

# Basal cell carcinoma: a retrospective clinicopathological analysis of 100 cases derived from the Histopathological Registry of the Institute of Pathology in Niš

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## Abstract

Basal cell carcinoma (BCC) is the most common malignant tumor of the skin. This study was conducted to analyze patients with BCC, their age and sex distribution, occupation, site distribution of tumors, clinical types, and histopathological characteristics of lesions. Based on the data obtained from the Histopathological Registry, a clinical and histopathological analysis of the surgically excised BCCs was performed.

The study included 100 randomly selected patients out of 263 consecutive patients with histopathologically diagnosed BCC at the Institute of Pathology of the Clinical Center in Niš in the period of 15 months. The sex ratio was 1.4:1 in favor of men ( $p < 0.05$ ). Two thirds of patients were over the age of 60 ( $p < 0.0001$ ). The average age of patients was  $66.6 \pm 12.2$  years (range 23 – 90). In agreement with the age distribution, 53 patients were retired (mostly retired farmers), 12 were workers, 14 farmers, 12 without permanent employment, 5 were housewives, and 4 clerks. A substantial majority of 61% of examinees lived in the country ( $p < 0.001$ ). The employment status was related to the age of examinees, but also with the altered demographic structure in the country: many workers lived in the country, or returned to the country after retirement.

BCC was commonly found on the face (77%), and rarely on the trunk (11%) and extremities (2%).

There were no data about exposition to X-rays or chemicals (except for pesticides and insecticides), scars resulting from burns or genodermatoses. In 87% of cases, BCC was significantly most often found at sites continually exposed to the sun (head including face and scalp, and neck). The most commonly diagnosed was the nodular type (57%), then the superficial (7%), ulcerative (5%), ulcero-sclerotic (4%), pigmented (1%), and morpheaform (1%). In 27% of cases, there were no data about the histopathological type of BCC in the Histopathological Registry, based on which accurate histological type of BCC could have been established. Based on histopathological analysis, apart from the nodular (40%), other types were rarely diagnosed, like the adenoid (12%) ( $p < 0.0001$ ), mixed types (nodular-adenoid, nodular-adenoid-fibroblastic and mixed) (9%), superficial (7%), fibroblastic (2%), infiltrative (1%), pigmented (1%), and morpheaform (1%). Surgical excision is the gold standard in the treatment of BCC: conventional, conducted in our patients, and Mohs micrographic surgery, which takes an important place in the treatment of high-risk BCCs. In 6% of cases, the tumor process was found in the margins of the excision.

In conclusion: Basal cell carcinoma was more common in males than in females. Significantly more patients with excised basal cell carcinoma lived in the country. An age-related increase in the number of patients with BCC has been established, and most patients with excised basal cell carcinomas belonged to the age group of 61 to 81 years of age. In most patients the tumor site was on the face, whereas clinically and histopathologically, nodular type was the most common.

## Key words

Carcinoma, Basal Cell + diagnosis + classification + etiology+ epidemiology; Skin Neoplasms + surgery; Age Factors; Neoplasms by Site; Sunlight

**B**asal cell carcinoma (BCC) is the most common malignant tumor of the skin. It is composed of cells similar to those in the basal area of the epidermis and the matrix cells of the skin appendages. Tumor cells originate from pluripotent cells of the basal layer of the epidermis, of the outer root sheath of the hair follicle, sebaceous and sweat glands (1, 2, 3). BCC is a malignant tumor of the follicular germinative cells (4). BCC is a slow growing neoplasm which shows minimal invasion to the soft tissue. Sometimes, however, BCC is characterized by aggressive growth, deep invasion, local recurrence and metastases (5, 6). Metastatic BCC is extremely rare, occurring in 0.0028% to 0.55% of all BCCs. This low rate is believed to be because the tumor cells require supporting stroma to survive (7). The histological variability originates from the pluripotentiality of immature cells of the epidermis (1).

BCC is more common in males than females: the annual incidence for males and females ranges from 175 to 849 and 124 to 605 per 100000 people, respectively (8,9,10). In Australia, it is three times more common than any other skin cancer (11). The comparison of age-specific incidence rates of BCCs in two studies from Sweden and Australia indicate that its rate in northern Europe is approximately three to four times lower than that estimated in Australian population [11,12,13].

Most investigations indicate that BCCs account for more than 70% of cases of NMSC (non-melanoma skin cancer). In non-immunosuppressed, fair-skinned individuals, a ratio of 4:1 between BCC and SCC (squamous cell carcinoma) incidence rates has been described as a relatively constant, but this ratio differs between countries with low and high ambient sun exposure. With increasing sun exposure, there is a disproportionate increase in SCC in relation to BCC (1).

The prevalence of skin cancer like BCC depends on the population susceptibility, skin type and exposure to ultraviolet radiation (1, 14), but also on other factors such as ionizing radiation, chemical carcinogens (arsenic found in insecticides), scars from previous diseases or burns, long-term ulcers on the lower extremities, some genodermatoses such as albinism, xeroderma pigmentosum, Rombo syndrome (basal cell carcinoma, atrophoderma vermiculata, milia, hypotrichosis, trichoepithelioma, and peripheral vasodilatation), Bazex's syndrome

(basal cell carcinoma, follicular atrophoderma, hypotrichosis, localized anhidrosis), Gorlin's syndrome (basal cell carcinoma, palmoplantar pits, odontogenic keratocysts, bifid ribs, frontal bossing, and central nervous system defects), immunodeficiency, as well as some therapeutic procedures (2, 15-19). The role of human papillomavirus (HPV) in the development of BCC in immunocompromised persons requires further research (20).

Although the exact incidence of BCC is unknown, it clearly differs in regard to geographical regions (21), type of skin, long-term sun exposure and progressive aging of the population (22). According to statistical data, the incidence of BCC in Netherlands in 1999 was 53 men and 38 women per 100000 inhabitants (23), whereas in 2004 it increased to 93 men and 82 women per 100000 inhabitants (24). In France, 70 new cases are registered annually per 100000 inhabitants (25). In Germany, in the period 1998 – 2003, the incidence for men was 112, and 118 for women per 100000 inhabitants (26). The incidence of BCC increases by 10% each year (27).

In 1986, there were 112 (59 male and 53 female) histopathological examinations for BCC at the Institute of Pathology in Niš, whereas in 1996 there were 207 (113 male and 94 female) – nearly double in 10 years time (28). In the municipality of Niš, in 1990 there were 113 (75 male and 38 female) patients with non-melanoma skin cancer, and in 2000, there were 229 (124 male and 105 female) (29). The number is probably much higher, since not all patients were registered.

We may only presume just how high the prevalence of BCC will be, knowing about the depletion of the ozone layer, which is known to absorb most of the harmful ultraviolet B and C radiation (30), while it is estimated that in 2015, in Europe, there will be 50 million people older than 80 years of age (31).

The aim of this clinicohistopathological analysis is to establish clinical and pathological characteristics of basal cell carcinomas diagnosed at the Institute of Pathology of the Clinical Center in Niš.

## Material and methods

The study included 100 randomly selected patients out of the total number of out of 263 consecutive patients with histopathologically established basal cell

carcinoma at the Institute of Pathology of the Clinical Center in Niš in the period of 15 months. Based on the data obtained from the Histopathological Registry, a clinical (demographic data, anamnesis, clinical picture), and histopathological analysis of surgically excised tumors (routine staining techniques including haematoxylin and eosin – H&E, periodic acid–Schiff–PAS, and Van Gieson staining) were performed.

Statistical methods included the T-test of significance for difference in percentages,  $\chi^2$  test for testing and comparing random distribution of frequencies, as well as the test of statistically significant deviation of obtained data in the contingency table of theoretical frequencies.

## Results

Out of 100 patients with BCC who were included in this study, 58 were men and 42 women (male to female ratio 1,4: 1) (Table 1). The difference between

the percentage of men and women with BCC was statistically significant  $p<0,05$ . The average age of patients was  $66.6 \pm 12.2$  years. The youngest patient was a female patient aged 23 with a BCC on her face, and the oldest patient was a man aged 90, also with a facial tumor. Most patients were over 60 years of age, that is 75% of the total number of examined patients with BCC (Table 1). The age distribution of patients shown in Table 1. significantly differs from random distribution, due to an increased number of aged patients ( $\chi^2(7)=97.6$ ;  $p<0.0001$ ).

In accordance with the age distribution, 53 patients were retired, 12 workers, 14 farmers, 12 without permanent employment, 5 housewives, and 4 clerks. Among the retired, many used to be farmers, both men and women. Thirtyeight patients resided in the town, and 62 in the country. The difference between patients from the town and from the country is statistically significant  $p<0.001$ .

Table 1. Demographic characteristics of patients with basal cell carcinoma (n=100)

Patients	Number (n=100)
<b>Male:Female</b>	1,4:1
<b>Age (years)</b>	
<20	0
21-30	3
31-40	0
41-50	6
51-60	16
61-70	36
71-80	27
>80	12
<b>Occupation</b>	
Retired	53
Indoor workers	12
Farmers	14
Without permanent employment	12
Housewives	5
Clerks	4
<b>Place of residence</b>	
Town	38
Country	62

Table 2. Distribution of basal cell carcinomas by site

Location	Number (n=100)
<b>Continually sun-exposed areas</b>	87
H-zone	48
Nose	29
Periorbital region	10
Ear area	2
Forehead	3
Cheek	2
Lip	1
Chin	1
Face (not specified)	29
Neck	5
Scalp	5
<b>Frequently sun-exposed</b>	2
Dorsal hand surface	1
Shoulder	1
<b>Non-sun-exposed</b>	11
Trunk	4
Lower extremity	1
Back	6

Sun exposure was certainly professional for a great number of examinees, because many of them were employed in factories and worked on farms, but also recreational and/or both.

There were no data about exposition to X-rays and chemicals (except for pesticides and insecticides), burn scars or genodermatoses.

BCCs were most commonly found in continually sun-exposed skin areas (87%), than on the trunk (11%), and on extremities (2%) (Table 2). Head and neck are considered to be continually sun-exposed. The most common site of BCC was the face in 77 persons, mostly in the H-zone in 48 patients (Table 2).

In regions which are frequently, but not continually sun-exposed, BCC was found in 2 patients: on the dorsal hand surface in one patient, and one on the shoulder in another. In non-sun-exposed regions, BCC was found in 11 patients: 4 on the trunk, 1 on

the leg, and 6 on the back. The percentage of patients with BCCs found on continually sun-exposed regions (87%) significantly differed from the percentage of patients with BCCs on non-sun-exposed regions (11%), with high significance ( $p < 0.0001$ ), whereas the percentage of patients in the second group (BCCs on non-sun-exposed regions) was significantly higher than in patients with BCCs in regions which are not frequently, but often sun-exposed (2%),  $p < 0.05$ .

Table 3. shows the site and age distribution of patients with BCC. There were only 9 patients with BCC under the age of 50 years, and all 9 (100%) had head and/or neck tumors. There were 12/16 (75%) of patients aged 50 – 60 years with BCC, also located on the head and/or neck; 28/36 (77.7%) patients aged 60 – 70 years, 27/27 (100%) aged 70 – 80 years, and 11/12 (91.66%) in the ninth decade of life.



Table 3. Distribution of basal cell carcinoma regarding its site and age of patients

Age (years)	Location			Total (n=100)
	Head and neck	Trunk	Extremities	
21-30	3	0	0	3
31-40	0	0	0	0
41-50	6	0	0	6
51-60	12	3	1	16
61-70	28	7	1	36
71-80	27	0	0	27
>80	11	1	0	12
Total	87	11	2	100

The distribution of patients with BCC located on the head and/or neck, regarding their age, does not significantly differ from the distribution of patients with BCC located on the trunk or extremities ( $X^2(5)=6.18$ ;  $p<0.05$  with Yates correction). The greatest number of patients with both locations was aged between 61 – 70 years.

Testing the difference between the obtained distribution of all patients in regard to the site of lesions in certain age groups and the theoretical distribution expected based on probability showed a statistically significant result ( $X^2(6)=72.86$ ;  $p<0.0005$ ). The greatest deviation of the random distribution of patients occurred in the group of patients aged between 61 and 80 years.

Table 4. shows results related to the frequency of certain clinical and histopathological types of BCC.

The most common type was the nodular type (Figure 1), without or with ulcerations, in a total of 57 patients (Table 4), which was significantly more frequent than all the other types together (43%) ( $p<0.05$ ), whereas there were significantly more ( $p<0.01$ ) nodular tumors without (38%) than with ulcerations (19%) (Figure 2). Ulcerative type (Figure 3) was found in 5 patients, and 4 presented with ulcersclerotic type (Figure 4). The Histopathological Registry missed data about the histological type of BCC in 27 examinees.

Based on the results of histopathological analysis presented in Table 4, nodular type was the most commonly diagnosed (40%) (Figure 5), while together with mixed types (nodular-adenoid, nodular-adenoid-fibroblastic and mixed) it occurred in 49 examinees, followed by the adenoid (12%). The difference between the percentage of patients with



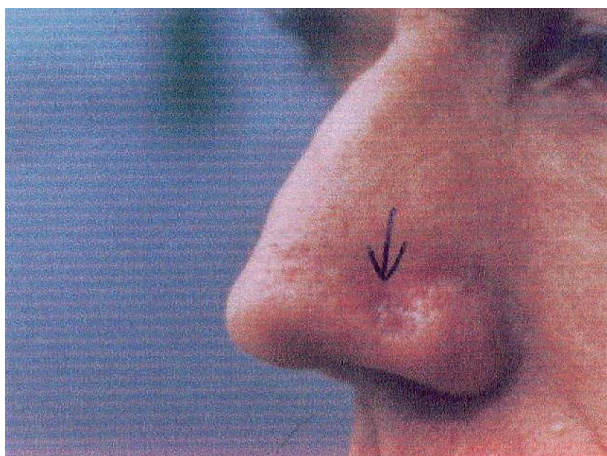
Figure 1. Basal cell carcinoma: nodular type



Figure 2. Basal cell carcinoma: noduloulcerative type



**Figure 3.** Basal cell carcinoma: ulcerative type



**Figure 4.** Basal cell carcinoma: ulcersclerosis type

nodular versus adenoid type of BCCs was statistically significant ( $p < 0.0001$ ), contrary to all nonspecific types together (27%) which is on the borderline of statistical significance ( $p = 0.05$ )

Tumor process was found on excision margins in 6% of patients (Table 4).

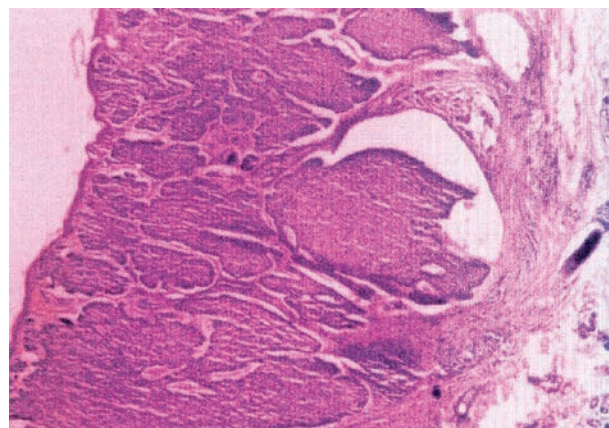
## Discussion

This study included 58 men and 42 women selected by random sampling. The sex ratio was 1.4:1 in favour of men ( $p < 0.05$ ), which is in accordance with literature data showing a range of 1.1-1.4 : 1 in favour of men (32, 33, 34).

The average age of examinees was  $66.6 \pm 12.2$  years (range 23 – 90 years), with similar data found in

other studies, where the average age of patients with BCC ranged between 64.5 to 71 years (32, 33, 34, 35, 36).

The employment status was related to the age of the examined patients, but also with the altered demographic structure in the country: workers living in the country, or returned to the country after retirement (37). Taking into consideration the fact that most examinees lived in the country ( $p < 0.001$ ), whether as retired workers, farmers or housewives, and that they were engaged in agriculture, it is easy to assume that UV radiation played a significant role in the development of the disease. According to our results, BCC was most commonly ( $p < 0.0001$ ; 87%) located on continually sun-exposed areas (head including face and scalp, and neck), which is in agreement with literature data showing that BCC commonly affects the head and neck, with a prevalence between 85% and 56.9% (19, 36, 38). Martel (19) described BCC located on the head and neck in 85% of examinees (28% of which were on the nose), while Meneses and associates (36) found them in 74.5% of examinees. Artis and associates reported a lower prevalence (38): in their patients BCC was also most commonly found on the head and neck, but in around half of them (55.9%) on the trunk (33.9%), upper extremities (3.6%), and on lower extremities in 6.0%. According to the results of Dauden and associates (33), BCC was located on the face in 45.8% of patients, on the trunk in 29.3%, upper extremities in 19.5%, and on lower extremities in 4.7%. In our patients BCC was commonly located on the face (77%), and less



**Figure 5.** Basal cell carcinoma: histological presentation of the nodular (solid) type (HE staining x100)



Table 4. Clinical and histopathological types of basal cell carcinomas

Basall cell carcinoma	Number n=100
<b>Clinical types</b>	
Nodular	38
Nodulo-ulcerative	19
Ulcerative	5
Superficial	7
Pigmented	1
Ultero-sclerotic	4
Morpheaform	1
Non specified	25
<b>Histopathological subtypes</b>	
Nodular (solid)	40
Adenoid	12
Solid adenoid	5
Fibroblastic	2
Solid adenoid fibroblastic	2
Superficial	7
Infiltrative	1
Morpheaform	1
Mixed	2
Pigmented	1
Non specified	27
<b>Excision</b>	
Total	72
Partial	6
Non-specified	22

commonly on the trunk (11%) and extremities (2%), probably due to exposure to UV radiation.

According to Abeldano and associates (39), BCCs located on the head and neck were caused by sun irradiation in 85 – 90% of cases, while BCCs on non-exposed regions are very rare and may point to another etiological mechanism. In 11% of our examinees with BCC on non-sun-exposed areas, we were not able to establish data on other etiological factors. Given the current hypothesis that reduced immune status caused by UV radiation at distant sites can be a BCC pathomechanism in places protected

from the sun (40), this could mean that in these 11% of cases the role of UV radiation may not be completely excluded. Literature data show that BCCs may occur in atypical and unusual locations (40): on the vulva (41,42; in the axilla (43,44). BCC was found on the dorsal side of the hand in one of our patients, which is extremely rare, although this region is mostly exposed to the sun, which may be explained by low concentration of pilosebaceous units in that skin region (36). Apart from exposition to ultraviolet radiation, the prevalence of BCC also depends on skin types (1). Due to retrospective features of this study, we could not

completely process data concerning types of skin, in order to obtain adequate and conclusive statistical data.

There are four main clinical types of BCC: nodular, pigmented, superficial, and morpheaform (45). Some authors classify BCCs into 7 clinical types (46), others into 5 (47), or into 5 basic, 2 atypical, and 3 rare clinical types (48), or 10 types (49). None of the classifications coincide completely. Taking into account locations of BCCs in our patients, the most common registered clinical type was nodular (57%), with a significantly higher number of nodular BCCs without than with ulcerations ( $p < 0.01$ ). The clinical classification itself has little or no importance for the prognosis. However, the prognosis of basal cell carcinoma is clearly related to its size (1).

There are also differences among authors when the terminology of histological types is concerned (47, 48, 50, 51, 52, 53), but most of them described the following types: nodular, adenoid, superficial, keratotic, pigmented, morpheaform, infiltrative, cystic, metatypical, fibroepithelioma, and basosquamous carcinoma. There is also a classification of differentiated and non-differentiated types. The differentiation pathway is directed towards cutaneous adnexa (keratotic, cystic, adenoid), while non-differentiated includes the nodular type (46). It is particularly valuable to classify the histologic appearance, because of the existing relationship between histologic subtype and clinical behavior: aggressive histologic variants include the micronodular, infiltrative, morpheaform; basosquamous, and mixed subtypes; nodular and superficial subtypes are characterized with a less aggressive clinical course (52). In 2006, WHO published classification of skin tumors which recognizes 8 histological types of BCC: superficial, nodular, micronodular, infiltrating, fibroepithelial, basosquamous, keratotic and basal cell carcinoma with adnexal differentiation (53). There are still differences in the terminology of histological types (1). Considering the fact that in our patients nodular type of BCC (40%) was most commonly (significantly more often than the second, adenoid type,  $p < 0.0001$ ) diagnosed, it is in accordance with Meneses and associates who analyzed histopathological preparations in 269 patients with BCC, and found the nodular type in most cases (36). Rigell and associates (46) reported the nodular type of BCC in 60% of all histological subtypes, mostly

located on the head and neck, but it may also be found on the trunk and extremities. Meneses and associates found that the next most commonly diagnosed were multifocal, superficial, and adenoid types, whereas morpheaform, metatypical and cystic were rather rare. None of our patients presented with metatypical (basosquamous) basal cell carcinoma. Interesting results were obtained by Aguilar Bernier and associates (21) who conducted a comparative epidemiological study of the differences in the prevalence of certain histological types of BCCs between Spaniards on the one hand, and the Europeans originating from northern and central Europe on the other hand, who were settled on the sunny Riviera, Spanish Costa del Sol. In both examined groups of inhabitants the most common type of BCC was superficial (20.4% and 28.2%), then infiltrative (20.8% and 19.6%), nodular (16.7% and 9.9%), undetermined (7.0% and 10.0%), and micronodular (0.9% and 0.4%). Such a high prevalence of superficial BCCs can be a result of patients' education. In our patients, the superficial type was diagnosed only in 7%.

In Australia, although still less common than the nodular type, compared with Europe, there are proportionately more superficial basal cell carcinomas, and in females the incidence is maximum in the 40–49 years age group (27). According to Raasch and associates, the superficial type of BCC accounts for 25%–26% of all BCCs in sun-exposed Australians, and for 15%–16% of all types in Europe: the most common are located on the trunk and extremities, excluding the population highly exposed to sun, who may have them on the face (27, 54).

Current therapy of BCC includes destructive and surgical procedures (55). Surgical excision is the gold standard for BCC: conventional, conducted in our patients, and Mohs micrographic surgery, which takes a significant place in the treatment of high-risk BCCs (56). When choosing therapeutic modalities, factors that increase the risk of recurrence and/or incidence of metastasis spread should be considered, such as: BCCs at high-risk sites (nasolabial fold, periocular and nose), BCCs greater than 2 cm in diameter, certain histological subtypes (morpheaform, infiltrative, micronodular, basosquamous), and recurrent BCCs (1). According to ANEAS (Agence Nationale d'Accreditation et Evaluation en Santé) (57) moderately risky locations for surgical excision



include the anterior part of the head, temples, cheeks, neck, chin and scalp, while high risk locations are the nose, ear, orbit and lips.

The excised area must be surrounded by healthy tissue to make the excision adequate (58, 59), highly affecting its outcome (56). In 6% of our patients a tumor process was found on the margins of excision. Santiago and associates found 90 (9.5%) incomplete excisions out of 947 BCC excisions. In 29 (32.2%) of these patients, recurrence was confirmed. The median recurrence was 12 months (range 1 – 57) (60). Depending on the location, size, margins of the tumor, previous treatment and histology, excision of BCC margins from 3 – 10mm may be rational in at least 95% of cases (61, 62). Thus, Rigell and associates used a margin of 4mm and adequately removed 98% of nonmorpheaform tumors less than 2cm in diameter (46). Dermoscopy of excised margins provides histologic confirmation of the complete excision in 98.5% of cases (63). It has been established that the risk for the development of new BCCs decreases with time: it is 11.6 in the first year, and 6.3 in the second (32). In cases where incomplete excision is performed on lateral margins only, it may be reasonable not to re-excise if the BCC is a primary tumor on a non-critical site and non-aggressive histology (1).

## Conclusion

In our sample, basal cell carcinoma was more common in males than in females. Significantly more people with excised basal cell carcinoma lived in the country. An age-related increase in the number of patients with BCC has been established, and most patients with excised basal cell carcinoma belonged to the age group of 61 to 81 years. In most patients the tumor was located on the face, whereas clinically and histopathologically, nodular type was the most common.

## References

1. Quinn AG, Perkins W. Non-melanoma skin cancer and other epidermal skin tumours. In: Burns T, Breathnach S, Cox N, Griffiths C, eds. *Rook's textbook of dermatology*. 6<sup>th</sup> ed. Oxford: Blackwell Publishing Ltd; 2010. p. 52.1-48.
2. Ančevski A. Bazocelularni karcinom. In: Karadaglić Đ, ed. *Dermatologija*. Beograd: Vojnoizdavački zavod, Versalpres; 2000. p. 825-34. Serbian.
3. Murphy GM, Moloney F. The pathogenesis of skin cancer in organ transplant recipients. In: Otley CC, Stasko T, Griffin MD, Murphy GM, Hirose R, Chong AH. *Skin disease in organ transplantation*. Cambridge: Cambridge University Press; 2008. p. 137-41.
4. Owens DM, Wat FM. Contribution of stem cells and differentiated cells to epidermal tumours. *Nat Rev Cancer* 2003;3:444-51.
5. Kleydman Y, Manolidis S, Ratner D. Basal cell carcinoma with intracranial invasion. *J Am Acad Dermatol* 2009;60(6):1045-9.
6. Robinson JK, Dahiya M. Basal cell carcinoma with pulmonary and lymph node metastasis causing death. *Arch Dermatol* 2003;139:643.
7. James WD, Berger TG, Elston DM. *Andrews' diseases of the skin: clinical dermatology*. Philadelphia: Elsevier Inc; 2006.
8. Chuang TY, Popescu A, Su WP, Chute CG. Basal cell carcinoma: a population-based incidence study. *J Am Acad Dermatol* 1990;22:413-7.
9. Marks R, Staples M, Giles GG. Trends in non-melanocytic skin cancer treated in Australia: the second national survey. *Int J Cancer* 1993;53:585-90.
10. Reizner GT, Chuang TY, Elpern DJ, Stone JL, Farmer ER. Basal cell carcinoma in Kauai, Hawaii: the highest documented incidence in the United States. *J Am Acad Dermatol* 1993;29:184-9.
11. Giles GG, Marks R, Folly P. Incidence of non-melanocytic skin cancer treated in Australia. *Br Med J* 1988;296:13-6.
12. Holme SA, Malinovsky K, Roberts DL. Changing trends in non-melanoma skin cancer in South Wales, 1988-98. *Br J Dermatol* 2000;143:1224-9.
13. Dahl E, Aberg M, Rausing A, Rausing EL. Basal cell carcinoma: an epidemiologic study in a defined population. *Cancer* 1992;70:104-8.
14. Mijušković ŽP, Kandolf-Sekulović L, Zečević RD. Kliničke karakteristike bazocelularnog karcinoma-analiza 83 pacijenta [Clinical characteristics of basal cell carcinoma – analysis of 83 patients]. In: *Zbornik rezimea XV Beogradski dermatološki dani* [Book of abstracts of the 15th Belgrade days of Dermatology]; 2010 Nov 12-13; Beograd (Srbija). Beograd: Srpsko Lekarsko Društvo; 2010. p. 37-8. Serbian.
15. Segura S, Puig S, Carrera C, Lecha M, Borges V, Malvehy J. Non-invasive management of non melanoma skin cancer in patients with cancer predisposition genodermatosis: a role for confocal microscopy and photodynamic therapy. *J Eur Acad Dermatol Venereol* 2011;25:819-27.
16. Abuzahra F, Parren LJMT, Frank J. Multiple familial and pigmented basal cell carcinomas in early childhood - Basex-Dupré-Christol Syndrome. *J Eur Acad Dermatol Venereol* 2012;27:117-21.
17. Pauwels C, Mazereeuw-Hautier J, Basset-Seguin N, Livideanu C, Viraben R, Paul C, et al. Topical methyl aminolevulinate photodynamic therapy for management of basal cell nevus syndrome improves patient's satisfaction and reduces the need for surgical procedure. *J Eur Acad Dermatol Venereol* 2011;25:861-4.
18. Bagazgoitia L, Bea S, Santiago JL, Cuevas J, Juarranz A, Jaen P. Multiple basal cell carcinomas arising on a thermal burn scar. Successful treatment with photodynamic therapy. *J Eur Acad Dermatol Venereol* 2002;23:459-61.
19. Harwood CA, Proby CM, Mc Gregor JM, Sheaff MT, Leigh IM, Cerio R. Clinicopathologic features of skin cancer in organ

- transplant recipients: a retrospective case - control series. *J Am Acad Dermatol* 2006;54:290-300.
20. Escutia B, Ledesma E, Serra-Guillen C, Gimeno C, Vilata JJ, Guillen C, et al. Detection of human papilloma virus and nodular basal cell carcinomas in immunocompetent subjects. *J Eur Acad Dermatol Venereol* 2011;25:32-8.
  21. Aguilar Bernier M, Rivaz Ruiz F, De Troya M, Blazquez Sanchez N. Comparative epidemiological study of non-melanoma skin cancer between Spanish and North and Central European residents on the Costa del Sol. *J Eur Acad Dermatol Venereol* 2012;26:41-7.
  22. Roewert-Huber J, Lange-Asschenfeldt B, Stockfleth E, Kerl H. Epidemiology and aetiology of basal cell carcinomas. *Br J Dermatol* 2007;157(Suppl 2):47-51.
  23. Stern RS. The mysteries of geographic variability in nonmelanoma skin cancer incidence. (editorial). *Arch Dermatol* 1999;135:843-4.
  24. Madan V, Lear JT, Szeimies RM. Non-melanoma skin cancer. *Lancet* 2010;375: 673-85.
  25. Guillaume JC. Carcinomes basocellulaires. In: Saurat JH, Grosshans E, Laugier P, eds. *Dermatologie et infections sexuellement transmissibles*. 4<sup>th</sup> ed. Paris: Masson; 2004. p. 640-7.
  26. Stang A, Ziegler S, Buchner S, Ziegler B, Jockel KH, Ziegler U. Malignant melanoma and nonmelanoma skin cancers in Northrhine-Westphalia, Germany: a patient-vs diagnosis based incidence approach. *Int J Dermatol* 2007;46:564-70.
  27. Raasch BA, Buettner PG, Garbe C. Basal cell carcinoma: histological classification and body-site distribution. *Br J Dermatol* 2006;155:401-7.
  28. Paravina M. Epidemiologija epitelnih malignih tumora kože [Epidemiology of epithelial malignant tumors of the skin]. Proceedings of the 16<sup>th</sup> Congress of Yugoslav dermatovenerologists; 2000 Sep 20-23; Igalo. Beograd: Yugoslav Association of Dermatovenerologists; 2000. p. 25. Serbian.
  29. Paravina M, Spalević Lj, Janković A, Đokić S. Faktori rizika i neki epidemiološki pokazatelji malignih epitelnih tumora kože [Risk factors and some epidemiological characteristics of malignant epithelial tumors of the skin]. Zbornik rezimea XXXV Dani preventivne medicine [Book of abstracts 35th Days of Preventive Medicine]; 2001. Niš: Medicinski fakultet; 2001. p. 99-100. Serbian.
  30. Pons M, Quintanilla M. Molecular biology of malignant melanoma and other cutaneous tumours. *Clin Transl Oncol* 2006;8:466-74.
  31. Trakatelli M, Ulrich C, del Marmol V, Euvard S, Stockfleth E, Abeni D. Epidemiology of nonmelanoma skin cancer (NNSC) in Europe: accurate and comparable data are needed for effective public health monitoring and interventions. *Br J Dermatol* 2007;156(Suppl 3):1-7.
  32. Mc Loone NM, Tolland J, Walsh M, Dolan OM. Follow-up of basal cell carcinomas: an audit of current practice. *J Eur Acad Dermatol Venereol* 2006;20(6):698-701.
  33. Dauden E. Effectiveness and satisfaction with imiquimod for the treatment of superficial basal cell carcinoma in daily dermatological practice. *J Eur Acad Dermatol Venereol* 2011;25:1304-10.
  34. Fantini F, Greco A, Dell Giovane C, Cesinaro AM, Venturini M, Zane C, et al. Photodynamic therapy for basal cell carcinoma: Clinical and pathological determinants of response. *J Eur Acad Dermatol Venereol* 2011;25:896-901.
  35. Tiftikcaglu JO, Karaaslan D, Aksoy HM, Aksoy B, Koçer U. Basal cell carcinoma in Turkey. *J Dermatol* 2005;32:946-50.
  36. Meneses N, Guides R, Moreira A, Mota G, Baptista A. Basal cell carcinoma: epidemiology from 269 cases. *J Eur Acad Dermatol Venereol* 2010;24:1359-60.
  37. Paravina M, Jovanović S, Randelović J, Stanojević M, Spalević Lj, Todorović J, i dr. Karcinomi kože: analiza kliničkih i histoloških karakteristika [Skin carcinomas: analysis of clinical and histological characteristics]. *Acta Dermatovenerol Jugosl* 1990;17:157-61.
  38. Arits AH, Schlangen MH, Nelemans PJ, Kelleners-Smeets NW. Trends in the incidence of basal cell carcinoma by histopathological subtype. *J Eur Acad Dermatol Venereol* 2011;25:565-9.
  39. Abeldano MA, Pincay Cedeno L, Neglia V, Brea P, Retamar R, Kien M, et al. Basal cell epithelioma of atypical localisation. *J Eur Acad Dermatol Venereol* 2001; 15(Suppl 2):167.
  40. Gibson GE, Ahmed I. Perianal and genital basal cell carcinoma: a clinicopathologic review of 51 cases. *J Am Acad Dermatol* 2001;45:68-71.
  41. Mulayin N, Silver DF, Ocal JT, Babalola E. Vulvar basal cell carcinoma: two unusual presentation and review of the literature. *Gynecol Oncol* 2001;85:531-7.
  42. Pisani E, Poggiali S, La de Padova, Andreassi A, Bilenchi R. Basal cell carcinoma of the vulva. *J Eur Acad Dermatol Venereol* 2006;20:446-8.
  43. Woo SH, Kim IH, Son SW. Axillary basal cell carcinoma. *J Eur Acad Dermatol Venereol* 2006;20:222-3.
  44. Betti R, Crosti C, Moneghini L, Crespi E, Menni S. Axillary basal cell carcinoma: Additional 25 patients and consideration. *J Eur Acad Dermatol Venereol* 2011;25: 858-60.
  45. Crowson AN. Basal cell carcinoma: biology, morphology and clinical implications. *Modern Pathol* 2006;19:S127-47.
  46. Rigell DS, Cockerell CJ, Caruci J, Wharton J. Actinic keratosis, basal cell carcinoma and squamous cell carcinoma. In: Bologna JL, Jarizzo JL, Rapini RP. *Dermatology*. 2<sup>nd</sup> ed. St. Louis: Mosby Elsevier; 2008. p. 1641-60.
  47. Wolff K, Johnson KA, Suurmond D. *Fitzpatrick's color atlas and synopsis of clinical dermatology*. New York: McGraw-Hill; 2005. p. 282-9.
  48. Stojanović S, Poljački M. Klinička slika bazocelularnog karcinoma kože [Clinical picture of basal cell carcinoma of the skin]. In: Poljački M, Ed. *Bazocelularni i spinocelularni karcinomi kože* [Basal cell and spinocellular skin cancers]. Novi Sad: Medicinski fakultet; 1997. p. 43-7. Serbian.
  49. Višnjić MM. Hirurgija tumora kože i mekih tkiva. [Surgery of skin tumors and soft tissues]. Niš: Prosveta; 1997. str. 16-25.
  50. Rippey JJ. Why classify basal cell carcinomas? *Histopathology* 1998;32:393-8.
  51. Vučković N, Vučković D. Histogeneza i mikroskopske karakteristike [Histogenesis and microscopic characteristics]. U: Poljački M, Ed. *Bazocelularni i spinocelularni karcinomi kože* [Basal cell and spinocellular skin cancers]. Novi Sad: Medicinski fakultet; 1997. p. 35-42. Serbian.
  52. Rubin AJ, Chen EH, Ratner D. Basal cell carcinoma. *N Engl J Med* 2005;353: 2262-9.
  53. LeBoit PE, Burg G, Weedon D, Sarasin A, eds. *World Health Organisation classification of tumors: pathology and genetics of skin tumors*. Lyon: IARC Press; 2006. p. 10-33.
  54. Popadić S, Tanasilović S, Živanović D, Medenica Lj. Genital

superficial basal cell carcinoma: a case report. *Serb J Dermatol Venereol* 2010;2(3):106-9.

55. Stang A, Weichenthal M. Micrographic surgery of skin cancer in German hospitals 2005-2006. *J Eur Acad Dermatol Venereol* 2011;25:422-8.

56. Perrot JL, Labelle B, Cambazard F, Godard W, Gentil A, Chanoz Poulard G, et al. Assessment of microscopic surgical margins used in the excision of basal cell carcinoma in the Loire and Haute-Loire regions from 2006 to 2008. *Journées dermatologiques de Paris. The key moments of today's dermatology*. Paris: Société Française de dermatologie; 2009. p. 46-7.

57. Coulomb A, Agence Nationale d'Accreditation et d'Evaluation (ANAES). Recommendations for basal cell carcinoma. *Ann Dermatol Venereol* 2004;131(6-7 Pt2):661-756.

58. Smeets NWJ, Kuijpers DJM, Nelemans P, Verhaegh MEJM, Kreckels GAM, Neuman HAM. Mohs' micrographic surgery for treatment of basal cell carcinoma of the face: results of a

retrospective study and review of the literature. *Br J Dermatol* 2004;151:141-7.

59. Dabrera G, Wakeel R. Is the adequacy of excision of basal cell carcinoma related to operator experience? *Clin Exp Dermatol* 2006;32:103-4.

60. Santiago F, Serra D, Vieira R, Figueiredo A. Incidence and factors associated with recurrence after incomplete excision of basal cell carcinomas: a study of 90 cases. *J Eur Acad Dermatol Venereol* 2010;24:1421-4.

61. Laloo MT, Sood S. Head and neck basal cell carcinoma: treatment using a 2mm clinical excision margin. *Clin Otolaryngol Allied Sci* 2000;25:370-3.

62. Dandurand M, Petit T, Martel P, et al. Management of basal cell carcinoma in adults: clinical practice guidelines. *Eur J Dermatol* 2006;4:394-401.

63. Caresana G, Giardini R. Dermoscopy-guided surgery in basal cell carcinoma. *J Eur Acad Dermatol Venereol* 2010;24:1395-9.

## Bazocelularni karcinom: retrospektivna kliničko-histološka analiza 100 slučajeva na osnovu Histopatološkog registra Instituta za patologiju u Nišu

### Sažetak

Uvod: Bazocelularni karcinom najčešći je maligni tumor kože. Tumorske ćelije potiču od pluripotentnih ćelija bazalnog sloja epiderma, spoljašnjeg omotača folikula dlake (eng. *outer root sheath of the hair follicle*), lojnih i znojnih žlezda.

Cilj: Cilj ispitivanja bio je da se analizom bolesnika sa bazocelularnim karcinomom kože utvrdi distribucija oboljenja prema polu, životnom dobu, profesiji, lokalizaciji, kliničkim oblicima i patohistološkim karakteristikama promena.

Materijal i metode: U ovoj retrospektivnoj studiji urađena je, na osnovu Histopatološkog registra Instituta za patologiju u Nišu, klinička obrada (demografski podaci, anamneza, klinička slika) i patohistološka analiza hirurški ekscidiranih tumora kod 100 osoba koje su izdvojene metodom slučajnog izbora iz grupe od 263 pacijenata, kod kojih je konsekutivno u periodu od petnaest meseci na osnovu patohistološkog nalaza, postavljena dijagnoza bazocelularnog karcinoma.

Rezultati i diskusija: Odnos polova (muškarci : žene) bio je 1,4 : 1 ( $p < 0,05$ ), što je u skladu sa podacima iz literature, po kojima se ovaj odnos kreće od 1,1-1,4 : 1 (muškarci : žene). Dve trećine obolelih bilo je starije

od 60 godina. Prosečna starost iznosila je  $66,6 \pm 12,2$  godina (raspon 23-90 godina), a slični podaci nalaze se i u drugim studijama u kojima se prosečna starost osoba sa bazocelularnim karcinomom kože kretala u rasponu 64,5-71 godine. U skladu sa starosnom strukturom, 53 pacijenta bili su penzioneri (uglavnom poljoprivredni), 12 radnici, 14 zemljoradnici, 12 bez stalnog zaposlenja, 5 domaćice i 4 pacijenta bili su službenici. S obzirom na mesto stanovanja, 61% osoba je živelo na selu. Status zaposlenosti bio je u skladu sa godinama života, ali i u skladu sa izmenjenom strukturom našeg sela, tj. stanovanjem radnika na selu ili povratka u selo po završetku radnog veka. Kada se uzme u obzir da je značajna većina ispitanika živela na selu ( $p < 0,001$ ), bilo da su penzionisani radnici, poljoprivrednici ili domaćice i da su se bavili poljoprivredom, onda se može pretpostaviti značajna uloga izlaganja ultravioletnom zračenju u nastanku oboljenja: bazocelularni karcinom kože bio je češće lokalizovan na licu (77%) a ređe na trupu (11%) i ekstremitetima (2%). Nije bilo podataka o ekspoziciji x-zracima i hemikalijama (izuzev pesticida i insekticida), ožiljcima od opekotina i genodermatozama. U 87% slučajeva, bazocelularni

karcinom kože je značajno najčešće ( $p < 0,0001$ ) bio lokalizovan na mestima stalno izloženim suncu (glava, tj. lice i poglavina i vrat), što se slaže sa podacima iz literature, prema kojima se bazocelularni karcinom kože najčešće javlja na glavi i vratu, a prevalencija se kreće između 85% i 56,9%. Prema podacima iz literature, bazocelularni karcinom kože lokalizovan na glavi i vratu je u 85–90% slučajeva izazvan sunčanom radijacijom, a na fotoneeksponiranim regijama javlja se retko i može značiti prisustvo nekog drugog etiološkog mehanizma. Kod 11% naših ispitanika, kod kojih je lokalizacija bazocelularnog karcinoma kože bila na fotoneeksponiranim regijama, mi nismo mogli utvrditi podatke o drugim etiološkim faktorima. S obzirom na postojeću hipotezu da smanjeni imunonadzor izazvan ultravioletnom radijacijom na udaljenim mestima, može predstavljati patomehanizam nastanka bazocelularnog karcinoma kože na mestima zaštićenim od sunca, to bi moglo značiti da se i u ovih 11% slučajeva nije mogla u potpunosti isključiti uloga ultravioletnog zračenja.

U literaturi su objavljeni slučajevi bazocelularnog karcinoma kože sa atipičnim i neuobičajenim lokalizacijama – na vulvi i u aksili. Bazocelularni karcinom kože je registrovan na dorzalnoj strani šake kod jedne naše pacijentkinje, što se izuzetno retko viđa, iako je ova regija često izložena suncu, što bi se moglo objasniti malom koncentracijom pilosebacealnih jedinica na toj regiji kože.

Najčešći klinički oblik bio je nodularni (57%), a bili su dijagnostikovani i superficijalni (7%) ulcerozni (5%), ulcerosklerotični tip (4%), pigmentni (1%) i morfeaformni (1%). U 25% slučajeva, u Histopatološkom registru nisu postojali podaci na osnovu kojih bi se mogao tačno odrediti klinički tip bazocelularnog karcinoma kože. Pojedini autori klasifikuju bazocelularni karcinom kože u 7 kliničkih tipova, drugi u 5, ili u 5 osnovnih, 2 atipična i 3 reda klinička tipa, ili u 10 tipova. Nijedna od podela se ne poklapa u potpunosti. S obzirom na lokalizaciju kod naših pacijenata, najčešće je bio registrovan nodularni klinički oblik pri čemu je značajno više bilo nodularnih bez ulceracije nego sa ulceracijom ( $p < 0,01$ ). Sama za sebe, klinička klasifikacija je od malog značaja za prognozu. Veličina lezije predstavlja faktor rizika koji utiče na prognozu.

S obzirom na lokalizaciju i kliničku sliku bazocelularnog karcinoma kože kod naših ispitanika, najčešće

dijagnostikovani histološki tip bio je nodularni, što je u saglasnosti sa rezultatima u literaturi. Smatra se da nodularni histološki tip ovog karcinoma čini do 60% svih histoloških tipova, najčešće se lokalizuje u predelu glave i vrata, ali se može lokalizovati i na trupu i ekstremitetima. Na osnovu rezultata patohistološke analize u našem ispitivanju, pored nodularnog tipa (40%), bili su dijagnostikovani značajno ređe i adenoidni (12%) ( $p < 0,0001$ ), mešoviti tipovi (nodulo-adenoidni, nodulo-adenoidno-fibroblastični i mikstni) (9%), superficijalni (7%), fibroblastični (2%), infiltrativni (1%), pigmentni (1%) i morfeaformni (1%). U 25% slučajeva u Histopatološkom registru nisu postojali podaci na osnovu kojih bi se mogao tačno odrediti klinički tip bazocelularnog karcinoma kože.

Histološka klasifikacija je od velikog značaja s obzirom da histološka građa tumora utiče na njegov klinički tok: agresivni histološki suptipovi (mikronodularni, infiltrativni, morfeaformni; bazoskvamozni i mešoviti); manje agresivni histološki suptipovi (nodularni i superficijalni). I u terminologiji histoloških formi postoje razlike među autorima. Svetska zdravstvena organizacija je objavila klasifikaciju sa 8 histoloških tipova: superficijalni, nodularni, mikronodularni, infiltrativni, fibroepitelijalni, bazoskvamozni, keratotični i bazocelularni karcinom sa adneksalnom diferencijacijom.

Terapija: Zlatni standard u terapiji bazocelularnog karcinoma kože jeste hirurška ekscizija: konvencionalna koja je sprovedena u ovom radu i Mohsova mikrograf-ska koja ima značajno mesto u lečenju visokorizičnih bazocelularnih karcinoma kože. Mesto ekscizije mora biti okruženo zdravim tkivom da bi ekscizija bila adekvatna, što određuje njen uspeh. Kod 6% naših bolesnika nađen je tumorski proces na ivicama ekscizije. Santiago i saradnici su od 947 bazocelularnih karcinoma kože koje su ekscidirali nekompletnu eksciziju našli kod 90 (9,5%) bolesnika. Kod 29 (32,2%) ovih bolesnika potvrđen je recidiv. Prosečno trajanje remisije je iznosilo 12 meseci (raspon od 1 do 57 meseci). Zavisno od mesta, veličine, ivica tumora, prethodnog tretmana i histologije, ekscizija margina bazocelularnog karcinoma kože od 3–10 mm, može biti racionalna u najmanje 95% slučajeva. Tako su Rigel i saradnici, sa marginom od 4 mm, adekvatno uklonili 98% nemorfeaformnih tumora manjih od 2 cm u prečniku. Dermoskopskom detekcijom ekscizionih ivica može se dobiti histološka potvrda kompletne ekscizije u



98,5% slučajeva. Utvrđeno je da rizik od razvoja novih bazocelularnih karcinoma kože vremenom opada: u prvoj godini iznosi 11,6, u drugoj godini iznosi 6,3. U slučajevima da se inkompletna ekscizija odnosi samo na lateralne ivice tumorskog tkiva, a da se radi o primarnom tumoru koji se ne nalazi na kritičnom mestu i nema agresivnu histološku građu, odluka da se ne radi reekscizija može biti opravdana.

Zaključak: Bazocelularni karcinom je bio značajno

češći kod osoba muškog pola. Značajno veći broj osoba sa ekscidiranim bazocelularnim karcinomom živeo je na selu. Utvrđen je značajan porast broja obolelih sa starošću i najveći broj osoba sa ekscidiranim bazocelularnim karcinomom pripadao je starosnoj kategoriji od 61. do 81. godine života. Kod najvećeg broja osoba tumor je bio lokalizovan na koži lica, a najčešći klinički i patohistološki dijagnostikovan tip bio je nodularni tip.

## Ključne reči

Bazocelularni karcinom + dijagnoza + klasifikacija + etiologija + epidemiologija; Neoplazme kože + hirurgija; Starosni faktori; Neoplazme po mestu nastanka; Sunčeva svetlost