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Original Research Article

ASSESSMENT OF MORPHOLOGICAL PARAMETERS DEFINING RISK STRATIFICATION IN CUTANEOUS BASAL CELL CARCINOMA. A SINGLE-CENTRE STUDY

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ABSTRACT

Background: *Basal cell carcinoma (BCC) is the most common skin malignancy worldwide, yet its clinical risk is heterogeneous and strongly influenced by histomorphological features. Data from Pakistan are limited, and local evidence is needed to inform treatment strategies based on histology-defined risk.* ***Objective:*** *To evaluate histomorphological parameters for risk stratification in cutaneous basal cell carcinoma in a Pakistani population.* ***Study Design:*** *Single-centre observational study.* ***Setting:*** *Department of Histopathology, Chughtai Lab, Pakistan.* ***Duration of Study:*** *1 March 2023 to 30 September 2024.* ***Methods:*** *Histopathology reports of 382 unique BCC specimens were retrieved from the laboratory information system (Nexus Pro). Extracted variables included age, gender, anatomical site, and maximum tumor diameter. Histological subtypes were categorized as nodular, infiltrative, superficial, keratotic, adenoid, micronodular, or mixed. Depth of invasion was measured from the reconstructed epidermal surface to the deepest tumor nest and stratified into clinically relevant groups. Adverse features, including perineural invasion (PNI), lymphovascular invasion (LVI), and ulceration, were documented. High-risk histology was defined a priori as any infiltrative or micronodular component (pure or mixed). Descriptive statistics were performed in line with STROBE guidance.* ***Results:*** *The mean age was 63.11 ± 14.48 years; 50.5% were female, and 63.9% were ≥60 years. The majority of lesions arose on the head and neck. Nodular BCC was the most common pure subtype (62.3%), followed by infiltrative (19.9%) and superficial (7.9%); mixed subtypes constituted 7.3%. Depth of invasion was ≥7 mm in 52.4% of tumors, while 36.2% measured ≥20 mm clinically. Adverse features included PNI in 6.5%, LVI in 0.5%, and ulceration in 86.9%. Overall, 25.1% of cases were classified as high-risk and 74.9% as low-risk histology.* ***Conclusion:*** *Nodular BCC was the predominant subtype, but one in four tumors exhibited high-risk histology. A substantial proportion of lesions were large (≥20 mm) or deeply invasive (≥7 mm) at presentation. Morphology-based risk stratification is practical for routine reporting and can inform surgical margins, surveillance intensity, and multidisciplinary referral decisions. Early detection, particularly for head and neck lesions, may reduce the burden of advanced disease.*

Keywords: Basal Cell Carcinoma; Depth of Invasion; Pakistan; Risk Stratification; Skin Cancer

INTRODUCTION

The increasing incidence of cutaneous basal cell carcinoma (BCC) is a pressing health concern worldwide, and particularly in Pakistan, where environmental factors, including high ultraviolet (UV) radiation exposure, contribute to a higher susceptibility to this common skin malignancy. Basal cell carcinoma accounts for approximately 80% of all non-melanoma skin cancers, rendering it the most prevalent type of skin cancer globally (1, 2). In Pakistan, the disease is primarily associated with sun exposure and other risk factors, including genetic predispositions and regional climatic conditions, necessitating an understanding of the morphological parameters influencing risk stratification (3, 4). With the mounting number of cases diagnosed each year, it has become essential to refine risk assessment tools that not only include classic clinical features but also incorporate detailed histopathological evaluations (5, 6).

Histologically, BCC can present in various forms, such as nodular, infiltrative, and adenoid subtypes, each exhibiting distinctive morphological characteristics that can inform prognosis (7, 8). Notably, characteristics like tumor growth patterns, involvement of perineural spaces, and skin ulceration have been recognized as critical elements defining the malignant potential of the carcinoma and its risk of recurrence (9, 5). The significance of these morphological features is further enhanced when viewed through the lens of Pakistani demographics, where genetic diversity and environmental factors can significantly impact the course of disease and clinical outcomes (10, 11). Recent studies emphasize the need to integrate comprehensive morphological analyses into risk stratification processes for the management of BCC. Research indicates that specific histological subtypes of BCC, like infiltrative, sclerosing, and micronodular, demonstrate aggressive biological behaviors and higher rates of tumor recurrence as compared to typical BCC (8). Enhanced understanding of the various morphological presentations, as well as their behavioral traits, could lead to more informed treatment strategies and improved patient outcomes in Pakistan, where treatment access and awareness may still be evolving (12, 6).

This study aims to assess the morphological parameters that define risk stratification for BCC in a Pakistani population. By conducting a detailed evaluation of clinical and histopathological characteristics, we hope to delineate a more precise risk stratification model tailored to local conditions. This approach not only has implications for clinical practice but may also influence public health strategies aimed at early detection and management of BCC.

METHODOLOGY

This was a single-centre, cross-sectional study conducted in the Department of Histopathology, Chughtai Lab (Pakistan). We reviewed all skin specimens reported between March 1, 2023, and September 30, 2024, that had a final diagnosis of cutaneous basal cell carcinoma (BCC). Cases were extracted through our laboratory information system (Nexus Pro). If more than one specimen came from the same lesion, we retained only the first (index) sample to avoid counting it twice. Only excisional biopsies were included. We excluded records that were missing basic details such as age, sex, histologic subtype, or at least one measure of depth or size. Ethical

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approval was obtained from the Chughtai institute of pathology (CIP) IRB before data extraction, and only de-identified information was analyzed.

From Nexus Pro, we recorded patient age at diagnosis, sex, tumor site, and the largest clinical tumor diameter noted at presentation. To make the sites easy to read and compare, we grouped them into head and neck, trunk, upper limb, lower limb, or other/unspecified categories, while keeping common sub-sites (e.g., nose, eyelid) available for description. Clinical size was categorized into practical bands (1.0–<7.0, 7.0–<11.0, 11.0–<15.0, 15.0–<20.0, 20.0–<24.9, and 24.9–85.0 mm) that reflect everyday decision points and match the distribution of our data.

On histology, each tumor was assigned a harmonized subtype (nodular, infiltrative, superficial, keratotic, adenoid, or micronodular). When more than one pattern was present, we labelled it as "mixed" (e.g., nodular + infiltrative). The maximum depth of invasion was measured from the surface granular layer to the deepest connected tumor nest. In ulcerated lesions, we drew a straight, "reconstructed" surface line across the ulcer and measured from that point, which is standard practice. Because depths were right-skewed, we grouped them into narrow, clinically meaningful ranges (1.0–<3.0, 3.0–<5.0, 5.0–<7.0, 7.0–<7.6, 7.6–<8.2, and 8.2–30.0 mm). We also recorded perineural invasion, lymphovascular invasion, and ulceration using routine, widely accepted definitions. For risk stratification, we maintained a morphology-focused and straightforward approach. Any tumor with an infiltrative, sclerosing, or micronodular component (pure or mixed) was classified as "high-risk histology." Tumors that were nodular, superficial, keratotic, or adenoid without aggressive components were classified as "low-risk histology." Other adverse features (depth of invasion, large size, ulceration, and perineural/lymphovascular invasion) were described in the results but did not alter the primary risk label; this approach maintained transparency in our analysis and aligns with common clinical thinking about aggressive BCC growth patterns.

Before analysis, we checked ranges (e.g., age, size units), confirmed outliers by a quick slide re-review when needed, and locked the dataset. Continuous variables are reported as mean ± standard deviation, depending on distribution; categorical variables are shown as counts and percentages. Analyses were performed using IBM SPSS Statistics (v26), and our work was reported following the STROBE guidance for observational studies.

RESULTS

The mean age at diagnosis is 63.11 ± 14.48 years, reflecting a predominantly older population. Sex distribution is balanced (50.5% female, 49.5% male). Age is right-skewed toward later decades, with 63.9% of individuals aged 60 years or older (26.7% in the 60–69 years age group and 37.2% in the 70 years or older group), and only 1.3% being younger than 30 years. This age profile aligns with cumulative sun-exposure risk in an elderly population. (Table 1)

predominance of head-and-neck involvement, with far fewer tumors on the trunk and extremities. This pattern is consistent with chronic ultraviolet exposure of cosmetically and functionally critical sites. (Figure 1). Figure 1 depicts the anatomic distribution of lesions and shows a clear.

Pure nodular BCC is the leading subtype (62.3%), followed by pure infiltrative (19.9%) and superficial (7.9%) patterns; keratotic, adenoid, and micronodular variants are uncommon individually. No case of sclerosing/morphoeic BCC is reported during this time period. Mixed histologies account for 7.3% of tumors, most often nodular with an infiltrative component (3.4%). The presence of infiltrative and/or micronodular components—observed as pure or mixed patterns- highlights a meaningful subset with aggressive growth characteristics relevant to risk categorization. (Table 2)

Table 1: Baseline demographics of patients with cutaneous basal cell carcinoma (n = 382)

Measure	n	% of total
Age (years), Mean ± SD	63.11 ± 14.48	
Gender		
Female	193	50.5%
Male	189	49.5%
Age group (years)		
<30	5	1.3%
30–39	12	3.1%
40–49	45	11.8%
50–59	76	19.9%
60–69	102	26.7%
≥70	142	37.2%

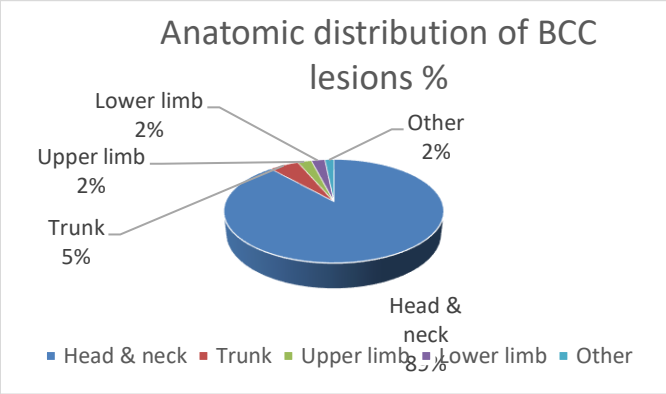

Figure 1: Anatomic distribution of BCC lesions (n = 382)

Table 2. Histopathological subtypes (harmonized) (n = 382)

Subtype	N	%
Pure subtypes		
• Nodular	238	62.3%
• Infiltrative	76	19.9%
• Superficial	30	7.9%
• Keratotic	6	1.6%
• Adenoid	3	0.8%
• Micronodular	1	0.3%
Mixed subtypes		
• Nodular + Infiltrative	13	3.4%
• Nodular + Superficial	6	1.6%
• Nodular + Micronodular	2	0.5%
• Infiltrative + Micronodular	2	0.5%
• Infiltrative + Adenoid	2	0.5%
• Nodular + Keratotic + Adenoid	3	0.8%

Table 3 presents the grouped maximum depth of invasion. Over half of tumors (52.4%) extended to a depth of ≥7.0 mm, while 16.0% measured 5.0–<7.0 mm and 13.6% were limited to 1.0–<3.0 mm. The sizeable fraction with deeper invasion underscores a morphological burden that can upstage risk in standard stratification schemas.

Table 4 reports clinical tumor size at presentation. The distribution was bimodal, with peaks at 7.0–<11.0 mm (20.9%) and 20.0–<24.9 mm (19.9%). Notably, 36.2% of lesions were ≥20 mm, while 12.3% were <7.0 mm. The appreciable number of larger tumors at first presentation suggests delayed care-seeking or indolent, late-

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recognized growth, both of which are pertinent to the high-risk designation in cosmetically sensitive areas.

Table 3. Maximum depth of invasion (grouped, mm) (n = 382)

Depth category (mm)	n	%
1.0–<3.0	52	13.6%
3.0–<5.0	69	18.1%
5.0–<7.0	61	16.0%
7.0–<7.6	69	18.1%
7.6–<8.2	67	17.5%
8.2–30.0	64	16.8%

Table 4. Clinical tumor size at presentation (grouped, mm) (n = 382)

Size category (mm)	n	%
1.0–<7.0	47	12.3%
7.0–<11.0	80	20.9%
11.0–<15.0	49	12.8%
15.0–<20.0	68	17.8%
20.0–<24.9	76	19.9%
24.9–85.0	62	16.3%

Table 5 summarizes key adverse pathological features and the resulting overall risk classification. Perineural invasion was identified in 6.5% and lymphovascular invasion in 0.5% of specimens, while ulceration was frequent (86.9%). Integrating these morphological parameters, one-quarter of cases (25.1%) were classified as high risk, and three-quarters (74.9%) as low risk. Collectively, these findings indicate that although nodular BCC predominates, a substantial minority exhibit aggressive histology, deeper invasion, larger size, or destructive surface change, features that concentrate the cohort's high-risk burden.

Table 5. Key pathological features and overall risk stratification (n = 382)

Parameter	Category	n	%
Perineural invasion	Seen	25	6.5%
	Not seen	357	93.5%
Lymphovascular invasion	Seen	2	0.5%
	Not seen	380	99.5%
Skin ulceration	Seen	332	86.9%
	Not seen	50	13.1%
Overall Risk Stratification	High risk	96	25.1%
	Low risk	286	74.9%

DISCUSSION

Basal cell carcinoma is the most common type of skin neoplasm, with its incidence increasing worldwide over the past few decades. Although mortality attributable to BCC is negligible, the disease is associated with substantial morbidity. Thus, it imposes a considerable burden on health care services. Risk factors associated with basal cell carcinoma include excessive exposure to ultraviolet radiation, non-ionizing radiation therapy, mutations in genes such as p53 and PTCH, skin types I and II, arsenic exposure, and immunosuppression (19). We designed this study to survey patients with BCC within our sphere and compare the clinical and morphological parameters that define risk stratification of BCC in our population with those reported in the literature. The current study provides essential insights into the morphological characteristics and risk stratification of cutaneous basal cell carcinoma (BCC) in a Pakistani cohort. Our findings indicate a mean age at diagnosis of 63.11 years, consistent with the trend in the global literature, where BCC predominantly affects older populations. The study by Dika et al. (13) corroborates this trend, noting that aging is a significant risk factor for non-melanoma skin cancers, with cumulative sun exposure playing a critical role in these demographics. Similarly, Wisdorf et al. (14) highlighted that higher incidences of BCC are frequently observed in older patients, which resonates with the 63.9% of our cases being 60 years old or older.

The sex distribution balance observed in our study also aligns with recent findings from regional studies, which show that BCC incidence is nearly equal between men and women. A similar trend is identified in a study by Asif et al., in which males make up 53.2% of cases, with a male-to-female ratio of 1.2:1 (17). Moreover, our data revealed that more than half (52.4%) of tumors exhibited a maximum depth of invasion of ≥7.0 mm, which is indicative of an aggressive clinical behavior. This finding is crucial, especially in the context of the morphological burden affecting patient prognosis—earlier research by Akhlaghdoust et al. (15) emphasized that deeper invasions and higher Clark's levels correlate with an increased risk of recurrence and distant metastasis. In our cohort, larger tumor sizes at presentation, with 36.2% measuring ≥20 mm, underscore the delayed detection and possible late referral patterns, highlighting an issue similar to that raised by Wisdorf et al. (14), who noted a higher proportion of larger tumors. The present study reflects a bimodal distribution of tumor sizes with notable peaks around 7.0–<11.0 mm and 20.0–<24.9 mm. Lesion size is a significant predictor of patient outcomes, as Cohen (16) reported that larger tumor diameters are frequently associated with aggressive clinical behaviors. Parts of the body exposed to sunlight are the most common sites of BCC occurrence. In our Cohort, 89.5% of BCC were in the head and neck regions, particularly on the nose, periocular areas, cheek, and forehead. The results from other international studies are also similar to ours and align with the existing literature. A study by Sonia et al. identified the face as being responsible for 66% of the lesions, primarily due to its exposure to the most significant amount of UV radiation.[18] Furthermore, the prominent ulceration rate (86.9%) among our cases suggests that the presence of ulceration, a critical adverse pathological feature addressing risk within clinical contexts, aligns with findings observed in a similar population by Safia Rana et al, where 4 out of the total 09 cases demonstrated skin ulceration (23). The incorporation of morphological parameters such as perineural and lymphovascular invasion, identified in 6.5% and 0.5% of specimens, respectively, is pivotal. These aspects are highlighted by Dika et al. (13), who noted that the presence of perineural invasion is indicative of a more aggressive disease. In our study, the single most predominant subtype was nodular BCC, accounting for 62.3% (238 cases) of the total 382 cases, a finding supported by available locoregional and international data. A similar study conducted by Afridi et al. reported that the nodular subtype is the most prevalent in a Pakistani cohort, with an overall frequency of 51% (20). Mixed morphological patterns constituted 7.8% of total cases in this study, and the nodular subtype was the leading pattern found in combinations with other histological subtypes. An extensive literature search did not reveal studies with similar details regarding mixed patterns of BCC. Morphological subtype is the most critical parameter to predict the risk of a second BCC. Nodular, superficial, adenoid, keratotic, and pigmented BCCs are considered low-risk subtypes, whereas infiltrative BCC, micronodular BCC, and sclerosing BCC are considered high-risk subtypes (21). The classification of our cases into high-risk (25.1%) and low-risk (74.9%) groups reflects the complexity and diversity of BCC histopathology in our sample, while also providing crucial information to clinicians regarding the impending risk of recurrence. A study conducted by Vornicescu et al. aimed to assess the histopathological characteristics of tumors that recurred after surgery and revealed that all recurrent tumors were assigned to the high-risk

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category for recurrence (22). This study is an original effort to investigate the morphological subtypes of BCC in the Pakistani population. We hope that the results of this study will provide benchmark data and a valuable reference for future higher-level research and genetic studies related to skin cancer. We recommend that a cancer registry be maintained to precisely record the frequency of the disease and aggressive histological features, which, if present, utterly demand attentive surveillance and subsequent action. Since BCC is a preventable disease, public awareness programs highlighting the importance of solar protection against UV radiation and the use of sunscreens should be encouraged. Seeking medical advice promptly ultimately leads to early diagnosis and effective management, which should be promoted.

CONCLUSION

Nodular BCC remains the leading subtype in our population (62.3%), and the notable presence of aggressive histological features necessitates careful monitoring and follow-up strategies tailored to local demographic profiles. The findings not only indicate a pressing need for increased awareness and early detection strategies but also suggest that multidisciplinary management approaches are vital in improving patient outcomes in the Pakistani context. Thus, this study lays a foundation for enhanced clinical pathways and further research focused on the specific morphological attributes of BCC within our region.

DECLARATIONS

Data Availability Statement
All data generated or analysed during the study are included in the manuscript.
Ethics approval and consent to participate
Approved by the department Concerned. (CIP/IRB/1172A)
Consent for publication
Approved
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Not applicable

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTION

MARIAM FATIMA
Conceived the study, collected data, performed analysis, and prepared the first draft of the manuscript
FATIMA KHALID
Assisted in data collection, literature review, and manuscript editing
MUHAMMAD AHSAN
Contributed to statistical analysis, interpretation of results, and manuscript formatting
OMAR CHUGHTAI
Provided supervision, expert guidance, and critical review of the manuscript
SAIRA RATHORE
Contributed to methodology development, data organization, and final proofreading of the manuscript
All authors read and approved the final version of the manuscript.

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