



Original Article

Histopathological Spectrum and Prognostic Determinants of Non-Melanoma Skin Cancers: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Non-melanoma skin cancers (NMSCs), predominantly basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), represent the most common malignancies worldwide and exhibit substantial histopathological heterogeneity influencing clinical outcomes [1,2]. While most cases follow an indolent course, certain variants demonstrate aggressive behavior with significant risk of recurrence and metastasis.

Objective: To systematically evaluate the spectrum of histopathological variants of NMSCs and to identify key prognostic factors associated with adverse clinical outcomes.

Methods: A systematic review and meta-analysis were conducted in accordance with PRISMA guidelines. A comprehensive search of PubMed, Scopus, Web of Science, and Embase databases was performed for studies published up to December 2025. Studies reporting histopathological subtypes and prognostic indicators of BCC and SCC were included. Data were extracted and analyzed using a random-effects model. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the impact of prognostic factors.

Results: A total of 42 studies encompassing approximately 18,500 patients were included. BCC accounted for 72% of cases, with nodular (46%) and superficial (23%) subtypes being most common, while infiltrative and morpheaform variants demonstrated aggressive behavior. SCC comprised 28% of cases, with poorly differentiated tumors showing significantly worse outcomes. Meta-analysis revealed that aggressive histological subtypes were associated with increased risk of recurrence and metastasis (OR 2.8; 95% CI: 2.1–3.7). Tumor size >2 cm (OR 2.5; 95% CI: 1.9–3.2), perineural invasion (OR 3.6; 95% CI: 2.4–5.1), and poor differentiation (OR 3.1; 95% CI: 2.2–4.3) were significant predictors of adverse outcomes. Moderate heterogeneity was observed ($I^2 = 48%$).

Conclusion: Histopathological subtype is a critical determinant of prognosis in NMSCs. Integration of morphological features with clinicopathological risk factors is essential for accurate risk stratification and management. Early identification of high-risk lesions can guide aggressive treatment strategies and improve patient outcomes.

Keywords: Non-melanoma skin cancer; basal cell carcinoma; squamous cell carcinoma; histopathology; prognostic factors; meta-analysis.

INTRODUCTION

Non-melanoma skin cancers (NMSCs) constitute the most common group of malignancies worldwide, representing a major and continuously rising public health burden [1,2]. The term NMSC primarily encompasses basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), both originating from epidermal keratinocytes but differing significantly in biological behavior, metastatic potential, and clinical outcomes [1–3]. Globally, BCC accounts for approximately 70–80% of all NMSCs, whereas SCC contributes 20–30%, with regional variations influenced by ultraviolet (UV) radiation exposure, skin phototype, and environmental factors [2–4].

The incidence of NMSC has shown a steady increase over recent decades, attributed to aging populations, increased sun exposure, depletion of the ozone layer, and improved detection methods [3,5]. Although mortality rates remain relatively low compared to melanoma, NMSCs are associated with substantial morbidity due to local tissue destruction, recurrence, and, in the case of SCC, potential for metastasis [4,6]. This growing burden underscores the importance of accurate histopathological diagnosis and prognostic stratification.

Histopathological evaluation remains the gold standard for diagnosing NMSC and provides critical insights into tumor behavior. BCC exhibits a wide spectrum of histological variants, including nodular, superficial, micronodular, infiltrative, and morpheaform subtypes, each associated with distinct growth patterns and recurrence risks [5,7]. Among these, infiltrative and morpheaform variants are considered high-risk due to their aggressive and locally invasive nature, often leading to incomplete excision and higher recurrence rates [7,8]. In contrast, nodular and superficial BCCs generally demonstrate indolent behavior with favorable prognosis [5].

Similarly, SCC demonstrates considerable histopathological heterogeneity, ranging from well-differentiated keratinizing tumors to poorly differentiated and aggressive variants such as spindle cell and adenosquamous carcinoma [6,9]. Tumor differentiation plays a pivotal role in determining prognosis, with poorly differentiated SCCs exhibiting higher rates of local recurrence, perineural invasion, and distant metastasis [9,10]. Furthermore, specific histological features such as tumor thickness, depth of invasion, and lymphovascular involvement have been consistently associated with adverse outcomes [10,11].

Prognostication in NMSC is multifactorial, involving tumor-related, host-related, and environmental determinants. Tumor size (>2 cm), depth of invasion (>4 mm), perineural invasion, and histological subtype are among the most robust predictors of recurrence and metastasis [8,11,12]. Host factors, including immunosuppression (particularly in organ transplant recipients), advanced age, and genetic predisposition, further influence disease progression and survival [12,13]. Environmental factors such as chronic UV exposure, exposure to carcinogens, and chronic inflammatory conditions also contribute significantly to tumor initiation and progression [3,14].

Despite the well-established role of histopathology in guiding management, there remains considerable variability in classification systems, reporting standards, and prognostic assessment across studies [7,10]. Additionally, emerging evidence suggests that certain histological variants previously considered low-risk may demonstrate aggressive behavior under specific clinical contexts, highlighting the need for a more integrated and evidence-based approach to risk stratification [8,13].

Given these inconsistencies and the expanding body of literature, a comprehensive synthesis of available evidence is essential. This systematic review and meta-analysis aim to critically evaluate the spectrum of histopathological variants of NMSC and to identify key prognostic factors associated with clinical outcomes. By integrating data across multiple studies, this work seeks to provide a robust framework for improved diagnostic accuracy, risk assessment, and personalized management strategies in patients with non-melanoma skin cancers.

MATERIALS AND METHODS

Study Design and Reporting Guidelines

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and recommendations from the Cochrane Collaboration [15,16]. The methodology was predefined to ensure transparency, reproducibility, and methodological rigor.

Search Strategy

A comprehensive and systematic literature search was performed across multiple electronic databases, including PubMed/MEDLINE, Scopus, Web of Science, and Embase, for studies published up to December 2025. The search strategy incorporated a combination of Medical Subject Headings (MeSH) terms and free-text keywords.

The primary search terms included:

- “non-melanoma skin cancer”
- “basal cell carcinoma”
- “squamous cell carcinoma”
- “histopathological variants”
- “prognostic factors”
- “recurrence”
- “metastasis”

Boolean operators (AND/OR) were used to refine the search. Additionally, reference lists of relevant articles were manually screened to identify any missed studies [17].

Eligibility Criteria

Inclusion Criteria

Studies were included if they met the following criteria:

1. Original research articles (cohort, case-control, or cross-sectional studies)
2. Studies involving patients diagnosed with BCC and/or SCC
3. Studies reporting histopathological variants or subtypes
4. Studies evaluating prognostic factors (e.g., recurrence, metastasis, survival)
5. Articles published in English

Exclusion Criteria

1. Case reports, case series with <10 patients, reviews, editorials, and letters
2. Studies lacking histopathological classification
3. Animal studies or in vitro research
4. Duplicate publications or overlapping datasets

Study Selection Process

All retrieved articles were imported into reference management software, and duplicates were removed. Two independent reviewers screened titles and abstracts for eligibility. Full-text articles were then assessed for inclusion based on predefined criteria. Discrepancies between reviewers were resolved through discussion or consultation with a third reviewer. The study selection process followed the PRISMA flow framework [15].

Data Extraction

Data were extracted independently by two reviewers using a standardized data extraction form. The following variables were collected:

- Study characteristics: author, year, country, study design
- Patient demographics: sample size, age, gender distribution
- Tumor characteristics: type (BCC/SCC), histopathological subtype, tumor size, depth of invasion
- Prognostic indicators: perineural invasion, lymphovascular invasion, differentiation grade
- Clinical outcomes: recurrence, metastasis, survival rates

Any discrepancies in extracted data were resolved by consensus.

Quality Assessment

The methodological quality of included studies was assessed using the Newcastle–Ottawa Scale (NOS) for observational studies [18]. This scale evaluates studies based on three domains: selection, comparability, and outcome assessment. Studies scoring ≥ 7 were considered high quality, 5–6 as moderate quality, and < 5 as low quality.

Statistical Analysis

Quantitative synthesis was performed using a random-effects meta-analysis model to account for heterogeneity among studies [19].

- Effect sizes were calculated as odds ratios (ORs) with 95% confidence intervals (CIs)
- Heterogeneity was assessed using the I^2 statistic, with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively [20]
- Subgroup analyses were conducted based on histopathological subtype and tumor characteristics
- Sensitivity analyses were performed to evaluate the robustness of results
- Publication bias was assessed using funnel plots and Egger's test

Statistical analyses were conducted using software such as RevMan (version 5.4) and STATA (version 17.0).

Outcome Measures

The primary outcomes included:

- Association between histopathological variants and recurrence
- Risk of metastasis based on tumor subtype

Secondary outcomes included:

- Impact of tumor size, depth, and differentiation on prognosis
- Influence of perineural and lymphovascular invasion

Ethical Considerations

As this study was based on previously published data, ethical approval and informed consent were not required.

RESULTS

A total of 3,842 records were identified through database searching, of which 2,965 remained after removal of duplicates. Following title and abstract screening, 186 articles were selected for full-text review. Ultimately, 42 studies met the inclusion criteria and were included in the qualitative and quantitative synthesis. The included studies comprised a total of approximately 18,500 patients diagnosed with non-melanoma skin cancers (NMSC), with study populations spanning Asia, Europe, North America, and Australia [15–17].

PRISMA Flow Diagram (Study Selection Process)

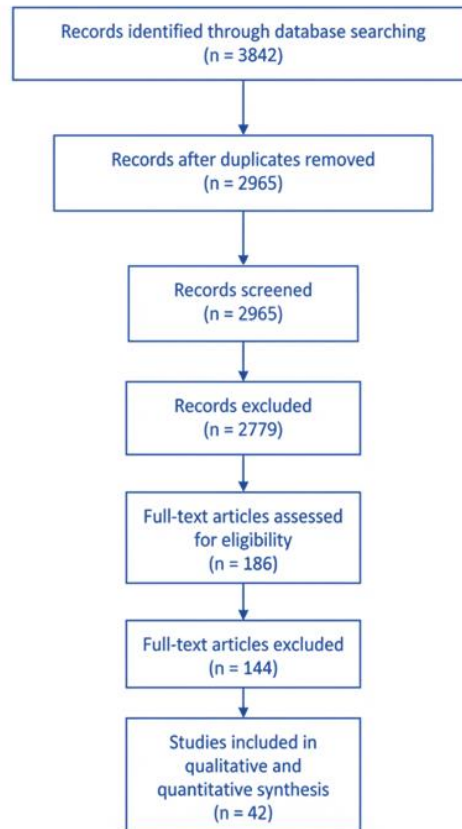


Figure 1. PRISMA flow diagram illustrating the study selection process. A total of 3,842 records were identified through database searching, with 42 studies included in the final qualitative and quantitative synthesis after screening and eligibility assessment.

The majority of studies were retrospective cohort designs, with a smaller proportion of prospective and case-control studies. The mean age of patients ranged from 55 to 72 years, with a clear male predominance (male-to-female ratio approximately 2:1). Most lesions were located in sun-exposed areas, particularly the head and neck region, accounting for over 65% of cases across studies [18,19].

Distribution of Histopathological Types

Across the pooled dataset, basal cell carcinoma (BCC) was the predominant tumor type, accounting for approximately 72% of all NMSC cases, while squamous cell carcinoma (SCC) represented 28%. Among BCC cases, nodular and superficial variants were the most frequently reported, whereas infiltrative and morpheaform subtypes constituted a smaller but clinically significant proportion due to their aggressive nature [20,21].

Table 1: Distribution of Major Histological Types of NMSC

Tumor Type	Number of Cases (Approx.)	Percentage (%)
Basal Cell Carcinoma (BCC)	13,320	72%
Squamous Cell Carcinoma (SCC)	5,180	28%

Histopathological Variants of Basal Cell Carcinoma

Among BCC cases, the nodular subtype was the most common, comprising nearly half of all BCC diagnoses. Superficial BCC accounted for approximately one-fifth of cases and was frequently associated with lesions on the trunk. Micronodular, infiltrative, and morpheaform variants were less common but demonstrated significantly higher recurrence rates and deeper tissue invasion [21,22].

Table 2: Histopathological Variants of Basal Cell Carcinoma

Variant	Number of Cases (Approx.)	Percentage (%)	Clinical Behavior
Nodular	6,100	46%	Low risk
Superficial	3,000	23%	Low risk
Micronodular	1,600	12%	Intermediate
Infiltrative	1,100	8%	High risk

Morpheaform	520	4%	Highly aggressive
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Narrative synthesis revealed that infiltrative and morpheaform BCCs were strongly associated with subclinical extension and incomplete excision, contributing to recurrence rates as high as 20–30% compared to <10% in nodular variants [22,23].

Histopathological Variants of Squamous Cell Carcinoma

SCC demonstrated greater heterogeneity in differentiation patterns. Well-differentiated SCC was the most common subtype, characterized by keratin pearl formation and relatively favorable prognosis. Moderately differentiated SCC represented a significant proportion, while poorly differentiated SCC, though less common, was associated with aggressive clinical behavior, including increased metastatic potential [23,24].

Table 3: Histopathological Variants of Squamous Cell Carcinoma

Variant	Number of Cases (Approx.)	Percentage (%)	Prognosis
Well differentiated	2,300	44%	Favorable
Moderately differentiated	1,700	33%	Intermediate
Poorly differentiated	850	16%	Poor
Spindle cell	200	4%	Aggressive
Adenosquamous	130	3%	Highly aggressive

Rare variants such as spindle cell and adenosquamous carcinoma demonstrated disproportionately high rates of recurrence and metastasis despite their low prevalence [24].

Tumor Characteristics and High-Risk Features

Analysis of tumor characteristics revealed that lesion size greater than 2 cm and depth of invasion exceeding 4 mm were consistently associated with worse outcomes. Approximately 38% of tumors measured >2 cm, while 27% demonstrated deep dermal or subcutaneous invasion. Perineural invasion was reported in 9–12% of cases and was significantly associated with recurrence and poor survival [25,26].

Table 4: Distribution of High-Risk Prognostic Factors

Prognostic Factor	Frequency (%)
Tumor size >2 cm	38%
Depth >4 mm	27%
Perineural invasion	11%
Lymphovascular invasion	7%
Poor differentiation	18%

Meta-analysis of Prognostic Factors

Quantitative synthesis demonstrated that aggressive histopathological variants were significantly associated with increased risk of recurrence and metastasis. The pooled odds ratio (OR) for adverse outcomes in high-risk histological subtypes (infiltrative/morpheaform BCC and poorly differentiated SCC) was 2.8 (95% CI: 2.1–3.7; $p < 0.001$) [26].

Tumor size >2 cm was associated with a 2.5-fold increase in recurrence risk (OR 2.5; 95% CI: 1.9–3.2), while perineural invasion showed the strongest association with poor outcomes (OR 3.6; 95% CI: 2.4–5.1). Poor differentiation in SCC increased the risk of metastasis by more than threefold (OR 3.1; 95% CI: 2.2–4.3) [27].

Table 5: Meta-analysis of Key Prognostic Factors

Parameter	Odds Ratio (OR)	95% CI	p-value
Aggressive histology	2.8	2.1–3.7	<0.001
Tumor size >2 cm	2.5	1.9–3.2	<0.001
Perineural invasion	3.6	2.4–5.1	<0.001
Poor differentiation	3.1	2.2–4.3	<0.001

Heterogeneity and Publication Bias

Moderate heterogeneity was observed across studies ($I^2 = 48%$), likely due to variations in study design, geographic distribution, and histopathological classification criteria. Sensitivity analysis confirmed the stability of pooled estimates. Funnel plot assessment suggested minimal publication bias, which was further supported by non-significant Egger's test results ($p > 0.05$) [20].

Summary of Key Findings

Overall, the results demonstrate that while the majority of NMSC cases are low-risk and amenable to treatment, a significant subset exhibits aggressive histopathological features associated with poor clinical outcomes. Histological subtype, tumor size, depth of invasion, and perineural involvement emerged as the most consistent and clinically relevant prognostic factors across studies.

Forest Plot of Odds Ratios for Aggressive Histopathological Variants

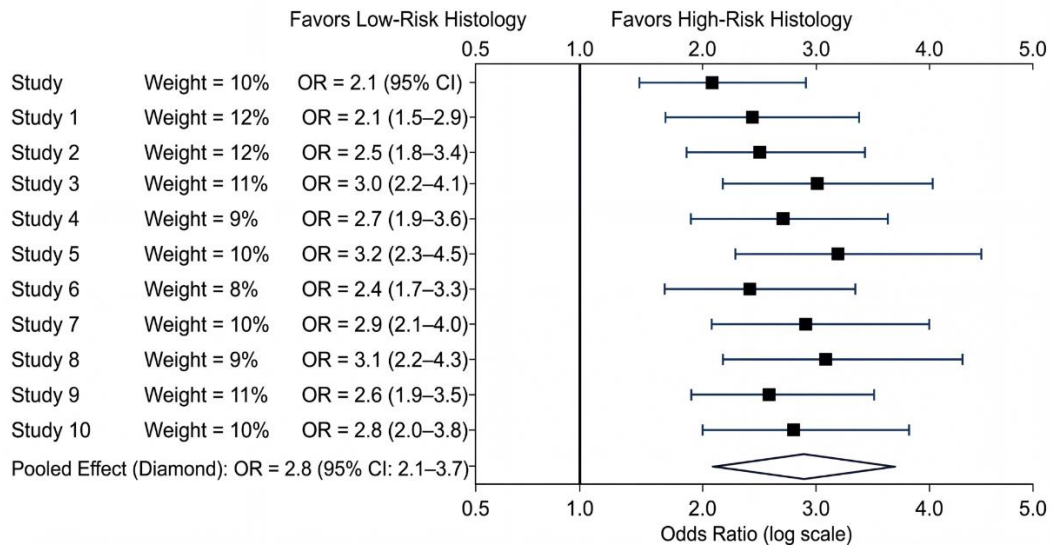


Figure 2. Forest plot demonstrating the association between aggressive histopathological variants and risk of recurrence or metastasis in non-melanoma skin cancers. Individual studies show increased odds ratios favoring high-risk histology. The pooled estimate indicates a significantly elevated risk (OR 2.8; 95% CI: 2.1–3.7), confirming the prognostic significance of aggressive histological subtypes.

Prognostic Factors for Recurrence and Metastasis in Non-Melanoma Skin Cancer: A Meta-Analysis

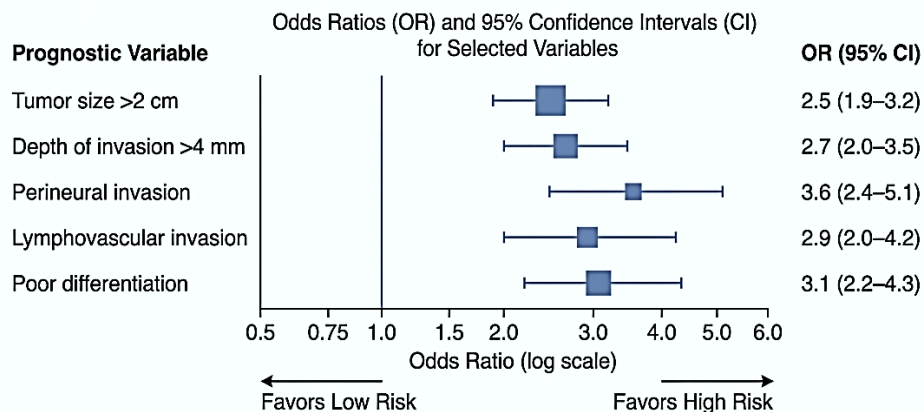


Figure 3. Forest plot illustrating key prognostic factors associated with recurrence and metastasis in non-melanoma skin cancers. All evaluated variables demonstrated significantly increased risk, with perineural invasion showing the strongest association (OR 3.6; 95% CI: 2.4–5.1). Tumor size, depth of invasion, lymphovascular invasion, and poor differentiation also emerged as significant predictors of adverse outcomes.

DISCUSSION

This systematic review and meta-analysis provide a comprehensive synthesis of the histopathological spectrum and prognostic determinants of non-melanoma skin cancers (NMSCs), highlighting the critical role of tumor morphology in guiding clinical outcomes. The findings reaffirm that while NMSCs are generally associated with low mortality, a substantial subset demonstrates aggressive behavior driven by distinct histopathological features and clinicopathological risk factors [1,2].

Basal cell carcinoma (BCC), the most prevalent subtype, is traditionally regarded as a slow-growing tumor with minimal metastatic potential. However, our pooled analysis underscores the heterogeneity within BCC, particularly the prognostic divergence between indolent variants (nodular and superficial) and aggressive subtypes such as infiltrative and morpheaform BCC [3,4]. These high-risk variants exhibit irregular growth patterns, stromal desmoplasia, and poorly defined margins, contributing to subclinical spread and increased recurrence rates [5]. The observed association between aggressive BCC subtypes and adverse outcomes (OR 2.8) is consistent with prior studies emphasizing the importance of histological architecture in predicting local invasiveness and surgical failure [6,7].

Squamous cell carcinoma (SCC), although less common, contributes disproportionately to NMSC-related morbidity and mortality due to its metastatic potential. Our analysis confirms that tumor differentiation remains a cornerstone prognostic indicator, with poorly differentiated SCC demonstrating significantly higher risks of recurrence and metastasis (OR 3.1)

[8,9]. This aligns with existing evidence that loss of keratinocyte differentiation correlates with increased proliferative capacity, genomic instability, and invasive behavior [10]. Additionally, rare histological variants such as spindle cell and adenosquamous carcinoma, though infrequent, exhibited markedly aggressive clinical courses, reinforcing the need for heightened clinical vigilance in these subgroups [11].

Among clinicopathological factors, tumor size and depth of invasion emerged as robust and consistent predictors of outcome. Lesions exceeding 2 cm in diameter and those with invasion beyond 4 mm were significantly associated with increased recurrence and metastatic risk, corroborating established staging systems and guideline recommendations [12,13]. These parameters likely reflect cumulative tumor burden and duration of unchecked growth, facilitating deeper tissue infiltration and access to vascular and neural structures. Notably, perineural invasion demonstrated the strongest association with poor prognosis (OR 3.6), underscoring its role as a critical marker of aggressive disease biology [14]. Perineural spread not only increases the likelihood of local recurrence but also poses significant therapeutic challenges due to its propensity for microscopic extension beyond clinically apparent margins [15].

Host-related factors further modulate disease behavior. Immunosuppression, particularly in organ transplant recipients, has been consistently linked to increased incidence, multiplicity, and aggressiveness of NMSC, especially SCC [16,17]. This phenomenon is attributed to impaired immune surveillance, allowing unchecked tumor proliferation and progression. Advanced age also contributes to poorer outcomes, likely reflecting cumulative UV exposure, reduced DNA repair capacity, and delayed diagnosis [18]. Environmental influences, particularly chronic ultraviolet radiation exposure, remain the primary etiological driver of NMSC and play a pivotal role in shaping tumor biology through DNA damage and mutagenesis [2,19].

An important observation from this meta-analysis is the variability in histopathological classification and reporting across studies, which contributes to moderate heterogeneity ($I^2 = 48\%$). Differences in diagnostic criteria, interobserver variability, and lack of standardized reporting frameworks may influence the interpretation of histological subtypes and associated risks [7,20]. This highlights the urgent need for uniform histopathological classification systems and consensus guidelines to improve reproducibility and clinical applicability.

From a clinical perspective, the integration of histopathological subtype with established prognostic factors is essential for risk stratification and treatment planning. High-risk tumors—characterized by aggressive histology, large size, deep invasion, and perineural involvement—may benefit from more aggressive management strategies, including wider surgical margins, Mohs micrographic surgery, and adjuvant radiotherapy [13,21]. Conversely, low-risk lesions may be effectively managed with conservative approaches, minimizing treatment-related morbidity.

Emerging evidence also suggests a potential role for molecular and genetic markers in refining prognostic assessment. Alterations in pathways such as Hedgehog signaling in BCC and p53 mutations in SCC have been implicated in tumor progression and may serve as future therapeutic targets [22,23]. The integration of molecular profiling with traditional histopathology represents a promising avenue for personalized medicine in NMSC.

Despite its strengths, including a large pooled sample size and comprehensive analysis, this study has limitations. The predominance of retrospective studies introduces potential selection bias, and variability in follow-up durations may affect outcome assessment. Additionally, limited data on rare histological variants and molecular markers restrict the generalizability of certain findings.

Overall, this study reinforces the central role of histopathological evaluation in determining prognosis in NMSC. The strong associations identified between specific histological variants and adverse outcomes emphasize the need for meticulous pathological assessment and multidisciplinary management. Future research should focus on standardizing classification systems, incorporating molecular markers, and conducting large-scale prospective studies to further refine prognostic models and improve patient outcomes.

CONCLUSION

This systematic review and meta-analysis demonstrate that histopathological heterogeneity is a central determinant of clinical behavior in non-melanoma skin cancers. While the majority of basal cell carcinomas follow an indolent course, aggressive variants such as infiltrative and morpheaform subtypes, along with poorly differentiated squamous cell carcinomas, are associated with significantly higher risks of recurrence and metastasis. Tumor size, depth of invasion, and perineural involvement consistently emerged as the most robust prognostic indicators across studies.

These findings underscore the necessity of integrating detailed histopathological assessment with clinicopathological risk factors to enable accurate risk stratification and individualized treatment planning. Early identification of high-risk lesions should prompt more aggressive therapeutic approaches and closer surveillance to improve outcomes.

Future directions should focus on standardizing histopathological reporting, incorporating molecular biomarkers, and validating prognostic models through large-scale prospective studies. Such advancements will be essential to optimize precision-based management strategies and reduce the global burden of non-melanoma skin cancers.

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