

BASAL CELL CARCINOMA OF THE SKIN – A FOUR-YEAR EXPERIENCE OF THE UNIVERSITY CLINICAL CENTER OF VOJVODINA

BAZOCELULARNI KARCINOM KOŽE – ČETVOROGODIŠNJE ISKUSTVO UNIVERZITetskOG KLINIČKOG CENTRA VOJVODINE

Nikolina KONSTANTINOVIĆ¹, Vanja TATALOVIĆ^{1,2}, Sveto BJELAN^{1,2}, Miroslav TOMIĆ^{1,2}, Mara AĐIĆ¹ and Marija MARINKOVIĆ^{1,2}

ORCID NUMBER

Nikolina Konstantinović – 0009-0003-8878-8110

Vanja Tatalović – 0009-0008-1942-706X

Sveto Bjelan – 0009-0008-7418-0717

Miroslav Tomić – 0000-0003-3352-9018

Mara Adić – 0009-0006-7361-9164

Marija Marinković – 0000-0002-5346-1922

University of Novi Sad, Faculty of Medicine Novi Sad¹

University Clinical Center of Vojvodina, Novi Sad

Clinic for Plastic and Reconstructive Surgery²

Original study

Originalni naučni rad

UDK 616.5-006.6

<https://doi.org/10.2298/MPNS2606090K>

Abstract

Introduction. Basal cell carcinoma is the most common non-melanoma skin cancer. It predominantly occurs in sun-exposed areas, in individuals older than 50 years, and more frequently in men. The most important risk factors are skin phototype and ultraviolet radiation exposure. Most lesions are located on the face, scalp, and neck. Surgical treatment remains the most effective approach as it enables complete tumour excision with clear margins and subsequent histopathological analysis. The study aimed to analyse the incidence, type, and distribution of basal cell carcinoma of the skin, as well as the association between risk factors, age, and sex, in patients treated at the Clinic for Plastic and Reconstructive Surgery, University Clinical Center of Vojvodina, between 2020 and 2023. **Material and Methods.** A retrospective study was conducted using data obtained from hospital medical records and the institutional information system. **Results.** A total of 802 patients were included; the mean age was 73.3 years. Lesions were most frequently located on the face (25.3%). The most common histopathological subtype was the mixed type, comprising nodular and infiltrative components (47.1%). The largest proportion of patients sought medical attention between one month and one year after first noticing the lesion (32.9%). A previous history of the disease was more common in men than in women. **Conclusion.** Basal cell carcinoma is often under-represented in cancer registries because of its relatively low mortality. Monitoring epidemiological trends is essential for prevention, early detection, and effective disease control.

Key words: Basal Cell Carcinoma; Skin Neoplasms; Epidemiology; Histology; Biopsy; Risk Factors

Introduction

Basal cell carcinoma is a slow-growing malignant tumour and the most common non-melanoma skin cancer, predominantly occurring on sun-exposed areas in fair-skinned individuals [1]. It originates from immature pluripotent cells of the basal layer of the epidermis, the outer root sheath of hair follicles, sebaceous

Sažetak

Uvod. Bazocelularni karcinom je najčešći nemelanomski maligni tumor kože. Najčešće se javlja na područjima izloženim suncu, kod osoba starijih od 50 godina i kod muškaraca. Najvažniji faktori rizika su fototip kože i ultraljubičasto zračenje. Većina lezija lokalizovana je na licu, glavi i vratu. Hirurško lečenje predstavlja najefikasniji terapijski pristup jer omogućava potpuno uklanjanje tumora sa rubom zdravog tkiva i patohistološku analizu. Cilj rada bio je da se analiziraju učestalost, tip i distribucija bazocelularnog karcinoma kože, kao i povezanost faktora rizika, starosti i pola kod pacijenata lečenih na Klinici za plastičnu i rekonstruktivnu hirurgiju Univerzitetskog kliničkog centra Vojvodine u periodu od 2020. do 2023. godine. **Materijal i metode.** Retrospektivna studija sprovedena je analizom podataka iz medicinske dokumentacije i informacionog sistema ustanove. **Rezultati.** U studiju su uključena 802 pacijenta, prosečne starosti 73,3 godine. Promene su najčešće bile lokalizovane na licu (25,3%). Najzastupljeniji histološki tip bio je mešoviti, koji je obuhvatao kombinaciju nodularnog i infiltrativnog tipa (47,1%). Najveći broj pacijenata javio se lekaru u periodu od jednog meseca do jedne godine nakon uočavanja promene (32,9%). Prethodna pojava bolesti bila je češća kod muškaraca. **Zaključak.** Bazocelularni karcinom se često ne evidentira u registrima karcinoma zbog niskog mortaliteta. Praćenje epidemioloških trendova važno je za prevenciju, rano otkrivanje i adekvatnu kontrolu bolesti.

Ključne reči: bazocelularni karcinom; tumori kože; epidemiologija; histologija; biopsija; faktori rizika

glands, and other cutaneous adnexal structures. Basal cell carcinoma is characterized by locally infiltrative and occasionally destructive growth [1]. Metastases are exceedingly rare, with an estimated incidence ranging from 0.0028% to 0.5% [2]. The disease occurs more frequently in individuals older than 50 years and is approximately twice as common in men as in women [3]. The highest incidence rates have been

✉ Corresponding author: Vanja Tatalović, E-mail: vanja.tatalovic@mf.uns.ac.rs

reported in Australia, where recent population-based estimates indicate approximately 770 new cases per 100,000 persons annually [4].

The most important aetiological factors include skin phototype - particularly Fitzpatrick skin types I and II - and environmental exposure, primarily to natural and artificial ultraviolet radiation, including tanning beds. Other factors implicated in skin carcinogenesis include X-ray exposure, alpha- and beta-radiation, chemical carcinogens such as tar, resins, soot, arsenic, asbestos, immunosuppressive therapy, a family history of skin cancer, and specific genodermatoses associated with oncogenic transformation, including Gorlin-Goltz syndrome, xeroderma pigmentosum, and albinism [5].

Cumulative exposure to solar ultraviolet radiation is considered the principal environmental risk factor for the development of basal cell carcinoma. Prolonged outdoor exposure, particularly among those who work outdoors, such as farmers, construction workers, and sailors, has been implicated in its development [6]. Furthermore, recreational sun exposure during childhood and adolescence significantly increases the risk of developing basal cell carcinoma later in life, suggesting that these periods may be critical in determining the risk of the disease in adulthood [7].

Ultraviolet radiation induces structural damage to epidermal deoxyribonucleic acid (DNA). Whilst such damage is normally repaired, inadequate cellular repair mechanisms may permit the persistence and replication of induced mutations, ultimately leading to malignant transformation of affected tissues. In addition to its mutagenic effects, ultraviolet radiation exerts local immunosuppressive activity by reducing the number of Langerhans cells and stimulating epidermal suppressor T lymphocytes [8].

The majority of basal cell carcinoma lesions occur on sun-exposed areas of the skin, particularly the face, scalp, and neck, accounting for approximately 90% of all such neoplasms. They are especially common on the head and neck above an imaginary line connecting the corner of the mouth and the earlobe [9]. The most common clinical presentation of early basal cell carcinoma is a light pink papule with a smooth, shiny surface and prominent telangiectasia. As the lesion progresses, central crusting or ulceration may develop. Patients frequently present with an enlarging, non-healing lesion that may occasionally bleed and may also be associated with pruritus. Tumour spread typically follows the path of least resistance, including along the periosteum, perichondrium, perineurium, and fascial planes. Recurrences have

been shown to occur more frequently in patients who delayed surgical treatment for a prolonged period [10].

Several clinical variants of basal cell carcinoma have been described, including nodular, ulcerative, superficial, pigmented, morpheaform, and cystic forms [11]. The prognosis of basal cell carcinoma is closely related to tumour size. Giant basal cell carcinoma, defined as a lesion exceeding 5 cm in diameter, is generally associated with the poorest prognosis [8].

In 2006, the World Health Organisation published a classification of skin tumours recognising eight histopathological subtypes of basal cell carcinoma: superficial, nodular, micronodular, infiltrative, fibroepithelial, basosquamous, keratotic, and basal cell carcinoma with adnexal differentiation [12]. From a surgical perspective, the distinction between aggressive and non-aggressive subtypes is particularly important. Aggressive variants include infiltrative, morpheaform, micronodular, basosquamous, and mixed infiltrative-morpheaform or nodular-infiltrative forms, whereas superficial, pigmented, and nodular subtypes are considered non-aggressive [13]. Aggressive subtypes characteristically grow as continuous strands of tumour cells along paths of least resistance, including nerves and fascial structures, and represent the most common cause of recurrence [1].

Treatment options may be either non-surgical or surgical. Non-surgical approaches include imiquimod, photodynamic therapy, and radiotherapy. Surgical excision remains the treatment of choice, as it enables complete removal of the lesion with an adequate margin of healthy tissue, and the excised specimen is subsequently submitted for histopathological examination, which provides definitive confirmation of the diagnosis [13].

This study aimed to analyse the demographic, clinical, and histopathological characteristics of patients with basal cell carcinoma and to evaluate associations between age, sex, smoking status and tumour-related variables.

Material and Methods

This study was conducted as a retrospective analysis. Patients with histopathologically confirmed basal cell carcinoma who were treated at the Clinic for Plastic and Reconstructive Surgery, University Clinical Center of Vojvodina, between 1 January 2020 and 31 December 2023, were included. The unit of analysis was the individual patient; in patients with more than one lesion, data were recorded at the patient level rather than separately for each lesion. The database was accessed after the end of the study period.

Table 1. Distribution of Lesion Locations

Location	N	%	Male	%	Female	%
Face	203	25.3	86	21.1	117	29.6
Back	184	22.9	94	23.1	90	22.8
Scalp	166	20.7	99	24.3	67	17
Upper extremity	83	10.3	47	11.5	36	9.1
Trunk	83	10.3	45	11.1	37	9.4
Lower extremity	43	5.4	16	3.9	27	6.8
Neck	40	5.0	20	4.6	20	5.1
Genital region	1	0.1	0	0	1	0.1

Disease-related data were collected from hospital medical records via the Clinical Information System. Patients were identified using diagnosis-specific search criteria. A total of 27 referral diagnosis codes according to the International Classification of Diseases, Tenth Revision, were recorded among patients who were subsequently confirmed to have histopathologically verified basal cell carcinoma. The diagnostic codes considered for inclusion were D48.5 and C44.0–C44.9.

The following variables were collected for all participants: sex, age, time interval between the appearance of the lesion and the first medical consultation, tumour location, histopathological subtype, and previous history of basal cell carcinoma. In this study, a previous history of basal cell carcinoma was defined as any earlier occurrence of the disease - that is, one or more histopathologically confirmed basal cell carcinomas diagnosed before the current presentation, irrespective of anatomical site - rather than local recurrence of a previously treated tumour at the same site. Local recurrence could not be reliably distinguished from new primary tumours arising in previously treated patients; accordingly, all patients with any prior history of basal cell carcinoma, including suspected local recurrences, were classified as having a previous history of the disease. Patients whose current tumour was their first diagnosed basal cell carcinoma were classified as having primary disease. Given the considerable variability in lesion locations, sites were categorised into eight anatomical groups. Lesions on the shoulders were included in the upper extremity group, whilst trunk lesions were divided into the anterior trunk (chest and abdomen) and posterior trunk (back).

Statistical analysis was performed using IBM SPSS Statistics software. Categorical variables were presented as frequencies (N) and percentages (%). The chi-square test was used for categorical variables and Student's t-test for continuous variables. Statistical significance was set at $p < 0.05$.

The study was approved by the Ethics Committee of the University Clinical Center of Vojvodina (approval number 00-251).

Results

A total of 802 patients were included in the study, comprising 407 men and 395 women. The mean age was 73.30 years (SD = 11.72; range 32-104 years). No statistically significant difference was observed in the sex distribution of patients ($p = 0.67$). However, men were significantly older than women (mean age 74.34 ± 11.02 vs 72.20 ± 12.31 years, respectively; $p < 0.01$).

Patients with a history of skin lesions at the time of presentation of the current presentation were significantly older than those without (75.32 ± 9.81 vs 72.49 ± 12.32 years, respectively; $p < 0.01$). A significant difference was also observed concerning smoking status, with non-smokers being older than smokers ($p = 0.02$), with a mean age difference of 3.15 years.

The majority of participants were residents of Novi Sad, accounting for 426 patients (53.1%).

The distribution of lesion locations is presented in **Table 1**. A statistically significant association was found between lesion location and sex ($p < 0.05$). Scalp lesions were significantly more common in men than in women (99 vs 67 cases), whereas facial lesions were more frequently observed in women than in men (117 vs 86 cases).

The most common histopathological finding was *Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi* (N = 378; 47.1%), followed by *Carcinoma basocellulare infiltrativum cutis et texti fibrosi* (N = 111; 13.8%). The distribution of histopathological diagnoses is presented in **Table 2**.

Significant sex-related differences were observed in the distribution of certain histopathological findings ($p < 0.01$). Specifically, *Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi* was more frequently diagnosed in women, whereas *Carcinoma basocellulare infiltrativum cutis*, *Carcinoma basocellulare cutis typus superficialis*, and *Carcinoma*

Table 2. Distribution of Histopathological Diagnoses

Histopathological Diagnosis	N	%	Male	%	Female	%
<i>Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi</i>	378	47.1	172	42.2	206	52.2
<i>Carcinoma basocellulare infiltrativum cutis</i>	91	11.3	57	14	34	8.6
<i>Carcinoma basocellulare exulceratum et infiltrativum cutis</i>	86	10.7	43	10.6	43	10.9
<i>Carcinoma basocellulare cutis typus superfitalis</i>	29	3.6	21	5.2	8	2.0
<i>Carcinoma basocellulare exulceratum et infiltrativum cutis typus superfitalis</i>	9	1.1	2	.5	7	1.8
<i>Carcinoma basocellulare cutis</i>	7	0.9	4	1	3	0.8
<i>Carcinoma basocellulare infiltrativum cutis typus superfitalis</i>	13	1.6	4	1	9	2.3
<i>Carcinoma basocellulare infiltrativum cutis et texti fibrosi</i>	111	13.8	68	16.7	43	10.9
<i>Carcinoma basocellulare exulceratum cutis</i>	8	1	5	1.2	3	0.8
<i>Carcinoma basocellulare exulceratum cutis typus superfitalis</i>	9	1.1	5	1.2	4	1
<i>Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi et adiposi subcutanei</i>	36	4.5	13	3.2	23	5.8
<i>Carcinoma basocellulare infiltrativum cutis et texti fibrosi et adiposi subcutanei</i>	2	0.2	0	0	2	0.5
<i>Carcinoma basocellulare infiltrativum cutis et texti fibrosi et adiposi subcutanei et texti muscularis</i>	4	0.5	3	0.7	1	0.3
<i>Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi et texti adiposi et muscoli striatii</i>	6	0.7	3	0.7	3	0.8
<i>Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi et texti adiposi et muscoli striatii et spatii perineuralis</i>	1	0.1	1	0.2	0	0
<i>Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi et muscoli arrector pili</i>	3	0.4	3	0.7	0	0
<i>Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi et chondroides et adiposi subcutanei</i>	2	0.2	2	0.5	0	0
<i>Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi et muscularis et spatii perineuralis</i>	2	0.2	1	0.2	1	0.3
<i>Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi et texti adiposi subcutanei et spatii perineuralis</i>	6	0.7	1	0.2	5	1.3

basocellulare infiltrativum cutis et texti fibrosi were more common in men. No statistically significant sex-related differences were identified for the remaining histopathological diagnoses.

Among scalp lesions, the most common histopathological findings were *Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi* (N = 77; 46.4%), *Carcinoma basocellulare infiltrativum cutis et texti fibrosi* (N = 24; 14.5%), and *Carcinoma basocellulare infiltrativum cutis* (N = 23; 13.9%). Similarly, among facial lesions, the most frequent diagnosis was *Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi* (N = 102; 50.2%), followed by *Carcinoma basocellulare infiltrativum cutis* (N = 26; 12.8%) and *Carcinoma basocellulare infiltrativum cutis et texti fibrosi* (N = 20; 9.9%).

No statistically significant association was found between histopathological subtype and lesion location ($p = 0.86$), nor between histopathological subtype and previous history of basal cell carcinoma ($p = 0.81$). Regarding the time interval before presentation, patients diagnosed with *Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi* most frequently sought medical attention between one and five years

after first noticing the lesion. No significant differences in the distribution of histopathological findings were observed according to smoking status ($p = 0.69$).

Patients differed with regard to the time interval between first noticing the lesion and seeking medical attention; the distribution of these intervals is presented in **Figure 1**. Within the study cohort, 572 patients (71.2%) presented with a primary lesion, whereas 231 patients (28.8%) reported a previous history of basal cell carcinoma.

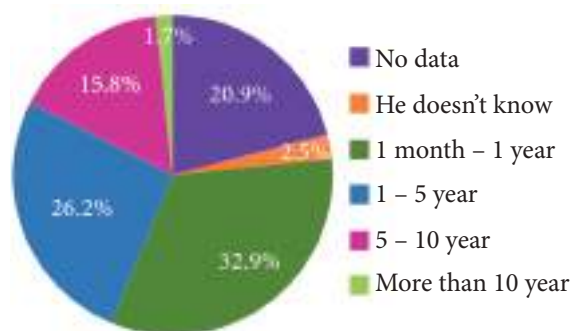


Figure 1. Time Interval Between Initial Detection of the Lesion and First Medical Consultation

Among male patients, data on time to presentation were unavailable for 72 individuals, and 7 patients were unable to specify the duration. A total of 140 men sought medical attention between 1 month and 1 year after noticing the lesion, 115 between 1 and 5 years, 65 between 5 and 10 years, and 8 after more than 10 years. Among female patients, data were unavailable for 96 individuals, and 13 were unable to recall the duration. A total of 124 women presented between 1 month and 1 year after lesion onset, 95 between 1 and 5 years, 61 between 5 and 10 years, and 6 after more than 10 years. Overall, information on the time interval between lesion onset and the first medical consultation could not be retrieved for 168 patients (20.9%), and a further 20 patients (2.5%) were unable to specify it; this variable was therefore available for analysis in 614 patients (76.6%).

No statistically significant association was found between sex and time to presentation ($p = 0.13$).

A statistically significant relationship was observed between lesion location and time to presentation ($p < 0.01$). Scalp lesions were more common among patients who sought medical attention between 1 and 5 years after first noticing the lesion, and less common among those presenting between 5 and 10 years. Trunk lesions were disproportionately less frequent among patients presenting between 1 and 5 years after lesion onset. Patients presenting between 5 and 10 years after first noticing the lesion more frequently had lesions located on the back. Facial lesions, by contrast, were more common among patients who sought medical attention relatively early - within 1 month to 1 year after lesion onset - and, as expected, less frequent among those presenting between 5 and 10 years.

A previous history of basal cell carcinoma was significantly more common in men ($N = 141$) than in women ($N = 90$) ($p < 0.01$; odds ratio for male sex 1.80, 95% CI 1.32–2.45). Among male patients, 266 had no previous history of the disease, compared with 305 female patients.

Borderline differences were observed in the distribution of previous disease according to lesion location ($p = 0.06$). Scalp and face lesions appeared somewhat more common among patients with a previous history of basal cell carcinoma, whereas back lesions were more frequently observed among those presenting for the first time.

Within the study population, 719 patients (89.5%) were non-smokers, and 84 (10.5%) were smokers. Significant differences in lesion location were observed according to smoking status ($p = 0.011$). Facial lesions were disproportionately more common among smokers, whilst back lesions were more frequently observed among non-smokers. No statistically significant as-

sociation was found between smoking status and the time to presentation.

Discussion

Basal cell carcinoma is a slow-growing malignant tumour arising from the basal layer of the epidermis, the outer root sheath of hair follicles, or sebaceous glands. It is the most common skin malignancy, accounting for up to 80% of all diagnosed skin cancers, and its incidence continues to increase worldwide [14].

Rising incidence rates of basal cell carcinoma have been reported globally for several decades. In Europe, the incidence is estimated to increase by approximately 5.5% per year [15]. The highest rates worldwide have been reported in Australia and New Zealand. A study conducted across 38 countries between 1955 and 2007 identified Australia as having the highest incidence, exceeding 1000 new cases per 100,000 population annually [16]. As basal cell carcinoma predominantly affects fair-skinned individuals, disease incidence varies according to the racial and ethnic composition of a given population [17]. Regrettably, no dedicated registry providing current epidemiological data on basal cell carcinoma in the Republic of Serbia could be identified. According to national cancer statistics, 1,830 and 1,715 new cases of non-melanoma skin cancer were diagnosed among men and women, respectively, in Serbia in 2018 [18].

Although basal cell carcinoma may occur earlier in life, either sporadically or in association with certain genodermatoses, increasing age is an independent risk factor [3]. The incidence approximately doubles between the ages of 40 and 70 years [8]. In our study, the mean age was 73.30 ± 11.72 years, consistent with previous epidemiological reports [3]. For example, German cancer statistics from 2014 reported a mean age of 72 years in patients with basal cell carcinoma, with men accounting for 52% of cases [19]. In contrast to studies reporting a male predominance with a male-to-female ratio ranging from 1.5:1 to 2:1, no statistically significant sex-related difference in disease occurrence was observed in our cohort [20].

Although mortality is low owing to the rarity of metastasis, basal cell carcinoma is associated with considerable morbidity and represents a substantial burden on healthcare systems worldwide. The most common anatomical sites are the head and neck, accounting for 70–98.4% of cases, followed by the upper extremities and back [21]. In our study, lesions were most frequently located on the face, followed by the back and scalp. Of particular note was the identification of a single case of genital basal cell carcinoma in a female patient, an exceptionally rare localisation.

As an example, Popadić et al. reported a case of genital basal cell carcinoma in a 55-year-old man, emphasising the rarity of this presentation [22].

A statistically significant sex-related difference was observed in lesion location. Scalp lesions were more common among men, whilst facial lesions were more frequently reported among women. These findings are consistent with those reported by Souza et al., who demonstrated a tendency for women to develop lesions on the central face - particularly the nose and upper lip - whilst men more commonly presented with lesions on the scalp, lateral facial regions, ears, and hair-bearing scalp [23]. These differences may be explained primarily by behavioural and anatomical factors, including longer hairstyles in women and a lower prevalence of severe androgenetic alopecia compared with men. Although several studies have reported a predilection for trunk lesions in men and lower-extremity lesions in women, no significant sex-related differences were observed at these anatomical sites in our study [24].

Numerous histopathological classifications of basal cell carcinoma have been proposed. The need for a simplified and clinically relevant classification led Sexton et al. to define six major histopathological subtypes: nodular (including ulcerated forms), superficial, micronodular, infiltrative, sclerosing, and mixed [25]. According to most authors, the nodular subtype is considered a low-risk, whilst the infiltrative subtype is classified as high risk [26]. Superficial basal cell carcinomas account for approximately 10% of all cases and are typically located on the trunk or extremities; although generally regarded as a low-risk, they demonstrate a tendency toward recurrence owing to their multifocal growth pattern [13].

To facilitate the interpretation of our results, lesions exhibiting both ulcerative and infiltrative features were classified as a mixed subtype. The most common histopathological finding in our study was mixed basal cell carcinoma involving the skin and subcutaneous tissue (*Carcinoma basocellulare exulceratum et infiltrativum cutis et texti fibrosi*), accounting for 47.1% of cases, followed by infiltrative basal cell carcinoma involving the skin and subcutaneous tissue (*Carcinoma basocellulare infiltrativum cutis et texti fibrosi*), which accounted for 13.8%. When all infiltrative variants were combined, irrespective of tissue depth or extent of involvement, the overall frequency of infiltrative basal cell carcinoma was 27.4%. The superficial subtype was identified in only 3.6% of cases, whilst the ulcerative subtype alone accounted for 2.1% of cases.

These findings differ from those reported in most previous studies [24], in which the nodular subtype

has consistently been the most common histopathological variant. For example, Roš et al. found that the nodular subtype represented 57% of all basal cell carcinomas examined [14]. One possible explanation is that our institution is a tertiary referral centre.

Significant sex-related differences in the distribution of histopathological subtypes were observed ($p < 0.01$). The mixed subtype was more frequently diagnosed in women, whilst infiltrative and superficial subtypes were more common in men. These findings are partially consistent with those reported by Pyne et al., who demonstrated a higher prevalence of both superficial and aggressive subtypes, including infiltrative basal cell carcinoma, in male patients [27]. However, Scrivener et al. reported somewhat different results, noting a higher proportion of nodular basal cell carcinomas in men than in women (79.9% vs 77.5%), whilst infiltrative subtypes were more frequent among women (7.2% vs 5.2%) [24].

Regarding scalp and facial lesions, the most common histopathological findings in our study were the mixed subtype (46.4% and 50.2%, respectively) and the infiltrative subtype (28.4% and 22.7%, respectively), consistent with previous studies reporting that infiltrative basal cell carcinoma most frequently occurs in the head and neck region [12]. No statistically significant association was observed between histopathological subtype and lesion location ($p = 0.86$), nor between histopathological subtype and previous history of basal cell carcinoma ($p = 0.81$). Regarding time to presentation, patients with the mixed subtype most commonly presented between one and five years after first noticing the lesion.

Patients differed in the interval between lesion onset and the first medical consultation. Within our study population, 572 patients (71.2%) presented with a first diagnosed basal cell carcinoma, whilst 231 patients (28.8%) had a previous history of the disease. The largest proportion of patients (32.9%) sought medical attention between one month and one year after first noticing the lesion, whilst 26.2% presented between one and five years. It has been reported that 30–50% of patients diagnosed with primary non-melanoma skin cancer will develop another within five years, representing a nearly tenfold increased risk of developing a subsequent basal cell carcinoma or cutaneous squamous cell carcinoma compared with the general population [28]. These findings highlight the importance of patient education and regular dermatological and dermoscopic follow-up.

Basal cell carcinomas are commonly classified as low-risk or high-risk tumours with respect to recurrence [7]. High-risk tumours include lesions larger than 2 cm in diameter, tumours located in the central

facial region (particularly around the eyes, nose, and lips), clinically ill-defined lesions, aggressive histopathological subtypes, and recurrent tumours [7,29]. Surgical margins are generally determined according to tumour size: lesions up to 10 mm are typically excised with 3–5 mm margins of clinically healthy tissue, whilst tumours measuring 10–20 mm usually require margins of at least 5 mm [29]. The primary goal of treatment is complete tumour excision with an adequate safety margin, followed by reconstruction of the resulting defect whilst preserving function and achieving the best possible aesthetic outcome [30].

In our study, a previous history of basal cell carcinoma was more common in men ($N = 141$) than in women ($N = 90$). Borderline differences were observed between previous disease history and lesion location ($p = 0.06$). Scalp and facial lesions appeared somewhat more frequent among patients with a previous history of the disease, whilst back lesions were more common in those presenting with a primary tumour. These findings are consistent with those of Bøgelund et al. [31], who reported that trunk lesions carried the most favorable prognosis, whilst tumours on the head carried the highest risk of recurrence. The authors also demonstrated that recurrence risk depends on tumour size, anatomical location, treatment modality, and the clinical experience of the treating surgeon. Notably, previous studies have shown that the risk of developing a new basal cell carcinoma decreases over time, from 11.6% in the first year after treatment to 6.3% in the second year [32].

Previous studies have demonstrated that basal cell carcinoma and cutaneous squamous cell carcinoma exhibit markedly different associations with cigarette smoking [33]. Specifically, Dusingize et al. reported that current smoking was associated with a reduced risk of basal cell carcinoma but an increased risk of cutaneous squamous cell carcinoma [33]. In our study, non-smokers accounted for the majority of participants (89.5%), whilst smokers represented 10.5% of the cohort. Facial lesions were disproportionately more common among

smokers, whilst back lesions were more frequently observed among non-smokers ($p = 0.011$). No comparable studies examining differences in the anatomical distribution of basal cell carcinoma between smokers and non-smokers could be identified, limiting direct comparison with previously published data.

Several limitations of this study should be acknowledged. First, the study relied on medical records held in the Clinical Information System, which were not uniformly documented. Second, variables such as the time to presentation and smoking status were obtained from patient medical histories and thus dependent on self-reporting, which could not be independently verified. These factors may have introduced information bias. Finally, this was a single-centre retrospective study conducted at a tertiary referral centre. As such, centres tend to manage more complex and advanced cases, which may have contributed to an over-representation of aggressive histopathological subtypes relative to the general population, and limit the generalisability of the findings to other clinical settings.

Conclusion

Basal cell carcinoma predominantly affects older individuals and remains an important public health challenge owing to its high incidence and potential for local tissue destruction. The predominance of mixed and infiltrative histopathological subtypes in our cohort, in contrast to findings reported in most epidemiological studies, may reflect specific characteristics of the treated population at a tertiary referral centre. Male patients more frequently had a previous history of the disease, and significant sex-related differences were observed in lesion localisation. The observed delays in seeking medical attention further emphasise the importance of patient education, regular skin examinations, and early treatment. Ongoing surveillance of epidemiological and clinicopathological patterns may facilitate earlier diagnosis, improve treatment outcomes, and reduce disease recurrence.

References

1. Lang PG, Maize J. Basal cell carcinoma. In: Rigel DS, Friedman R, Dzubow LM, Bystryń JC, Reintgen DS, Marks R. *Cancer of the skin*. Philadelphia: Elsevier Saunders; 2005. p. 101-25.
2. Walling HW, Fosko SW, Geraminejad PA, Whitaker DC, Arpey CJ. Aggressive basal cell carcinoma: presentation, pathogenesis, and management. *Cancer Metastasis Rev*. 2004;23(3-4):389-402.
3. Staples MP, Elwood M, Burton RC, Williams JL, Marks R, Giles GG. Non-melanoma skin cancer in Australia: the 2002 national survey and trends since 1985. *Med J Aust*. 2006;184(1):6-10.
4. Olsen CM, Pandeya N, Green AC, Ragaini BS, Venn AJ, Whiteman DC. Keratinocyte cancer incidence in Australia: a review of population-based incidence trends and estimates of lifetime risk. *Public Health Res Pract*. 2022;32(1):3212203.
5. Dimitrijević MV. Epitelni maligni tumori kože. In: Dimitrijević M, editor. *Maksilofacijalna hirurgija*. Beograd: Medicinski fakultet Univerziteta u Beogradu; 2020. p. 165-70.
6. Cameron MC, Lee E, Hibler BP, Barker CA, Mori S, Cordova M, et al. Basal cell carcinoma: epidemiology, pathophysiology, clinical and histological subtypes, and disease associations. *J Am Acad Dermatol*. 2019;80(2):303-17.
7. Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. *N Engl J Med*. 2005;353(21):2262-9.
8. Crowson AN. Basal cell carcinoma: biology, morphology and clinical implications. *Mod Pathol*. 2006;19 Suppl 2:S127-47.

9. Migden MR, Chen L, Silapunt S, editors. Basal cell carcinoma: advances in treatment and research. 1st ed. Cham: Springer; 2020. p. 290.
10. Leibovitch I, Huilgol SC, Selva D, Richards S, Paver R. Basal cell carcinoma treated with Mohs surgery in Australia I. Experience over 10 years. *J Am Acad Dermatol*. 2005;53(3):445-51.
11. Reifemberger J, Ruzicka T. Basal cell carcinoma. In: Braun-Falco O, Burgdorf WHC, Plewig G, Wolff HH, Landthaler M, editors. *Braun-Falco's dermatology*. Heidelberg: Springer Medizin Verlag; 2009. p. 1348-56.
12. LeBoit PE, Burg G, Weedon D, Sarasin A. World Health Organisation classification of tumors. Pathology and genetics of skin tumours. Lyon: IARC Press. 2006. p. 10-33.
13. Dimitrijević M, Brašanac D, Todorović N, Petrović M, Dimitrijević AM. Basal cell carcinoma—principles of treatment. *Srp Arh Celok Lek*. 2023;151(1-2):98-105.
14. Roš T, Gajić B, Rajić N, Ivkov-Simić M, Gajinov Z. Basal cell carcinoma: a frequent challenge/bazocelularni karcinom: čest izazov. *Serbian Journal of Dermatology and Venereology*. 2013;4(1):5-30.
15. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. *Br J Dermatol*. 2012;166(5):1069-80.
16. Vukić L. Etiopatogeneza, klinička slika, dijagnostika i liječenje bazocelularnog karcinoma [master thesis]. Rijeka: Sveučilište u Rijeci, Medicinski fakultet; 2023.
17. Gangan R. Basal cell carcinoma: epidemiology. *J Skin Sex Transm Dis*. 2022;4(2):157-63.
18. Institute of Public Health of Serbia "Dr Milan Jovanović Batut", Department for Prevention and Control of Noncommunicable Diseases. Malignant tumours in Republic of Serbia 2018. Serbian cancer registry. Beograd: Institute of Public Health of Serbia "Dr Milan Jovanović Batut"; 2020.
19. Robert Koch-Institut. Krebs in Deutschland für 2013/2014. 11. Ausgabe. Berlin: Robert Koch-Institut; 2017.
20. Andersen LK, Davis MD. Sex differences in the incidence of skin and skin-related diseases in Olmsted County, Minnesota, United States, and a comparison with other rates published worldwide. *Int J Dermatol*. 2016;55(9):939-55.
21. Griffiths RW, Suvarna SK, Stone J. Basal cell carcinoma histological clearance margins: an analysis of 1539 conventionally excised tumours. Wider still and deeper? *J Plast Reconstr Aesthet Surg*. 2007;60(1):41-7.
22. Popadić S, Tanasilović S, Živanović D, Medenica L. Genital superficial basal cell carcinoma - a case report/Bazocelularni karcinom kože u genitalnoj regiji - prikaz slučaja. *Serbian Journal of Dermatology and Venereology*. 2013;2(3):106-9.
23. Souza CF, Thomé EP, Menegotto PF, Schmitt JV, Shibue JR, Tarlé RG. Topography of basal cell carcinoma and their correlations with gender, age and histologic pattern: a retrospective study of 1042 lesions. *An Bras Dermatol*. 2011;86(2):272-7.
24. Scrivener Y, Grosshans E, Cribier B. Variations of basal cell carcinomas according to gender, age, location and histopathological subtype. *Br J Dermatol*. 2002;147(1):41-7.
25. Sexton M, Jones DB, Maloney ME. Histologic pattern analysis of basal cell carcinoma. Study of a series of 1039 consecutive neoplasms. *J Am Acad Dermatol*. 1990;23(6 Pt 1):1118-26.
26. Saldanha G, Fletcher A, Slater DN. Basal cell carcinoma: a dermatopathological and molecular biological update. *Br J Dermatol*. 2003;148(2):195-202.
27. Pyne JH, Myint E, Barr EM, Clark SP, Hou R. Basal cell carcinoma: variation in invasion depth by subtype, sex, and anatomic site in 4,565 cases. *Dermatol Pract Concept*. 2018;8(4):314-9.
28. Ciężńska M, Sławińska M, Kamińska-Winciorek G, Lange D, Lewandowski B, Reich A, et al. Clinical and epidemiological analysis of basosquamous carcinoma: results of the multicenter study. *Sci Rep*. 2020;10(1):18475.
29. Tatalović V, Bjelan S, Zeljković D, Marinković M, Višnjevac Lj, Jovanović M. From neglect to metastasis: a giant abdominal basal cell carcinoma. *Med Pregl*. 2024;77(9-12):344-7.
30. Dourmishev LA, Rusinova D, Botev I. Clinical variants, stages, and management of basal cell carcinoma. *Indian Dermatol Online J*. 2013;4(1):12-7.
31. Bøgelund FS, Philipsen PA, Gniadecki R. Factors affecting the recurrence rate of basal cell carcinoma. *Acta Derm Venereol*. 2007;87(4):330-4.
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. Dusingize JC, Olsen CM, Pandeya NP, Subramaniam P, Thompson BS, Neale RE, et al. Cigarette smoking and the risks of basal cell carcinoma and squamous cell carcinoma. *J Invest Dermatol*. 2017;137(8):1700-8.

Rad je primljen 6. VI 2026.

Recenziran 9. VI 2026.

Prihvaćen za štampu 11. VI 2026.

BIBLID.0025-8105:(2026):LXXIX:3-6:90-97.