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Original Article

MIF and MMP-9 expression levels positively correlate with pathological stages of gingival cancer

Xiaowei Lin[1], Xinxia Mao[1], Xuan Wei[2], Pengyi Zhang[1]

[1]*Department of Stomatology, Zhangye People's Hospital Affiliated to Hexi University, Zhangye, Gansu, China;* [2]*Medical College of Hexi University Zhangye, Gansu, China*

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Abstract: Objective: The aim of the current study was to investigate expression levels of macrophage migration inhibitory factor (MIF) and matrix metalloproteinase-9 (MMP-9) in gingival cancer, analyzing correlation levels of MIF and MMP-9 with pathological stages, differentiation degrees of gingival cancer, and prognosis. Methods: A total of 76 patients with gingival cancer (study group) and 64 healthy volunteers (control group) were prospectively analyzed. Enzyme-linked immunosorbent assays (ELISA) were conducted, detecting expression levels of MIF in serum and expression levels of MMP-9 in dental pulp tissues. Correlation levels between MIF, MMP-9, pathological stages, and differentiation degrees of gingival cancer were calculated. A 5-year-follow-up peroid was carried out, recording patient survival in the first, third, and fifth years. Results: There were significant differences in expression levels of MIF and MMP-9 between different pathological stages ($P < 0.001$), with the highest levels observed in stage IV ($P < 0.005$), followed by stages III and II. Significant differences were observed in expression levels of MIF and MMP-9 between different degrees of differentiation ($P < 0.001$), with the highest levels observed in poorly-differentiated tumors ($P < 0.05$), followed by moderately-differentiated tumors. Linear correlation analysis revealed that MIF and MMP-9 were positively correlated with clinical pathological stages ($r = 0.845, 0.828$, $P < 0.001$) and negatively correlated with tumor differentiation ($r = -0.630, -0.769$, $P < 0.001$). Survival analysis indicated that patients with lower expression levels of MIF and MMP-9 survived longer than those with higher expression levels of MIF and MMP-9 ($P = 0.042, 0.035$). Conclusion: MIF and MMP-9 were highly expressed in patients with gingival cancer. They were positively correlated with pathological stages of gingival cancer and negatively correlated with degrees of tumor differentiation and survival. Thus, these proteins may be useful targets in gingival cancer treatment.

Keywords: Matrix metalloproteinase-9, migration inhibitory factor, gingival cancer

Introduction

Gingival cancer is a common highly-differentiated squamous cell carcinoma [1]. Gingival cancer predominantly affects middle-aged and elderly individuals. It presents mostly in the lower gingiva. However, the average age of patients has continually decreased [2]. According to Keshaava et al. [3], there were approximately 450,000 newly diagnosed cases of gingival cancer in 2016, of which 24% of the cases were below 40 years of age. Compared to statistics from 10 years ago, the number of patients with gingival cancer had increased by more than 10-fold [4]. Many studies have suggested that [5, 6] the number of patients will continue to increase. Gingival cancer originates from the interdental papilla and palatal border area. It is easily misdiagnosed as gingivitis or periodontitis, causing patients to miss the best chance for treatment. Thus, upon diagnosis, the tumor has usually proceeded to middle and late stages [7].

Pan et al. [8] found that the 5-year survival rate of patients with advanced gingival cancer was 62%. Currently, the main treatment for gingival cancer is gingival resection. Total maxillary resection has often been applied for advanced or more severe cases [9]. Regardless of treatment method, the quality of life of patients is adversely impacted when the gingiva or entire maxilla is removed [10]. Therefore, studies examining methods for retaining gingival tissue will help improve the prognosis of patients. Matrix metalloproteinases (MMPs) have been

shown to effectively rebuild periodontal tissues and have been closely associated with the absorption capacity of the tooth root [11]. Macrophage migration inhibitory factor (MIF), a recently discovered cytokine, is abnormally expressed in various inflammatory diseases [12, 13]. De Faro Valverde et al. [14] detected the presence of MIF in oral cancer tissues, suggesting that MIF is associated with occurrence and development of oral cancer.

However, very few studies have examined MIF and gingival cancer. Therefore, the current study analyzed expression levels of MIF and MMP-9 in patients with gingival cancer, exploring association levels between MIF, MMPs, and gingival cancer.

Materials and methods

General information

A total of 127 Patients with gingival cancer, admitted to Stomatology and Oncology Departments, were enrolled and prospectively analyzed. They were included according to criteria for clinical symptoms compiled in the 2011 Oral Cancer Diagnosis Guidelines [15]: Gingival cancer was diagnosed by pathological biopsies, followed by treatment; Medical records of the patients were complete; Patients were cooperative to the arrangements of the medical staff; Patients were 20 to 70 years old. Exclusion criteria: Patients were administered with radiotherapy or chemotherapy; Patients with other tumors, cardiovascular diseases, pulmonary failure, infectious diseases, digestive tract infections, physical disabilities, mental disorders, and abnormal vital signs; Patients transferred to other hospitals and bedridden patients. In the end, a total of 76 cases were included as study subjects, including 54 males and 22 females, with an average age of 49.21 ± 10.57 years. Pathological stages and differentiation degrees were evaluated according to 2011 Gingival Cancer Disease Guidelines [16]. Results showed that 14 patients were in stage I, 18 patients were in stage II, 27 patients were in stage III, and 17 patients were in stage IV. Highly-differentiated, moderately-differentiated, and poorly-differentiated tumors were found in 36, 21, and 19 cases, respectively, in the study group. Additionally, 64 healthy volunteers were selected as the control group, including 42 males and 22 females, with an average age of 50.54 ± 9.87 years.

Methods

Two milliliters of venous blood were drawn from the two groups and centrifuged for 4 minutes (4,000 rpm/min) to obtain the supernatant. MIF-ELISA kits (from Thermo Fisher Scientific, Waltham, MA, USA) were used to detect MIF levels in the serum. Dental pulp tissues of the subjects were obtained. MMP-9 protein expression levels in the dental pulp tissue were detected by ELISA. Pulp tissues were lysed by cell lysis solution and protein concentrations were detected with a spectrophotometer. The proteins were placed in a water bath at 100°C for 10 minutes. SDS-PAGE gel was used for electrophoresis. After separation, the gel was transferred to polyvinylidene fluoride membranes and placed in blocking solution overnight at 4°C. Primary antibodies (1:200 anti-MMP-9 rabbit polyclonal antibody; 1:10,000 anti-beta-actin mouse monoclonal antibody) were added. They were incubated with gentle mixing for 3 hours, then discarded. After 3 washes with phosphate-buffered saline, the peroxidase-labeled secondary antibody was added. It was incubated with gentle mixing for 1 hour, then washed 3 times with phosphate-buffered saline. Luminescent substrate ECL-PLUS was added with β-actin as an internal reference for X-ray exposure and image development. This study was approved by the Ethics Committee of Zhangye People's Hospital Affiliated to Hexi University.

Outcome measures

Expression levels of MIF and MMP-9 were determined for the two groups. Expression levels of MIF and MMP-9 in gingival cancer patients at different pathological stages and different degrees of differentiation were determined, along with correlation levels and 1-year, 3-year, and 5-year survival rates. These levels and rates were based on 5-year follow-up periods.

Statistical analysis

SPSS 22.0 statistical software (SPSS, Inc., Chicago, IL, USA) was used to analyze present da-

Table 1. Comparison of clinical information between the two groups of patients [n (%)]

	Test group (n = 76)	Control group (n = 64)	X2 or t	P
Age	49.21 ± 10.57	50.54 ± 9.87		
Body weight	72.34 ± 12.84	71.52 ± 13.26		
Gender			0.475	0.491
Male	54 (71.05)	42 (65.63)		
Female	22 (28.95)	22 (34.38)		
Smokes			0.214	0.643
Yes	64 (84.21)	52 (81.25)		
No	12 (15.79)	12 (18.75)		
Sports habits			0.558	0.455
Yes	15 (19.74)	16 (25.00)		
No	61 (80.26)	48 (75.00)		
Living Environment			0.296	0.586
Downtown	52 (68.42)	41 (64.06)		
Suburbs	24 (31.58)	23 (35.94)		

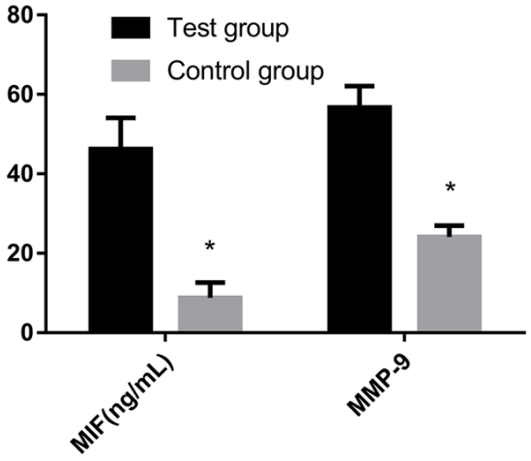

Figure 1. MIF and MMP-9 expression in both groups. *represents P < 0.001 compared to experimental group MIF or MMP-9 expression.

ta. Count data, such as gender, smoking habits, and other clinical information, are expressed as rates. Comparisons between groups were performed using Chi-square tests. Measurement data, such as MIF and MMP-9 expression levels, are expressed as mean ± standard deviation. Comparisons between multiple groups were performed by analysis of variance with post-hoc Bonferroni's tests. Comparisons between the two groups were carried out by independent *t*-tests. Linear correlation analysis was used for correlation analysis. Survival rates were calculated using the Kaplan-Meier method. Survival rates were compared by log-rank tests. P < 0.05 indicates statistical significance.

Results

Comparison of baseline data

Age, body weights, gender, smoking history, exercise habits, and living environments between the two groups of patients were not significantly different (P > 0.05), demonstrating that the two groups were comparable (**Table 1**).

MIF and MMP-9 expression levels in both groups

Expression levels of MIF in the study group were significantly higher than those in the control group (P < 0.001). Expression levels of MMP-9 in the study group were significantly higher than those in the control group (P < 0.001; **Figure 1**).

MIF and MMP-9 expression levels at different pathological stages and differentiation degrees

MIF levels in stages I, II, III, and IV were 24.86 ± 3.66, 35.21 ± 5.25, 46.37 ± 6.70, and 57.88 ± 4.75 ng/mL, respectively. MMP-9 levels in these stages were 37.66 ± 4.86, 45.96 ± 3.13, 59.14 ± 5.94, and 68.38 ± 5.07, respectively. Present results indicate significant differences in expression levels of MIF and MMP-9 in different pathological stages (P < 0.001), with the highest levels in stage IV (P < 0.005), followed by stages III and II. MIF and MMP-9 expression levels were lowest in patients with stage I disease (P < 0.005). For well-differentiated, moderately-differentiated, and poorly-differentiated patients, MIF expression levels were 31.88 ± 6.67, 47.70 ± 9.58, and 59.14 ± 7.27 ng/mL, respectively. MMP-9 expression levels were 41.37 ± 5.09, 52.68 ± 6.29, and 64.33 ± 6.40, respectively, revealing significant differences in expression levels of MIF and MMP-9 at different differentiation degrees (P < 0.001). Patients with poorly-differentiated tumors showed the highest expression levels (P < 0.05), followed by moderate-differentiation. Well-differentiated patients showed the lowest levels (P < 0.005, **Tables 2**, **3**).

Table 2. MIF and MMP-9 expression levels at different pathological stages

Stage	MIF (ng/mL)	MMP-9
Phase I (n = 14)	24.86 ± 3.66	37.66 ± 4.86
Phase II (n = 18)	35.21 ± 5.25*	45.96 ± 3.13*
Phase III (n = 27)	46.37 ± 6.70*,#	59.14 ± 5.94*,#
Phase IV (n = 17)	57.88 ± 4.75*,#,Δ	68.38 ± 5.07*,#,Δ
F	117.324	139.824
P	< 0.001	< 0.01

Note: *compared with levels of expression of MIF or MMP-9 in patients at stage I, P < 0.005; #compared with levels of MIF or MMP-9 expression in patients at stage II, P < 0.005; Δcompared with expression levels of MIF or MMP-9 in patients at phase III, P < 0.005.

Table 3. Different levels of MIF and MMP-9 expression

Differentiation	MIF (ng/mL)	MMP-9
Highly differentiated (n = 36)	31.88 ± 6.67	41.37 ± 5.09
Medium differentiation(n = 21)	47.70 ± 9.58*	52.68 ± 6.29*
Poor differentiation (n = 19)	59.14 ± 7.27*,#	64.33 ± 6.40*,#
F	82.894	100.916
P	< 0.001	< 0.001

Note: *compared with expression levels of MIF or MMP-9 in patients with high differentiation, P < 0.05; #compared with expression levels of MIF or MMP-9 in patients with moderate differentiation, P < 0.05.

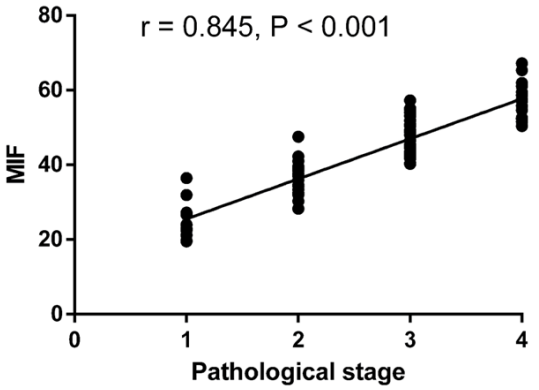

Figure 2. Correlation analysis of MIF and pathological stage. Linear correlation analysis shows a positive correlation between MIF and pathological staging (r = 0.845, P < 0.001).

Correlation analysis of MIF and MMP-9 with pathological stages and differentiation

Linear correlation analysis showed that MIF and MMP-9 were positively correlated with clinical pathological stages (r = 0.845, 0.828, P < 0.001) and negatively correlated with differentiation degrees (r = -0.630, -0.769, P < 0.001, **Figures 2**-**5**).

Prognosis survival rates

Of the 76 cases with gingival cancer, 72 cases were successfully followed-up. According to median expression levels, patients were divided into the MIF high-expression group (MIF > 46.24 ng/mL based on the median, 34 cases in total), MIF low-expression group (MIF ≤ 46.24 ng/mL based on the median, 38 cases in total), MMP-9 high-expression group (MMP-9 > 56.72, 40 cases in total), and MMP-9 low-expression group (MMP-9 ≤ 56.72, 32 cases in total). Moreover, 1-, 3-, and 5-year survival rates of the MIF low expression group were 97.14%, 85.64%, and 70.27%, respectively, significantly higher than values of 87.15%, 69.68%, and 38.32% observed in the MIF high-expression group (P = 0.042). The 1-, 3-, and 5-year survival rates of the MMP-9 low-expression group were 97.06%, 93.71%, and 67.28%, respectively, also significantly higher than 92.08%, 71.33%, and 42.36% values observed in the MMP-9 high-expression group (P = 0.035, **Figures 6**, **7**).

Discussion

The pathogenesis of gingival cancer remains unclear. Studies have suggested that [17, 18] long-term gingival injuries and genetic factors cause the deterioration of gingival tissue lesions. These induce gingival cancer. Radiotherapy and chemotherapy have been used to treat gingival cancer in clinical practice. However, efficacy levels are approximately 30% [19]. Thus, tissue resection remains the most effective treatment. However, excising gingival tissues or even jaw bones greatly decreases the quality of life of patients. Therefore, it is a major challenge to treat gingival cancer while retaining original tissues. Many studies [20, 21] have shown that occurrence and development of gingival cancer is closely associated with changes in multiple biological factors. Exploring the presence of abnormally-expressed factors in the pathogenesis of gingival cancer and changes in the biological mechanisms of gingival cancer can reveal target treatments for gingival cancer. These treatments may enable

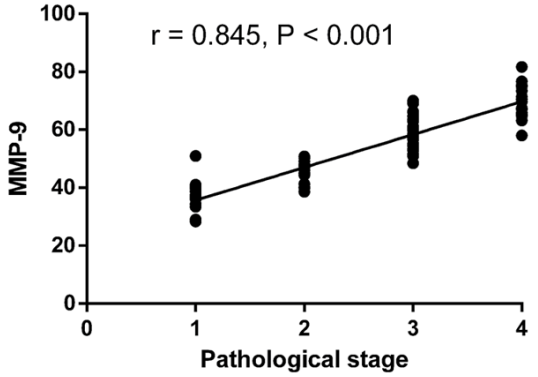

Figure 3. Analysis of the correlation between MMP-9 and pathological stage. Linear correlation analysis shows a positive correlation between MMP-9 and pathological staging (r = 0.828, P < 0.001).

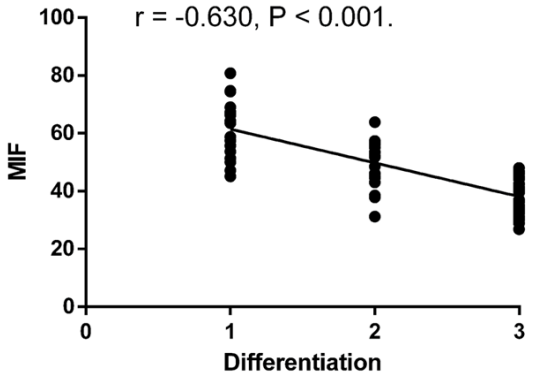

Figure 4. Correlation analysis of MIF and tumor differentiation. Linear correlation analysis shows that MIF was negatively correlated with the degree of tumor differentiation r = -0.630, P < 0.001. 1- represents poorly differentiated, 2- represents moderate differentiation, and 3- represents high differentiation.

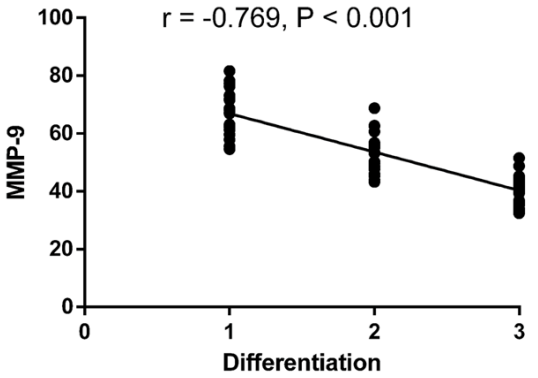

Figure 5. Correlation analysis of MMP-9 and tumor differentiation. Linear correlation analysis shows that MMP-9 was negatively correlated with the degree of tumor differentiation r = -0.769, P < 0.001. 1- represents poorly differentiated, 2- represents moderate differentiation, and 3- represents high differentiation.

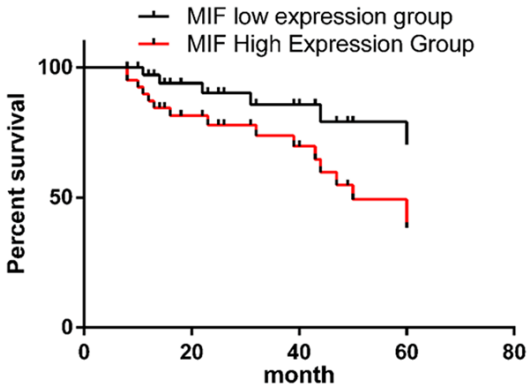

Figure 6. Prognosis 5-year survival rate in high- and low-expression MIF groups. Survival rates of the MIF low-expression group were 97.14%, 85.64%, and 70.27%, significantly better than those of the MIF high-expression group (87.15%, 69.68%, 38.32%, P = 0.042).

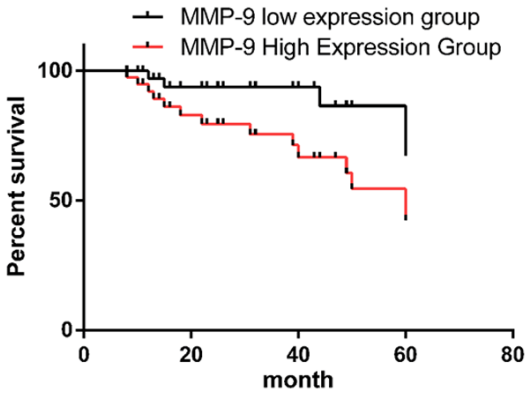

Figure 7. Prognosis for 5-year survival rates of MMP-9 high and low-expression groups. Survival rates of the MMP-9 low-expression group were 97.06%, 93.71%, and 67.28%, significantly better than those in the MMP-9 high-expression group (92.08%, 71.33%, 42.36%, P = 0.035).

patients to retain original gingival tissues. MIF can activate macrophage or monocyte cytokines. The cytokines strongly regulate the activation of inflammatory cytokines. This has been shown to be significant for abnormal expression in periodontitis [22]. MMP-9 is abnormally-expressed in many tumor diseases, acting as a carcinogenic factor closely associated with metastasis and invasion of tumor lesions [23]. Therefore, detection of MIF and MMP-9 expression levels in patients with gingival cancer may provide a foundation for targeted therapy of gingival cancer.

Current results showed that both MIF and MMP-9 were highly-expressed in patients with

gingival cancer, suggesting that these proteins are closely associated with gingival cancer. MIF and MMP showed positive correlation levels with pathological stages and negative correlation levels with degrees of differentiation. Results suggest that MIF and MMP-9 are involved in the development of gingival cancer. MIF can malignantly transform oncogenes by inhibiting the division of normal cells [24]. It has been predicted that MIF activates macrophages and inflammatory factors in the cells, resulting in a continuously damaged environment of gingival tissues. In this case, cancer cells are more susceptible to invasion. As the cancer deteriorates, cancer cells phagocytose normal cells in the gingival tissue of patients, promoting the proliferation of macrophages and mononuclear cytokines. This results in additional deterioration. Therefore, patients with more severe disease show higher expression levels of MIF. Moreover, MIF is a powerful regulator of the anti-inflammatory effects of renal epithelial hormone, accelerating the formation of new blood vessels and increasing growth rates of tumors. MMP-9, a factor that degrades extracellular matrix components, significantly destroys cells [25]. MMP-9 induces local tissue and organ damage by activating inflammatory factors, including interleukin-1, tumor necrosis factor-α, and transforming growth factor-β [26]. Its high expression in gingival cancer demonstrates that MMP-9 is present in gingival cancer cells. It has been thought that, during disease progression, MMP-9 secretion increases, causing synthesis in basal cells to be significantly lower than the degradation rate, damaging gingival tissue. Results of Monteiro et al. [27] are consistent with current results, demonstrating the validity of the current experiment. Investigation of prognosis survival showed that survival rates of patients with high MIF and MMP-9 expression levels were significantly lower than those of patients with low expression, suggesting that MIF and MMP-9 can be targeted for treatment of gingival cancer. However, the mechanisms of MIF and MMP-9 in promoting occurrence and development of gingival cancer require further investigation.

There were some limitations to the current study, however. The subject population was small and relatively simple. Statistical analysis was not carried out on other types of gingival cancer, in which differences in expression levels between MMP-9 and MIF may have existed.

In summary, MIF and MMP-9 were shown to be highly-expressed in patients with gingival cancer, positively correlated with pathological stages of gingival cancer, and negatively correlated with degrees of tumor differentiation. Therefore, they may be acceptable therapeutic targets for treatment of gingival cancer.

Disclosure of conflict of interest

None.

Address correspondence to: Xinxia Mao, Department of Stomatology, Zhangye People's Hospital Affiliated to Hexi University, No. 67 Huancheng West Road, Ganzhou District, Zhangye 734000, Gansu, China. Tel: +86-0936-8222165; E-mail: xinxiamaoyx@163.com

References

[1] Niu LX, Feng ZE, Wang DC, Zhang JY, Sun ZP and Guo CB. Prognostic factors in mandibular gingival squamous cell carcinoma: a 10-year retrospective study. Int J Oral Maxillofac Surg 2017; 46: 137-143.

[2] Kim DW, Lee BD, Lim JH, Park JH, Nam W, Kim HJ and Cha IH. Elective neck dissection versus observation in early stage oral squamous cell carcinoma: recurrence and survival. J Korean Assoc Oral Maxillofac Surg 2016; 42: 358-364.

[3] Keshava A, Gugwad S, Baad R and Patel R. Gingival squamous cell carcinoma mimicking as a desquamative lesion. J Indian Soc Periodontol 2016; 20: 75-78.

[4] Huang C and Yu Y. Synergistic cytotoxicity of beta-Elemene and cisplatin in gingival squamous cell carcinoma by inhibition of STAT3 signaling pathway. Med Sci Monit 2017; 23: 1507-1513.

[5] Cheng CS, Chang CM, Hsiao YL, Chan MY, Lee CY, Lee LT and Wong YK. Clinical implications of recent exodontia before diagnosis of gingival squamous cell carcinoma: a new classification. Head Neck 2016; 38:

[6] Nishio K, Motozawa K, Omagari D, Gojoubori T, Ikeda T, Asano M and Gionhaku N. Comparison of MMP2 and MMP9 expression levels between primary and metastatic regions of oral squamous cell carcinoma. J Oral Sci 2016; 58: 59-65.

[7] Noda Y, Kishino M, Sato S, Hirose K, Sakai M, Fukuda Y, Murakami S and Toyosawa S. Galectin-1 expression is associated with tumour immunity and prognosis in gingival squamous cell carcinoma. J Clin Pathol 2017; 70: 126-133.

[8] Pan H, Gu L, Liu B, Li Y, Wang Y, Bai X, Li L, Wang B, Peng Q, Yao Z and Tang Z. Tropomyosin-1 acts as a potential tumor suppressor in human oral squamous cell carcinoma. PLoS One 2017; 12: e0168900.
[9] Lubek JE and Magliocca KR. Evaluation of the bone margin in oral squamous cell carcinoma. Oral Maxillofac Surg Clin North Am 2017; 29: 281-292.
[10] Bark R, Mercke C, Munck-Wikland E, Wisniewski NA and Hammarstedt-Nordenvall L. Cancer of the gingiva. Eur Arch Otorhinolaryngol 2016; 273: 1335-1345.
[11] Sorsa T, Gursoy UK, Nwhator S, Hernandez M, Tervahartiala T, Leppilahti J, Gursoy M, Kononen E, Emingil G, Pussinen PJ and Mantyla P. Analysis of matrix metalloproteinases, especially MMP-8, in gingival creviclular fluid, mouthrinse and saliva for monitoring periodontal diseases. Periodontol 2000 2016; 70: 142-163.
[12] Otvos B, Silver DJ, Mulkearns-Hubert EE, Alvarado AG, Turaga SM, Sorensen MD, Rayman P, Flavahan WA, Hale JS, Stoltz K, Sinyuk M, Wu Q, Jarrar A, Kim SH, Fox PL, Nakano I, Rich JN, Ransohoff RM, Finke J, Kristensen BW, Vogelbaum MA and Lathia JD. Cancer stem cell-secreted macrophage migration inhibitory factor stimulates myeloid derived suppressor cell function and facilitates glioblastoma immune evasion. Stem Cells 2016; 34: 2026-2039.
[13] Cattaneo A, Ferrari C, Uher R, Bocchio-Chiavetto L, Riva MA, Consortium MRCI and Pariante CM. Absolute measurements of macrophage migration inhibitory factor and interleukin-1-beta mrna levels accurately predict treatment response in depressed patients. Int J Neuropsychopharmacol 2016; 19.
[14] Valverde Lde F, Pereira Tde A, Dias RB, Guimaraes VS, Ramos EA, Santos JN and Gurgel Rocha CA. Macrophages and endothelial cells orchestrate tumor-associated angiogenesis in oral cancer via hedgehog pathway activation. Tumour Biol 2016; 37: 9233-9241.
[15] Olivo M, Bhuvaneswari R and Keogh I. Advances in bio-optical imaging for the diagnosis of early oral cancer. Pharmaceutics 2011; 3: 354-378.
[16] Katz J, Onate MD, Pauley KM, Bhattacharyya I and Cha S. Presence of Porphyromonas gingivalis in gingival squamous cell carcinoma. Int J Oral Sci 2011; 3: 209-215.
[17] Li C, Lin J, Men Y, Yang W, Mi F and Li L. Does medullary versus cortical invasion of the mandible affect prognosis in patients with oral squamous cell carcinoma? J Oral Maxillofac Surg 2017; 75: 403-415.
[18] Garzino-Demo P, Zavattero E, Franco P, Fasolis M, Tanteri G, Mettus A, Tosco P, Chiusa L, Airoldi M, Ostellino O, Schena M, Rampino M, Ricardi U, Evangelista A, Merletti F, Berrone S and Ramieri G. Parameters and outcomes in 525 patients operated on for oral squamous cell carcinoma. J Craniomaxillofac Surg 2016; 44: 1414-1421.
[19] Obata K, Shimo T, Okui T, Matsumoto K, Takada H, Takabatake K, Kunisada Y, Ibaragi S, Nagatsuka H and Sasaki A. Tachykinin receptor 3 distribution in human oral squamous cell carcinoma. Anticancer Res 2016; 36: 6335-6341.
[20] Baba Y, Maeda T, Suzuki A, Takada S, Fujii M and Kato Y. Deguelin potentiates apoptotic activity of an EGFR tyrosine kinase inhibitor (AG1478) in PIK3CA-Mutated head and neck squamous cell carcinoma. Int J Mol Sci 2017; 18.
[21] Inaba H, Tagashira M, Kanda T, Murakami Y, Amano A and Matsumoto-Nakano M. Apple- and hop-polyphenols inhibit porphyromonas gingivalis-mediated precursor of matrix metalloproteinase-9 activation and invasion of oral squamous cell carcinoma cells. J Periodontol 2016; 87: 1103-1111.
[22] Castro SA, Collighan R, Lambert PA, Dias IH, Chauhan P, Bland CE, Milic I, Milward MR, Cooper PR and Devitt A. Porphyromonas gingivalis gingipains cause defective macrophage migration towards apoptotic cells and inhibit phagocytosis of primary apoptotic neutrophils. Cell Death Dis 2017; 8: e2644.
[23] Lin YW, Lee LM, Lee WJ, Chu CY, Tan P, Yang YC, Chen WY, Yang SF, Hsiao M and Chien MH. Melatonin inhibits MMP-9 transactivation and renal cell carcinoma metastasis by suppressing Akt-MAPKs pathway and NF-kappaB DNA-binding activity. J Pineal Res 2016; 60: 277-290.
[24] Zou M, Zhang X and Xu C. IL6-induced metastasis modulators p-STAT3, MMP-2 and MMP-9 are targets of 3,3'-diindolylmethane in ovarian cancer cells. Cell Oncol (Dordr) 2016; 39: 47-57.
[25] Kalafatovic D, Nobis M, Son J, Anderson KI and Ulijn RV. MMP-9 triggered self-assembly of doxorubicin nanofiber depots halts tumor growth. Biomaterials 2016; 98: 192-202.
[26] Candido S, Abrams SL, Steelman LS, Lertpiriyapong K, Fitzgerald TL, Martelli AM, Cocco L, Montalto G, Cervello M, Polesel J, Libra M and McCubrey JA. Roles of NGAL and MMP-9 in the tumor microenvironment and sensitivity to targeted therapy. Biochim Biophys Acta 2016; 1863: 438-448.
[27] Monteiro LS, Delgado ML, Ricardo S, do Amaral B, Salazar F, Pacheco JJ, Lopes CA, Bousbaa H and Warnakulasuryia S. Prognostic significance of CD44v6, p63, podoplanin and MMP-9 in oral squamous cell carcinomas. Oral Dis 2016; 22: 303-312.