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# Perineural Invasion as a Prognostic Marker in Oral and Oropharyngeal Carcinoma — A Review

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### KEYWORDS

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### ABSTRACT:

Perineural invasion (PNI) is a well-recognised pathological phenomenon in which malignant cells infiltrate, surround, or track along nerve sheaths. It represents an alternative route for tumour spread in oral and oropharyngeal squamous cell carcinomas and is increasingly identified as a marker of aggressive tumour biology. The presence of PNI is associated with increased local recurrence, nodal metastasis, and reduced disease-free and overall survival. Mechanistic studies reveal a dynamic and reciprocal interaction between tumour cells and neural elements mediated by neurotrophic factors, chemokines, and matrix-remodelling enzymes that facilitate tumour migration along perineural pathways. Despite strong evidence of its adverse prognostic impact, inconsistencies in histopathological definitions and variations in reporting practices have hindered its uniform application in staging and treatment planning. Contemporary research supports incorporating PNI into multidisciplinary decision-making, particularly for adjuvant therapy considerations. This review synthesises current evidence regarding the epidemiology, biological mechanisms, diagnostic standards, prognostic significance, and clinical management implications of PNI in oral and oropharyngeal carcinomas. It also highlights the need for standardised pathological criteria and prospective validation to establish PNI as a reliable and independent prognostic marker, ultimately aiding in precise risk stratification and improved patient outcomes.

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### Introduction

Perineural invasion (PNI) is defined histologically as tumour cell infiltration in, around, or through nerve sheaths or the perineural space and is recognised across several malignancies as a marker of neurotropism and

aggressive behaviour. <sup>[1]</sup> In head and neck oncology, particularly in oral cavity and oropharyngeal squamous cell carcinomas, PNI has long been observed and variably reported as an adverse pathological finding. <sup>[2]</sup> The clinical significance of PNI is that it provides a



conduit for local extension beyond the primary tumour margins, may be associated with skip lesions and perineural tumour spread detectable radiologically, and is implicated in higher rates of local recurrence and worse survival. [3] Despite this, there remains debate about the magnitude of its independent prognostic impact and how PNI should influence staging, surgical margins and adjuvant therapy recommendations. [4]

## Epidemiology and incidence

Reported prevalence of PNI in oral and oropharyngeal squamous cell carcinoma varies widely, commonly ranging from approximately 10% to over 40% depending on study population, tumour subsite, tumour stage, the thoroughness of histopathologic sampling, and the criteria used to define PNI. [5] Systematic reviews and meta-analyses demonstrate pooled prevalence estimates and reinforce that PNI is common enough to be clinically relevant while also highlighting substantial heterogeneity among studies. [6] Some series focusing on early-stage tumours emphasise that even small, early lesions may harbour PNI and that its presence in early disease is particularly prognostic for recurrence and survival. [7]

## Pathobiology and molecular mechanisms

PNI is now understood not simply as passive tumour extension along pre-existing anatomical planes, but as an active, reciprocal process of cancer–nerve interaction. [8] Tumour cells secrete neurotrophic factors such as NGF, GDNF, and artemin, which promote neurite outgrowth and attract tumour cells, while nerves secrete chemokines and provide a permissive extracellular matrix for tumour invasion. [9] Matrix metalloproteinases remodel perineural connective tissue to allow tumour infiltration, and Schwann cells actively participate in the crosstalk that facilitates the migration and survival of tumour cells along nerves. [10] Experimental models identify signalling axes such as CXCL12–CXCR4 and NGF–TrkA as mediators of PNI, suggesting therapeutic targets to disrupt neurotropic spread. [11]

## Histopathological definitions and reporting issues

Variation in histopathological definitions and reporting practices complicates prognostic interpretation. [12] Some define PNI as tumour cells in an intraneural location, while others include tumour encasing nerves or within the perineural space. [13] Classification systems stratify PNI by nerve calibre, extent, and location, with studies

reporting that extra-tumoural or large-nerve PNI portends a worse prognosis. [14] Immunohistochemical stains like S100 can increase detection rates, but standardised thresholds for significance remain debated. [15]

## Prognostic evidence: outcomes and effect sizes

Retrospective cohorts and meta-analyses show that PNI correlates with higher risk of recurrence and reduced survival. [16] Pooled analyses reveal PNI increases the hazard of death and recurrence independently of T and N stage in many models. [17] Studies on oral tongue cancer found that PNI predicts poorer survival and higher cervical metastasis, influencing elective neck dissection and adjuvant therapy. [18]

## PNI in early-stage disease and implications for surgical margins

PNI in early-stage cancers identifies a subgroup at higher risk of occult nodal metastasis and local recurrence. [19] The finding of PNI on pathology in low-risk resections may prompt adjuvant radiotherapy. [20] The absolute risk attributable to PNI varies by site, and integrating PNI with other features like depth of invasion provides better risk stratification. [21]

## Radiologic perineural tumour spread versus histologic PNI

Microscopic PNI must be distinguished from radiologic perineural tumour spread (PNTS), which involves larger cranial nerves. [22] PNTS indicates advanced disease with major implications for radiotherapy and surgery. [23] Radiologic detection of nerve involvement warrants multidisciplinary management. [24]

## Clinical management and therapeutic implications

PNI often alters adjuvant-treatment decisions. [25] It is considered a high-risk pathological feature supporting postoperative radiotherapy. [26] Intensity-modulated radiotherapy with nerve-target delineation is recommended when PNI or PNTS is present. [27] The role of chemotherapy in PNI-positive disease without other risk factors remains uncertain. [28]

## Integrating PNI into staging and prognostic models

The current AJCC staging does not include PNI as a parameter for oral squamous cell carcinoma, although



several prognostic models do.<sup>[29]</sup> Standardisation of definitions and prospective data collection are essential to refine staging systems.<sup>[30]</sup>

### Limitations and controversies

Some reports suggest that small-nerve or focal PNI has limited prognostic value, whereas extra-tumoral or multifocal PNI retains significance.<sup>[31,32]</sup> Evolving radiotherapy may modify PNI's historical prognostic role.<sup>[33]</sup>

### Future directions and research priorities

Future work should standardise definitions, include nerve size and extent, and integrate PNI data into clinical trials.<sup>[34]</sup> Targeted therapies disrupting neurotrophic signalling may prevent perineural spread.<sup>[35]</sup> Combining radiologic nerve mapping with pathology data could improve treatment planning.<sup>[36-39]</sup>

### Conclusion

PNI is a biologically and clinically important feature of oral and oropharyngeal carcinomas associated with recurrence and reduced survival. Though substantial evidence supports PNI as a prognostic marker, variability in definitions and confounding factors limit its uniform use. Standardised reporting, granular data inclusion, and prospective studies are essential for defining its prognostic weight and guiding therapy.

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