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Review

Pathological extranodal extension in head and neck cancer: A prognostic biomarker with therapeutic ramifications and diagnostic pitfalls

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ABSTRACT

Extranodal extension (ENE), defined as the pathological spread of metastatic tumor cells beyond the lymph node capsule into adjacent soft tissues, represents a critical prognostic biomarker in head and neck squamous cell carcinoma (HNSCC). Its presence correlates with aggressive tumor biology, increased risk of locoregional recurrence, distant metastasis, and reduced survival, thereby influencing staging systems and therapeutic strategies. The 8th edition of the AJCC Cancer Staging Manual has formally incorporated ENE into nodal classification for select HNSCC subsites, with the 9th edition of UICC (2025) extending this to HPV-positive oropharyngeal carcinomas. Despite its prognostic significance, diagnostic evaluation of ENE—particularly microscopic ENE—remains challenging due to interobserver variability, ambiguous histological thresholds, and limitations of imaging modalities. The emergence of artificial intelligence and radiomics offers promising tools for improving ENE detection. Moreover, recent studies underscore the importance of quantifying ENE extent, with macroscopic ENE (>2 mm) portending a worse prognosis and guiding the need for adjuvant chemoradiotherapy. However, controversies persist, especially regarding its role in HPV-positive tumors and the utility of traditional cutoffs. This review synthesizes current evidence on the biological underpinnings, diagnostic complexities, therapeutic implications, and future research directions related to ENE in HNSCC, advocating for standardized assessment protocols to optimize patient management and outcomes.

1. Introduction

Extranodal extension (ENE) refers to the pathological extension of metastatic carcinoma beyond the lymph node, characterized by penetration and disruption of the tumor through the whole thickness of the LN capsule into the surrounding connective tissue or soft tissue stroma [1,2]. The presence of ENE is linked to several adverse clinical outcomes [3,4]. ENE is indicative of a more aggressive tumor phenotype, characterized by the ability of cancer cells to infiltrate beyond the lymph node capsule. This invasive behavior complicates surgical management by increasing the risk of incomplete resection and residual microscopic disease, which in turn raises the chances of local recurrence [3,5]. Moreover, ENE is a strong predictor of distant metastasis, as tumor cells that have breached the nodal capsule are more likely to disseminate to distant organs [6,7]. This heightened metastatic potential contributes significantly to a poorer overall prognosis and reduced survival rates in patients with ENE-positive disease.

ENE was first recognized in 1930 during a retrospective analysis of autopsy samples from 20 patients with head and neck cancer [8]. Later, in 1971, Bennett and colleagues identified a notable correlation between the presence of ENE and decreased survival outcomes in cancers of the larynx and hypopharynx [9]. Further, ENE was identified as a negative prognostic factor in several cancers including colorectal carcinoma and breast cancer [2,6,10–12]. Initial observations of ENE primarily focused on its prognostic significance, revealing that its presence correlated with increased rates of regional and distant recurrence, as well as poorer overall and disease-free survival outcomes.

In the context of head and neck squamous cell carcinoma (HNSCC), ENE serves as a potent biomarker of tumor aggressiveness and a determinant of adverse clinical outcomes [2,4]. It indicates the tumor's enhanced ability to invade, infiltrate, and disseminate beyond local anatomic confines, thereby correlating with a significantly higher risk of locoregional recurrence, distant metastasis, and reduced overall survival [2,4]. The biology underlying ENE reflects a phenotype characterized by

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increased invasiveness, enhanced motility, and potential resistance to conventional therapies [2,13]. Given the consistent association of ENE with poor clinical outcomes, the 8th edition of the *American Joint Committee on Cancer (AJCC) Cancer Staging Manual* introduced a pivotal change by incorporating ENE into the pathological nodal (pN) classification for select head and neck cancer subsites, particularly oral cavity, oropharynx (human papilloma virus (HPV)-negative), larynx, and hypopharynx SCC [14,15]. In contrast, the 7th edition (2010) did not include ENE in the pN classification, relying primarily on lymph node size, laterality, and number of metastatic nodes for staging. This transition in the 8th edition underscores the prognostic significance of ENE and its role in guiding therapeutic decisions and prognostication [14–16]. 9th edition (2025) of Union for International cancer control (UICC), TNM Classification of malignant tumors, defines Clinical Extranodal Extension (cENE) by the presence of tumor invasion beyond the lymph node capsule, manifesting as involvement of overlying skin, infiltration into adjacent soft tissues with deep fixation to underlying musculature or nearby anatomical structures, or clinical signs indicative of perineural involvement. Increasingly, imaging modalities are being adopted as standard tools to detect clear evidence of extranodal extension in the clinical setting. Pathological Extranodal Extension (pENE) should be diagnosed only when tumor cells, initially confined within a lymph node, are observed to extend completely through the lymph node capsule into the surrounding connective tissue. This transgression may occur with or without an accompanying stromal or desmoplastic reaction. Moreover, the presence of a soft tissue tumor deposit at an anatomical location corresponding to a regional lymph node basin should be regarded as equivalent to a lymph node harboring extranodal extension. They have also introduced documentation of ENE in HPV positive oropharyngeal carcinoma [17].

Despite its acknowledged prognostic value, the practical assessment of ENE remains fraught with challenges [2,13]. From a histopathological perspective, the diagnosis of ENE—particularly microscopic ENE—is subject to inter-observer variability, with pathologists differing in thresholds for interpreting tumor extension beyond the nodal capsule [18]. The lack of universally accepted histologic criteria, such as the extent of extranodal spread or the degree of stromal reaction, contributes to variability in diagnosis and reporting.

Radiologic evaluation of ENE is similarly problematic. Imaging modalities including computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography-computed tomography (PET-CT) may suggest ENE based on indirect signs, such as nodal irregularity, infiltration into adjacent fat, or obliteration of fascial planes [19,20]. However, the sensitivity and specificity of these features are modest, particularly in detecting microscopic ENE [21]. Furthermore, there is no consensus on standardized imaging criteria for diagnosing ENE, leading to inconsistencies in clinical and radiologic staging [2].

Another emerging area of uncertainty relates to the prognostic role of ENE in HPV-associated oropharyngeal squamous cell carcinoma (OPSCC) [22,23]. HPV-positive OPSCC exhibits distinct biological behavior, marked by better treatment response and overall prognosis compared to HPV-negative HNSCC. Retrospective data suggest that the presence of ENE may not confer the same adverse prognostic implications in HPV-positive cases, raising important questions about its staging and therapeutic relevance in this context [24–27]. Consequently, the AJCC 8th edition staging system notably omits ENE from nodal classification in HPV-positive OPSCC, further emphasizing the nuanced and evolving understanding of this feature [28]. It is important to acknowledge, however, that the majority of these investigations involved limited sample sizes and may have lacked sufficient statistical power to draw definitive conclusions regarding the prognostic significance of pathological (p) ENE in HPV-related OPSCC, particularly in this subset of patients who generally exhibit favorable survival outcomes and a lower incidence of adverse events. In recent years, accumulating evidence has indicated that pENE (particularly when exceeding 1 mm) in HPV-positive OPSCC is associated with poorer survival outcomes and diminished regional disease control [13,29–31]. In fact, in meta-analysis by Benchetrit et al., authors systematically analyzed pooled data of 1349 patients from 6 studies to determine whether the presence of ENE in HPV-positive OPSCC was independently associated with poorer clinical outcomes. Their meta-analysis revealed that ENE in this setting does, in fact, correlate with significantly worse overall survival and loco-regional control. Notably, the adverse impact was more pronounced in cases of macroscopic ENE, particularly when the extension exceeded 1 mm [29].

In light of these complexities, this review comprehensively examines the biological rationale, clinical utility, diagnostic challenges, and therapeutic implications of ENE in head and neck cancers. By incorporating insights from recent clinical trials, meta-analyses, and evolving guidelines, we aim to elucidate the current state of knowledge on ENE and highlight the unresolved issues and future directions in its application.

2. Biological basis and clinical significance of ENE

ENE refers to the phenomenon where tumor cells breach the lymph node capsule, invading the surrounding perinodal tissues [1]. The presence of ENE is a significant prognostic factor. In colorectal cancer, patients exhibiting ENE have demonstrated worse cancer-specific survival and disease-free survival rates [34]. Similarly, in HNSCC, ENE has been associated with increased locoregional recurrence and distant metastasis, underscoring its role in tumor aggressiveness [32].

Biological Hypothesis Underpinning the Process of Extranodal Extension (ENE): The biological hypothesis underlying ENE is rooted in the concept that tumor cells upon colonizing lymph nodes, can acquire or retain invasive and migratory phenotypes that allow them to breach the nodal capsule and invade surrounding extranodal tissues [2,10]. This process is thought to mirror the epithelial-to-mesenchymal transition (EMT) and is facilitated by complex interactions within the tumor microenvironment (TME) of the lymph node, involving immune modulation, stromal remodeling, and angiogenesis [33,34].

At the molecular level, ENE is hypothesized to result from a cascade of sequential, yet highly interrelated biological events that transform tumor cells within the lymph node into an invasive, immunoevasive, and migratory phenotype [7]. These processes enable cancer cells not only to survive and proliferate within the lymphatic system but also to breach the lymph node capsule and infiltrate surrounding soft tissues [33,35]. The major biological steps implicated in ENE include:

a) **Acquisition of an Invasive Phenotype via Epithelial-Mesenchymal Transition (EMT):** Similar to the primary tumor, one of the earliest and most critical steps enabling tumor cells to invade beyond the lymph node capsule must be the acquisition of a mesenchymal, motile phenotype via EMT [36,37]. This process is characterized by the downregulation of epithelial markers, notably E-cadherin—a calcium-dependent transmembrane glycoprotein that maintains intercellular adhesion and epithelial tissue architecture—and the upregulation of mesenchymal markers such as vimentin, N-cadherin, and fibronectin [38,39]. Loss of E-cadherin is particularly central, as it disrupts adherens junctions, allowing tumor cells to lose cohesion, detach from the nodal metastatic mass, and migrate through the extracellular matrix (ECM) [40,41]. EMT is not only a phenotypic switch but also an orchestrated gene expression program often driven by transcription factors such as Snail, Slug, Twist, and ZEB1/2 [42].

Importantly, EMT is facilitated by cues from the TME, including hypoxia, inflammatory cytokines like TGF-β and TNF-α, and matrix-remodeling enzymes [33]. These microenvironmental factors activate intracellular signaling pathways (e.g., SMAD, NF-κB, PI3K/Akt), promoting transcriptional reprogramming and fostering a more invasive and migratory phenotype that favors capsular invasion [33,43,44].

b) **Matrix Degradation and Capsule Invasion:** Following EMT, tumor cells require enzymatic assistance to breach physical barriers. This is achieved through the secretion of matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, which are capable of degrading components of the ECM (collagen, laminin, fibronectin) and the fibrous capsule [45,46]. These proteolytic enzymes are either secreted directly by tumor cells or induced in adjacent cancer-associated fibroblasts (CAFs) and tumor-associated macrophages (TAMs) through paracrine signaling [47–49]. The combined enzymatic degradation of ECM and capsular structures will facilitates the physical invasion of surrounding soft tissue, establishing extranodal disease [50].

c) **Immunoevasion and Immune Modulation:** For successful ENE, tumor cells must evade immune surveillance [51]. Within lymph nodes with metastasis, there is often a dominance of immunosuppressive cell populations, including regulatory T cells (Tregs), M2-polarized TAMs, and myeloid-derived suppressor cells (MDSCs) [52–54]. These cells secrete immunosuppressive cytokines (e.g., IL-10, TGF-β) and inhibit cytotoxic T cell activity. Additionally, upregulation of immune checkpoint molecules such as PD-L1 on tumor or stromal cells inhibits T-cell activation via PD-1 signaling [54]. This local immune suppression may creates a permissive environment for tumor cells to migrate beyond the nodal capsule without being eliminated by host immunity [55–57].

d) **Hypoxia and Angiogenic Switch:** As nodal metastases expand, hypoxic microenvironments emerge due to inadequate vascularization [55]. Hypoxia-inducible factors (HIFs), particularly HIF-1α, become stabilized under these conditions, activating downstream genes that support tumor progression. These include VEGF (vascular endothelial growth factor), which promotes neoangiogenesis, providing metabolic support for the expanding tumor mass [55, 58–60]. Hypoxia also enhances EMT and promotes an aggressive, migratory phenotype by altering mitochondrial metabolism, upregulating glycolytic enzymes, and influencing cell motility pathways [61,62].

e) **Stromal Co-option and Mechanical Stress-Induced Rupture:** Beyond cellular and enzymatic processes, **mechanical forces** may play a role in ENE. As tumor burden within a confined lymph node increases, intratumoral pressure may mount, which may contribute to capsular rupture or extrusion of tumor cells [63]. Additionally, tumor cells may **c**o-opt and reprogram stromal elements, such as lymph node fibroblasts similar to the fibroblast in primary tumor, into myofibroblasts or CAFs [64,65], which in turn produces ECM components (e.g., tenascin-C, collagen I/III) and **pro-invasive factors** [64,66]. This stromal remodeling may weaken capsular integrity and provides directional cues for tumor egress. The interplay of biological invasion and mechanical stress synergistically accelerates extranodal dissemination.

This hypothesis positions ENE not as a passive consequence of tumor size, but as an active, biologically driven process reflecting aggressive tumor behavior. This underpins its value as a prognostic marker in cancers such as HNSCC, where ENE correlates with higher recurrence rates and poorer survival.

Clinically, ENE is a powerful independent predictor of poor outcomes in patients with HNSCC [67]. Numerous studies have confirmed its association with worse overall survival (OS), disease-free survival (DFS), and disease-specific survival (DSS) [67]. Further, several meta-analysis involving significant number of patients has demonstrated that the presence of ENE is associated with a two- to eight-fold increased risk of disease recurrence and mortality, after adjusting for other independent prognostic factors including positive margins and smoking. [4,68,69]. These associations persist even after adjusting for other nodal parameters such as number and size of involved nodes, suggesting that ENE reflects distinct biological aggressiveness rather than simply advanced nodal disease [2]. The value of these studies lies in their ability to isolate the impact of ENE on survival outcomes. They demonstrated that the presence of ENE could reduce survival by up to 50 % and highlighted that ENE serves as a more reliable prognostic indicator than traditional staging systems [70–72]. Patients with ENE-positive nodal metastases frequently require more aggressive multimodal therapy, including surgery followed by adjuvant chemoradiotherapy (CRT) [29,72].

Based on the observations of histopathological prognostication, Johnson et al. demonstrated that adding chemotherapy to adjuvant radiation therapy progressively lowered the risk of death and recurrence, including local, regional, and distant relapse in patients of HNSCC with ENE [73,74]. Further, studies have demonstrated that in patients with ENE, incorporating adjuvant CRT can improve outcomes. In their study, de Almeida et al. investigated the treatment implications of postoperative CRT in patients with oral cavity squamous cell carcinoma (OCSCC) exhibiting minor versus major ENE. The study stratified ENE into minor (≤2 mm) and major (>2 mm) and analyzed outcomes following surgery and adjuvant CRT. Results showed that patients with major ENE experienced improved disease control and survival with the addition of chemotherapy to postoperative radiotherapy, supporting the use of aggressive multimodal therapy. However, in cases of minor ENE, the benefit of adding chemotherapy was less pronounced, raising questions about the necessity of intensified treatment in this subgroup [75]. Furthermore, a multi-center retrospective study conducted in Japan focused on OSCC patients with a single lymph node metastasis and ENE. The study found that adjuvant therapy (radiotherapy or concomitant CRT) after surgery was associated with better disease-specific survival and overall survival rates compared to surgery alone, suggesting the importance of adjuvant treatment in such cases [76].

3. Diagnostic and interpretive challenges

In the 7th edition of the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) staging system, the presence or extent of ENE was not formally incorporated into the nodal (N) classification for HNSCC. While the extent of pENE was occasionally described as macroscopic or microscopic, this distinction remained purely descriptive and had no impact on staging. Macroscopic pENE referred to soft tissue invasion that was evident either clinically or on gross examination, while microscopic pENE was characterized by tumor extension beyond the lymph node capsule detectable only under a microscope. Consequently, nodal staging was determined solely by the size, number, and laterality of metastatic lymph nodes, with ENE status excluded from the classification criteria [16]. It was only in 8th edition (2017) that prognostic significance of ENE was underscored and noted, for its role in guiding therapeutic decisions and prognostication [14,15].

In HNSCC, research after the publication of 7th edition of UICC/AJCC staging manual, moved beyond simply detecting the presence of ENE to also quantifying its extent, recognizing that the degree of ENE may carry additional prognostic significance. This shift reflects an effort to refine risk stratification and improve prognostic accuracy, ultimately guiding more tailored therapeutic approaches [2]. Study by Yamada et al., aimed to assess whether ENE progression levels could effectively identify OCSCC patients at high risk of recurrence who would benefit most from intensified adjuvant therapy. ENE progression was categorized into three levels (A-C), and their associations with patient outcomes were analyzed (A: few tumor cells outside of the capsule, B: slight invasion of soft tissue with capsular destruction and C: macroscopic invasion, with visible tumor invasion into perinodal fat or muscle). Out of 441 OSCC patients, 87 exhibited ENE. The recurrence rate was highest in those with type C ENE at 69.8 %. Thirteen of these patients died due to distant metastasis. The 3-year disease-specific survival rate for type C patients was 49.0 %, and these patients had significantly worse prognoses ($P < 0.01$). Multivariate analysis further indicated that ENE progression, particularly type C, was a key factor influencing patient prognosis ($P < 0.01$). Overall, the findings support the level of ENE

progression as a valuable prognostic marker in OCSCC [77]. Further emerging evidence suggested that a threshold around 2 mm could serve as a critical cutoff for assessing the prognostic significance of ENE; however, the available data were limited and showed inconsistent results across studies. Wreesmann et al., investigated the prognostic significance of ENE in OCSCC through a pathological review of 245 neck dissection specimens. ENE was present in 44 % of cases. Time-dependent receiver operating characteristic (ROC) analysis identified 1.7 mm as the optimal cutoff point for ENE extent, distinguishing between minor ($\leq$1.7 mm) and major (>1.7 mm) ENE. Multivariate analysis revealed that patients with major ENE had significantly lower disease-specific survival (DSS) compared to those with minor ENE, whose DSS was comparable to patients without ECS. The study concluded that ENE becomes clinically relevant in oral cavity SCC when it extends more than 1.7 mm beyond the nodal capsule [78]. Mamic et al. investigated the prognostic significance of ENE in patients with OCSCC presenting with occult neck metastases. Among the cohort, 90 patients (51.7 %) were found to have occult nodal disease, and ENE was identified in 41 cases (23.6 %). Using ROC curve analysis, the study determined 1.9 mm as the optimal threshold for ENE in relation to both DFS and OS. Patients with ENE exceeding 1.9 mm exhibited significantly poorer OS and DFS compared to those with ENE $\leq$ 1.9 mm or no ENE. Multivariate analysis confirmed that ENE > 1.9 mm served as an independent predictor of adverse outcomes, emphasizing that the measurable extent of ENE—rather than its mere presence—holds important prognostic value in OCSCC, particularly in patients with clinically negative necks [79]. A systematic review and meta-analysis by Mermod et al., noted a direct correlation between the level of ENE and poor prognosis. The meta-analysis confirmed that patients with extensive ENE had higher rates of loco-regional recurrence and distant metastasis, emphasizing the need for precise assessment of ENE extent in prognostication and treatment planning [68]. Based on the emerging evidences, UICC/AJCC staging system 8th edition, categorized ENE into microscopic ENE ($\leq$ 2 mm) and macroscopic ENE (> 2 mm), aiming to distinguish between minimal and extensive tumor spread beyond the lymph node [14,15,80], as a more specific measurement according to research findings was difficult to use in clinical practice. This stratification appeared to have clinical relevance; several retrospective and prospective analyses have since shown that macroscopic ENE is more strongly associated with poor overall survival, increased rates of locoregional recurrence, and distant metastasis compared to microscopic ENE. A study by Joshi et al., observed that patients with macroscopic ENE (>2 mm) exhibited a 2-year survival rate of 0 %, in contrast to a 72.6 % survival rate in those with microscopic ENE. Additionally, the distant failure rate was higher in the macroscopic ENE group (44.83 %) compared to the microscopic ENE group (22.22 %) [81]. Similarly, an analysis utilizing the National Cancer Database (in year 2022) examined 7975 patients with OSCC who underwent primary surgical intervention. The study reported that both microscopic and macroscopic ENE were associated with decreased OS compared to patients without ENE. Specifically, macroscopic ENE conferred a higher hazard ratio for mortality, highlighting its more detrimental impact on prognosis. Interestingly, the study also noted that the addition of chemotherapy to adjuvant radiation did not provide a significant survival benefit for patients with either form of ENE, suggesting that treatment strategies might need to be tailored based on ENE extent [82].

Accurately detecting and classifying ENE in HNSCC however presents significant challenges, particularly when distinguishing between microscopic ($\leq$2 mm beyond the nodal capsule) and macroscopic (>2 mm) ENE. The absence of universally standardized definitions exacerbates these difficulties, particularly in the pathological assessment of ENE [4]. Microscopic ENE, defined as tumor cells extending just beyond the lymph node capsule and detectable only by histological examination, remains a challenging and variably interpreted diagnostic feature in HNSCC. The lack of consensus regarding its definition and assessment introduces significant variability in both clinical decision-making and research outcomes [4].

When the lymph node capsule is obliterated, the extent of extranodal spread can be approximated by reconstructing the capsule's original boundary (Fig. 1). However, this approach is often challenging or unfeasible, particularly in cases where the lymph node is completely replaced by metastatic tissue, as seen in soft tissue metastases. Histological signs such as small tumor clusters breaching the capsule, perinodal desmoplasia (Fig. 2), and inflammatory changes are often subject to interobserver variability, contributing to diagnostic inconsistency among pathologists. The presence of desmoplastic reaction—fibrous tissue responses to tumor invasion (reduplicated capsule)—can resemble the lymph node capsule, leading to potential misinterpretation; in these cases the original capsule can be presumed to be the innermost aspect of the thickened capsule closest to the lymph node parenchyma (Fig. 2) [52,78].To clarify regarding the thickened capsule, HN CLEAR (Head and Neck Collaborative for Laboratory and Epidemiologic Annotation of Risk) gave recommendations; as the host tissue response may lead to the formation of multiple layers of capsule-like structures even when the original capsule is no longer distinctly visible. In such cases, the original capsule is typically inferred to be the innermost layer of the thickened fibrous tissue adjacent to the lymph node parenchyma. Tumor extension beyond this inferred original capsule is considered evidence of ENE [83].

In some instances, the lymph node capsule may be inherently thin, disrupted, or discontinuous—particularly near the hilum, where blood vessels and nerves enter and exit the node. This natural deficiency or absence of a clearly defined capsule can make it challenging to determine whether tumor cells have truly breached the capsule or are simply adjacent to it (Fig. 3 and Fig. 4) [1,4,83]. When the capsule is incomplete or partially missing, pathologists may attempt to infer or virtually reconstruct its boundaries based on the remaining identifiable segments. However, this interpretive process introduces subjectivity, potentially leading to diagnostic variability and reduced reproducibility [4,83]. These challenges are further compounded when the lymph node is entirely replaced by tumor (soft tissue metastasis). Such ambiguities can lead to inconsistencies in diagnosing ENE, as pathologists may need to infer the capsule's boundaries based on surrounding structures, potentially affecting diagnostic accuracy and inter-observer reliability [1,4]. However, according to the 8th edition of the TNM Classification of Malignant Tumors (2025), a discrete soft tissue tumor deposit located in the anatomical region corresponding to a regional lymph node basin—in the absence of identifiable nodal tissue—should be considered equivalent to a metastatic lymph node exhibiting extranodal extension (ENE). This recommendation aligns with the clinical implications of such deposits, which often reflect aggressive tumor biology and worse prognosis [17].

Another diagnostic difficulty arises when evaluating grossly

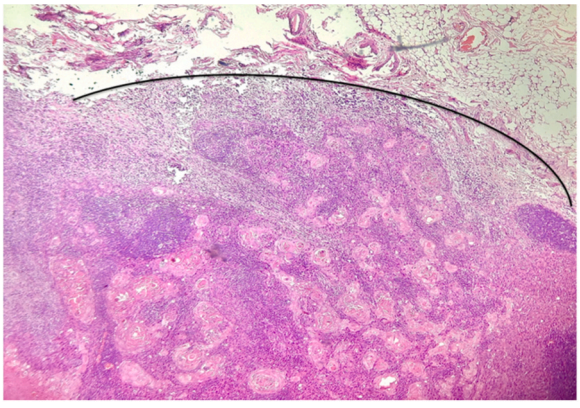

Fig. 1. Reconstruction by extrapolating the original boundary of the lymph node capsule, in cases with obliterated lymph node capsule.

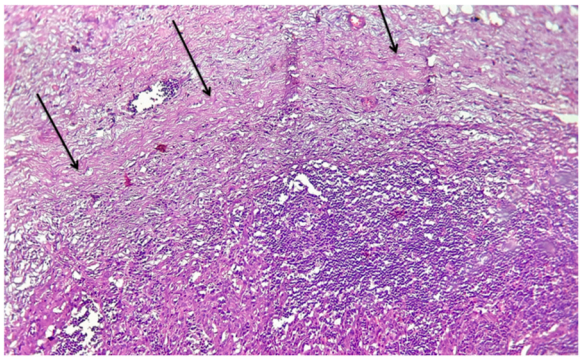

Fig. 2. Peri-nodal desmoplastic response, difficult to ascertain the capsule.

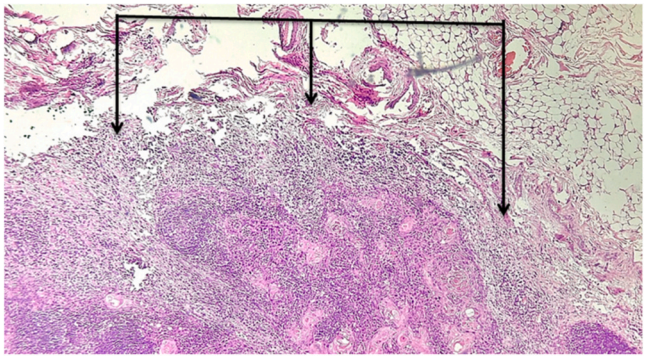

Fig. 3. Thin peri-nodal capsule.

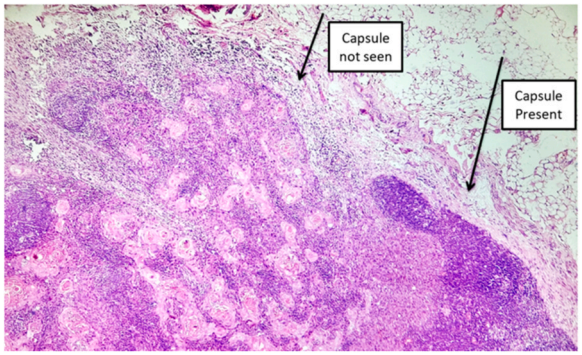

Fig. 4. Partially broken peri-nodal capsule.

confluent lymph nodes, often termed matted or coalescent nodes. To determine whether ENE is genuinely present, it is recommended to review deeper or step sections. These confluent nodes may simply reflect closely aggregated lymph nodes with fibrotic or thickened capsules, rather than actual histological evidence of tumor invasion beyond the nodal capsule [84]. Further dilemma may arises, when a primary tumor appears to merge directly with a nearby lymph node. In such cases, some pathologists may choose to classify it as ENE due to the inability to conclusively rule it out. Conversely, others may limit the diagnosis of pathological ENE (pENE) only to instances where a residual lymph node capsule is present and clearly disrupted by tumor invasion, distinguishing it from direct tumor continuity [84].

Because ENE can be focal, it may be overlooked if the entire lymph node is not submitted for microscopic assessment or if sections are taken from suboptimal planes. Thorough embedding and deliberate orientation of nodes suspected for ENE are essential for accurate detection [1]. Artifactual displacement of tumor cells into perinodal tissue [Toothpaste Effect] during surgical manipulation can resemble ENE under the microscope. This is often suggested by scattered, non-cohesive tumor fragments without a directional infiltration pattern. Recognizing such surgical artifacts is crucial to avoid misdiagnosis [1,85]. While IHC may assist in difficult cases, it is not routinely necessary for evaluating ENE. Inappropriate application of markers such as p63 or CK5/6 can highlight background reactive or inflammatory cells, potentially complicating interpretation. Histologic architecture should always guide the diagnosis [83].

Further, diagnostic pitfalls can arise from tissue processing artifacts or tangential sectioning of lymph nodes, that mimic or obscure true capsular invasion [83]. Distinguishing true microscopic ENE from pseudo-invasion or reactive perinodal fibrosis can be particularly challenging. The variability in how different institutions define and report microscopic versus macroscopic ENE further compounds the issue, potentially influencing staging, prognosis, and therapeutic decisions. These challenges underscore the urgent need for clearly defined histopathological criteria and improved interobserver agreement to enhance diagnostic reliability and patient stratification [4].

Several studies have highlighted the low interobserver agreement in assessing ENE. For instance, a study involving Danish head and neck pathologists, evaluating ENE in oropharyngeal SCC cases demonstrated only moderate reliability and agreement. Even after implementing standardized evaluation methods, significant inconsistencies persisted in histopathological diagnoses of ENE, underscoring the need for more precise diagnostic criteria [86]. Similarly, research by van den Brekel et al. assessed the interobserver and intraobserver agreement among ten pathologists diagnosing ENE in 41 tumor-positive lymph nodes. The study revealed considerable variability, with interobserver kappa values ranging from 0.14 to 0.75 and overall kappa values of 0.42 and 0.49 in two scoring sessions. These findings indicate substantial discrepancies in ENE assessment, which could impact treatment decisions and prognostication [87]. The lack of consensus on histopathological definitions further complicates ENE evaluation. A systematic review identified 44 distinct definitions of ENE in HNSCC literature, reflecting significant variability in diagnostic criteria. This inconsistency diminishes the external validity of study results and challenges the perception of histopathological diagnosis as the gold standard [1]. To address these issues, the Head and Neck Cancer International Group (HNCIG) conducted a three-round modified Delphi process with 19 international pathology experts. The outcome was a set of consensus recommendations for histologically detected ENE diagnostic criteria, terminology, and reporting. These guidelines aim to standardize ENE assessment, thereby improving diagnostic accuracy and consistency across institutions [32].

The HNCIG has provided a comprehensive set of consensus-based recommendations aimed at standardizing the histopathological diagnosis of ENE in HNSCC [32]. The consensus focused on standardizing the terminology and diagnostic criteria for ENE in head and neck cancers. ENE was precisely defined as the extension of metastatic tumor cells beyond the lymph node capsule into the surrounding perinodal soft tissue, differentiating it from related but distinct findings such as capsular involvement or perinodal inflammation. A significant advancement was the sub-classification of ENE into minor ($\leq$2 mm) and major (>2 mm) categories based on the depth of extension, reflecting growing evidence that the extent of ENE has important prognostic value.

To support accurate histopathologic diagnosis, the panel delineated essential features such as unequivocal tumor infiltration beyond an intact lymph node capsule. Supplementary findings—like capsule disruption, desmoplastic response, and lymphovascular invasion—reinforce the diagnosis, while ancillary changes such as perinodal fibrosis or involvement of adjacent structures serve as supportive but non-definitive clues. The consensus emphasized that benign reactive changes should not be misread as ENE. Thorough gross examination protocols, including inking the nodal capsule and comprehensive sectioning, were advised to facilitate the precise identification and measurement of ENE, particularly in subtle cases. Uniform pathology

reporting was strongly advocated, requiring clear statements on the presence and extent of ENE (minor or major) and the identification of soft tissue metastases. The use of ambiguous language like "indeterminate" was discouraged unless adequately explained. The adoption of synoptic reporting formats was recommended to ensure consistency, especially in multicenter trials. The broader aim of these guidelines is to improve staging accuracy, inform therapeutic decisions, and foster international research collaboration. Training and quality assurance, including digital pathology exercises, were highlighted as essential to ensure consistent application of these criteria and enhance patient outcomes in head and neck cancer care [32].

International Consensus Recommendations of Diagnostic Criteria and Terminologies for Extranodal Extension in Head and Neck Squamous Cell Carcinoma: An HN CLEAR Initiative (Update 1, published in *Head and Neck Pathology* [2025]), presents updated international consensus guidelines on the diagnosis and terminology of ENE in HNSCC. The recommendations emerged from the HN CLEAR (Head and Neck Collaborative for Laboratory and Epidemiologic Annotation of Risk) initiative, aiming to standardize ENE assessment to enhance diagnostic accuracy, clinical communication, and prognostic consistency across pathology practices worldwide. The consensus panel, consisting of pathologists and clinical experts from various countries, addressed key areas such as histological criteria for identifying ENE, the distinction between microscopic and macroscopic ENE, and the challenges in cases with equivocal features, including capsular fragmentation, inflammatory responses, and capsular reduplication. The panel emphasized that ENE should be defined as tumor extending beyond the lymph node capsule into perinodal soft tissue, with microscopic ENE being limited and only detectable histologically, while macroscopic ENE is grossly evident or causes architectural distortion. Importantly, the update also provides recommendations for reporting terminology to ensure clarity and clinical utility, advocating for descriptive language that includes the extent and certainty of ENE. The guidelines encourage pathologists to document cases where the capsule is not clearly identifiable and to use defined criteria to infer ENE based on tumor localization relative to lymph node structures. These harmonized criteria are expected to reduce interobserver variability and enhance prognostication, treatment decisions, and research in head and neck oncology [83].

Since the release of the eighth edition of the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) staging manual in 2019, multiple studies have sought to validate the 2-mm threshold distinguishing major from microscopic ENE in HNSCC, yielding mixed results. Mamic et al. identified a 1.9 mm threshold as prognostically significant through ROC curve analysis in their multivariate assessment of OCSCC. Notably, their study focused exclusively on cases with clinically occult nodal metastases [79]. Conversely, other research has challenged the prognostic value of the 2-mm cutoff. In their 2021 study, Arun et al. noted that ENE extending beyond 5 mm was linked to worse outcomes but only in univariate analysis., and larger metastatic deposits were more likely to exhibit ENE. Multivariate analysis identified metastasis to lower neck levels as an independent predictor negatively impacting both DFS and OS [88]. In 2025, Panda et al. conducted a retrospective single-center analysis, the study focused on treatment-naïve head and neck cancer patients whose final histopathology revealed ENE. Out of the patient cohort, 122 individuals (12.4 %) exhibited pathological ENE. Traditionally, ENE is categorized into minor (Mi-ENE, $\leq$2 mm extension) and major (Ma-ENE, >2 mm extension) based on a 2 mm cutoff. However, this study found no significant differences in OS and DFS between patients with Mi-ENE and Ma-ENE, both in unmatched and propensity score-matched analyses. Specifically, in the unmatched cohort, OS was 40.9 % for Mi-ENE versus 33.6 % for Ma-ENE ($p = 0.7$), and DFS was 34.05 % versus 26.12 %, respectively ($p = 0.5$). In the matched cohort, hazard ratios (HR) for OS and DFS were 1.08 ($p = 0.82$) and 0.95 ($p = 0.89$), respectively. Further analysis using ROC curves suggested that a 4 mm cutoff for ENE extent provided a better prognostic distinction, with an area under the curve (AUC) of 0.52. When assessing the impact of adjuvant CRT, only patients with Ma-ENE demonstrated significant OS (HR: 0.42, 95 % CI: 0.18–0.9) and DFS (HR: 0.33, 95 % CI: 0.15–0.70) benefits from CRT. Additionally, the revised 4 mm cutoff was predictive of therapeutic benefit with adjuvant CRT (HR: 0.27, 95 % CI: 0.1–0.73). These findings suggest that the traditional 2 mm threshold may not adequately stratify risk in ENE-positive head and neck cancer patients. A 4 mm cutoff appeared more effective in identifying patients who would benefit from treatment intensification with adjuvant CRT [89]. The findings by Panda et al. suggest that the traditional 2 mm threshold may not adequately stratify risk in ENE-positive head and neck cancer patients. A 4 mm cutoff appears more effective in identifying patients who would benefit from treatment intensification with adjuvant CRT. However further prospective studies with larger sample size including both HPV-negative and HPV-positive tumors are needed to validate this and challenge the 2 mm cut-off.

Radiologic identification of ENE is also limited [90]. While imaging modalities such as contrast-enhanced CT, MRI, and PET/CT can suggest ENE based on features like irregular nodal margins, infiltration into adjacent fat, or loss of nodal architecture, these findings are not definitive [90]. Abdel-Halim et al. by systematic review and meta-analysis evaluated the diagnostic accuracy of various imaging modalities—such as CT, MRI, and PET/CT—in detecting histopathological ENE in head and neck cancer. The study synthesized data from multiple sources to determine the sensitivity, specificity, and overall reliability of imaging techniques compared to histopathological findings, which remain the gold standard. Results indicated that while imaging can aid in preoperative assessment, its accuracy in identifying ENE is limited, with variable sensitivity and specificity across modalities. The authors concluded that imaging alone should be interpreted cautiously and in conjunction with clinical and pathological findings [91]. Park et al. in their systematic review and diagnostic meta-analysis, noted that both CT and MRI show moderate diagnostic accuracy for detecting ENE, with MRI generally offering slightly higher sensitivity. However, both modalities demonstrated limitations, emphasizing the need for cautious interpretation and potential integration with clinical and histopathological data for accurate diagnosis [92]. Maxwell et al. reported that although CT imaging could detect some radiologic indicators suggestive of ENE, its overall diagnostic accuracy was suboptimal. They concluded that CT alone is not a reliable tool for predicting extracapsular spread (ECS), noting considerable inter-observer variability and limited diagnostic performance, with the area under the ROC curve ranging between 0.65 and 0.69 [93].

Moreover, the criteria for radiologic ENE are not standardized across institutions, leading to inconsistencies in diagnosis and staging [94]. A study by Su et al. concluded that imaging, especially MRI and PET/CT, plays a valuable role in the preoperative evaluation of ECS, but highlighted the need for standardized imaging criteria and further research to improve diagnostic performance and consistency in clinical practice [95]. Emerging technologies, including radiomics and artificial intelligence (AI)-driven imaging analysis, offer potential to improve ENE detection, but these approaches are still in early stages of clinical validation [96]. Huang et al. explored the use of an evolutionary learning model to predict ENE in patients with HNSCC using contrast-enhanced CT images. Recognizing the prognostic significance of ENE and the limitations of traditional radiologic assessments, the researchers developed a machine learning model based on genetic algorithms to optimize feature selection and classification. The model was trained and validated on a dataset of patients with pathologically confirmed HNSCC and demonstrated superior performance compared to conventional radiologic evaluation, with higher sensitivity, specificity, and AUC. The findings highlight the potential of integrating artificial intelligence with imaging data to enhance preoperative prediction of ENE, thereby supporting more accurate clinical decision-making and individualized treatment planning [97].

The Head and Neck Cancer International Group (HNCIG) has tried to

established consensus recommendations to standardize the diagnosis of ENE detected through radiological imaging in head and neck cancers [90]. These guidelines aim to harmonize clinical practice and research by providing clear diagnostic criteria and a classification system for imaging-detected ENE (iENE).

Key Diagnostic Criteria for iENE:

1. Indistinct or Irregular Nodal Margins: Blurred or uneven edges of lymph nodes on imaging.
2. Extension into Perinodal Fat: Tumor infiltration spreading into the fat surrounding the lymph node.
3. Extension into Adjacent Structures: Tumor spread into nearby tissues or organs.
4. Conglomerate/Matted/Coalescent Nodes: Multiple lymph nodes appearing fused or clustered together.

Conversely, the panel advises against using nodal necrosis and capsular thickening as criteria for identifying iENE. Implementing these guidelines is expected to refine patient selection for treatments such as transoral robotic surgery (TORS). Accurate preoperative identification of iENE can prevent under treatment or overtreatment, thereby optimizing therapeutic outcomes and minimizing unnecessary morbidity [90].

4. ENE and HPV-positive oropharyngeal cancer

The clinical implications of ENE in HPV-positive OPSCC remain a subject of ongoing investigation. While HPV-positive OPSCC generally has a favorable prognosis, recent studies suggest that the presence of ENE may still confer a worse outcome [5,98].

While earlier studies did not find a significant prognostic impact of ENE in HPV-positive OPSCC [22,68,99–102], more recent large-scale analyses have demonstrated that ENE is associated with worse survival outcomes. A study by An et al., analyzed 1043 patients with HPV-positive OPSCC who underwent primary surgery. It found that ENE was associated with decreased 3-year OS (89.3 % vs. 93.6 %; $P = .01$). However, among ENE-positive patients, there was no significant difference in OS between those who received adjuvant chemoradiotherapy and those who received radiotherapy alone, suggesting that the addition of chemotherapy may not provide additional survival benefit in this subgroup [98]. Another large scale study, study involving 4153 patients with HPV-positive OPSCC showed that ENE was an independent predictor of decreased 5-year OS (84.0 % for ENE-positive vs. 92.6 % for ENE-negative; $P < 0.001$). Further, after adjusting for confounding variables, ENE-positivity was associated with almost twice the hazard of death (HR = 1.90; 95 % CI: 1.35–2.67) compared to ENE-negative cases [30]. A comprehensive review by Beltz et al., also highlighted that ENE is associated with poor prognosis in HPV-positive OPSCC [5]. Notably, the AJCC 8th edition staging system does not incorporate ENE into the nodal classification for HPV-positive OPSCC, reflecting the ambiguity in existing evidence [14,15,80]. Accordingly with the data available, we advocate for the systematic documentation of both the presence and extent of ENE in HPV positive OPSCC in the forthcoming AJCC manual. Ongoing trials, such as those evaluating treatment de-escalation strategies in HPV-positive disease, may further help clarify the true clinical utility of ENE in this context. Infact, the 9th edition (2025) of UICC have introduced the documentation of ENE for HPV positive OPSCC, similar to the criteria for HPV negative OPSCC i.e., tumor is present within the lymph node with evidence of definite transgression through the entire thickness of the capsule into the surrounding soft tissue, with or without stromal reaction [17].

5. Implications for treatment and prognostication

The identification of ENE carries profound implications for both treatment planning and prognostic evaluation in HNSCC. Several clinical trials have attested this [Table 1]. In patients undergoing surgical resection for HNSCC, the detection of ENE is a well-established criterion for escalation of adjuvant therapy. Specifically, ENE is a major indication for the administration of postoperative CRT rather than radiotherapy alone, based on high-level evidence from pivotal randomized controlled trials such as RTOG 9501, EORTC 22931 and others [Table 1]. These landmark studies demonstrated that the addition of concurrent chemotherapy significantly improves locoregional control and overall survival in high-risk patients, including those with ENE and/or positive surgical margins or locoregionally advanced HNSCC [104–106].

Despite these findings, the clinical application of ENE status in therapeutic decision-making requires careful consideration of multiple factors. One major challenge lies in the heterogeneity of ENE itself, particularly the distinction between macroscopic (gross) and microscopic (subclinical) ENE. While macroscopic ENE is clearly associated with a more aggressive disease phenotype and worse outcomes, the prognostic significance of microscopic ENE remains less definitive. Some studies suggest that in microscopic ENE concurrent CRT is not associated with improved OS relative to radiotherapy [107], raising questions about the necessity of intensive CRT in these patients. Given the potential for increased toxicity with CRT and the unclear survival benefit in patients with microscopic ENE, treatment decisions should be individualized [106]. Clinicians must weigh the risks and benefits of adding chemotherapy to adjuvant radiotherapy in patients with microscopic ENE, considering factors such as patient comorbidities, performance status, and preferences. Furthermore, the presence of ENE must be interpreted in the context of HPV status, especially in OPSCC. HPV-positive OPSCC is typically associated with a more favorable prognosis, and there is growing interest in whether patients with HPV-related tumors and ENE should be treated with the same aggressive postoperative regimens as their HPV-negative counterparts [13,108]. The potential for overtreatment in this subgroup, with its attendant risks of treatment-related morbidity—including mucositis, xerostomia, fibrosis, and long-term dysphagia—necessitates a more nuanced, risk-adapted approach.

6. Future directions and research needs

Several promising avenues for future research exist in the field ENE assessment and management, each with the potential to significantly enhance diagnostic accuracy, prognostication, and individualized therapy [2,97,109]. A critical first step is the standardization of histopathologic definitions and reporting criteria for ENE. Current variability in how ENE is defined, particularly with respect to microscopic versus macroscopic extension and soft tissue invasion, hampers reproducibility and interobserver agreement across institutions. Establishing universally accepted histologic thresholds, along with structured reporting templates, would promote consistency in diagnosis, improve staging accuracy, and facilitate comparison across clinical trials.

In parallel, the integration of digital pathology and machine learning (ML) algorithms into routine histopathologic evaluation, may offer a transformative approach to ENE detection [110,111]. By leveraging computational image analysis, these technologies can identify subtle features indicative of ENE, reduce observer variability, and enhance diagnostic precision, particularly in borderline or ambiguous cases. AI-driven pattern recognition may also support the development of predictive models that incorporate histologic and molecular features to estimate the likelihood of ENE prior to definitive histologic confirmation [112,113].

From an imaging standpoint, the emergence of radiomics—the extraction of high-dimensional quantitative features from medical imaging—combined with artificial intelligence (AI)-based segmentation tools [96,114], holds great promise for improving the preoperative prediction of ENE. These techniques can detect nuanced imaging biomarkers that are beyond the resolution of human interpretation [96,114,

Table 1
Clinical trials for treatment efficacy and prognostication of ENE.

Trial Title	Phase	Status	Objective	Key Findings / Interim Results pertaining to ENE
European Organization Research and Treatment of Cancer; EORTC 22931	Phase III RCT	Completed	Effectiveness of combining cisplatin with radiation therapy versus using radiation therapy alone as adjuvant treatment in patients with stage III or IV HNSCC	Confirmed that ENE-positive patients benefit from combined chemoradiotherapy, establishing ENE as a high-risk factor.
Radiation Therapy Oncology Group; RTOG 9501 (NCT00002670)	Phase III	Completed	Postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck	Demonstrated improved survival in ENE-positive cases treated with concurrent chemoradiation.
RTOG 0234, (NCT00084318)	Phase II	Completed	Postoperative chemoradiotherapy with cetuximab for high-risk HNSCC + cisplatin or docetaxel	Identified an optimal regimen for ENE-positive patients, with ENE serving as a key stratification factor.
Cooperative Group Metaanalysis Bernier et al. [103]	–	–	Pooled analysis of RTOG 9501 and EORTC 22931	ENE-positive patients and/or microscopically involved surgical margins were the only risk factors for which the impact of CERT was significant in both trials.
PATHOS Trial, (NCT02215265)	2015–2025 Phase II/III	Ongoing	To evaluate the feasibility and efficacy of risk-stratified, reduced-intensity adjuvant treatment following transoral surgery in patients with HPV-positive oropharyngeal cancer.	Interim analyses reaffirm that histopathologic ENE remains a critical prognostic marker guiding treatment de-intensification or escalation.
ECOG-ACRIN E3311, (NCT01898494)	2013–2018 Phase II	Completed	To determine if transoral surgery followed by low-dose intensity modulated radiation therapy could maintain oncologic control while reducing treatment-related toxicity in resectable, locally advanced p16-positive oropharyngeal cancer.	Highlighted that histopathologic ENE is a determinant for adjuvant treatment intensification in this subgroup.
ORATOR Trial, (NCT01590355)	Phase II	Completed	Compare surgery versus radiotherapy in early-stage oropharyngeal carcinoma with ENE analysis	Noted that the incidence of ENE was low in this early-stage cohort, suggesting that its impact on post-operative quality of life and functional outcomes was minimal.

CERT: chemotherapy-enhanced radiation therapy

115], offering the potential to identify ENE with higher sensitivity and specificity. Enhanced imaging analysis could thus enable more precise surgical planning, guide neck dissection strategies, and improve patient counseling regarding prognosis and treatment options [116,117].

Importantly, future research should also prioritize well-designed prospective trials to evaluate the feasibility and outcomes of treatment de-escalation strategies in patients with ENE, especially in the context of HPV-positive OPSCC. Given the favourable prognosis associated with HPV-positive disease, it remains uncertain whether all patients with ENE require aggressive multimodal therapy. Identifying subgroups of patients who may benefit from less intensive treatment regimens without compromising oncologic outcomes could reduce treatment-related morbidity and improve quality of life.

7. Application of AI (ML and DL) in the context of ENE with real world examples

The application of Artificial Intelligence (AI)—particularly machine learning (ML) and deep learning (DL)—in the context of ENE is an emerging frontier in oncologic imaging and pathology [118]. Given the significant prognostic and therapeutic implications of ENE, AI algorithms are being developed and validated to assist in its detection, quantification, and prediction, especially in ***HNSCC*** and other solid tumors like breast, lung, and colorectal cancers.

7.1. Machine learning (ML) approaches for ENE prediction

ML techniques—such as support vector machines (SVM), random forests, and logistic regression—have been employed using radiomic features extracted from imaging modalities like contrast-enhanced CT and MRI [119,120]. Radiomics involves converting medical images into mineable data by quantifying features such as shape, texture, intensity, and spatial relationships [121,122].

Real world example: Kann et al. investigated the application of AI, specifically deep learning convolutional neural networks (CNNs), to detect nodal metastasis and ENE in patients with HNSCC. Given the significant prognostic implications of ENE in HNSCC, the authors aimed to develop a non-invasive, automated method to identify these features on standard pre-treatment contrast-enhanced CT scans. The researchers trained and validated CNN models using a large dataset of annotated CT images from patients with pathologically confirmed nodal disease and ENE status. Importantly, the models were developed to function without requiring manual segmentation of lymph nodes, a task that is often time-consuming and subject to inter-observer variability. The study compared the performance of the deep learning models with that of expert radiologists to assess the potential utility of AI in clinical diagnostics. The results demonstrated that the CNN models could accurately identify both nodal metastasis and ENE, achieving an area under the curve (AUC) of 0.91 for nodal metastasis and 0.86 for ENE, which was comparable to or exceeded the diagnostic accuracy of experienced radiologists. This finding is particularly significant as ENE detection on imaging has traditionally been challenging due to its subtle and variable radiographic presentation. In conclusion, the study provided compelling evidence that deep learning algorithms can serve as effective tools in the non-invasive identification of high-risk features such as ENE in head and neck cancer. The authors suggest that such models could support clinical decision-making by enabling early and accurate risk stratification, potentially guiding more personalized treatment approaches. This work represents an important step toward integrating artificial intelligence into radiological evaluation and cancer management [118].

7.2. Deep learning (DL) in ENE detection from imaging

DL, particularly convolutional neural networks (CNNs), can learn hierarchical features directly from raw image data without manual feature engineering [123,124]. CNNs have shown superior performance in detecting complex spatial patterns of ENE, especially when used with cross-sectional imaging like CT or PET-CT.

Real world examples: Ariji et al. investigated the use of DL techniques to improve the detection of ENEin patients with OCSCC. The researchers developed a DL model based on a CNN, specifically using the AlexNet architecture, to analyze contrast-enhanced CT images. The goal was to differentiate between lymph nodes with and without ENE. The training dataset included manually labeled CT slices of lymph nodes confirmed by histopathology after surgical resection. The model was trained to recognize subtle features associated with capsular invasion that might

be overlooked in conventional radiological assessments. The study results demonstrated that the CNN-based model achieved a high classification accuracy of up to 84.0 %, significantly outperforming human radiologists, whose accuracy ranged between 55 % and 63 %. Importantly, the model showed superior sensitivity in identifying both macroscopic and microscopic ENE, suggesting that DL could assist in preoperative risk stratification and improve diagnostic confidence in challenging cases. In conclusion, this study provided promising evidence that DL-based analysis of CT images can enhance the detection of ENE in OCSCC. The integration of such AI tools into clinical workflows could support more accurate, objective, and early identification of high-risk patients, ultimately guiding more personalized and effective treatment strategies [125]. In conclusion, this study provides promising evidence that DL-based analysis of CT images can enhance the detection of ENE in OSCC. The integration of such AI tools into clinical workflows could support more accurate, objective, and early identification of high-risk patients, ultimately guiding more personalized and effective treatment strategies. In another study, Kann and colleagues evaluated a CT-based DL algorithm for detecting ENE in patients with HPV-associated OPSCC. The study utilized imaging data from a multicenter, randomized de-escalation trial (NRG-HN002) to assess the performance of the AI model in a real-world clinical context. The algorithm was trained to identify ENE using contrast-enhanced CT scans and was validated against expert radiologist interpretation and histopathologic confirmation. The DL model demonstrated higher sensitivity and comparable specificity compared to expert radiologists, particularly in identifying subtle or microscopic ENE. Importantly, the study highlighted the potential of AI to standardize and improve pre-treatment ENE assessment, which is critical for treatment de-intensification strategies in HPV-positive OPSCC [126]. This work supports the clinical integration of AI tools for risk stratification and personalized therapy planning in head and neck cancer.

7.3. *Multimodal AI integration: imaging + pathology + genomics*

Recent advances in AI have led to the development of multimodal AI integration pipelines that combine imaging, histopathology, and genomic data to enhance the prediction and characterization of ENE [127]. These multi-omics AI models leverage radiomic features from contrast-enhanced CT scans—such as lymph node shape, border irregularity, and internal heterogeneity—alongside digital pathology-based assessments of capsular invasion and stromal remodeling [128]. Additionally, they incorporate molecular signatures associated with EMT, such as downregulation of E-cadherin and upregulation of transcription factors like Snail and ZEB1, which are known to correlate with invasiveness and ENE risk. Emerging research initiatives from institutions like MD Anderson and Stanford University are exploring such integrated models to provide a comprehensive, biologically informed risk stratification of ENE before surgery. These pipelines not only improve diagnostic accuracy but also enable personalized treatment planning by identifying patients who may benefit from more aggressive surgical approaches or tailored adjuvant therapies based on a combination of morphological, histologic, and molecular predictors. [127,129].

8. Conclusion

ENE represents a pivotal prognostic marker in HNSCC, with well-documented implications for staging, risk stratification, and therapeutic decision-making. Defined as the extension of metastatic tumor cells beyond the lymph node capsule into the surrounding perinodal soft tissue, ENE is recognized as a harbinger of aggressive disease behavior and poor clinical outcomes. Numerous studies have demonstrated that the presence of ENE correlates with increased risks of locoregional recurrence, distant metastasis, and decreased overall survival. Consequently, ENE has been incorporated into the AJCC 8th edition TNM staging system, significantly altering nodal classification and contributing to refined prognostic grouping.

The presence of ENE often necessitates intensification of treatment, such as the addition of adjuvant chemoradiotherapy following surgical resection, especially in high-risk patients. However, the management of ENE-positive cases remains complex and nuanced. Despite its clear adverse prognostic value, challenges persist in the consistent and accurate histopathological diagnosis of ENE. Interobserver variability among pathologists and lack of universally accepted diagnostic criteria—particularly regarding the extent of soft tissue involvement required to define clinically significant ENE—can lead to discrepancies in staging and treatment planning.

Moreover, the biological and clinical relevance of ENE appears to vary across different subtypes of head and neck cancer. For example, in HPV-associated OPSCC, the prognostic impact of ENE may be less pronounced compared to its HPV-negative counterparts, raising questions about the appropriateness of applying uniform treatment protocols across heterogeneous disease entities. Similarly, the therapeutic benefit of treatment intensification in ENE-positive patients remains uncertain in some contexts, especially given the potential for added toxicity without a clear survival advantage.

CRediT authorship contribution statement

Zaheer Sufian: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Shikhar Chohan:** Resources, Data curation.

Informed consent and ethical considerations

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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