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# Perineural Invasion in Head and Neck Cancer: An Overview of Challenges and Implications for Treatment

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**ABSTRACT**
In India, 30% of all cancers are head and neck cancers [1]. It ranks as the sixth most prevalent form of cancer worldwide [2]. A high-risk characteristic of oral cavity cancer called peri-neural invasion (PNI) justifies radiation therapy. Better tumour control and survival results have been obtained with the use of radiation therapy in adjuvant situations. According to studies, PNI results from a dynamic interaction between cancer cells and neurons that involves the secretion of signalling molecules by these cells. It has been proposed that radiation works by impairing nerve microenvironment and decreasing tumour cell survival. The difficulties encountered with PNI in head and neck cancer, its clinical result, and methods for identifying high-risk groups in PNI and lowering the likelihood of recurrence in such individuals are all covered in this review paper.

**Keywords:** throat and head cancer Squamous cell carcinoma of the oral cavity invaded the peri-neural radiation treatment

## I. INTRODUCTION

Oropharyngeal and oral cavity cancers are the most typical head and neck cancers in India, followed by larynx and hypopharynx cancers. For resectable oral cavity squamous cell carcinoma (OSCC), surgery is the mainstay of care, while radiation therapy is the most common form of treatment for oropharyngeal, laryngeal, and hypopharyngeal malignancies. In order to enhance the result of treatment, adjuvant radiation therapy is required in post-operative patients with pathological risk factors. In oral cavity cancer, peri-neural invasion (PNI) is a prognostic marker that predicts lymph node recurrence and has a negative impact on both disease-free survival and overall survival [3]. Due to its neurotropic character, PNI is most often found in squamous cell cancer [4]. Yet, owing to its closeness and pathology, it is also observed in skin squamous cell carcinoma, melanoma, and high grade salivary gland tumours. Larynx and hypopharynx show a tendency for PNI of around 20-46%, but the oral cavity and oropharyngeal cancer have a strong predilection of about 25-71% [5].

PNI is an accidental finding in the majority of patients with resected oral cavity cancer and is initially asymptomatic. When the tumour encloses and invades the sizable nerve feeding the organ, it produces pain and paraesthesia.

The prognosis is determined by the PNI's involvement, which may be determined by elements like clinical symptoms, imaging, and its detection in pathology specimens. Smaller nerves (1mm), unifocal, and intra-tumoral PNI, respectively, are thought to have better prognoses than large nerves (>1mm), multifocal, and extra-tumoral PNI.

### 1. PNI's difficulties with head and neck cancer

There are three layers that make up nerve cells: the endoneurium, perineurium, and epineurium. The epineurium is the outermost layer of thick connective tissue encasing nerves, whereas the perineurium surrounds nerve fascicles and the endoneurium is the deepest layer that protects individual axons and Schwann cells. According to Liebig's definition of PNI from 2009, it is a tumour that is "in close proximity to the nerve and involves at least 1/3 of the epineurium or tumour cells inside any of the three layers of the nerve" [6]. Nevertheless, owing to the absence of an uniform definition and universal rules as well as the pathological diversity of how tumours interact with nerves, pathologists' judgement of PNI on histologic sections remains extremely subjective [7].

The biopsy process, slide/tissue block preparation, number of tissue sections investigated, and application of neural stains are all factors in the histological examination that determines the discovery of PNI. When neural stains are utilised, there is a significant range in the reported incidence of PNI in oral cavity squamous cell carcinoma, ranging from as low as 2% to a high of 82% [8]. This obvious discrepancy is due to the absence of a reliable PNI detection technique.

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It has been shown that the expression of certain biomarkers, such as intercellular adhesion molecules, growth factors, and basement membrane proteins, correlates with the existence of PNI in resected specimens. This shows that the mutual interactions between tumour cells and nerves are what cause PNI. The process for finding these biomarkers must be standardised among all pathologists since it is a difficult endeavour.

The preferred investigation for head and neck cancer is magnetic resonance imaging (MRI), particularly for the detection of PNI in unresectable OSCC and the evaluation of recurrence in post-operative patients. Depending on the degree of expansion, it is divided into perineural invasion zones. Zones 2 and 3 are intracranial and are thought to be unresectable, whereas Zone 1, which extends from the tumour to the base of the skull, is thought to be resectable. On MRI, it may be detected in individuals who are clinically symptomatic as (a) direct nerve invasion, (b) nerve enlargement, (c) nerve enhancement, (d) widening or erosion of the skull base foramina, and/or (e) obliteration of the perineural fat at foraminal apertures or the pterygopalatine fossa [9]. During MRI imaging, it might be challenging to spot individuals who are clinically asymptomatic. Fluorodeoxyglucose positron emission tomography (FDG-PET) may detect PNI early in these situations, which can help Doctors design treatments and assess patient responses [10].

**2. PNI results for head and neck cancer**

According to studies, PNI has varying effects depending on the main tumor's stage and location in cases of head and neck cancer.

PNI in OSCC considerably reduced both overall survival and recurrence-free survival, according to earlier studies conducted between 1978 and 1989 [[11], [12], [13], [14], [15], [16]]. In one of these investigations, O'Brien et al. found that the presence of PNI in early-stage OSCC substantially increased recurrence rate ($p = 0.003$) and reduced survival ($p = 0.002$) after a follow-up of 24 months [13].

According to Laske et al., the 5-year recurrence-free survival rates for early stage (stages I-II) and advanced stage (stages III-IV) OSCC with PNI were 60.0% and 41.7%, respectively. The 5-year recurrence-free survival rates for those without PNI were 94.1% for early stage OSCC and 73.5% for advanced stage OSCC. PNI was linked to reductions in 5-year overall survival and recurrence-free survival of 30.3% and 33.3%, respectively [17]. Adjuvant therapy was indicated because to the increase in loco-regional recurrence caused by PNI involvement.

Nair et al. included 1500 patients with PNI and early-stage node-negative OSCC in a retrospective analysis. After doing a multivariate analysis with a median follow-up of 24 months, they discovered that patients with PNI had considerably worse disease-free and overall survival, and that adjuvant radiation significantly increased survival (HR 2.9, $p = 0.022$) [18]. Rajappa et al. examined 118 individuals with T1-2N0 OSCC who tested positive for PNI in a different retrospective research carried out in India. Patients were split into two groups: those receiving adjuvant radiation and those receiving observation, with a 45-month median follow-up. Those who received postoperative radiation had less nodal recurrence than those who underwent observation (8 vs 10 patients, respectively; $p = 0.013$). On Kaplan-Meier analysis, adjuvant therapy was also linked to improved disease-free survival ($p = 0.047$), but no overall survival advantage ($p = 0.54$) [19].

There was no statistically significant relationship between PNI and clinical outcome at other head and neck cancer locations. In oropharyngeal tumours with HPV positivity, PNI was linked to a higher T-stage, according to a research by Albergotti et al. [20]. Nevertheless, Tassone et almeta-analysis .'s found no difference in survival between HPV-associated oropharyngeal malignancies with and without PNI [21]. Hypopharyngeal and laryngeal cancers in a research by Fagan et al. did not exhibit any correlation between PNI and node metastasis [22].
[10:41, 02/04/2023] Sp: 4. PNI high risk categories for head and neck cancer are identified.

Each site in head and neck cancer with PNI responds to radiation therapy differently, thus it follows that each site must have certain high-risk characteristics that increase the likelihood of loco-regional recurrence. The degree of PNI involvement, which might alter loco-regional recurrence, may be the cause of this variation in prognosis.

The number, size, and location of damaged nerves are used to categorise the amount of PNI involvement.

PNI in OSCC includes cranial nerves that innervate tissues including the tongue, buccal mucosa, and palate (maxillary branch of trigeminal nerve V2, mandibular branch of trigeminal nerve V3, and facial nerve VII). These cranial nerves go a long way via the bone and soft tissue structures before reaching the brainstem. Some head and neck locations, on the other hand, are not innervated by a major nerve and have involvement of small calibre nerves inside and around the main tumour.

Miller et al. discovered a strong correlation between the degree of PNI beyond the tumour margin and the duration of disease-free survival. PNI was classified by him as being absent, intra-tumoral (inside the tumour mass), and extra-tumoral (outside tumour edge). As compared to intra-tumoral PNI, he discovered that extra-tumoral PNI was linked with a shorter time to recurrence [23]. In a retrospective research, 229 patients with OSCC and PNI who had major surgery were included. It was determined if they had extra-tumoral or intra-tumoral PNI. As compared to intra-tumoral PNI, extra-tumoral PNI illness had inferior 5-year locoregional control (63.7% vs. 79.5%), disease-free survival (53.8 vs. 72.9%), and overall survival (54.1% vs. 72%). Multivariate study confirmed this importance, demonstrating that extra-tumoral PNI is more aggressive than intra-tumoral PNI [24]. In a similar manner, Caponio et al. reviewed patient records retrospectively to determine the associations between survival and unifocal, multifocal, intra-tumoral, or peritumoral PNI. They discovered that whereas multifocal PNI indicated poor disease-specific survival, intra-tumoral PNI rather than peritumoral PNI was related with lymph node metastasis [25].

PNI was divided into unifocal (1 nerve) and multifocal (many nerves) PNI, and nerves were divided into size categories by Aivazian et al. Both tumours with multifocal PNI and individuals with PNI in nerves under 1 mm had considerably greater rates of local failure [26].

**3. PNI therapy for head and neck cancer is advancing.**

For patients with ECE and/or surgical margins that were microscopically involved, a pooled study of the RTOG 9501 and EORTC 22931 studies from 2006 revealed that concurrent chemo-radiation was superior to radiotherapy alone in terms of outcome [27]. However the subgroup analysis also showed a tendency for chemoradiation to be beneficial in individuals with perineural infiltrate. The degree of PNI participation, however, remained unknown in these research. Thus, more recent research are needed to examine the impact of chemo-radiation while taking the severity of PNI into account. Concurrent chemotherapy may enhance the benefits of radiation over radiotherapy alone because extra-tumoral PNI has poorer loco-regional control than intra-tumoral PNI. Multifocal nerves or a significant nerve involvement (>1mm) may also fall under this.

In resectable OSCC, surgical excision of gross disease with macroscopic nerve involvement is suggested. Gluck et al. published a paper on pattern of failure analysis in OSCC with PNI in 2007. He showed that the cranial nerves that supplied the original tumour site were the most common location for recurrence. When PNI is present, skip metastasis may cause a tumour to advance up to 10 cm from its place of origin [28]. Hence, it was suggested that the target volume for radiation therapy comprise sections of the nerve proximal and distal to the tumour location, as well as the skin innervated by the implicated nerve [29].

Targeted therapeutics are being researched as a means of blocking the paracrine and Schwann cell-mediated PNI pathways. In co-cultures with pancreatic cancer cells, Bakst et al. (2012) demonstrated that exposure to 4Gy of single fraction radiation dramatically decreased GDNF expression and suppressed PNI. It also shown that in mice injected with pancreatic cancer cells, 8Gy of radiation to the sciatic nerve lowered GDNF expression, decreased PNI, and retained nerve function [30]. In order to lower the incidence of PNI, how may radiation treatment change the nerve microenvironment in head and neck squamous cell cancer? Its therapeutic ramifications are yet unknown.

Another potential source of innovative medicines for treating tumours with PNI and extending life in patients with OSCC is inhibitors that specifically target neurotrophins and their receptors, such as anti-GDNF inhibitors [31]. The treatment of head and neck squamous cell carcinoma with PNI may undergo a revolutionary change as a result of recent significant advancements in immunotherapies. By changing how tumour cells, nerves, and Schwann cells interact, targeted medicines may be able to lower morbidity and enhance prognosis in patients with OSCC.

## II. CONCLUSION

The identification of neurotrophins and the characterization of PNI based on imaging, surgery, and pathology are essential for the creation of individualised treatment plans. The radiologist, oncologist, and pathologist should aggressively look for it while evaluating oral cancer. Combining radiation with concurrent chemotherapy, immunotherapy, or anti-GDNF inhibitors has the potential to improve locoregional control and survival. PNI was divided into extra-tumoral and intra-tumoral PNI in the eighth edition of the American Joint Committee on Cancer (AJCC) Staging Manual. Therefore, it will be challenging to categorise such individuals and develop a treatment plan in the absence of a standardised detection technique, characterization, and pathology criteria for PNI.

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