DERMATOSCOPY IN PREDICTING BASAL CELL CARCINOMA MARGINS

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Introduction: Basal cell carcinoma (BCC) is a slow-growing epithelial tumor that rarely metastasizes, and has the rising incidence in the last decades. Complete surgical removal to reduce local recurrence is the therapy goal. *Aim:* To investigate the efficacy of dermatoscopy in distinguishing superficial from other histopathologic BCC subtypes and in predicting the required surgical margins to reduce recurrence rate. *Methods:* We conducted a single-center, retrospective study in the period between January 1, 2011 and December 31, 2020. After BCC diagnosis was established, skin lesions were evaluated using dermatoscopy. After surgical excision, histopathologic analysis of the tumor and peritumoral tissue was performed by an experienced pathologist. Correlation between dermatoscopy and histopathology findings were evaluated. *Results:* All tumors were up to 20 mm in largest diameter with head and neck being the most affected skin site (56%). There was an absolute correlation between dermatoscopy and histopathology in superficial BCC subtype (kappa coefficient 1.000; p<0.001), lower in nodular (kappa 0.847; p<0.001) and infiltrative subtype (kappa value 0.846, p<0.001). A large majority of tumors were 1-2 mm from the inked margins (81%), belonging to pT1 category. Regarding the recurrence rate, there was no statistically significant relationship with tumor size, margin or base status or tumor thickness; 8.8% of patients had recurrence in the median follow-up period of 120 months. There was a significantly poorer survival period regarding recurrence in infiltrative BCC subtype when compared to superficial (51 vs. 108 months; p<0.001) and nodular subtype (51 vs. 72 months, p<0.001). *Conclusion:* Dermatoscopic evaluation of the BCC margins could be helpful in preoperative assessment, with emphasis on inking of surgical specimen margins.

Key words: basal cell carcinoma, dermatoscopy, margins, inking

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INTRODUCTION

Basal cell carcinoma (BCC) is the most common malignancy in the fair skin population (1,2). Standard treatment of BCC includes surgical removal, while the application of imiquimod, 5-fluorouracil or photodynamic therapy should be restricted to low-risk superficial tumors (1). Since the recurrent BCC becomes more aggressive, the lesion should be completely surgically removed (1,3). In addition, the appropriate margins for complete removal of recurrent BCC should be twice as large as those for complete removal of the primary BCC (4,5). The main factors that can influence recurrence rates are histologic BCC subtype and surgical margins (1,4,5). Recurrence rates vary from 2% to 8% at 5 years after complete surgical removal to up to 41% after incomplete removal (1,4-6). Therefore, a valid and easily applied preoperative method to define BCC margins can be useful for the clinicians. Dermatoscopy, by providing a more accurate assessment of the true extension of the tumor, allows a more precise estimation of the required surgical margins helping to minimize the BCC recurrence rate (1,6). While the diagnostic significance of pigmented structures, such as blue-gray ovoid nests, blue-gray globules and dots or maple leaf-like areas is proven, the usefulness of vascular structures in defining surgical margins of BCC remains to be further elucidated (6,7). Preoperative use of dermatoscopy may improve recognition of the BCC margins and complete excision rate (8-10).

The aim of this study was to investigate the efficacy of dermatoscopy in distinguishing superficial from other histopathologic BCC subtypes and the efficacy in predicting the required margins of surgical excision to reduce recurrence rate.

MATERIALS AND METHODS

We conducted a single-center, retrospective study in the period between January 1, 2011 and December 31, 2020. Dermatoscopic criteria applied to diagnose BCC were the following: arborizing vessels, ulceration, leaflike areas, spoke wheel areas, large blue-gray ovoid nests, and multiple blue-gray globules (8). After BCC diagnosis was established, perilesional skin was evaluated using dermatoscopy. Dermatoscopic analysis and photo documentation in the period between January 1, 2011 and December 31, 2014 was performed with a Dermlite II Pro HR 3 GEN digital dermatoscope (DermLite LLC, USA) and Nikon Coolpix 5400 camera (Nikon, Japan), saved in PhotoMax program. In the period between January 1, 2015 and December 31, 2020, we used a FotoFinder ATBM system digital dermatoscope (FotoFinder Systems GmbH, Germany). During dermatoscopy, minimal pressure and immersion with the use of antiseptic fluid (Octenisept, Schulke & Mayr GmbH, Germany) were used to preserve vascular morphology and to obtain the clearest possible visualization of the tumor formation. Evaluation of dermatoscopic images was based on the combined dermatoscopic criteria (1,2,8). The BCC margins were marked with tissue dye and surgical sutures, i.e., one suture in the lateral part and two sutures in the medial part. After surgical excision, an experienced pathologist performed histopathologic analysis of the tumor and peritumoral tissue. Specimens were processed by fixation in 10% formalin for 24-72 hours, embedded in paraffin, cut at 4 µm and stained by hematoxylin-eosin (H&E) (11). The distance between the tumor margins and the nearest inked margins was measured on H&E stained slides by a computer program and expressed in millimeters (BX51, Olympus, Issa PACS software). The study was done on archival material taken from the files of the Department of Pathology, School of Medicine, University of Zagreb, Croatia.

Dermatoscopic definition of the BCC surgical margins was based on vessel evaluation, detection of satellite BCC clues in perilesional tissue including whitish to erythematous translucent to opaque areas free of vascular structures, satellite pigmented dots and small, superficial ulcerations (1,8). Tumoral vessels and telangiectasia of the healthy skin were distinguished because BCC vessels are bright-red, appear sharply in focus, and exhibit evident ramifications to finer capillaries (1,8). Instead, the telangiectatic vessels of the surrounding undamaged skin were more blurred, unfocused, and showed few, if any, branches (1,2,8).

All included patients gave written informed consent for participating in the study, which was conducted in accordance with the principles of Good Clinical Practice and the current version of the Declaration of Helsinki.

Statistical analyses were performed using licensed IBM SPSS Statistics software, version 25.0 (https://www.ibm. com/analytics/spss-statistics-software). The distribution of variables was tested using Kolmogorov-Smirnov test. Categorical variables were expressed as absolute values and percentages. Categorical variables were compared by Fisher exact test and Fisher-Freeman-Halton test in cases of contingency tables larger than 2x2 format. Continuous data were expressed as means and standard deviations or median with corresponding interquartile range (IQR) in case of skewed distribution, and differences were analyzed by Kruskal-Wallis test. ROC analysis analyzed the effectiveness (sensitivity and specificity) of dermatoscopy in distinguishing superficial from other histopathologic subtypes of BCC, as well as the optimal size of the required surgical margin in relation to recurrence. The kappa coefficient was used as a measure of concordance between dermatoscopic and histopathologic findings. Kendall's tau-b correlation coefficients were calculated to analyze the association of tumor size, base, margins, and tumor thickness with recurrence. The analysis of freedom to recurrence was performed by a Kaplan-Meier curve with a log-rank test. A p-value of <0.05 was pre-specified to indicate statistical significance.

RESULTS

This retrospective, single-center study included 57 Caucasian patients with a skin lesion having clinical and dermatoscopic features of BCC. Mean age of the study group was 66 (range, 20-91) years, 72% were fe-

male. All tumors were up to 20 mm in largest diameter (range 3 to 20 mm) and therefore classified as pT1 (12). The most affected skin site was head and neck in 32 (56%) patients, followed by trunk in 18 (32%) and extremities in 7 (12%) patients. Superficial BCC subtype using dermatoscopy was diagnosed in 24 (42%), nodular in 22 (39%) and infiltrative in 11 (19%) patients (Table 1). Histopathologic analysis revealed superficial subtype in 24 (42%), nodular in 18 (32%), infiltrative in 14 (25%) cases and mixed in one (1.8%) case. Baseline demographic characteristics, histopathology and dermatoscopy findings of the study population are shown in Table 1. In this study, no complications were noted during dermatoscopy evaluation.

Table 1. Demographic characteristics, histopathology and	
dermatoscopy findings in the study population	

		n	%	95%	6 CI
Condor	Male	16	28.1	17.7	40.6
Genuer	Female	41	71.9	59.4	82.3
	<60	15	26.3	16.3	38.7
	60-70	13	22.8	13.4	34.9
Aye yloup (yeals)	70-80	17	29.8	19.2	42.5
	>80	12	21.1	12.1	32.9
	Superficial	24	42.1	29.9	55.0
Histopathologia subtura	Nodular	18	31.6	20.7	44.3
nisiopalilologic sublype	Infiltrative	14	24.6	14.8	36.8
	Mixed	1	1.8	0.2	7.9
Illegration	No	38	66.7	53.8	77.8
UICEIAUUII	Yes	19	33.3	22.2	46.2
	0	4	7.0	2.4	15.8
Cubaroup according to baco	1	21	36.8	25.2	49.8
Subgroup according to base	2	26	45.6	33.2	58.5
IIIVOIVEIIIEIIL	3	6	10.5	4.5	20.4
	4	1	1.8	0.2	7.9
	0	3	5.3	1.5	13.4
Subgroup according to	1	27	47.4	34.8	60.2
border	2	19	33.3	22.2	46.2
	3	7	12.3	5.7	22.6
	Superficial	24	42.1	29.9	55.0
Diagnosed with dermato-	Nodular	22	38.6	26.8	51.5
scopy	Infiltrative	11	19.3	10.7	30.9
	Mixed	0	0.0		
Dermatoscopic features:					
arborizing (tree-like) telan-	No	18	31.6	20.7	44.3
giectasia with or without	Yes	39	68.4	55.7	79.3
blue/gray dots					
	Face and scalp	30	52.6	39.8	65.2
Localization	Neck	2	3.5	0.7	10.8
	Body	18	31.6	20.7	44.3
	Foot	7	12.3	5.7	22.6
Palanca	No	52	91.2	81.8	96.6
neiapoe	Yes	5	8.8	3.4	18.2

There was absolute correlation between dermatoscopy and histopathology in superficial BCC subtype (kappa coefficient 1.000; p<0.001). Correlation regarding nodular subtype (22 *vs.* 18 case) was lower (kappa 0.847; p<0.001), while kappa value was 0.846 (p<0.001) comparing dermatoscopic and histopathologic diagnosis of infiltrative BCC (Table 2).

Table 2. Histopathologic subtype findings in relation to
dermatoscopy findings

		Diagnosed with dermatoscopy							
		Supe	rficial	Nod	ular	Infiltrative			
		n	%	n	%	n	%		
	Superficial	24	100	0	0.0	0	0		
Histopathologic	Nodular	0	0	18	th dermatoscopy dular Infiltrativ % n % 0.0 0 0 81.8 0 0 13.6 11 10 4.5 0 0	0			
subtype	Infiltrative	0	0	3	13.6	11	100		
	Mixed	0	0	1	4.5	0	0		

The most common dermatoscopic feature in the perilesional skin was superficial, bright-red, fine arborizing telangiectasia (51%), followed by a combination of gray dots and fine telangiectasias (8.7%), larger arborized blood vessels (5.2%), fine telangiectasias in combination with dotted vessels (3.5%), and scattered gray dots (1.8%). A total of 17 (30%) patients did not show dermatoscopic structures suspicious of BCC extension in perilesional skin (Table 3, Figure 1).

Table 3. Dermatoscopic features seen in perilesional skin

	BCC subtype									
Dermatoscopic features	Superficial		Nodular		Infiltrative		Mixed		Total	
	n	%	n	%	n	%	n	%	n	%
None	10	41.7	3	16.7	4	28.6	0	0	17	29.8
Arborizing (tree-like) telangiectasia	12	50	12	66.7	9	64.3	1	100	34	59.6
Blue/gray dots without telangiectasia	1	4.2	0	0.	0	0	0	0.0	1	1.8
Arborizing (tree-like) telangiectasia with blue/gray dots	1	4.2	3	16.7	1	7.1	0	0.0	5	8.8

After a median follow-up of 36 (IQR 12-60, min 6, max 108) months, patients with superficial and nodular BCC subtypes did not have any recurrence, however, recurrence was recorded in 45.5% (5/11) of patients with infiltrative BCC subtype. There were three (5.3%) cases with positive lateral margins detected on histopathologic slides despite negative dermatoscopic finding. The large majority of tumors (46 cases, 81%) were 1 to 2 mm from the inked margins, belonging to pT1 category (2,12). The tumor was observed on the base of the specimen in 4 cases, however, 82% (47 cases) of tumors were 1-2 mm from the base of the specimen (Table 1, Figure 2). Regarding recurrence rate, there was no statistically significant relationship with tumor size, margin or base status, and tumor thickness. There was a significantly lower survival period to recurrence in infiltrative BCC subtype when compared to the superficial subtype (51 months, 95% CI 30-72 vs. 108 months, 95% CI 108-108; p<0.001) and nodular subtype (51 months, 95% CI 30-72 vs. 72 months, 95% CI: 72-72; p<0.001) (Figure 3). In addition, the optimal distance of the surgical excision margins in relation to the recurrence rate, with the best ratio of sensitivity and specificity, in superficial BCC tumors was 4 mm, in nodular subtype 8 mm and in infiltrative >8 mm of dermatoscopic structures associated with the tumor.



Figure 1. Dermatoscopic features of margins of basal cell carcinoma (A) and basal cell carcinoma after inking of tumor and surgical margins (B).



Figure 2. A. Gross photograph of surgical specimen of basal cell carcinoma after inking with tissue dyes (A) and microscopic features of basal cell carcinoma after inking of specimen margins with tissue dyes (B) (hematoxylin and eosin, X40).



Figure 3. Kaplan-Meier survival analysis regarding dermatoscopic findings of basal cell carcinoma recurrence.

DISCUSSION

The main findings of this single-center, retrospective cohort study which included 57 patients with BCC were as follows: 1) all tumors were up to 20 mm in largest diameter with head and neck being the most affected skin site; 2) there was an absolute correlation between dermatoscopy and histopathology in superficial BCC subtype (kappa coefficient 1.000; p<0.001), lower but still high in nodular subtype (0.847; p<0.001) and infiltrative subtype (0.846, p<0.001); 3) regarding recurrence rate, there was no statistically significant relationship with tumor size, margin, base status or tumor thickness; and 4) there was a significantly lower survival period regarding recurrence in infiltrative BCC subtype when compared to superficial (51 vs. 108 months; p<0.001) and nodular subtype (51 vs. 72 months, p<0.001).

The mean age of the study group was 66 years, which is within the age at which BCC most commonly occurs, however, with a rather strong female predominance (13). In our study, all tumors were up to 20 mm in largest diameter, which is in line with previous studies, unlike the superficial subtype predominance (42%) and head and neck being the most affected skin site (56%) instead of thorax (10,13,14).

The large majority of tumors were 1-2 mm from the inked margins (81%), all of them belonging to pT1 category, which is also in line with previous studies (12-16). Therefore, there was a low recurrence rate, especially in superficial and nodular BCC subtypes. We could state that certain dermatoscopic vascular (fine telangiectasia and punctuate vascular changes) and structural characteristics (gray spots) could be taken into consideration when predicting BCC extension into the surrounding tissues. In addition, current data show that the inci-

dence of these criteria are similar in BCCs located in different areas, implicating that these are tumor specific, which is in line with a previous study (13). Although dermatoscopy is nowadays an indispensable tool in clinical evaluation of skin tumors, there is still no standard protocol for determination of BCC margins prior to surgical treatment (9,10,15-17). There are some studies showing the value of dermatoscopy in assessing surgical margins during Mohs microscopic surgery, however, not decreasing the number of stages obtained during this procedure (1,9-11,18-21). Dermatoscopy, as a noninvasive method, is free of complications, which was proven again in our study (1,13-21). Moreover, several noninvasive methods, such as reflectance confocal microscopy (RCM) and optical coherence tomography (OCT), have been proposed to improve margin marking precision, however, dermatoscopy among these is likely to be fastest and least expensive (16,18). High costs with mandatory additional training to adequately interpret the resulting images largely limit the widespread availability of OCT and RCM (19-21).

Regarding correlation between dermatoscopy and histopathology findings, dermatoscopy proved to be highly efficient in all three BCC subtypes, especially in superficial BCC (kappa coefficient 1.000; p<0.001), which was higher when compared to previous studies (1,2,9,10,13,14). This could be explained by the fact that we used the already known and adopted BCC characteristics gaining more experience. Caresana and Giardini used dermatoscopy to determine peripheral BCC margins consequently reducing surgical margins to 2 mm for conventional surgery (9). They achieved 98.5% of complete tumor excision, higher in comparison to our 93%, which was still high when compared to similar studies, especially for nodular subtype (14,15).

Considering recurrence rate, there was no statistically significant relationship with tumor size, margin, base status or tumor thickness, but there was an expected significantly lower survival period without recurrence in infiltrative BCC subtype despite a high total surgical excision rate. This fits well with previous results, where the higher recurrence rate was proven for this BCC subtype (2,13-20). Our study showed that the optimal distance of surgical margins in relation to the recurrence rate, with the best ratio of sensitivity and specificity, in superficial BCC tumors was 4 mm, in nodular subtype 8 mm and in infiltrative >8 mm of dermatoscopic structures associated with the tumor, which is higher than currently accepted recommendations (1,2). Moreover, it is much more difficult to determine distance between the tumor and the base of surgical specimen. Infiltrative subtype due to unpredictable tumor features and subclinical spread below visible margins dermatoscopically should be removed with a wider resection margin than proposed with a depth reaching to the fascia, perichondria and periosteum. Dermatoscopic structures characteristic of BCC at tumor margin were more frequently observed in pigmented BCC, and in unpigmented BCCs we used blood vessels to predict the margins. The data suggest that dermatoscopy could be useful in perioperative assessment of BCC margins, but there is still space for improvement.

CONCLUSION

According to our findings, dermatoscopic evaluation of the BCC margins could be helpful in preoperative assessment of the required surgical margins aiming to reduce the BCC recurrence rate. Randomized controlled studies comparing dermatoscopic findings with histopathologic evaluation of complete surgical excision are required to confirm the real usefulness of dermatoscopy in defining the preoperative tumor margins.

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S A Ž E T A K

PREDVIĐANJE RUBOVA KARCINOMA BAZALNIH STANICA POMOĆU DERMOSKOPIJE

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Uvod: Bazocelularni karcinom kože je spororastući tumor koji vrlo rijetko metastazira, a incidencija kojega se povećava tijekom posljednjih nekoliko desetljeća. Liječenje je većinom kirurško s ciljem kompletnog odstranjenja i smanjenja mogućnosti nastanka lokalnih recidiva. Neki se podtipovi tumora mogu liječiti i konzervativno. Cilj: Analizirati uspješnost dermoskopije u identifikaciji kirurških rubova sa svrhom smanjenja učestalosti nastanka recidiva te razlikovanje superficijalnog od ostalih podtipova. Metode: Klinički dio studije je proveden u Poliklinici Manola, a analiza patohistoloških preparata na Zavodu za patologiju Medicinskog fakulteta Sveučilišta u Zagrebu u razdoblju od 1. siječnja 2011. do 31. prosinca 2020. godine. Nakon postavljanja kliničke dijagnoze bazocelularnog karcinoma tumori su pregledani dermoskopski. Nakon kirurškog odstranjenja iskusni patolog je analizirao tumor i peritumorsko tkivo s naglaskom na korelaciju kliničkog i patohistološkog nalaza. Rezultati: Većina tumora bila je lokalizirana u području glave i vrata (56 %), a svi su bili manji od 20 mm u najvećem promjeru (pT1). Utvrđena je potpuna korelacija između dermoskopskog i patohistološkog nalaza superficijalnog podtipa (kappa koeficijent 1,000, p<0.001), ali manja podudarna glede nodularnog (kappa 0,847, p<0.001) i infiltrativnog podtipa (kappa 0,846, p<0,001). Većina tumora (81 %) se nalazila na 1-2 mm od bližeg resekcijskog ruba označenog bojom za tkiva. Tijekom razdoblja praćenja recidiv tumora je dijagnosticiran u 8,8 % pacijenata. Međutim, nije utvrđena statistički značajna povezanost između veličine odnosno debljine tumora i statusa rubova i baze materijala. Utvrđena je statistički značajna razlika između infiltrativnog i superficijalnog bazocelularnog karcinoma u odnosu na razdoblje od dijagnoze do nastanka recidiva (51 u odnosu na 108 mjeseci, p<0,001) odnosno infiltrativnog i nodularnog podtipa (51 napram 72 mjeseca, p<0,001). Zaključak: Dermoskopska evaluacija rubova i baze bazocelularnog karcinoma je uspješna u većini slučajeva osim infiltrativnog podtipa. U patohistološkoj analizi je nužno označavanje resekcijskih rubova poradi procjene potpunosti ekscizije i predviđanja mogućnosti nastanka lokalnih recidiva.

Ključne riječi: bazocelularni karcinom, dermoskopija, rubovi, označavanje bojom