Original Article doi: 10.5146/tjpath.2014.01277

Metastasis-Associated Protein 1 Expression in Oral Squamous Cell Carcinomas: Correlation with Metastasis and Angiogenesis

Metastaz İlişkili Protein 1 Ekspresyonunun Oral Skuamöz Hücreli Karsinomlarda Metastaz ve Anjiyogenez ile İlişkisi

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ABSTRACT

Objective: Metastasis-associated protein 1 (MTA1) has been associated with poor prognosis in several carcinomas. Recent investigation has found that in different tumors, MTA1 protein significantly correlates with tumor angiogenesis, suggesting that MTA1 may be a possible angiogenesis-promoting molecule in malignant tumors. Thus, the current study was performed to determine the role of MTA1 protein in the biological behavior of oral squamous cell carcinoma and its relation with tumor angiogenesis.

Material and Method: In this study, 44 oral squamous cell carcinomas and 15 normal epitheliums were reviewed by IHC staining for MTA1 and CD105.

Results: Frequency of MTA1 expression in SCCs was recorded as 97.7%, which was significantly higher than that of the control group (33.3%). Mean percentage of MTA1 expression in oral squamous cell carcinomas was 76.88 ± 25.33% which was significantly higher than that of the control group (22.81 ±10.83). Our data showed a correlation between MTA1 expression with lymph node metastasis, tumor size and, stage. Evaluation of the correlation between MTA1 protein expression and micro vessel density showed that high micro vessel density was detected more frequently in tumors with MTA1 protein overexpression than in those without overexpression.

Conclusion: In the present study, high expression of the MTA1 protein was seen in oral squamous cell carcinoma, and was closely associated with tumor progression and increased tumor angiogenesis. The findings may indicate that MTA1 protein has clinical potentials as a useful indicator of progressive phenotype, a promising prognostic predictor to identify patients with poor prognosis and may be a potential novel therapeutic target of anti-angiogenesis for patients with oral squamous cell carcinoma.

Key Words: MTA-1 protein, Squamous cell carcinoma, Immunohistochemistry, Metastasis, Head and neck neoplasms

ÖZ

Amaç: Metastaz ilişkili protein 1 (MTA1) bazı karsinomlarda kötü prognoz ile ilişkilidir. MTA1 proteinin farklı tümörlerde anjiyogenez ile ilişkisini gösteren son çalışmalar MTA1 in malign tümörlerde anjiyogenezi uyarmada rolünü olabileceğini desteklemektedir. Bu çalışma, oral skuamöz hücreli karsinomun biyolojik davranışının saptanmasında MTA1 in rolü ve MTA1 proteinin tümör anjiyogenezi ile ilişkisini göstermek amacıyla yapılmıştır.

Gereç ve Yöntem: Çalışmada, 44 oral skumöz hücreli karsinom ve 15 normal epitel immünhistokimyasal olarak MTA1 ve CD105 ile boyanmıştır.

Bulgular: Skuamoz hücreli karsinomlarda MTA 1 ekspresyonu %97,7 iken kontrol grubunda bu oran %33,3 olup karsinomlarda belirgin olarak yüksek saptanmıştır. MTA1 ekspresyonunun oral skuamoz hücreli karsinomlarda ortalama yüzdesi 76,88±%25,33 olup, kontrol grubundan belirgin olarak yüksektir (22,81±10,83). Sonuçlarımız lenf nodu metastazı, tümör boyutu ve evre ile MTA1 ekspresyonu arasında ilişkiyi desteklemiştir. MTA1 protein ekspresyonu ve mikrodamar dansitesi ilişkisi araştırıldığında yüksek mikrodamar dansitesinin MTA1 overekspresyonu gösteren tümörlerde, overekspresyon göstermeyen tümörlere göre daha sık olduğu saptanmıştır.

Sonuç: Çalışma, oral skuamöz hücreli karsinomlarda yüksek MTA1 protein ekspresyonunun görüldüğünü ve bu ekspresyonun tümör progresyonu ve artmış tümör anjiyogenezi ile yakın ilişkisini göstermiştir. Bulgular MTA1 proteinin tümörün progresiv fenotipinin saptanmasında kullanılabileceğini, kötü prognozu belirleyen prognostik bir belirteç olarak klinik potansiyeli olabileceğini göstermektedir ve ayrıca oral skuamöz hücreli karsinom hastalarında antianjiyogenezise yönelik hedef tedavilerinde kullanılabilme potansiyeline sahip olabileceğini düşündürmektedir.

Anahtar Sözcükler: MTA-1 protein, Skuamöz hücreli karsinom, İmmünohistokimya, Metastaz, Baş boyun tümörleri

(Turk Patoloji Derg 2015, 31:9-15)

Received : 01.04.2014 **Accepted :** 08.07.2014

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INTRODUCTION

Oral cancer is the eleventh most common cancer in the world, and squamous cell carcinoma (SCC) constitutes approximately 94% of all oral malignancies. The overall 5-year survival rate for intra oral carcinoma ranges from 27% to 68% and a great majority of deaths occur within the first 5 years (1). Equivocal results are shown for various molecular markers associated with carcinoma, and for determining patient prognosis. However, considerable differences in survival exist among patients with the same pathologic stage, so it is not sufficient to accurately predict a patient's prognosis on the basis of the current staging system alone (2,3). Therefore, it is necessary to find novel biomarkers that could be used as predictors so that the conventional staging system risk stratification can be improved (4). These biomarkers can help us to find patients who will benefit from adjuvant therapy with poor prognosis after surgery (5).

Metastasis is the result of complicated events including factors such as those important for the separation of neoplastic cells from the initial tumor, penetration into the blood and lymphatic, arrest at remote sites by adhesion to endothelial cells, extravasation, induction of angiogenesis, evasion of host antitumor responses, and growth at metastasis sites (6). As molecular biology has improved, novel molecules involved in carcinogenesis and tumor progression have been discovered. Metastasis-associated genes (MTA) are a recently found group of tumor progression-related genes with three different members: MTA1, MTA2 and MTA3 (7).

Among them, metastasis-associated protein 1 (MTA1) is a component of the nucleosome remodeling and histone deacetylation (NURD) complex, and is involved in remodeling of adenosine triphosphate-dependent chromatin and function of histone deacetylase (8). The MTA1 protein functions in conjunction with other components of NURD to mediate transcriptional repression as it facilitates the association of repressor molecules with the chromatin (9,10). Few studies have shown that MTA1 has an effect on invasiveness of oral squamous cell carcinoma (OSCC), although cancer progression and metastatic state are thought to be affected by the great invasive potential of cancer cells (11).

Tumor angiogenesis occurs in the early stage during cancer pathogenesis and is basically required for carcinogenesis, progression, and metastasis of malignant tumors (12,13). Micro vascular density (MVD) is a good predictor of angiogenesis. Since 1991, many markers have been introduced to stain the vessels. However, none of them can distinguish between neovasculature and preexisting ones except CD105 (14). CD105, also known as endoglin, is a good marker for measuring MVD (15,16). It is a 180KDa homotypedipolymer glycoprotein in the endothelial cell membrane that modulates responses to TGFβ (14). Its gene is located on chromosome 9q34 (17).

Recent investigations have found that in different tumors, MTA1 protein significantly correlates with tumor angiogenesis, suggesting MTA1 may be a possible angiogenesis-promoting molecule in malignant tumors (4,14,15,16,17). Accordingly, the present study aimed to determine the role of MTA1 protein in the biologic behavior of oral SCC and its relation with tumor angiogenesis.

MATERIALS and METHOD

In this cross-sectional study, the specimen from 44 patients with OSCC (29 males and 15 females) with the mean age of 54.47 (range 35-81) from the archives of Khalili Hospital between 2008 and 2012 were studied. The control group consisted of 15 cases of normal oral epithelium.

Immunohistochemical (IHC) staining and analysis: First, H&E slides of available blocks were reviewed and then cases with definite diagnosis and adequate cellular tissue were selected for immunohistochemical staining (IHC). IHC staining was performed using the Envision Labeled Peroxidase System (DAKO, Carpentaria, CA, USA). All the samples were fixed at 10% buffered formalin and were embedded in paraffin. Sections with 4μ thickness were prepared, deparaffinized in xylene, rehydrated in graded alcohol and were washed with distilled water. Antigen retrieval for MTA1 and CD105 was performed using DAKO estimation, target retrieval solution with PH = 9, for 20 minutes. Internal peroxidase activity was inhibited by 3% H2O2.

Tissue sections were then incubated for 30 minutes with the anti-MTA1 monoclonal antibody (mouse, Abcam Corporation, ab64214, UK) and anti-CD105 monoclonal antibody (mouse, novocastra Corporation, NCL_CD105, Germany) at 1/10 dilution. Brown cytoplasmic staining for CD105 and both cytoplasmic and nuclear staining for MTA1 was considered as positive. Omission of the primary antibody was employed as negative control, while liver tissue was used as positive control for CD105 and an esophageal cancer tissue known to overexpress MTA1 protein was used as positive control for MTA1 protein staining.

Intratumoral micro vessel density was quantified according to a recent consensus statement (18). Briefly, in an optical

microscope, hotspot areas for CD105 expression with discrete blood vessels were initially identified by scanning the entire tumor at low power (x40). The number of CD105 highlighted vessels in 10 of these areas was then counted with high-power magnification (x400).

For MTA1 protein assessment, immunoreactivity was evaluated using a semiquantitative scoring system for both staining intensity (**0,** negative staining; **1,** weak staining; **2,** moderate staining; **3,** intense staining) and percentage of positively stained cancer cells (**0;**0-5%; **1;**6-25%; **2;**26-50%; **3;**51-75%; **4;** ≥76%). The final staining score was the sum of the scores of staining intensity and percentage of positive cells, and was further graded as follows: (0), 0-1; (1), 2-3; (2), 4-5; (3), 6-7. Tumors with the final staining score ≥ 4 were defined as overexpressing MTA1 protein, a system that had been validated in previous studies (19).

Statistical analysis: Student's t test, the Mann-Whitney test, chi_square test, Spearman's correlation coefficient test and Pearson's correlation coefficient test were used to compare the results between the two groups and the relation with clinic-pathologic features such as age, sex, tumor size, histopathological grade, lymph node metastasis and tumor stage. We used the SPSS15 software to statistically analyze the data. A P-value ≤ 0.05 was considered significant in all the statistical analyses.

RESULTS

Expression of MTA1 in oral cancer: In the present study, MTA1 was expressed in both the cytoplasm and nucleus of the tumor cells; however, in control cases, its expression was only cytoplasmic (Figure 1-3). Frequency of MTA1 expression in OSCCs was recorded as 97.7%, which was significantly higher than that of the control group (33.3%) (p<0.001). Mean percentage of MTA1 expression in OSCCs was 76.88 ± 25.33 and was significantly higher than that of the control group (22.81 ±10. 83) (p<0.001).

Our data showed a positive correlation between MTA1 expression and stage (r= 0.6, p<0. 001) (Table I). MTA1 expression was significantly higher in node positive patients (Median: 2) than node negative cases (Median: 0), (p<0.001). MTA1 expression was not related to tumor size and grade (p>0.05).

The mean CD105-MVD value was significantly higher in tumoral tissue (20.02±8.03) when compared to normal tissues (8.67±1.75) (p<0.001). CD105 MVD in OSCC was associated with lymph node status (p=0. 005) and clinical stage (p<0. 001), but it was not related to age, sex, tumor size and grade (p>0.05).

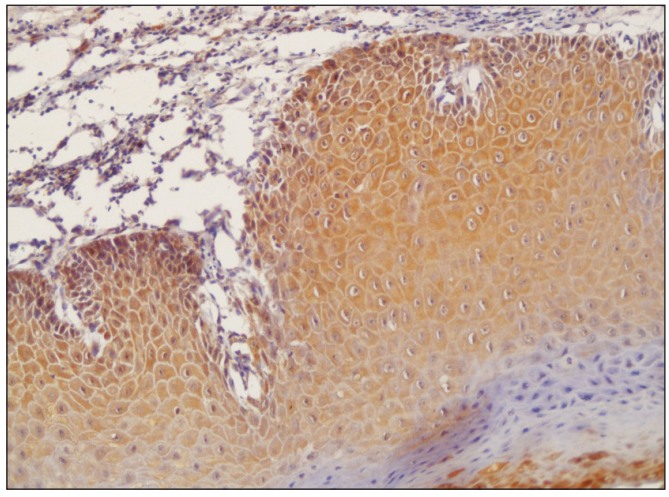

Figure 1: Cytoplasmic MTA-1 expression in normal oral mucosa (MTA-1; x200).

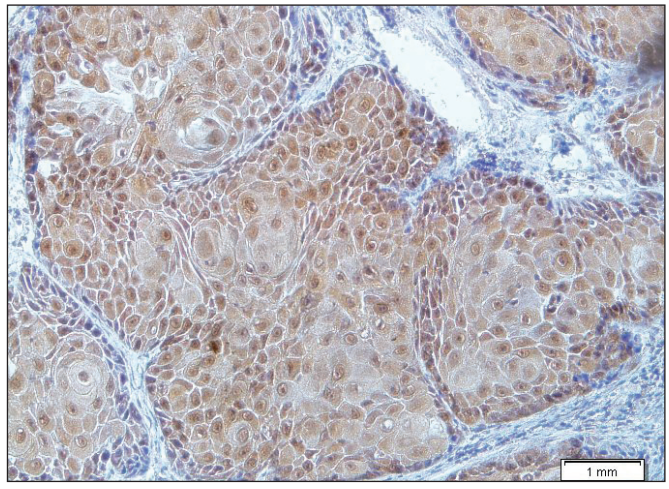

Figure 2: Intense cytoplasmic MTA-1 expression in oral squamous cell carcinoma (MTA-1; x200).

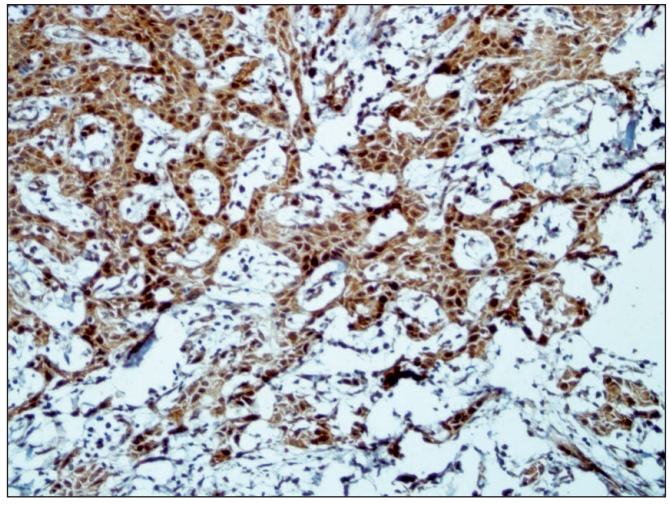

Figure 3: Nuclear and cytoplasmic MTA-1 expression in oral squamous cell carcinoma (MTA-1; x200).

Table I: Correlation of clinicopathological data with MTA1[1] expression and MVD[2] of the patients included in this study

	Frequency (n) (%)	Intratumoral MVD	p value	Final MTA1 Score (-,+) (%)	(++,+++) (%)	p value
Sex						
Male	29 (66.7)	15.11±5.5	p= 0.9	14 (48.3)	15 (51.7)	p = 0.8
Female	15 (33.3)	15.64±4.61		7 (46.7)	8 (53.3)	
Tumor size						
T1	14 (31.8)	13.62±3.57		6 (42.9)	8 (57.1)	
T2	21 (47.7)	15.63±5.62	P= 0.1	13 (61.9)	8 (38.1)	p= 0.3
T3	7 (15.9)	17.13±6.64		2 (28.6)	5 (71.4)	
T4	2 (4.6)	15.50±0.70		0 (0.0)	2 (100)	
Lymph node involvement						
N0	21 (47.7)	13.19±2.96	p= 0.005	19 (90.5)	2 (9.5)	p < 0.001
N1	23 (52.3)	18.40±5.85		2 (8.7)	21 (91.3)	
Grade						
G1	28 (63.7)	16.67±5.89		13 (46.4)	15 (53.6)	
G2	12 (27.2)	12.75±2.05	p=0.08	6 (50)	6 (50)	p=0.5
G3	4 (9.1)	13.00±1.00		2 (50)	2 (50)	
Stage						
I	9 (20.5)	12.22±1.48		8 (88.9)	1 (11.1)	
II	10 (22.7)	13.60±4.00	p<0.001	10 (100)	0 (0.0)	p < 0.001
III	14 (31.8)	16.21±5.13		2 (14.3)	12 (85.7)	
IV	11 (25)	18.78±6.68		1 (9.1)	10 (90.9)	

MTA: Metastasis-associated protein-1, **MVD:** Micro vessel density

*Correlation of MTA1 protein with MVD***:** Evaluation of the correlation between MTA1 protein expression and MVD showed that high MVD was detected more frequently in tumors with MTA1 overexpression than in those without overexpression (Figure 4,5) (r=0. 5, p<0. 001).

DISCUSSION

Oral squamous cell carcinoma (OSCC) forms nearly 3% of all malignancies in the United States and about 28900 new cases of oral cancer are noticed yearly, resulting in 7400 deaths (20). Prognosis of patients with OSCC is primarily determined by the stage of disease at the time of diagnosis. However, the staging system is not sufficient for the prediction of prognosis (21,22). Thus, to optimize treatment for oral cancer patients, new biomarkers may be employed as an adjunct to the staging system that could be used as a possible therapeutic target or a prognostic predictor (23).

Our study proved that the CD105-MVD value was significantly higher in OSCCs than normal tissue. It was in line with previous studies (24-27) and verified that CD105 is expressed more in tumoral tissues and may have a major role in tumor development. We also observed a positive relation between CD105 expression and lymph node metastasis. This finding is compatible with previous investigations (28-32) and suggests that the marker can be helpful in predicting the possibility of metastasis.

MTA1, the basic member of the MTA family was primarily recognized via differential screening of the cDNA Library from rat metastatic breast tumors as an upregulated gene (33-35). MTA1 upregulation was seen in various human cancers and shown to be involved in tumorigenesis, tumor invasion, and metastasis (36,37). So far, there has only been one clinical study of MTA1 expression in OSCCs; it has reported that MTA1 expression in control tissues was significantly lower than carcinomas, and showed MTA1 protein production was strongly associated with cancer cell invasion, and there was clinically a correlation between lymph node metastasis and MTA1 protein production. The

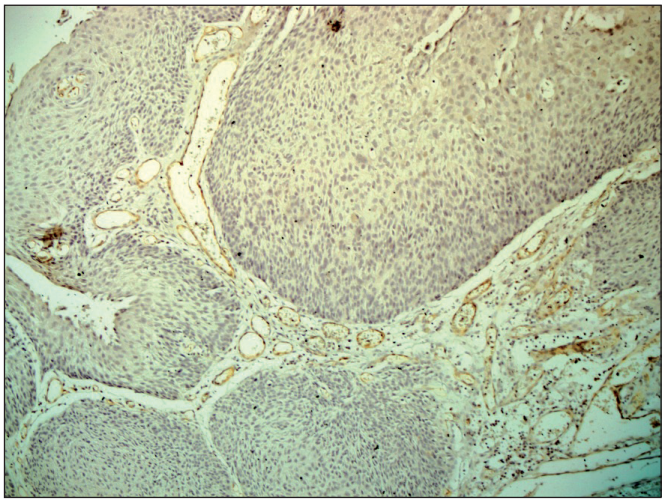

Figure 4: High CD105-MVD in oral squamous cell carcinoma (CD105; x200).

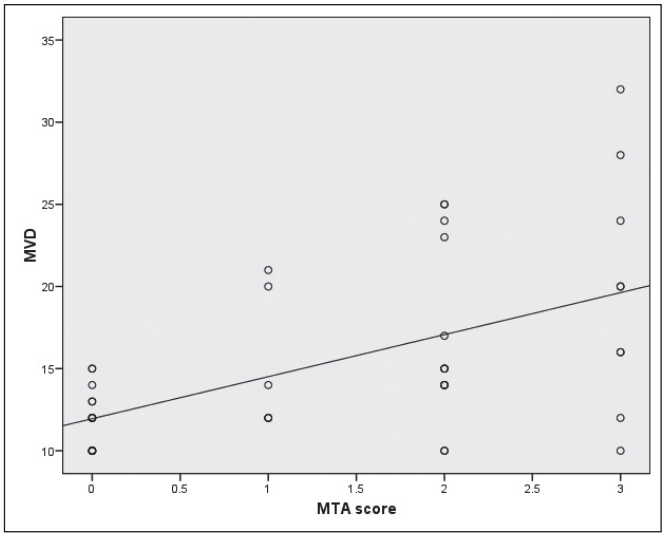

Figure 5: Correlation between MTA score and MVD (r=0.5, p<0.001, n=44).

authors stated that MTA1 overexpression in OSCC may lead to increased invasive ability and lymph node metastasis (11).

In the present study, we found a relationship between MTA1 expression and clinicopathological factors such as metastasis to lymph node and stage. The obtained result indicates that MTA1 might play a role in tumor progression and is consistent with other studies (4,11,14). The mechanism by which MTA1 protein contributes to the progressive potential of OSCC has not been investigated; however, evidence has shown that MTA1 protein is significantly correlated with tumor angiogenesis, and MTA1 protein contributes to angiogenesis through regulating hypoxia-inducible factor-1α (HIF-1α), suggesting that MTA1 may be a possible angiogenesis-promoting molecule in malignant tumors (16,17).

Shu_Hai Li et al. reported that overexpression of the MTA1 protein is common in esophageal SCC (ESCC), and is closely related to tumor progression, increased tumor angiogenesis, and poor survival. These results reveal that MTA1 protein can be a useful indicator of progressive phenotype, a promising prognostic predictor to identify patients with poor prognosis, and a potential novel therapeutic target of antiangiogenesis for patients with ESCC (4).

In another study, Shu-hai Li et al. found that MTA1 protein overexpression was common in early-stage non small cell lung cancer and was correlated with tumor angiogenesis and relapse. Moreover, MTA1 protein overexpression could affect patient survival and was an independent prognostic factor for disease-free, overall, and disease specific survival (18).

However, to the best of the authors' knowledge, the present study is the first clinical report to investigate the role of MTA1 protein in relation to angiogenesis in OSCCs. The findings of our study showed that MTA1 protein overexpression was common in OSCC tissues and significantly associated with increased angiogenic activity suggesting that MTA1 protein might promote tumor progression and development of aggressive phenotypes by the induction of tumor angiogenesis but further studies is recommended to investigate the relationship of these markers with the more accurate method for proving this finding. The mechanism by which MTA1 protein contributes to the angiogenic potential of cancer cells and formation of new tumor microvessels is unclear and still needs to be further investigated.

Mazudmar et al. reported in general, the MTA proteins contain basic nuclear localization signals and are predominantly localized in the nucleus. Analysis of various mouse tissues suggested that variable, but easily detectable, levels of MTA1 protein are present in multiple organ systems including lung, liver, kidney, heart and testes, thus suggesting a physiologic function of MTA1 in normal cellular functions (38).

Manavathi and Kumar have documented the predominantly nuclear localization of MTA1 in various cancerous tissues, including ovarian, lung, gastric and colorectal cancers (39). However, Moon et al. showed in human hepatocarcinoma (HCC) cells, MTA1 localizes to both the nucleus and cytoplasmic compartments (19). Li et al. also reported both cytoplasmic and nuclear expression of MTA1 in NSCLC

(18). In our study, we have seen MTA1 expression in both the nucleus and cytoplasm, which was consistent with the results obtained by Moon et al. (19) and Li et al. (18).

The expression of MTA family members is not restricted to cancer cells, but one of the most important issues in MTA family research is that little information about the physiological functions and underlying mechanisms in normal cells is available. According to the recent researches and the findings that MTA1 is a master co-regulatory molecule, it is quite possible that MTA1 deregulation may interfere in other human diseases than cancer.

Because MTA family members were found in distinct subcellular compartments, it is important to understand the underlying biochemical basis of differential sub cellular localization and whether it is further affected by extracellular signals or not. Furthermore, to fully appreciate the master regulatory function of MTA1 (or other MTA family members), it is of paramount importance to understand the nature of the biochemical switch responsible for corepressor versus coactivator activity of MTA1. In addition to further researching the cellular functions of MTA1, there is a clear need to intensify research connecting various domains of MTA1 (or other MTA family members) with specific cellular functions.

In conclusion; In this study, high expression of the MTA1 protein was seen in OSCC, and was closely associated with tumor progression and increased tumor angiogenesis. These findings may indicate that MTA1 protein has clinical potentials as a useful indicator of progressive phenotype, a promising prognostic predictor to identify patients with poor prognosis and may be a potential novel therapeutic target of anti-angiogenesis for patients with OSCC, but to confirm this relationship in the context of MTA1 expression leading to enhanced angiogenesis, further experimentation using OSCC cell lines overexpressing or silencing MTA1 and examining the incidence of angiogenesis should be performed.

Acknowledgements: This manuscript is based on the post-graduate thesis of Dr. Fereshteh Kamali. The authors are also grateful to Dr. M. Vossoughi from Dental Research Development Center of the Dental School, for the statistical analysis.

Funding Source: This research program was supported by Vice-Chancellor of Shiraz University of Medical Sciences (Grant# 91-01-03-5257).

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