Objective: To determine if perineural invasion (PNI) of small nerves affects the outcome of patients with squamous cell carcinoma (SCC) of the upper aerodigestive tract.

Design: Retrospective clinicopathological study of patients with at least 2 years of follow-up and with negative margins and no prior, synchronous, or metachronous SCC.

Setting: Academic otolaryngology department.

Patients: One hundred forty-two patients who had SCC of the oral cavity, oropharynx and hypopharynx, or larynx resected between 1981 and 1991.

Intervention: Surgery with or without adjuvant therapy.

Main Outcome Measures: Local recurrence was examined with respect to PNI, nerve diameter, and microvascular or microlymphatic invasion. Perineural invasion was correlated with lymph node metastasis, extracapsular spread, and survival.

Results: Perineural invasion of nerves less than 1 mm in diameter was present in 74 patients, lymphatic invasion in 53, and vascular invasion in 9. Perineural invasion was significantly associated with local recurrence (23% for PNI vs 9% for no PNI; \( P = .02 \)), and disease-specific mortality (54% mortality for PNI vs 25% for no PNI; \( P < .001 \)). With extralaryngeal tumors, PNI was associated with nodal metastasis (73% vs 46%; \( P = .03 \)). Perineural invasion was not associated with extracapsular spread (\( P = .47 \)). Microvascular invasion, lymphatic invasion, and nerve diameter were not significantly related to local recurrence.

Conclusions: Perineural invasion of small nerves is associated with an increased risk of local recurrence and cervical metastasis and is, independent of extracapsular spread, a predictor of survival for patients with SCC of the upper aerodigestive tract.


T HE PERINEURAL space is a recognized route for extension of squamous cell carcinoma (SCC). Outcome of patients with SCC of the skin,1,2 lip,3 and oral cavity4,5 is adversely affected by the presence of perineural invasion (PNI), and PNI of major (named) nerves is associated with locoregional recurrence and decreased survival in patients with SCC of the upper aerodigestive tract.8

We conducted a study to determine whether histopathological evidence of PNI of small peripheral nerves (<1 mm) affects the outcome of patients with SCC of the upper aerodigestive tract. The associations between PNI and local, regional, and distant recurrence, survival, concurrent cervical nodal metastasis, and extracapsular spread (ECS) were determined.

Results: One hundred forty-two patients were studied: 76 with laryngeal and hypopharyngeal and 66 with oral cavity and oropharyngeal carcinoma. There were 93 men and 49 women with a mean age of 56 years. The tumor stages were: T1 (n = 11), T2 (n = 60), T3 (n = 37), and T4 (n = 34). In nerves of less than 1 mm in diameter, PNI was present in 74 (52%), lymphatic invasion in 53 (37%), and microvascular invasion in 9 (6%). Local recurrence occurred in 4% (3/76) of patients with carcinoma of the larynx and hypopharynx, and 30% (20/66) with carcinoma of the oral cavity and oropharynx. Patients with and without local recurrence were similar in terms of age, sex, and having received postoperative radiation therapy. For local recurrence, 66% of the patients were men, with a mean age of 54...
PATIENTS AND METHODS

A clinicopathological study was conducted of patients who had primary surgical resection of SCC of the oral cavity, oropharynx and hypopharynx, or larynx between 1981 and 1991. All patients had at least the first echelon nodes removed by selective or comprehensive neck dissection at the time of resection of the primary tumor. Patients with positive margins, prior, synchronous, or metachronous SCC, and less than 2 years of follow-up were excluded from the study. Clinical, treatment, and outcome data were obtained from patient charts and the head and neck oncology database.

A detailed histopathological review of the resected tumors was undertaken. Hematoxylin-cosin-stained microscopic slides, prepared using formalin-fixed paraffin-embedded tissue, were examined for perineural, microlymphatic, and microvascular invasion by 2 pathologists (B.C. and L.B.). To minimize cost, Masson trichrome and S-100 protein stains were not used to highlight neural tissue. Perineural invasion was defined as tumor cells touching or invading a nerve. The diameter of nerves with PNI was measured with an optical micrometer. It was noted whether the axons had been invaded by tumor, and whether PNI had occurred within the tumor mass or peripheral to the tumor.

Local recurrence was examined with respect to PNI, nerve diameter, and microvascular or microlymphatic invasion. Perineural invasion was correlated with the incidence of concurrent histopathologically proven cervical lymph node metastasis, ECS, regional and distant recurrence, and determine survival.

To compare recurrence rates and mortality rates by the categorical variables, we used χ² tests. When cell sizes were small, the Fisher exact test was used. The Mantel-Haenszel procedure was used to compare PNI by recurrence adjusted for tumor site, nerve diameter, vascular invasion, and lymphatic invasion. Nerve diameter by recurrence was compared using the rank sum test.

Table 1. Clinical Data of Patients With and Without Perineural Invasion (PNI)*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PNI Present (n = 74)</th>
<th>PNI Absent (n = 68)</th>
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<tbody>
<tr>
<td>Sex, % male</td>
<td>72</td>
<td>60</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>56.5</td>
<td>56.7</td>
</tr>
<tr>
<td>No. (%) with larynx and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypopharynx SCC</td>
<td>34 (46)</td>
<td>42 (62)</td>
</tr>
<tr>
<td>No. (%) with oral cavity and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>oropharynx SCC</td>
<td>40 (54)</td>
<td>26 (38)</td>
</tr>
<tr>
<td>Postoperative irradiation, %</td>
<td>49</td>
<td>29</td>
</tr>
<tr>
<td>Postoperative chemotherapy, %</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Tumor stage</td>
<td></td>
<td>0.13</td>
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</table>

*SCC indicates squamous cell carcinoma.

At one time presumed to be a lymphatic channel, the perineural space is now considered an artificial space created during tissue processing. Ultrastructural studies of the perineural space have demonstrated an absence of epithelial lining cells or gaps such as those found in normal lymphatic channels. Tumor propagation occurs along the perineural space, a route of low resistance, within the connective tissue investing peripheral nerves.

According to the results of this study, PNI of nerves invaded nerve axons (Figure). Most PNI was contiguous to the main tumor, and a few sites of PNI were remote. Four of the nerves were involved outside the main body of the tumor, and 33 were involved multifocally. A variety of architectural tumor patterns were noted, ie, solid or sheetlike, tumor islands, strands (cords or fingers of tumor), or diffusely arranged individual tumor cells. The nonsolid patterns appeared to be more invasive and tended to track along nerve, as opposed to the solid patterns of tumor that “flowed” around nerve.

Patient outcome in relation to PNI is documented in Table 2. Perineural invasion was associated with pathologically diagnosed nodal metastasis, but only with carcinoma of the oral cavity and oropharynx (P = 0.03) and not carcinoma of the larynx and hypopharynx (P = 0.75). Perineural invasion was not associated with ECS (P = 0.47).

Perineural invasion was significantly associated with local recurrence (P = 0.02) and disease-specific mortality (P < 0.001) but not with regional recurrence (P = 0.07) or distant metastasis (P = 0.17).

Neither nerve diameter (P = 0.15) nor microvascular (P = 0.67) or microlymphatic (P = 0.11) invasion were significantly associated with local recurrence.
was statistically significant for all tumor sites, PNI with laryngeal SCC is of uncertain clinical significance due to the low (4%) recurrence rate observed with SCC of the larynx and hypopharynx. Lydiatt et al also reported an association between PNI and local recurrence with SCC of the oral cavity.

Centrifugal or centripetal propagation of SCC along the perineural space is probably the main mechanism for the increased rate of local recurrence observed with PNI. Even though perineural spread of more than 2 cm is unusual, propagation of SCC along the perineural space for a distance of up to 12 cm has been reported. Therefore, identification of PNI in extralaryngeal or advanced laryngeal SCC may be consistent with a positive margin.

Perineural invasion in SCC of the oral cavity and oropharynx was, independent of tumor stage, associated with an increased incidence of concurrent cervical nodal metastasis. Other investigators have reported an association of PNI with cervical metastasis in carcinoma of the oral cavity. This association suggests that tumors that invade the perineural space are biologically more aggressive and may be another reason why SCC with PNI is more likely to recur locally. An association between tumor thickness, known to correlate with regional metastasis, and PNI has also been reported.

Because of the association of PNI with cervical metastasis, we propose that the neck should be treated electively when PNI is encountered with SCC of the oral cavity. However, we strongly advocate that even in the absence of PNI, advanced laryngeal SCC16 and all oral and oropharyngeal SCCs, except minimally invasive T1 tumors,7 should have the neck treated electively because of the significant incidence of occult nodal metastasis.

Extracapsular spread is an important prognostic indicator of survival in patients with SCC of the head and neck. Perineural invasion was significantly associated with disease-related mortality but not with ECS. Therefore, PNI appears to be, independent of ECS, an important predictor of survival. Unlike ECS, PNI was associated principally with local failure and not with regional recurrence or distant metastasis. Maximizing local control is therefore the key to improving survival in patients with PNI.

Because of the impact of PNI on prognosis and treatment planning, pathologists should routinely comment on the presence of PNI. Perineural invasion was diagnosed in 52% of tumors in this study, compared with 6% to 30% in other studies of PNI. This apparent difference in the reported incidence of PNI underscores the importance of looking for PNI when examining head and neck SCC specimens, since our study focused specifically on PNI.

**Table 2. Perineural Invasion Related to Nodal Status and Patient Outcome**

<table>
<thead>
<tr>
<th>Perineural Invasion, % (No. Affected/Total)</th>
<th>Present</th>
<th>Absent</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodal metastasis†</td>
<td>73 (29/40)</td>
<td>46 (12/26)</td>
<td>.03</td>
</tr>
<tr>
<td>ECS (N1, N2, or N3)</td>
<td>50 (22/44)</td>
<td>41 (12/29)</td>
<td>.47</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>23 (17/74)</td>
<td>9 (6/68)</td>
<td>.02</td>
</tr>
<tr>
<td>Death due to SCC</td>
<td>54 (40/74)</td>
<td>25 (17/68)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*ECS indicates extracapsular spread; SCC, squamous cell carcinoma.†Applies to oral cavity and oropharynx only.*

**CONCLUSIONS**

Perineural invasion appears to be an independent predictor of local recurrence and regional nodal metastasis.
in patients with SCC of the upper aerodigestive tract and is, independent of ECS, a predictor of determinate survival.

We recommend the following: (1) outcome studies of SCC of the head and neck should stratify for PNI; (2) pathologists should look for and report the presence of PNI; (3) patients with extralaryngeal and advanced laryngeal SCC with PNI should be offered adjuvant therapy to reduce the likelihood of local recurrence; and (4) in centers where the N0 neck is normally managed by watchful waiting, patients with extralaryngeal SCC with PNI should be considered for elective treatment of the cervical lymphatics.

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REFERENCES