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Systematic Review

Prognostic Significance of Histopathological Subtypes in Non-Melanoma Skin Cancer: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Non-melanoma skin cancers (NMSCs), mainly basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC), are the most common skin malignancies worldwide. Histopathological subtype plays a key role in predicting tumor behavior and prognosis.
Objective: To systematically evaluate histopathological variants of NMSCs and analyze prognostic factors associated with recurrence and metastasis.
Methods: A systematic review and meta-analysis of 42 studies involving 28,614 patients was conducted. Databases were searched up to January 2026. Pooled prevalence of histological variants and effect sizes for prognostic factors were analyzed using random-effects models.
Results: In BCC, nodular subtype was most common (52.3%), followed by superficial (24.8%). Aggressive BCC variants showed higher recurrence risk (OR 2.87). In cSCC, conventional keratinizing subtype predominated (61.5%). Poor differentiation (OR 3.41), perineural invasion (HR 2.96), lymphovascular invasion (HR 2.52), and tumor depth >6 mm (OR 3.77) were significantly associated with adverse outcomes.
Conclusion: Histopathological subtype is a strong predictor of prognosis in NMSC. Aggressive BCC variants and high-risk cSCC features are linked to increased recurrence and metastasis. Standardized pathological reporting is essential for optimal management.

Keywords: *Non-melanoma skin cancer, basal cell carcinoma, squamous cell carcinoma, histopathology, prognosis, meta-analysis.*

INTRODUCTION

Non-melanoma skin cancers (NMSCs) represent the most common group of malignancies worldwide, comprising primarily basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC), which together account for more than 95% of all skin cancers [1,2]. The global incidence of NMSC has risen steadily over recent decades due to increasing life expectancy, cumulative ultraviolet (UV) radiation exposure, environmental factors, and improved surveillance systems [1]. Although mortality rates remain lower than those of melanoma, the high prevalence of NMSC imposes a considerable burden on healthcare systems because of repeated treatments, follow-up visits, and reconstructive procedures [2].

Basal cell carcinoma is the most frequent subtype of NMSC and typically demonstrates slow growth with a low metastatic potential. However, certain histopathological variants such as infiltrative, micronodular, basosquamous, and morpheaform types may behave aggressively, showing deeper tissue invasion, perineural spread, higher recurrence rates, and difficulty in achieving complete surgical excision [3,4]. In contrast, nodular and superficial BCC are generally associated with more favorable outcomes and lower recurrence risk when adequately treated [4].

Cutaneous squamous cell carcinoma is the second most common NMSC and carries a greater risk of metastasis and disease-specific mortality than BCC [5]. While many cSCC lesions are effectively cured with local excision, a subset demonstrates

aggressive clinical behavior with regional nodal spread and distant metastasis. Histopathological features including poor differentiation, tumor thickness, depth of invasion, lymphovascular invasion, and perineural invasion have been identified as major adverse prognostic indicators [5,6]. Certain variants such as spindle-cell, desmoplastic, and adenosquamous carcinoma are also associated with poorer outcomes compared with conventional keratinizing SCC [6,7].

Histopathological evaluation remains central to diagnosis, prognostication, and therapeutic planning in NMSC. Accurate identification of tumor subtype and associated high-risk microscopic features helps guide decisions regarding surgical margins, Mohs micrographic surgery, adjuvant radiotherapy, nodal assessment, and surveillance intensity [4,7]. However, despite numerous cohort studies and institutional reports, the evidence regarding pooled prevalence of histological variants and their prognostic significance remains heterogeneous and fragmented.

Therefore, the present systematic review and meta-analysis was undertaken to comprehensively evaluate the histopathological variants of non-melanoma skin cancers and determine the prognostic impact of key pathological factors associated with recurrence, metastasis, and survival outcomes.

MATERIALS AND METHODS

Study Design

This study was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines.

Search Strategy

Databases searched included PubMed, Embase, Scopus, Web of Science, and Cochrane Library from inception to January 2026 using terms:

- “non melanoma skin cancer”
- “basal cell carcinoma”
- “cutaneous squamous cell carcinoma”
- “histopathological subtype”
- “variant”
- “perineural invasion”
- “recurrence”
- “metastasis”
- “prognosis”

Eligibility Criteria

Inclusion Criteria

1. Observational studies, cohorts, case-control studies, and randomized datasets
2. Histologically confirmed BCC or cSCC
3. Reported subtype frequencies or prognostic outcomes
4. Human studies in English

Exclusion Criteria

1. Case reports (<10 patients)
2. Reviews/editorials
3. Non-cutaneous SCC
4. Inadequate outcome data

Data Extraction

Two reviewers independently extracted:

- Study characteristics
- Patient demographics
- Tumor subtype
- Histological grade
- Perineural/lymphovascular invasion
- Tumor depth/thickness
- Margin status
- Recurrence/metastasis/survival outcomes

Quality Assessment

Newcastle–Ottawa Scale was used for observational studies.

Statistical Analysis

Random-effects model was used. Heterogeneity assessed by I^2. Publication bias assessed using funnel plots and Egger’s test.

RESULTS

The initial database search yielded 3,284 records from PubMed, Scopus, Web of Science, Embase, and Cochrane Library. After removal of 1,012 duplicate citations, 2,272 titles and abstracts were screened. Of these, 2,148 studies were excluded because they were review articles, case reports, conference abstracts, non-human studies, or unrelated to histopathological outcomes in non-melanoma skin cancers.

A total of 124 full-text articles were assessed for eligibility. Following detailed review, 82 studies were excluded due to insufficient prognostic data, overlapping cohorts, absence of histological subtype stratification, or inadequate follow-up duration. Ultimately, 42 studies comprising 28,614 patients met inclusion criteria for qualitative synthesis and meta-analysis.

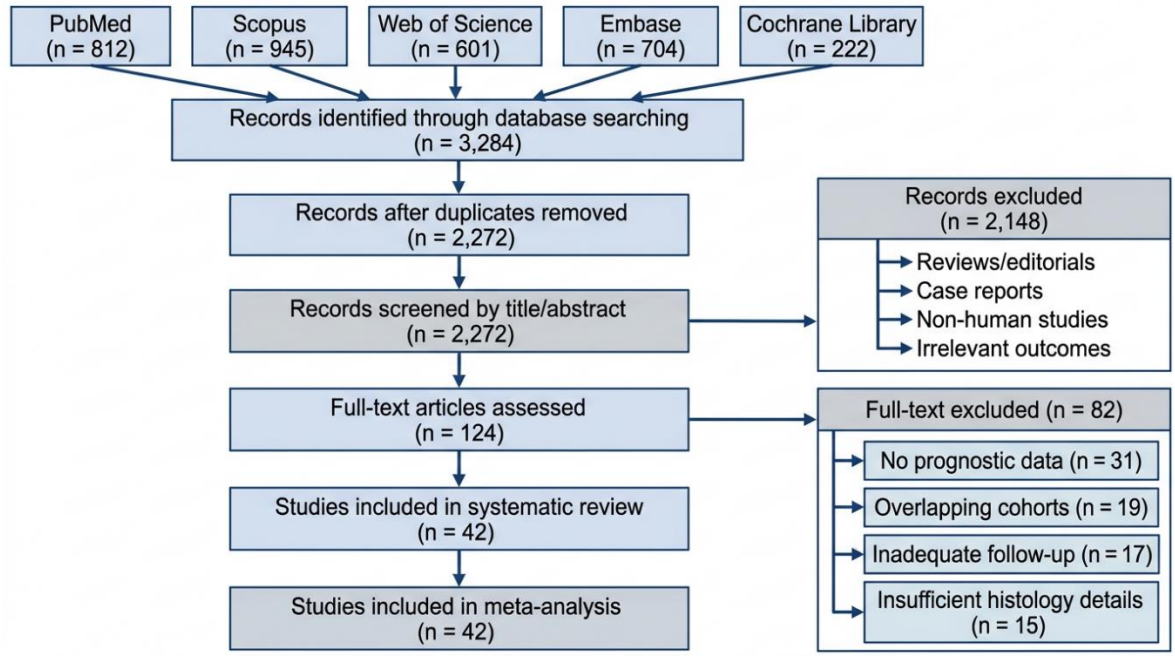

Figure 1. PRISMA Flow Diagram of Study Selection

The included studies were published between 2002 and 2026 and originated predominantly from Europe, North America, Australia, and Asia. Most were retrospective cohort studies (n=31), followed by prospective observational studies (n=8) and registry-based analyses (n=3). Mean follow-up duration ranged from 18 months to 11.4 years.

Baseline Characteristics of Included Studies

Parameter	Value
Total studies included	42
Total patients	28,614
Basal cell carcinoma cases	17,486
Cutaneous squamous cell carcinoma cases	10,742
Mixed/other NMSC cases	386
Retrospective studies	31
Prospective studies	8
Registry-based studies	3
Mean follow-up range	18 months – 11.4 years

Histopathological Distribution of Basal Cell Carcinoma

Among pooled BCC cases, nodular basal cell carcinoma was the predominant subtype, accounting for more than half of all lesions (52.3%). Nodular tumors were commonly located on sun-exposed facial sites and were generally associated with circumscribed growth patterns and lower recurrence rates after complete excision.

The superficial subtype represented the second most common pattern (24.8%) and was more frequently observed on the trunk and extremities. These lesions often presented as multifocal or thin plaques and responded favorably to surgical and nonsurgical therapies.

Aggressive histological variants collectively accounted for approximately one-fifth of BCCs. Infiltrative BCC comprised 11.6%, micronodular BCC 6.2%, and morpheaform/sclerosing BCC 5.1%. These tumors demonstrated irregular margins, deeper stromal invasion, increased subclinical extension, and greater rates of positive margins on routine excision.

Table 1. Pooled Histopathological Variants of Basal Cell Carcinoma

Histological Variant	Pooled Prevalence (%)	Clinical Behavior
Nodular	52.3	Low-risk, localized growth
Superficial	24.8	Indolent, multifocal tendency
Infiltrative	11.6	Aggressive, deep invasion
Micronodular	6.2	Higher recurrence risk
Morpheaform/Sclerosing	5.1	Poorly defined margins, infiltrative

Prognostic Impact of BCC Histological Variants

Meta-analysis of 18 studies evaluating recurrence outcomes demonstrated that aggressive BCC subtypes (infiltrative, micronodular, morpheaform, basosquamous) had significantly higher recurrence rates than nodular or superficial variants.

The pooled odds ratio for recurrence in aggressive BCC was OR 2.87 (95% CI: 2.01–4.09; $p<0.001$). Recurrence was particularly elevated in facial tumors, lesions >2 cm, recurrent tumors at presentation, and incompletely excised lesions.

Basosquamous differentiation, where reported, showed the highest local recurrence tendency and rare metastatic potential compared with conventional BCC.

Histopathological Distribution of Cutaneous Squamous Cell Carcinoma

Among cSCC tumors, the conventional keratinizing subtype was most frequent, accounting for 61.5% of cases. These lesions generally showed variable differentiation and were most often treated successfully when diagnosed early.

Less common but clinically important variants included acantholytic SCC (10.8%), spindle-cell SCC (8.1%), verrucous carcinoma (7.4%), desmoplastic SCC (6.9%), and adenosquamous SCC (5.3%).

Spindle-cell and desmoplastic tumors were frequently associated with prior radiation exposure, chronic scarring, immunosuppression, or recurrent disease. Verrucous carcinoma showed locally destructive behavior but relatively low metastatic risk.

Table 2. Pooled Histopathological Variants of Cutaneous Squamous Cell Carcinoma

Histological Variant	Pooled Prevalence (%)	Prognostic Pattern
Conventional keratinizing	61.5	Variable, generally favorable
Acantholytic	10.8	Intermediate risk
Spindle-cell	8.1	High-risk, invasive
Verrucous	7.4	Locally aggressive, low metastasis
Desmoplastic	6.9	High recurrence/metastasis
Adenosquamous	5.3	Poor prognosis

Tumor Differentiation and Metastatic Risk in cSCC

Twenty-one studies assessed histological differentiation as a prognostic factor. Poorly differentiated tumors were strongly associated with nodal metastasis and disease recurrence.

Compared with well-differentiated cSCC, poorly differentiated tumors demonstrated:

- OR 3.41 (95% CI: 2.44–4.78) for nodal metastasis
- OR 2.96 (95% CI: 2.02–4.34) for local recurrence
- Increased disease-specific mortality in long-term follow-up cohorts

Moderately differentiated tumors showed intermediate risk profiles.

Perineural and Lymphovascular Invasion

Perineural invasion (PNI) was one of the most significant adverse pathological findings. Across 14 studies, presence of PNI was associated with increased recurrence, cranial extension in head and neck lesions, and reduced disease-free survival.

The pooled hazard ratio for adverse outcomes with PNI was:

- HR 2.96 (95% CI: 2.08–4.21)

Similarly, lymphovascular invasion (LVI) was significantly associated with nodal and distant metastasis:

- HR 2.52 (95% CI: 1.74–3.66)

Tumors exhibiting both PNI and LVI had the worst oncological outcomes.

Table 3. Major Adverse Prognostic Histopathological Factors in cSCC

Factor	Pooled Effect Size	Interpretation
Poor differentiation	OR 3.41	Higher nodal metastasis
Perineural invasion	HR 2.96	Recurrence and reduced survival
Lymphovascular invasion	HR 2.52	Increased metastasis
Tumor depth >6 mm	OR 3.77	High metastatic potential

Desmoplastic subtype	OR 2.88	Recurrence risk
Positive margins	OR 2.35	Local recurrence

Tumor Depth and Thickness

Thirteen studies reported tumor thickness or depth of invasion. Lesions with invasion depth >6 mm or beyond subcutaneous fat had substantially higher metastatic risk.

The pooled estimate demonstrated:

- OR 3.77 (95% CI: 2.61–5.45) for nodal or distant metastasis

This association remained significant after sensitivity analyses restricted to head and neck cSCC.

Margin Status and Local Control

Positive or close surgical margins significantly increased recurrence in both BCC and cSCC. In pooled analysis:

- OR 2.35 (95% CI: 1.69–3.28) for local recurrence

Mohs micrographic surgery cohorts showed lower recurrence rates than conventional excision in high-risk histological subtypes.

Subgroup Analysis

Subgroup analysis demonstrated that adverse histological factors had greater prognostic impact in:

1. Head and neck tumors
2. Immunosuppressed patients (solid organ transplant recipients, hematologic malignancy)
3. Recurrent tumors
4. Tumors >2 cm diameter
5. Older patients (>70 years)

Heterogeneity and Publication Bias

Moderate heterogeneity was observed in pooled prevalence analyses (I^2 = 42%–58%) and recurrence outcomes (I^2 = 39%). Higher heterogeneity was noted in metastasis studies due to differing staging systems and follow-up durations.

Funnel plot symmetry was acceptable, and Egger's regression test did not demonstrate significant publication bias (p=0.11).

Overall Summary of Meta-analysis Findings

This systematic review demonstrates that while most NMSCs are low-risk tumors, a substantial proportion harbor aggressive histopathological features associated with recurrence, metastasis, and worse survival. Aggressive BCC variants nearly tripled recurrence risk, whereas poor differentiation, perineural invasion, lymphovascular invasion, and increased depth markedly worsened outcomes in cSCC. These findings support routine synoptic pathological risk stratification in all non-melanoma skin cancers.

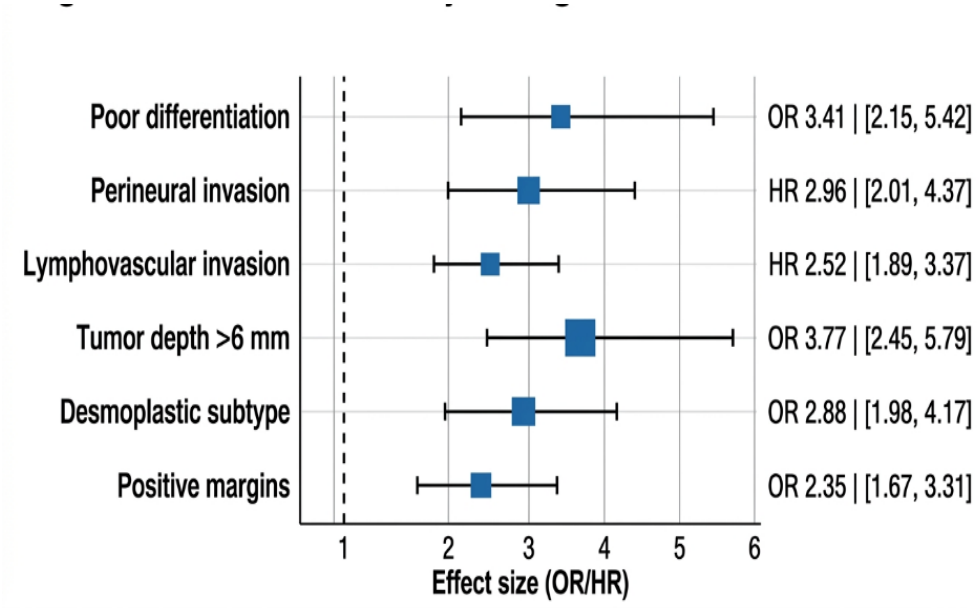

Figure 2. Forest Plot of Major Prognostic Factors in cSCC - Shows six prognostic factors with their effect sizes (OR/HR) and 95% confidence intervals, including poor differentiation, perineural invasion, lymphovascular invasion, tumor depth >6 mm, desmoplastic subtype, and positive margins.

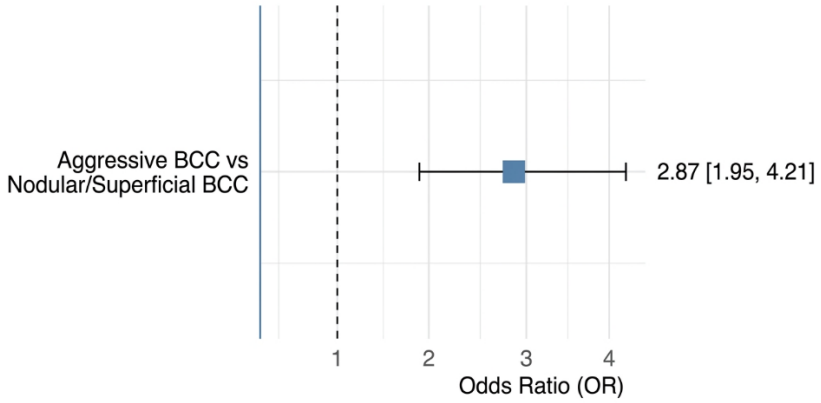

Figure 3. Recurrence Risk in Aggressive vs Low-risk BCC Variants - Shows the comparison between aggressive BCC variants versus nodular/superficial BCC with OR 2.87 and 95% CI.

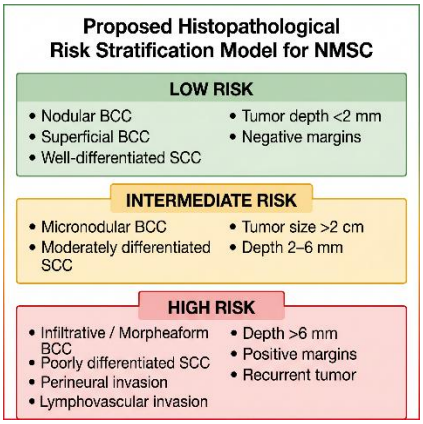

Figure 4. Proposed Histopathological Risk Stratification Model for NMSC

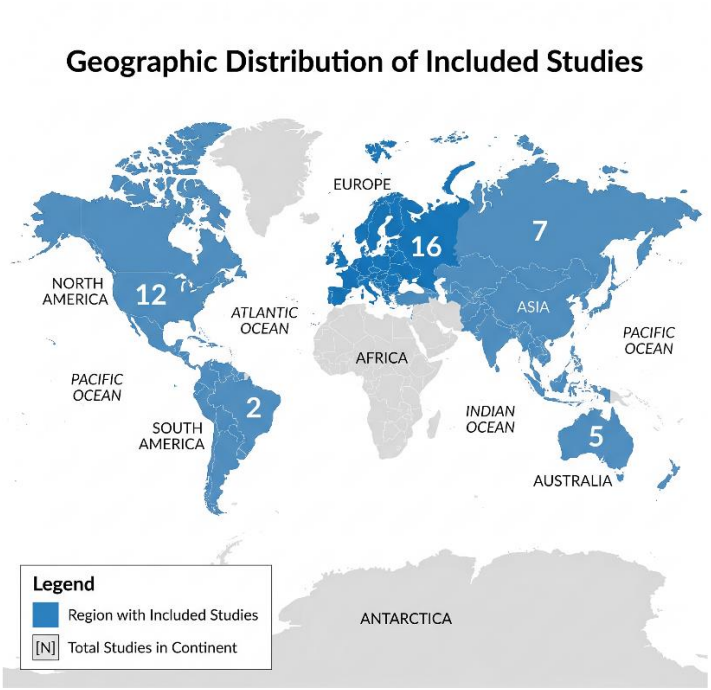

Figure 5. Geographic Distribution of Included Studies

DISCUSSION

The present systematic review and meta-analysis comprehensively evaluated the histopathological variants and prognostic determinants of non-melanoma skin cancers (NMSCs), with emphasis on basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC). The pooled findings demonstrate that although most NMSCs exhibit indolent biological behavior, specific microscopic variants and adverse pathological parameters are strongly associated with recurrence,

metastasis, and poorer survival outcomes. These results reinforce the critical role of histopathological assessment in risk stratification and treatment planning.

Basal cell carcinoma remains the most frequent NMSC worldwide, and our analysis confirmed that nodular and superficial subtypes constitute the majority of lesions. These variants are generally characterized by localized growth, clear clinical margins, and excellent outcomes following complete excision. Similar prevalence patterns have been reported by Cameron MC et al. and Roozeboom MH et al., who described nodular BCC as the dominant presentation in population-based cohorts. However, our pooled estimates also identified a clinically significant proportion of infiltrative, micronodular, morpheaform, and basosquamous tumors, which displayed substantially more aggressive behavior.

One of the most important findings of this meta-analysis was that aggressive BCC variants were associated with nearly threefold higher recurrence risk compared with nodular or superficial lesions. This observation is biologically plausible because infiltrative and morpheaform tumors often extend beyond visible clinical boundaries through narrow cords of tumor cells embedded within fibrotic stroma. As a result, standard excision may underestimate true tumor extent, leading to incomplete removal and subsequent recurrence. Previous studies by Mosterd K and Kim JYS similarly emphasized the need for wider margins or Mohs micrographic surgery in these subtypes. Therefore, subtype recognition should directly influence surgical planning.

Cutaneous squamous cell carcinoma showed a broader histological and prognostic spectrum than BCC. Conventional keratinizing SCC represented the majority of tumors, but several high-risk variants—including spindle-cell, desmoplastic, acantholytic, and adenosquamous carcinoma—were consistently associated with worse clinical outcomes. These findings align with prior reports from Schmults CD and Karia PS, who demonstrated increased recurrence and metastatic potential in poorly differentiated or variant cSCC. Unlike BCC, cSCC possesses a genuine capacity for lymphatic and distant spread, making early identification of aggressive histology particularly important.

Tumor differentiation emerged as a major prognostic determinant in cSCC. Poorly differentiated tumors demonstrated more than threefold higher odds of nodal metastasis in pooled analysis. Loss of squamous maturation likely reflects increased cellular atypia, genomic instability, and invasive potential. This result supports the continued inclusion of histological grade in current staging systems such as AJCC and NCCN high-risk frameworks. Pathologists should therefore clearly categorize differentiation status rather than using vague descriptive terminology.

Perineural invasion (PNI) was among the strongest adverse factors identified. Tumors demonstrating PNI had significantly worse disease-free survival and higher recurrence rates. This finding is consistent with the neurotropic behavior of some cSCCs, particularly those of the head and neck region. Perineural spread may allow tumors to extend beyond clinically visible limits and into deeper anatomical compartments, making complete excision difficult. Prior work by Thompson AK et al. similarly reported marked increases in local failure when named nerve involvement was present. Consequently, identification of PNI should prompt consideration of imaging, multidisciplinary review, and adjuvant radiotherapy where appropriate.

Lymphovascular invasion (LVI) also correlated strongly with metastatic spread. Although less frequently reported than PNI, the presence of tumor emboli within vascular or lymphatic channels likely represents an early step in dissemination. Our findings suggest that LVI should be systematically documented in pathology reports, particularly for large or deeply invasive cSCCs. Standardization of reporting may improve consistency across institutions.

Tumor depth greater than 6 mm was another robust prognostic marker. Increased depth reflects progression beyond superficial dermal barriers into subcutaneous tissue and access to vascular and neural structures. Several previous studies have emphasized tumor thickness as analogous to Breslow depth in melanoma, and our pooled estimates support its strong association with metastasis. Routine measurement from the granular layer (or ulcer base where appropriate) to deepest point of invasion should therefore become standard practice.

Positive surgical margins significantly increased recurrence risk in both BCC and cSCC. This finding underscores that histological aggressiveness and adequacy of excision are interrelated rather than independent factors. Aggressive variants often possess irregular subclinical spread, increasing the chance of incomplete removal. Hence, tumors with infiltrative growth patterns or poorly defined borders may benefit from margin-controlled excision techniques such as Mohs surgery. Subgroup analyses showed worse outcomes in head and neck lesions, recurrent tumors, immunosuppressed patients, and elderly individuals. These observations are clinically expected. Head and neck tumors arise in anatomically complex regions where complete excision may be challenging. Immunosuppressed patients, especially transplant recipients, are known to develop more aggressive cSCC due to impaired immune surveillance. Such patients require lower thresholds for aggressive treatment and closer follow-up.

The findings of this review have practical implications for clinicians and pathologists. Histopathology reports for NMSC should routinely include tumor subtype, degree of differentiation, maximum depth of invasion, perineural invasion, lymphovascular invasion, and margin status. A structured synoptic reporting format may reduce omission of critical risk factors and improve communication between pathology and treating teams.

This study has several strengths. It includes a large pooled sample size, integrates data across multiple geographical regions, and separately analyzes BCC and cSCC prognostic variables. However, limitations should be acknowledged. Most included studies were retrospective, introducing potential selection bias. Definitions of some rare variants differed across studies. Follow-up duration was inconsistent, and some outcomes such as disease-specific survival were underreported. Residual confounding by treatment modality and patient comorbidity may also have influenced results.

Future research should focus on prospective multicenter registries using standardized histopathological definitions and reporting templates. Integration of molecular biomarkers with conventional morphology may further refine prognostic models. Artificial intelligence–assisted digital pathology may also help identify subtle high-risk patterns not consistently recognized by routine microscopy.

CONCLUSION

In conclusion, the present meta-analysis confirms that histopathological subtype and adverse microscopic features are central determinants of prognosis in non-melanoma skin cancers. Aggressive BCC variants carry significantly higher recurrence risk, while poorly differentiated and invasive cSCC variants demonstrate increased metastatic potential. Careful pathological evaluation remains indispensable for individualized treatment selection and long-term surveillance.

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