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Review

Cutaneous head and neck basal and squamous cell carcinomas with perineural invasion ☆

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SUMMARY

Perineural invasion (PNI) occurs in 2% to 6% of cutaneous head and neck basal and squamous cell carcinomas (SCCs) and is associated with mid-face location, recurrent tumors, high histologic grade, and increasing tumor size. Patients may be asymptomatic with PNI appreciated on pathologic examination of the surgical specimen (microscopic), or may present with cranial nerve (CN) deficits (clinical). The V and VII CNs are most commonly involved. Magnetic resonance imaging (MRI) may be obtained to detect and define the extent of PNI; computed tomography (CT) or ultrasound-guided fine needle aspiration cytology (UGFNAC) may assist with detecting or excluding regional lymph node metastases. Patients with apparently resectable cancers undergo surgery, usually followed by postoperative radiotherapy (RT). Patients with unresectable cancers are treated with definitive RT. Moreover, RT may be considered if significant functional or cosmetic impairment is expected after surgical treatment. The 5-year outcomes after treatment for clinically unsuspected microscopic compared with clinical PNI are: local control, 80% and 55%; cause-specific survival, 75% and 65%; and overall survival, 55% and 50%, respectively. The incidence of grade $\geqslant 3$ complications is higher after treatment for clinical PNI versus microscopic PNI; approximately 35% compared with 15%, respectively. Proton beam RT may be used to reduce the risk of late complications by reducing RT dose to the visual apparatus and central nervous system (CNS).

Introduction

The vast majority of skin carcinomas are basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs), and are treated successfully with surgery or radiotherapy (RT).[1,2] Perineural invasion (PNI) occurs infrequently but is more common than was previously thought and is associated with a poorer prognosis.[3–16] The frequency of PNI varies according to different factors, such as the number of histologic sections examined, the stains used and the diligence of the pathologist. In 2005, Hassanein et al.[17] evaluated 706 BCCs and 264 SCCs and observed that PNI was present in 2.1% and 2.6% of the cases, respectively. In the same year, Leibovitch et al.[18,19] noted PNI in 283 of 10,035 BCCs (2.74%) and 70 of 1177 SCCs (5.95%) that were treated with Mohs surgery in Australia between 1993 and 2002. The risk of PNI is increased with mid-face location, male gender, increasing tumor size, recurrence after prior treatment, and poor histologic differentiation.[18–22] Another pathologic feature associated with a high incidence of PNI (up to 73% of cases) was desmoplastic (sclerosing) response to the SCC.[23] The nerves most commonly involved are the second division of cranial nerve (CN) V and CN VII.[21]

Patients with tumors with PNI may be asymptomatic (incidental PNI) or may present with CN deficits (clinical PNI) because of tumor invasion.[24,25] Incidental PNI is also referred to as microscopic or focal but the key point is that the patient is asymptomatic and there are no radiographic findings. Patients with clinical PNI

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are symptomatic and/or have radiographic evidence of PNI; radiographic evidence of PNI is rare in an asymptomatic patient. Clinical PNI may also be referred to as macroscopic. It is likely that the majority of patients with PNI have microscopic, as opposed to clinically overt PNI. The initial symptoms of PNI are often subtle and may consist with paresthesia such as a feeling of ants crawling underneath the skin (formication).[21] The symptoms may slowly progress to pain, numbness, and/or facial weakness over 6 months to 2 years before the diagnosis is made. The patient may be incorrectly diagnosed as having Bell's palsy or trigeminal neuralgia and undergo one or more non-diagnostic magnetic resonance imaging (MRI) scans before the presence of PNI is appreciated. Given the prognostic significance of PNI, in 2011 this parameter was included among the high-risk features in the T classification of the new 7th edition AJCC staging system for cSCC.[26]

Attempts have been made to identify molecular factors associated with this type of tumor growth. In this context expression of alphaB-crystallin has been studied and was found to be decreased in cutaneous SCC with clinical PNI whereas expression of neural cell adhesion molecule (N-CAM) did not differ between SCC with or without PNI.[27,28] More research is needed to understand the processes underlying the growth pattern of PNI.

The optimal diagnostic evaluation and treatment of patients with skin cancer and PNI is unclear and is the topic of this review.

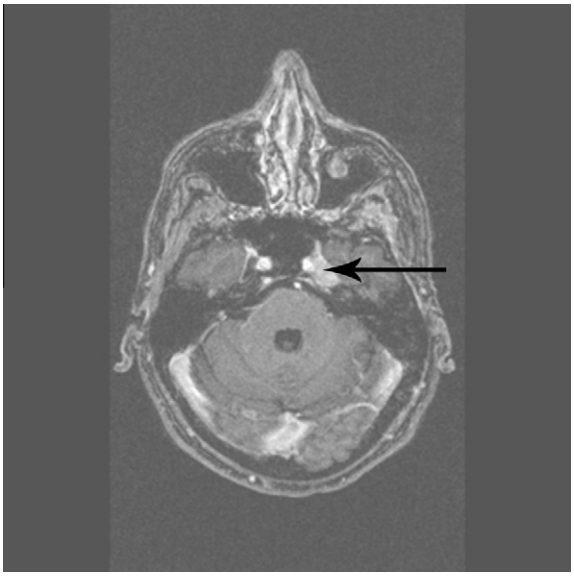

Fig. 1 Patient with SCC of the skin with clinical PNI of the second division of the trigeminal nerve and the facial nerve. Gross tumor extends through the skull base and invades the left cavernous sinus. (Arrow).

Diagnosis

Most of the time, PNI is identified on histologic examination of a relatively asymptomatic skin cancer following excision. Histologically, the tumor cells may surround the nerve and extend along the nerve. Skip lesions are common and, although proximal spread towards the central nervous system (CNS) is the usual mode of extension, distal spread may also be observed.[10,21] Occasionally, it may be necessary to biopsy a CN suspected of being involved to confirm the diagnosis.[29]

PNI may be difficult to appreciate histologically. Peritumoral fibrosis, which is the presence of concentric layers of fibrous tissue that surround or are surrounded by tumor, may mimic PNI.[17] In 2006, Lewis Kelso et al.[30] retrospectively evaluated 34 cutaneous SCCs for PNI with hematoxylin and eosin (H&E) stains as well as immunostains for S-100 and $p75^{NGFR}$ (nerve growth factor receptor). The latter is part of a membrane receptor complex that binds nerve growth factor.[30] PNI was appreciated in 6 of 34 cases (18%) with the H&E stain, 13 of 34 cases (38%) with the $p75^{NGFR}$ immunostain, and 12 of 34 cases (35%) with the S-100 immunostain. Two cases that were positive for PNI on the $p75^{NGFR}$ immunostain were negative with the S-100 immunostain, and one case that was positive for PNI on the S-100 immunostain was negative on the $p75^{NGFR}$ immunostain. Thus, the addition of the $p75^{NGFR}$ immunostain to the H&E stain with or without the S-100 immunostain may enhance the detection of PNI.[30] Forkhead box P3 (FoxP3) belongs to a family of transcriptional regulatory proteins, and is a marker for regulatory T lymphocytes. FoxP3 expression was found to be strongly associated with PNI in SCC, and could be a marker of value to identify cases with PNI.[31]

It is rare to observe radiographic evidence of PNI in an asymptomatic patient.[24] MRI is the most sensitive radiographic study to detect and define the extent of PNI.[25] Expansion of neural foramina and canals such as the inferior alveolar canal, infraorbital foramen, foramen rotundum or facial (Fallopian) canal may be apparent on plain radiographs or computed tomography (CT) scan. Radiographic evidence of PNI includes enlargement or abnormal enhancement of the nerve, obliteration of the fat plane surrounding the nerve, and/or erosion or enlargement of the related foramen (Fig. 1).[25] Abnormal enhancement implies diffuse enhancement of the nerve with loss of the distinction between the nerve and the perineural vascular plexus.[25] The interpretation of MRI findings consistent with PNI may be less certain in irradiated patients. The use of high-field 3T MRI could increase the sensitivity in detecting PNI.[32]

Patients with PNI have an increased risk of metastases to the regional lymph nodes.[4,9,33] These regional nodes can also be assessed on MRI but alternatively, patients should undergo contrast-enhanced CT and/or ultrasound-guided fine needle aspiration cytology (UGFNAC), and/or sentinel lymph node biopsy (SLNB).[34] CT may also be considered to assess bone destruction in addition to MRI.[25]

Prognostic factors and treatment

PNI is a form of tumor spread exhibited by neurotropic malignancies that correlates with aggressive behavior, disease recurrence and increased morbidity and mortality.[35] Other than being diagnosed on a biopsy, patients with microscopic PNI have almost always undergone excision of the primary lesion prior to the diagnosis. Whether or not to routinely add postoperative RT following complete excision is controversial. In 2010, Jambusaria-Pahlajani et al.[15] conducted a survey of randomly selected trained Mohs surgeons to evaluate their management of patients with high-risk cutaneous SCCs regarding radiographic nodal staging, SLNB, and the use of adjuvant RT. Approximately 25% of the membership of the American College of Mohs Surgery completed the survey regarding the management of high-risk cutaneous SCC ($n = 117$) or SCC with PNI ($n = 118$). The survey revealed that most respondents considered in-transit metastases and PNI as the major factors leading to consideration of radiographic staging, SLNB, and adjuvant RT. In 2009, Jambusaria-Pahlajani et al.[36] reported on a literature review of reports on high-risk SCC with PNI treated with either surgery alone or surgery and adjuvant RT. They observed that, for 74 patients with PNI, the outcomes after surgery alone and surgery plus RT were similar and concluded that, in the presence of clear surgical margins, the benefit of adjuvant RT was unclear. The disadvantage of retrospective literature reviews is that the patients at higher risk for recurrence are probably more likely to receive adjuvant RT, thus biasing the comparison. In relation to