Journal of Pain Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Measurement of the Association of Pain with Clinical Characteristics in Oral Cancer Patients at Diagnosis and Prior to Cancer Treatment

Caroline M Sawicki[1], Malvin N Janal[2], Sung Hye Gonzalez[3], Angie K Wu[3], Brian L Schmidt[3–5,*], Donna G Albertson[3–5,*]

[1]Department of Pediatric Dentistry, New York University College of Dentistry, New York, NY, USA; [2]Department of Epidemiology & Health Promotion New York University College of Dentistry, New York, NY, USA; [3]NYU Dentistry Translational Research Center, New York University College of Dentistry, New York, NY, USA; [4]Department of Oral and Maxillofacial Surgery, New York University College of Dentistry, New York, NY, USA; [5]NYU Pain Research Center, New York University College of Dentistry, New York, NY, USA

*These authors contributed equally to this work

Correspondence: Donna G Albertson, NYU Dentistry Translational Research Center, New York University College of Dentistry, 421 First Avenue, Room 233W, New York, NY, 10010, USA, Tel +1 212-998-9396, Fax +1 212-995-4843, Email da66@nyu.edu

Aim: Oral cancer patients suffer pain at the site of the cancer, which degrades quality of life (QoL). The University of California San Francisco Oral Cancer Pain Questionnaire (UCSFOCPQ), the only validated instrument specifically designed for measuring oral cancer pain, measures the intensity and nature of pain and the level of functional restriction due to pain.

Purpose: The aim of this study was to compare pain reported by untreated oral cancer patients on the UCSFOCPQ with pain they reported on the Brief Pain Inventory (BPI), an instrument widely used to evaluate cancer and non-cancer pain.

Patients and Methods: The correlation between pain measured by the two instruments and clinical characteristics were analyzed. Thirty newly diagnosed oral cancer patients completed the UCSFOCPQ and the BPI.

Results: Pain severity measurements made by the UCSFOCPQ and BPI were concordant; however, the widely used BPI average pain over 24 hours score appeared less sensitive to detect association of oral cancer pain with clinical characteristics of patients prior to treatment (nodal status, depth of invasion, DOI). A BPI average score that includes responses to questions that measure both pain severity and interference with function performs similarly to the UCSFOCPQ in detection of associations with nodal status, pathologic T stage (pT stage), stage and depth of invasion (DOI).

Conclusion: Pain assessment instruments that measure sensory and interference dimensions of oral cancer pain correlate with biologic features and clinical behavior.

Keywords: pretreatment oral cancer pain, University of California San Francisco Oral Cancer Pain Questionnaire, Brief Pain Inventory, pain severity, pain interference with functioning

Introduction

Oral cancer pain produces severe pain in over half of patients.[1,2] At the time of diagnosis and prior to treatment, quality of life (QoL) is diminished in patients with late stage tumors (stage III and IV vs I and II) and in patients reporting greater pain.[3–5] Pretreatment pain predicts head and neck squamous cell carcinoma (HNSCC) patient survival.[6] Head and neck cancers include those that develop in or around the throat, nose, larynx, sinuses, and oral cavity (oral tongue, gingiva, floor of mouth and other oral cancers, ICD145). Incidence of oral and oropharyngeal cancer is increasing in young patients (≤45).[7,8]

Symptom scores reported by patients differ by tumor site.[4] Oral cancer patients report intense function-related pain prior to surgery. Pain is alleviated by surgical resection.[2] Pain interferes with talking, eating and drinking. Oral cancer pain is poorly managed by analgesics. Opioids may not be effective and/or dose escalation is required as tolerance develops. Accurate and

Received: 29 May 2023
Accepted: 25 September 2023
Published: 2 February 2024

reliable pain measurement instruments are needed to guide treatment and support clinical trials to identify additional pain therapies, as well as translational studies investigating the responsible peripheral nociceptive mechanisms and the molecular features and clinical characteristics such as metastasis, that are associated with painful oral cancers. [9–11]

Pain is subjective, with biological, psychological and social dimensions.[12] It has been suggested that patients' description of pain can be captured by two dimensions – sensory discrimination of pain and reaction to pain – with one dimension or the other perhaps being more meaningful for different sources of pain (eg, cancer versus non-cancer).[13] Two instruments, the University of California San Francisco Oral Cancer Pain Questionnaire (UCSFOCPQ) and the Brief Pain Inventory (BPI) have been used to measure pain experienced by HNSCC patients.

The UCSFOCPQ, the only validated instrument specifically tailored to oral cancer,[1,2] asks about both sensory and interference aspects of pain. The first six UCSFOCPQ questions ask about the intensity, sharpness and throbbing nature of pain and whether these pain qualities are experienced spontaneously or with function. Question 7 asks about sensitivity to touch and question 8 about interference of pain with function. In addition to risk for metastasis,[1,11] studies have reported association of UCSFOCPQ scores with clinical and pathologic features, including gender,[1,14] perineural invasion (PNI),[15] depth of invasion (DOI) and pathologic (pT) and clinical (cT) tumor stage.[16]

The Brief Pain Inventory (BPI), a widely used instrument for measurement of cancer and non-cancer pain, asks patients about the intensity and quality of pain, effectiveness of pain treatment, and how much pain interferes with physical and psychological aspects of one's life.[17] The BPI has been validated across several cultures and languages in numerous countries.[17] Although there are four questions querying pain intensity, only the single pain severity item, average pain over 24 hours, has been used as the measure of pain intensity in a variety of studies, including for example, the association of cancer pain with; QoL,[5] circulating biomarkers[12] and drug monitoring,[18] as well as in comparisons of the interference of pain with physical and psychological functioning in cancer and non-cancer chronic pain patients.[13] In studies of HNSCC patients at diagnosis, average pain over 24 hours was reported in association with T stage and nodal status, as well as with QoL.[5]

The aim of this study was to compare the pain reported by untreated oral cancer patients on the UCSFOCPQ with pain they reported on the BPI. We show that the commonly used BPI metric, average pain over 24 hours, appears less sensitive to measure the association of oral cancer pain with clinical characteristics. By contrast, a BPI average score that measures both the sensory and interference dimensions of oral cancer pain is a sensitive indicator of clinical correlates of oral cancer pain prior to treatment, similar to the UCSFOCPQ. Recognition of the need to measure both sensory and interference dimensions of oral cancer pain has implications for clinical practice and pain research.

Materials and Methods

Patients

The patients comprising the current study are part of a larger, ongoing study focused on the study of pain in oral cancer patients. Patients are screened and enrolled through the New York University (NYU) Oral Cancer Center. Eligible patients are at least 18 years of age, have received a diagnosis of oral squamous cell carcinoma, and have not yet received treatment for their cancer, including surgery, chemotherapy or radiation. Informed consent was obtained from each study participant prior to study activities. The study is being carried out in accordance with the Declaration of Helsinki, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), the National Institutes of Health requirements for human subjects research, and institutional research policies and procedures of the Institutional Review Board (IRB) at New York University. The Committee on Human Research at NYU Langone Medical Center approved this study (10–01261, 15 September 2020).

Thirty patients enrolled in the ongoing study between 2015 and 2021 met the inclusion criteria and completed the UCSFOCPQ and BPI. Twelve patients were members of a previously published cohort of 72 patients.[11] Patients completed a demographic questionnaire that included age, sex, ethnicity, race, and employment status. Patients also complete a smoking and alcohol history questionnaire. The demographics of the cohort studied here (Table 1) are representative of the population of patients seen at the New York University (NYU) Oral Cancer Center over a ten year period (2011–2021) and who were 18 years or older with a diagnosis of oral squamous cell carcinoma prior to treatment (n=111). The demographics of the cohort of 111 patients were: age 65, 49.5% (vs 46.7%, Table 1); women, 49.5% (vs 46.7%, Table 1); majority white, 64.9% (66.7%, Table 1);

Table 1 Patient Demographic and Clinical Characteristics

Characteristic	Number	Percent
Age (years)		
< 65	14	46.7
≥ 65	16	53.3
Gender		
Female	14	46.7
Male	16	53.3
Tumor site		
Tongue	18	60.0
Gingiva	8	26.7
Floor of mouth	2	6.7
Buccal mucosa	1	3.3
Hard palate	1	3.3
Nodal status		
N0	17	60.7
N+	11	39.3
pT stage		
T1	10	37.0
T2	7	25.9
T3	3	11.1
T4	7	25.9
Self-reported ethnicity		
Hispanic/Latino	1	3.3
Not Hispanic/Latino	29	96.7
Self-reported race		
White	20	66.7
African American	7	23.3
Asian/Pacific Islander	3	10.0
Employment status		
Currently employed	11	42.3
Previously employed/retired	6	23.1
Never employed	3	11.5
Unknown/not indicated	6	23.1
Tobacco use		
Previous/Never	22	73.3
Current	8	26.7
Alcohol use		
Previous/Never	11	36.7
Current	19	63.3

non-Hispanic, 86.5% (vs 96.7%, Table 1); current smoker, 22.5% (vs 26.7%, Table 1); current drinker, 61.3% (vs 63.3%, Table 1).

Pathology reports were reviewed for information on primary tumor stage, PNI, DOI and nodal status. Eleven patients were determined to have positive nodes by pathologic examination of the neck dissection specimen following surgery (pN+). All, but one of the 17 pN0 patients, have been followed for a year or more. None developed neck disease during the 1-year follow-up period.

Pain Measures

Patients completed the UCSFOCPQ[1,2] and the BPI[17] at a preoperative clinic visit before being prescribed analgesics for their oral cancer pain and before any treatment (median time to surgery was 16 days), as previously described.[1] If patients were currently taking pain medication, they were asked to refrain for 24 hours All patients consented to participate in the study.

The UCSFOCPQ includes eight questions that are answered by the patient on a visual analogue scale of 0–100 mm. Dr. Schmidt developed the UCSFOCPQ to provide information on the quality of pain experienced by oral cancer patients in order to better understand the nociceptive mechanisms underlying oral cancer pain. Questions were designed to distinguish between functional and spontaneous pain and to query whether pain was dull or sharp – activation of Aδ nerve fibers being suggested by a response of functionally induced intense sharp pain and spontaneous dull pain by activation of Aδ and C fibers. Questions 1, 3, and 5 ask about spontaneous intensity, sharpness, and aching, while questions 2, 4, and 6 ask about these sensations when talking, eating, or drinking. Question 7 asks about sensitivity to touch and question 8 asks how significantly pain interferes with function.

Patients were instructed to place a vertical line transecting the 100 mm horizontal scale to approximate their pain level (if any) for each question. The median angle of the vertical line relative to the horizontal line was 90° (interquartile range 86–90°, n=240 responses), indicating good patient comprehension of the task. The average of the eight questions was used as the measure of the response to the UCSFOCPQ, as previously described.[11]

On the BPI, patients rated the intensity of pain experienced during the past week at its worst and average on a numeric rating scale of 0 (“no pain”) to 10 (“excruciating pain”). They were also asked to rate the number of hours pain lasts on days with pain (0–24) and the number of days pain interferes with mood and/or activities (0–7). Patients rated the extent to which their pain interfered with four physical QoL domains (general activity, normal work, walking ability, sexual ability) and four psychological QoL domains (mood, relations with others, enjoyment of life, and sleep) on a scale of 0 (“does not interfere”) to 10 (“interferes completely”). Participants answered questions related to the occurrence of cancer- and non-cancer related pain and pain qualities. Additionally, if participants had previously been treated for pain, they answered how much relief they received from their pain medication on a percent scale of 0 (“no relief”) to 100 (“complete relief”), and “How satisfied are you with the results of your pain treatment overall?” They rated their satisfaction on a numeric rating scale of 0 (“extremely dissatisfied”) to 10 (“extremely satisfied”).

Statistical Analysis

Data were analyzed using GraphPad Prism for Mac OSX (version 9.3.1, GraphPad, San Diego, CA, USA). Hierarchical clustering was performed using ClustVis.[19] Correlational analyses utilized a pairwise deletion approach to missing data. A p-value of <0.05 was considered statistically significant.

Results

Patients and Responses to Pain Questionnaires

Characteristics of the study cohort of 30 patients who completed both the UCSFOCPQ and BPI are presented in Table 1. The median age of patients enrolled in the study was 66 years. The majority of patients were diagnosed with tongue cancers and identified as White/non-Hispanic.

Patient responses to the UCSFOCPQ and the BPI are presented in Supplementary Table 1. Cronbach’s alpha coefficient for the UCSFOCPQ was 0.92. Figure 1 shows two UCSFOCPQ response patterns – one cluster of patients (n=12) reporting low scores in response to all questions (average UCSFOCPQ pain score = 7.9) and a second cluster of 18 patients (60%) reporting higher scores on questions 2, 4, 6, 7 and/or 8 (average UCSFOCPQ pain score = 48.9). The latter group included all but one of the node positive (N+) cases. A subcluster of the 18 patients reporting pain included patients reporting the highest pain scores, female gender and N+ nodal status (n=7). Associations of pain measurements with clinical characteristics are presented in Table 2 and Supplementary Table 2. Patients with N+ cancers reported higher pain scores, pain increased with pT stage – pT1 vs pT2, pT3, pT4, stage – I and II vs III and IV and DOI. Pain score was not associated with gender, age or PNI.

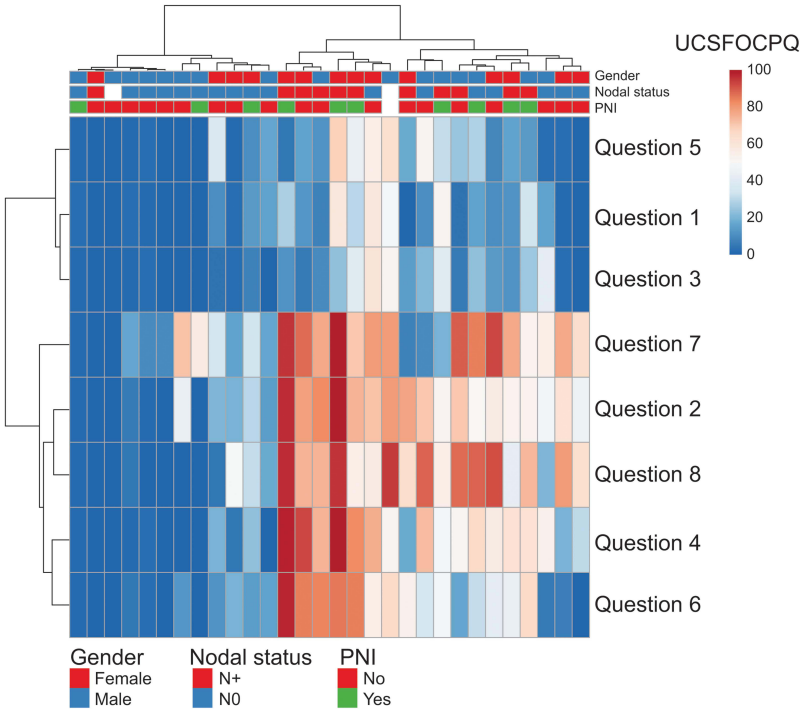

Figure 1 Responses of patients on the UCSFOCPQ. Shown are individual patients' responses to each of the eight questions on the UCSFOCPQ in columns and responses to the UCSFOCPQ questions across patients in rows. Both columns and rows were clustered by Euclidean distance and Ward linkage. Patients' pain scores are distributed among low (mostly blue) and medium or high responses to questions 2, 4, 6, 7 and 8 (shades of red), representing the range of responses observed in a larger cohort of patients.
Note: Some patients included in Figure 1 were from Bhattacharya A, Janal MN, Veeramachaneni R, et al. Oncogenes overexpressed in metastatic oral cancers from patients with pain: potential pain mediators released in exosomes. *Sci Rep.* 2020;10(1):14724.[11]

On the BPI, all but five patients reported experiencing pain (25/30). Pain due to cancer was reported by 24 patients (24/30) and one patient reported pain was not due to cancer (1/30). Ten patients reported experiencing both cancer and non-cancer pain (10/29). Cronbach's alpha coefficients for pain severity and interference scales were 0.78 and 0.93, respectively. Patients reporting higher BPI average pain over 24 hours scores were more likely to have N+ cancers and present with higher stage – I and II vs III and IV, but not with higher tumor stage – pT1 vs pT2, pT3, pT4, PNI or DOI (Table 2, Supplementary Table 2).

Table 2 Association of Pain Measurement Instruments with Clinical Characteristics

	Nodal Status	pT Stage (pT1 vs pT2, pT3, pT4)	Stage (I, II vs III, IV)	PNI	DOI
UCSFOCPQ pain score					
Pearson r	0.5354	0.4226	0.6370	0.3747	0.5610
p value	0.0033	0.0281	0.0005	0.0593	0.0124
N	28	27	29	29	22
BPI average pain over 24 hours					
Pearson r	0.3772	0.3431	0.3780	0.1717	0.4122
p value	0.0478	0.0798	0.0432	0.3731	0.0566
N	28	27	29	29	22
BPI average score					
Pearson r	0.5900	0.5055	0.5380	0.3620	0.7490
p value	0.0016	0.0072	0.0028	0.3127	0.0003
N	28	27	29	29	22

Correlation of UCSFOCPQ with BPI Pain Characteristics and Interferences

The average UCSFOCPQ pain score correlated positively with responses to the BPI pain questions measuring severity of pain (Supplementary Table 2). Pain severity, as measured by both the UCSFOCPQ and the BPI average pain over 24 hours score, correlates positively with interference with physical and psychological functioning (average of the four physical and psychological features, respectively) (Supplementary Table 2). The UCSFOCPQ pain score correlated negatively with the BPI question "overall satisfaction with pain treatment" (r=−0.50, p=0.014).

A BPI Average Pain Score Has Greater Sensitivity to Discriminate Associations of Pain with Clinical Characteristics

The UCSFOCPQ appeared to have greater sensitivity to measure the association of pain with clinical characteristics than the single BPI question "average pain over 24 hours." The UCSFOCPQ queries both pain severity and interference with function, suggesting that scores that incorporate pain severity and interference with functioning have potential to better measure the complexity of pain. Similar to the UCSFOCPQ score, which is an average of the eight questions, we defined a BPI average score as the average of the responses to the questions "average pain over 24 hours" plus the eight physical and psychological interference questions. The BPI average score performed similarly to the UCSFOCPQ (Table 2). We note, that significant association of pain and PNI was not observed with any of the three pain measurements, likely due to under reporting unless special stains are used to highlight PNI.[20]

Pain Qualities

The most common descriptors of the quality of pain on the BPI were "sharp" "aching", "tender" and "nagging" (Figure S1, Supplementary Table 1). Descriptors associated with neuropathic etiology include throbbing, aching, numb, tender, miserable, tiring, exhausting, burning, and nagging. [21] Descriptors associated with nociceptive etiology include sharp, stabbing, and gnawing. [21] We carried out a preliminary investigation into whether different pain qualities were associated with demographic (gender, age) and clinical characteristics reported in association with pain (nodal status, PNI, pT stage, stage),[4–6,15,16] as well as DOI. The descriptors "shooting" (r=0.59, p=0.0006) and "sharp" (r=0.41, p=0.023) were associated with female gender; "aching" (r=0.40, p=0.034) "exhausted" (r=0.38. p=0.046) and "unbearable" (r=0.39, p=0.04) with positive nodal status; "miserable" (r=0.37, p=047) with T stage (pT1 vs pT2, pT3, pT4); "aching" (r=0.38, p=0.040), "sharp" (r=0.38, p=0.04), "exhausting", (0.38, p=0.040), "numb" and "unbearable" (r=0.44, p=0.017) with stage (I, II vs III, IV) and "sharp" (r=0.48, r=0.024) and "miserable" (r=0.59, p=0.0039) with DOI.

Discussion

The correlations between the UCSFOCPQ and BPI measure "average pain over 24 hours" (Supplementary Table 2) suggest there is good agreement between the two instruments for measuring the severity of pretreatment oral cancer pain. The single BPI question "average pain over 24 hours" appeared less sensitive to detect associations of pretreatment oral cancer pain with clinical features (pT stage, DOI) than the UCSFOCPQ average pain score (Table 2). An average BPI pain score incorporating the BPI pain intensity and interference items, however, performed similarly to the UCSFOCPQ in discriminating associations with clinical characteristics (nodal status, pT stage, stage and DOI). These observations suggest that both dimensions (intensity and interference) are needed to fully capture variability in the clinical presentation of oral cancers. The UCSFOCPQ appears to more efficiently capture both intensity and interference dimensions of the pain experience. Patients are required to answer fewer questions, and they typically complete the UCSFOCPQ in about 8 minutes compared to 15 minutes to complete the BPI.

There are limitations to our study. The sample size is small compared to prior studies of HNSCC pain and QoL[4,5] and the cohort included a small proportion of subjects from a larger previously published cohort.[11] The mean UCSFOCPQ scores, however, were similar in the two cohorts and the patient demographics are similar to those of all patients enrolled in our studies over the 10 year period, 2011–2021 (Methods and Table 1). Future work with larger cohorts should develop and evaluate BPI average scores for measurement of pain in oral cancer patients prior to treatment and compare performance with the UCSFOCPQ. The UCSFOCPQ, however, is recommended given its simplicity and brevity.

Pain may be an initial symptom that causes patients to seek treatment.[22] Oral precancerous lesions, oral epithelial dysplasia, are not painful. Oral cancer pain has nociceptive and neuropathic components.[23] Oral cancer pain has been attributed to release from the cancer and/or cells of the cancer microenvironment of soluble mediators and extracellular vesicles carrying pain mediators that sensitize or activate primary afferent neurons.[11,24] Two receptors on peripheral neurons – TRPV1 (transient receptor potential cation channel subfamily V member 1) and TRPA1 (transient receptor potential cation channel subfamily A member 1) have been implicated in oral cancer pain.[25] Pain mediators include lipids,[26] ATP,[27] nerve growth factor,[28] proteases,[29–33] cytokines,[34,35] genes involved in pain processing[36,37] and micro RNAs.[38,39] The heterogeneity of cancers suggests that the etiology of oral cancer pain – the relative contributions of the many pain mediators, in addition to psychological and social dimensions – is patient specific. The personal nature of pain highlights the need to accurately and reliably measure pain in newly diagnosed oral cancer patients in order to better manage treatment to optimize QoL and guide surgical planning.

Conclusion

Pain measurement instruments that incorporate oral cancer patient responses to queries of pain severity and interference with function appear more sensitive to discriminating associations of pretreatment oral cancer pain with biological features and clinical characteristics. Larger studies should develop and evaluate BPI average scores for measurement of pain in oral cancer patients prior to treatment and compare performance with the UCSFOCPQ.

Acknowledgments

Brian L Schmidt and Donna G Albertson are co-senior authors for this study. The work was supported by the National Institutes of Health (NIH) Grants R01 CA228525, R01 CA231396, R01 DE026806, R01 DE029694, R01 DE029951, and K23 DE029844. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The funder had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Disclosure

The authors declare no conflicts of interest in this work.

References

1. Connelly ST, Schmidt BL. Evaluation of pain in patients with oral squamous cell carcinoma. *J Pain*. 2004;5(9):505–510. doi:10.1016/j.jpain.2004.09.002
2. Kolokythas A, Connelly ST, Schmidt BL. Validation of the University of California San Francisco oral cancer pain questionnaire. *J Pain*. 2007;8(12):950–953. doi:10.1016/j.jpain.2007.06.012
3. Borggreven PA, Verdonck-de Leeuw IM, Muller MJ, et al. Quality of life and functional status in patients with cancer of the oral cavity and oropharynx: pretreatment values of a prospective study. *Eur Arch Otorhinolaryngol*. 2007;264(6):651–657. doi:10.1007/s00405-007-0249-5
4. Hammerlid E, Bjordal K, Ahlner-Elmqvist M, et al. A prospective study of quality of life in head and neck cancer patients. Part I: at diagnosis. *Laryngoscope*. 2001;111(4 Pt 1):669–680. doi:10.1097/00005537-200104000-00021
5. Oliveira KG, von Zeidler SV, Podesta JR, et al. Influence of pain severity on the quality of life in patients with head and neck cancer before antineoplastic therapy. *BMC Cancer*.2014;14(1):39. doi: 10.1186/1471-2407-14-39.
6. Reyes-Gibby CC, Anderson KO, Merriman KW, Todd KH, Shete SS, Hanna EY. Survival patterns in squamous cell carcinoma of the head and neck: pain as an independent prognostic factor for survival Research Support. *Extramural J Pain*. 2014;15(10):1015–1022. doi:10.1016/j.jpain.2014.07.003
7. Hussein AA, Helder MN, de Visscher JG, et al. Global incidence of oral and oropharynx cancer in patients younger than 45 years versus older patients: a systematic review. *Eur J Cancer*. 2017;82:115–127. doi:10.1016/j.ejca.2017.05.026
8. Tota JE, Anderson WF, Coffey C, et al. Rising incidence of oral tongue cancer among white men and women in the United States, 1973-2012. *Oral Oncol Apr*. 2017;67:146–152. doi:10.1016/j.oraloncology.2017.02.019
9. Parikh AS, Puram SV, Faquin WC, et al. Immunohistochemical quantification of partial-EMT in oral cavity squamous cell carcinoma primary tumors is associated with nodal metastasis. *Oral Oncol*. 2019;99:104458. doi:10.1016/j.oraloncology.2019.104458
10. Puram SV, Tirosh I, Parikh AS, et al. Single-Cell Transcriptomic Analysis of Primary and Metastatic Tumor Ecosystems in Head and Neck Cancer. *Cell*. 2017;171(7):1611–1624 e24. doi: 10.1016/j.cell.2017.10.044.
11. Bhattacharya A, Janal MN, Veeramachaneni R, et al. Oncogenes overexpressed in metastatic oral cancers from patients with pain: potential pain mediators released in exosomes. *Sci Rep*. 2020;10(1):14724. doi: 10.1038/s41598-020-71298-y.
12. Oliveira KG, von Zeidler SV, Lamas AZ, et al. Relationship of inflammatory markers and pain in patients with head and neck cancer prior to anticancer therapy. *Braz J Med Biol Res*. 2014;47(7):600–604. doi:10.1590/1414-431x20143599

13. Holen JC, Lydersen S, Klepstad P, Loge JH, Kaasa S. The Brief Pain Inventory: pain's interference with functions is different in cancer pain compared with noncancer chronic pain. *Clin J Pain*. 2008;24(3):219–225. doi:10.1097/AJP.0b013e31815ec22a
14. Scheff NN, Bhattacharya A, Dowse E, et al. Neutrophil-Mediated Endogenous Analgesia Contributes to Sex Differences in Oral Cancer Pain. *Front Integr Neurosci*. 2018;12:52. doi:10.3389/fnint.2018.00052
15. Salvo E, Campana WM, Scheff NN, et al. Peripheral nerve injury and sensitization underlie pain associated with oral cancer perineural invasion. *Pain*. 2020;161(11):2592–2602. doi:10.1097/j.pain.0000000000001986
16. Naik K, Janal MN, Chen J, et al. The Histopathology of Oral Cancer Pain in a Mouse Model and a Human Cohort. *J Dent Res*. 2021;100 (2):194–200. doi:10.1177/0022034520961020
17. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singap*. 1994;23(2):129–138.
18. Klepstad P, Borchgrevink PC, Dale O, et al. Routine drug monitoring of serum concentrations of morphine, morphine-3-glucuronide and morphine-6-glucuronide do not predict clinical observations in cancer patients. *Palliat Med*. 2003;17(8):679–687. doi:10.1191/0269216303pm835oa
19. Metsalu T, Vilo J. ClustVis: a web tool for visualizing clustering of multivariate data using Principal Component Analysis and heatmap. *Nucleic Acids Res*. 2015. doi: 10.1093/nar/gkv468. 43(W1):W566–70
20. Schmitd LB, Beesley LJ, Russo N, et al. Redefining Perineural Invasion: integration of Biology With Clinical Outcome. *Neoplasia*. 2018;20 (7):657–667. doi:10.1016/j.neo.2018.04.005
21. Wilkie DJ, Huang HY, Reilly N, Cain KC. Nociceptive and neuropathic pain in patients with lung cancer: a comparison of pain quality descriptors. *J Pain Symptom Manage*. 2001;22(5):899–910. doi:10.1016/s0885-3924(01)00351-7
22. Lam DK, Schmidt BL. Orofacial pain onset predicts transition to head and neck cancer. *Pain*. 2011;152(5):1206–1209. doi:10.1016/j.pain.2011.02.009
23. Viet CT, Schmidt BL. Biologic mechanisms of oral cancer pain and implications for clinical therapy. *J Dent Res*. 2012;91(5):447–453. doi:10.1177/0022034511424156
24. Dubeykovskaya ZA, Tu NH, Garcia PDR, Schmidt BL, Albertson DG. Oral Cancer Cells Release Vesicles that Cause Pain. *Adv Biol (Weinh)*. 2022;6(9):e2200073. doi:10.1002/adbi.202200073
25. de Almeida AS, Bernardes LB, Trevisan G. TRP channels in cancer pain. *Eur J Pharmacol*. 2021. 904;174185. doi:10.1016/j.ejphar.2021.174185
26. Ruparel S, Bendele M, Wallace A, Green D. Released lipids regulate transient receptor potential channel (TRP)-dependent oral cancer pain. *Mol Pain*. 2015. 11;30. doi:10.1186/s12990-015-0016-3
27. Ye Y, Ono K, Bernabe DG, et al. Adenosine triphosphate drives head and neck cancer pain through P2X2/3 heterotrimers. *Acta Neuropathol Commun*. 2014;2(1):62. doi: 10.1186/2051-5960-2-62.
28. Ye Y, Dang D, Zhang J, et al. Nerve growth factor links oral cancer progression, pain, and cachexia. *Research Support, N I H, Extramural Mol Cancer Ther*. 2011;10(9):1667–1676. doi:10.1158/1535-7163.MCT-11-0123
29. Lam DK, Dang D, Flynn AN, Hardt M, Schmidt BL. TMPRSS2, a novel membrane-anchored mediator in cancer pain. *Pain*. 2015;156(5):923–930. doi:10.1097/j.pain.0000000000000130
30. Lam DK, Dang D, Zhang J, Dolan JC, Schmidt BL. Novel animal models of acute and chronic cancer pain: a pivotal role for PAR2. Research Support, N.I.H., Extramural. *J Neurosci*. 2012;32(41):14178–14183. doi:10.1523/JNEUROSCI.2399-12.2012
31. Lam DK, Schmidt BL. Serine proteases and protease-activated receptor 2-dependent allodynia: a novel cancer pain pathway. *Pain*. 2010;149 (2):263–272. doi:10.1016/j.pain.2010.02.010
32. Tu NH, Inoue K, Chen E, et al. Cathepsin S Evokes PAR2-Dependent Pain in Oral Squamous Cell Carcinoma Patients and Preclinical Mouse Models. *Cancers (Basel)*. 2021;13(18):4697. doi:10.3390/cancers13184697
33. Tu NH, Jensen DD, Anderson BM, et al. Legumain Induces Oral Cancer Pain by Biased Agonism of Protease-Activated Receptor-2. *J Neurosci*. 2021;41(1):193–210. doi: 10.1523/JNEUROSCI.1211-20.2020.
34. Scheff NN, Ye Y, Bhattacharya A, et al. Tumor necrosis factor alpha secreted from oral squamous cell carcinoma contributes to cancer pain and associated inflammation. *Pain*. 2017;158(12):2396–2409. doi:10.1097/j.pain.0000000000001044
35. Andratsch M, Mair N, Constantin CE, et al. A key role for gp130 expressed on peripheral sensory nerves in pathological pain. *J Neurosci*. 2009;29 (43):13473–13483. doi: 10.1523/JNEUROSCI.1822-09.2009.
36. Viet CT, Dang D, Ye Y, Ono K, Campbell RR, Schmidt BL. Demethylating drugs as novel analgesics for cancer pain. *Clin Cancer Res*. 2014;20 (18):4882–4893. doi:10.1158/1078-0432.CCR-14-0901
37. Viet CT, Ye Y, Dang D, et al. Re-expression of the methylated EDNRB gene in oral squamous cell carcinoma attenuates cancer-induced pain. *Pain*. 2011;152(10):2323–2332. doi:10.1016/j.pain.2011.06.025
38. Li X, Chen Y, Wang J, Jiang C, Huang Y. Lung Cancer Cell-Derived Exosomal let-7d-5p Down-Regulates OPRM1 to Promote Cancer-Induced Bone Pain. *Front Cell Dev Biol*. 2021;9:666857. doi:10.3389/fcell.2021.666857
39. Hoshikawa N, Sakai A, Takai S, Suzuki H. Targeting Extracellular miR-21-TLR7 Signaling Provides Long-Lasting Analgesia in Osteoarthritis. *Mol Ther Nucleic Acids*. 2020. 19;199–207. doi:10.1016/j.omtn.2019.11.011