Diagnostic accuracy of basal cell carcinoma in dermatology setting in Serbia – a single-center study

Pouzdanost dijagnoze bazocelularnog karcinoma u dermatologiji – monocentrična studija u Srbiji

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Abstract

Background/Aim. The growing incidence of skin tumors requires an accurate diagnosis. Dermoscopy, especially *in vivo*, enhances the diagnosis of basal cell carcinoma (BCC). Total body skin examination (TBSE), a visual inspection of the patient's total body surface, is considered a basic step in the dermatological exam, especially in skin cancer screening. However, TBSE is still a matter of debate regarding its expediency in a real clinical setting. The aim of this study was to analyze the diagnostic accuracy of BCC detected and treated by referred dermatologists. **Methods.** The retrospective analysis included a five-year period of BCC detection during TBSE by visual inspection and dermoscopy. We calculated sensitivity, specificity and positive predictive value for BCC using histopathological results as the correct diagnosis. **Results.** Out of 3,346 biopsied skin tumors, 49.58% were malignant and 50.42% benign. The most common malignant tumor was BCC, accounting for 84.09%. Localization of BCCs was mainly on the trunk (38.92%) and the H-zone of the face (37.63%). Other localizations were face (non-H-zone) (6.67%), neck (3.01%), scalp (3.37%), arms (6.88%) and limbs (3.51%). Of all BCCs, 0.83% were recurrent BCC. The sensitivity for the diagnosis of BCC was 97.71%, and the positive predictive value was 95.08%. **Conclusion.** In the dermatology setting, TBSE and visual inspection with *in vivo* dermoscopy result in a very good diagnostic performance of BCC.

Key words:
dermoscopy; diagnosis; histological techniques; neoplasms, basal cell; sensitivity and specificity; serbia.

Apstrakt

Uvod/Cilj. Zbog povećane incidence tumora kože potrebna je njihova pouzdana dijagnoza. Dermoskopija, posebno *in vivo*, poboljšava dijagnozu bazocelularnog karcinoma (BCK). Pregled kompletne kože tela (PKKT) podrazumeva inspekciju cele površine kože bolesnika i predstavlja osnov dermatološkog pregleda, a posebno pregleda „skrininga" kože na premaligne i maligne lezije. Međutim, svrsishodnost PKKT u svakodnevnoj kliničkoj praksi je i dalje predment debate. Cilj rada bio je da se ispita pouzdanost dijagnostike BCK, detektovanog i lečenog od strane iskusnog dermatologa. **Metode.** Retrospektivna analiza obuhvatila je petogodišnji period detekcije BCK prilikom PKKT vizuelnom ispekcijom i dermoskopskim pregledom. Određivana je senzitivnost, specifičnost i pozitivna prediktivna vrednost dijagnoze BCK korišćenjem histopatoloških rezultata kao tačne dijagnoze. **Rezultati.** Od 3 346 bioptiranih tumora kože, 49,58% su bili maligni a 50,42% benigni. Najčešći maligni tumor bio je BCK (84,09%). Njegova najčešća lokalizacija je bio trup (38,92%) i H-regija lica (37,63%). Ostale lokalizacije bile su: lice (izvan H-regiona) (6,67%), vrat (3,01%), poglavina (3,37%), ruke (6,88%) i noge (3,51%). Od ukupnog broja BCK, 0,83% su bili recidivantni. Senzitivnost dijagnostike BCK iznosila je 97,71%, a pozitivna prediktivna vrednost bila je 95,08%. **Zaključak.** U dermatologiji, PKKT vizuelnom ispekcijom i *in vivo* dermoskopijom omogućava veoma dobru dijagnostiku BCK.

Ključne reči:
dermoskopija; dijagnoza; histološke tehnike; karcinom, bazocelularni; senzitivnost i specifičnost; srbija.

Introduction

The growing incidence of skin tumors is a worldwide problem. In Serbia, the incidence of non-melanoma skin cancer (NMSC) is increased for both genders, with an annual percent change of 2.32%, in the period from January 1999 to December 2015. This continuously increasing incidence rate of NMSC in Serbia urges engagement of all practitioners

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dealing with skin tumors and education about preventive measures in the population, in general, as part of the national preventive strategy [1]. Today, the etiology and pathogenesis of basal cell carcinoma (BCC) are much better understood [2]. BCC is the most common skin cancer in Caucasians, slow-growing, with low metastatic potential. If left untreated, locally invasive BCC can jeopardize the aesthetics and function of the anatomical region and eventually become life-threatening. BCC is still a challenge for dermatologists and other practitioners since its accurate and early diagnosis reduces not only the morbidity rate but also the costs of treatment [3]. For a long time, clinical examination, with naked-eye inspection, was standard for detecting skin tumors, and diagnostic accuracy of BCC with visual inspection alone has been superior to other skin tumors [4–6]. Dermoscopy was introduced into clinical practice about 20 years ago as an additional noninvasive tool for visual inspection; at the beginning, its primary use was for skin tumors [7]. Our knowledge of dermoscopy of BCC has been significantly enriched since dermoscopy was introduced to clinical practice. Variability of dermoscopic structures in BCCs, not only augments the clinical differential diagnosis but also provides additional significant information for guiding type and the management of BCC [8–11]. In recently published meta-analyses, the diagnostic accuracy of skin tumors, BCC of particular interest, with visual inspection and dermoscopy, has been analyzed. Great heterogeneity between studies was found, but it was shown that when dermoscopy is used by specialists, especially in person (*in vivo*), it may be a valuable tool to support visual inspection of a suspicious skin lesion for the diagnosis of BCC [12, 13]. Besides, total body skin examination (TBSE), a visual inspection of the patient's total body surface, is considered a basic step in a dermatological exam, especially in skin cancer screening, but also a matter of debate of its expediency in real clinical setting [14–18]. The diagnostic accuracy of BCC has been studied very rarely in the context of TBSE specified. Papers on BCC diagnostic accuracy in Serbia are lacking.

The main aim of this study was to analyze the diagnostic accuracy of BCC detected and treated by referred dermatologists in the Skin Cancer Unit of the Dermatology and Venereology Clinic, University Clinical Center of Vojvodina, Novi Sad, Serbia with an emphasis on the influence of total body skin examination.

Methods

Clinical setting

This retrospective study included consecutive five-year referrals (from January 1st, 2015, to December 31st, 2019) to the Skin Cancer Unit (SCU) at the Clinic of Dermatology and Venereology, University Clinical Center of Vojvodina in Novi Sad, Serbia (coordinates longitude: 19°51 east, latitude: 45°20 north). The referral Center covers health services for the city of Novi Sad and the Serbian province of Vojvodina, with a population of nearly 2,000,000 inhabitants.

In the SCU, four dermatologists were mainly engaged in the diagnosis and treatment of skin tumors and procedural dermatology. Four clinical specialists were part-time engaged in daily SCU practice. Dermoscopy is incorporated into everyday clinical work. All specialists were practicing dermoscopy, three of them at the level of expert dermoscopy (experience > 10 years and PhD thesis and published papers in the field of dermoscopy), two intermediate (dermoscopy experience 5–10 years), and three with basic knowledge and experience in dermoscopy. Routine protocol in the SCU is held for all dermatologists working in the SCU. Patients were referred to the SCU by general practitioners or dermatologists. Waiting time for a consultant varied from several days to three weeks. For all patients, it was mandatory to perform a TBSE. Every patient was examined by visual inspection and dermoscopy in person. Handheld dermoscope DermLite DL100® was at the disposal of every doctor all the time.

For every lesion planned for biopsy, a digital dermoscopy with photo documentation was performed. Clinical and contact polarized dermoscopic photographs were obtained for each lesion using a Nikon Coolpix 4300® camera attached to a DermLite Foto II Pro®. The dermoscopic diagnosis of BCC was based on pattern analysis: looking for the absence of melanocytic specific criteria (network, aggregated globules, streaks, and homogeneous blue pigment) and by identifying features of BCC: arborizing telangiectasia, large blue/gray ovoid nests, ulceration, multiple blue/gray globules, maple-leaf like areas, spoke-wheel areas, short fine superficial telangiectasia, multiple small erosions, concentric structures, multiple in-focus blue/gray dots. It was mandatory for the dermatologist, who made the decision for surgery, to give a preoperative clinical and dermoscopic diagnosis for any tumor or dermatosis, as a first or as a second – to exclude malignancy and to record it in a database of all biopsies, where diagnoses from histopathology reports have also been collected. When inflammatory dermatosis was considered a referral diagnosis, usually, an incisional biopsy was taken. When a skin tumor was considered a referral diagnosis, usually, an excisional biopsy was taken. The sample was fixated in 4% formalin, and standard paraffin vertical sections, treated with hematoxylin-eosin, were examined by one of three pathologists at the Pathology and Histology Center, University Clinical Center of Vojvodina in Novi Sad. In the SCU, we treat skin tumors less than 20 mm in diameter on all anatomic regions of the skin, while bigger lesions are mainly referred to a surgeon for plastic and reconstructive surgery or maxillofacial surgery. In our SCU, some flat lesions on the trunk or limbs larger than 20 mm, quite suspicious for superficial BCC, are treated with imiquimod or 5-fluorouracil therapy after incisional biopsy and histopathological confirmation. Out of all malignant skin tumors, BCC is the most common lesion treated in the SCU. Before the SCU was established in our Department in 2011, all skin tumors were treated by plastic or maxillofacial surgeons. Still, around 400 malignant tumors a year are treated outside the SCU.

Study design

For this study, we underwent a retrospective analysis of referral and histopathological diagnoses of all consecutive biopsies from the SCU database. We excluded biopsies referred to as inflammatory dermatoses and those suspected of T cell lymphoma. The rest were biopsies suspected of skin tumors. When multiple referral diagnoses were present, we took the first one into account. Lesions were detected following accepted SCU protocol.

The study protocol was approved by the Ethics Committee of the University Clinical Center of Vojvodina from February 27, 2017 (00-15/1222).

Statistical analysis

We calculated sensitivity, specificity, positive and negative predictive value (PPV and NPV, respectively) for BCC using histopathological results as the correct diagnosis. For statistical analysis, we used Statistica® Version 13.5 software.

Results

In the study period, there were 4,033 biopsies. From them, we excluded biopsies with suspicion of inflammatory dermatoses and suspicion of cutaneous T cell lymphoma, 687 (17.03%). The remaining 3,346 biopsies were suspected skin tumors. Of all 3,346 biopsied skin tumors, 49.58% were malignant and 50.42% benign (Table 1).

The most common malignant tumor was BCC, accounting for 1,395 (84.09%) of all malignant tumors. The median age of patients with BCC was 75 years (range 20–95, mean ± standard deviation: 72 ± 12); 48.55% were men and 51.45% were women. Localization of BCCs was mainly on the trunk (38.92%) and the H-zone of the face (37.63%). In all, in the head and neck region, the localization of BCC lesions was 50.68% (Table 2). Referral recurrent BCC was found in 25 cases; histopathology verified 12 of them. Of all BCCs, 0.83% were recurrent BCC.

BCC was a referral diagnosis in 1,459 lesions. Histopathological diagnosis of BCC was made in 1,395 biopsies. In 32 lesions, the referral diagnosis was not BCC,

Table 1

Histopathological diagnosis of excised tumors

Diagnosis	n (%)
Malignant	
basal cell carcinoma	1,395 (84.09)
squamous cell carcinoma	119 (7.17)
Morbus Bowen	78 (4.70)
keratoacanthoma	40 (2.41)
malignant other	27 (1.63)
Total	1,659 (100)
Benign	
actinic keratosis	112 (6.64)
seborrheic keratosis	221 (13.10)
dernatifubrina	78 (4.62)
nevus intradermalis	351 (20.81)
nevus dysplasticus	315 (18.67)
nevus ceruleus	15 (0.89)
haemangioma	78 (4.62)
angiokeratoma	2 (0.12)
fibroma	110 (6.52)
cystis	141 (8.36)
verruca vulgaris	94 (5.57)
benign other	122 (7.23)
no tumor	48 (2.85)
Total	1,687 (100)

Table 2

Localization of basal cell carcinoma lesions

Localization	Lesions, n (%)
Head and neck	
head	
face	
H region	525 (37.63)
non-H region	93 (6.67)
scalp	47 (3.37)
neck	42 (3.01)
Trunk	543 (38.93)
Arms	96 (6.88)
Legs	49 (3.51)
Total	1,395 (100)

but BCC was the histopathological diagnosis. In 96 biopsies, the referral diagnosis was BCC, but it was not proven by histopathology (Table 3). We calculated diagnostic accuracy for BCC as sensitivity, specificity, PPV and NPV (Table 4). Sensitivity was 97.71%, specificity 95.08%, the PPV was 93.42% and the NPV 98.3% (Table 5).

Recently, it was shown that diagnostic accuracy of skin tumors, BCC of particular interest, with visual inspection and dermoscopy, if performed by specialists experienced in dermoscopy, may be a useful tool to help diagnose BCC correctly when compared with visual inspection alone [12, 13].

Our study addressed BCC and investigated the diagnostic accuracy of visual inspection and dermoscopy during TBSE.

Table 3

Diagnostic accuracy of basal cell carcinoma

Diagnoses	FP (unnecessary excisions) n (%)	FN (missed BCC) n (%)
SCC	12 (12.50)	17 (53.14)
Morbus Bowen	3 (3.13)	8 (25.00)
Keratoacanthoma	2 (2.07)	0 (0.00)
Malignant other	1 (1.04)	1 (3.12)
Actinic keratosis	17 (17.71)	3 (9.37)
Other benign	28 (29.17)	3 (9.37)
No tumor	33 (34.38)	0 (0.00)
Total	96 (100)	32 (100)

FP – false positive diagnoses; FN – false negative diagnoses; SCC – squamous cell carcinoma; BCC – basal cell carcinoma.

Table 4

Calculation of diagnostic accuracy for basal cell carcinoma (BCC)

Clinical and dermoscopic diagnosis of BCC*	Histopathological diagnosis of BCC	
	positive	negative
Positive	True positive (n = 1,363)	False positive (n = 96)
Negative	False negative (n = 32)	True negative (n = 1,855)

***Clinico-dermoscopic approach with total body skin examination.**

Table 5

Calculated diagnostic accuracy for basal cell carcinoma as sensitivity, specificity, positive and negative predictive value

Statistical parameters	Value (%)	95% CI (%)
Sensitivity: TP/(TP + FN)	97.71	96.78–98.43
Specificity: TN/(FP + TN)	95.08	94.02–96.00
Positive predictive value: TP/(TP + FP)	93.42	92.11–94.52
Negative predictive value: TN/(FN + TN)	98.3	97.63–98.79

TP – true positive; FP – false positive; FN – false negative; TN – true negative; CI – confidence interval.

Discussion

Seeking the simplest and best diagnostic and therapeutic method for BCC, diagnostic accuracy was investigated from different perspectives. Several previous studies have addressed the diagnostic accuracy of skin cancer based on clinical examination with the naked eye [4–6]. They have considered skin tumors, in general, in different settings, with different profiles of physicians enrolled in the study, such as general practitioners, general practitioners with a special interest in skin cancer, plastic surgeons and general surgeons, and dermatologists. In these studies, the sensitivity of BCC detection was superior to other skin tumors and varied between 63.9–90% [4–6].

Attitude toward TBSE is rarely specified in studies [5]. We have endorsed the concept of TBSE and the clinico-dermoscopic approach as we feel more confident with the diagnosis of skin tumors in general, and we wanted to test it from a perspective of diagnostic accuracy of BCC. Ahnlide and Bjellerup [19] conducted a similar study in Sweden. Both studies had a similar setup and results, with the exception of their study being prospective and our retrospective. TBSE was not specified in the methodology, but given the percentage of BCCs detected on different parts of the skinhead and neck (53.3%), arms (5.9%), legs (10.0%), trunk (30.8%), indicated that a full-body check was performed. Important similarities include the clinical setting of the studies, with only dermatologists as diagnosticians. Anhlide and Bjellerup [19] mentioned for their study that it was "the first

European study with such design". Their study lasted 3 and a half years and included dermatologists familiar with dermoscopy. In their study, 2,953 lesions were analyzed, and 55.1% of the excised lesions were malignant. The most common malignant tumor was BCC, accounting for 72.6% of the malignant tumors. Squamous cell carcinoma (SCC) (including invasive SCC, keratoacanthoma, and SCC *in situ*) accounted for 18% of malignant tumors and 8.4% were melanoma. In our study, there were 49.58% of malignant tumors; of them, 84.09% were BCCs, 14.28% were invasive SCCs, keratoacanthoma, and Morbus Bowen, while other malignant tumors, including melanoma, accounted for 1.63%. In a study by Ahnlide and Bjellerup [19], there were 54 (55.5%) false negative (FN) or misdiagnosed BCCs, of them, 30 (55.5%) were diagnosed as SCCs. In our study, out of 32 FN or missed BCCs, SCCs were diagnosed in 52%, Morbus Bowen in 24%, and actinic keratosis was diagnosed in 9% of cases. Although BCC was missed and incorrectly diagnosed, excision was still justifiable, as there was malignancy in 76% or actinic keratosis in 9% of cases.

Some evidence showed that dermatologists did not routinely perform TBSE while examining patients for skin cancer [14]. Some of them stated that factors influencing such an attitude were the lack of evidence about its efficacy, lack of time, or inadequate reimbursement [16]. Furthermore, in 2009, the US Preventive Services Task Force (PSTF) concluded that for the general adult population, TBSE is questionable as a result for several different reasons. They claimed that current evidence is insufficient to assess the harms and benefits of TBSE for the early detection of skin cancer. They accepted that screening could result in the early detection of skin cancers and pointed out that there was not enough evidence that early detection of skin malignancies was related to morbidity or mortality. Moreover, the US PSTF mentioned potential harms from screening and that their magnitude could not be assessed [14]. Some of the harms they referred to were false positive findings, namely lesions that needed not be biopsied or excised as benign lesions and potential anxiety in screened patients. They also mentioned cancers detected by screening were possibly overtreated because of their slow growth, low metastatic potential, and low mortality rate [14]. In 2012, Argenziano et al. [15] conducted research to give more evidence on TBSE in the light of the US PSTF announcement from 2009. Currently, the US PSTF does not recognize anymore the previous statements for early detection of skin cancer in the view of screening the adult population [20].

Argenziano et al. [15] calculated that in order to find one skin malignancy, 47 patients had to be examined by TBSE, and to detect one melanoma, 400 patients were needed. If TBSE was not performed, the risk of missing one malignancy was 2.17% (95% confidence interval was 1.25–3.74%). A similar prevalence of 2.0% of skin tumors detected by TBSE in dermatology settings was found by other dermatologists [17, 18]. We calculated that 2.17% (n = 30) of 1,395 BCCs found in our study could have been missed. In our study, among 96 FP results (unnecessary excisions), 12 were SCC, and 23 were other malignant tumors and precancerous lesions. Measuring potential harms of TBSE concerning false positive results and 2% of potentially missed tumors, we consider performing TBSE

reasonable and justified. We share the opinion of Argenziano et al. [15] that TBSE is a safe procedure that can be easily and rapidly performed by dermatologists who are specifically trained. It has been shown that the median time needed for TBSE performed by well-trained dermatologists was only 70 sec, regardless of whether the patients had few or many lesions [21]. In the study of Ahnlide and Bjellerup [19], the sensitivity for BCC diagnosis was 95.4%, and PPV 85.9%, whereas in the present study, sensitivity was 97.71% and PPV 93.42%. Sensitivity in our study was slightly superior to that from Anhlide and Bjellerup study [19], PPV was also superior, but to a higher extent. It is commonly acknowledged that PPV is influenced by the prevalence of the disease in the population tested/studied. With all the other factors remaining constant, PPV increases with increasing prevalence. The superior result of PPV in our study is very likely the sign of the most important limitation of the present study. Namely, in our SCU, there is a slightly unbalanced frequency among malignant skin tumors, with more BCCs compared to SCCs and melanomas. BCC was found in 84.09% of all malignant tumors. As we stressed earlier, in the SCU, mainly NMSC smaller than 20 mm in diameter are treated, while suspected melanomas and bigger NMSC are referred to the Plastic Surgery Unit, which is equipped with facilities to perform sentinel lymph node biopsy.

Nelson et al. [22] conducted a study to estimate the proportion of BCC lesions that could be referred directly to definitive therapy of BCC escaping incisional biopsy that is usually performed as a part of a treatment plan. In the study based on diagnosing BCC through dermoscopy, it was concluded that clinicians were confident enough to refer about two-thirds of BCCs directly to definitive surgery. With dermoscopy and TBSE, regarding our results and other experiences, we are very confident with the diagnosis of BCC, and we already perform excisional biopsies of BCC upon detection, with very satisfactory results concerning recurrent BCCs.

Another limitation of this study, usually occurring in similar studies, concerns the true sensitivity of the study. The true sensitivity of a referral diagnosis can be determined only if all relevant skin lesions are assessed histologically to give the correct number of FN results. Namely, to assess accuracy and sensitivity completely, each lesion clinically and dermoscopically inspected had to be biopsied. However, this is ethically unacceptable, unnecessary, and reasonably unrealistic in a typical clinical setting.

Conclusion

In the dermatology setting, TBSE and visual inspection with *in vivo* dermoscopy result in a very good diagnostic performance of BCC.

The results of our study appear to be superior in sensitivity and specificity with respect to other referred studies. In our opinion, this can be attributed to TBSE and visual inspection aided with dermoscopy. We also believe that this is a consequence of strengthening the coworking of a small number of experienced specialists engaged in diagnosing and treating BCC in our dermatology setting.

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