DOI: https://doi.org/10.3126/njdvl.v24i1.89756

Histopathological Subtypes of Basal Cell Carcinoma and Associated Pathological Features: A Prospective Study from Western Nepal

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Abstract

Background: Basal cell carcinoma (BCC) is the most common skin malignancy globally. Histopathological subtype influences prognosis and treatment selection, yet prospective data from Nepal remain limited.

Objectives: To determine BCC subtype distribution, describe associations between morphology and pathological parameters, and identify high-risk features relevant to treatment planning at a Western Nepal referral center.

Materials and Methods: We prospectively studied 35 consecutive histopathologically confirmed BCC cases at a tertiary care hospital in Western Nepal from September 1st, 2023 to August 31st 2025. Two observers independently reviewed hematoxylin and eosin-stained slides, evaluating subtype distribution, demographics, anatomical site, tumor depth, surgical margin status, perineural invasion, and ulceration.

Results: Nodular BCC predominated (68.6%, n=24), with pigmented nodular variant most frequent (45.7% of all cases, n=16). Male to female ratio was 1.7 to 1; mean age 64.3±9.2 years. All cases were from head and neck sites, cheek/periocular region most common (57.1%, n=20), followed by nose/ear (31.4%, n=11). High-risk subtypes (n=7, 20%) showed higher biopsy margin involvement (71.4% vs 14.3%), greater mean invasion depth (2.8±1.1 mm vs 1.4±0.6 mm), and increased ulceration (57.1% vs 17.9%) compared to low-risk subtypes.

Conclusion: Pigmented nodular BCC is the predominant subtype in Western Nepal. High-risk histopathological patterns suggested increased adverse features including higher biopsy margin involvement. These findings are consistent with previously reported associations between high-risk histological patterns and adverse pathological features; however, validation with clinical outcome data is required.

Key words: basal cell carcinoma; biopsies; Nepal; skin malignancy; surgical margins

Introduction

Basal cell carcinoma (BCC) is the most common skin malignancy, accounting for approximately 80% of non-melanoma skin cancers worldwide.[1] Despite exceptionally low metastatic potential, BCC causes substantial morbidity through progressive local tissue destruction, with recurrence rates reaching 5–20% depending on histopathological subtype.[2] Histopathological classification directly influences treatment selection and prognosis. Low-risk subtypes including nodular and superficial BCC typically respond

Date of Submission: 2025-07-06
Date of Acceptance: 2026-01-02
Date of Publication: 2026-05-01

How to cite this article
Ghimire PG, Ghimire P, Paudel R, Aryal A, Jaiswal R. Histopathological Subtypes of Basal Cell Carcinoma and Associated Pathological Features: A Prospective Study from Western Nepal: BCC Subtypes in Western Nepal. NJDVL 2026;24(1):35-40

https://doi.org/10.3126/njdvl.v24i1.89756

Funding: None
Conflict of Interest: None

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favorably to conventional surgical excision with 4 mm margins.[3] High-risk variants including infiltrative, micronodular, morpheaform, and basosquamous carcinoma show irregular infiltrative growth patterns that frequently extend beyond clinically visible borders and require wider excision margins or Mohs micrographic surgery.[3] Basal cell carcinoma exhibits several histopathological growth patterns that carry different biological behavior. Commonly recognized variants include nodular, superficial, infiltrative, micronodular, pigmented, basosquamous, and morpheaform (sclerosing) subtypes. Nodular BCC shows large basaloid tumor nests with peripheral palisading and stromal retraction. Superficial BCC demonstrates budding tumor islands arising from the epidermis with limited dermal invasion. Infiltrative and micronodular variants show small irregular tumor nests or cords infiltrating the dermis and are considered aggressive forms. Pigmented BCC demonstrates melanin deposition within tumor cells and surrounding stromal melanophages. Basosquamous carcinoma shows features of both basal cell carcinoma and squamous differentiation, while morpheaform BCC is characterized by thin tumor strands embedded within dense fibrotic stroma. Recognition of these histological patterns is clinically important because aggressive variants are associated with higher recurrence risk and may require wider surgical margins.

BCC incidence continues to rise globally due to cumulative ultraviolet radiation exposure, aging population, and enhanced diagnostic facilities.[4] In Nepal, limited published data exist characterizing BCC histopathological patterns. One retrospective study from Kathmandu documented that non-melanoma skin cancers comprised 40% of cutaneous malignancies with 67% head and neck distribution.[5] Populations in Western Nepal may face elevated risk due to intense agricultural sun exposure, though systematic data are lacking.

Our hospital serves as the principal referral center for Western Nepal. We conducted this prospective study to characterize BCC histopathological subtypes and associated pathological features consecutively. Specific objectives were to determine subtype distribution, describe associations between morphology and pathological parameters including demographics, anatomical site, depth of invasion, and margin status, and identify high-risk features relevant to treatment planning. We hypothesized that pigmented variants would be more common than in Caucasian populations given regional skin phototypes.

Materials and Methods

This prospective cross-sectional study was conducted at the Department of Pathology of a tertiary care teaching hospital in Western Nepal from September 1st, 2023 to August 31st 2025, following approval by the Institutional Review Committee (Reference: 72/080-081 dated August 14, 2023).

Inclusion criteria: Adult patients (18 years or older) with histopathologically confirmed primary BCC and complete clinical documentation including age, gender, and anatomical site.

Exclusion criteria: Recurrent BCC, specimens with inadequate tissue for subtyping due to crush artifact or insufficient sampling, and incomplete clinical records.

Specimens underwent routine formalin fixation, paraffin embedding, and sectioning at 4–5 µm thickness with hematoxylin and eosin (H&E) staining. Most specimens represented diagnostic biopsies performed prior to definitive treatment, including both incisional biopsies and small excisional biopsies depending on lesion size and clinical judgment. Because many samples were obtained primarily for diagnostic confirmation rather than therapeutic excision, margin status reflects biopsy sampling rather than definitive surgical clearance.

One consultant pathologist and one pathology resident independently reviewed all slides using an Olympus CX23 microscope (10×–40× magnification), resolving discrepancies by consensus. Histopathological subtyping followed World Health Organization (WHO) Classification of Skin Tumors 2023 criteria[6]: nodular, superficial, and infundibulocystic BCC including several variants like pigmented, infiltrative, micronodular, morpheaform/sclerosing, and basosquamous carcinoma.

The following pathological parameters were systematically evaluated:

- Tumor size: Maximum diameter in millimeters
- Pigmentation: Melanin deposition within tumor cells and/or stromal melanophages involving ≥10% of tumor area
- Perineural invasion (PNI): Tumor infiltration within nerve sheath or circumferential involvement exceeding 33% of nerve circumference[7]
- Surgical margin status: Positive (tumor at inked margin) or negative (clear margins).
- Ulceration: Loss of epithelial continuity
- Tumor depth: Vertical invasion depth measured from overlying epidermis (or ulcer base if ulcerated) to deepest tumor extension, in millimeters

Data were analyzed using SPSS version 26.0 (IBM Corporation, Armonk, NY, USA). Descriptive statistics are presented as frequencies with percentages for categorical variables and means with standard deviations (SD) for continuous variables. Ninety-five percent confidence intervals (95% CI) were calculated using the Wilson score method. Interobserver agreement was quantified using Cohen's kappa statistic.

BCC subtypes were categorized for comparative analysis as:

- Low-risk: Nodular (all variants) and superficial
- High-risk: Infiltrative, micronodular, morpheaform, and basosquamous

Due to small sample sizes in subgroups, formal statistical hypothesis testing was not performed. Comparative statistics are presented descriptively.

Results

Thirty-five patients were enrolled: 22 males and 13 females (male to female ratio 1.7 to 1; 62.9% male, 95% CI 45.8–77.9%). Ages ranged from 42 to 82 years with mean 64.3±9.2 years (95% CI 61.1–67.5), demonstrating peak incidence in the sixth to seventh decades (71.4%, n=25; 95% CI 53.7–84.9%). a wide confidence interval reflecting modest sample size.

All cases originated from the head and neck sites. Cheek and periocular regions were most common (57.1%, n=20; 95% CI 39.4–73.7%), followed by nose and ear (31.4%, n=11; 95% CI 16.9–49.3%), and forehead and scalp (11.4%, n=4; 95% CI 3.2–26.7%). Mean tumor diameter was 12.4±5.6 mm (95% CI 10.4–14.4).

Table 1. Demographic and Clinical Characteristics (n=35)

Characteristic	Number	Percentage (%)	95% CI
Gender			
Male	22	62.9	45.8–77.9
Female	13	37.1	22.1–54.2
Age Group			
40–59 years	10	28.6	14.6–46.3
60–69 years	15	42.9	26.3–60.6
≥70 years	10	28.6	14.6–46.3
Anatomical Site			
Head and neck			
Cheek/Periocular	20	57.1	39.4–73.7
Nose/Ear	11	31.4	16.9–49.3
Forehead/Scalp	4	11.4	3.2–26.7

CI = confidence interval

Nodular BCC was the predominant subtype (68.6%, n=24; 95% CI 50.8–82.8%). Pigmented nodular variant was most frequent overall, accounting for 45.7% of all cases (n=16; 95% CI 29.4–62.8%). The tissues were mostly lined by keratinized stratified squamous epithelium with surface erosion and crust with nests of atypical basaloid cells showing peripheral palisading and haphazard arrangement of cells in the center. Rare mitoses and apoptotic bodies were seen along with pigment deposition within the macrophages. Fibromyxoid stroma surrounding the nest showed artifactual clefting, thus, confirming the diagnosis as Pigmented Basal Cell Carcinoma. Pigmented nodular BCC demonstrated characteristic large tumor nests of atypical basaloid cells and melanin deposition intra as well as extra cellularly within the stromal melanophages. Non-pigmented nodular BCC including one case of rare low risk infundibulocystic variant comprised 22.9% (n=8). (Figure 1-6)

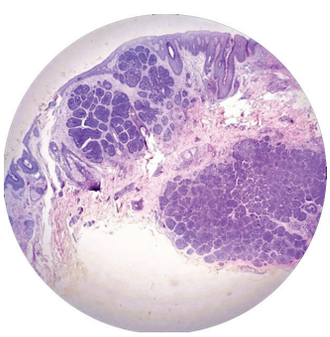

Figure 1. Micronodular BCC: Photomicrograph showing tumor cells in small pushing nodules infiltrating the deeper dermis and resection margins. (H&E stain, scanner view)

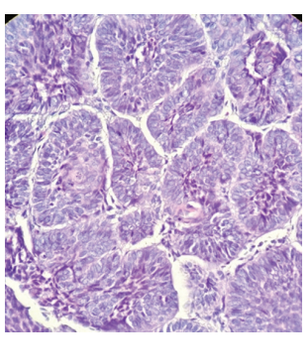

Figure 2. Superficial BCC: High power view from tumor proper showing nests of dark, hyperchromatic basaloid cells with peripheral palisading and artifactual retraction(clefting). (H&E stain x 40)

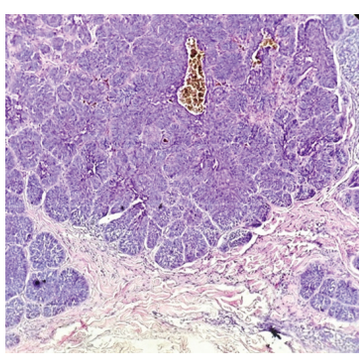

Figure 3. Pigmented nodular BCC: Photomicrograph showing melanin deposition within tumor cells. Tumor nests with rounded pushing borders and clefting seen lower down. (H&E stain x40)

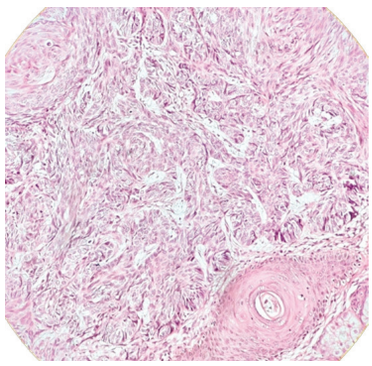

Figure 4. Infiltrative BCC: Photomicrograph showing basaloid tumor cells in small irregular tongues embedded in the fibromyxoid stroma. Hair follicle is seen lower down. (H&E stain x40).

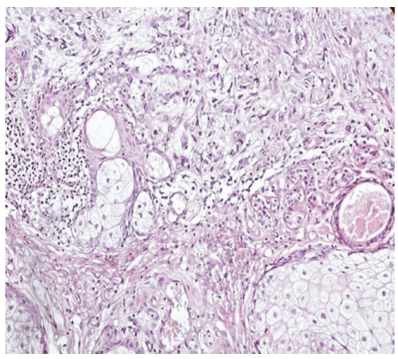

Figure 5. Infundibulocystic BCC: Photomicrograph showing keratin filled cyst with surrounding pale myxoid stroma infiltrated by anastomosing malignant basaloid cells. (H&E stain x 40)

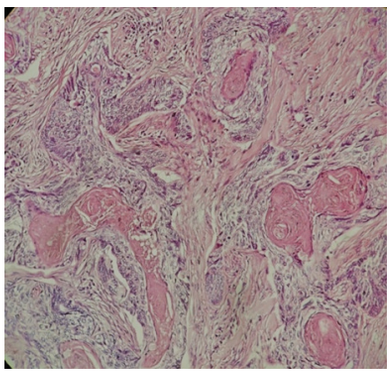

Figure 6. Basosquamous BCC: Photomicrograph showing irregular jagged cords and strands of basaloid cells with poor circumscription and deep dermal penetration lacking pushing borders and foci of neoplastic squamous differentiation. Note the irregular spiky borders contrasting with nodular BCC. (H&E stain x40).

Superficial BCC comprised 11.4% of cases (n=4; 95% CI 3.2–26.7%), characterized by budding of basaloid cells from the lower epidermal margin without deep dermal invasion. High-risk subtypes totaled 20.0% (n=7; 95% CI 9.1–36.0%): infiltrative (n=3, 8.6%), micronodular (n=2, 5.7%), and basosquamous (n=2, 5.7%). These demonstrated characteristic irregular infiltrative cords, small tumor nests, and in basosquamous cases squamoid differentiation. Interobserver agreement was substantial for overall histopathological subtype classification (Cohen's kappa 0.82; 95% CI 0.71–0.93). Minor discrepancies occurred mainly in differentiating nodular from micronodular patterns in small biopsy specimens where architectural features were limited. These cases were resolved by multiple tissue sectioning, joint slide review and consensus.

Table 2 compares pathological features between high-risk and low-risk subtypes. High-risk subtypes demonstrated higher rates of biopsy margin involvement (71.4%, 5/7) compared with low-risk subtypes (14.3%, 4/28). Mean invasion depth was greater in high-risk subtypes (2.8±1.1 mm) compared to nodular BCC (1.4±0.6 mm) and superficial BCC (0.4±0.2 mm).

Deep invasion (>2 mm) occurred in 25.7% of cases overall (n=9; 95% CI 12.0–44.9%), more commonly in high-risk subtypes (57.1%, 4/7) than low-risk subtypes (17.9%, 5/28).

Perineural invasion was rare (5.7%, n=2; 95% CI 0.7–19.2%), both cases demonstrating infiltrative morphology at head and neck sites. Ulceration was present in 25.7% of cases overall (n=9; 95% CI 12.0–44.9%), more frequently in high-risk subtypes (57.1%, 4/7) than low-risk subtypes (17.9%, 5/28).

Table 2. Histopathological Subtypes and Associated Pathological Features (n=35)

Subtype	n (%)	95% CI	Depth (mm ± SD)	Biopsy Margin Involvement n (%)	PNI n (%)	Ulceration
n (%)						
Nodular (pigmented + non-pigmented)	24 (68.6)	50.8–82.8	1.4±0.6	4 (16.7)	0 (0)	5 (20.8)
Superficial	4 (11.4)	3.2–26.7	0.4±0.2	0 (0)	0 (0)	0 (0)
High-risk*	7 (20.0)	9.1–36.0	2.8±1.1	5 (71.4)	2 (28.6)	4 (57.1)
Total	35 (100)	—	1.7 ±1.0	9 (25.7)	2 (5.7)	9 (25.7)

*High-risk subtypes: infiltrative (n=3), micronodular (n=2), basosquamous (n=2)

PNI = perineural invasion; SD = standard deviation; CI = confidence interval

Discussion

This prospective study of 35 BCC cases from Western Nepal demonstrates nodular morphology predominance (68.6%), with pigmented variants comprising nearly half of all cases (45.7%). High-risk subtypes (20%) exhibited increased adverse features including higher diagnostic biopsy margin positivity, greater invasion depth, and more frequent ulceration compared to low-risk subtypes.

Our findings confirm that nodular BCC is the most common subtype in Western Nepal, consistent with global data reporting nodular morphology prevalence of 50–80%.[3,8] However, the high frequency of pigmented variants (45.7%) likely reflects regional population characteristics. South Asian populations typically have Fitzpatrick skin phototypes III to IV, wherein melanin accumulates more readily within tumor nests and stromal melanophages.[9] We did not systematically assess patient skin phototypes, and comparative data from Caucasian populations at our institution are unavailable. Further studies correlating skin phototype with pigmented variant frequency would clarify this association.

High-risk subtypes demonstrated numerically higher positive margins in diagnostic biopsies (71.4% vs 14.3%). Several factors limit interpretation of this finding. First, these were diagnostic biopsies without planned therapeutic margins, so margin positivity may simply reflect incomplete sampling. Second, infiltrative growth patterns may be more difficult to clinically delineate, leading to smaller initial biopsies. Third, our small sample size (n=7 high-risk cases) precludes formal statistical testing. Nevertheless, this pattern aligns with established literature documenting that high-risk BCC subtypes frequently extend beyond visible clinical borders,[3] supporting existing guideline recommendations for wider excision or Mohs surgery. Importantly, we cannot determine from our data whether these cases actually required wider margins at definitive excision or experienced higher recurrence rates. Clinical outcome studies are needed to validate treatment recommendations in our population.

High-risk subtypes also demonstrated approximately twice the invasion depth of nodular BCC (2.8 mm vs 1.4 mm) and higher frequencies of ulceration.

In our study, there was an exclusive head and neck distribution (100%) that exceeds typical published rates of 70-80%. This may reflect referral patterns to our tertiary center or regional sun exposure patterns in Western Nepal's agricultural communities. [10] High-risk subtypes similarly occurred exclusively at head and neck sites (100%, 7/7), consistent with the overall distribution. Nasal involvement present in 31.4% of all cases presents particular therapeutic challenges due to limited soft tissue depth and cosmetic prominence. Our study strengths include prospective consecutive enrollment, standardized WHO 2023 classification, dual independent review with excellent reproducibility (kappa 0.82), and comprehensive pathological documentation. Important limitations must be acknowledged. First, the modest sample size (n=35) with few high-risk subtype cases (n=7, some subtypes n=2) limits statistical power and subtype-specific interpretation. Confidence intervals are wide, and formal comparative statistics could not be performed. Second, margin assessment reflects diagnostic biopsies rather than therapeutic excisions, limiting clinical inference about adequate treatment margins. Third, absence of clinical outcome data including treatment modalities, definitive surgical margins achieved, and recurrence rates prevents validation of treatment recommendations. Fourth, single-center referral patterns may introduce selection bias. Fifth, routine H&E evaluation without immunohistochemistry limits additional insights, though this reflects standard practice at most institutions. Our findings align with international guidelines supporting risk-stratified treatment approaches.[3,11] It is considered that for nodular and superficial BCC, a standard 4 mm excision margins are appropriate. When high-risk features including infiltrative, micronodular, morpheaform, or basosquamous morphology, depth greater than 2 mm, or perineural invasion are identified on diagnostic biopsy or Mohs micrographic surgery, guidelines recommend wider margins (≥6 mm).[11]

However, several contextual factors require consideration. Mohs surgery is not widely available in Nepal, and cost may be prohibitive for many patients. Alternative approaches for high-risk cases in resource-limited settings include staged excision with frozen section margin assessment, wider planned margins (6–10 mm) with permanent section evaluation, and close clinical follow-up with low threshold for re-excision. The feasibility and outcomes of these approaches in Western Nepal warrant prospective evaluation. When high-risk features are identified on biopsy, definitive surgical planning should account for the likelihood of more extensive disease than clinically apparent, and clear communication between clinicians and pathologists is essential.

Several research directions would strengthen the evidence base for BCC management in Nepal. First, multicenter collaboration could achieve adequate sample sizes for subtype-specific analysis with formal statistical testing. Second, prospective outcome studies linking histopathological features with treatment modalities, achieved surgical margins, and recurrence rates are critically needed. Third, systematic assessment of environmental and occupational risk factors including sun exposure and skin phototype specific to Terai populations would clarify epidemiology. Fourth, cost-effectiveness analysis comparing Mohs surgery with alternative approaches in resource-limited settings would inform policy. Fifth, digital pathology validation for subtype classification may enhance diagnostic consistency.[12] This systematic

characterization establishes baseline histopathological data for Western Nepal BCC, providing foundation for evidence-based, context-appropriate treatment protocols.

Conclusion

Pigmented nodular basal cell carcinoma was the predominant histopathological subtype (45.7%) at our Western Nepal institution, likely reflecting regional population skin phototypes. High-risk morphological patterns demonstrated greater invasion depth, and ulceration, and biopsy margin involvment compared to low-risk subtypes. However, interpretation is limited by the small sample size and absence of treatment and follow-up data. These findings provide preliminary regional data and emphasize the importance of recognizing aggressive histological patterns during pathological evaluation. Larger multicenter studies incorporating clinical outcomes and recurrence data are required to clarify the true clinical significance of these observations in Nepali populations.

Acknowledgments

The authors acknowledge the pathology faculty members and technical staff of the Department of Pathology for their support in this study.

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