

Review

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Review

A Proposal for Making Perineural Invasion Measurable in HNSCC Preclinical Research

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Abstract

Perineural invasion (PNI) is associated with poor outcomes in head and neck squamous cell carcinoma (HNSCC), yet neural invasion is seldom the outcome around which preclinical models are designed. Perineural infiltration has been observed in orthotopic tumors, but its occurrence alone does not establish whether a model can reproducibly measure nerve entry, extension along a nerve, or response to treatment. In this paper, the criteria for developing PNI-focused models are proposed, by which these outcomes can be distinguished from primary-tumor growth. Some recent studies provide two useful starting points: HO-1-u-1 tongue xenografts exhibit nerve-directed invasion, while direct infraorbital-nerve inoculation of murine oral cancer cells reproduces neural injury, nociceptive responses and impaired oral function. The former permits investigation of invasion from a mucosal tumor; the latter bypasses nerve entry and permits study of established neural disease. Model selection should therefore incorporate this experimental distinction while validation should require prespecified pathological definition, blinded and reproducible sampling, and analysis of neural involvement alongside tumor burden. Imaging and functional measurements should also be tested against histology, and the host immune context should match the mechanism or therapy under investigation. Establishing these measures would allow studies [and scientists] to determine whether an intervention prevents nerve entry, restricts neural spread or preserves function, and whether those effects extend beyond a reduction in tumor size.

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Introduction

Perineural invasion (PNI) describes microscopic tumor involvement of a nerve or its surrounding sheaths [1]. It is distinct from perineural tumor spread (PNTS), which is the clinically or radiologically detectable extension of a tumor along a named nerve [2]. Tumor–nerve contact, microscopic invasion and longitudinal spread represent related but distinguishable observations [3]. For experimental studies, the distinction determines both the model and the outcome, in which a system that measures tumor-cell attraction toward a nerve does not necessarily measure invasion into it.

The clinical association between PNI and adverse outcomes provides a cogent rationale to study these events separately from tumor growth. A meta-analysis of 18 HNSCC studies comprising 3,894 patients associated PNI with worse overall, disease-free and disease-specific survival [1]. A later analysis of 101 studies and 26,062 patients with oral squamous cell carcinoma (OSCC) also found poorer survival and locoregional control in PNI-positive disease [4]. These associations vary with tumor subsite, stage, pathological definition and analytical approach. They establish prognostic relevance, while leaving open the mechanisms through which neural invasion contributes to disease progression and treatment outcomes.

PNI already occurs in some preclinical HNSCC models, and perineural infiltration has been described as a common histological finding in an orthotopic tongue xenograft study designed

primarily to examine lymphangiogenesis and cervical lymph-node metastasis [5]. Other orthotopic studies have likewise placed emphasis on tumor take, volume, survival and nodal dissemination [6,7]. In such systems, neural involvement may be observed without a sampling plan that establishes how often it occurs or how extensively nerves are invaded. A treatment-associated decrease in PNI is therefore difficult to interpret because it may reflect a direct effect on neural invasion, reduced tumor size and fewer opportunities for nerve contact, or differences in tissue sampling.

It is therefore proposed that perineural invasion be prospectively defined and quantified during initial model characterization. Key preliminary evaluations should determine if neural invasion occurs consistently, whether it can be quantified independently of overall tumor volume, and if inter-observer and inter-experimental measurements are reproducible. Addressing these parameters is essential for validating targeted therapies aimed at PNI, associated cancer pain, and clinical outcomes.

What Existing Models Can Establish

Model choice depends on which part of the tumor-nerve interaction is being tested. Two-dimensional culture permits controlled perturbation of tumor cells but lacks tissue architecture; while organoids and organotypic cultures preserve selected tumor features and can support drug-response studies, although neural, vascular, immune and stromal components may require deliberate incorporation [7,8]. Subcutaneous xenografts permit measurement of tumor growth and treatment response outside the oral neural environment. Orthotopic tongue and buccal tumors are better at reproducing local anatomical constraints and can develop invasive and nodal disease, with results that depend on tumor source, implantation site, host and endpoint [9].

Therefore, orthotopic placement nevertheless requires its own validation for a PNI study. Tongue xenografts from different cell lines vary in growth, stromal organization and nodal spread [6,10]; neural invasion must also be characterized rather than inferred from location. Host selection also creates another constraint; human xenografts permit study of human tumor-cell biology but cannot reproduce intact adaptive immunity in an immunodeficient mouse [5]. Syngeneic models retain immune interactions, but their neural phenotype must still be evaluated against human disease. Direct nerve inoculation ensures consistent tumor-nerve contact but bypasses the natural progression of a mucosal tumor toward and into a nerve.

Table 1 relates these models to the questions they can address. A mechanistic finding may require testing in more than one system, particularly when the proposed effect involves both tumor cells and the host response.

Table 1. Comparison of preclinical HNSCC model classes for PNI research.

Model class	Main strength	Relevance to PNI	Principal limitation
Two-dimensional culture and tumor-only spheroids	Rapid perturbation and scalable screening	Can identify tumor-intrinsic migration or survival programs	No intact nerve, tissue architecture, or host response
Nerve-tumor co-culture and organotypic systems	Direct measurement of neurite attraction, tumor migration, and candidate signaling	Permits perturbation of individual tumor-nerve interactions	Limited pharmacokinetics, immunity, and anatomical spread
Subcutaneous xenograft or patient-derived xenograft (PDX)	Reproducible tumor growth and treatment exposure	Can compare growth at subcutaneous and oral sites	Lacks the oral and cranial neural niche; human grafts require immune-deficient hosts
Conventional orthotopic tongue or buccal model	Site-relevant growth, local invasion, and nodal dissemination	PNI may occur and can be recovered by systematic pathology	Requires PNI-specific characterization and a prespecified sampling plan

Carcinogen-induced or genetically engineered model	Multistep tumorigenesis in an immunocompetent host	Can test whether PNI emerges during natural tumor evolution	Long latency, heterogeneity, and uncertain PNI penetrance
Direct sciatic or cranial nerve inoculation	High control over nerve engagement and longitudinal spread	Useful for neural pathology, pain, and intervention studies	Bypasses tumor-to-nerve recruitment and may introduce injection injury
PNI-focused orthotopic platform	Mucosal origin combined with prospective neural endpoints	Intended to measure entry, extension, and treatment response along nerves	Requires formal validation before it can be used predictively

Recent Models Separate Nerve Entry from Established Neural Disease

Hani and colleagues compared five OSCC cell lines implanted into nude mouse tongues and identified a nerve-directed invasion phenotype in HO-1-u-1. Transcriptomic analysis of the cell lines showed enrichment of neural- and glial-related pathways in this line [11]. HO-1-u-1 therefore provides a candidate reference for developing a human PNI xenograft model. Its usefulness for treatment studies will depend on further characterization of PNI frequency, variation between cohorts and the relationship between neural invasion and tumor growth. The immunodeficient host also limits the immune mechanisms that can be examined.

Zhang and colleagues established a syngeneic model by directly inoculating murine oral cancer cells into the infraorbital nerve. The mice developed spontaneous and evoked nociception, impaired oral function, sensory alterations, axonal and myelin pathology, and immune-cell involvement in both tumor and nerve compartments [12]. This model permits investigation of established neural disease and its functional consequences. Because tumor cells are placed within the nerve, it does not test the earlier steps by which a mucosal tumor reaches and enters the neural compartment.

Sciatic-nerve implantation of oral cancer cells has also been used to examine nerve injury and sensitization associated with PNI [13]. Also, a whisker-pad model of cutaneous head and neck squamous cell carcinoma allows assessment of cranial-nerve involvement after tumor growth at a head and neck site [14]. These systems extend the available experimental approaches, but their anatomical and tumor contexts are essential when interpreting results alongside mucosal HNSCC.

These models can be used together to investigate a defined mechanism. A human tongue xenograft could determine whether perturbing tumor cells alters nerve entry, whereas a syngeneic model could assess whether the effect depends on immune interactions. A direct-nerve model could then evaluate disease progression or neural function after invasion is established. Co-culture experiments could clarify whether the response is mediated by tumor-cell migration, neurite growth, Schwann-cell behavior or soluble factors. Hence, concordant findings across models are most informative when each system tests the same proposed mechanism using appropriate outcomes.

Validation of a PNI-Focused Orthotopic Model

The following requirements are proposed for an orthotopic model intended to measure PNI. These measurements should be specified before treatment experiments begin, ensuring that neural invasion and the reliability of its detection are established independently of the intervention being evaluated.

i. Define the anatomical question

The implantation site should correspond to the disease process of interest. Oral tongue, floor-of-mouth, buccal and oropharyngeal tumors arise in different anatomical and biological settings; one implantation protocol cannot be assumed to represent them all. Pilot dissection and histology should identify nearby nerves and establish a site and depth that allow a mucosal tumor to form without direct intraneural injection. Placement near a nerve may increase the frequency of PNI, but tumor

cells must still approach and enter the neural compartment if those steps are the intended subject of study.

The protocol should document the relevant peripheral branches and tissue planes, together with the mouse strain, age, sex and positioning method. Injection coordinates require empirical validation in that setting. Anatomical landmarks alone are insufficient without histological confirmation of where the inoculum and subsequent tumor lie relative to the nerve.

ii. Match tumor source and host to the question

A candidate high-PNI line such as HO-1-u-1 should be compared with a line showing less neural invasion [11]. This comparison would establish whether the assay distinguishes neural phenotypes rather than differences in growth. Cell identity, mycoplasma status, relevant HPV and driver status, growth rate and neural behavior should be documented for each tumor source. Because a larger or longer-established tumor has more opportunity to encounter nerves, comparisons should account for both time and tumor burden.

The host must support the mechanism being tested. Human xenografts are useful for human tumor-intrinsic signaling, whereas studies of intact adaptive immune responses require an appropriate immunocompetent model. Syngeneic, carcinogen-induced and genetically engineered models offer routes to studying those interactions, but their PNI incidence and distribution must first be measured [7,15].

iii. Establish reproducible pathological assessment

Histopathology should provide the reference measure of neural invasion. A prespecified serial-sectioning plan should cover the tumor and the expected proximal nerve trajectory. Hematoxylin and eosin sections can be supplemented by epithelial, neural or Schwann-cell markers where these help resolve the tumor–nerve relationship. In addition, observers should be blinded to experimental group.

Reports should distinguish tumor adjacent to a nerve, circumferential involvement, invasion of a nerve-sheath compartment and extension along the nerve beyond the main tumor. The number and caliber of involved nerves, intratumoral or extratumoral location, and focal or multifocal distribution should be recorded. Length or distance of spread is useful where it can be measured reproducibly. These component observations will allow readers to interpret a proposed score and assess how it relates to existing pathological definitions [1,16]. It is also important that interobserver agreement be established before the score is used as a treatment endpoint.

iv. Measure neural invasion alongside tumor burden

Tumor shrinkage may reduce opportunities for nerve invasion without directly altering tumor–nerve interactions. Conversely, an intervention could restrict neural spread while having little effect on bulk tumor volume. Studies should therefore report PNI incidence and extent alongside primary-tumor burden, with nodal disease and survival included where relevant. The primary question should specify whether treatment is intended to prevent nerve entry, restrict extension along an invaded nerve, modify established neural disease or relieve dysfunction.

Pilot estimates of the selected PNI outcome should inform sample size. Randomization, blinded assessment and transparent reporting of exclusions are particularly important because tissue sampling affects whether invasion is detected. If PNI occurs infrequently or varies widely between control cohorts, an apparent treatment effect may be difficult to distinguish from that variability; the model may need further development before therapeutic comparisons are feasible.

v. Relate imaging and function to pathology

Bioluminescence and fluorescence imaging can follow tumor burden, but their signals do not establish microscopic nerve invasion. A proposed imaging measure, including small-animal magnetic resonance neurography, should be evaluated against blinded histology in the specific nerve and model. Validation should report detection sensitivity, specificity and spatial agreement, as well as the conditions in which the signal fails to distinguish PNI from adjacent tumor.

Functional measurements address consequences that histology alone cannot capture. The infraorbital- and sciatic-nerve studies demonstrate approaches to measuring nociception, oral

function, sensory physiology and nerve morphology [12]. Their interpretation requires matched controls: tumor inflammation can produce pain without PNI, and an intraneural procedure can itself injure a nerve. Sham procedures and appropriately characterized tumor-bearing controls are therefore needed to relate functional changes to invasion rather than surgery or tumor growth alone.

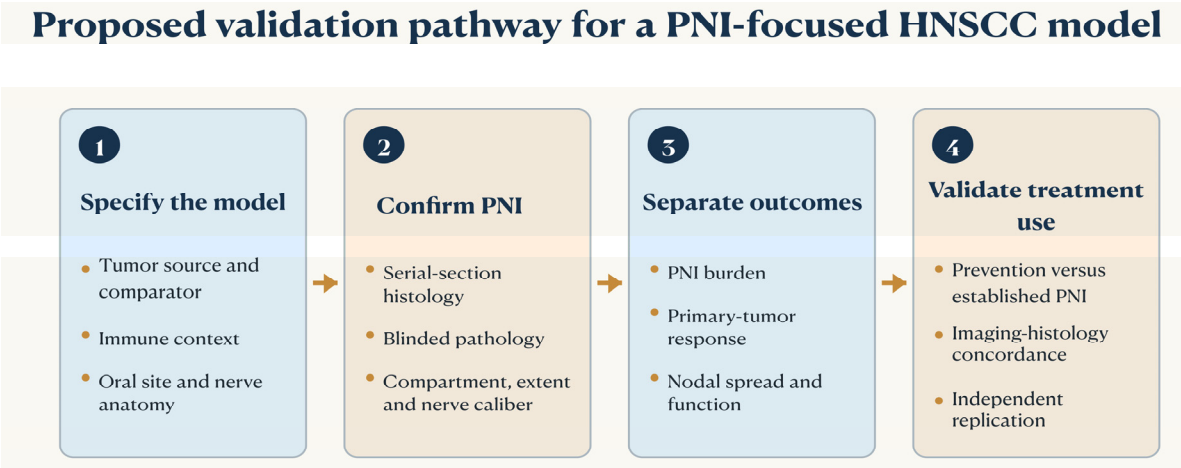


Figure 1. Minimum validation pathway for a PNI-focused HNSCC model. Tumor source, host and implantation site are selected for the intended biological question. Blinded histopathology establishes neural invasion, which is measured alongside primary-tumor burden. Reproducibility and the relationship between pathological and functional measures are assessed before treatment effects are interpreted.

Mechanisms That Can Be Tested with Defined Neural Endpoints

Existing studies identify tumor–nerve signals that could be tested against these outcomes. Human nerve explants and OSCC cells exhibit reciprocal paracrine effects on tumor migration, invasion and growth [17]. In HNSCC specimens and dorsal-root-ganglion co-culture, nerve-derived glial cell line-derived neurotrophic factor was linked to PNI and induced tumor-cell PD-L1 through JAK2–STAT1 signaling [18]. Tumor cells can also alter neuronal behavior: loss of TP53 changes microRNA signaling and promotes adrenergic reprogramming of sensory neurons in oral cancer models [19]. A model with defined PNI measurements would allow these effects on signaling or growth to be related to nerve entry and extension.

Neural signaling also affects the immune response. Studies in syngeneic HNSCC models show that calcitonin gene-related peptide (CGRP) can suppress activated CD8-positive and T helper 1 responses, while interruption of sensory signaling changes tumor growth and immune-cell composition [20,21]. A separate OSCC study connected trigeminal adenosine A2A-receptor signaling with CGRP release and tumor progression [22]. These findings raise a specific question: does the immune effect depend on microscopic nerve invasion, or can it arise through signaling from non-invaded nerves? Pairing PNI histology with spatial immune measurements would help distinguish those possibilities.

Epigenetic regulators, extracellular-matrix programs and axon-guidance pathways have also been associated with PNI in reviews and transcriptomic analyses [23,24]. Spatially matched samples could establish whether tumor cells at invaded nerves differ from cells elsewhere in the same tumor. Perturbation experiments would then be needed to determine whether a chromatin or metabolic difference contributes to invasion or follows from it. At present, a local kynurenine–AHR mechanism

or a therapy-resistant perineural compartment should be treated as a hypothesis requiring direct measurement.

Characterization and Treatment Studies

The first stage is to establish that the assay measures neural invasion consistently: agree on a pathological definition, test the sampling plan, quantify variation between observers and determine how PNI relates to tumor burden. The next stage is to reproduce the phenotype across cohorts and, where feasible, laboratories using characterized reference tumors. Treatment studies can then ask whether a change in neural invasion adds information beyond the primary-tumor response. Preclinical reproducibility alone would not establish prediction of clinical benefit, which requires a separate translational assessment.

Shared tissue-orientation maps, pathological definitions and reference samples would make comparisons between laboratories more interpretable. High- and lower-PNI tumors provide comparators for the assay, while sham and vehicle controls address procedural and treatment effects. Human xenografts and immunocompetent murine tumors should be analyzed within their respective biological contexts. Direct-nerve models can test established neural disease; mucosal orthotopic models are needed when the question concerns recruitment and entry into nerves.

A therapeutic study should ultimately be able to distinguish reduced tumor size from prevented nerve entry, restricted neural extension and preserved function. These outcomes may occur together, but reporting each allows the proposed mechanism of treatment to be evaluated. It also makes a negative result informative: an intervention that reduces bulk growth without altering neural spread may require a different strategy for PNI-associated disease.

Conclusion

Orthotopic tumors with perineural infiltration, the HO-1-u-1 xenograft phenotype, and direct cranial- and sciatic-nerve models already provide experimental access to different stages and consequences of neural involvement [5,11–13]. The next step is to characterize those phenotypes with measurements that can be reproduced and interpreted alongside tumor growth.

An appropriate starting point would be an orthotopic model in which the tumor approaches and invades a nerve, evaluated by blinded histopathology and benchmarked against reference tumors with characterized PNI phenotypes. Such a model would help distinguish whether an intervention prevents nerve entry, limits extension along an invaded nerve, or modifies established neural disease. Once these outcomes can be measured reproducibly and interpreted independently of tumor burden, PNI could serve as a prespecified endpoint in HNSCC studies rather than an incidental finding at the end of an experiment.

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