Diagnostic concordance among dermatopathologists in basal cell carcinoma subtyping: Results of a study in a skin referral hospital in Tehran, Iran

Azita Nikoo, MD [1]
Zahra Naraghi, MD [1]
Kambiz Kamyab, MD [1]
Alireza Ganadan, MD [1]
Zohre Khodashenas, MD [2]
Azadeh Goodarzi, MD [3]
Fatemeh Mohaghegh, MD [1,4]

1. Department of Pathology, Tehran University of Medical Sciences, Tehran, Iran
2. Department of Dermatology, Tehran University of Medical Sciences, Tehran, Iran
3. Department of Dermatology, Iran University of Medical Sciences, Tehran, Iran
4. Department of Pathology, Isfahan University of Medical Sciences, Isfahan, Iran

Corresponding Author:
Fatemeh Mohaghegh, MD
Department of Pathology, Al Zahra Hospital, Isfahan, Iran
Email: f.mohaghegh@med.mui.ac.ir

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Background: Basal cell carcinomas (BCC) are the most prevalent among non-melanoma skin cancers (NMSC), which correspond to the most common skin cancers. BCC histopathological subtyping is a problem in therapeutic management. Therefore, we have decided to perform a histopathologic study for better classification of BCCs based on interobserver diagnostic judgment.

Methods: We conducted this cross-sectional study on 100 randomly selected pathologically confirmed BCC cases of various subtypes at Razi Hospital, Tehran, Iran during 2013 and 2014. A total of four dermatopathologists independently reviewed each pathology slide to evaluate the interobserver concordance rate.

Results: The overall Fleiss' kappa statistic (kappa) for the BCC subtypes was 0.18 (P<0.001), which indicated slight agreement. We observed moderate agreement on superficial and nodular BCC (kappa: 0.0-0.4); fair agreement on infiltrative and keratotic BCC (kappa: 0.2-0.4); and slight agreement on pigmented, micronodular, and metatypical BCC (kappa: 0.0-0.2). There was moderate agreement diagnosis for the low and high risk growth pattern categories.

Conclusion: Overall, we found that the dermatopathologists had inconsistent nomenclature for the BCC subtypes, however they had better agreement for the diagnosis of superficial, nodular, and infiltrative subtypes and the high risk growth pattern.

Keywords: basal cell carcinomas, diagnostic concordance, histopathology subtyping, interobserver study

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INTRODUCTION

Skin cancers are the most common cancers. Non-melanoma skin cancers (NMSCs) account for the most prevalent skin cancers and include basal cell carcinomas (BCC) and squamous cell carcinomas (SCCs) [1]. BCC comprises approximately 80% of NMSCs [2-4] potentially encountered by dermatologists in daily practice. BCC is a malignant epithelial neoplasm that originates from pluripotent cells in the epidermis and hair follicles [5]. Although considered a low grade malignancy, BCC is locally aggressive. If improperly managed or untreated, BCC could eat away at the tissues, deeply penetrate the bone, and result in ulceration (rodent ulcer). The metastasis rate of BCC is rare (0.03%) with a low mortality rate, however it needs specific attention due to considerable functional impact and cosmetic deformities [5,6].

Experienced dermatologists can usually clinically diagnose typical cases of BCC based on morphology, anatomic location, and dermoscopic guides.

However, biopsies should always be performed to confirm the initial clinical diagnosis [2].

There are multiple well-known histopathologic subtypes of BCC. Each subtype is associated with a specific biologic behavior that could affect the likelihood ratio of tumor recurrence and treatment modality [3].

A major purpose of tumor classification is better therapeutic management because different tumor subtypes behavior in different manners [3,6]. In one classification, BCC could belong to either indolent growth-pattern or aggressive growth-pattern tumors. The indolent-growth variants include superficial and nodular BCC, whereas aggressive-growth types comprise infiltrative, metatypical, morpheaform, and sclerosing BCC [7]. Such classifications aid communication between clinicians and pathologists, allow for comparison between different case groups, and facilitate research. It is considered as one of the tumor's characteristics that affects the choice of therapeutic approach [6,8].

Classification of BCC in most recent textbooks is complex and usually lacks uniformity in terminologies and clear definitions [6,9]. For this reason, different dermatopathologists could report one BCC with different histopathologic subtypes. Nedved *et al.* assessed the concordance of BCC subtypes between different dermatopathologists with interesting results [10]. We decided to measure interobserver diagnostic concordance in BCC subtyping between four dermatopathologists as a cross-sectional study at the Razi Skin Center to obtain a better interpretation of the pathology reports. The new classification proposed based on the study results could increase relative agreement between different dermatopathologists on BCC pathologic subtyping and facilitate decision making for BCC management.

METHODS

In this retrospective cross-sectional study, we investigated BCC cases diagnosed in 2013 and 2014 at the Department of Pathology, Razi Hospital, Tehran, Iran. We randomly selected 100 cases of BCC without considering their subtypes. We selected a single representative slide with no artifact from each case that met our inclusion criteria. Our cases had the following characteristics: a) originally diagnosed as BCC and primary tumor (non-recurrent), b) no evidence of prior surgery because scar tissue could interfere with the diagnosis, and c) presence of a good margin that allowed for assessment of the growth pattern (at least 1 mm).

We distributed the study slides to four dermatopathologists for individual review and diagnosis. These dermatopathologists obtained their primary board certification in pathology and received training in dermatopathology fellowship programs. Their work experience in dermatopathology ranged from 6 to 30 years.

The dermatopathologists were informed that the selected cases represented BCC but they received no other information about subtyping. They were blinded to each other's diagnosis and only noted BCC subtype. After their diagnosis, we categorized the cases as high or low risk. Study cases that reported by the dermatopathologists as composite subtype were considered as high risk if at least one of the individual subtypes was high risk.

We received permission for using the archived pathology material from the Vice-Chancellor of Research and Ethical Committee of Tehran University of Medical Sciences for conducting our research.

Diagnosis concordance and overall and individual Fleiss' kappa statistics were calculated to determine concordance between pairs of observers with Stata (StataCorp. 2011. Stata: Release 12. Statistical Software. College Station, TX, USA). Fleiss' kappa statistic statistics were calculated and interpreted using the nomenclature set forth by Landis and Koch for following kappa ranges [10,11]:

- 0: poor agreement (agreement expected by chance)
- 0.01-0.2: slight agreement
- 0.21-0.4: fair agreement
- 0.41-0.6: moderate agreement
- 0.61-0.8: substantial agreement
- 0.81-1: almost perfect agreement

RESULTS

Out of 100 cases, there were 66 male and 34 female cases whose ages ranged from 32 to 91 years (mean: 66 years). The cases were originally reported as having composite (49%), nodular (23%), superficial (12%), infiltrative (3%), morpheaform (3%), micronodular (3%), metatypical (3%),

sclerosing (2%), and basosquamous (2%) BCC patterns. The dermatopathologists reported all 100 cases as BCC. Table 1 shows the subtypes reported by each dermatopathologist. Nodular BCC was the most common pattern followed by composite.

In terms of risk assessment, 62% of cases were low risk and 38% high risk.

There was agreement between all four observers on 26 of 100 cases. These 26 cases included 13 nodular BCC, 12 superficial, and one pigmented-nodular BCC.

Concordance in subtyping between any two dermatologists ranged from 13.9 to 22.2 (Table 2). The overall kappa in BCC subtyping was 0.18 (P<0.001), which was considered slight agreement. In Table 3, interobserver precision is placed with their subtype.

The individual kappa values of 3 subtypes - fibroepithelial, clear, and eccrine could not be calculated because they were reported only once.

There was moderate agreement on superficial and nodular BCC (kappa: 0.41-0.6); fair agreement on infiltrative and keratotic BCC (kappa: 0.21-0.4); and slight agreement on pigmented, micronodular, and metatypical BCC (kappa: 0.01-0.2).

Table 2. Fleiss' kappa values for the individual basal cell carcinoma (BCC) subtypes.

Subtype	Kappa	*P*
Nodular	0.4819	<0.001
Infiltrative	0.3278	<0.001
Superficial	0.5249	<0.001
Pigmented	0.1562	<0.001
Morpheaform	-0.0204	0.6914
Micronodular	0.1874	<0.001
Fibroepithelial	-0.0076	0.5734
Infundibulocystic	-0.0050	0.5490
Nodulocystic	-	-
Keratotic	0.2340	<0.001
Basosquamous	-0.0050	0.5490
Metatypical	0.1220	0.0015
Adenoid	0.0756	0.0321
Squamatized	-0.0050	0.5490
Sclerosing	0.0028	0.4722
Follicular differentiation	-0.0152	0.6454
Clear cell	-0.0025	0.5245
Adamantinoid	-	-
Eccrine differentiation	-0.0025	0.5245
Composite	0.2477	<0.001
High risk	0.5084	<0.001

However, when we categorized BCC into low and high risk growth patterns, the observers had moderate agreement (Table 2).

Table 1. Frequencies of basal cell carcinoma (BCC) subtypes diagnosed by each observer*.

Subtype	Observer					
	A	B	C	D	Total	%
Nodular	51	76	38	60	225	56.25
Infiltrative	13	20	16	9	58	14.5
Superficial	36	21	28	11	96	24.0
Pigmented	0	23	2	12	37	9.25
Morpheaform	0	0	8	0	8	2.0
Micronodular	19	4	8	26	57	14.25
Fibroepithelial	0	0	0	3	3	0.75
Infundibulocystic	0	1	1	0	2	0.50
Nodulocystic	0	0	0	0	0	0.00
Keratotic	1	4	3	3	11	2.75
Basosquamous	0	0	1	1	2	0.50
Metatypical	0	7	13	0	20	5.0
Adenoid	0	0	17	8	25	6.25
Squamatized	0	1	0	1	2	0.50
Sclerosing	0	0	13	23	36	9.0
Follicular differentiation	0	4	0	2	6	1.5
Clear cell	0	1	0	0	1	0.25
Adamantinoid	0	0	0	0	0	0.00
Eccrine differentiation	0	0	1	0	1	0.25
Composite	17	30	34	31	112	28.0
High risk	31	28	46	47	152	38.0

*There were four independent dermatopathologists who recorded the histopathological subtypes of each sample (overall 100 patients) and finally 400 filled-out files were gathered for analysis.Any one sample could have had more than one main histopathological feature and could, therefore, be recorded in more than one subtype group.Hence, the total frequency and relative frequencies noted here are depicted as more than 100 and 100%, respectively.

Table 3. Concordance rate (%) between the observers.

Observer	A	B	C	D
A	-	22.02	20.71	19.95
B	22.02	-	13.99	21.90
C	20.71	13.99	-	16.85
D	19.95	21.9	16.85	-

DISCUSSION

The present study differed from the Nedved *et al.* study [10] in the selection of the cases. Our selection of cases was random from our archives. Nedved *et al.* selected a broad diversity of BCC cases that included common and less common BCC subtypes.

The original reports of BCC cases included composite (49%); nodular (23%); superficial (12%); metatypical, micronodular, morpheaform and infiltrative (3%); and basosquamous and sclerosing (2%) subtypes. The prevalence of these subtypes were consistent with a study by Sexton *et al.* [12] who reviewed 1039 consecutive cases of BCC with mixed (38.6%), nodular (21%), and superficial (17.9%) subtypes.

The current study had an overall kappa of 0.18 (P<0.001), which was considered slight agreement. Nedved *et al.* reported an overall kappa of 0.30 (P<0.001), which was considered fair agreement. On the basis of these results we could conclude that the dermatopathologists in both studies have used inconsistent nomenclature when reporting BCC subtypes. Hence there is an essential need to change the classification of BCC subtyping to obtain more consistent reports.

Evaluation of individual kappa values showed moderate agreement on superficial BCC with a kappa of 0.52 (P=0.001), BCC risk assessment with a kappa of 0.50 (P=0.001), and nodular BCC with a kappa of 0.48 (P<0.001). However, Nedved *et al.* reported substantial agreement (kappa: 0.61-0.8) for superficial and high risk BCC.

There was lower agreement for the other subtypes (Table 2), which again represented different subtyping of BCC in the scientific literature. A number of dermatopathology text books consider metatypical BCC and basosquamous carcinoma to be synonymous, while other texts define them as different entities [10,13]. The term basosquamous BCC has been defined by the presence of mixed features of both BCC and SCC by two of the current study dermatopathologists. We suggest a consensus on using the high risk growth pattern which may be more useful than the exact nomenclature since, in the current study, we have moderate agreement in risk assessment BCC but fair agreement in basosquamous (kappa: 0.23, P=0.01) and metatypical subtypes.

The importance of different histological types is due to the necessity for different treatments according to the National Comprehensive Cancer Network (NCCN). Low risk BCC should be excised with 4 mm margins and high risk lesions with 10 mm margins [14]. Other nonsurgical treatment options such as cryosurgery can be used in low risk BCC such as the superficial subtype which has a cure rate of 95% to 97% [8].

The current study dermatopathologists had less agreement on each of the high risk BCC subtypes, which included the infiltrative (kappa: 0.3278), micronodular (kappa: 0.1874), and metatypical (kappa: 0.1220) subtypes. However, in terms of risk assessment with high risk BCCs in one single group or low risk BCC in another group (Table 2), the dermatopathologists showed moderate agreement with a kappa of 0.50 (P=0.001).

Nedved *et al.* suggested a reporting system which consisted of superficial, nodular, and infiltrative or high risk subtypes as the high risk group. Hence, a therapeutic algorithm would be based on these three histopathologic subtypes: superficial, nodular, and high risk BCC [10].

Although the dermatopathologists in the current study evaluated the cases with inconsistent nomenclature of the BCC subtyping, they have shown better agreement for the superficial, nodular, infiltrative or high risk BCC subtypes. Therefore,we suggest that physicians use the classification by Nedved *et al.* However further studies are needed to validate this classification.

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