Imaging of Perineural Spread in Head and Neck Cancer

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KEYWORDS

• Perineural spread • Perineural invasion • Head and neck cancer • Skull base imaging

KEY POINTS

- Perineural spread (PNS) of tumor is a recognized pattern of metastasis occurring in the head and neck.
- Imaging plays a critical role in identifying PNS for adequate staging and treatment planning.
- Understanding the major branches and pathways of cranial nerves V and VII, key anatomic landmarks, interconnections between these nerves, and pearls and pitfalls of PNS imaging can aid in early detection, appropriate therapy, and the best possible chance for cure.

INTRODUCTION

Perineural tumor growth is a recognized pattern of malignant tumor metastasis occurring along the potential space between the nerve and the surrounding sheath. It is important to differentiate between perineural tumor spread (PNS) and perineural tumor invasion (PNI) whenever possible, as they are frequently used interchangeably in the literature and clinical practice. This interchange leads to ambiguity regarding their implications, although such differentiation may not always be feasible or accurate. We define PNS as the macroscopic tumor extension away from the primary tumor site detectable by imaging and PNI as a diagnosis made on histology, typically in a specimen including the primary tumor. Much of what is known about the prognosis and incidence of perineural tumor growth comes from pathologic studies investigating PNI, which we apply to PNS because this is done broadly in the literature and at some point they exist on the same spectrum.

The overall frequency of PNI in head and neck cancers has been reported in the range of 2.5% to 5.0%,[1] with PNS suspected to be lower. Such nerve involvement can be seen in all head and neck cancers, but certain tumors demonstrate a particular proclivity for this method of metastasis and should prompt the careful attention of the radiologist. The most commonly encountered histology is mucosal (5%) or cutaneous (5%–14%) squamous cell carcinoma (SCC), given that it is by far the most common head and neck malignancy, accounting for up to 95% of the approximately 650,000 head and neck cancers diagnosed each year worldwide.[2] The most common sites of mucosal SCC are the larynx, oral cavity, and the tonsils.[3] Adenoid cystic carcinoma (ACC) of the minor or major salivary glands is probably the most notorious offender, with reported rates of PNI in up to 50% of cases, although it comprises only 1% to 3% of all head and neck malignancies.[4] Basal cell carcinoma (BCC), melanoma, especially the desmoplastic type (1%–2%), mucoepidermoid carcinoma, and lymphoma round out the list of additional culprits.[5]

Only 30% to 40% of patients with PNI are symptomatic at presentation,[2] but the percentage is likely higher in clinical PNS, as noted in a series

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of patients with skin cancer in which 59 of 62 patients with PNS were symptomatic.[6] Symptoms include pain, paresthesias, dysesthesias, weakness, or paralysis. Symptoms attributed to multiple nerve distributions suggest more central involvement, such as the cavernous sinus, spread from one cranial nerve (CN) to another, or leptomeningeal disease.[7,8] As in most cases, the clinical history is important to guide a careful search pattern for PNS. The clinical scenarios with which PNS presents include the following:

1. At the time of diagnosis of a primary head and neck malignancy. In this setting, PNS-specific symptoms are often absent or overshadowed by symptoms related to the primary tumor.
2. Recurrence of a previously treated tumor. In this setting, symptoms usually precede imaging diagnosis, although occasionally PNS demonstrated on imaging may be the only manifestation of recurrent disease.
3. Symptoms such as pain, paresthesia, or diplopia with no known primary tumor. Because this presentation is rare and the primary tumors are often occult, patients are frequently misdiagnosed as having, for example, trigeminal neuralgia.

The risk of developing PNI in skin cancer is higher in poorly differentiated tumors, larger primary tumor size, male gender, history of recurrence after treatment, and midface location.[9] PNI is also associated with the increased risk of local recurrence and portends a poor overall outcome with the likelihood of residual disease proportionate to the proximal extent of the tumor[6] and the diameter of the involved nerves.[10] The 5-year local control rate in one series was 25% in patients with skin carcinoma with PNI.[6] Thus, the identification of PNS has important therapeutic and prognostic implications and is critical for adequate staging and treatment planning. Changes in planned treatment may include expansion of the radiation field and/or the surgical resection; for example, the need for mastoidectomy and/or temporal bone resection in case of a parotid tumor with PNS extending into the facial canal. Failure to identify early perineural disease may delay or prevent potentially curative treatment. Knowledge of the commonly involved nerve pathways and vigilance in assessing key landmarks can allow for accurate assessment of disease extent and allow for the best chance of obtaining durable control of the disease.

GROWTH PATTERN AND PATHOPHYSIOLOGY

The pattern of growth in PNS most commonly occurs in a contiguous retrograde fashion from the primary tumor or resection site toward the intracranial cavity, although it may spread in an antegrade direction as well. Early tumor growth is described as preferentially spreading along the axis of the nerve greater than concentric growth.[1] This may explain why some patients with PNS are initially asymptomatic, as concentric growth results in compression of the nerve fibers and the previously described symptomatology. Nerve enlargement may eventually expand or erode the skull base canals and foramina. In addition, "skip" or "resurfacing" lesions with sites of tumor separated by uninvolved nerve may be present, although this pattern has been questioned in a recent study by Panizza and Warren,[11] in which they examined 50 cases of SCC and found no skip lesions. Regardless, evaluation of key landmarks distal from the tumor site remain important from an imaging standpoint.

The pathophysiology of PNS is not well understood. Previous theories suggesting spread occurring passively along paths of least resistance or via epineural lymphatics have been rejected.[12] The most recent theories describe complex interactions in the nerve environment that promote perineural tumor growth. Tumor cells have been shown to upregulate genes that increase cell proliferation and decrease rates of apoptosis in the nerve mileu.[2] Proinvasive signals, such as brain-derived neurotrophic factor, nerve growth factor, neurotrophin-3 and neurotrophin-4, glial cell line–derived neurotrophic factor, substance P, and various chemokines,[2] have been shown to facilitate tumor growth along the nerve. Neural cell adhesion molecule, which mediates cell-to-cell adhesion in neuroectodermal tissues, was found to be expressed in 93% of patients with ACC with PNS.[13] The desmoplastic type of melanoma, a variant with increased incidence of PNS, stains for high levels of p75 neurotrophin receptors mediating PNS.[14]

PNS in the head and neck most commonly involves branches of the trigeminal and facial nerves, as these are the 2 nerves responsible for most of the sensory (**Fig. 1**) and motor innervation of the face. The trigeminal nerve provides sensory information from the face and motor innervation to the muscles of mastication. Understanding the CN anatomy is critical to identifying PNS. Our goal here is to review the major branches and pathways of CNs V and VII, key anatomic landmarks, interconnections between these nerves, and pearls and pitfalls of PNS imaging.

CRANIAL NERVE V1

PNS involving the ophthalmic branch of the trigeminal nerve is uncommon compared with involvement of the maxillary and mandibular