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REVIEW

Decoding Occult Cervical Lymph Node Metastasis in Head and Neck Squamous Cell Carcinoma: From AI-Driven Multimodal Fusion to Clinical Translation

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Abstract

Purpose of Review This review examines the limitations of conventional macroscopic approaches in detecting occult cervical lymph node metastasis (OCLNM). It also explores how multi-omics technologies and artificial intelligence (AI) driven cross-scale multimodal integration are reshaping precision diagnosis for patients with clinically node-negative (cN0) head and neck squamous cell carcinoma.

Recent Findings Recent studies show that combining high-throughput omics data, such as genome-wide DNA methylation and spatial transcriptomics, with radiomics through deep learning models leads to markedly better performance than conventional imaging alone. New computational strategies, including habitat radiomics and cross-modal fusion networks, allow more detailed characterization of spatial tumor heterogeneity. They also provide insights into how the tumor microenvironment evolves during early metastatic spread. In addition to improving detection of microscopic disease, these approaches are beginning to support more reliable survival risk stratification.

Summary The integration of AI with multi-omics data is moving the field toward a noninvasive "panoramic virtual biopsy." This framework offers a practical path to address a long-standing clinical challenge, balancing overtreatment against undertreatment in cN0 patients. With further validation, it may support safer surgical de-escalation and enable more personalized treatment strategies.

Keywords Head and Neck Squamous Cell Carcinoma (HNSCC) · Occult Cervical Lymph Node Metastasis (OCLNM) · Artificial Intelligence (AI) · Multi-omics · Radiopathomics · Multimodal fusion

Introduction

Head and neck squamous cell carcinoma (HNSCC), a heterogeneous group of malignancies originating from the mucosal epithelium of the oral cavity, pharynx, and larynx, represents a significant global oncology burden. According to recent GLOBOCAN estimates, HNSCC accounts for approximately 900,000 incident cases and 450,000 disease-related deaths annually worldwide [1]. As the single most critical prognostic determinant in HNSCC, cervical lymph node metastasis (CLNM) is associated with a significantly reduced 5-year survival rate [2, 3]; consequently, and its occult presentation (OCLNM) is linked to poor long-term patient outcomes even in patients with small primary tumors (low T stage) [4].

In clinical practice, the care of patients with clinically node negative (cN0) HNSCC presents a formidable challenge. Despite advances in conventional imaging, macroscopic assessments often fail to detect microscopic tumor deposits; as a result, 20% to 40% of patients with cN0 disease harbor occult CLNM (OCLNM; i.e., cN0-pN+) [5, 6]. Consequently, clinical guidelines typically recommend elective

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neck dissection when the estimated risk of occult metastasis exceeds 20% [7, 8]. However, in the 60% to 80% of patients with pathologically negative (cN0-pN0) cervical lymph nodes, elective neck dissection represents overtreatment. For these patients, prophylactic elective neck dissection offers no survival benefit but may result in significant surgical complications, such as spinal accessory nerve dysfunction, dysphagia, and lymphedema [9]. Resolving this pervasive clinical dilemma, i.e., forego elective neck dissection and miss some cases of OCLNM or proceed with elective neck dissection and overtreat a substantial proportion of patients, necessitates the development of high-fidelity, noninvasive approaches that encompass both macroscopic (e.g., advanced radiomics) and microscopic (e.g., machine learning assessment risk stratification of digitized pathology images) tools.

Research into detecting OCLNM and elucidating the mechanisms underlying OCLNM in HNSCC has entered the era of integrated application of diagnostic imaging, digital pathology, multi-omics and artificial intelligence (AI). Although conventional cross-sectional imaging and pathological evaluation remain the cornerstones of clinical assessment, these approaches have limited sensitivity in the identification of early microscopic dissemination and are based on individual assessment and diagnosis of a single pathologist with varying experience with head and neck pathology [10]. In recent years, the integration of high-throughput imaging and multi-omics technologies—spanning genomics, transcriptomics, epigenetics and spatial omics—with advanced machine learning architectures has opened new frontiers in detection of OCLNM [11]. By decoding multidimensional data from digital whole-slide images and medical scans, this integration of multi-omics and AI offers unprecedented insights into the metastatic cascade and facilitates individualized decision-making.

In this article, we comprehensively review the contemporary landscape of OCLNM assessment (Fig. 1). We systematically evaluate the molecular mechanisms underlying OCLNM, conventional and emerging diagnostic modalities for OCLNM, and the paradigm shift in OCLNM assessment brought about by AI-assisted diagnosis. Furthermore, we critically analyze hurdles to clinical translation of new CLNM assessment methods and outline future trajectories, emphasizing the transformative potential of radiogenomics and cross-scale multimodal fusion (integration of imaging, pathology, and epigenetics data) to improve assessment of OCLNM.

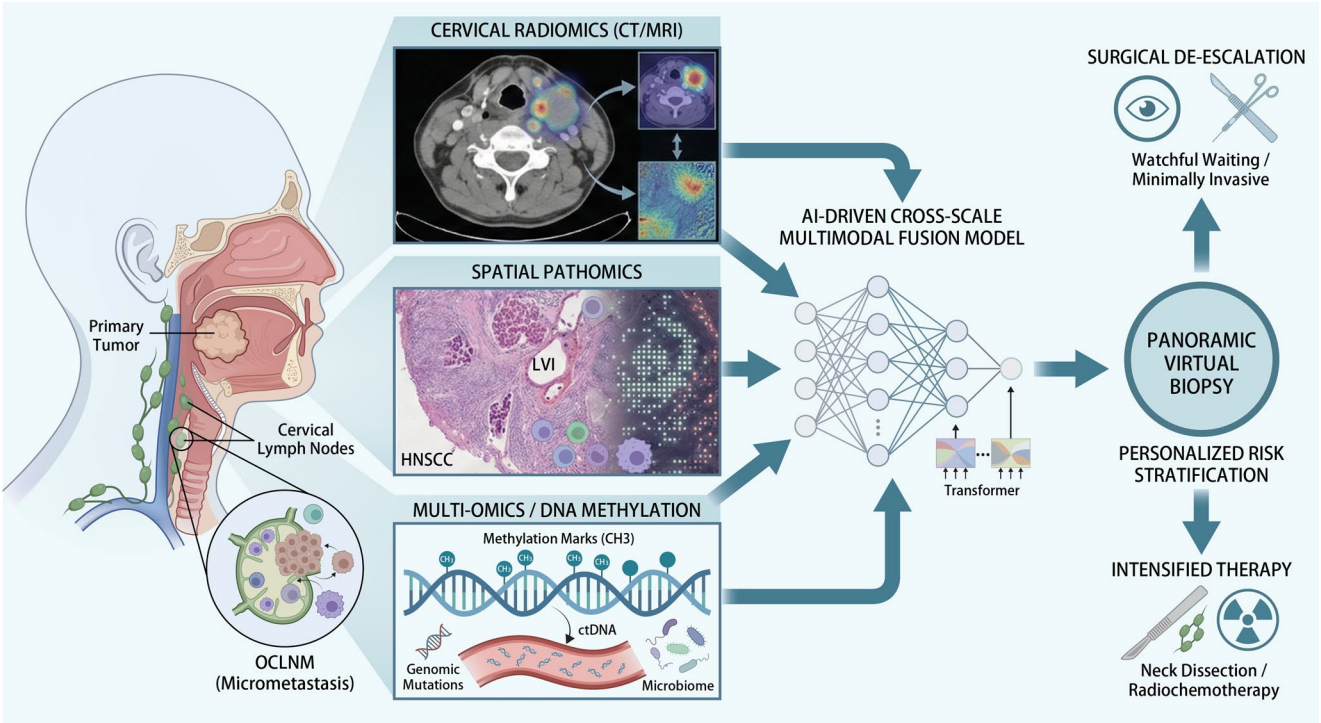

Fig. 1 AI-driven cross-scale multimodal fusion model for precision assessment of OCLNM in cN0 HNSCC. Macroscopic cervical radiomics data derived from contrast-enhanced CT/MRI capture spatial heterogeneity and peritumoral habitat features within the head and neck region. Microscopic spatial pathomics data extracted from whole-slide images quantify tumor budding, lymphovascular invasion (LVI), and immune-stromal niches at cellular resolution. At the molecular level, genome-wide DNA methylation, mutational landscapes, and circulating tumor-derived analytes provide stable epigenetic and genomic predictors of metastatic potential. These complementary data layers converge within a unified artificial intelligence framework to generate a noninvasive "panoramic virtual biopsy," enabling individualized risk stratification and guiding rational surgical de-escalation versus intensified therapeutic strategies. This cross-scale paradigm aims to transcend the intrinsic diagnostic ceiling of unimodal assessment. ctDNA, circulating tumor DNA

Epidemiology and Molecular Mechanisms of OCLNM

Epidemiology

The prevalence of OCLNM in clinically node negative (cN0) HNSCC exhibits considerable heterogeneity and is heavily influenced by the primary anatomical subsite, histologic grade, and depth of invasion [5]. The incidence of OCLNM in HNSCC typically ranges from 20% to over 40%, and OCLNM is most commonly observed in malignancies of the oral cavity (particularly the oral tongue), pharynx, and larynx [12–14]. Large cohort analyses have consistently demonstrated that approximately 20% to 30% of patients presenting with cN0 HNSCC harbor occult microscopic dissemination at the time of primary diagnosis [13].

The genesis of OCLNM has been linked to a spectrum of aggressive clinicopathological parameters. Larger primary tumor (e.g., ≥ 20 mm or T3/T4 classification) and poor histologic differentiation (grade 3) are established macroscopic predictors of OCLNM [15–17]. At the microscopic level, lymphovascular invasion and perineural invasion are universally recognized as robust, independent risk factors linked to regional lymphatic dissemination [18, 19]. Tumor budding and microscopic extranodal extension [18, 20] have also been associated with OCLNM. Crucially, these micro-morphological features are the critical biological features that modern AI and radiopathomics models strive to capture and quantify to risk-stratify patients [20].

Molecular Mechanisms and Tumor Microenvironment Remodeling

At the molecular level, the metastatic cascade of OCLNM is orchestrated by a complex interplay of genomic aberrations, epigenetic reprogramming, and tumor microenvironment remodeling. Recent multi-omics interrogations of the HNSCC cohort of The Cancer Genome Atlas have begun to decode these underlying vulnerabilities, revealing distinct mutational landscapes, genome-wide methylation alterations, and specific immune-stromal ecotypes that robustly differentiate patients with cN0-pN+ disease from those with cN0-pN0 disease [21].

From a genomic perspective, the acquisition of metastatic potential is closely tied to the dysregulation of chromatin remodeling and cytoskeletal dynamics. For instance, while true node-negative (cN0-pN0) tumors frequently exhibit mutations in chromatin remodeling regulators—notably NSD1 (19% vs. 2% in cN0-pN+) and SMARCA4 (10% vs. 0%)—tumors harboring occult metastases (cN0-pN+) are characterized by a distinct genomic landscape enriched for alterations affecting cytoskeletal dynamics, including ARHGAP15 (9% vs. 1% in cN0-pN0) and ATP8A2 (9% vs. 1%) [21]. Although the functional consequences of these specific mutations require further experimental validation, the enrichment of alterations in cytoskeleton-associated genes raises the possibility that perturbed cellular motility and matrix degradation may predispose these tumors to early lymphatic invasion.

Beyond genomic alterations, gene expression programs and epigenetic plasticity serve as primary driver of the metastatic phenotype [22, 23]. Comprehensive DNA methylation profiling has identified extensive genome-wide hypomethylation alongside targeted promoter hypermethylation in OCLNM. Gene set enrichment analysis indicates that these epigenetic shifts robustly activate the epithelial-mesenchymal transition program, hypoxia-response pathways, and gamma-tubulin binding [24]. Such genome-wide epigenetic reprogramming destabilizes cellular adhesion and enhances the invasive capacity requisite for regional nodal dissemination.

The metastatic transition is also linked to the spatiotemporal remodeling of the tumor immune microenvironment. OCLNM-positive tumors frequently harbor aggressive tumor microenvironment ecotypes, such as the CE1 (TGF-β/epithelial-mesenchymal transition signaling-enriched) and CE4 (myogenic signature) states. Specifically, the expansion of unique cellular subsets—including CARNS1-positive natural killer cells and CBX1-positive epithelial populations—within these ecotypes suggests the formation of a profound immunosuppressive and stroma-reactive niche. This reprogrammed microenvironment nurtures tumor budding and facilitates immune evasion during the tumor cells' transit through the lymphatic network [25] **(**Fig. 2**)**.

Conventional Cross-Sectional Imaging

Currently, conventional imaging modalities, i.e., computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography, and positron emission tomography/computed tomography (PET/CT) are the mainstays of preoperative nodal staging. These techniques rely heavily on macroscopic morphological criteria to differentiate malignant from benign nodes. Standard macroscopic criteria used to identify LNM include a short-axis diameter exceeding 10 mm, the presence of central necrosis, a rounded contour (reflecting loss of the normal reniform shape), and obliteration of the fatty hilum [26].

However, the fundamental pathological hallmark of OCLNM is microscopic colonization of tumor cells within the lymph node cortex, which frequently occurs well before

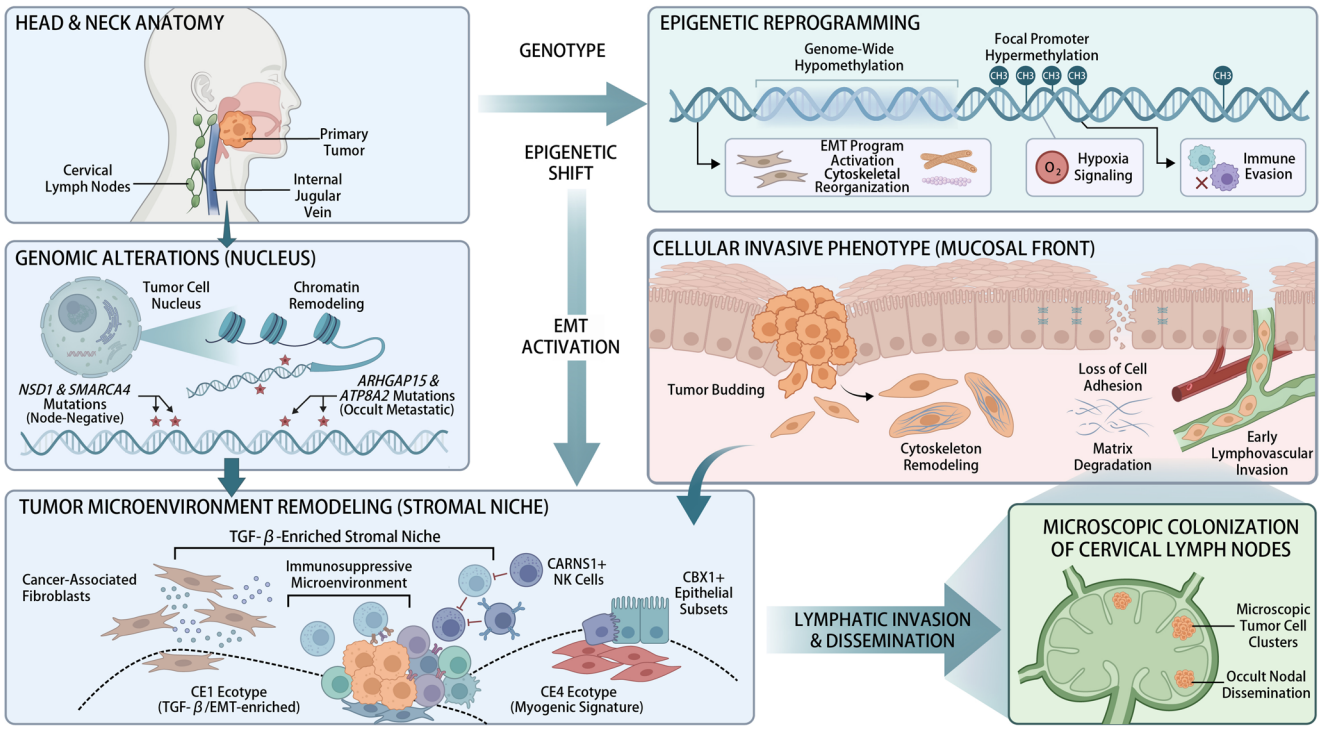

Fig. 2 Molecular and microenvironmental cascade underlying OCLNM in HNSCC. Genomic divergence constitutes the initiating layer of multimodal fusion; node-negative tumors (cN0–pN0) frequently harbor mutations in chromatin remodeling regulators such as *NSD1* and *SMARCA4*, whereas tumors with occult metastasis (cN0–pN+) frequently exhibit enrichment for mutations affecting cytoskeletal dynamics, including *ARHGAP15* and *ATP8A2*. These genomic distinctions converge on epigenetic reprogramming, which is characterized by genome-wide hypomethylation and focal promoter hypermethylation, which transcriptionally activate epithelial-mesenchymal transition (EMT), hypoxia-response programs, cytoskeletal reorganization pathways and immune evasion. At the cellular level, these epigenetic shifts destabilize intercellular adhesion and promote tumor budding, extracellular matrix degradation, and early lymphovascular invasion at the invasive front. Concomitantly, the tumor immune microenvironment undergoes spatiotemporal remodeling, which gives rise to aggressive ecotypes such as CE1 (TGF-β/EMT-enriched) and CE4 (myogenic signature), accompanied by expansion of distinct cellular subsets including CARNS1-positive (CARNS1+) natural killer cells and CBX1+epithelial subsets. This immunosuppressive and stroma-reactive niche facilitates immune evasion and supports tumor cell transit through the cervical lymphatic network. Ultimately, these coordinated genomic, epigenetic, and microenvironmental alterations culminate in microscopic tumor cell colonization within morphologically normal cervical lymph nodes, i.e., clinically occult metastasis

any gross anatomical enlargement or structural necrosis becomes evident on imaging. The sensitivity of conventional CT and MRI for detecting these subtle micrometastases in cN0 cohorts is notoriously low, frequently below 50% to 60% [13]. Furthermore, while comprehensive meta-analyses suggest that 18 F-FDG PET/CT exhibits higher patient-level diagnostic accuracy than any of the other standard imaging modalities, its utility in detecting sub-centimeter occult lesions is limited. For metastatic foci smaller than 5 mm, PET/CT is hindered by the partial volume effect and frequent false-positive results arising from nonspecific inflammatory radiotracer uptake [27]. These intrinsic physical resolution limits and the subjective nature of human visual interpretation underscore the urgent need for advanced computational paradigms, such as radiomics and deep learning, capable of extracting high-dimensional, microscopic imaging features [28].

Pathological Evaluation and Emerging Molecular Diagnostics

Historically, ultrasound-guided fine-needle aspiration cytology has been the frontline diagnostic tool for nodal evaluation. However, sampling errors are common in patients with microscopic lesions, which leads to an unacceptably high false-negative rate in patients with cN0 cervical nodes. Similarly, intraoperative frozen section analysis, even when augmented by rapid immunohistochemistry, frequently misses micrometastases or isolated tumor cells due to restricted tissue sampling and sectioning artifacts [29].

Sentinel lymph node biopsy(SLNBx), which enables ultrastaging of the first echelon of lymphatic drainage, avoids the sampling issues with fine-needle aspiration cytology and intraoperative frozen section analysis and has gained significant traction as a targeted surgical adjunct in

early-stage HNSCC [30]. A standard practice in Europe, the utility of this staging procedure, is being studied in a large multi-center prospective clinical trial by NRG Oncology.

More recently, the adoption of liquid biopsy technologies, which measure tumor-derived molecular byproducts in blood or saliva, has demonstrated tremendous potential to identify cN0 patients who are pN+, as it provides a highly sensitive, non-invasive window into subclinical lymphatic dissemination prior to surgical intervention. Moreover, the noninvasive nature of liquid biopsy facilitates longitudinal, dynamic monitoring of metastatic evolution, heralding a new era of precise molecular staging and individualized therapeutic intervention for HNSCC.

Extensive research has validated the predictive efficacy of a diverse array of circulating biomarkers in detecting OCLNM. These include specific microRNAs (e.g., miR-203 and miR-205), systemic inflammatory indices (such as the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio) and circulating tumor DNA and cell-free DNA [31]. Furthermore, high-throughput profiling has identified localized intratumoral and nodal markers, including overexpression of PARVB and IL-32 and the unique colonization of the intratumoral microbiome (by *Fusobacterium nucleatum*), as potent indicators of elevated metastasis risk [32].

Integrated Application of Multi-Omics Technologies and AI

Multi-Omics Technologies in OCLNM Assessment

The contemporary integration of multi-omics technologies in OCLNM assessment is focused on translating multidimensional molecular data into clinically actionable predictive tools and algorithmic inputs.

Genomics and Epigenetics: The Molecular Bedrock

At present, to predict the risk of OCLNM, targeted next-generation sequencing and epigenetic microarrays are used to construct quantitative risk-stratification models. For instance, genomic panels demonstrating 11q13 amplification (encompassing driver genes such as *CCND1*, *CTTN*, and *FADD*) have been used to identify patients requiring aggressive prophylactic neck dissection [33, 34]. More importantly, DNA methylation signatures have emerged as stable and optimal targets for clinical translation. Because DNA methylation alterations (e.g., hypermethylation of specific tumor-suppressor promoters) occur as early, ubiquitous events in metastasis, these epigenetic footprints are currently being transformed into robust, PCR-based biomarker panels for liquid biopsies. In the realm of AI, these genome-wide methylation matrices are no longer analyzed in isolation but are increasingly utilized as high-fidelity, vectorized inputs for multimodal machine learning classifiers, acting as the molecular anchor for predicting occult nodal status.

Transcriptomics, Proteomics, and Metabolomics

For prediction of OCLNM in clinical practice, transcriptomic and proteomic discoveries are translated into spatial pathology and multiplexed clinical assays. Advanced spatial transcriptomics and multiplex immunohistochemistry are applied directly to whole-slide images. This allows for precise in situ quantification of metastasis-associated proteins (e.g., PARVB, VEGF, and the E-cadherin/N-cadherin ratio) within specific tumor microenvironment niches [35]. By digitizing these proteomic and cellular interactions, pathologists can generate "spatial pathomic signatures." These signatures can be seamlessly integrated with macroscopic imaging data to augment the predictive accuracy of AI-assisted diagnostic pipelines.

Liquid Biopsy and the Microbiome

The most direct clinical application of multi-omics in predicting OCLNM is the development of noninvasive, dynamic monitoring pipelines. Liquid biopsy technologies quantifying circulating tumor DNA, cell-free DNA, and exosomal contents are shifting OCLNM assessment from surgical pathology assessments, which provide a snapshot of a single point in time, to real-time surveillance. Furthermore, the application of machine learning has unlocked the diagnostic value of the intratumoral microbiome. A prime example is the MicroAIbiome framework, an applied machine-learning pipeline that bypasses traditional mechanistic analysis, using the relative abundance of microbes at the genus level (e.g., *Fusobacterium*) as algorithmic features to classify major malignancies, including HNSCC, with an accuracy of 78.23% [36]. These computational pipelines exemplify the transition from histological approaches to identifying OCLNM to automated, AI-driven clinical approaches.

AI and Machine Learning in OCLNM Assessment

In recent years, the application of AI and machine learning in predicting tumor LNM has advanced at an unprecedented pace. To overcome the inherent limitations of conventional morphological imaging, investigators have advanced AI methodologies across underlying computational models, feature extraction algorithms, and overarching research paradigms. These technological leaps, from basic image classification networks to the decoding of complex spatial heterogeneity and progressing toward cross-modal fusion

and survival-driven risk stratification, have reshaped the landscape of precision diagnosis.

Convolutional Neural Networks and Baseline Models

Early AI applications for assessing the risk of LNM predominantly employed classical convolutional neural networks (CNNs), such as ResNet and VGG architectures, for the binary classification of nodal status on the basis of data from CT or MRI [37, 38]. These pioneering end-to-end models bypassed the need for complex hand-crafted features by autonomously extracting hierarchical textures, edge delineations, and morphological patterns from manually cropped regions of interest or image patches. Clinical validations of these baseline models have consistently demonstrated performance comparable to or even exceeding that of mid-level radiologists. For instance, a recent prospective study by Xu et al. utilized a CNN model trained on a massive dataset of contrast-enhanced CT images to diagnose CLNM in oral SCC. The model consistently achieved an area under the receiver operating characteristic curve ranging from 0.85 to 0.90, substantially better than the results reported with human visual assessment [39]. Similar large-scale retrospective evaluations have further corroborated the robust baseline efficacy of CNNs in diagnosing CLNM in head and neck malignancies [40].

However, despite these promising performance metrics, standard CNNs typically processes the entire primary tumor or lymph node as a monolithic, homogeneous region. This whole-region pooling approach inevitably averages out the pixel intensities across the lesion, thereby diluting critical high-risk signals (e.g., microvascular proliferation) with the "noise" of necrotic cores or dense fibrotic stroma. Consequently, standard CNNs have limited capacity to capture highly localized, microscopic spatial cues and intratumoral heterogeneity, which are the fundamental biological prerequisites for identifying early-stage OCLNM.

Evolution of Feature Extraction: Interrogation of Spatial Heterogeneity

The internal architecture of HNSCC is heterogeneous, frequently characterized by central ischemic necrosis, fibrosis, and a proliferative peripheral invasive front with dense microvascular infiltration.

In contrast with traditional CNNs, which treat the tumor as homogeneous, recent research paradigms emphasize refined interrogation of spatial heterogeneity. Peritumoral radiomics represents a major advance in this field. By algorithmically expanding the tumor boundary outward (e.g., by 3 to 5 mm), this approach captures features of the tumor invasive front, early lymphovascular invasion, and desmoplastic responses. Xu et al. [41] demonstrated in hypopharyngeal SCC that combined extraction of gross tumor volume and peritumoral margins on contrast-enhanced CT significantly improved prediction of lymphovascular invasion and metastatic potential compared with extraction of intratumoral features alone.

Habitat radiomics further dissects intratumoral microecology. Using unsupervised clustering algorithms such as K-means, habitat radiomics allows tumors to be automatically partitioned into physiologically distinct subregions ("habitats"), such as low-enhancement ischemic/necrotic zones and high-enhancement hypervascular zones [42]. Targeted extraction of deep learning features from high-risk habitats reduces interference from necrotic tissue and amplifies predictive signals for occult metastasis.

Multi-Regional Spatial Linkage and Cross-Modal Fusion

Regional LNM involves clonal evolution of the primary tumor, basement membrane invasion, lymphatic migration, and regional nodal colonization. Restricting analysis to the primary lesion leads to incomplete predictive information.

Recent computer vision architectures, particularly Vision Transformers, have facilitated clinical implementation of multi-regional spatial linkage. Song et al. [43], in a large real-world cohort of 811 patients with oropharyngeal carcinoma, employed a Swin Transformer architecture to simultaneously extract features from both the primary tumor and cervical lymph nodes. Through global self-attention mechanisms, the model captured intrinsic associations between anatomically distant regions. Notably, even morphologically normal cN0 lymph nodes may exhibit subtle internal texture alterations reflecting biological remodeling driven by the primary tumor.

To overcome the limitations of single-modality data, cross-modal fusion strategies have been widely introduced. Li et al. [44] rigorously evaluated various fusion approaches in a multicenter cohort of tongue SCC. Their findings indicated that late fusion (decision-level fusion), which integrates MRI-based deep learning probability scores, intratumoral heterogeneity radiomic features, and key clinical anchor variables (e.g., depth of invasion, T category) through logistic regression, demonstrated better generalizability and robustness than early feature concatenation did.

Furthermore, Qi et al. [45]. used dual-energy CT-based deep learning models employing channel stacking techniques to input iodine maps, fat maps, and virtual monoenergetic images (70 keV) into a Crossformer Transformer network, providing a functional imaging perspective beyond morphology. The integration of anatomical and perfusion-related information offers improved diagnostic performance for detecting very small occult nodal metastases.

Toward Clinical Trust: Uncertainty Awareness and Survival Risk Reshaping

As AI diagnostic performance approaches technical limits, research emphasis has shifted toward clinical safety and interpretability.

Occult metastases often exhibit subtle and ambiguous imaging characteristics. Conventional deep neural networks tend to be overconfident, assigning definitive predictions even for uncertain lesions, thereby posing potential clinical risks. Uncertainty-aware deep learning has emerged as a solution. De Biase et al. [46] introduced Bayesian mechanisms or Monte Carlo dropout into multicenter segmentation models, enabling quantification of predictive uncertainty. In addition to segmentation outputs, the models generated tumor probability maps, highlighting low-confidence regions and guiding targeted radiologist intervention within a human-in-the-loop framework.

More fundamentally, the ultimate clinical objective of AI in assessing possible OCLNM is shifting from binary diagnosis toward survival risk stratification and restaging. In a study published in *Journal of Clinical Oncology*, Ye et al. developed an automated deep learning pipeline to quantify total nodal burden and extranodal extension from preoperative imaging in oropharyngeal carcinoma [20]. These AI-derived metrics were incorporated into Cox proportional hazards models to predict overall survival and progression-free survival. The results demonstrated that AI could identify a substantial subset of patients misclassified as "low risk" by the clinical staging system in the eighth edition of the *AJCC Cancer Staging Manual* who actually exhibited poor outcomes. This AI-driven risk reshaping provides robust evidence to guide future treatment de-escalation or intensified neoadjuvant therapy.

Digital Pathology and Spatial Transcriptomics

Digital pathology (whole-slide imaging) and high-resolution image analysis have promoted the informatized management of large samples. AI improves the detection ability of microscopic signs such as minimal extranodal extension, tumor budding, and metastatic nodules in pathological Sect [47]. Recent studies show that integrating molecular labels with digital pathology images can achieve automatic quantification of immune cell composition in the microenvironment and quantitative correlation of substructures, providing a high-throughput tool for establishing "microscopic pathological scales" and dynamic follow-up [48].

In a study published in *Cell Reports Medicine*, Oh et al. used spatial analysis techniques and found that the spatial organization of CCR7-positive dendritic cells in niches predicted patient response to pembrolizumab treatment and overall survival better than traditional combined positive score did [49]. This finding highlights the importance of spatial omics in understanding the tumor immune microenvironment and predicting treatment response.

Cross-Scale Multimodal Fusion

In addressing the challenge of precision diagnosis for OCLNM, reliance on the single data modality leaves "information blind spots." Medical imaging (e.g., contrast-enhanced CT or MRI) provides a global view of macroscopic spatial heterogeneity but lacks cellular-level resolution. Conversely, whole-slide digital pathology images, despite being the microscopic gold standard, are constrained by spatial sampling bias.

To overcome these intrinsic limitations, cross-scale multimodal fusion, integration of imaging, pathology, and epigenetic data, has emerged as the ultimate precision oncology paradigm [50]. Combining macroscopic peritumoral habitat features from medical imaging with microscopic indicators from whole-slide images significantly improves predictive performance in various solid tumors, including HNSCC [51–53].

Emerging research is embedding genome-wide DNA methylation profiles into this multidimensional architecture [54]. Local epigenetic reprogramming, such as methylation-driven angiogenesis, inevitably translates into altered tissue density and abnormal imaging textures [55]. By capturing the tumor ecosystem from phenotype to genotype, these high-fidelity multi-omics signatures enable a noninvasive "panoramic virtual biopsy," providing an integrated anatomical, cellular, and molecular basis for resolving the OCLNM clinical dilemma **(**Fig. 3**)**.

Critical Appraisal: Biological Plausibility and Translational Bottlenecks

The "Curse of Dimensionality" and Fusion Architecture Flaws

Multimodal models generally report better mathematical performance than single-modality tools, but these numbers warrant a closer look. The strikingly high AUCs (often > 0.90) seen in recent studies are sometimes more indicative of the 'curse of dimensionality' than true predictive power. When mapping massive genomic arrays onto thousands of radiomic features within relatively small patient cohorts, the risk of overfitting skyrockets; the algorithms simply memorize cohort-specific noise. Another

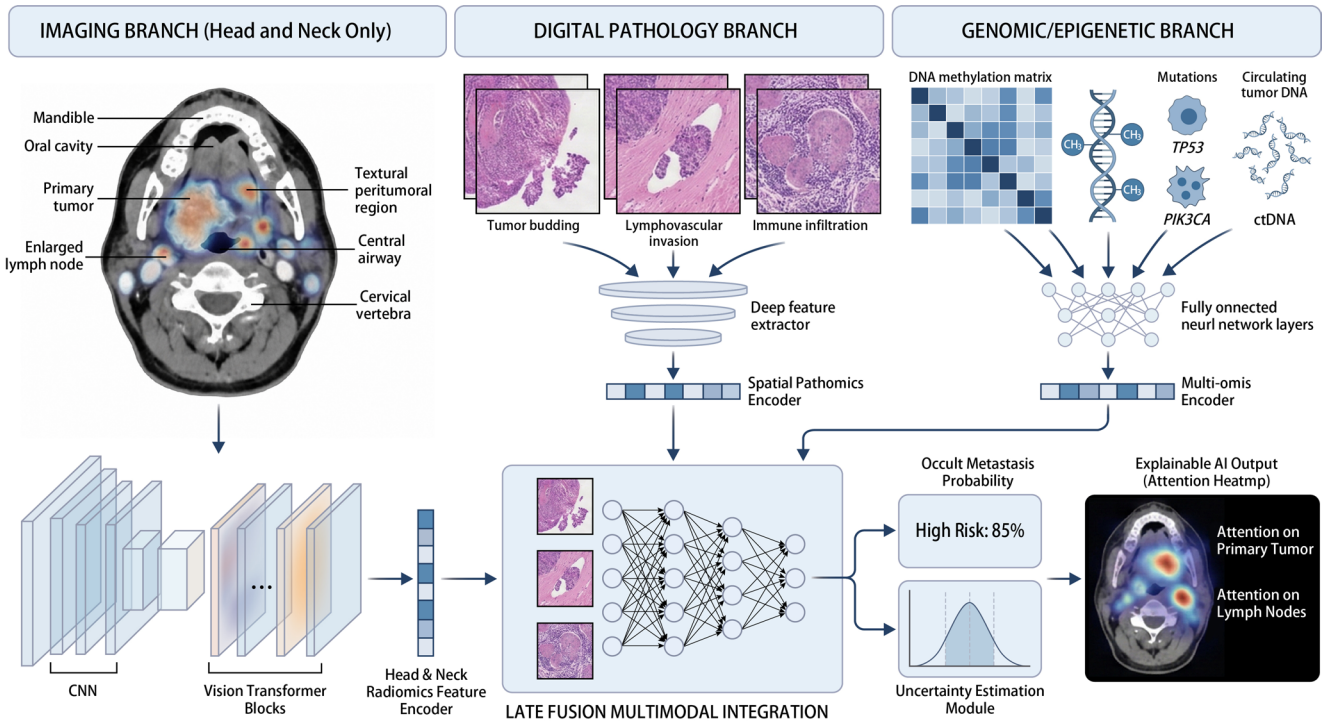

Fig. 3 Multimodal deep learning architecture for head and neck–specific OCLNM prediction. The imaging branch encodes radiomic features from axial cervical CT/MRI slices encompassing the primary tumor and regional lymphatic basin. The digital pathology branch extracts high-dimensional spatial features from whole-slide images, capturing microinvasion and immune features. The genomic/epigenetic branch integrates vectorized DNA methylation matrices and mutation signatures as stable molecular predictors. Feature embeddings from each modality are harmonized through late-fusion integration to generate probabilistic metastasis predictions. Auxiliary modules incorporate uncertainty quantification and explainable attention mapping to enhance clinical interpretability and safety. This architecture exemplifies the transition from single-modality classification toward biologically informed, uncertainty-aware multimodal risk modeling

issue is the field's heavy reliance on 'late-fusion' designs. Simply averaging the final probability scores of two separate networks misses the point of multi-omics. It ignores the actual biological crosstalk—for instance, how an *ARHGAP15* mutation biologically drives the macroscopic tissue changes eventually captured on an MRI.

Ground Truth Integrity and the "Black Box" Dilemma

There is also a persistent problem with how we define the 'ground truth' for training these models. We typically rely on routine H&E staining to classify a node as pN0, but standard pathology inherently misses a certain percentage of micrometastases and isolated tumor cells. This introduces baseline label noise right from the start. Compounding this is the interpretability issue. Instead of chasing higher accuracy metrics through pure statistical pattern recognition, future AI architectures need to be anchored in biology. A practical step forward would be cross-validating abstract radiomic textures against concrete spatial pathomics—like the CARNS1 + and CBX1 + immunosuppressive niches discussed earlier. This is necessary to prove an algorithm is actually detecting pre-metastatic tissue remodeling, rather than just overfitting to random scanner artifacts.

Temporal Asymmetry in Clinical Feasibility

Finally, we must consider the reality of surgical oncology workflows. Many proposed multi-omics models assume all data types are equally accessible, ignoring massive disparities in cost and turnaround time. Radiomics can be extracted rapidly and non-invasively from standard preoperative scans. Spatial transcriptomics and deep sequencing, however, are expensive, take weeks to process, and suffer from biopsy sampling bias. These constraints often clash with urgent surgical scheduling. Because of this, trying to force all available data into a simultaneous fusion model is clinically impractical. A more realistic strategy is a hierarchical, step-wise integration. Fast, low-cost radiomics should serve as the first-line screening tool, while deep molecular profiling is reserved as a second-tier triage, triggered only when the initial radiomic algorithms flag a case as highly uncertain.

Current Challenges and Future Directions

Clinical Translation Hurdles and Technical Limitations

Although the convergence of multi-omics, machine learning, and digital pathology has catalyzed a paradigm shift in OCLNM research, the transition from silico discovery to real-world clinical application is impeded by several formidable challenges, discussed below.

Data Heterogeneity and Absence of Harmonization: The lack of standardized protocols for omics sequencing and image acquisition across different institutions severely hinders the development of generalizable algorithms. Variations in imaging scanners, contrast protocols, and bioinformatics pipelines inevitably introduce batch effects, making large-scale, multicenter data integration exceptionally challenging.

Lack of External Validation: Currently, most AI models are trained on relatively homogeneous, single-center retrospective cohorts. Lack of rigorous external validation across diverse demographics limits model generalizability.

The "Black Box" Conundrum: The opaque, "black box" nature of deep learning architectures obscures the underlying biological rationale, thereby significantly diminishing trust and adoption among clinical practitioners.

Class Imbalance in Model Training: Given that the true incidence of OCLNM in cN0 HNSCC ranges from 20% to 40%, training datasets are inherently skewed. This substantial positive/negative class imbalance often biases AI classifiers toward the majority class (pN0), compromising the sensitivity required to detect the critical minority class (pN+).

Data Silos: The formulation of high-fidelity multimodal models requires massive longitudinal datasets. However, strict data privacy regulations and ethical constraints regarding patient information-sharing create isolated "data silos," severely restricting international and multicenter data pooling.

Strategic Directions and Technological Solutions

To overcome the challenges described above and permit clinical translation of AI models for OCLNM assessment, future research endeavors must prioritize the following strategic frameworks:

Federated Learning and Standardized Cohorts: To overcome data silos and privacy barriers, adoption of federated learning frameworks is paramount. Federated learning would allow multiple institutions to collaboratively train global AI models without sharing raw patient data. Concurrently, establishing open source, standardized multicenter cohorts with unified longitudinal follow-up is essential for rigorous external validation.

High-Fidelity Spatial Omics and Cross-Scale Mapping: Moving beyond bulk sequencing, the field must embrace cutting-edge spatial transcriptomics and spatial proteomics. These technologies enable in situ, high-resolution mapping of the tumor microenvironment.

Integrating these micro-spatial features with macroscopic imaging will facilitate a truly "cross-scale" understanding of how local immune landscapes and intratumoral heterogeneity drive nodal dissemination.

Explainable AI and Human-in-the-Loop Paradigms: To demystify the AI 'black box' and address the interpretability issues raised above, future pipelines must incorporate explainable AI techniques (e.g., attention maps, SHapley Additive exPlanations) that link computational predictions directly to identifiable biological or morphological features. Furthermore, promoting a so-called human-in-the-loop paradigm, in which AI acts as an augmentative co-pilot rather than an autonomous decision-maker, will dramatically enhance clinical acceptance and enable dynamic, individualized risk monitoring **(**Fig. 4**)**.

Next-Generation Nanodiagnostics and Theranostic Convergence: Clinical translation can be accelerated by optimizing ultra-sensitive liquid biopsy assays and integrating nanotechnology. For instance, the development of novel molecular contrast agents and nanoparticle-enhanced imaging could push the resolution limits of traditional MRI or PET, permitting direct visualization of micro-lesions in vivo.

Fostering Medical-Engineering Interdisciplinary Research: Breaking the boundaries between oncology, bioinformatics, and bioengineering is the ultimate key to clinical translation of AI models for OCLNM assessment. Emerging medical-technical convergences, such as utilizing engineered dendritic cell–derived exosomes for targeted locoregional immune regulation of the lymphatic basin, exemplify the immense therapeutic potential of this interdisciplinary synergy.

Conclusion

The precise assessment of OCLNM remains a formidable challenge in the clinical management of clinically node negative (cN0) HNSCC. Reliance on unimodal conventional imaging or traditional pathological evaluation is inadequate to capture the highly complex and covert nature of microscopic metastatic cascades. The advent of high-throughput multi-omics, spanning genomics, epigenetics, and spatial transcriptomics, coupled with advanced AI has ushered in a transformative era of precision oncology.

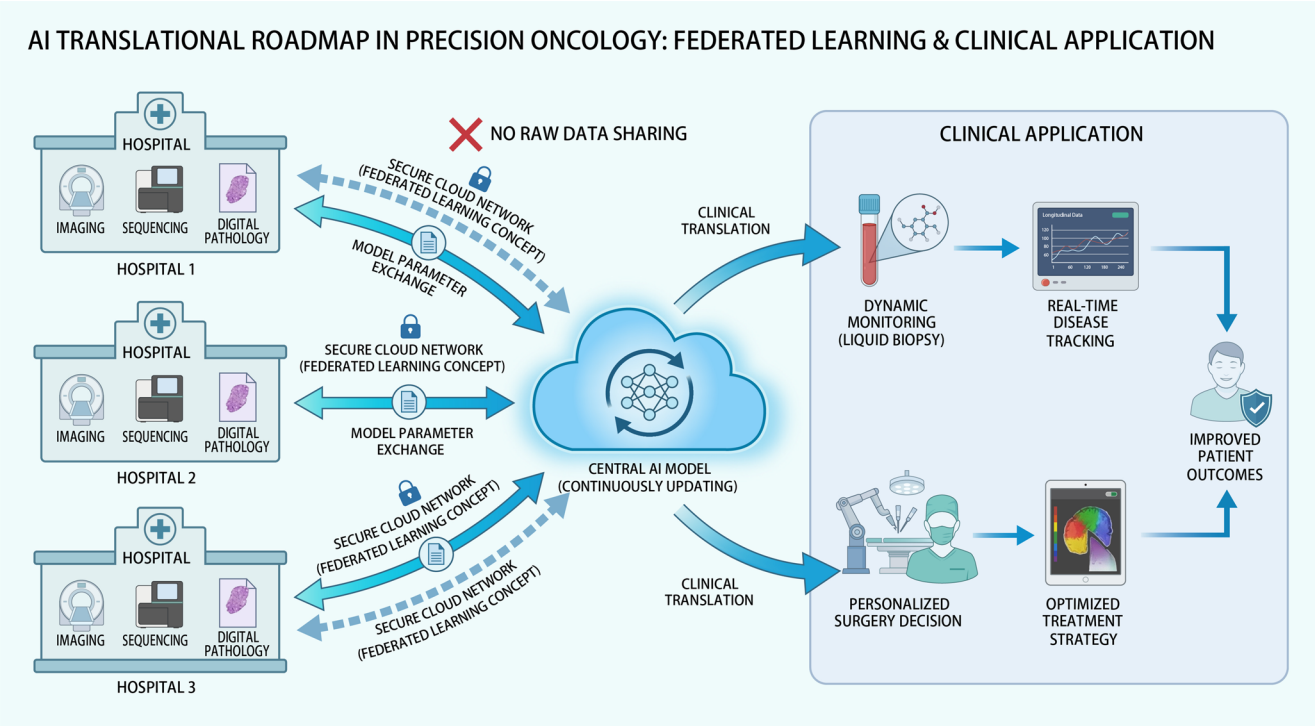

Fig. 4 Translational roadmap: from data silos to federated, explainable, and clinically deployable AI ecosystems. This roadmap can be followed to translate multimodal OCLNM prediction from research to clinical implementation. Distributed institutional datasets, including imaging, multi-omics, and digital pathology profiles, are integrated via federated learning frameworks that preserve data privacy while enabling collaborative model training. Standardized acquisition protocols and cross-center validation mitigate heterogeneity and enhance generalizability. Explainable AI modules and human-in-the-loop paradigms foster clinician trust by linking computational outputs to interpretable biological features. Ultimately, integration with liquid biopsy–based dynamic monitoring and next-generation nanodiagnostics enables continuous, noninvasive surveillance of metastatic evolution. This ecosystem-level strategy aims to overcome clinical translational hurdles and embed precision risk stratification into routine head and neck oncology practice

By decoding multidimensional biological data, AI-driven liquid biopsy and radiopathomic pipelines offer unprecedented sensitivity for early detection and risk stratification. Ultimately, the future of OCLNM diagnosis lies in cross-scale multimodal fusion. Integrating macroscopic imaging habitats, microscopic spatial pathomic signatures, and underlying epigenetic reprogramming (e.g., genome-wide DNA methylation) into a cohesive "panoramic virtual biopsy" represents the ultimate diagnostic paradigm. This integrative architecture will not only shatter existing diagnostic ceilings but also resolve the pervasive clinical dilemma of "overtreatment versus undertreatment." By translating these multi-omics computational models into routine clinical practice, we can pave the way for highly individualized, safe de-escalation of surgical interventions, thereby maximizing both survival outcomes and the quality of life for HNSCC patients.

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    - By systematically evaluating histopathological predictors of metastasis, this study highlights the critical micro-morphological features that advanced radiopathomics models must target to improve risk stratification.
- Shen H, Zhang T, Wang S. A Prediction Model for Lymph Node Metastasis of Oral Squamous Cell Carcinoma

Based on Multiple Risk Factors. Clin Exp Dent Res. 2024;10:e70046. https://doi.org/10.1002/cre2.70046.

○ This paper demonstrates the clinical utility of integrating multiple macroscopic and microscopic risk factors into a cohesive prediction model, serving as a foundational concept for multimodal risk assessment.

- Oh J, Hoelzl J, Carlson JCT, Bill R, Peterson HM, Faquin WC, et al. Spatial analysis identifies DC niches as predictors of pembrolizumab therapy in head and neck squamous cell cancer. Cell Rep Med. 2025;6:102100. https://doi.org/10.1016/j.xcrm.2025.102100.

  ○ This study elegantly demonstrates the power of spatial transcriptomics in identifying highly specific immune-stromal niches that predict treatment response in head and neck cancer. It provides crucial microscopic validation for evaluating the tumor immune microenvironment, a core component of modern spatial pathomics.

- Zhou Y, Wang Y, Shi X, Wang J, Zang Z, Zhang L, et al. Multi-center multi-omics integration predicts individualized prognosis in medullary thyroid carcinoma. Nat Commun. 2026;17:432. https://doi.org/10.1038/s41467-025-67533-7.

  ○ This study represents a major breakthrough in multi-omics integration. It successfully demonstrates how federated, multi-center omics data can be harnessed to achieve highly individualized prognostic predictions, a strategy highly applicable to HNSCC.

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  ○ This paper provides a robust framework for cross-scale fusion by integrating macroscopic MRI data with microscopic whole-slide images using deep learning architectures, highlighting its direct utility in clinical treatment prediction for HNSCC.

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  ○ This research elegantly illustrates the power of integrating radiomics with biopsy-adapted immunoscores. It provides a strong proof-of-concept for the cross-scale "panoramic virtual biopsy" approach advocated in this review.

- Cai D, Zhu C, Huang H, Cao Y, Cai G, Chen Z, et al. Lymph Node Metastasis-Associated Spatiotemporal Mapping of the TFF3-Linked Niche in Breast Cancer: Integrating Radiogenomic Signatures with Immune-Ecosystem Remodeling. Research (Wash D C). Washington, D.C.; 2026;9:1016. https://doi.org/10.34133/research.1016.

  ○ The authors successfully integrated radiogenomic signatures with immune-ecosystem remodeling mapping to predict lymph node metastasis. This research offers a highly translational "cross-scale" paradigm that directly supports the feasibility of utilizing panoramic virtual biopsies in clinical oncology.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

Conflict of interest The authors confirm that there are no conflicts of interest.

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