



Editorial

Neural invasion: A distinct pathologic pathway in tumor progression

Indranil Chakrabarti^{1*}

¹Dept. of Pathology, All India Institute of Medical Sciences, Kalyani, West Bengal, India

Received: 28-09-2025; Accepted: 17-10-2025; Available Online: 29-10-2025

This is an Open Access (OA) journal, and articles are distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License](#), which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprint@ipinnovative.com

Neural invasion (NI) represents a unique pattern of tumor spread characterized by the infiltration of malignant cells into, around, or through nerves. It occurs across several morphologic patterns and plays a pivotal role in diagnostic pathology as well as in prognostic stratification. Importantly, NI serves as a distinct route of cancer dissemination— independent of lymphatic or vascular invasion and has emerged as a potent indicator of aggressive tumor biology.

Clinically and histopathologically, neural invasion bears particular significance in malignancies of the head and neck, pancreas, biliary tract, colorectum, stomach, prostate, cervix, vulva, and penis, where it often correlates with recurrence, lymph node metastasis, and reduced disease-free survival.¹

In certain neoplasms, perineural invasion (PNI) may even constitute the exclusive route of metastatic spread, extending beyond the confines of local infiltration.

Peripheral nerves possess a well-organized, layered structure comprising the endoneurium, perineurium, and epineurium. The endoneurium surrounds individual axons and Schwann cells, forming fascicles encased by the perineurium, a multilamellar barrier regulating the intraneural environment. These fascicles, together with their connective tissue matrix, are enclosed by the epineurium, which provides mechanical protection. The perineural space is an anatomical potential space that exists between the neural axons and their surrounding perineural layer.²

Histologically, NI may be classified into two broad subtypes:

1. Perineural invasion (PNI) is tumor cells infiltrating the perineural space.
2. Intraneural (endoneural) invasion (INinv) tumor cells invading within the endoneurium or fascicular structures.

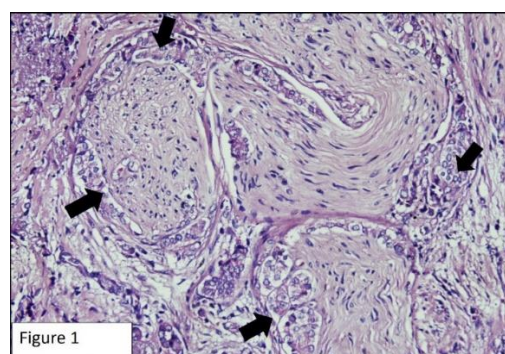


Figure 1: PNI: Tumor cells (black arrows) in the perineural spaces involving >33% of the nerve circumference (Hematoxylin and eosin stain; 200X magnification)

Notably, intraneural spread without accompanying perineural invasion remains uncommon.¹

Historically, Jean Cruveilhier first described neural involvement in head and neck cancer in 1835. Batsakis, in 1985, defined PNI as tumor cell infiltration in, around, and through nerves.^{3,4} Later, Liebig et al. elaborated objective

*Corresponding author: Indranil Chakrabarti
Email: drinch@rediffmail.com

criteria, describing PNI as either tumor presence within any of the 3 layers of neurolemma (Type A) and/or tumor in close proximity to the nerve involving more than one-third (> 33%) of the nerve circumference (Type B).^{4,5} (**Figure 1**)

Brown proposed reserving the term “perineural spread” (PNS) for larger, named nerves that are often clinically or radiologically evident while referring microscopically detected involvement of smaller nerves as PNI.²

More recently, the terminology is increasingly evolving, with “perineural tumor spread” (PNTS) used to describe the presence of cancer cells invading the outer surfaces of nerves while their invasion into the interior being referred to as PNI.^{5,6}

On the other hand, entrapment of an intact nerve within tumor tissue, without true contact or invasion by malignant cells, should not be misinterpreted as PNI, as it lacks comparable biological significance.

Several groups have attempted to establish objective scoring systems, notably in head and neck squamous cell carcinoma (HNSCC) and pancreatic ductal adenocarcinoma (PDAC).^{7,8} Histological parameters evaluated in various studies include the number and size of involved nerves, depth of tumor, location of PNI (intratumoral i.e. located within the malignancy or extratumoral i.e. separated at least 1 mm from the main lesions), circumferential extent of infiltration (focal, circumferential or intraneural), and mitotic activity in the perineural region. Higher composite scores are strongly associated with adverse outcomes, including recurrence and metastasis.

Accurate identification of neural invasion sometimes may require deeper histologic sections and immunohistochemical correlation is employing S-100 for nerve structures and cytokeratin for tumor cells—to confirm definitive involvement.

In conclusion, meticulous gross sampling and systematic histopathologic examination remain essential for accurately recognising and categorising neural invasion. Awareness of its subtypes and diagnostic thresholds is particularly vital in organs where PNI serves as an independent prognostic marker, guiding both prognostication and therapeutic decisions.

Conflict of Interest

None.

References

1. Dwivedi S, Krishnan A. Neural invasion: a scenic trail for the nervous tumor and hidden therapeutic opportunity. *Am J Cancer Res.* 2020;10(8):2258–70.
2. Brown IS. Pathology of Perineural Spread. *J Neurol Surg B Skull Base.* 2016;77(2):124–30. <https://doi.org/10.1055/s-0036-1571837>.
3. Batsakis JG. Nerves and neurotropic carcinomas. *Ann Otol Rhinol Laryngol.* 1985;94(4 pt 1):426–7.
4. Liebig C, Ayala G, Wilks JA, Berger DH, Albo D. Perineural invasion in cancer: a review of the literature. *Cancer.* 2009;115(15):3379–91.
5. Chen SH, Zhang BY, Zhou B, Zhu CZ, Sun LQ, Feng YJ. Perineural invasion of cancer: a complex crosstalk between cells and molecules in the perineural niche. *Am J Cancer Res.* 2019;9(1):1–21.
6. Bakst RL, Glastonbury CM, Parvathaneni U, Katabi N, Hu KS, Yom SS. Perineural invasion and perineural tumor spread in head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2019;103(5):1109–24. <https://doi.org/10.1016/j.ijrobp.2018.12.009>.
7. Totonchy MB, McNiff JM, Suozzi KC, Leffell DJ, Christensen SR. A histopathologic scoring system for perineural invasion correlates with adverse outcomes in patients with cutaneous squamous cell carcinoma. *Dermatol Surg.* 2021;47(4):445–51. <https://doi.org/10.1097/DSS.0000000000002923>.
8. Nozzoli F, Catalano M, Messerini L, Cianchi F, Nassini R, De Logu F, et al. Perineural invasion score system and clinical outcomes in resected pancreatic cancer patients. *Pancreatol.* 2024;24(4):553–61.

Cite this article: Chakrabarti I. Neural invasion: A distinct pathologic pathway in tumor progression. *IP J Diagn Pathol Oncol.* 2025;10(3):99-100.