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Correlation between clinically and histopathologically measured tumor width in basal cell carcinoma

Korelacija između kliničke i histopatološke izmerene širine tumora kod bazocelularnog karcinoma kože

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Abstract

Introduction/Aim. Basal cell carcinoma (BCC) is the most common malignant skin tumor in fair-skinned populations. Although it has low metastatic potential, it can be highly locally invasive and, in addition to impairing function, may even pose a threat to life itself. The majority of BCCs can be successfully reated by classical surgical excision with appropriate safety margins. The aim of this study was to evaluate the correlation between clinical and histopathological tumor width in excised BCCs. **Methods.** A prospective clinical and histopathological study included 45 subjects consecutively examined at the Department of Dermatologic Surgery and Skin Tumors, University Clinical Center of Vojvodina, Novi Sad, Serbia, with a total of 60 primary BCC specimens obtained by classical surgical excision. Medical history was recorded, and dermatological examination was performed. Prior to the excisional biopsy, an incision was made along the edge of the clinically visible tumor to the level of the papillary dermis, and the standard recommended safety margin was added. Histopathological assessment involved microscopic analysis at various magnifications. The histopathological tumor width was measured using a millimeter ocular. The total clinically estimated tumor width was determined as the distance between the two stated skin incisions, and the distance from the incision to the histopathological tumor margin was also recorded. **Results.** A statistically significant correlation was found between clinically determined and microscopically measured total tumor width ($p < 0.05$). The mean clinically estimated width was 9.55 ± 5.13 mm, while the histopathological width was 7.98 ± 4.75 mm. The statistically determined difference between the clinically marked and microscopically measured tumor width was less than 2.0 mm in 96.7% of cases, i.e., in 88.4% of cases, this difference in assessment was 1.0 mm or less. **Conclusion.** There is a positive correlation between the clinically assessed and histopathologically verified width of the BCC.

Key words:
carcinoma, basal cell; dermoscopy; histological techniques; skin neoplasms.

Apstrakt

Uvod/Cilj. Bazocelularni karcinom (*basal cell carcinoma* – BCC) je najčešći maligni tumor kože kod ljudi svetle puti. Iako ima nizak metastatski potencijal, lokalno može biti visoko invazivan, te pored funkcije dela tela na kome se nalazi može ugroziti i sam život. Većina BCC-a se može uspešno lečiti klasičnom hirurškom ekscizijom uz odgovarajuće sigurnosne margine. Cilj rada bio je da se proceni korelacija između kliničke i patohistološke širine kod ekscidiranih BCC-a. **Metode.** Prospektivna klinička i histopatološka studija obuhvatila je 45 bolesnika pregledanih na Odeljenju za dermatohirurgiju i tumore kože, Univerzitetskog kliničkog centra Vojvodine, Novi Sad, Srbija, gde je analizirano ukupno 60 uzoraka primarnih BCC-a dobijenih klasičnom hirurškom ekscizijom. Uzeti su anamnestički podaci i obavljen je dermatološki pregled. Pre ekscizione biopsije, načinjen je rez duž ivice klinički vidljivog tumora do nivoa papilarnog dermisa i dodata standardno preporučena sigurnosna margina. Histopatološka obrada uključila je mikroskopsku analizu na različitim uveličanjima. Histopatološka širina tumora merena je milimetarskim okularom. Ukupna klinički procenjena širina tumora određena je kao razdaljina između dva navedena reza na koži, a zabeležena je i razdaljina između reza i histopatološke margine tumora. **Rezultati.** Utvrđena je statistički značajna korelacija između klinički određene i mikroskopski izmerene ukupne širine tumora

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($p < 0,05$). Prosečna klinički procenjena širina bila je 9,55 ± 5,13 mm, dok je histopatološka širina bila 7,98 ± 4,75 mm. Statistički utvrđena razlika između klinički obeležene i mikroskopski izmerene širine tumora bila je u 96,7% slučajeva manja od 2,0 mm, tj. u 88,4% slučaja ova razlika u proceni bila je 1,0 mm ili manja. **Zaključak.** Postoji pozitivna korelacija između klinički procenjene i histopatološki verifikovane širine BCC-a.

Ključne reči:
karcinom, bazocelularni; dermoskopija; histološke tehnike; koža, neoplazme.

Introduction

Basal cell carcinoma (BCC) is a slow-growing malignant skin tumor of epidermal origin, representing the most common malignant tumor in fair-skinned populations [1, 2]. It accounts for approximately 80% of non-melanoma skin cancers, whereas squamous cell carcinoma makes up the remaining 20% [3]. Although BCC shows a very low tendency for metastases (0.0028–0.55%), if left untreated, it can be locally destructive, compromising the function and esthetics of the region and even endangering life itself [4]. The incidence of BCC is constantly increasing, and it is associated with significant morbidity and high cost of treatment [5].

The etiology and pathogenesis of BCC are complex. Apart from genetic characteristics, exposure to ultraviolet (UV) radiation stands out as a significant environmental risk factor [6]. From a molecular perspective, BCC is linked to mutations in keratinocyte progenitor cells [7]. Most of these mutations occur due to deoxyribonucleic acid damage induced by UVB radiation. In almost all cases of BCC, there is an activation of the hedgehog signaling pathway [3]. Certain genodermatoses and autoimmune diseases, as well as immunosuppression, are associated with a higher incidence of BCC.

There are several clinical types of BCC. The most frequent are nodular and superficial, while others include sclerosing, ulcerated (ulcus rodens), and destructive (ulcus terebrans) types. According to the World Health Organization classification, other subtypes, which are mainly based on histological findings and are difficult to differentiate clinically, include micronodular, fibroepithelial, basosquamous and metatypical, keratotic, cystic, infundibulocystic, and adenoid subtypes [4]. In individuals with darker skin phototypes, BCC can have a different clinical presentation and can frequently present as pigmented BCC, where dermoscopy, as an ancillary diagnostic method, is especially useful [8].

Given that BCC is characterized by local tissue destruction and a very low rate of metastasis, the tumor, node, metastasis (TNM) staging system provides limited value in its assessment. The T stage is nonspecific, while N and M status are negative in more than 99% of cases [4].

Factors used to assess the risk of recurrence include tumor localization, size, histopathological subtype, and whether the tumor is primary or recurrent [9]. Localizations with a higher incidence of tumor occurrence and recurrence serve as important indicators for the diagnosis and prognosis of BCC. The high-risk area for BCC recurrence, the "H zone", includes the following regions: nose, eyebrows, upper lids, lips, mandibular angles, earlobes, preauricular region, hands, feet, and genital area. The second, so-called "M zone", involves the regions of the remaining parts of the face, scalp, neck, and pretibial region. These are the zones with a moderate risk of recurrence, while the "L zone" includes the trunk and extremities (excluding hands, feet, and pretibial region) and shows a lower likelihood of BCC recurrence. Another important prognostic factor of the risk of recurrence is the tumor size. The likelihood of recurrence in the "H zone" is higher for tumors with a diameter of over 6.0 mm, while in the "M zone" it applies to tumors larger than 10.0 mm. Moreover, larger BCCs are more likely to exhibit subclinical spread beyond the clinically visible tumor margins and thus, the risk of tumor recurrence on the resection margin of the histopathological specimen is much higher in larger tumors. Regarding histopathological subtype, a high risk of recurrence is observed in the following subtypes of BCC: sclerosing, infiltrating, metatypical, and micronodular, while a low risk is typical for superficial, nodular, adenoid, tubercular, infundibulocystic, cystic, and fibroepithelial (Pinkus tumor) subtypes [4].

Mohs micrographic surgery is the most effective treatment for BCC, especially for recurrent tumors and for those located in high-risk, cosmetically sensitive areas [10]. The most common treatment is surgical excision. The majority (more than 95%) of BCCs can be definitely treated with a classical surgical excision with appropriate safety margins [4]. Punch or excision biopsy provides a definite diagnosis by determining the histological characteristics of a lesion [9]. Non-surgical topical treatment (i.e., imiquimod, 5-fluorouracil), photodynamic therapy, superficial radiation therapy, and surgical curettage with electrodessication are reserved for low-risk BCCs or for patients in whom other therapeutic modalities are contraindicated. Systemic therapy is indicated in cases of locally advanced or metastatic BCCs. Targeted therapy with inhibitors of the hedgehog signaling pathway is currently in clinical use [4].

According to current clinical guidelines, a safety margin of 3.0–5.0 mm is generally recommended for BCCs at low risk of recurrence, whereas margins greater than 5.0 mm are advised for high-risk tumors [4]. Others, however, suggest that the safety margin of 6.0 mm should be sufficient for both tumor variants [9], even for those 5.0 to 10.0 mm in size [11].

The study is based on the assumption that clinical assessment of BCCs can reliably predict histopathological outcomes regarding tumor size. We postulate that in dermatology settings, clinical estimation of tumor width and margin position will significantly correlate with

histopathological width and histopathological margin position, respectively.

The aim of this study was to evaluate the correlation between clinical and histopathological tumor width in excised BCCs.

Methods

Clinical study

The study was conducted at the University Clinical Center of Vojvodina, Novi Sad, Serbia. This prospective clinical and histopathological study included 60 specimens of both low- and high-risk primary BCCs, taken from 45 subjects consecutively examined at the Department of Dermatologic Surgery and Skin Tumors by an attending dermatologist. The subjects who had immunocompromising diseases at the same time and/or were receiving immunosuppressive therapy were excluded from the study, as were the subjects with genodermatoses accompanied by multiple BCCs, as well as those with tumors larger than 25 mm and recurrent tumors. The study was approved by the Ethics Committee of the Clinical Center of Vojvodina (No. 00-05/277, from April 30, 2012). Written informed consent was obtained from all participants prior to their inclusion in the study.

The following patient data were registered: sex, age, personal and family history of previous BCC, possible presence of multiple BCCs, and absence of other genetic syndromes. The clinical examination included a complete skin examination and dermoscopy. As for the tumors, we recorded the size (measured by a millimeter ruler) and localization of each BCC.

Clinically assessed tumor width was marked with a No. 15 surgical scalpel to make it visible on a histopathological specimen by placing an incision to the level of the papillary dermis. A classical surgical excision with 3 mm safety margins was performed, oriented along relaxation tension lines of the skin and adjoining anatomical structures. These markings were necessary for later measurements. The specimens were placed into a formalin solution and further processed using routine histopathological preparation, given that histopathological analysis remains the "gold standard" for confirming clinically established diagnoses of BCC. Histopathological evaluation involved microscopic analysis at various magnifications (×40, ×100, ×200, ×400). We measured histopathological tumor width using a millimeter ocular. The total clinically estimated tumor width was measured as the distance between the two stated incisions.

Specimens were divided into three groups according to both clinically and histopathologically measured tumor width: 0–10.0 mm, 10.1–20.0 mm, and 20.1 mm or more. Additionally, the distance of the incision from the histopathological tumor margin was measured. This third measure was applied to adequately verify whether the clinically estimated tumor width corresponded to the true, histopathologically confirmed width.

The data obtained were analyzed in comparison with each other and in relation to whether the incision was made within or outside the histopathologically verified tumor. Furthermore, the results were compared based on whether the difference between the clinically marked and histopathologically determined tumor width in the excised BCC specimen was greater or less than 2.5 mm. All these procedures and measurements were needed to determine the correlation between the clinically estimated and histopathologically determined tumor width.

Statistical analysis

Statistical analysis was performed using SPSS version 21 software. Descriptive statistics were primarily employed. Using univariate analysis, we determined which anamnestic, clinical, and histopathological factors showed a statistically significant difference between the corresponding groups. Odds ratios with corresponding 95% confidence intervals and *p*-values were calculated. A *p*-value of less than 0.05 was considered statistically significant.

Results

The study involved 45 subjects and histopathological analysis of 60 primary BCC tumors, both with low and high risk of recurrence.

The sample included 45 subjects, 26 (57.8%) females and 19 (42.2%) males.

The sex ratio was 1.37 in favor of females. The mean age of the study population was 63 years (range 28–85). The largest number of subjects (40.0%) was in the 40–59 age range. Subjects in the range of age 60–79 years comprised 37.8% of the sample. Those aged 80 years or above made up 17.8%, and those aged 20–39 years accounted for 4.4% of subjects.

Out of the total number of subjects, 40.0% had a history of BCC at another site, whereas 60.0% had no history of prior BCC. Additionally, 48.9% of subjects had more than one BCC. Regarding the histopathological subtype of tumor, nodular (51.7%) and superficial (40.0%) BCC comprised the largest percentage, while other subtypes accounted for 8.0% of the samples. The largest number of tumors in the specimens (65.0%) were located in the head and neck region. The next frequent localization was the trunk and shoulders (31.7%), and only 3.2% of our specimens were localized elsewhere.

Most tumors (78.4%) were up to 10.0 mm wide, 18.3% were 10.1–20.0 mm wide, and only 3.3% were wider than 20.1 mm (Table 1).

The mean clinically measured width of the sampled tumors was 9.55 ± 5.13 mm, while the mean histopathological tumor width was 7.98 ± 4.75 mm ($n = 60$) (Table 2).

The mean difference between the clinically measured and histopathologically verified tumor width was 1.57 mm, with a 95% confidence interval of 1.0–2.13 mm.

Further statistical analysis determines that the mean distance from the incision to the histopathologically verified

Table 1

Distribution of histopathological tumor width in the study population

Histopathological tumor width, mm	n (%)
0–10.0	47 (78.4)
10.1–20.0	11 (18.3)
≥ 20.1	2 (3.3)
Total	60 (100)

n – number of excised tumors.

Table 2

Mean clinical and histopathological tumor width with standard deviation (SD) in the study population

Tumor width, mm (n = 60)	Mean ± SD
Clinical	9.55 ± 5.13
Histopathological	7.98 ± 4.75

n – number of excised tumors.

tumor width was 0.62 mm (range 0.10–2.50 mm). Of 60 samples, two (3.3%) tumors had an incision distance ≥ 2.0 mm, whereas in 96.7% of tumors, the incision distance was less than 2.0 mm. More precisely, in 88.4% of the samples, the incision was 1.0 mm or less from the histopathologically verified tumor width. Regarding incision placement, 25.0% of incisions were made within the tumor, whereas 75.0% were made outside the tumor. In more than 95.0% of cases, the incision was at a distance of less than 1.5 mm.

Discussion

In our conditions, following clinical and dermoscopic examination, we performed excisional biopsy for tumors smaller than 25 mm, with a 3 mm safety margin, serving both as a diagnostic (establishing a definite histopathological type) and treatment procedure. Demographic characteristics from our study show that the mean age of subjects with BCC was 63 years, consistent with published data [1], with a female-to-male sex ratio of 1 : 1.37. Although these data support a higher incidence of this type of carcinoma in males, the sample size is too small to make the difference in trends statistically significant. Still, the findings align with global trends of increasing BCC incidence in females. This is most likely because women are increasingly exposed to risk factors by assuming traditionally "male" tasks. Furthermore, following current tanning trends involving natural and/or artificial sources of UV radiation represents a serious problem that should be addressed through adequate primary prevention measures. Similar preventive efforts are needed regarding exposure to different household chemical agents, as well as to various chemicals present in hair-care and styling products [12]. Our study also reveals that 40.0% of subjects report a history of BCC, while clinical examination shows one or more BCCs in 48.9% of subjects, which aligns with findings from another study (46.7%) [13].

Regarding the skin tumor localization in our study, the largest percentage of carcinoma (65.0%) is excised from the region of head and neck, which aligns with the results of other researchers, and with the known fact that this region bears the highest risk of BCC occurrence [4]. We are aware that a punch biopsy is the first and mandatory procedure in the most developed countries when establishing a definite diagnosis of BCC, but, because of the insufficient financial resources and the burden of healthcare, we opt to plan further treatment only for high-risk histopathological type of tumor [9]. For high-risk histopathological subtypes of BCCs and/or those located in the H-zone and/or recurrent tumors, we perform additional Mohs micrographic surgery after excisional biopsy [10].

The most common pathohistological subtype of tumor, according to our study, is the nodular type (51.7%), followed by the superficial type (40.0%), while only 8.0% account for other BCC subtypes. In comparison with the data from another study [13], where a nodular BCC is also the most common one (57.1%), a superficial BCC (19.5%) and other subtypes (14.1%) are present in larger proportions. This is likely due to the relatively small sample size in our study.

Our research shows a potential bias in the measurement of histopathological tumor width, as the study was conducted within a single healthcare institution. It should be noted that all measurements were made by dermato-oncology subspecialists, and since other institutions in our country do not provide comparable conditions, this approach can be considered representative in the given context. The result's authenticity would have been better if histopathological tissue processing had included a horizontal section. However, complete circumferential margin assessment is performed only in micrographic surgery, unlike the conventional vertical-section histopathological analysis applied in this study. Mohs micrographic surgery is both efficient and cost-effective, offering the highest cure rates, and is considered the gold standard for treating high-risk nonmelanoma skin cancers in most developed countries [5].

The methodology of our study, which involves placing an incision in the papillary dermis before excision, enables us to avoid the difference in tumor width measurement between clinical and histopathological assessments, which

results from specimen tissue contraction. On the other hand, this could be considered a shortcoming when the results are compared to another study [11].

Statistical analysis in this study reveals a significant correlation between the clinically estimated tumor width and the actual histopathological tumor width ($p < 0.05$). This finding emphasizes the importance of precise clinical margin assessment in standard surgical excision, which remains the most effective treatment for primary BCCs. Accurate estimation of safety margins is essential for optimizing cure rates while minimizing morbidity [10]. Our results support the continued use of excisional biopsy as a reliable and sufficient diagnostic and therapeutic approach for all primary BCCs with low-risk histopathological subtypes [11].

In 95.0% of the specimens, the difference between the clinically and histopathologically measured tumor widths was up to 1.5 mm, while 96.7% of specimens showed a difference of less than 2.0 mm. The single specimen in which the distance from the incision to the tumor exceeded 2.0 mm (specifically 2.40 mm) was a nodular BCC located in the so-called "cancerization field". This skin area typically contains numerous precancerous lesions; thus, clinically, the lesion cannot be exactly differentiated from carcinoma that is not clinically visible, although it may be present in a histopathological analysis. This circumstance indirectly affects the above-mentioned statistics.

The results of our study favor the views expressed in the study that suggest that it is actually needed to consider a potential reduction of the current safety margins [9]. In our study, a uniform safety margin of 3.0 mm is applied for both low and high-risk BCCs, and histopathological analysis confirms this margin as adequate in all cases. However, our recommendation of a 3.0 mm safety margin applies specifically to low-risk tumors. In order to determine whether this margin is sufficient for high-risk BCCs as well, long-term prospective studies with extended follow-up are necessary to evaluate the rate of recurrence at excision sites.

Conclusion

This study shows a positive correlation between the clinically assessed and histopathologically verified basal cell carcinoma width. Returning to the initial observation that the incidence of basal cell carcinoma continues to rise, it is evident that appropriate surgical treatment (with adequate safety margins) and prevention of recurrence will remain the focus of interest for a long time. In perspective, clinical guidelines should consider a decrease of safety margins during surgical treatment of basal cell carcinomas at a low risk of recurrence, to achieve maximal tissue salvage, and at the same time, minimize recurrence rates and resource consumption.

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