Pain may predict poor prognosis in patients with oral squamous cell carcinoma

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Objective. We have previously reported that the histologic mode of invasion of oral squamous cell carcinoma (OSCC) is a significant risk factor for pain. Here we sought to determine whether pain is a risk factor for poor prognosis in patients with OSCC.

Study design. We evaluated the relationships between overall survival rates and clinicopathologic variables, including gender, age, T- and N-stages, pathologic findings, and pain in 109 consecutive patients with untreated OSCC.

Results. Of these 109 patients, 40 (37%) reported spontaneous pain. Univariate analysis showed that the overall survival rates of patients with spontaneous pain was significantly lower than those of patients without pain ($P = 0.002$). Multivariate analysis revealed that spontaneous pain and N-stage were significant independent predictors of overall survival rates.

Conclusions. This is the first report showing that spontaneous pain before treatment may be associated with poor prognosis in patients with OSCC. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:587-592)
The primary tumor sites were the tongue in 53 patients, the lower gingiva in 20, the buccal mucosa in 13, the floor of the mouth in 10, the upper gingiva in 11, and the palate in 2. All patients underwent radical treatment for OSCC consisting of surgery in 104 patients and radiation therapy in 5. We excluded patients who received palliative treatment and those who could not answer questions during the medical interview. We also excluded patients who had already been biopsied or treated for OSCC.

All subjects gave informed consent to biopsy and histologic examination, and the study protocol was approved by our Institutional Review Board (no. 100,930).

Clinicopathologic data
Clinical data reviewed include patient gender, age, primary tumor sites, T-stage, and N-stage. Of the 109 primary tumors, 19 were T1, 44 were T2, 21 were T3, and 25 were T4a; 82 (75%) were staged as N0.17 Tumors were evaluated histopathologically by 2 authors (YY and JS) using hematoxylin and eosin–stained slides prepared from pretreatment biopsy specimens. The degree of histologic differentiation was determined in accordance with the criteria of the World Health Organization (1997). We found that 48 patients had grade 1 tumors, 58 grade 2, and 3 grade 3.

The histologic mode of invasion was classified according to the YK classification system,16,18 in which tumors classified as YK-1 had well defined borderlines and those classified as YK-4 were diffuse or invasive. Of the 109 primary tumors, 5 were classified as YK-1, 26 as YK-2, 36 as YK-3, and 42 as YK-4 (Table I).

The chief compliant at first visit was “pain” in 32 patients, “swelling” in 44, “bleeding” in 4, “trismus” in 2, “loss of sensation” in 3, “delay of wound healing after extraction” in 1, and “nothing” or “request for further examination” in 23 cases.

Presence or absence of pain in the cancerous oral lesion
All subjects were regularly examined by 5 trained oral surgery specialists. The presence or absence of pain in the region around the tumor was determined at first patient visit by examination and medical interview.15 Spontaneous and function-related pain were evaluated separately. All the examiners asked the patients the same questions, such as “Have you felt a lasting pain in the oral lesion, even while resting, during the past 1 or 2 days?” The examiners took care to distinguish spontaneous pain from other types of pain and to distinguish a sensation of pain from discomfort or incongruity. Moreover, the examiners asked the patients about function-related pain, using questions such as “Do you feel definite pain during actions such as opening the mouth, drinking, eating, swallowing saliva, and talking?” Pain was evaluated as “present” or “absent” regardless of intensity. Effort was made to distinguish pain due to OSCC and pain due to other sources, such as temporomandibular disorders, headache, ear pain, teeth pain, periodontal disease, and sinusitis. There were no patients with systemic diseases, such as autoimmune disease, metastatic lesion in the oral cavity, or psychologic disease in this study. We also excluded tumor-associated pain after palpation or biopsy. We did not compare pain results between examiners, nor did we revise results of the examiners, because patients were evaluated using simple standard questions.

Statistical analyses
Patients were divided into 2 groups based on gender (male vs. female), age (under vs. over median), T-stage (T1 + T2 vs. T3 + T4), N-stage (N0 vs. N1 + N2), spontaneous and function-related pain (presence vs. absence), degree of histologic differentiation (grade I vs. grades II + III), and mode of invasion (YK-1 + YK-2 vs. YK-3 + YK-4).

Overall survival (OS) curves were plotted using the Kaplan-Meier method and compared using log-rank test and Cox multivariate proportional hazards regression analysis. Multiple logistic regression analysis was also used to evaluate the relationships between the presence of pain at the first visit examination and the above-mentioned clinical and demographic factors. All statistical analyses were performed using Stat View J-5.0 statistical software (Abacus Concepts, Berkeley, CA, USA), with \( P \) values of <.05 considered to be statistically significant.

RESULTS
Presence of spontaneous and function-related pain
At first examination, 40 of the 109 patients (37%) reported spontaneous pain and 72 (66%) reported function-related pain at primary tumor sites. All patients with spontaneous pain also reported function-related pain.
Correlations between the clinical factors and pain

Multiple logistic regression analysis showed that spontaneous pain was significantly correlated with the histologic mode of invasion (P = .007; odds ratio 6.2, 95% confidence interval [CI] 1.6-23.6) after adjustment for other factors (Table II).

Patient outcomes

The median follow-up duration was 48 months (range 3-66 months), and the mean follow-up duration was 43 ± 19 months. The percentages of the patients followed for 2, 3, and 5 years were 80%, 71%, and 42%, respectively. The 2-, 3-, and 5-year OS rates (OSRs) for all patients were 94%, 89%, and 85%, respectively.

Factors associated with OSR

The OSR was significantly lower in patients with than without spontaneous pain (P = .002; Fig. 1). OSR, however, did not differ significantly between patients with and without function-related pain (P = .10; Fig. 2). The OSR was significantly lower in patients with T3 + T4 tumors than in those with T1 + T2 tumors (P = .03; Fig. 3), as well as being significantly lower in patients with N1 + N2 tumors than in patients with N0 tumors (P < .0001; Fig. 4). OSR, however, was not significantly associated with gender (P = .93), patient age, (P = .13), primary tumor sites (P = .74), degree of histologic differentiation (P = .37), or histologic mode of invasion (P = .15; data not shown).

Factors associated with OSR by multivariate statistical analysis

Cox multivariate proportional hazards regression analysis revealed that spontaneous pain (P = .01; risk ratio [RR] 0.18, 95% CI, 0.45-0.72) and N-stage (P = .001; RR 0.10; 95% CI 0.02-0.40) were independent risk factors for OSR (Table III).

DISCUSSION

We previously reported that a histologically invasive pattern of tumor growth (mode of invasion) was a significant risk factor for pretreatment pain in patients with OSCC. Because significant correlations have been reported between the histologic mode of invasion and patient prognosis, we hypothesized that pain in patients with oral cancer may be significantly correlated with patient poor prognosis.

Orofacial pain in cancer patients may be due to underlying pathophysiologic mechanisms (e.g., nociceptive/inflammatory, neuropathic), tumor location (local or distant), or the primary initiating agent (tumor or tumor treatment). Usually, cancer pain is classified into 3 categories: pain caused by tumor growth, pain caused by treatment, and pain unrelated to cancer.

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**Table II. Results of multiple logistic regression analysis of spontaneous pain**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Chi-square</th>
<th>P value</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>0.18</td>
<td>.67</td>
<td>0.79</td>
<td>0.27-2.31</td>
</tr>
<tr>
<td>Age</td>
<td>0.64</td>
<td>.42</td>
<td>0.69</td>
<td>0.28-1.70</td>
</tr>
<tr>
<td>T-stage</td>
<td>1.06</td>
<td>.3</td>
<td>1.61</td>
<td>0.65-4.00</td>
</tr>
<tr>
<td>N-stage</td>
<td>0.063</td>
<td>.8</td>
<td>1.14</td>
<td>0.45-3.21</td>
</tr>
<tr>
<td>Histologic grading</td>
<td>1.92</td>
<td>.17</td>
<td>1.92</td>
<td>0.76-4.82</td>
</tr>
<tr>
<td>Mode of invasion</td>
<td>7.2</td>
<td>&lt;.01</td>
<td>6.22</td>
<td>1.64-23.61</td>
</tr>
</tbody>
</table>

CI, Confidence interval.
Because our patients had not yet been treated before evaluation, we could discount pain caused by cancer treatment. Tumor growth may cause pain by compressing and invading surrounding tissues, including muscles, bones, and peripheral nerves. The rich blood supply and large numbers of nerves in the head and neck may affect tumor growth and/or pain. Peripheral nociceptive mechanisms consistent with mechanical allodynia and hypersensitivity have been reported to be responsible for producing pain in patients with oral cancer. For example, metabolic products of arachidonic acid, such as prostaglandins, are produced by OSCC cells, which sensitize primary afferent nociceptors and produce hyperalgesia. This type of pain is histologically associated with tumor infiltration and compression of peripheral nerves and nociceptive receptors. Highly invasive tumors may directly stimulate peripheral nerve endings and nociceptive receptors. Because we previously reported that tumor size was not correlated with pain, oral cancer pain likely does not result from the mass effect of the tumor. In locally invasive tumors, inflammation is probably the initial cause of pain. Local inflammatory responses may lead not only to increased sensitivity of local nociceptors, but also to distant effects at the level of the central nervous system.

Many clinical and pathologic factors have been reported to be risk factors for cervical lymph node metastasis and OS. These include tumor size, tumor differentiation, mode of invasion, mitotic activity, microvascular invasion, and histologic grade of malignancy. Tumor depth of invasion and vascular invasion were recently reported to be risk factors for cervical lymph node metastasis in patients with SCC of the head and neck. Interestingly, patients with lymph node metastasis tended to report increased levels of spontaneous pain, suggesting that the process of tissue infiltration leading to metastasis may be responsible for increased spontaneous pain.

Increased preoperative CRP concentration was found to be associated with worse OS in patients with OSCC. CRP is easy to measure, reproducible, and familiar to clinicians. Synthesis of CRP is regulated by proinflammatory cytokines, such as IL-1 and IL-6, and increased serum concentrations of IL-6 have been shown to correlate with increased serum concentration of CRP in patients with head and neck cancer. Inflammatory mechanisms are activated by cancer-induced tissue damage and by factors locally released by certain tumors. Recruited inflammatory cells release cytokines that induce cancer-related pain. Thus, proinflammatory cytokines produced by invasive cancer cells may increase local pain and reduce its threshold in patients with OSCC, with IL-6 thought to play an important role in the initiation of painful neuropathies.
Carcinomas rated YK-4 have a mostly endophytic growth pattern,\textsuperscript{29} and a high local recurrence rate. Patients with these tumors have an extremely poor prognosis, apparently because tumor cells metastasize more easily in these types of cancer.\textsuperscript{30} We found, however, that the histologic mode of tumor invasion (i.e., YK classification) was not significantly associated with patient prognosis, even in univariate statistical analysis. There are 2 possible explanations for this unexpected finding. The first is based on the morphologic structures of the oral cavity. The thickness of the submucosal layer differs at different oral subsites, resulting in different depths of major lymphatics and blood vessels.\textsuperscript{1} Because our patients had tumors at different subsites, the thickness of the submucosal layers differed. The second explanation arises from the pathologic evaluation of biopsy specimens. Biopsy materials were usually taken from the edge of the tumor rather than from the most invasive front.\textsuperscript{7} It may be difficult to evaluate the characteristics of an entire tumor from a small amount of biopsy material.

We found that function-related pain did not significantly correlate with patient prognosis, even in univariate statistical analysis. Function-related pain may be greatly influenced by tumor location and the function characterization of the tumor site rather than nature of the tumor. Our patients had tumors at various primary sites, thus confusing any possible correlation between function-related pain and patient prognosis.

In patients with advanced pancreatic cancer, the onset of pain after radical resection was found to be significantly prognostic for patient survival.\textsuperscript{31,32} For example, back pain correlated with nonresectability and shorter survival.\textsuperscript{32} Large pancreatic cancers and invasion of the pancreatic capsule and intrapancreatic nerves may cause back pain.\textsuperscript{31} In contrast, we could not observe these correlations in patients with oral lesions.

One of the major limitations of the present study is the lack of information about the intensity and nature of pain. The severity of pain at the diagnosis of OSCC is usually of low intensity (mean visual analog scale 3).\textsuperscript{22} Spontaneous pain disturbs night sleep and daily activities in particular. We therefore distinguished between spontaneous and function-related pain. However, we were unable to identify any other study concerning the intensity of spontaneous pain in patients with OSCC. Because pain is a personal sensation, it is difficult to compare the intensity and nature of pain in different patients. Before we started this study, we verified that there was a difference in patients with OSCC between the presence and absence of spontaneous pain, without regard to the intensity or nature of pain. We therefore concluded that the presence or absence of pain may be an important risk factor for patient prognosis.

In conclusion, our findings suggest that the presence of spontaneous pain before treatment may be associated with poor prognosis in the patients with OSCC.

REFERENCES


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