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REVIEW ARTICLE

PERINEURAL SPREAD IN HEAD AND NECK CANCER: CURRENT PERSPECTIVES

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ABSTRACT:
Perineural spread is mechanism of tumor dissemination along a nerve in the head and neck with decreased survival and a higher risk of local recurrence and metastasis. Even though several theories have been proposed, pathogenesis of perineural spread is poorly understood. Advances in diagnostic imaging and the development of new fronts like skull base surgery have brought a transcending change in the treatment of perineural spread in head and neck cancer. Present review is an attempt to discuss pathogenesis, pathways of spread, various diagnostic modalities and treatment protocol.
Key words: Head and neck cancer, Perineural invasion, perineural spread.

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INTRODUCTION

Perineural spread is an under-recognized mechanism of tumor dissemination in the head and neck. It is associated with decreased survival and a higher risk of local recurrence and metastasis.[1]It is very important to distinguish perineural spread from perineural invasion. Perineural invasion is a histologic diagnosis which is beyond the resolution of macroscopic imaging modalities whereas perineural spread is dissemination of tumor cells along a nerve which can be detected with imaging techniques.[2]

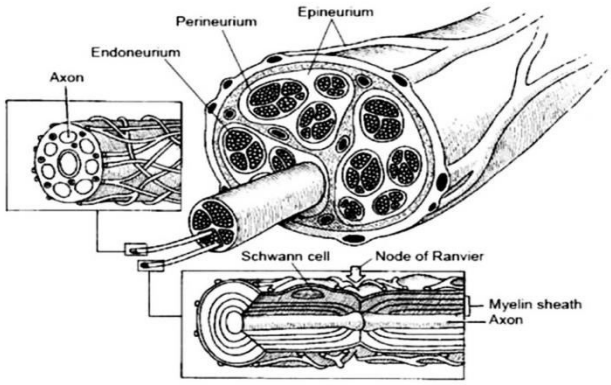

Figure 1: Structure of peripheral nerve sheath

In order to understand the mechanism of perineural spread, it is important to study and perceive the pathogenesis of perineural invasion. This requires the knowledge of the basic structure of peripheral nerve sheath (Fig. 1). The nerve sheath is composed of three connective tissue layers, from outside to inwards – the epineurium, perineurium and the endoneurium.[3] According to Batsakis (1985)[4] perineural invasion can be defined as tumor cell invasion in around and through the nerves. To clarify further, Liebig et al. (2009)[5] suggested that perineural invasion could be stated as finding of tumor cells within any of the three layers of the nerve sheath, tumor in close proximity to the nerve and involving at least 33% of its circumference.

PATHOGENESIS:

The pathogenesis of perineural invasion is poorly understood and was initially thought to be due to spread of tumor through perineural lymphatics. According to this theory, perineural spread occurs by emboli along theperineural lymphatics. As a direct inference, skip metastasis could occur with no direct continuity with the main tumor mass.

However, if this theory was true, it would be impossible to achieve negative surgical margins with enbloc resection of tumor.[4,6] This theory was subsequently discarded as definitive studies demonstrated that lymphatic channels do not penetrate the inner layer of nerve sheath.[4,7,8]

Following the rejection of the above theory, a new mechanism was proposed, which suggested that tumor cells spread along nerve sheath due to the availability of a low resistance pathway. In contradiction, it is now believed that the multiple layers of collagen and basement membrane that compose the nerve sheath make access to this pathanything but low resistance.[4,6]

More recent studies have shown that perineural invasion occurs by way of signaling interactions between tumor cells and nerves. There are several neurotrophic factors involved such as nerve growth factor (NGF),[9,10] glial cell line derived neurotrophic factor (GDNF) and brain derived neurotrophic factor (BDNF).[9] Also, there has been extensive investigation about tumor expression of neural cell adhesion molecule (NCAM), also known as CD56, which is strongly associated with perineural spread. In one of the studies on adenoid cystic carcinoma, 89% of all lesions and 93% of those associated with perineural spread, expressed neural cell adhesion molecule (NCAM).[11]

nerves which are often involved in tumors of skull base,[13] the tumor cells may eventually reach the trigeminal ganglion, pterygopalatine ganglion or cavernous sinus (Fig. 2). These neural pathways acts as "relay stations" to provide access for further perineural spread in a centrifugal (peripheral) or centripetal (towards the brain) fashion.[12]

HISTOLOGIC SUBTYPES:

Squamous cell carcinoma (SCC) is the most prevalant histologic subtype, probably because this malignancy has the highest incidence among all cancers of head and neck. However it is adenoid cystic carcinoma that exhibits the highest association with perineural spread (approximately 60%). Other malignancies exhibiting perineural spread include mucoepidermoid carcinoma, melanoma - desmoplastic variant, lymphoma, basal cell carcinoma, adenocarcinoma, rhabdomyosarcoma, chondrosarcoma, malignant mixed tumor and esthesioneuroblastoma.[14-17]

PATHWAYS OF SPREAD:

The pathway of spread involves different nerves along the skull base (Fig. 3), which include – maxillary nerve, mandibular nerve, facial nerve, auriculotemporal nerve, hypoglossal nerve, vidian nerve and greater superficial petrosal nerve. Along these paths the tumor cells may spread to

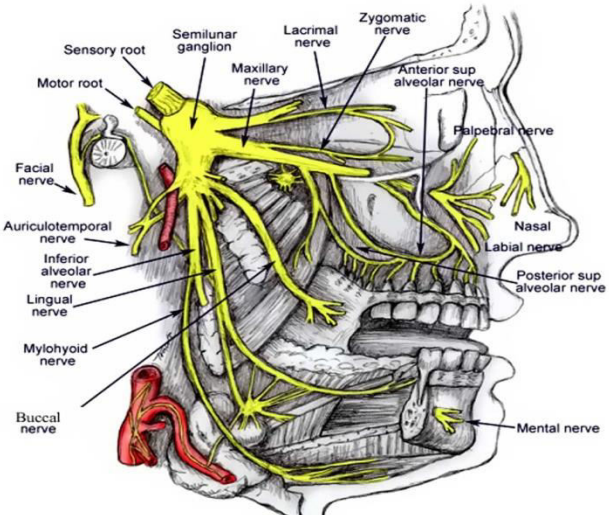

Figure 2: Perineural spread

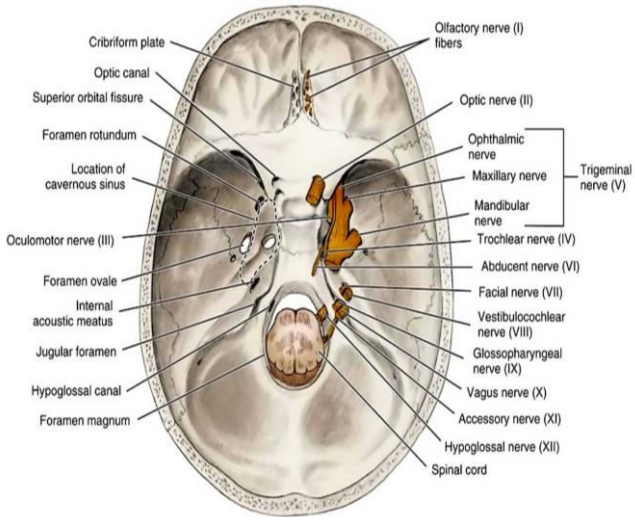

Figure 3: Pathways of spread along different nerves

Perineural spread can occur in an axial and circumferential pattern along the involved nerve. It may progress in a retrograde or antegrade direction.[12] For the maxillary, mandibular and vidian intracranial fossae.[1] However the most dreaded complication is leptomeningeal carcinomatosis, In leptomeningeal carcinomatosis, the continuity between perineurium and leptomeninges and the

communication of perineural space and subarachnoid space permit the dissemination of neoplastic cells from the involved nerves in to the meninges. Hence, it denotes a poor prognosis.[18]

RADIOLOGIC DIAGNOSIS:

Imaging diagnosis of perineural spread include CT, MRI[12] and ^{18}F-FDG PET/ CT.[1] The criteria of involvement on CT include bony changes in the foramina, fissures or canals where the nerves normally transverse the skull base. Typical changes include bonyerosion, sclerotic margins and widening of the normal diameter of these cranial base channels. However these changes are late to occur.[13]Earlier detection is possible with MRI because of better soft tissue delineation. The ability of MRI to detect the different signal intensity of tumor, nerve, fat, CSF, meninges and brain, is believed to allow better assessment of perineural spread. The criteria of nerve involvement on MRI include replacement of normal perineural fat with tumor, enhancement with gadolinium (regardless of size) and increased size of nerve in question (regardless of enhancement).[12]

PET/CT[1] reveals area of perineural spread as location of abnormal FDG uptake. There are different sites of uptake highlighted according to the different nerves involved:

1. Maxillary nerve – pteygopalatine fossa, foramen rotundum, cavernous sinus;
2. Mandibular nerve – foramen ovale, cavernous sinus, lateral mandible;
3. Facial nerve or auriculotemporal nerve – parotid space, infratemporal fossa, stylomastoid foramen, temporal bone;
4. Hypoglossal nerve – hypoglossal nerve, pterygopalatine ganglion;
5. Maxillary nerve, vidian nerve, greater superficial petrosal nerve – vidian nerve, pterygopalatine fossa.

TREATMENT PROTOCOLS:

Through there is no general consensus on the treatment protocols, it may be stated that treatment plan for the cancer of head and neck with perineural invasion and concomitant skull base involvement, consists of surgery followed by radiotherapy and/ or chemotherapy.[12,19,20] Surgical approaches to resection of perineural invasion involve different skull base approaches developed over years of diligent research.[12] The anterior skull base may be approached through transfacial approach,[21] anterior subcranial approach, facial translocation,[22]maxillary swing,[23] trans-naso-orbito-maxillary approach[24] and transmandibular-transpterygoid approach.[25] Even the involvement of cavernous sinus is considered a relative contraindication and not a definite one. In expert hands resection at cavernous sinus carries good prognosis. Currently the most definite contraindications to anterior skull base surgery include bilateral orbital involvement and encroachment of internal carotid artery.[22] The lateral skull base may be approached through the transzygomatic approach,[26] the transzygomatic-transmandibular approach,[27] the lateral approach (by Sekhar and Schramm)[21] and the far lateral approach (by George and Laurian).[21] The surgery might involve combined extracranial and intracranial resection.[12]As far as radiotherapy is concerned , the current protocol suggests that if perineural spread is suspected along nerve of one side , radiation must be applied bilaterally , along the pathway of nerve toward skull base.[20,28]Chemotherapy is reserved for specific chemosensitive tumors such as rhabdomyosarcoma or as an adjunctive therapy.[28]

PROGNOSIS:

Considerable debate has been related to the prognostic value of preoperative detection of perineural spread in cases of head and neck cancer. The vast majority have concluded that the presence of perineural invasion is associated with higher risk of local recurrence, higher risk of metastasis and decreased survival rate.[5,29] The prognostic value varies among the histologic type and location of head and neck malignancies. In mucosal derived squamous cell carcinoma the 3 year survival rate is approximately 23% in those with perineural spread, compared with 49% in those without perineuralspread.[5] The 5 year survival rate associated with treatment of adenoid cystic carcinoma is only 37% in presence of perineural spread, compared to 94% when no perineural spread is evident.[30]

METHODS:

Using Pubmed and Google™ Scholar, a literature search was performed up until December 2015, for articles published in English, using the search terms 'Perineural spread' and 'head neck cancer'. The abstracts of all the studies found in the search were analysed to judge their relevance and inclusion. Articles with insufficient data were excluded. References of the selected articles were searched to identify further related studies. The lack of

prospective studies and randomization precluded a formal meta-analysis.

RESULTS:

Perineural spread in head and neck cancer is an under recognised mode of spread and metastasis of cancer. There are no definite guidelines on the treatment strategy and its management depends on the respective institutional guidelines. Surgical treatment based onwell defined surgical approaches to skull base, are used in advanced surgical centers where the required expertise is available.

CONCLUSION:

Advances in diagnostic imaging and the development of new fronts like skull base surgery have brought a transcending change in the treatment of perineural spread in head and neck cancer.

REFERENCES:

1. Paes FM, Singer AD, Checkver AN, Palmquist RA, Vega MDL, Sidani C. Perineural Spread in Head and Neck Malignancies: Clinical Significance and Evaluation with 18F-FDG PET/CT. Head and neck neoplasms 2013;33(6):1717-35.
2. Ginsberg LE. Imaging of perineuraltumour spread in head and neck cancer. Semin Ultrasound CT MR. 1999; 20 (3) : 175-186.
3. Peters A. Connective tissue sheaths of peripheral nerves. In: Peters A, Palay SL, Webster H, eds. The Fine Structure of the Nervous System: Neurons and Their Supporting Cells, 3rd ed. New York, NY: Oxford University Press; 1991: 494.
4. Batsakis JG. Nerves and neurotropic carcinomas. Ann OtolRhinolLaryngol. 1985; 94: 426-427.
5. Liebig C, Ayala G, Wilks JA, Berge DH, Albo D. Perineural Invasion in Cancer: A Review of the Literature. Cancer.2009; 115(15) :3379-3391.
6. Larson DL, Rodin AE, Roberts DK, O'Steen WK. Rapperport AS, Lewis SR. Perineural lymphatics: myth or fact. Am J Surg. 1966; 112: 488-492.
7. Hassan MO, Maksem J. The prostatic perineural space and its relation to tumour spread: an ultrastructural study. Am J Surg Pathol. 1980; 4: 143-148.
8. Rodin AE, Larson DL, Roberts DK. Nature of the perineural space invaded by prostatic carcinoma. Cancer. 1967;20:1772-1779.
9. Ketterer K, Rao S, Friess H, et al. Reverse transcription-PCR analysis of laser-captured cells points to potential paracrine and autocrine actions of neurotrophins in pancreatic cancer. Clin Cancer Res. 2003;9:5127-5136.
10. Zhang Y, Dang C, Ma Q, et al. Expression of nerve growth factor receptors and their prognostic value in human pancreatic cancer. Oncol Rep. 2005;14:161-171.
11. Barrett AW, Speight PM. Perineural invasion in adenoid cystic carcinoma of the salivary glands: a valid prognostic indicator ? Oral Oncol. 2009;45(11): 936-940.
12. Hanna E, Vural E, Prokopakis E, Carrau R, Snyderman C, Weissman J. The Sensitivity and Specificity of High-Resolution Imaging in Evaluating Perineural Spread of Adenoid Cystic Carcinoma to the Skull Base.Arch Otolaryngol Head Neck Surg. 2007;133(6): 541-5.
13. Hanna E, Janecka IP. Perineural spread in head and neck and skull base cancer. Crit Rev Neurosurg. 1994; 4: 109-115.
14. Elsen MD, Yousem DM, Montone KT, et al. Use of preoperative MR to predict dural, perineural, and venous sinus invasion of skull base tumours. AJNR Am J Neuroradiol. 1996;17:1937-1945.
15. Parker GD, Hamsberger HR. Clinical-radiologic issues in perineuraltumour spread of malignant diseases of the extra-cranial head and neck. Radiographics. 1991;11:383-399.
16. Laine FJ, Braun IF, Jensen ME, Nadel L, Som PM. Perineuraltumour extension through the foramen ovale: evaluation with MR imaging. Radiology. 1990;174:65-71.
17. De Pena CA, Lee YY, Van Tassel P. Lymphomatous involvement of the trigeminal nerve and Meckel Cave: CT and MR appearance. AJNR Am J Neuroradiol. 1989;10 (suppl):S15-S17.
18. Dunn M, Morgan MB, Beer TW. Perineural invasion: identification, significance, and a standardized definition. DermatolSurg 2009;35(2):214-221.
19. Panizza B, Solares CA, Redmond M, Parmar P, Rourke PO. Surgical resection for clinical perineural invasion from cutaneous squamous cell carcinoma of the head and neck. Head Neck. 2012;34(11):1622-7.
20. Barnett CM, Foote MC, Panizza B. Cutaneous head and neck malignancies with perineural spread to contralateral cranial nerves: an argument for extending postoperative radiotherapy volume. J ClinOncol. 2013; 31(18): e291-3.
21. Donald PJ, editor. Surgery of the skull base. Philadelphia: Lippincott-Raven Publishers, 1998.
22. Kuriakose MA, Trivedi NP, Kekatpure V. Anterior skull base surgery. Indian J SurgOncol. 2010; 2: 133–145
23. Wei WI, Lam KH, Sham JST. New approach to the nasopharynx: the maxillary swing approach. Head Neck. 1991;13:200-207.
24. Salins PC. The transnaso-orbito-maxillary approach to the anterior and middle skull base. Int J Oral Maxillofac Surg. 1998;27:53-57.
25. Yumoto E, Gyo K, Yanagihara N. Resection of Persistent Nasopharyngeal Carcinoma.Skull Base Surgery. 1994;4(2):59-64.

26. Sammy LL, Girgis IH. Transzygomatic approach for nasopharyngeal fibromata with extrapharyngeal extension. J Laryngol Otol. 1965;79:782-95.
27. Timoshenko AP, Asanau A, Gavid M, Colin V, Martin C, Prades JM. Preauriculartransmandibular and transzygomatic approach for tumors of the infratemporal fossa revisited.J OtorhinolaryngolRelat Spec. 2013; 75(4):250-5.
28. James Paul O'Neill and Jatin P. Shah, eds. Self-Assessment in Head and Neck Surgery and Oncology. Philadelphia: Elsevier Saunders, 2014.
29. Johnston M, Yu E, Kim J. Perineural invasion and spread in head and neck cancer. Expert Rev Anti-cancer Ther. 2012;12(3):359-371.
30. Majoie CB, Hulsmans FJ, Verbeeten B Jr, et al. Perineural tumour extension along the trigeminal nerve: magnetic resonance imaging findings. Eur J Radiol. 1997; 24(3): 191-205.

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