

**SIGNIFICANCE OF MMPS EXPRESSION ON OSCC CLINICAL OUTCOME: A
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ABSTRACT

Aim and background: Oral squamous cell carcinoma (OSCC) is an invasive neoplasm that spreads either locally through regional lymph nodes or cause distant metastasis. Matrix metalloproteinase (MMP) degrades the extracellular matrices (ECMs) and have been thought to play an important role in both the invasion and metastasis of tumors. The aim of this study was to review the expression of MMPs in OSCC and explore the significance of MMPs expression in clinical outcome of these patients. **Material and Methods:** The most recognized data Bases such as PubMed, Google scholar, Science direct, etc. were searched using keywords as OSCC, MMP, prognosis, clinical outcome, prognosis, metastasis, invasion, stage and other related ones During 1999 to 2016. **Results:** Among 24 reviewed in this study, MMP-9 was reported in association with invasion, metastasis recurrence, prognosis and patient survival in 7 ones but in no association with survival in only 1 research. Also, it is reported MMP-2 incorporation with poor differentiation, invasion and metastasis of OSCC in 5 studies, MMP-7 in relation with biological behavior, invasion and metastasis in 3 ones, MMP-1 and 10 as indicators of OSCC cancer risk and also potential oral cancer markers in 2 studies, MT1-MMP in association with prognosis and patient survival in 3 research and in relation with invasion and metastasis in only 1 study. 3 studies suggested MMP family was associated with prognosis and metastasis of OSCC. MMP 28 and 12 were also evaluated in 2 studies and researches could not find any correlation with them and any clinical evaluated parameters. **Conclusion:** Evaluation of the clinical data along with the expression of MMPs could be useful in predicting the post-therapeutic outcome and prognosis of OSCC patients. Furthermore, among members of MMP family, MMP 2, 7 & 9 considered to association with clinical outcome and late evidences in oral cancerogenesis but MMP 1 & 10 might be related to early consequences occurred in this field as indicators or markers for initiation of OSCC.

KEYWORDS: MMP, Oral squamous cell carcinoma, Invasion, Metastasis.**INTRODUCTION**

Oral squamous cell carcinoma (OSCC), is the most common cancer in oral cavity. Nowadays, although notable advancement was reported in treatment modalities of these patients but related survival rate and quality of life did not improved for them, yet.^[1] This cancer is considered as a global public health problem and it has shown a high degree of local invasiveness and also metastasis for progressed cases. Recent studies have been focused on expression of markers in association of clinical outcome of cancers.^[2-5] Early detection of invaded malignant cells might be helpful for prevention of more proceeded stages as distant metastasis of tumoral cells. Metastasis includes a series of tumor host interactions that involve multiple extracellular matrix degrading enzymes specially matrix metalloproteinase (MMPs).^[6] MMPs consists a family of at least 22 secreted, membrane-bound zinc- and calcium-dependent

proteases that characterize as degradation and remodeling of extracellular matrix proteins. These enzymes are categorized to five groups according to their substrate specificity: collagenases (MMP-1, -8, and -13), gelatinases (MMP-2 and -9), stromelysins (MMP-3, -10), and membrane-type MMPs (MT-MMPs) (MMPs 14-17, 24, and 25) and other MMPs (MMPs 11, 19 and 20).^[7]

Tumor cells have capacity for utilizing MMPs produced by stromal cells and they have an active role for stroma in tumor invasion. MMPs are produced by cancer cells or through the induction of surrounding stromal cells. Previous studies have shown a correlation between MMP-2/MMP-9 and the invasive/metastatic potential of cancer cells.^[8,9] Somehow, studies related to evaluation of these important enzymes in OSCC samples demonstrated this importance, too. It seems, it is important to review and more evaluation around the expression of MMPs and tissue inhibitors of MMP

(TIMPs) in OSCC to early diagnosis of its malignant potential. So, this study was aimed to review the expression of MMPs in OSCC and its clinical significance.^[8-11]

MATERIAL AND METHODS

The most recognized data Bases such as PubMed, Google scholar, Science direct, etc. were searched using keywords as OSCC, MMP, prognosis, clinical outcome, prognosis, metastasis, invasion, stage and other related ones During 1999 to 2016.

RESULTS

24 studies which are reviewed in this research (Table1), evaluated association of MMP Families in histopathological & clinical parameters related to cancerogenesis and clinical outcome of patients suffered from OSCC. In this case, among most recognized

members, MMP-9 was reported in association with invasion, metastasis recurrence, prognosis and patient survival in 7 ones but in no association with survival in only 1 research. MMP-2 was introduced for incorporation with poor differentiation, invasion and metastasis of OSCC in 5 studies. MMP-7 was considered in relation with biological behavior, invasion and metastasis in 3 ones. MMP-1 and 10 were reported to be an indicator of OSCC cancer risk and also potential oral cancer markers in 2 studies. MT1-MMP was considered to in association with prognosis and patient survival in 3 research and in relation with invasion and metastasis in only 1 study. 3 studies suggested MMP family was associated with prognosis and metastasis of OSCC. Other less recognized members as MMP 28 and 12 were also evaluated in 2 studies and researches could not find any correlation with them and any histopathological and clinical evaluated parameters in this field.

Table 1: Summary of reviewed studies around expression of MMPs in OSCC samples.

NO	Subject	Author/year of publication	Samples	Materials and method	Conclusion
1	Prognostic value of matrix metalloproteinase in oral squamous cell carcinoma and its association with angiogenesis. ^[6]	Andisheh-Tadbir A 2016	61	Samples were studied by Immunohistochemical staining approached for MMP-2, MMP-7, MMP-9 and MMP-13.	No significant differences in the MMPs immunoreactivity between tumor cells and stroma were observed. Application of MMPs as prognostic indicators for the malignancy potential of OCSS might be considered in every case of tumor examination.
2	Immunohistochemical expression of MMP-2 and MMP-8 in oral squamous cell carcinoma. ^[10]	Lawal AO 2015	36	Immunohistochemical staining approached for MMP2 & 8	A higher proportion of poorly differentiated OSCC strongly expressed MMP-2.
3	The role of MMP-2 and MMP-9 as prognostic markers in the early stages of tongue squamous cell carcinoma. ^[8]	Aparna M 2015	59	Immunohistochemical staining of tongue OSCC in T1N0M0 and T2N0M0 stages with MMP-2 and MMP-9 antibodies	Expression of MMP-2 and MMP-9 was observed in patients who subsequently developed local recurrence, regional and distant metastasis of the tumor.
4	COX-2, MMP-7 expression in oral lichen planus and oral squamous cell carcinoma. ^[12]	Li TJ 2013	43	The immunohistochemical method and RT-PCR were applied to detect the expression of COX-2 and MMP-7.	The abnormal expression of COX-2 and MMP-7 are closely related to the biological behavior of OSCC, the MMP-7 may be induced by COX-2 and further lead to the invasion and metastasis of OSCC.
5	Changes in the expression of MMP2, MMP9, and CollIV in stromal cells in oral squamous tongue cell carcinoma: relationships and prognostic implications ^[9]	Hai-Xia Fan 2012	48	Immunohistochemistry was approached	clinical application of agents that may inhibit MMP-9 secretion by stromal cells may be a key to achieving clinical control of invasion and metastasis of oral tumors

6	The immunohistochemical characterization of MMP-2, MMP-10, TIMP-1, TIMP-2, and podoplanin in oral squamous cell carcinoma. ^[11]	Mashahadiabbas F 2012	40	Forty cases of OSCC were analyzed by IHC.	The results are suggestive of important roles that MMP-2, MMP10, TIMP and podoplanin play in pathologic processes of OSCC, including invasion.
7	Serum level of MMP-3 in patients with oral squamous cell carcinoma- Lack of association with clinico pathological features. ^[13]	Tadbir AA 2012	45	Using an ELISA kit to assess and compare the circulating levels of MMP-3 in blood serum of 45 OSCC patients with 45 healthy control samples.	Measurement of serum MMP-3 concentration might be helpful to diagnose OSCC but not to predict prognosis.
8	Prognostic value of transforming growth factor beta 1 (TGF-B) and matrix metalloproteinase 9 in oral squamous cell carcinoma. ^[14]	Elahi M 2011	48	Immunohistochemical staining of 48 OSCC biopsies with MMP-9 and TGF-B1 markers	Unlike TGF-B1, MMP-9 might be useful for prognosis determination of OSCC
9	Expression of MMP-1 in histopathological different grades of OSCC and in normal buccal mucosa. ^[15]	George A 2010	30	Immunohistochemically stained for the expression OF MMP-1.	100% OF OSCC showed cytoplasmic immune reactivity for MMP-1 in the epithelial and connective tissue cells.
10	Immunoexpression of matrix metalloproteinase-2 and matrix metalloproteinase-9 in the metastasis of squamous cell carcinoma of the human tongue. ^[16]	Zhou CX 2010	61	Expressions of MMP-2/MMP-9 were detected by immunohistochemistry	MMP-2 and/or MMP-9 play an important role in invasion and metastasis in tongue cancer, and that analysis of MMP expression and/or activity in primary tumors may have a predictive value for the actual or potential presence of cervical metastases.
11	MMP-1 and MMP-10 but not MMP-12 are potential oral cancers markers. ^[17]	Yen CY 2009	114	Tissue samples collected included 51 oral tumors, and matched internal control tissue included 25 samples from the oral safe margin and 38 samples from neck platysma muscle	There were no significant differences for MMP1, MMP10 and MMP12 in different stages, invasion and locations or different habits. Therefore, MMP1 and MMP10 but not MMP12 are potential oral cancer markers.
12	Expression of MMP-7 and MT1-MMP in oral squamous cell carcinoma as predictive indicator for tumor invasion and prognosis. ^[18]	de Vicente JC 2007	69	immunohistochemically studied using specific antibodies against MMP-7 and MT1-MMP proteins.	MMP-7 and MT1-MMP displayed a survival relevance, and in multivariate analysis they were independent prognostic indicators, particularly in neck node-positive cases.
13	Studies on the expression of MMP-9 and significance of a macrophage assay in oral squamous cell carcinoma. ^[19]	Taiming DAI 2007	42	immunohistochemical expression of MMP-9 and CD-68 in 42 cases of OSCC and 10 normal tissue.	Both MMP-9 and macrophages may play an important role in the process of invasion and metastasis in OSCC.

14	Characterization of 3 OSCC lines with different invasion and/or metastatic potentials. ^[20]	N FazilErdem 2007	3	Using IHC and flow cytometry in 3 OSCC cell lines and HNEC. The cell morphologies of these 4 cell lines were compared using transmission electron microscopy (TEM).	MMPs play an important role in the invasion and metastasis of oral cancer. MMP-9 play a more important role than MMP-2 during invasion.
15	Functional role of matrix metalloproteinase-28 in the oral squamous cell carcinoma. ^[21]	Lin MH 2006	92	Assessment of this proteinase by RT-PCR.	The results showed that expression of MMP-28 was significantly higher in 92 oral squamous cell carcinomas.
16	CD44 expression and its relationship with MMP-9 clinicopathological factors and survival in OSCC. ^[22]	A.Kosuen 2006	138	Immuohistochemically stained for the expression of CD44 and MMP-9.	MMP-9 expression showed no statistical significance in survival analyses.
17	Expression of MMP-2 and its tissue inhibitor in OSCC. ^[23]	Gao ZB 2005	40	Expression of MMP-2 was evaluated in 40 cases with semi-quantitative RT-PCR and immunohistochemical techniques.	MMP-2 may play important roles in the invasion and metastasis of OSCC.
18	MMP-2 and MMP-9 in OSCC: manifestation and localization of their activity. ^[24]	Kato 2005	31	Freshly frozen samples from 31 OSCC patients were analyzed. Serial frozen sections were used by routine hematoxylin and eosin staining, IHC and film in situ zymography (FIZ) for gelatinolytic activity.	These results indicate that two types of MMPs, MMP-2 and MMP-9 are present in OSCC.
19	Expression and clinical significance of MMP-2 and MMP-9 in OSCC. ^[25]	de Vicente JC 2005	68	The expression of MMP-2 and MMP-9 in series of 68 OSCC by IHC.	MMP-2 and MMP-9 are involved in the invasion process of oral cancer and MMP-9 is related to poor prognosis in the subset of patients without neck node metastasis.
20	Expression of MMP-9, TIMP-1, CD-34 and factor-8 as prognostic markers for squamous cell carcinoma of the tongue. ^[26]	Guttman D 2004	23	Immunohistochemistry analysis was performed	Tumor and adjacent tissue and the relationship between the histopathologic findings and clinical outcome were evaluated.
21	Expressions of matrix metalloproteinases in early-stage oral squamous cell carcinoma as predictive indicators for tumor metastases and prognosis. ^[27]	Katayama A 2004	53	Expressions of MMP-2, MMP-9, MT1-MMP, and TIMP-2 were examined using immunohistological methods on the sections of tumor biopsy samples	Expressions of MMP-9 and TIMP-2 have predictive value for tumor metastases and cause-specific survival. High expression of TIMP-2 is the most independent factor for worse prognosis in early-stage oral SCC.
22	Correlation between functional genotypes in the matrix metalloproteinases-1 promoter and risk of oral squamous cell carcinomas. ^[28]	Lin SC 2004	121	Genomic DNA from the blood of OSCC, OSF and controls were amplified by PCR-based genotyping.	The results showed that 2G genotype in MMP-1 promoter was associated with the risk of OSCC.

23	Expression of membrane type1-matrix metalloproteinase in oral squamous cell carcinoma. ^[29]	Myoung H 2002	46	MT1-MMP expression was examined in 46 OSCCs via immunohistochemistry and non-radioisotope in situ hybridization.	These results suggest that MT1-MMP is primarily secreted in the OSCC cells and is involved in the invasiveness of the OSCC and LNM. Moreover, MT1-MMP combined with other markers may be used to predict the metastatic potential of an OSCC.
24	Expression of MMPs,MT-MMP and TIMPs in OSCC of the oral cavity. ^[30]	Kurahara S 1999	96	Immunohistochemical study of MMPs expression	Tumor progression and metastasis of tumors is regulated by many types of MMPs and the overproduction of MMPs appears to be more important for metastasis.

DISCUSSION

The expression and activation of proteolytic enzymes, which are involved in the ECM degradation, is crucial for the invasion and spread of tumoral cells to the distant sites.^[31,32] Initially, a carcinoma develops within the epithelium, surrounded by the basement membrane. This structure has several components (laminin, type IV collagen, and heparan-sulphate proteoglycan) and its degradation is a crucial step for progression from carcinoma in situ to invasive carcinoma.

Tumor cells initially penetrate the basement membrane and lately migrate through the stroma. Thus, proteolysis of extracellular matrix macromolecules is an essential step in cancer invasion and metastasis. The cancer cells produce different extracellular matrix degrading enzymes, such as MMPs, cathepsins, and plasminogen activators, and it is considered that all of them play a role in the malignant behavior of the neoplasms.^[28] MMPs are overexpressed in many tumor types, and several studies have been carried out to explore their prognostic significance, but without conclusive results. These reports have used mainly immunohistochemistry, in situ hybridization and gelatin zymography to evaluate expression of MMPs and their tissue inhibitors (TIMPs). Previous attempts to correlate MMPs expression with clinical outcome for patients with oral or head and neck cancer have been inconclusive which is summarized in this review study too. (Table 1).

Several researches were conducted in this category and majority of them suggested a significant correlation between expressions of MMP members and clinical outcome of OSCC patients as prognosis, stage, survival rate, metastasis, etc. In this study, we reviewed their objectives, methods and conclusion and summarize the exist data and try to achieve a complementary points in this field. In summary, it can be notify that, combination of the clinical data with the expression of MMPs could be useful in predicting the post-therapeutic outcome and prognosis of OSCC patients.

CONCLUSION

Due to reports of evaluated studies reviewed in this research, evaluation of the clinical data along with the expression of MMPs could be useful in predicting the post-therapeutic outcome and prognosis of OSCC patients. Furthermore, among members of MMP family, MMP 2,7 & 9 considered to association with clinical outcome and late evidences in oral cancerogenesis but MMP 1 & 10 might be related to early consequences occurred in this field as indicators or markers for initiation of OSCC.

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