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Molecular and clinicopathological predictors of cervical lymph node metastasis in oral squamous cell carcinoma: A narrative review

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Abstract

Cervical lymph node metastasis (CLNM) remains the principal determinant of survival in oral squamous cell carcinoma (OSCC), conferring significant reductions in disease-specific and overall survival even in early-stage disease. Despite advances in imaging and surgical staging, accurate identification of occult nodal involvement in clinically node-negative patients continues to represent a major clinical challenge. This narrative review synthesizes contemporary evidence on clinicopathological and molecular predictors of CLNM in OSCC, with emphasis on biological determinants that may refine risk-adapted neck management. A structured literature search of PubMed, Scopus, and Web of Science was conducted, prioritizing high-quality cohort studies, meta-analyses, and translational investigations evaluating histopathological parameters, molecular alterations, tumor microenvironment features, and integrative predictive models. Among clinicopathological factors, depth of invasion, lymphovascular invasion, perineural invasion, tumor budding, and infiltrative invasion patterns consistently demonstrate strong associations with nodal metastasis. Molecular drivers include epithelial–mesenchymal transition, activation of the phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin signaling pathway, hypoxia-mediated angiogenesis and lymphangiogenesis, immune checkpoint upregulation, and dysregulated non-coding RNAs. Emerging multivariable models that integrate pathological and molecular determinants demonstrate improved predictive performance compared to conventional tumor–node–metastasis staging. Collectively, CLNM reflects a coordinated biological process involving invasive tumor architecture and molecular reprogramming. Incorporation of validated biological predictors into routine pathological assessment may support precision-based neck management and enhance oncologic stratification in OSCC.

Keywords: Oral squamous cell carcinoma; Cervical lymph node metastasis; Depth of invasion; Tumor budding; Epithelial–mesenchymal transition; Precision neck management

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1. Introduction

Oral squamous cell carcinoma (OSCC) represents the predominant histologic subtype of oral cavity malignancies and remains a substantial contributor to global cancer burden.[1,2] Despite advances in surgical techniques, radiotherapy, and systemic therapies, survival

improvement has been modest over recent decades.[2] This limited progress is largely attributed to locoregional recurrence and cervical lymph node metastasis (CLNM), which remain the most critical determinants of outcome.

Among all prognostic variables, the presence of CLNM consistently confers the greatest impact on survival. Nodal involvement reduces disease-specific and overall survival by approximately 40–50%, independent of primary tumor size.[3] Furthermore, nodal metastasis increases the risk of distant dissemination and complicates therapeutic planning. Therefore, accurate prediction of cervical lymph node status is central to optimizing treatment strategies in OSCC.

Management of the clinically node-negative (cN0) neck remains controversial. Randomized trials and meta-analyses have demonstrated improved regional control and survival with elective neck dissection (END) in selected early-stage OSCC patients.[4] However, a considerable proportion of patients undergoing END ultimately demonstrate no pathological nodal metastasis, exposing them to potential surgical morbidity without therapeutic benefit. Conversely, observation strategies carry the risk of delayed detection of occult nodal disease, which may adversely affect prognosis.[4]

Conventional risk assessment has historically relied on tumor size and anatomical staging systems, including the American Joint Committee on Cancer (AJCC) tumor–node–metastasis (TNM) classification.[5,6] The incorporation of depth of invasion (DOI) into the 8th edition TNM system has improved prognostic stratification.[6] Nevertheless, tumor size alone does not fully reflect metastatic potential. Increasing evidence suggests that nodal dissemination is driven by a combination of invasive tumor characteristics and underlying molecular alterations.

Histopathological factors, such as DOI, lymphovascular invasion (LVI), perineural invasion (PNI), tumor budding, and pattern of invasion, have demonstrated consistent associations with CLNM.[7-11] These parameters provide insight into tumor aggressiveness beyond anatomical extent. In parallel, molecular mechanisms—including epithelial–mesenchymal transition (EMT), activation of the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) signaling pathway, hypoxia-mediated processes, and immune modulation—have been implicated in metastatic progression.[12-18]

Given the complexity of metastatic biology, reliance on a single parameter is unlikely to achieve optimal predictive accuracy. Integration of clinicopathological variables with molecular determinants may offer a more refined framework for risk stratification and personalized neck management. This narrative review critically evaluates established and emerging predictors of CLNM in OSCC and discusses their potential implications for precision-based oncologic care.

2. Methodological framework

This review adopts a narrative methodological approach to synthesize heterogeneous evidence spanning histopathology, molecular oncology, tumor immunology, and translational research related to CLNM in OSCC.[8,9] A narrative design was selected due to the conceptual objective of integrating mechanistic insights with clinicopathological predictors, which were often evaluated across diverse study designs and analytical frameworks.

A structured literature search was conducted using PubMed, Scopus, and Web of Science databases. Search strategies incorporated combinations of the following key terms: "oral squamous cell carcinoma," "cervical lymph node metastasis," "depth of invasion," "tumor budding," "lymphovascular invasion," "epithelial–mesenchymal transition," "PI3K/AKT/mTOR," "hypoxia," and "immune checkpoints." Only English-language publications were considered.

Literature published between January 2000 and January 2026 was considered. Inclusion criteria comprised original cohort studies, systematic reviews, and meta-analyses evaluating clinicopathological or molecular predictors of CLNM in OSCC.[4,8] Exclusion criteria included case reports, non-human studies, conference abstracts without full text, and studies lacking explicit analysis of nodal outcomes. When multiple publications addressed overlapping cohorts, the most comprehensive or methodologically robust study was prioritized.[4,8]

An example search string used in PubMed was: ("oral squamous cell carcinoma" AND "cervical lymph node metastasis") AND ("depth of invasion" OR "tumor budding" OR "epithelial–mesenchymal transition" OR "PI3K/AKT/mTOR" OR "hypoxia" OR "immune checkpoint"). This approach was designed to capture both established clinicopathological predictors and emerging molecular determinants of nodal dissemination.[8,19]

Priority was given to systematic reviews, meta-analyses, multicenter cohort studies, and translational investigations that examined clinicopathological or molecular predictors of nodal metastasis.[4,8] When multiple studies addressed similar variables, preference was given to those incorporating multivariable statistical analyses or demonstrating external validation.

Studies were considered high quality if they included

multivariable analyses adjusting for established prognostic variables, clearly defined nodal endpoints, and adequate sample sizes (generally >100 patients where feasible).[8,19] Preference was given to studies reporting hazard ratios or odds ratios with corresponding confidence intervals to enhance interpretability and comparability of effect estimates.

Given the integrative and hypothesis-generating nature of this review, a formal Preferred Reporting Items for Systematic Reviews and Meta-Analysis-guided systematic review methodology was not applied. Instead, emphasis was placed on biological plausibility, methodological robustness, and clinical applicability in the selection and synthesis of evidence.[4,8]

3. Clinicopathological predictors of cervical lymph node metastasis

3.1. Depth of invasion

Depth of invasion is widely regarded as one of the most robust and clinically relevant predictors of CLNM in OSCC.[10,11] In contrast to conventional tumor thickness measurements, DOI specifically quantifies the perpendicular distance from the reconstructed basement membrane of the adjacent normal mucosa to the deepest point of tumor infiltration. This distinction is critical, as exophytic growth patterns may overestimate tumor thickness without accurately reflecting invasive potential.

The incorporation of DOI into the 8th edition of the AJCC TNM staging system reflects accumulating evidence supporting its prognostic significance.[6,20] Numerous cohort studies, including recent validation analyses, have demonstrated a progressive increase in the likelihood of occult nodal metastasis with increasing DOI values.[10,11,20] Several investigators have proposed cutoff thresholds of 3–5 mm to inform decisions regarding END in early-stage tumors, particularly in cN0 patients.[4,10,11]

Despite its recognized utility, certain methodological challenges remain. Variability in specimen orientation, tissue shrinkage, and interpretation of the mucosal reference line may contribute to interobserver differences in DOI measurement.[10] Furthermore, DOI alone does not fully capture qualitative aspects of tumor invasion, such as infiltrative growth patterns or stromal interaction, which may also influence metastatic behavior. Consequently, while DOI represents a cornerstone parameter in risk assessment, it may be most informative when interpreted in conjunction with additional histopathological and molecular indicators.

3.2. Lymphovascular and perineural invasion

Lymphovascular invasion and PNI represent direct histopathological evidence of tumor dissemination pathways and are consistently associated with adverse oncologic outcomes in OSCC.[10,11] Unlike surrogate indicators of invasiveness, such as tumor size, LVI, and PNI, which provide morphological confirmation of active tumor infiltration into anatomical conduits that facilitate regional spread.

Lymphovascular invasion reflects the presence of intraluminal tumor emboli within lymphatic or blood vessels and has been independently correlated with increased risk of CLNM, locoregional recurrence, and reduced survival.[10] The identification of LVI suggests early access of tumor cells to the lymphatic system, thereby increasing the likelihood of occult nodal involvement even in cN0 patients.

Perineural invasion, characterized by tumor cell invasion along or around nerve sheaths, is similarly indicative of aggressive biological behavior.[11] Beyond its association with local recurrence and pain, PNI has been linked to higher rates of nodal metastasis and poorer disease control. Mechanistically, PNI reflects enhanced migratory capacity and interaction with neural microenvironmental factors, which may promote tumor progression and dissemination.

Importantly, the prognostic impact of LVI and PNI is magnified when present alongside increased DOI, high-grade tumor budding, and infiltrative patterns of invasion. In such contexts, these features contribute to cumulative metastatic risk and frequently influence decisions regarding END and adjuvant therapy.

Despite their clinical relevance, variability in pathological reporting and interobserver interpretation can affect reproducibility. Therefore, standardized diagnostic criteria and consistent reporting practices are essential to ensure reliable incorporation of LVI and PNI into integrated risk stratification models.

3.3. Tumor budding and pattern of invasion

Tumor budding is characterized by the presence of isolated single tumor cells or small clusters (typically fewer than five cells) at the invasive front and is increasingly recognized as a reproducible marker of aggressive biological behavior in OSCC.[11,21] Histologically, tumor budding reflects partial loss of epithelial cohesion and acquisition of migratory capacity, features that are closely linked to EMT processes.[20,22]

Multiple studies have demonstrated that high-grade

tumor budding is significantly associated with CLNM, local recurrence, and reduced overall survival.[11,20] Importantly, budding provides insight into the dynamic interaction between tumor cells and the surrounding stromal microenvironment, capturing invasive potential that may not be adequately reflected by tumor size alone. In this context, tumor budding serves as a morphological indicator of early metastatic competence rather than merely a descriptive histopathological finding.

Tumor budding assessment methods vary across studies, with some using hotspot counting under high-power fields and others applying standardized criteria such as those proposed in the International Tumor Budding Consensus Conference. Most contemporary studies adopt hotspot-based evaluation at × 20 magnification, categorizing budding into low- and high-grade groups based on defined cut-off values.[4,20] However, heterogeneity in assessment techniques and threshold definitions may affect inter-study comparability and reproducibility.

Similarly, the pattern of invasion at the tumor–host interface has been shown to possess independent prognostic value. Infiltrative growth patterns, particularly Yamamoto–Kohama types 4C and 4D, are consistently associated with increased nodal dissemination and adverse outcomes.[23] These patterns are characterized by diffuse, cord-like, or satellite tumor infiltration into adjacent tissues, indicating reduced structural containment and enhanced invasive capacity.

Collectively, tumor budding and infiltrative growth patterns complement DOI by capturing qualitative aspects of tumor aggressiveness.[11,21] Their integration into routine pathological assessment may enhance risk stratification for occult nodal metastasis beyond conventional staging parameters.

3.4. Histological grade and tumor thickness

Conventional histological grading, based on the degree of keratinization, nuclear pleomorphism, and mitotic activity, has been incorporated into prognostic assessment in OSCC. However, when evaluated independently, histological grade demonstrates limited predictive accuracy for CLNM.[19] Although poorly differentiated tumors tend to exhibit more aggressive clinical behavior, grade alone does not consistently discriminate between patients with and without occult nodal involvement.

Importantly, the prognostic value of histological grade appears to increase when considered alongside other adverse pathological features, such as increased DOI, LVI, PNI, and tumor budding.[19] This observation supports the concept that metastatic risk reflects cumulative biological aggressiveness rather than a single morphological parameter.

Tumor thickness, previously used as a surrogate measure of invasive potential, has largely been superseded by DOI. Unlike tumor thickness, DOI accounts for the anatomical reference of the mucosal basement membrane and more accurately reflects true infiltrative growth.[6] Multiple studies have demonstrated the superior prognostic performance of DOI compared to tumor thickness in predicting nodal metastasis and survival outcomes.[6]

In contemporary practice, histological grade and tumor thickness retain descriptive value but are insufficient as standalone indicators for guiding neck management decisions. Their optimal utility lies within integrated multivariable models that combine quantitative invasion metrics with molecular and microenvironmental determinants of metastatic competence.

A summary of principal clinicopathological predictors of CLNM in OSCC is presented in Table 1.

4. Molecular predictors of cervical lymph node metastasis

4.1. Epithelial–mesenchymal transition

Epithelial–mesenchymal transition represents a central biological mechanism underlying tumor invasion and metastatic dissemination in OSCC.[12,13] Through EMT, epithelial tumor cells progressively lose cell–cell adhesion and apico-basal polarity while acquiring mesenchymal characteristics that enhance motility and invasive capacity. This phenotypic shift is mediated by transcription factors, such as Snail, Slug, Twist, and zinc finger E-box binding homeobox, which repress epithelial markers and promote cytoskeletal remodeling.[12]

In OSCC, reduced expression of E-cadherin and increased expression of mesenchymal markers, including vimentin, have been correlated with tumor budding, infiltrative growth patterns, and CLNM.[12,13,24] These molecular alterations provide a biological explanation for the morphological features observed at the invasive front. Thus, EMT serves as a mechanistic bridge linking histopathological aggressiveness with metastatic competence.

Importantly, EMT is not a binary process but exists along a dynamic spectrum. Partial or hybrid EMT states may enable tumor cells to retain proliferative capacity while acquiring migratory properties, thereby facilitating lymphatic dissemination. Moreover, EMT programs interact with hypoxia signaling, PI3K/AKT/mTOR activation, and immune modulation, reinforcing a coordinated pro-metastatic phenotype.[12,13]

Table 1. Clinicopathological predictors of CLNM in oral squamous cell carcinoma

Predictor	Definition	Association with CLNM	Key references	Clinical implication
DOI	Perpendicular distance from reconstructed basement membrane to deepest tumor infiltration	Strong, independent predictor; stepwise increase in nodal risk with increasing depth	6,10,11,20	Guides END; incorporated into AJCC 8th edition
Tumor budding	Isolated single tumor cells or small clusters (<5 cells) at the invasive front	Associated with higher nodal metastasis, recurrence, and reduced survival	4,11,22	Reflects early metastatic competence; enhances risk stratification when combined with DOI
Pattern of invasion (Yamamoto–Kohama 4C/4D)	Diffuse, cord-like infiltrative growth at the tumor–host interface	Increased nodal dissemination and adverse outcomes	19,23	Identifies aggressive invasive phenotype beyond tumor size
LVI	Presence of tumor emboli within lymphatic or vascular channels	Independent predictor of occult nodal metastasis and poorer survival	10	Suggests early lymphatic access; supports END and adjuvant therapy
PNI	Tumor infiltration along or around nerve sheaths	Associated with higher nodal involvement and recurrence	11	Indicates aggressive biological behavior; influences adjuvant treatment planning
Histological grade	Degree of keratinization, pleomorphism, and mitotic activity	Limited standalone predictive value; stronger when combined with other factors	19	Adjunct parameter within multivariable prognostic models
Tumor thickness	Maximum vertical tumor dimension	Less predictive than DOI; weaker association with CLNM	3,6	Historically used; largely replaced by DOI

Abbreviations: AJCC: American Joint Committee on Cancer; CLNM: Cervical lymph node metastasis; DOI: Depth of invasion; END: Elective neck dissection; LVI: Lymphovascular invasion; PNI: Perineural invasion.

Although EMT-related markers consistently associate with nodal metastasis and adverse prognosis, their incorporation into routine clinical decision-making remains limited. Standardized assessment methods and prospective validation are required to determine whether EMT profiling provides incremental predictive value beyond established pathological parameters such as DOI and tumor budding.

Beyond classical EMT markers, increasing attention has been directed toward epithelial–mesenchymal plasticity, in which tumor cells dynamically transition between epithelial and mesenchymal phenotypes rather than undergoing a fixed binary switch. Hybrid EMT states may confer simultaneous proliferative and migratory advantages, potentially enhancing metastatic efficiency. In OSCC, partial EMT signatures have been associated with increased tumor budding, invasive front heterogeneity, and nodal dissemination.[12,13,24,25] This plasticity may also contribute to therapeutic resistance, particularly in hypoxic microenvironments where EMT-related transcription factors are upregulated. Such findings suggest that EMT represents not merely a histological correlate of aggressiveness but a dynamic process underpinning metastatic competence.

Importantly, EMT does not occur in isolation but is regulated by microenvironmental signals, including hypoxia, inflammatory cytokines, and activation of oncogenic pathways. Crosstalk between EMT transcription factors and PI3K/AKT/mTOR signaling further reinforces invasive phenotypes, creating a feed-forward loop that promotes sustained tumor progression.[12-15] These interconnections highlight the necessity of integrating molecular pathway analysis with histopathological features when evaluating metastatic risk.

4.2. Activation of the phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin signaling pathway

Aberrant activation of the PI3K/AKT/mTOR signaling axis plays a central role in the biological progression of OSCC.[12-14] This pathway regulates critical cellular processes, including proliferation, metabolic adaptation, survival under hypoxic stress, and resistance to apoptosis. Persistent activation, whether through upstream receptor tyrosine kinase signaling, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) alterations, or downstream pathway dysregulation, has been associated with more aggressive tumor phenotypes.

Clinical studies have demonstrated correlations between PI3K/AKT/mTOR pathway activation and advanced tumor stage, presence of CLNM, and unfavorable survival outcomes in OSCC.[12-14,17] Importantly, this signaling cascade does not function in isolation. Crosstalk between PI3K-mediated signaling and EMT transcription factors enhances migratory and invasive capabilities, while interactions with hypoxia-inducible pathways further support metastatic adaptation within the tumor microenvironment.[15-18]

These cooperative molecular interactions suggest that PI3K/AKT/mTOR dysregulation contributes not only to primary tumor growth but also to the acquisition of metastatic competence. Consequently, this pathway represents both a mechanistic explanation for nodal dissemination and a potential therapeutic target in biologically aggressive OSCC, with ongoing clinical investigations evaluating PI3K-targeted strategies in head and neck squamous cell carcinoma.[12,17,26]

In head and neck squamous cell carcinoma, alterations affecting the PI3K pathway—including PIK3CA mutations and phosphatase and tensin homolog loss—are among the most frequently reported genomic events. Although not all alterations translate directly into aggressive behavior, activation of this pathway has been associated with increased cell survival, resistance to anoikis, and enhanced motility.[14-17] These properties are particularly relevant to lymphatic dissemination, where tumor cells must survive detachment, intravasation, and colonization of nodal microenvironments.

Therapeutically, targeting the PI3K/AKT/mTOR axis has emerged as an area of active clinical investigation in head and neck cancers.[26] While most trials have focused on recurrent or metastatic disease, the biological rationale suggests potential relevance in high-risk early-stage tumors exhibiting pathway activation. However, predictive biomarkers for response remain incompletely defined, and toxicity profiles have limited widespread adoption. Future studies may clarify whether molecular stratification can identify subgroups of OSCC patients who derive meaningful benefit from pathway-directed interventions.

4.3. Hypoxia, angiogenesis, and lymphangiogenesis

Hypoxia is a fundamental microenvironmental condition that promotes tumor progression and metastatic dissemination in OSCC.[15,20] As tumor growth outpaces vascular supply, reduced oxygen tension stabilizes hypoxia-inducible factors (HIFs), particularly HIF-1α, which activate transcriptional programs that support metabolic adaptation, cellular survival, and invasive behavior. Hypoxia-driven signaling enhances glycolytic metabolism and promotes resistance to apoptosis, thereby facilitating tumor persistence under adverse conditions.

A major downstream consequence of HIF activation is the upregulation of angiogenic mediators, including vascular endothelial growth factor (VEGF), which stimulates neovascularization and sustains tumor expansion.[15,20] Beyond supporting primary tumor growth, angiogenesis contributes to metastatic spread by increasing vascular permeability and enabling tumor cell entry into the circulation. Elevated VEGF expression has been correlated with advanced stage and CLNM in OSCC.[16,25]

In addition to blood vessel formation, lymphangiogenesis plays a crucial role in nodal dissemination. Hypoxia-induced signaling can stimulate the expression of lymphangiogenic factors such as VEGF-C and VEGF-D, promoting the proliferation and remodeling of lymphatic vessels within and around the tumor microenvironment.[20,24,25] Enhanced lymphatic density provides structural pathways that facilitate tumor cell migration toward regional lymph nodes. Several studies have reported associations between increased lymphatic vessel density and a higher incidence of nodal metastasis in OSCC.[24,25]

Importantly, hypoxia does not operate in isolation. It interacts with EMT programs and PI3K/AKT/mTOR signaling pathway, reinforcing invasive phenotypes and metastatic competence.[16-18] These coordinated biological processes suggest that hypoxia-driven angiogenic and

lymphangiogenic remodeling contribute directly to the establishment of a pro-metastatic microenvironment.

Recent investigations have also explored the interaction between hypoxia-driven signaling and immune modulation. Hypoxic tumor microenvironments may enhance programmed death ligand-1 (PD-L1) expression through HIF-1α–dependent mechanisms, thereby linking metabolic stress with immune evasion.[16-18] This interaction suggests that hypoxia contributes not only to vascular remodeling but also to immune escape, reinforcing a multifaceted pro-metastatic niche.

Furthermore, variability in lymphatic vessel density and VEGF-C/D expression across tumor subsites may partly explain differences in nodal metastatic patterns observed in oral cavity tumors. While such markers demonstrate biological plausibility, inter-study heterogeneity in immunohistochemical scoring and cut-off values limits their immediate translational applicability. Standardized quantification approaches are therefore necessary to determine their additive predictive value beyond established pathological parameters.

Although biomarkers related to hypoxia and lymphangiogenesis show promise for risk stratification, heterogeneity in assessment methods and lack of standardized thresholds currently limit their routine clinical application. Prospective validation studies are needed to clarify their additive value beyond established histopathological parameters.

4.4. Immune microenvironment and immune checkpoints

The tumor immune microenvironment plays a pivotal role in determining metastatic potential in OSCC.[16-18] Beyond intrinsic tumor cell alterations, successful nodal dissemination requires evasion of immune surveillance within both the primary tumor site and the regional lymphatic basin. The density, spatial distribution, and functional polarization of tumor-infiltrating immune cells significantly influence disease progression.

Tumor-infiltrating lymphocytes, particularly cytotoxic $CD8^+$ T cells, have been associated with improved local control and survival in several studies.[27] Conversely, immunosuppressive components—including regulatory T cells, myeloid-derived suppressor cells, and M2-polarized tumor-associated macrophages—create a permissive microenvironment that facilitates tumor invasion and lymphatic spread.[26] An imbalance favoring immunosuppression may therefore enhance the likelihood of CLNM.

Immune checkpoint pathways represent a critical mechanism of immune escape. Upregulation of PD-L1 on tumor cells or stromal immune cells can attenuate T-cell-mediated cytotoxicity through engagement of the programmed cell death protein 1 receptor. Increased PD-L1 expression has been correlated with advanced stage, nodal involvement, and unfavorable prognosis in OSCC.[16-18] These findings suggest that immune evasion is not merely a consequence of tumor progression but may actively contribute to metastatic competence.

Importantly, immune checkpoint signaling interacts with hypoxia-driven pathways and PI3K/AKT/mTOR activation, reinforcing a pro-tumorigenic microenvironment.[17,18] Hypoxic conditions may enhance PD-L1 expression, while oncogenic signaling cascades can modulate immune regulatory molecules, indicating convergence between metabolic stress, molecular dysregulation, and immune escape.

Although immune checkpoint inhibitors have demonstrated clinical benefit in recurrent or metastatic head and neck cancers, their predictive value in the context of occult nodal metastasis remains incompletely defined. Further investigation is required to determine whether immune microenvironment profiling can improve risk stratification in cN0 OSCC beyond established histopathological predictors.

4.5. Non-coding RNAs

Non-coding RNAs (ncRNAs), including miRNAs, long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), have emerged as important post-transcriptional regulators of tumor progression in OSCC.[12-14] These molecules influence gene expression networks involved in proliferation, apoptosis, EMT, and metastatic dissemination, thereby contributing to the biological heterogeneity of the disease.

Several miRNAs have been implicated in CLNM. Dysregulated expression of oncogenic miRNAs may promote invasive behavior by modulating EMT-related transcription factors and activation of pro-survival pathways, such as PI3K/AKT/mTOR.[12,17] Conversely, tumor-suppressive miRNAs can inhibit migration and invasion by targeting genes involved in cytoskeletal remodeling and extracellular matrix degradation.[13,14] Altered miRNA expression profiles have been correlated with nodal metastasis, advanced stage, and reduced survival in OSCC patients.[11-13]

Long non-coding RNAs and circRNAs further contribute to metastatic regulation by functioning as competing endogenous RNAs that sponge tumor-suppressive miRNAs, thereby enhancing oncogenic signaling cascades.[17] Through these interactions, ncRNAs

modulate pathways governing EMT, hypoxia response, and immune evasion, reinforcing a pro-metastatic phenotype.

Importantly, the relative stability of certain ncRNAs in tissue and circulating biofluids suggests potential utility as minimally invasive biomarkers for predicting nodal involvement. However, variability in study design, detection platforms, and normalization strategies currently limits standardization. Prospective validation in large, well-characterized cohorts is necessary before ncRNA profiling can be integrated into routine clinical risk assessment for occult cervical metastasis.

The translational potential of ncRNAs extends beyond tissue-based assessment. Circulating miRNAs and lncRNAs detected in plasma or saliva have shown promise as minimally invasive biomarkers in OSCC. However, pre-analytical variability, normalization strategies, and inter-platform differences represent substantial barriers to clinical implementation. Additionally, most ncRNA studies remain retrospective and single-institutional, underscoring the need for large, prospectively validated cohorts before integration into routine risk models.

Collectively, molecular predictors offer mechanistic insight into nodal dissemination, yet their optimal clinical utility likely resides in combination with robust clinicopathological parameters rather than as standalone markers. A structured overview of the principal molecular determinants associated with CLNM in OSCC is summarized in Table 2. Integrating these molecular drivers with established invasive histopathological features provides a comprehensive framework for understanding metastatic competence, as schematically illustrated in Figure 1.

5. Biological determinants of cervical lymph node metastasis in oral squamous cell carcinoma

Cervical lymph node metastasis remains the most decisive prognostic factor in OSCC, yet accurate identification of occult nodal disease in cN0 patients continues to present a major clinical challenge. The present review highlights that metastatic risk cannot be adequately captured by anatomical staging alone; rather, it reflects the convergence of invasive histopathological features and coordinated molecular reprogramming.

Among clinicopathological parameters, DOI has demonstrated the most consistent and reproducible association with nodal metastasis, justifying its incorporation into the 8th edition TNM staging system.[6] However, DOI primarily quantifies the extent of vertical infiltration and does not fully account for qualitative aspects of tumor aggressiveness. Tumor budding, infiltrative growth patterns, LVI, and PNI provide complementary information, capturing the dynamic interaction between tumor cells and the surrounding microenvironment.[4-11] Importantly, these features often coexist, suggesting that metastatic potential is cumulative rather than attributable to a single parameter.

Molecular alterations further refine understanding of nodal dissemination. Activation of EMT programs promotes loss of cell adhesion and acquisition of migratory capacity, with recent meta-analytic evidence confirming its association with nodal metastasis in OSCC.[12,13,24] Similarly, dysregulation of the PI3K/AKT/mTOR pathway contributes to enhanced proliferation, metabolic adaptation, and survival under hypoxic stress, all of which support metastatic competence.[12-15] Hypoxia-induced signaling and angiogenic remodeling, including VEGF-mediated vascular and lymphatic expansion, create structural and biochemical conditions favorable for tumor cell dissemination.[16,17] Immune microenvironmental factors, particularly PD-L1–mediated immune escape, further facilitate survival of disseminated tumor cells within regional lymphatic tissue.[18]

Taken together, these data support a model in which CLNM is not a random event but the biological consequence of coordinated invasion, stromal remodeling, metabolic adaptation, and immune evasion. This integrative perspective helps explain why reliance on a single pathological or molecular variable yields suboptimal predictive performance.

While DOI remains the most reproducible pathological determinant of nodal risk, its predictive accuracy is enhanced when interpreted alongside qualitative indicators of invasive behavior. Tumor budding and infiltrative patterns of invasion reflect localized disruption of epithelial cohesion and stromal remodeling, phenomena that mechanistically correspond to EMT activation.[4,11-13] The convergence of these features supports the concept that nodal metastasis arises from coordinated biological processes rather than isolated morphological findings. In practical terms, this underscores the importance of comprehensive pathological assessment rather than reliance on single metrics.

Notably, variation in metastatic propensity across oral cavity subsites further illustrates the multifactorial nature of CLNM. Tumors of the tongue and floor of the mouth exhibit higher rates of occult nodal involvement than other subsites, potentially reflecting differences in lymphatic density, microenvironmental exposure, and molecular profiles. Subsite-specific risk modeling may therefore represent an additional refinement of precision

Table 2. Molecular predictors of CLNM in oral squamous cell carcinoma

Molecular pathway/marker	Biological role	Association with CLNM	Key references	Clinical translation status
EMT	Loss of epithelial adhesion and acquisition of migratory phenotype via transcription factors (Snail, Twist, ZEB)	Increased tumor budding, invasion, and nodal metastasis	12,13,24	Promising biomarker; requires standardized assessment
PI3K/AKT/mTOR signaling	Regulates proliferation, metabolism, and survival under hypoxia	Associated with the advanced stage and nodal involvement	14-17,26	Therapeutic target under investigation; predictive markers evolving
Hypoxia (HIF-1α)	Cellular adaptation to low oxygen promotes angiogenesis and metabolic reprogramming	Correlates with aggressive phenotype and metastatic potential	16,20	Potential adjunct biomarker; not standardized
Angiogenesis/VEGF	Promotes vascular and lymphatic remodeling	Increased nodal metastasis and poorer survival	16,17,24	Prognostic indicator; limited routine use
Immune checkpoints (PD-L1)	Immune evasion through T-cell inhibition	Higher expression is linked to nodal involvement and poor prognosis	18,22	Established therapeutic target; prognostic value variable
Non-coding RNAs (miRNAs, lncRNAs)	Post-transcriptional regulation of EMT and invasion pathways	Associated with nodal metastasis and recurrence	19,25	Investigational; requires prospective validation
Radiogenomic profiling	Integration of imaging phenotypes with molecular signatures	Potential non-invasive prediction of metastatic risk	27	Emerging field; requires external validation

Abbreviations: AKT: Protein kinase B; CLNM: Cervical lymph node metastasis; EMT: Epithelial–mesenchymal transition; HIF: Hypoxia-inducible factor; lncRNAs: Long non-coding RNAs; mTOR: Mechanistic target of rapamycin; PD-L1: Programmed death-ligand 1; PI3K: Phosphoinositide 3-kinase; VEGF: Vascular endothelial growth factor; ZEB: Zinc finger E-box binding homeobox.

neck management.

From a methodological perspective, most molecular investigations remain retrospective and are frequently limited by modest sample sizes, heterogeneity in biomarker quantification, and inconsistent reporting standards. For example, variability in immunohistochemical scoring systems for PD-L1 or VEGF complicates cross-study comparisons.[16-18] Similarly, ncRNA analyses often employ different normalization strategies, which can affect reproducibility.[19,25] These limitations emphasize that while molecular markers are biologically compelling, their integration into routine practice requires standardized methodologies and external validation.

Most molecular studies included in this review are retrospective and observational in design, frequently derived from single-center cohorts with limited sample sizes.[12-15,21,25] Variability in biomarker detection techniques, antibody selection, RNA normalization strategies, and cut-off definitions further complicates reproducibility and cross-study comparison. These methodological constraints

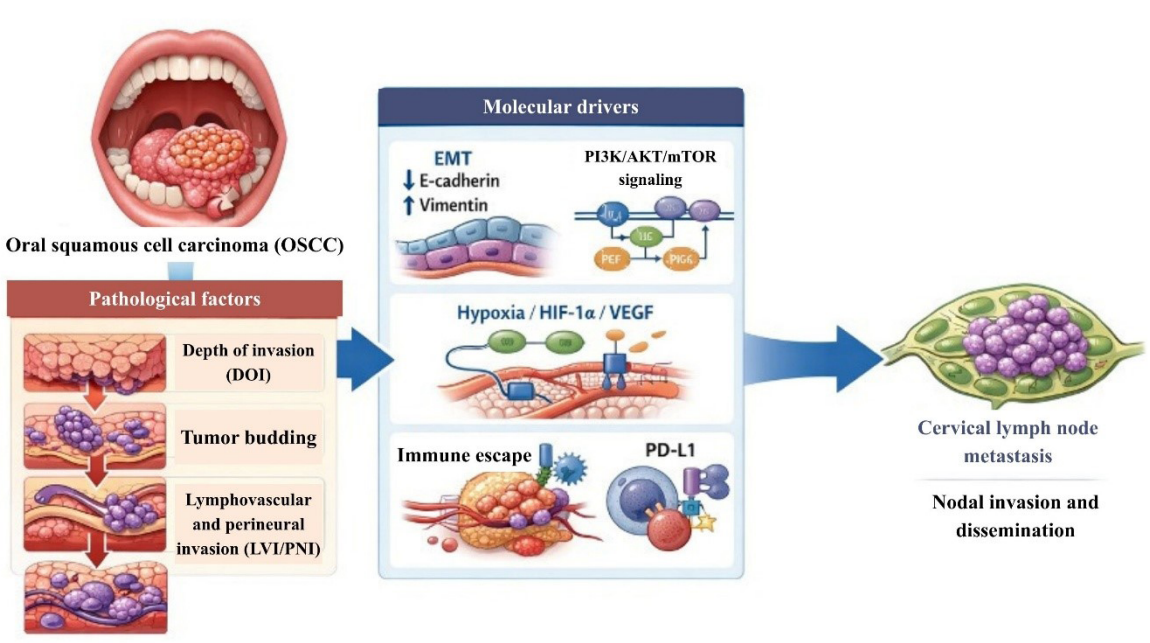

Figure 1. Conceptual model of integrated clinicopathological and molecular determinants of cervical lymph node metastasis in OSCC. Invasive histopathological features, including DOI, tumor budding, LVI, and PNI, interact with molecular drivers, such as EMT, PI3K/AKT/mTOR activation, hypoxia signaling, immune checkpoint modulation, and non-coding RNA dysregulation to promote lymphatic dissemination and nodal colonization.
Abbreviations: AKT: Protein kinase B; DOI: Depth of invasion; EMT: Epithelial–mesenchymal transition; HIF: Hypoxia-inducible factor; LVI: Lymphovascular invasion; mTOR: Mechanistic target of rapamycin; OSCC: Oral squamous cell carcinoma; PD-L1: Programmed death-ligand 1; PI3K: Phosphoinositide 3-kinase; PNI: Perineural invasion; VEGF: Vascular endothelial growth factor. Figure created by authors.

restrict the immediate clinical applicability of numerous proposed molecular predictors and underscore the need for prospective, multicenter validation before routine implementation.

Emerging computational tools offer potential solutions to some of these challenges. Digital pathology platforms can enhance the reproducibility of tumor budding quantification, while machine learning approaches may identify complex feature interactions that are not readily apparent in traditional statistical modeling.[19,27] Radiogenomic integration represents a particularly promising frontier, enabling correlation of imaging phenotypes with molecular signatures.[27] Such approaches may facilitate non-invasive risk estimation and preoperative stratification. However, current evidence remains predominantly retrospective, and prospective outcome-based validation is essential before clinical deployment.

Implementation of integrated risk models must also consider practical and ethical dimensions. Adoption of biology-informed neck management strategies requires multidisciplinary coordination, access to molecular testing infrastructure, and careful communication with patients regarding risk-benefit tradeoffs. Overreliance on unvalidated biomarkers may introduce unnecessary complexity, whereas failure to incorporate validated predictors risks continued overtreatment or undertreatment.

Cost-effectiveness represents another important consideration. While advanced molecular profiling and radiogenomic tools offer theoretical advantages, their economic impact must be weighed against the incremental improvements in predictive accuracy. In resource-limited settings, where OSCC burden is often highest, emphasis on standardized pathological assessment of DOI, tumor budding, LVI, and PNI may provide the greatest immediate clinical benefit.

Ultimately, the transition from anatomy-based staging toward biology-informed prognostication reflects a broader paradigm shift in oncology. Rather than viewing nodal metastasis as an inevitable extension of tumor size, contemporary evidence supports its characterization as the product of coordinated molecular and microenvironmental interactions. Integrative models that combine quantitative invasion metrics with validated biological markers may enable more nuanced risk stratification, guiding selective

END while preserving function in low-risk patients.

The development of multivariable prognostic models integrating clinicopathological and molecular determinants represents a logical evolution in risk assessment. Recent precision prognostication efforts have demonstrated that composite scoring systems outperform TNM staging in predicting nodal metastasis and survival outcomes.[8,19] Such models are particularly relevant in early-stage OSCC, where the decision between END and observation remains nuanced. More accurate risk stratification may reduce overtreatment in low-risk patients while ensuring timely intervention for those with biologically aggressive disease.

Nevertheless, several limitations in the current evidence base warrant consideration. Most studies evaluating molecular biomarkers remain retrospective, with heterogeneous methodologies and variable cut-off definitions. Interobserver variability in pathological assessment, particularly for tumor budding and LVI, also affects reproducibility. Moreover, few integrated models have undergone prospective multicenter validation. Without standardized measurement protocols and external validation, clinical implementation remains premature.

Future research should prioritize the harmonization of pathological reporting criteria, external validation of molecular biomarkers and predictive models in large prospective cohorts, and evaluation of integrated models in real-world clinical workflows across diverse populations. Standardized methodologies and assessment of patient-centered outcomes will be essential to establish clinical utility and reproducibility. In addition, the incorporation of digital pathology and computational analytics, including machine learning approaches, may enhance reproducibility and predictive accuracy. However, their incremental benefit must be demonstrated through rigorous outcome-based studies before clinical implementation. Only through such comprehensive validation can precision neck management transition from a conceptual framework to routine clinical practice.

This narrative review has inherent limitations. As a non-systematic synthesis, study selection may be influenced by publication bias and language restriction. Formal quality scoring and quantitative meta-analysis were not performed, reflecting the conceptual objective of integrating mechanistic and clinicopathological evidence. Consequently, conclusions should be interpreted within the context of heterogeneous methodologies and evolving biomarker validation.

In summary, the contemporary understanding of CLNM in OSCC underscores the need to transition from purely anatomical staging to biology-informed prognostication. Integration of invasive morphology with molecular determinants offers a rational framework for precision neck management, though careful validation remains essential before widespread adoption.

6. Integrated risk models and precision neck management

Increasing recognition of the limitations of anatomy-based staging has prompted the development of integrated risk models that combine clinicopathological and molecular variables to improve the prediction of CLNM. Multivariable nomograms incorporating DOI, tumor budding, LVI, PNI, and selected biological markers have demonstrated superior discriminative performance compared with TNM staging alone.[8,19] These composite models more accurately estimate the probability of occult nodal disease in cN0 patients.

Importantly, such models move beyond static anatomical parameters and instead reflect the biological aggressiveness of the primary tumor. By integrating quantitative measures of invasion with molecular indicators of metastatic competence, they offer a more individualized assessment of metastatic risk. This approach is particularly relevant in early-stage OSCC, where overtreatment and undertreatment remain competing clinical concerns.

Emerging computational strategies further expand this paradigm. Artificial intelligence–based algorithms combining digital histopathology, genomic profiling, and radiomic features have shown promise in refining risk stratification.[19,27] These technologies may detect subtle architectural or molecular patterns not readily apparent through conventional assessment. However, current evidence remains largely retrospective, and external validation across diverse populations is limited. Radiogenomic profiling, which links imaging phenotypes to molecular signatures, represents a promising extension of integrated predictive modeling in head and neck cancer.[27]

From a clinical perspective, integrating validated risk models into preoperative decision-making may enable more selective application of END. Patients categorized as low risk could potentially be managed with careful surveillance, whereas those identified as high risk may benefit from early surgical intervention or intensified adjuvant therapy. Such biology-driven stratification aligns with contemporary precision oncology principles and aims to balance oncologic control with preservation of function.

Nevertheless, before widespread implementation, standardized pathological assessment, reproducible biomarker measurement, and prospective validation

studies are required.[8,19] The ultimate goal is to establish clinically practical, evidence-based algorithms that can be incorporated into routine head and neck oncology workflows. A schematic representation of this biology-informed risk stratification framework is presented in Figure 2.

7. Clinical implications and future directions

Biology-driven risk stratification has important implications for the management of cN0 OSCC. Current decision-making regarding END remains largely guided by anatomical staging and DOI. However, as demonstrated in recent precision prognostication studies, integration of clinicopathological and molecular determinants may substantially improve risk estimation for occult CLNM.[8,19]

In clinical practice, more accurate prediction models could reduce unnecessary surgical morbidity in low-risk patients while ensuring timely intervention for those with biologically aggressive disease. This is particularly relevant in early-stage tumors, where the balance between oncologic safety and functional preservation is critical. Selective use of END based on validated multivariable risk algorithms may therefore represent a rational evolution in neck management.

Standardization remains a prerequisite for implementation. Uniform measurement of DOI, reproducible grading of tumor budding, and consensus criteria for lymphovascular and PNI are essential for consistent risk assessment across institutions. Similarly, molecular biomarkers—including EMT-related markers, PI3K pathway activation, hypoxia-associated signatures, immune checkpoint expression, and ncRNA profiles—require harmonized detection platforms and validated cutoff thresholds before routine clinical adoption.

Future research priorities should include prospective multicenter validation of integrated predictive models, incorporation of digital pathology and artificial intelligence tools into standardized workflows, and evaluation of minimally invasive biomarkers such as circulating tumor DNA or circulating ncRNAs. Importantly, clinical utility must be demonstrated not only in predictive accuracy but also in improved patient-centered outcomes, including survival, quality of life, and treatment-related morbidity.

Ultimately, translation of integrated clinicopathological–molecular models into pragmatic decision-support systems could facilitate individualized neck management

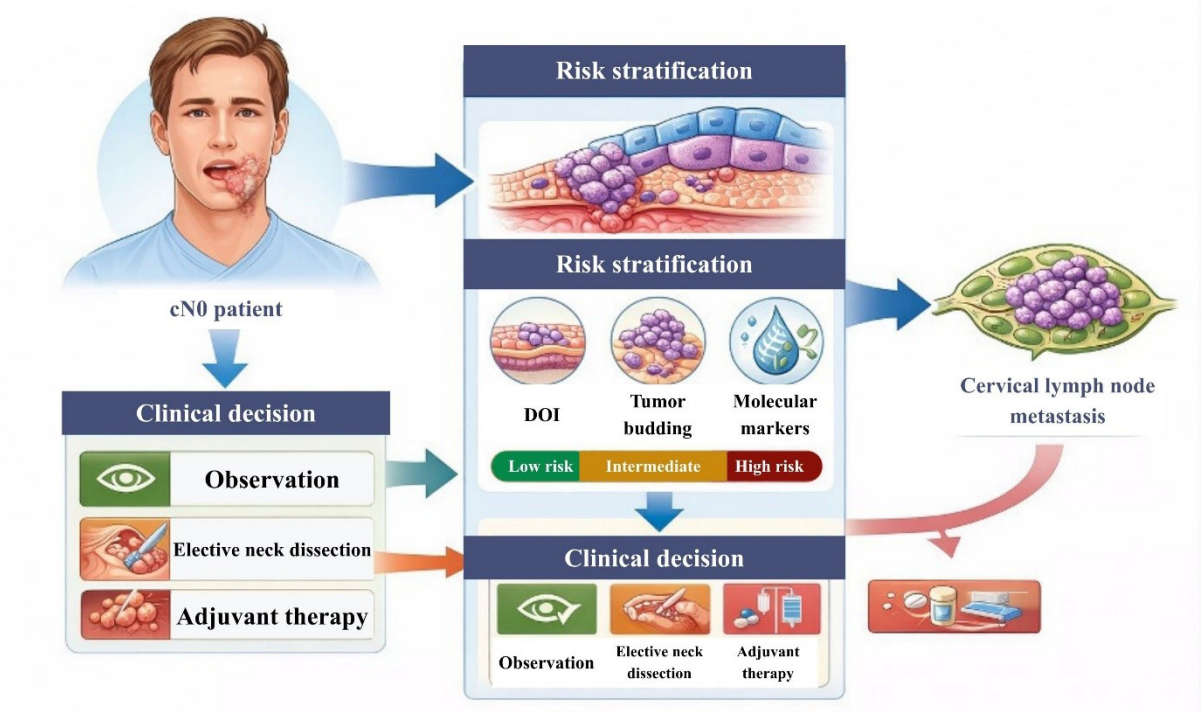

Figure 2. Biology-informed risk stratification framework for cN0 OSCC. This schematic depicts integration of pathological and molecular markers to stratify patients into low-, intermediate-, and high-risk groups, guiding decisions ranging from observation to elective neck dissection and adjuvant therapy.
Abbreviations: cN0: Clinically node-negative; DOI: Depth of invasion; OSCC: Oral squamous cell carcinoma. Figure created by authors.

strategies. Such an approach aligns with contemporary precision oncology principles and may improve oncologic control while minimizing overtreatment in OSCC.

8. Conclusion

Cervical lymph node metastasis in OSCC reflects the convergence of invasive histopathological features and coordinated molecular reprogramming. While DOI, tumor budding, LVI, and PNI remain the most reliable pathological predictors, mounting evidence demonstrates that metastatic competence is also shaped by EMT, PI3K/AKT/mTOR activation, hypoxia-driven remodeling, immune escape, and ncRNA dysregulation.

Anatomy-based staging alone is insufficient to fully capture this biological complexity. Integrated clinicopathological–molecular risk models provide a more comprehensive framework for predicting occult nodal disease and refining management strategies.[8,19] In cN0 patients, such models may support a more selective application of END, balancing oncologic safety with functional preservation.

However, before routine clinical implementation, standardized pathological assessment, reproducible biomarker evaluation, and prospective validation in multicenter cohorts are essential. The future of neck management in OSCC lies in developing practical, evidence-based decision-support algorithms that translate biological insights into individualized treatment strategies.

By aligning prognostic assessment with tumor biology, precision neck management has the potential to improve oncologic outcomes while reducing overtreatment, representing a meaningful advancement in contemporary head and neck oncology care.

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