows a slow growth, the destructive character not being a feature of it. Patients often describe the condition as a lesion that does not improve and sometimes bleeds spontaneously or as a result of minor trauma.

However, there are rare cases of perineural invasion, which is a negative prognosis factor, suggesting an aggressive form of basal cell carcinoma with high rates of metastasis and loco-regional recurrence [32,33].

Scientific data also reveals an increased incidence of nodular subtype, representing an average of 60-80% from the cases in most of the reports, being followed in varying percentages by other subtypes of basal cell carcinomas [34].

Repeated and prolonged exposure to ultraviolet radiation is the most important risk factor for basal cell carcinoma. According to scientific data, 80% of cases are located on the face.

Between exposure to UV radiation and the appearance of skin carcinomas there is a latency period between 20-50 years. This explains why basal cell carcinoma is more common in the elderly and explains the frequent placement on the head and neck [35].

The more frequent localisation of basal cell carcinoma on the trunk and extremities in the case of patients from rural areas can be explained by the different clothing style, often imposed by the high ambient temperatures in which the professions specific to rural areas are performed.

In this case, areas such as trunk become repeatedly and prolonged exposed to ultraviolet radiation, turning into risk areas for the development of skin malignancy.

High blood pressure is an age-related pathology and is therefore present in patients with basal cell carcinoma.

Other studies have shown that there is a significantly higher incidence of skin cancers, including basal cell carcinoma, in patients with diabetes.

A previous study showed that skin cancers are the most common malignancies after liver transplantation.

The connection between basal cell carcinoma and chronic kidney disease has been previously studied.

A higher incidence of malignancy has been shown in both dialysis and pre-dialysis patients.

Epilepsy has been previously associated with nevoid basal-cell carcinoma syndrome (Gorlin syndrome) [36-39].

Conclusions

In conclusion, basal cell carcinoma is the most frequent type of skin cancer worldwide, being caused primarily by UV exposure.

The results of our study are, as expected, very similar to the results in other scientific studies.

Most cases were located on photo-exposed areas, such as head or neck, for patients living in both rural and urban areas.

Patients from rural areas registered a higher number of cases both in photo-exposed and non-exposed areas, thus underlining one more time the impact of UV rays on this type of skin cancer.

Conflicts of interests

None to declare.

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