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

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Abstract

Objectives: We have previously reported that the histological mode of invasion of oral squamous cell carcinoma (OSCC) is a significant risk factor for pain. 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 (OSRs) and clinicopathological variables, including gender, age, T- and N-stages, pathological 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 OSR of patients with spontaneous pain was significantly lower than that of patients without pain ($p=0.002$). Multivariate analysis revealed that spontaneous pain and N-stage were significant independent predictors of OSR.

Conclusion: This is the first report showing that spontaneous pain before treatment may be associated with poor prognosis in patients with OSCC.

Introduction

Several tumor markers have been investigated for their ability to predict the biological behavior and prognosis of patients with oral squamous cell carcinoma (OSCC), but none is used in day-to-day clinical practice.^{1, 2} Determining the prognosis of patients with OSCC is very difficult,³ with studies showing contradictory results.^{3, 4-6} For example, tumor thickness has been reported to predict survival in patients with oral tongue carcinoma,⁷ and tumor shape and other pathologic factors have been reported to predict outcomes in patients with head and neck cancers.⁷⁻⁹ Nevertheless, some pathological malignant grading systems are too complex for use by clinicians, and some are inconsistent.¹⁰ Recently, an increased preoperative concentration of C-reactive protein (CRP) was found to be associated with poorer overall survival in patients with OSCC.² Synthesis of CRP is regulated by pro-inflammatory cytokines, such as interleukin (IL)-1 and IL-6.² These pro-inflammatory cytokines may be a source of pain around the tumor site.

Pain is a common symptom in patients with cancer, including those with cancers of the head and neck.¹² Pain can affect physical functions, emotional states, and quality of life of patients.¹¹⁻¹⁴ Since the mechanisms underlying of cancer-associated pain are very complex, many factors may affect pain. We recently performed a clinical study assessing risk factors significantly associated with pain in patients with untreated OSCC.¹⁵ We found that histological mode of tumor invasion was a significant risk factor for spontaneous pain. Due to the strong correlation between the histological mode of invasion and the clinical course in patients with OSCC,¹⁶ we hypothesized that cancer pain may be a risk factor predicting poor patient prognosis. To date, however, the correlation between cancer pain and

patient prognosis has not been assessed in patients with oral cancer lesions. We therefore sought to determine whether cancer pain was predictive of poor prognosis in patients with OSCC.

Materials and Methods

1. Patients

We evaluated 109 consecutive patients (79 males, 30 females, median age 63 yrs, range, 29-87 yrs) with untreated primary OSCC who had undergone medical examinations at the Department of Oral Medicine and Oral Surgery of Hokkaido University Hospital; these subjects had been included in our previous study.¹⁵ Histologic examination of biopsy specimens from all 109 patients showed that all were SCC. 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 medical interview. We also excluded the patients who had already been biopsied or treated for OSCC.

All subjects gave informed consent to biopsy and histological examination, and the study protocol was approved by our institutional review board (Number: 100930).

2. Clinicopathological 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 two authors (YY and JS) using haematoxylin- and eosin-stained slides prepared from pre-treatment biopsy specimens. The degree of histological differentiation was determined in accordance with the criteria of the World Health Organization (WHO) (1997). We found that 48 patients had grade 1 tumors, 58 had grade 2, and 3 had grade 3.

The histological 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, 3 and 42 as YK-4. (Table 1)

The chief complaint 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.

3. 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. We have made an effort to distinguish pain from OSCC and pain from other sources, such as temporomandibular disorders (TMD), 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 psychological 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, since patients were evaluated using simple standard questions.

4. Statistical analysis

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

OS curves were plotted using the Kaplan-Meier method and compared using log-rank test and Cox’ s multivariate proportional hazards regression analysis. Multiple logistic regression analysis was also utilized to evaluate the relationships between the presence of pain at the first visit examination

and the abovementioned 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 less than 0.05 were considered statistically significant.

Results

1. 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.

2. Correlations between the clinical factors and pain.

Multiple logistic regression analysis showed that spontaneous pain was significantly correlated with the histological mode of invasion ($p=0.007$, odds ratio [OR]=6.2, 95% confidence interval [CI]=1.6-23.6) after adjustment for other factors (Table 2).

3. 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 OSRs for all patients were 94%, 89%, and 85%, respectively.

4. Factors associated with OSR

The OSR was significantly lower in patients with than without spontaneous pain ($p=0.002$; Fig. 1). OSR, however, did not differ significantly between patients with and without function-related pain ($p=0.10$; Fig. 2). The OSR was significantly lower in patients with T3+4 tumors than in those with T1+2 tumors ($p=0.03$; Fig. 3), as well as being significantly lower in patients with N1+2 tumors than in patients with N0 tumors ($p<0.0001$; Fig. 4). OSR, however, was not significantly associated with gender ($p=0.93$), patient age, ($p=0.13$), primary tumor sites ($p=0.74$), degree of histological differentiation ($p=0.37$), or histological mode of invasion ($p=0.15$)(data not shown).

5. Factors associated with OSR by multivariate statistical analysis

Cox' s multivariate proportional hazards regression analysis revealed that spontaneous pain ($p=0.01$; risk ratio [RR], 0.18; 95% CI, 0.45-0.72) and N-stage ($p=0.001$; RR, 0.10; 95% CI, 0.02-0.40) were independent risk factors for OSR (Table 3).

Discussion

We previously reported that a histologically invasive pattern of tumor growth (mode of invasion) was a significant risk factor for pre-treatment pain in patients with OSCC.¹⁵ Since significant correlations have been reported between the histological mode of invasion and patient prognosis,^{15, 16, 19-21} 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 pathophysiological mechanisms (*e.g.*, nociceptive/inflammatory, neuropathic), tumor location (local or distant), or the primary initiating agent (tumor or tumor treatment).²² Usually, cancer pain is classified into three categories: pain caused by tumor growth, pain caused by treatment, and pain unrelated to cancer.²³ Because our patients had not yet been treated prior to 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.^{23, 24} Peripheral nociceptive mechanisms consistent with mechanical allodynia and hypersensitivity have been reported responsible for producing pain in patients with oral cancer.²⁵ For example, metabolic products of arachidonic acid, such as prostaglandins, are produced by OSCC cells, which sensitize primary afferent nociceptors and produce hyperalgesia.²⁵ This type of pain is histologically associated with tumor infiltration and compression of peripheral nerves and nociceptive receptors.²⁴ Highly invasive tumors may directly stimulate peripheral nerve endings and nociceptive receptors. Since we previously reported that tumor size was not correlated with pain,¹⁵ 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.¹² Local inflammatory responses may lead not only to increased sensitivity of local nociceptors, but to distant effects at the level of the central nerve system.¹²

Many clinical and pathological factors have been reported to be risk factors for cervical lymph node metastasis and overall survival. These include tumor size, tumor differentiation, mode of invasion, mitotic activity,

microvascular invasion, and histologic grade of malignancy.^{2, 7, 10, 18, 26, 27}

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.²⁶ 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.²⁵

Increased preoperative CRP concentration was found to be associated with worse OS in patients with OSCC.² CRP is easy to measure, reproducible and familiar to clinicians. Synthesis of CRP is regulated by pro-inflammatory cytokines such as IL-1 and IL-6,² 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.^{2, 28}

Inflammatory mechanisms are activated by cancer-induced tissue damage and by factors locally released by certain tumors.²³ Recruited inflammatory cells releases cytokines that induce cancer-related pain.²³ Thus, pro-inflammatory 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.

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Carcinomas rated YK-4 have a mostly endophytic growth pattern,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 type of cancer.³⁰ We found, however, that the histological mode of tumor invasion (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 morphological 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.¹ Since our patients had tumors at different subsites, the thickness of the submucosal layers differed. The second explanation arises from the pathological evaluation of biopsy specimens. Biopsy materials were usually taken from the edge of the tumor rather than from the most invasive front.⁷ It may be difficult to evaluate the characteristics of an entire tumor from small amount of biopsied 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 following radical resection was found to be significant prognostic for patient survival.^{31, 32} For example, back pain correlated with nonresectability and shorter survival.³² Large pancreatic cancers and invasion of the pancreatic capsule and intrapancreatic nerves may cause back pain.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 analogue scale=3).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. Since 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.

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Captions to illustrations

Figure 1: Kaplan-Meier curves of overall in patients with and without spontaneous pain. The overall survival rate was significantly lower in patients with than without spontaneous pain (log-rank test: $p=0.002$).

Figure 2: Kaplan-Meier curves of overall survival in patients with and without function-related pain. There was no significant difference in overall survival rate between patients with and without function-related pain (log-rank test: $p=0.10$).

Figure 3: Kaplan-Meier curves of overall survival in patients with T-I+II and T-III+IV tumors. The overall survival rate was significantly lower in patients with T-III+IV than in patients with T-I+II tumors (log-rank test: $p=0.03$).

Figure 4: Kaplan-Meier curves of overall survival in patients with N-0 and N-1+2 tumors. The overall survival rate was significantly lower in patients with N-1+2 than in patients with N-0 tumors (log-rank test: $p<0.0001$).

**Table 1: Histological grade of mode of invasion by Yamamoto-Kohama et al.
(so-called Y-K classification) ^{16, 18}**

<i>YK-1</i>	Well defined borderline
<i>YK-2</i>	Cords, less marked borderline
<i>YK-3</i>	Groups of cells, no distinct borderline
<i>YK-4</i>	Diffuse invasion

Table 2: Results of multiple logistic regression analysis of spontaneous pain

Factors	Chi-square	P value	Odds ratio	95% CI
<i>Sex</i>	0.18	0.67	0.79	0.27-2.31
<i>Age</i>	0.64	0.42	0.69	0.28-1.70
<i>T-stage</i>	1.06	0.30	1.61	0.65-4.00
<i>N-stage</i>	0.063	0.80	1.14	0.45-3.21
<i>Histological grading</i>	1.92	0.17	1.92	0.76-4.82
<i>Mode of invasion</i>	7.20	<0.01	6.22	1.64-23.61

CI: confidence interval

Table. 3: Cox's multivariate proportional hazards regression analysis for overall survival rate

Factors	Chi-square	<i>P</i>-value	Risk ratio	95% CI*
<i>Spontaneous pain</i>	5.93	0.01	0.18	0.45-0.72
<i>N-stage</i>	10.42	<0.01	0.10	0.02-0.40
<i>T-stage</i>	0.43	0.51	0.66	0.19-2.28
<i>Histological grading</i>	1.06	0.30	1.98	0.54-7.25
<i>Mode of invasion</i>	0.20	0.66	1.54	0.23-10.61
<i>Sex</i>	0.98	0.32	0.53	0.15-1.86
<i>Age</i>	2.16	0.14	0.43	0.14-1.32

*** CI: confidence interval**







