Frequency of Pain and Correlation with Clinical and Histologic Parameters in T1 Squamous Cell Carcinoma of the Tongue: A Retrospective Pilot Study

Nikolaos G. Nikitakis, MD, DDS, PhD
Assistant Professor
Department of Oral Medicine and Pathology
School of Dentistry
University of Athens
Athens, Greece

Eleni Sarlani, DDS, PhD
Private Practice Limited to Orofacial Pain
Athens, Greece

Antonia Kolokythas, DDS, PhD
Assistant Professor
Department of Oral and Maxillofacial Surgery
University of Illinois College of Dentistry
Chicago, Illinois, USA

Mark A. Scheper, DDS, PhD
Assistant Professor
Department of Oncology and Diagnostic Science
School of Dentistry
University of Maryland, Baltimore
and Greenebaum Cancer Center
Baltimore, Maryland, USA

Georgios Kamperos, DDS, MSc
Private Practice
Athens, Greece

Richard A. Ord, DDS, MD, MS
Professor and Head
Department of Oral and Maxillofacial Surgery/Oncology
University of Maryland, Baltimore
Baltimore, Maryland, USA

Alexandra Sklavounou-Andrikopoulou, DDS, MSc, PhD
Professor and Head
Department of Oral Medicine and Pathology
School of Dentistry
University of Athens
Athens, Greece

Correspondence to:
Dr Georgios Kamperos
2-4, Alkmaionidon St
16121 Athens
Greece
Email: gkamperos@yahoo.gr

Aims: To conduct a pilot retrospective study to investigate the frequency of pain among patients with early-stage oral squamous cell carcinoma (OSCC) of the tongue and to correlate the pain with clinical and histopathologic parameters. **Methods:** Twenty-four archival cases of T1 OSCC of the tongue were reviewed. No power analysis was conducted due to the pilot nature of the study. Tumors were classified into two groups according to the presence or not of pain (P+ and P– groups). Clinical and histopathologic parameters, such as grade of differentiation, depth of invasion, and presence of vascular, muscular, and perineural invasion were recorded. Statistical analyses included parametric (Student *t*) and nonparametric (chi-square) tests. **Results:** Pain was reported by 13 of the 24 patients. In the P+ group, 11 of the 13 had moderately differentiated and 2 well-differentiated tumors; in contrast, P– patients had moderately differentiated tumors in 5 of the cases and well-differentiated tumors in 6 cases ($P = .082$). Vascular invasion was observed in 5 of the 13 P+ and 5 of the 11 P– patients, muscular invasion in 5 P+ and 2 P– patients, and perineural invasion in 4 P+ and 1 P– patients, respectively. The mean depth of invasion was 1.51 mm for P+ patients and 1.25 mm for P– patients. Only lymphoplasmocytic infiltration differed significantly, with P+ tumors exhibiting more intense inflammation ($P = .041$). **Conclusion:** Despite the limited number of cases, the results of this study suggest that painful OSCCs of the tongue may be associated with more intense inflammation.
J Oral Facial Pain Headache 2014;28:46–51. doi: 10.11607/jop.969

Key words: *histologic grade, pain in cancer, perineural invasion, squamous cell carcinoma, tongue*

Oral squamous cell carcinoma (OSCC) is the most common type of cancer of the oral cavity, since it accounts for more than 90% of cancer cases in this anatomic region.[1–3] OSCC may present with various clinical forms, including endophytic and/or exophytic presentations. Most commonly, patients present with a painless mass or an ulceration that fails to heal after minor trauma.[4] The tongue is the most common location for OSCC development; the lingual musculature provides little restriction to tumor growth, and as a result, cancers of the tongue can reach a significant size before any symptoms occur or the symptoms may vary and be nonspecific. Referred otalgia and/or pharyngeal pain may be one of the first symptoms experienced by a patient with a mass in the oropharynx following a well-described neural pathway via cranial nerves IX and X.[5] Intense pain associated with major nerve trunk involvement is more often correlated with more advanced disease.[6]

The lack of accompanying painful symptoms in the early stages of OSCC may result in a delay in seeking medical attention, thus further compromising the prognosis. The 5-year survival rates vary between 60% and 85% for TNM (T, tumor size; N, lymph node metastases; M, distant metastases) stages I and II, and 10% and 40% for TNM stages III and IV.[1,3]

The purpose of this pilot retrospective study was to investigate the frequency of pain among patients with early-stage OSCC of the tongue and to correlate the pain with clinical and histopathologic parameters.

Table 1 Malignant Grading System of OSCC (by Anneroth et al,[7] modified by Bryne et al[8])

Morphologic parameter	Grade			
	1	2	3	4
Degree of keratinization	High (> 50% of the cells)	Moderate (20%–49% of the cells)	Minimal (5%–19% of the cells)	None (0%–4% of the cells)
Nuclear polymorphism	Little (> 75% mature cells)	Moderately abundant (50%–74% mature cells)	Abundant (25%–49% mature cells)	Extreme (0%–24% mature cells)
Number of mitoses / High power field	0–1	2–3	4–5	> 5
Pattern of invasion	Pushing, well-delineated infiltrating borders	Infiltrating solid cords, bands, and/or strands	Small groups or cords of infiltrating cells (n > 15)	Marked and widespread cellular dissociation in small groups of cells (n < 15) and/or in single cells
Lymphoplasmacytic infiltration	Marked	Moderate	Slight	None

Materials and Methods

A retrospective review of the medical records of patients with OSCC treated from 1991 to 2002 at the University of Maryland Medical Systems was undertaken. Thirty cases of T1 (tumor dimension 2 cm or less) squamous cell carcinomas of the oral tongue (anterior two-thirds of the tongue) were retrieved from a cohort of 685 cases. Of those 30 T1 OSCC cases, 24 cases were selected based on the absence of any previous therapeutic interventions and availability of microscopic slides (from both the biopsy and the final surgical specimens). All cases received surgery as their primary treatment modality. This study received Institutional Review Board approval, and informed consent was obtained from all patients.

The report of pain or any associated symptoms was retrieved from the patients' charts. History and clinical examination of all patients was performed by the same surgeon (RAO) with systematic questioning and recording of any symptomatology. Presence or absence of pain, numbness, or paresthesia was specifically indicated for every patient, none of whom reported numbness or paresthesia. For patients reporting pain, further questioning included duration, intensity, and location, as well as whether the pain was spontaneous or triggered by patients' activities, such as chewing or swallowing. Since in all these patients the pain was similar, ie, mild to moderate, of a few weeks' duration, located in the primary tumor site, and spontaneous but worsening by chewing or swallowing, the cases were classified into two groups according to the presence (P+ group) or absence (P– group) of pain at the time of the initial visit.

In addition, the medical charts were reviewed for nodal (N) status and presence or absence of distant metastasis (M) at the initial visit and at the last follow-up. The follow-up period ranged from 3 to 11 years, with a median value of 6.2 years.

Histopathologic reevaluation of both biopsy and surgical specimens (stained with hematoxylin and eosin) was undertaken by two oral pathologists independently (NN and MAS), who were not aware of the initial diagnosis or the presence or absence of pain. In case of disagreement, consensus was reached by discussion. The specimens were evaluated for: grade of differentiation according to the World Health Organization grading system, as well as the presence or absence of vascular, muscular, and perineural involvement. At least five serial sections of each specimen were examined. Furthermore, at the time of the study, all retrieved paraffin blocks were immunohistochemically stained with S-100 for confirmation of perineural invasion. Internal controls of peripheral nerve bundles present in the periphery of the tumor and external controls of benign neural tumors (neurofibromas and neurilemmomas from the archives of the Department of Oncology and Diagnostic Sciences, School of Dentistry, University of Maryland) were strongly stained with S-100 as expected.

Each specimen was scored according to the malignant grading system of Anneroth et al[7] for oral OSCC, as modified by Bryne et al[8] (Table 1). The depth of invasion, measured via an ocular micrometer attached to the microscope eyepiece, was defined as the distance from the surface of the epithelium to the deepest invading tumor island or cell, using a reconstructed line excluding any exophytic component and including the thickness of the epithelium lost due to ulceration.

Statistical Analysis

No power analysis was conducted because this was a pilot retrospective study. A freeware statistical program (PSPP) was used for data analysis (http://www.gnu.org/software/pspp/). Differences in the degree of keratinization, nuclear polymorphism, number of mitoses/high power field (HPF), pattern of invasion,

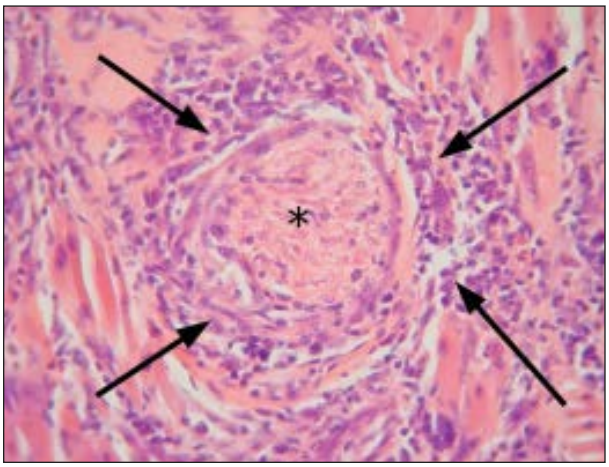

Fig 1a Perineural invasion in the form of tumor cells *(arrows)* surrounding a peripheral nerve branch (*). Hematoxylin and eosin stains, magnification ×200.

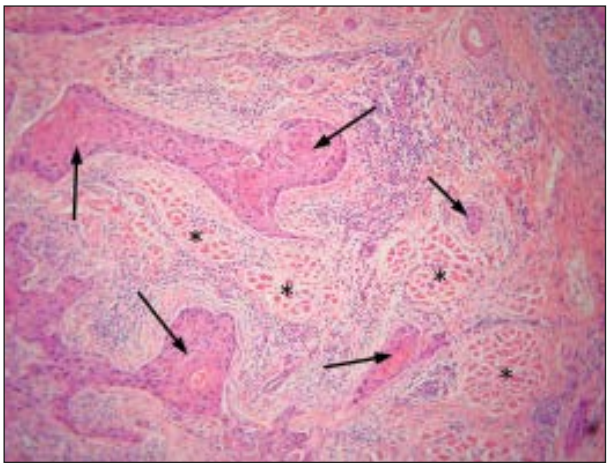

Fig 1b Muscular invasion with islands of tumor cells *(arrows)* extending between muscle fibers (*) in a case of painful OSCC of the tongue. Hematoxylin and eosin stains, magnification ×100.

Table 2 Mean Grading Scores (± Standard Deviation) of the Biopsy Specimens

	Degree of keratinization	Nuclear polymorphism	No. of mitoses/HPF	Pattern of invasion	Lymphoplasmacytic infiltration	Total
P+	1.85 (0.69)	2.38 (1.04)	1.77 (0.73)	2.08 (1.04)	2.00 (0.71)	10.08 (2.66)
P–	1.73 (0.79)	2.09 (0.83)	1.91 (0.70)	2.00 (0.89)	2.55*(0.52)	10.27 (2.57)

P+ and P– groups refer to patients with and without pain, respectively.
HPF: high power field; *statistically significant difference, $P = .041$.

lymphoplasmacytic infiltration, and depth of invasion between P+ and P– patients were analyzed by means of parametric tests (Student *t* test), while differences in the degree of tumor differentiation, and the presence of vascular, muscular, and perineural infiltration, were analyzed by means of nonparametric tests (chi-square test). Statistical significance was set at $P \leq .05$.

Results

Out of 24 patients with T1-stage OSCC of the tongue, 11 were male and 13 female (1:1.18). Their ages varied between 41 and 82 years (mean 66 years, SD 12 years). Eleven patients were smokers (including those who quit less than 10 years before) and 13 nonsmokers; 6 were alcohol drinkers and 18 nondrinkers.

At the time of the first visit, 13 patients (54.17%) did report pain of a few weeks duration (P+ group) located at the site of the primary tumor (ie, tongue); 1 of these patients additionally reported intermittent ear pain. Four of these patients (16.7%) indicated that pain was the chief complaint prompting medical evaluation. The remaining 11 patients (45.8%) were pain free (P– group) and the lesions were discovered on routine clinical examination.

In the P+ group, 11 (84.6%) patients had moderately differentiated and 2 (15.4%) had well-differentiated tumors; in contrast, the tumors of the P– patients were moderately differentiated in 5 (45.5%) cases and well differentiated in 6 (54.6%) cases. The difference in the prevalence of well-differentiated tumors between the two groups did not reach statistical significance ($P = .082$). In addition, within the P+ group, 5 (38.5%) patients had vascular invasion, 5 (38.5%) muscular invasion, and 4 (30.8%) perineural invasion (Fig 1). In the P– group, the presence of vascular, muscular, and perineural invasion was found in 5 (45.5%), 2 (18.2%), and 1 (9.1%) patients, respectively. None of these parameters reached a statistically significant difference between the two groups ($P > .05$).

The results of the analysis of the specimens according to the Anneroth et al and Bryne et al malignant grading system are described in Table 2; also see Figs 2 and 3. Only the lymphoplasmacytic infiltration differed significantly among the two groups, with P+ group cases receiving lower scores ($P = .041$), corresponding to a more intense infiltrate (Fig 3). The mean depth of invasion was 1.51 mm (SD 1.19 mm) for the P+ group and 1.25 mm (SD 1.19 mm) for the P– group, the difference being not statistically significant ($P > .05$).

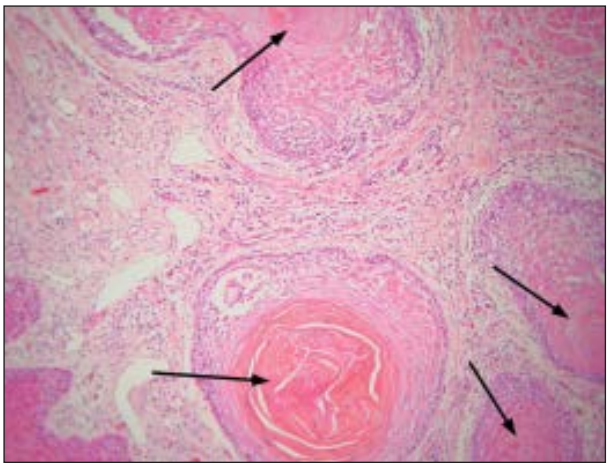

Fig 2a High degree of keratinization with formation of keratin pearls *(arrows)* and limited nuclear polymorphism in a case of nonpainful OSCC of the tongue. Hematoxylin and eosin stains, magnification ×100.

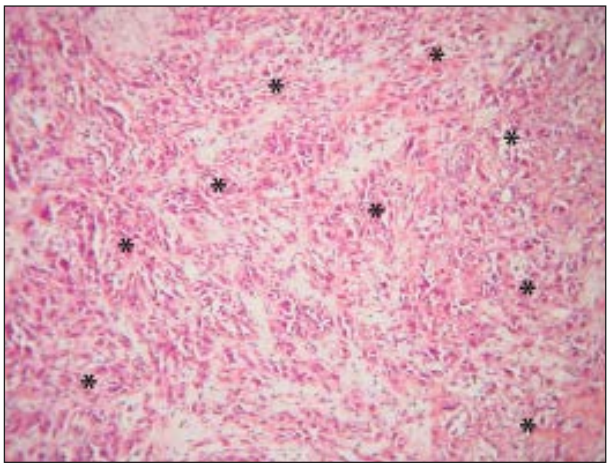

Fig 2b Low degree of keratinization and high nuclear polymorphism with variably sized and shaped hyperchromatic nuclei in a case of painful OSCC of the tongue (*). Hematoxylin and eosin stains, magnification ×100.

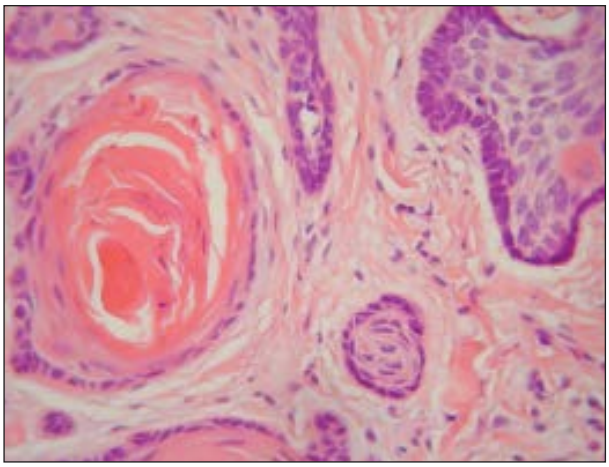

Fig 3a Lack of lymphoplasmacytic infiltration in a case of nonpainful OSCC of the tongue. Hematoxylin and eosin stains, magnification ×200.

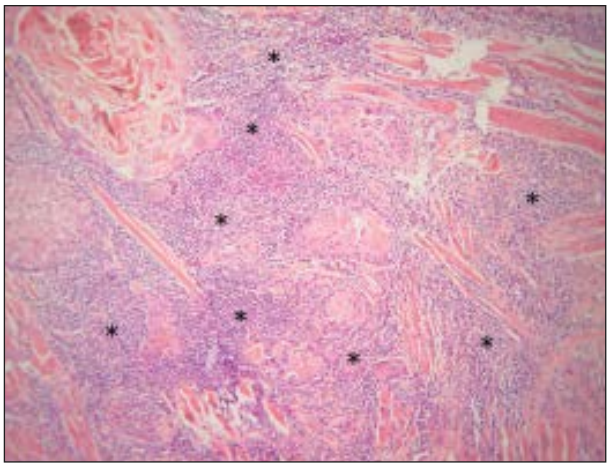

Fig 3b Intense and diffuse infiltration by numerous lymphocytes and plasma cells (*) in a case of painful OSCC of the tongue. Hematoxylin and eosin stains, magnification ×100.

All patients underwent partial glossectomy performed by the same surgeon (RAO). All frozen sections at time of surgery were negative and all margins were clear. Only 2 out of the 24 patients exhibited regional lymph node metastasis (N1), both belonging to the P+ group (statistical analysis of these observations was not feasible due to the small sample sizes). One of the patients with regional lymph node involvement died of the disease; all other patients were alive and well without evidence of locoregional recurrence during the follow-up period.

Discussion

According to previous studies, between 54.4% and 74.2% of patients with OSCC of all stages report pain.[9–11] The anterior two-thirds of the tongue, which is the most common OSCC localization, is also the area in which the painful symptoms are usually localized regardless of the OSCC stage.[2,3,9,11] The pain typically varies in intensity, increases as cancer progresses, and is usually triggered by physical activities such as chewing, swallowing, and speaking.[1,2,9,12,13] There is a general presumption that pain is absent or minimal in the early stages of OSCC, a fact that has been linked to delayed diagnosis with adverse consequences on patients' prognosis. Indeed, Cuffari et al reported that pain was the first symptom in only 19.2% of OSCC patients.[11] The present pilot retrospective study suggests, however, that in patients with early-stage OSCC of the tongue, pain of a few weeks duration may occur more often than generally thought, as it was reported by 54.17% of the patients.

Such recognition on behalf of the patients and clinicians alike may prompt appropriate diagnostic investigation. In contrast, perpetuation of the common belief that early-stage oral cancer is painless may result in inappropriate delays in diagnosis.

The pain has been etiologically associated with increased lymphoplasmacytic infiltration, perineural invasion, and muscular invasion, thus emphasizing the role of inflammation and infiltration of nerves and muscles in generating pain.[12] The inflammatory reaction produces algogenic substances that sensitize nociceptors causing pain, usually localized to the region.[12] The role of inflammation in the pathogenesis of cancer pain is under constant research. It has been estimated that 15% to 20% of all cancers are associated with inflammation, especially of the chronic type.[14] Tumor cells are known to produce inflammatory agents in order to alter the stroma and facilitate infiltration.[15] Increased proinflammatory cytokine levels are found in many cancer cell lines including oral OSCC. [15] Moreover, acute inflammation caused by high doses of tumor necrosis factor (TNF), interleukin-1 (IL-1), or lipopolysaccharides (LPS) leads to increased infiltration and metastases.[14] Inflammation is also related to the expression of several oncogenes.[16] Therefore, painful symptoms may be a reflection and potentially a surrogate marker of the occurrence and intensity of cancer-related inflammatory reactions in the tumor bed.

In this study, muscular and perineural invasions were found more often in patients with pain than without pain, although the difference did not reach statistical significance, which may be due to the lower power of the study. Muscular invasion is linked to increased depth of invasion, which is another factor partially responsible for pain generation.[7,17] Invasion of nerves by cancer cells may cause nerve stimulation and provoke pain, although nerve involvement may not be accompanied by pain, at least until the tumor has reached significant size and has spread to branches of cranial nerves IX and X.[4,5] A large number of patients with cancers of the skin of the head and neck with perineural invasion may be asymptomatic even though major nerve trunks are affected.[18] In general, the perineural invasion by cancer cells can assume the following histologic patterns: *(1)* lamination of tumor cells around the nerve, *(2)* capping of the nerve by tumor cells, *(3)* surrounding of the nerve by tumor cells, or *(4)* "sandwiching" of the nerve by tumor cells and invasion of the nerve by tumor cells.[19] Perineural invasion may interfere with the nerve's blood supply, resulting in local edema, demyelinization, or segmental infarction.[20] The frequency of perineural invasion increases along with increases in tumor size. Tumors greater than 7 mm have a 67% probability to show a perineural invasion,[17] although the frequency of perineural invasion varies according to the number of histologic sections examined and the diligence of the pathologist.[4]

Besides its potential involvement in pain generation, perineural invasion may play a significant role in cancer progression. The perineural space may serve as a route of spread for various types of cancer.[21] Once cancer cells enter the perineural space, they may spread proximally or distally, allowing tumor migration and increasing the risk of metastatic spread. Perineural invasion, reported to occur in up to 52% of head and neck squamous cell carcinomas, has been associated with an increased risk of local, regional, and locoregional recurrence.[14,22–28] For tongue OSCC in particular, Maddox et al, in their review of 136 patients with OSCC of the anterior two-thirds of the tongue, found that perineural invasion, along with tumor size and gender, could identify patients at high risk for occult metastasis.[29] Further, 71% of the patients with cancer of the tongue and floor of the mouth with perineural invasion and stage N0 developed lymph node metastasis, and this was significantly different compared with patients without perineural invasion.[17]

Sato et al[30] reported a statistically significant association between pain and some histologic features such as histologic differentiation and depth of invasion in OSCC. The present study could not confirm this finding, as the OSCCs of patients with pain did not exhibit lower differentiation than that in patients without pain.

Lymph node metastasis is an infrequent finding among patients with T1 tumors, and its presence significantly worsens patients' prognosis. In the present study, both patients with metastatic spread belonged to the P+ group; however, the small sample size did not allow for statistical analysis of this observation, which should be further explored in a larger cohort of metastatic versus nonmetastatic cases.

This study had two main limitations. First, the small sample size due to the rarity of T1 OSCCs of the oral tongue did not allow drawing firm conclusions. In the future, a careful recording of a pain history in patients with this tumor may provide a better insight in the role that inflammation and other pain-related features play in early-stage carcinogenesis. Second, the pain was only recorded as part of the patient's history, and no specific questionnaire was used for a more objective pain evaluation. Nevertheless, the authors are confident that the simplified categorization of the patients into just two groups (P+ versus P–) based on detailed questioning by a highly qualified clinician was acceptable for this pilot retrospective study. However, future studies investigating the frequency and significance of pain in oral cancer patients should use pain questionnaires such as the oral cancer pain questionnaire

recently developed at the University of California San Francisco, a reliable tool for quantifying the pain experienced by OSCC patients.[31] Future prospective studies correlating pain from patients with early oral cancer and clinical and histologic parameters of tumor aggressive behavior are needed. Quantification of pain, with well-established and easy-to-use pain questionnaires, and careful examination of the pathology specimen for presence of perineural invasion, especially in early-stage tumors, may guide treatment choices.

Acknowledgments

The authors report no conflicts of interest related to this study.

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