



Clinical perineural invasion of cutaneous head and neck cancer: Impact of radiotherapy, imaging, and nerve growth factor receptors on symptom control and prognosis

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ABSTRACT

Objectives: Clinical perineural invasion (CPNI) of cutaneous head and neck cancer is associated with poor prognosis and presents a therapeutic dilemma. The purpose of this study was to determine the relationship between CPNI and nerve growth factor receptors (NGFR), and the impact of radiotherapy (RT), imaging, and NGFR on symptom control and disease-related outcomes.

Materials and methods: We retrospectively reviewed patients with CPNI of cutaneous head and neck cancer who were treated with RT between 2010 and 2015 at our institution. Exact chi-square and Wilcoxon rank-sum tests compared patients with positive versus negative staining for TrkA and/or CD271. Gray's test determined differences in cumulative incidences of 1- and 2-year locoregional recurrence (LRR) and cancer-specific mortality (CSM).

Results: Twenty-three patients had a median overall follow-up of 31.4 months from initial clinical symptoms and 19.7 months from pathological confirmation of PNI. The most prevalent symptoms were numbness (70%) and pain (57%). Sixteen patients (70%) experienced symptom improvement or control, especially decreased pain (85%), within a median of 2.6 months from starting RT. The 1- and 2-year rates of overall LRR were 37% and 71%, while those of overall CSM were 11% and 25%, respectively. Patients who stained positively for TrkA and/or CD271 had significantly worse LRR compared to patients who stained negatively for both markers ($p = 0.046$).

Conclusion: Positive TrkA and/or CD271 staining predicts worse outcomes. Patients may benefit from aggressive RT for local control and symptom improvement. Future research is needed to identify the potential for anti-nerve growth factor therapies in CPNI.

Introduction

Perineural invasion (PNI) is a relatively rare but notable risk factor for poor prognosis in patients with cutaneous head and neck cancer [1–4]. Pathologically, PNI is characterized by tumor cells within the nerve sheath or tumor foci outside the nerve that involve $\geq 33\%$ of the nerve's circumference and spread along the length of the nerve [5–7].

The reported incidence of PNI is 2.5–14% in patients with squamous cell carcinoma (SCC) and 0.18–2.74% in patients with basal cell carcinoma (BCC), with worse outcomes in those with PNI of SCC compared to BCC [3,8–13].

There are two categories of PNI: clinical (CPNI) and incidental (IPNI). Although patients with CPNI show symptoms of cranial neuropathy or radiographic evidence of tumor involvement along the nerve,

Abbreviations: PNI, perineural invasion; CPNI, clinical perineural invasion; IPNI, incidental perineural invasion; NGFR, nerve growth factor receptor; SCC, squamous cell carcinoma; BCC, basal cell carcinoma; RT, radiotherapy; CRT, chemoradiotherapy; S, surgery; NED, no evidence of disease; MRI, magnetic resonance imaging; CT, computed tomography; FoxP3, Forkhead box P3; CSM, cancer-specific mortality; LRR, locoregional recurrence

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those with IPNI are asymptomatic with nerve invasion only detectable on histologic review [4,14,15]. Initial symptoms, including paresthesia or formication, may be subtle, with insidious progression to numbness, pain, weakness, or motor or sensory deficits over 6 months to 2 years preceding diagnosis [14,16–18]. CPNI is associated with even higher rates of recurrence and metastases and worse survival outcomes than IPNI [2,3,14,19,20].

Early detection of CPNI has clinical significance, as certain patients may benefit from radiotherapy (RT) with early detection and subsequent treatment [14,16,21]. Magnetic resonance imaging (MRI) and computed tomography (CT) have been shown to successfully identify and define the extent of perineural spread [10,15,16]. Gadolinium-contrast MRI with fat suppression further increases earlier detection of PNI [11].

Other studies have attempted to predict the presence of PNI via immunohistochemical markers. One retrospective evaluation of cutaneous SCC samples found that the addition of a p75^{NGFR} (nerve growth factor receptor) immunostain to a hematoxylin and eosin stain with or without a S-100 immunostain may enhance PNI detection [22]. Another study found that Forkhead box P3 (FoxP3) expression, a marker of regulatory T lymphocytes, was strongly associated with PNI in SCC [23]. Higher levels of Trk receptor expression, a high affinity NGFR, may also predict PNI, as PNI-positive cutaneous SCCs generally stain stronger with Trk A, B, and C than PNI-negative cutaneous SCCs [24,25]. Furthermore, CD271, a low affinity NGFR, has been associated with greater tumorigenicity, invasiveness, and metastases of head and neck SCC and melanoma [26–29].

CPNI presents a clinical dilemma, as its diverse manifestations have made diagnosis and treatment challenging, with limited data on how to detect and manage this rare condition. The purpose of this exploratory study is to share our institution's experience treating CPNI with RT and examine outcomes based on immunohistochemical staining patterns, with the goal of providing data that may guide future management. In particular, we stained for TrkA and CD271, both NGFRs associated with cancer aggressiveness. We hypothesized that perineural tumors that stained positive for either of these markers could pave the way for future research examining nerve growth factor inhibitors as therapeutic options for these patients with historically poor outcomes.

Materials and methods

Study population

This study was approved by our institutional review board, and a waiver of informed consent was granted. We performed a retrospective analysis of consecutive patients with CPNI of SCC or BCC, who were treated with RT between 2010 and 2015 at our institution. Criteria for study inclusion were presence of CPNI, defined as clinical symptoms and/or radiologic evidence of PNI [14], subsequent pathologic confirmation of PNI, and treatment with RT. Patients' medical records were reviewed for demographic and clinical data.

Pathologic analysis

Fourteen patients (61%) had specimens available for additional immunohistochemical staining; all available specimens were reviewed for this study. The pathologist was blinded to the patient outcome at the time of slide review. Specimens were fixed in 10% buffered formalin, processed, and embedded in paraffin using standard histologic methods. Sections 4 μm thick were stained for TrkA and CD271. Positive immunohistochemical staining was defined as > 26% membranous expression. The slides were also reviewed for pathologically confirmed PNI, defined as the presence of tumor cells within any of the 3 layers of the nerve sheath [5–7].

Statistical analysis

Differences between groups of patients who stained positive versus negative for TrkA or CD271 were determined with exact chi-square and Wilcoxon rank-sum tests. Cancer-specific mortality (CSM) was determined using cumulative incidence estimates and was defined as the time from the date of primary pathologic diagnosis until death from SCC or BCC, with any other cause of death considered a competing risk. Estimates for cumulative incidence of locoregional recurrence (LRR), defined as time from pathologic diagnosis to first locoregional recurrence, were calculated with all-cause death considered a competing risk. Censoring occurred at the date of last follow-up visit. One patient who did not achieve complete remission after primary treatments was excluded from LRR analyses. Differences between cumulative incidence of CSM and LRR were determined using Gray's test. Estimates of time to PNI detection based on clinical symptoms, imaging, and pathology were determined by the Kaplan-Meier method. All tests performed were 2-sided, with statistical significance set at 0.05. All analyses were conducted with the use of SAS version 9.4 (SAS Institute, Cary, NC).

Results

Patient characteristics

There were 23 patients at our institution with CPNI treated with RT. The median overall follow-up was 31.4 months from documentation of clinical symptoms and 19.7 months from pathological confirmation of PNI of SCC or BCC. The mean age of PNI diagnosis on pathology was 72 years (range: 45–86 years). Twenty-one patients (91%) presented with PNI of SCC and 2 with PNI of BCC. Six patients (26%) were immunosuppressed post-transplant or following treatment for lymphoma. Most patients had PNI along cranial nerves V (91%) and/or VII (35%). The most prevalent clinical symptoms were numbness (70%) and pain (57%). Table 1 summarizes each patient's clinical characteristics, treatments, and outcomes.

Radiographic imaging

All patients in our study received serial radiographic imaging in 2–5 month intervals to monitor for progression. Detection of progression led to potential salvage radiotherapy, chemotherapy, and/or surgery, based on shared decision making between physicians and patients. The median imaging follow-up from first abnormal imaging to last imaging available was 20.7 months. The median time from presentation of clinical symptoms to radiologic evidence of PNI was 6.1 months (range: 0–34 months). The median time from clinical symptoms to pathologic confirmation of PNI was 10.2 months (range: 0–35 months). Eighteen patients (78%) developed clinical symptoms at least two weeks prior to any abnormal imaging.

Twenty patients (87%) had identifiable PNI on initial imaging and were included in the imaging-positive group; MRI detected PNI in 16 of these patients (80%). Those without identifiable PNI on initial imaging were included in the imaging-negative group. There were no differences in clinical characteristics, LRR ($p = 0.84$), or CSM ($p = 0.92$) among imaging-positive and imaging-negative patients.

Radiotherapy and symptom control

Patients were treated with an External Beam Radiation Therapy (EBRT) dose range of 60–70 Gy in 30–35 fractions. Fifteen patients (65%) underwent surgical resection of gross tumor prior to radiation; five of these patients had clear margins, although all had residual perineural spread. Three patients were treated with initial and/or salvage CyberKnife radiosurgery. Sixteen patients received concurrent chemoradiotherapy, where eleven patients were treated with Cetuximab, four with Cisplatin, and one with Vismodegib. Fig. 1

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