Cutaneous Head and Neck Malignancies With Perineural Spread to Contralateral Cranial Nerves: An Argument for Extending Postoperative Radiotherapy Volume

Introduction

The incidence of nonmelanoma cutaneous head and neck malignancies is increasing worldwide. In a small percentage of cases, associated perineural spread (PNS) of cranial nerves occurs, resulting in poor prognosis, with a recorded 5-year survival rate of 50% to 64.3%. Patients with clinical PNS from cutaneous head and neck malignancies are treated with surgical resection and postoperative radiotherapy. Recent literature provides few reports of PNS that extends across the facial midline to affect the contralateral cranial nerves. This report describes patients with ipsilateral cranial nerve PNS that has subsequently progressed to contralateral cranial nerves, to both highlight and address the potential implications for the postoperative radiotherapy volume.

Case Reports

Within a cohort of 55 patients who were treated from 1996 to 2011 with confirmed PNS from a cutaneous malignancy, six patients with ipsilateral cranial nerve PNS and subsequent contralateral PNS were identified. Patient demographic and clinical characteristics were reviewed and are summarized in Table 1. Ethics approval was obtained from our institution’s Human Research Ethics Committee.

Case Example. A 49-year-old woman (Table 1, patient 4) presented with a 3-month history of increasing swelling and pain in the left cheek. Twelve years before, the patient had sustained a blast/burn injury to the left hemiface, and 18 months before presentation, had a squamous cell carcinoma (SCC) on the left side of the nose excised with adjuvant radiotherapy. A computed tomography scan indicated recurrence of the lesion, with bone erosion of the inferior orbit and anterior maxillary wall and extension into the antrum. A magnetic resonance imaging (MRI) scan showed involvement of V2 at the foramen rotundum to the anterior aspect of Meckel’s cave. Surgery involved en bloc removal of the left cheek skin, lateral nose wall, orbit floor, periorbita, and the infraorbital nerve to the gasserian ganglion. Reconstruction was performed with radial artery forearm flap and split skin graft. Histopathology confirmed SCC with PNS of left V2 to the anterior aspect of Meckel’s cave. The patient received postoperative radiotherapy to the operative bed, as previously described, back to the gasserian ganglion, using a total dose of 60 Gy in 30 fractions. The cutaneous branches of V2 (with some extension into V3 cutaneous distribution) were treated, but only the proximal part of V3. This was delivered by a mix of electrons and three-dimensional conformal photon radiotherapy. Five years after surgery, the patient developed paresthesia, formication, and pain in the right cheek. An MRI scan showed abnormally thickening and enhancement that were consistent with PNS along the intra- and extracranial segments of right V2 and V3. The patient refused additional treatment and died as a result of her contralateral disease 13 months after detection.

Discussion

The trigeminal (V) and facial (VII) nerves are the most common cranial nerves to be affected by PNS, and disease may progress slowly over a period of 6 months to 2 years before a diagnosis is made, which significantly affects prognosis. Symptoms of trigeminal nerve PNS include numbness, pain, formication, and paresthesia in the distribution of the affected branch. The orbit can also be accessed through spread along the ophthalmic nerve (V1), and patients may present with diplopia and/or visual impairment. Facial nerve involvement is characterized by a slowly progressive palsy of the affected hemiface. The anatomic extent of PNS seen on MRI has a previously described zonal classification and allows for surgical planning. Zone 1 boundaries are: V1 to the superior orbital fissure; V2 to the external aperture of the foramen rotundum; V3 to the external aperture of the foramen ovale; and VII to the external aperture of the stylomastoid foramen. Zone 2 boundaries are: V1, V2, V3 from zone 1 to the gasserian ganglion cistern; and VII from zone 1 to the lateral end of the internal auditory canal, with inclusion of the geniculate ganglion and the labyrinthine segment. Finally, zone 3 encompasses all nerves from the ganglion into the cisterns or into the brainstem.

The goal of surgical resection of the disease to a margin clear of disease is to prevent additional retrograde spread to the brainstem. In our experience, patients are classified as having inoperable disease if the disease extends proximally to the gasserian (V) or geniculate (VII) ganglion (zone 3).

A retrospective review of our department of 21 patients with clinical PNS from cutaneous SCC of the head and neck who underwent surgical resection to the gasserian or geniculate ganglion demonstrated a 5-year disease-specific survival rate for zone I and II disease of 80% and 55%, respectively, supporting our experience that surgical excision of the disease to the ganglion improves survival without significant additional morbidity.

Although published data are limited, postoperative radiotherapy is often relied on to prevent both cutaneous spread and central progression of disease. For local (cutaneous) spread from the original tumor with perineural infiltration, a generous margin of 2 to 3 cm around the resected disease is generally used. However, with large-pore PNS, the cutaneous distribution of the named nerve (V1, V2, or V3 to midline) needs to be treated to prevent cutaneous recurrence. If the disease involves more than one named nerve (eg, V2 and V3), then the cutaneous branches in those regions should be treated. For control of central disease, the whole operative bed including the path of the named cranial nerve is treated back to the ganglion (for resected zone 1 disease) or prepyramidal region (for resected zone 2 disease).

Local (cutaneous) spread from the original tumor site to other cutaneous branches across the midline to the corresponding contralateral cutaneous cranial nerve branches (eg, right V2 to left V2) or from adjacent cutaneous distributions on the ipsilateral face (eg, right
Table 1. Patient Demographic and Clinical Characteristics of Patients With Ipsilateral Cranial Nerve PNS and Subsequent Contralateral PNS

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Initial Presentation</th>
<th>History of Cutaneous Head and Neck Malignancy</th>
<th>Final Diagnosis</th>
<th>Ipsilateral Disease Management</th>
<th>Contralateral Disease Management</th>
<th>Time to Contralateral Spread</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75</td>
<td>F</td>
<td>2 years progressive left cheek paraesthesia</td>
<td>Excision of left lateral nose SCC and XRT 3 years before</td>
<td>PNS SCC along left V2 and right infraorbital nerve</td>
<td>Subcranial and intracranial surgery with PORT; peripheral recurrence treated with WLE and free flap</td>
<td>Subcranial surgery and PORT</td>
<td>3 years</td>
<td>Living with ipsilateral peripheral disease</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>F</td>
<td>2.5 years progressive left VII palsy and V3 involvement after right V2 SCC. PNS treatment 5 years before</td>
<td>Multiple facial SCCs excised over last 20 years, including a left nasal ala SCC and an aggressive recurrent right nose SCC</td>
<td>PNS SCC along right V2 followed by left V3 and VII</td>
<td>WLE and PORT</td>
<td>Skull base surgery and PORT</td>
<td>5 years</td>
<td>No evidence of disease 7 years after contralateral disease</td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>M</td>
<td>18 months right forehead paraesthesia and heat; lump appeared along right medial eyebrow and orbital rim 2 months before</td>
<td>Multiple skin lesions on nose previously treated with cryotherapy; no forehead/scalp lesions removed</td>
<td>PNS SCC along right V1 followed by left V1</td>
<td>Skull base surgery; PORT and chemotherapy (cisplatin and fluorouracil)</td>
<td>Palliative chemoradiotherapy</td>
<td>15 months</td>
<td>Living with contralateral disease</td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>F</td>
<td>3 months progressive swelling and pain in left cheek</td>
<td>Blast/burn injury in left face area 12 years before; SCC on left side of nose was excised 1.5 years before</td>
<td>PNS SCC along left V2 followed by right V2</td>
<td>Skull base surgery and PORT</td>
<td>Refused treatment</td>
<td>6 years</td>
<td>Died as result of contralateral disease 13 months after detection</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>M</td>
<td>6 months left forehead progressive paraesthesia and paralysis, 2 months left eye ptosis, and 1 month diplopia</td>
<td>Multiple facial SCCs, including excision of left nasal ala lesion 3-4 months before</td>
<td>PNS SCC along left V1 and upper VII followed by right V and VII and delayed left lower VII involvement</td>
<td>Skull base surgery; PORT and cisplatin</td>
<td>Palliative care</td>
<td>21 months</td>
<td>Died as result of central disease 18 months after initial treatment</td>
</tr>
<tr>
<td>6</td>
<td>69</td>
<td>F</td>
<td>6 months right forehead numbness</td>
<td>SCC right temporal region</td>
<td>PNS SCC along right V1 followed by left V1</td>
<td>Skull base surgery and PORT</td>
<td>Palliative radiotherapy</td>
<td>6 months</td>
<td>Died as result of peripheral out-of-field recurrence 3 months after detection</td>
</tr>
</tbody>
</table>

Abbreviations: PNS, perineural spread; PORT, postoperative radiotherapy; SCC, squamous cell carcinoma; V, trigeminal nerve; V1, ophthalmic nerve; V2, maxillary nerve; V3, mandibular nerve; VII, facial nerve; WLE, wide local excision; XRT, radiotherapy.
V2 to right V3) can occur. Current practice for postoperative radiotherapy includes irradiation of central disease, as previously described, but for the cutaneous distribution of the particular cranial nerve branch to the facial midline only.\(^8,11\)

Within our subset, patients 1, 3, 4, and 6 did not have evidence of a secondary primary on the contralateral hemiface that potentially could have been responsible for the clinical findings. Patients 1, 3, and 4 had primary lesions occur on the nose, close to the midline, whereas patient 6 had multiple recurrences at the midline margin of the radiotherapy volume. We propose that the disease extension occurred across the facial midline by local spread from the cutaneous peripheral branches of the affected cranial nerve and those of the contralateral side. Therefore, these patients could have potentially benefited from extending the radiotherapy volumes across the midline 2 to 3 cm to further prevent contralateral cutaneous spread.

At the time of postoperative radiotherapy, microscopic PNS across the midline to the contralateral peripheral trigeminal or facial nerve branch may have already occurred, and the standard radiotherapy volume used would have failed to sterilize that affected area. Extension of the radiotherapy volumes across the midline could potentially treat any microscopic PNS on the contralateral side, thus preventing any further spread. An exception was noted with patient 2, given that the ipsilateral disease was in the right V2 area and likely developed into a separate primary lesion with associated PNS of V3 and VII on the contralateral side; thus, this patient would not likely have benefited from extended volumes of postoperative radiotherapy. Additionally, extended volumes would not likely have benefited patient 5 because, unfortunately, his disease spread centrally.

For postoperative radiotherapy planning, detailed knowledge of the anatomy of the trigeminal and facial nerves is imperative to accurately include the cutaneous distribution of particular peripheral branches and follow the course of the nerve trunk to the desired level. The anatomic course of the trigeminal nerve, from the brainstem through the skull base to the peripheral branches, is well described.\(^12,13\) However, the precise boundaries of the areas of sensation supplied by the ophthalmic, maxillary, and mandibular branches and the interindividual variation present in the general population are not known. The anatomy of the facial nerve trunk and its five subsequent branches is also well known.\(^13\) Interconnections between the trigeminal and facial nerves on each side exist that could potentiate PNS from an affected branch to another on the same side.\(^14\) At present, no evidence exists that describes, in detail, the anatomic relationship of the terminal cutaneous branches of the trigeminal and facial nerves of each hemiface and whether they interconnect or overlap slightly along the facial midline. During radiotherapy planning, the cutaneous area to be irradiated is based on the boundaries described in this report but is ultimately at the discretion of the treating radiation oncologist.

The primary aim of this report was to provide evidence in support of an argument to extend postoperative radiotherapy volumes in this particular patient population. Previously, with older radiation planning and delivery, this was not practical because of the inherent increased morbidity that was associated with extending the radiotherapy volume across midline. Nowadays, these patients are treated postoperatively with intensity-modulated radiotherapy, which is an external beam radiotherapy that allows the radiation dose to conform more closely to the shape of the tumor by changing the intensity of the radiation beam. With more sophisticated radiotherapy like intensity-modulated radiotherapy, the treating oncologist may be able to extend the postoperative radiotherapy volumes without a significant increase in treatment morbidity.

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