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Original Article

Role of catecholamine levels and quality-of-life domains in patients with oral neoplasms

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Abstract: Background: Oral cancer has a profound impact on quality of life, but the relationship between quality of life and tumorigenesis, catecholamine levels, and disease stage in oral cancer patients is not well understood. Methods: Pre-surgical quality of life was determined using the Short Form 36 (SF-36) health-related quality of life questionnaire in 75 oral neoplasm patients, including 40 oral carcinoma patients and 35 benign oral tumor patients. The plasma epinephrine and norepinephrine concentrations were assessed using high performance liquid chromatography-mass spectrometry-mass spectrometry, and data were analyzed using multivariate logistic regression models. Results: There were significant differences in pain, general health, and mental health SF-36 subscores between the oral carcinoma and benign oral tumor groups. Multivariate logistic regression models showed that the SF-36 scores in the oral carcinoma group were significantly lower than those in the benign oral tumor group. Conclusions: These findings show that general health is affected in oral neoplasm patients and stress hormones can affect quality of life in oral carcinoma patients; furthermore, plasma catecholamines and mental health contribute to the progression of oral carcinoma.

Keywords: Oral neoplasm, catecholamine, mental health, logistic regression models, SF-36, quality of life

Introduction

The annual global incidence of head and neck carcinoma is greater than 600,000, representing the sixth most common type of cancer in the general population [1]. head and neck squamous cell carcinoma (HNSCC) comprises more than 90% of head and neck cnacer cases; moreover, there is evidence that the incidence is increasing [2]. Approximately two-third of patients suffer with dvanced stage disease (stages III and IV), while the remaining patients present with early stage disease (stages I and II) (stages III and IV) [3]. With advanced stages, the 5-year survival rate is < 50%, and survival is associated with considerable esthetic and functional problems following treatment [4, 5]. There is sufficient scientific evidence to suggest that HNSCC is largely related to lifestyle [6]. Changes in hormonal and immune status reportedly result from chronic stress, and other behavioral conditions might influence the development and progression of carcinoma [7]. Chronic stress is related toabnormality of the neuroendocrine system, with a secondary levels of catechalamine, mainly including norepinephrine (NE) and epinephrine (E) [8]. NE and E are catecholamines released from the adrenal medulla and neurons of the sympathetic nervous system [9]. Stress plays crucial roles in altering immunological and neurochemical functions, yet its role in cancer development and progression remains unclear.

The growth and progression of ovarian cancers might be influenced by increased noradrenergic responses [8], and intra-tumoral catecholamines such as NE increased with stress in an animal model; however, little is known about the change of tumor NE with disease grade or stage and tumor biological behavior in patients [10]. Available research suggests that circulating plasma NE concentrations are correlated with tumor grade and stage [11]. Some studies have implications from outcomes of ovarian cancer, indicating that beta-adrenergic signal-

ing is associated with key biological behaviors involved in cancer progression [12]. In a previous study, we found that the circulating stress hormones including catecholamines and glucocorticoid might impact the biological behavior of oral cancer by influencing the tumor microenvironment [11]; however, the association between quality of life (QoL) and stress-related hormones in primary oral neoplasm patients was not clear. Moreover, the relationship between general and mental health and tumorigenesis in HNSCC is less clear.

Oral carcinomas can significantly affect both the structure and function of head and neck region [13], especially in terms of swallowing, breathing, and speaking [14]. This could lead to a significant reduction in QoL and impair the functional capacity [15, 16].

In this study, the association between quality of life and stressor catecholamines in primary oral neoplasm patients was analysed. It was hypothesized that advanced stage HNSCC would be associated with higher circulating plasma catecholamine levels as well as a reduced QoL.

Materials and methods

Ethics statement

This study was conducted according to the guidelines in the Declaration of Helsinki and and approved by the Ethics Committee of the West China Hospital of Stomatology (Protocol No: WCHSIRB-D-2013-054). All participants in this study signed the written informed consents voluntarily.

Participants

The participants consisted of 75 patients > 18 years of age with a histological diagnosis of an oral neoplasm (49 men and 26 women). Inclusion was that primary oral neoplasms confirmed by pathologic diagnosis. Patients with metastatic lesions, systemic diseases, a history of alcohol abuse, or the use of drugs altering the immune response such as systemic corticosteroids or beta-blockers within the last 6 months were excluded. All tumor samples of included patients were verified by two pathologists who classified the tumors and judged the oral cancer stages according to TNM classification of UICC 2002. Two pathologists independently carried out the classification of tumours and oral cancer stages. Disagreements between the 2 pathologists were discussed with a third pathologist for consensus.

Quality of life, demographic, and medical assessments

During the pre-operative appointment, the Short Form 36 (SF-36) was completed to assess QoL [17], which is a 36-item questionnaire that scores physical function as well as social and mental wellbeing within 8 domains: physical functioning (PF, 10 questions), role limitations due to physical health problems (RP, 4 questions), bodily pain (BP, 2 questions), general health perceptions (GH, 5 questions), mental health (MH, 5 questions), role limitations due to emotional problems (RE, 3 questions), social functioning (SF, 2 questions), and vitality (VT, 4 questions). In addition, a question is included to record changes in health (HC, 1 question) [18]. The summary scores for the physical and mental components were also calculated. The SF-36 was translated into the Chinese language for the purposes of this study. Using the SF-36, Lam et al. and Lee et al. reported a high prevalence of clinical anxiety, depression, and severe impairment in QoL in a population of Chinese patients with chronic non-cancer pain, indicating that the SF-36 is a valid method to determine the QoL of Chinese patients [15, 16].

Blood samples were collected approximately 2 hours before surgery, and demographic, health behavior, clinical, and histopathological data were obtained from medical records. Detailed information on hours of sleep, smoking, alcohol intake, and caffeine intake during the 7 days immediately preceding surgery was also collected.

Measurement of catecholamines

High performance liquid chromatography with mass spectrometry (HPLC-MS/MS) was used to measure blood samples, as described previously [11, 19]. Briefly, blood samples were collected and stored at -80°C after centrifuging 10 minutes at 4°C at 1,000 g using a cold chilled EDTA Vacutainer tubes (BD Biosciences, Franklin Lakes, NJ). The supernatants were introduced in the HPLC-MS-MS system, as previously described [11]. Sample analysis was carried out using an UltiMate 3000 HPLC system (Dionex Corporation, Sunnyvale, CA). The eluents applied in sequence a 3200 Q TRAP tandem mass spectrometer (Applied Biosys-

Table 1. Comparison of SF-36 scores between the oral cancer and benign oral tumor groups

SF-36	Benign Tumor Group (n = 35)	Carcinoma Group (n = 40)	Z*	P
PF	29.4 ± 1.03	27.6 ± 2.46	4.34	< 0.01
RP	7.74 ± 0.61	6.40 ± 1.34	4.88	< 0.01
BP	4.34 ± 2.13	5.03 ± 1.73	-1.93	0.0436
GH	14.89 ± 1.66	15.90 ± 1.63	-2.42	0.0157
VT	13.86 ± 2.91	13.40 ± 2.45	0.49	0.6255
SF	6.71 ± 1.32	6.28 ± 1.40	1.33	0.1844
RE	5.83 ± 0.62	4.80 ± 1.26	4.03	< 0.01
MH	18.23 ± 2.34	17.65 ± 3.17	-0.89	0.3770
HC	3.20 ± 0.68	3.63 ± 0.81	-2.07	0.0387
TOTAL	104.20 ± 7.17	100.68 ± 7.22	-2.12	0.038

Values are reported as mean ± standard deviation. BP, bodily pain; HC, health change; GH, general health; MH, mental health; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality.

tems, Foster City, CA) operated in the electrospray positive mode and with multiple reaction monitoring (MRM).

Statistical analyses

The data were analysed with SPSS version 19.0 (IBM Corp., Armonk, NY). Catecholamine concentrations in each compartment were examined using Pearson's correlation coefficients. Either Chi-squared tests or analyses of variance (ANOVA) were used to test categorical variables. Following the detection of a possible tumorigenesis effect in any of the SF-36 indices, the mean scores of the SF-36 scales were compared using ANOVA, based on the two different diagnostic subgroups of oral cancer and oral benign tumor. To better understand the differences in catecholamines and QoL based on tumorigenesis, bivariate associations between each of the domain scales and catecholamine concentrations were assessed using logistic regression models, which estimated the odds ratios (OR) with 95% confidence intervals (CI) [20]. Statistically significance was determined by a *P*-value < 0.05.

Results

Participant characteristics

There were no significant differences in age, gender, tumor location, income, marital status, or educational status between the benign tumor and carcinoma groups. There were no significant correlations in catecholamine concentrations in any compartment (P > 0.34). Those 40 oral cancer tissue cases collected from head and neck ward of West China hospital of Stomatology, according to TNM classification of UICC 2002, 4 cases of stage I, 19 cases of stage II , 10 cases of stage III and 7 cases of stage IV.

SF-36 domains

There were significant differences between the two groups in most of the SF-36 domain scores (PF, P < 0.001; RP, P < 0.001; BP, P = 0.0436; GH, P = 0.0157; RE, P < 0.001; and HC, P = 0.0387) (**Table 1**).

Catecholamines and tumor histology

The mean catecholamine concentrations in peripheral blood in the carcinoma group (70.27 ± 34.50 pg/mL, E; 316.73 ± 109.22 pg/mL, NE) were significantly higher than in the benign tumor group (49.48 ± 31.04 pg/mL, E; 252.14 ± 81.80 pg/mL, NE; P < 0. 01).

Peripheral blood catecholamine levels were significantly different based on cancer stage, with lower concentrations in stages I and II (early stage) cancer (56.61 ± 23.09 pg/mL, E; 267.81± 89.77 pg/mL, NE) than in stages III and IV (advanced stage) cancer (88.75 ± 39.20 pg/mL, E; 382.91 ± 99.50 pg/mL, NE; P < 0.05) (**Table 2**).

Biobehavioral factors and catecholamines

In the bivariate analyses, only one SF-36 domain (GH) was significantly associated with tumorigenesis in oral neoplasm patients, indicating that better general health (OR 0.54, 95% CI 0.319-0.917) was associated with the lack of an oral tumor (**Table 3**).

There was also a difference in plasma E (OR 1.478, 95% CI 1.117-1.901, P = 0.0028) and plasma NE (OR 1.521, 95% CI 1.275-2.102, P = 0.075) levels based on carcinoma stage (**Table 4**). The combined estimate showed no difference in SF-36 based on carcinoma stage except for the BP (OR 0.995, 95% CI 0.694-1.427, P = 0.045) and MH (OR 1.304, 95% CI 1.012-2.014, P = 0.036) domains.

Discussion

In the present study, blood catecholamine levels in patients with primary oral cancer were

Table 2. Comparison of the concentration of catecholamine in plasma of peripheral blood between oral cancer and benign oral tumor patients

		Plasma E (pg/ml)			Plasma NE (pg/ml)		
		Mean ± Sd	t	p	Mean ± Sd	t	P
Tumor Type	Benign (N = 35)	49.48±31.04	-2.97	0.0030	252.14 ± 81.80	-2.89	0.0039
	Cancer (N = 40)	70.27 ± 34.50			316.73 ± 109.22		
Cancer Stage	Early (N = 23)	56.60 ± 23.09	-3.02	0.006	267.81 ± 89.77	-3.83	0.0005
	Advanced (N = 17)	88.75 ± 39.20			382.91 ± 99.50		

Table 3. Bivariate associations between quality of life and plasma catecholamine levels in peripheral blood and oral tumorigenesis in oral neoplasm patients (n = 75)

Variable	Estimate	Standard	Wald	P	OR	95% CI
SF-36 PF	0.1652	0.1759	0.8811	0.3479	1.18	0.836-1.665
SF-36 RP	0.3172	0.3853	0.6781	0.4102	1.373	0.645-2.922
SF-36 BP	-0.0259	0.1865	0.0192	0.8897	0.974	0.676-1.404
SF-36 GH	-0.6154	0.2697	5.205	0.0225	0.54	0.319-0.917
SF-36 VT	0.2338	0.1521	2.3622	0.1243	1.263	0.938-1.702
SF-36 SF	-0.0528	0.2755	0.0367	0.8481	0.949	0.553-1.628
SF-36 RE	0.2872	0.4286	0.4492	0.5027	1.333	0.575-3.087
SF-36 MH	0.1266	0.1362	0.8627	0.353	1.135	0.869-1.482
SF-36 HC	-1.0891	0.5782	3.5479	0.0596	0.337	0.108-1.045
SF-36 Total	-0.011	0.0538	0.0419	0.8378	0.989	0.89-1.099
Plasma E (pg/mL)	-0.0428	0.0222	3.7362	0.0532	0.958	0.917-1.001
Plasma NE (pg/mL)	-0.0126	0.00644	3.8211	0.0506	0.987	0.975-1

OR, odds ratio; CI, confidence interval; E, epinephrine; NE, norepinephrine; BP, bodily pain; HC, health change; GH, general health; MH, mental health; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality.

Table 4. Bivariate associations between quality of life and plasma catecholamine levels in peripheral blood and oral carcinoma progression (stage) in oral carcinoma patients (n = 40)

Variable	Estimate	Standard	Wald	P	OR	95% CI
SF-36 PF	0.036	0.1577	0.052	0.8195	1.037	0.761-1.412
SF-36 RP	-0.5771	0.3989	2.093	0.148	0.562	0.257-1.227
SF-36 BP	-0.3626	0.2881	1.5838	0.0451	0.995	0.694-1.427
SF-36 GH	-0.0284	0.2452	0.0134	0.9077	0.972	0.601-1.572
SF-36 VT	-0.2864	0.2197	1.6993	0.1924	0.751	0.488-1.155
SF-36 SF	-0.3508	0.3512	0.9979	0.3178	0.704	0.354-1.401
SF-36 RE	0.4568	0.3566	1.6407	0.2002	1.579	0.785-3.176
SF-36 MH	0.1978	0.179	1.2205	0.0351	1.304	1.012-2.014
SF-36 HC	0.0489	0.4988	0.0096	0.9219	1.05	0.395-2.792
SF-36 Total	0.0235	0.0459	0.2629	0.2804	1.024	0.940-1.118
Plasma E (pg/mL)	-0.022	0.0135	2.6612	0.0028	1.478	1.117-1.901
Plasma NE (pg/mL)	-0.0104	0.00388	7.1543	0.0075	1.521	1.275-2.102

OR, odds ratio; CI, confidence interval; E, epinephrine; NE, norepinephrine; BP, bodily pain; HC, health change; GH, general health; MH, mental health; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality.

related with both disease severity and QoL. General health might be particularly affected in patients with oral neoplasms, while patients with oral carcinoma experience mental health issues and have higher catecholamine levels than patients with a benign tumor.

All of the SF-36 subscale scores in the present study were lower than the norm for the local Chinese population with a similar age and sex distribution, indicating significant impairment in QoL [15, 16]. These findings, determined using logit models, provide support for a link between QoL and oral cancer, which is consistent with the findings of others [10] and suggests that

patients diagnosed with oral cancer have more physical distress than patients diagnosed with a benign oral tumor. However, patients with a benign oral tumor reported greater mental distress and poorer subjective symptoms, including pain, during the preoperative period. Most of the patients with oral cancer were not aware of the true nature of the disease, while patients with a suspected benign oral tumor were always aware of the disease status. The total SF-36 scores (OR 1.024, 95% CI 0.94-1.118, P = 0.2804) were not associated with carcinoma stage; however, the OR of plasma NE (OR 0.987, 95% CI 0.975-1, P = 0.0506) indicated that this result was consistent with other results and the association would likely be statistically significant in a larger sample.

In our previous study, we found associations between biobehavioral factors, measured using the Symptom Checklist-90-revised Inventory, and circulating blood catecholamine and glucocorticoid levels in oral neoplasm patients [11]. Based upon our findings, we showed that chronic stress influenced key biological behaviors of oral cancinoma by changing the tumor microenvironment though the circulating blood plasma. Although plasma E and NE levels did not differ by tumorigenesis in the present study, the data indicate a potential relationship between circulating catecholamine levels and cancer stage. The plasma E and NE levels were significantly higher in advanced stages of oral cancer than in the early stages.

Positive correlations between chronic stress and carcinoma progress have been emerged in both clinical and animal model studies. The locus ceruleus/norepinephrine (LC/NE) sympathetic system and catecholamine mediator (e.g., NE and E) production are involved in the stress response; because these arise both from the sympathetic system and adrenal medulla, it is possible that distinct information is provided by circulating plasma NE concentrations [21]. Chronic stress is associated with dysregulation of the LC/NE sympathetic system, with a consequent increase in NE and E levels released from the adrenal medulla and the neurons of LC/NE sympathetic system to promote tumor growth and angiogenesis [12]. Carcinomas in stressed animals indicated signally increased angiogenesis and over expression of VEGF, MMP2, and MMP9 [8].

Regarding our methodology for the measurement of NE and E, because NE and E rarely exist in peripheral blood, it is essential to determine an accurate method to precisely measure plasma NE and E concentrations. Because the HPLC-MS-MS monitors ion transitions using MRM, it has better specificity than LC-MS. Gu et al. [22] used two HPLC-MSMS methods in the MRM acquisition mode for quantitative analysis of 13 compounds in the catecholamine biosynthetic and metabolic pathways. Compared with other existing methods, the time-consuming sample pretreatment procedure was shortened. HPLC-MS-MS methods are simple, rapid, reproducible, and efficient to determine plasma catecholamine concentrations [11].

The findings of the present study support our hypothesis that patients with oral cancer have higher catecholamine levels in peripheral blood than patients with benign oral tumors. Plasma catecholamine levels and mental health play a larger role in the progression of oral carcinoma than oral tumorigenesis.

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Disclosure of conflict of interest

None.

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