

The Occurrence of Activated Leukocyte Cell Adhesion Molecule (ALCAM) and Its Predictive Factors in Patients with Oral Squamous Cell Carcinoma

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Abstract

Objectives: To determine the occurrence of Activated Leukocyte Cell Adhesion Molecule (ALCAM) and its predictive factors in patients with oral squamous cell carcinoma (OSCC). **Methods:** This cross sectional study was concocted on 102 patients with OSCC referred to Imam Khomeini Hospital of Tehran during 1997-2015. The data collection tool a checklist consisted of demographic and pathologic (lymph node involvement, differentiation, tumor size and tumor location) characteristics which extracted from patients' medical records. To evaluate ALCAM, a new sample of tumor tissue was prepared from archive. Finally, the multivariable logistic regression model was used to determine the predictive factors of ALCAM by STATA14. **Results:** the number (%) of men and women were 70 (68.6) and 32 (31.4%), respectively. The mean age (S.D) of participants was 61.7 (15.6) years. Of the total samples, 32 (38.2), 19 (18.6), 36 (35.3) and 8 (7.8%) samples were related to the tongue, oral mucosa, skin and lips, respectively. More than half of the tumors had good differentiation and lymph node involvement and 74.5% were ≥ 20 mm. Also, 79.41% of the samples were positive for the overall incidence of ALCAM. The most important predictors of the overall incidence of ALCAM were tumor size (OR: 3.46, 95% CI: 1.71 - 7.01) and tumor location (OR: 3, 95% CI: 1.03 - 8.72). Similarly, for incidence of cytoplasmic ALCAM were age (OR: 2.56, 95% CI: 1.38 - 4.76) and location of the tumor (OR: 3.23, 95% CI: 1.08 - 9.64). However, the only predictor of membranous ALCAM incidence was lymph node involvement (OR: 0.36, 95% CI: 0.19 - 0.66). **Conclusion:** The results of our study suggest preliminary evidence for the potential clinical application of ALCAM as a prognostic biomarker for OSCC which may be the basis for future clinical application, however further studies are recommended.

Keywords: Activated Leukocyte Cell Adhesion Molecule (ALCAM)- oral squamous cell carcinoma (OSCC)

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Introduction

Cancer is the second most common cause of death in most developing and developed countries. Among cancers, head and neck cancers are one of the leading causes of morbidity and the sixth leading cause of cancer deaths (Bray et al., 2018; Mirzaei et al., 2016). The anatomical areas involved in head and neck cancers are mostly the oral cavity, nose, nasopharynx, oropharynx, hypopharynx, larynx, thyroid and salivary glands (Krishnatreya et al., 2014; Narayan et al., 2022). More than 650,000 new cases of head and neck cancers (4.9% of incidence of all cancers) are diagnosed each year, and about 330,000 deaths (4.6% of all deaths from cancers) from these

cancers occur (Bray et al., 2018; Kiani et al., 2020). In general, head and neck cancers make up 2-4% of all malignancies. In the United States and Europe, 3% and 4% of all malignancies diagnosed are related to the head and neck, respectively, of which oral and laryngeal cancers are the most common (Bray et al., 2018; Gatta et al., 2015; Liu et al., 2021). In Iran, due to the incompleteness of the comprehensive cancer registration system, there are no accurate statistics on the incidence of head and neck cancers, however, according to a report by the Iranian Ministry of Health in 2014, head and neck cancers were among the top 10 most common cancers of men in many provinces (Roshandel et al., 2019). This type of cancers are usually more common in men than women, however,

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the sex ratio varies according to the geographical area and anatomical location of the lesion (Braakhuis et al., 2014). The most important risk factors for head and neck cancers are smoking, poor oral hygiene, poor nutrition, alcohol consumption and human papillomavirus infection (Karlighkoti et al., 2014; Keyghobadi et al., 2015).

Among head and neck cancers, oral squamous cell carcinoma (OSCC) is a subset of squamous cell carcinoma (SCC) in the head and neck, which is the eighth most common cancer (Elaiwy et al., 2020). The prognosis of patients with OSCC depends on the clinical stage of the disease at the time of diagnosis, which is determined by tumor size, lymph node status, distant metastases (Arun et al., 2021). Despite advances in treatment and extensive studies on the disease, survival rates have not improved significantly over the past few decades. Also, some studies have shown that despite the diagnosis of the tumor in the early stages and timely treatment, acceptable therapeutic results are not achieved. Therefore, the information obtained from conventional staging systems alone may not be sufficient to predict the biological characteristics and behavior of the tumor (Shokouhi et al., 2021)(Shokouhi et al., 2021)(Shokouhi et al., 2021).

Today, many studies have focused on the extensive and accurate study of various histopathological markers and molecular manifestations of malignant tumors such as OSCC, hopefully, those can be used by researchers to develop more effective combination stage methods that may have better predictive power for tumor behavior and, consequently, higher clinical value in determining treatment plans (AMINNEJAD et al., 2020; Daraghma et al., 2021). One of these effective molecules is the large family of adhesive molecules, which can be divided into several subgroups, including immunoglobulins, cadherins, selectins, integrins, and mucins. One of the members of the family of immunoglobulins is Activated leukocyte cell adhesion molecule (ALCAM / CD166), which is a glycoprotein and has two membrane and cytoplasmic components. The ALCAM molecule is physiologically involved in cell-to-cell attachment, cell-to-matrix, signal transduction from the matrix, migration of monocytes from the vascular wall, and in processes of embryogenesis, neurogenesis, angiogenesis, hematopoiesis and immune system responses. It is also known as the mesenchymal stem cell index (Asgharpour et al., 2020; Ronco et al., 2020; Yang et al., 2021). Considering the differences between OSCC and other SCCs in terms of pathogenesis and prognosis, identification of any more molecular and pathological indicators such as ALCAM, in addition to clarifying the etiology and pathogenesis of the lesion, it may open the door to access to new therapies. On the other hand, due to the different results obtained regarding the incidence and role of ALCAM in many of carcinomas and its paradoxical effect on the prognosis of the disease and also the limited studies conducted in this field in Iran, the aim of this research was to determine the occurrence of ALCAM and its predictive factors in patients with OSCC referred to Imam Khomeini Hospital of Tehran during 1997-2015.

Materials and Methods

Study Design and Subjects

This cross-sectional study was performed to evaluate the occurrence of ALCAM and its predictive factors in patients with OSCC referred to Imam Khomeini Hospital of Tehran during 1997-2015. Considering that all 102 patients with head and neck cancer were studied during this period, the study was conducted by census. Inclusion criteria consisted of patients with pathology diagnosis of squamous cell carcinoma of the mouth, skin, head and neck, no history of preoperative chemotherapy or radiotherapy and history of neck dissection surgery to examine the lymph nodes. Exclusion criteria also included recurrent tumors, the presence of lesions or concomitant tumors in other areas, small and insufficient samples for slide preparation, and medical records with incomplete information.

Data Collection

The data collection tool a standard checklist consisted of demographic and pathologic characteristics which extracted from patients' medical records of cancer Institute of Imam Khomeini Hospital. These variables included age, sex, lymph node involvement, differentiation, tumor size and tumor location. To evaluate ALCAM, a new sample of tumor tissue from the Cancer Institute's archive was prepared. These samples were then made available to the technician in the form of prepared paraffin blocks for immunohistochemical and histopathological examination, and immunohistochemistry (IHC) staining was performed according to the instructions of ALCAM (Novacastra) antibody manufacturer by high temperature antigen unmasking technique.

After preparing the slides, the overall incidence of ALCAM, membranous and cytoplasmic ALCAM were investigated using Olympus CX31-P polarized light microscope. To classify the samples into two positive or negative groups in terms of ALCAM index, the severity and degree of cytoplasmic and membrane ALCAM incidence in the samples were considered. A score of 0-3 (Not at all = 0, mild = 1, moderate = 2 and severe = 3) was considered for the severity of incidence and a score of 0-4 (0 = ≤ 10%, 1 = 11-30%, 2 = 31 - 50%, 3 = 51-70% and 4 = >70%) for the degree of incidence. For each sample, by summing the severity and degree of incidence scores, a total incidence score was calculated (0 -7 score), then cytoplasmic and membrane indices ≥ 2 were considered as positive (Sawhney et al., 2009). The location of the tumor was classified based on whether the main site of the lesion was inside the mouth (tongue or oral mucosa) or the skin of the head, neck, and lips. Tumor classification in terms of size was considered 20 mm according to the relevant references (<20 mm= T1 - ≥ 20 MM= T2 - T4). Samples were classified into three groups according to pathological criteria: good differentiated (W), moderate differentiation (M) and poor differentiation (P). In terms of lymph node involvement, they were divided into two groups: lymph node involvement (N1) and non-involvement (N0). Finally, by microscopic examination of the slides of the samples, the status of each of them in terms of ALCAM

incidence was determined.

Statistical analysis

Data were analyzed using STATA 14.0. For descriptive analyses, the mean, standard deviation (SD), and number (%) were used. Then, univariate and multivariate logistic regression model were used to determine the most important predictors of the overall incidence of ALCAM, membranous and cytoplasmic ALCAM. Finally, adjusted odds ratio (OR) with 95% confidence interval (CI) were estimated and P-value <0.05 was considered as a significant level.

Ethics considerations

This study was performed according to the principles expressed in the Declaration of Helsinki and was approved by the Deputy of Research and Ethics Committee of Tehran University of Medical Sciences (Iran).

Results

In the present study, 102 patients with OSCC referred to Imam Khomeini Hospital of Tehran for tumor surgery were studied. The number (%) of male and female participants were 68.6 and 31.4%, respectively. The mean age (S.D) of participants was 61.7 (15.6) years. The youngest and oldest patients were 26 and 94 years old, respectively. Only 12 (11.8%) patients were less than 40 years old. Of the total samples, 32 (38.2), 19 (18.6), 36 (35.3) and 8 (7.8%) samples were related to the tongue, oral mucosa, skin and lips, respectively. Also, the mean (S.D) size of the studied tumors was 36.1 (21.5) mm and the minimum and maximum sizes were 6 and 90 mm, respectively.

Table 1 shows demographic and pathological characteristics of patients according to tumor location. As can be seen, more than half of the tumors (58.8%) had good differentiation. Most tumors were 20 mm or larger in size (74.5%). Approximately half of the cases involved lymph node involvement. Also, lymph node involvement in oral mucosal tumors (63.2%) was more common than tongue (53.8%), skin and lips (45.5%). In

addition, all of the tumor lesions studied were significantly more common in men than women. Similarly, in the age group of 40 years and older, they were significantly higher than 40 years (Table 1).

Also, 79.41 (81), 77.5 (79) and 34.5% (35) of the samples were positive for the overall incidence of ALCAM, membranous and cytoplasmic ALCAM; respectively. Table 2 shows demographic and pathological characteristics of patients according to type of ALCAM. As is clear, cytoplasmic ALCAM is more common in the skin and lips (49.4%) than in the mouth (15.2%) and tongue (35.4%). Also, 80% of male samples and 87.1% of female samples were positive for the overall incidence of ALCAM. In addition, 78.6% of men and 75% of women were positive for cytoplasmic ALCAM. In the age group < 40 and ≥40 years, 66.7 and 88.1% of the samples were positive for the overall incidence of ALCAM, respectively. The results also indicated that 83.7% of patients without lymph node involvement and 75.5% with lymph node involvement were positive for the overall incidence of ALCAM. Similarly, 80% of the samples belonging to individuals with a good degree of tumor differentiation and 78.6% with a moderate and poor degree of differentiation were positive for the overall incidence. Finally, samples with tumor size <20 and ≥20 mm, 65.4 and 84.2% of the samples were positive for the overall incidence of ALCAM, respectively (Table 2).

Table 3 shows adjusted OR and 95% CI derived from multivariate logistic regression model for the effective factors on the overall occurrence of ALCAM, membranous and cytoplasmic ALCAM. As can be seen, after adjusting for the confounding variables, there was a statistically significant relationship between the overall occurrence of ALCAM with tumor size (OR: 3.46, 95% CI: 1.71 – 7.01) and tumor location (OR: 3, 95% CI: 1.03 – 8.72). For example, the odds of the overall occurrence of ALCAM in people with tumors ≥20 mm is 3.46 times higher than people with tumors < 20 mm (P-Value<0.05). The results also showed that the age (OR: 2.56, 95% CI: 1.38 – 4.76) and location of the tumor (OR: 3.23, 95% CI: 1.08 – 9.64) are the most important predictors of cytoplasmic ALCAM. However, the only predictor variable for membranous

Table 1. Demographic and Pathological Characteristics of Patients According to Tumor Location

Variable		Tumor location			
		Tongue (%)	Oral mucosa (%)	Skin and lips (%)	Total (%)
Sex	Female	17 (43.6)	6 (31.6)	9 (20.5)	32 (31.4)
	Male	22 (56.4)	13 (68.4)	35 (79.5)	70 (68.6)
Age	<40 years	7 (17.9)	3 (15.8)	2 (4.5)	12 (11.8)
	≥40 years	32 (82.1)	16 (84.2)	42 (95.5)	90 (88.2)
lymph node involvement	No	18 (46.2)	7 (36.8)	24 (54.5)	49 (48)
	Yes	21 (53.8)	12 (63.2)	20 (45.5)	53 (52)
Differentiation	Good	21 (53.8)	12 (63.2)	27 (61.4)	60 (58.8)
	Weak	14 (35.9)	4 (21.1)	13 (29.5)	31 (30.4)
Tumor size	Moderate	4 (10.3)	3 (15.8)	4 (9.1)	11 (10.8)
	<20 mm	15 (38.5)	4 (21.1)	7 (15.9)	26 (25.5)
	≥20 mm	24 (61.5)	15 (78.9)	37 (84.1)	74 (74.5)

Table 2. Demographic and Pathological Characteristics of Patients According to type of ALCAM

	Variable	Overall ALCAM		Cytoplasm ALCAM		Membranous ALCAM	
		Negative	Positive	Negative	Positive	Negative	Positive
Sex	Female	7 (21.9)	25 (78.1)	8 (25.0)	24 (75.0)	23 (71.9)	9 (28.1)
	Male	14 (20.0)	56 (80.0)	15 (21.4)	55 (78.6)	44 (62.9)	26 (37.1)
Age	<40 years	4 (33.3)	8 (66.7)	5 (41.7)	7 (58.3)	6 (50.0)	6 (50.0)
	≥40 years	17 (18.9)	73 (88.1)	18 (20.0)	72 (90.0)	61 (67.8)	29 (32.2)
lymph node involvement	No	8 (16.3)	41 (83.7)	10 (20.4)	39 (79.6)	28 (57.1)	21 (42.9)
	Yes	13 (24.5)	40 (75.5)	13 (24.5)	40 (75.5)	39 (73.6)	14 (26.4)
Differentiation	Good	12 (20.0)	48 (80.0)	14 (23.3)	46 (76.7)	39 (65.0)	21 (35.0)
	Weak + moderate	9 (21.4)	33 (78.6)	9 (21.4)	33 (78.6)	28 (66.7)	14 (33.3)
Tumor size	<20 mm	9 (34.6)	71 (65.4)	9 (34.6)	17 (65.4)	19 (73.1)	7 (26.9)
	≥20 mm	12 (15.8)	64 (84.2)	14 (18.4)	62 (81.6)	48 (63.2)	28 (36.8)
	Tongue	10 (47.6)	29 (35.8)	11 (47.8)	28 (35.4)	22 (32.8)	17 (48.6)
Tumor location	Oral mucosa	6 (28.6)	13 (16.0)	7 (30.4)	12 (15.2)	14 (20.9)	5 (14.3)
	Skin and lips	5 (23.8)	39 (48.1)	5 (21.7)	39 (49.4)	31 (46.3)	13 (37.1)

ALCAM after adjusting for confounding variables was lymph node involvement (OR: 0.36, 95% CI: 0.19 – 0.66) (P-Value<0.05) (Table 3).

Discussion

Recently, various studies have reported ALCAM / CD166 expression in various malignancies such as cancers of the head and neck, prostate, breast, lung and esophagus. These studies have shown the association of ALCAM with the prognosis of several carcinomas and have discussed this indicator as a potential therapeutic target (Clauditz et al., 2014; Fujiwara et al., 2014; Ni et al., 2013). In this study, the relationship between the occurrence of ALCAM in mucosal and lingual tumors of patients with OSCC with the variables of the sex, age and anatomical location of the tumor, tumor size, degree of differentiation and lymph node involvement as prognosis-related indicators was examined. The results of this study showed that the number (%) of men and women were 70 (68.6) and 32 (31.4%), respectively. The mean

age (S.D) of participants was 61.7 (15.6) years. Of the total samples, 32 (38.2), 19 (18.6), 36 (35.3) and 8 (7.8%) samples were related to the tongue, oral mucosa, skin and lips, respectively. More than half of the tumors had good differentiation and lymph node involvement and 74.5% were ≥20 mm. Also, 79.41% of the samples were positive for the overall incidence of ALCAM. The most important predictors of the overall incidence of ALCAM were tumor size (OR: 3.46, 95% CI: 1.71 - 7.01) and tumor location (OR: 3, 95% CI: 1.03 - 8.72). Similarly, for incidence of cytoplasmic ALCAM were age (OR: 2.56, 95% CI: 1.38 - 4.76) and location of the tumor (OR: 3.23, 95% CI: 1.08 - 9.64). However, the only predictor of membranous ALCAM incidence was lymph node involvement (OR: 0.36, 95% CI: 0.19 - 0.66).

One of the important findings of this study was the relationship between the overall incidence of ALCAM and tumor size so that the odds of the overall incidence of ALCAM in people with tumors ≥20 mm is 3.46 times higher than people with tumors <20 mm. This finding was consistent with different studies conducted in this field

Table 3. The Effective Factors on the Overall Occurrence of ALCAM, Membranous and Cytoplasmic ALCAM by Multivariate Logistic Regression Model

	Variable	Adjusted OR *	P-Value	Adjusted OR**	P-Value	Adjusted OR***	P-Value
		(95% CI)		(95% CI)		(95% CI)	
Sex	Female	Reference	0.933	Reference	0.843	Reference	0.411
	Male	1.05 (0.50 – 2.42)		0.92 (0.44 – 1.89)		1.31 (0.67 – 2.59)	
Age	<40 years	Reference		Reference		Reference	
	≥40 years	1.72 (0.53 – 5.59)	0.412	2.56 (1.38 – 4.76)	0.003	0.36 (0.12 – 1.09)	0.07
lymph node involvement	No	Reference		Reference		Reference	
	Yes	0.53 (0.17 – 1.65)	0.354	0.74 (0.25 – 2.17)	0.645	0.36 (0.19 – 0.66)	0.001
Differentiation	Good	Reference		Reference		Reference	
	Weak + moderate	1.33 (0.47 – 3.73)	0.614	1.38 (0.5 – 3.83)	0.521	1.25 (0.51 – 1.04)	0.632
Tumor size	<20 mm	Reference		Reference		Reference	
	≥20 mm	3.46 (1.71 – 7.01)	0.001	2.01 (0.67 – 6.06)	0.237	1.98 (0.69 – 5.74)	0.214
Tumor location	Tongue and oral mucosa	Reference		Reference		Reference	
	Skin and lips	3 (1.03 – 8.72)	0.045	3.23 (1.08 – 9.64)	0.041	0.36 (0.19 – 0.66)	0.229

*, Overall ALCAM; **, cytoplasmic ALCAM; ***, membranous ALCAM

(Burandt et al., 2014; Lu et al., 2018; Sawhney et al., 2009; Tan et al., 2014; Verma et al., 2005). However, in some other studies, no significant relationship was observed between ALCAM incidence and tumor size (Davies et al., 2008; Mikaeili et al., 2022; Tachezy et al., 2012). The significant relationship between ALCAM expression and tumor size can be related to the role of ALCAM in its proliferative stages and anti-apoptotic properties as well as the increase of ALCAM-ALCAM junctions in larger cell islets. On the other hand, the role of ALCAM in angiogenesis should not be forgotten, angiogenesis is an important factor in advancing the size of malignant tumors, which is achieved by proliferation, differentiation and migration of endothelial cells (Darvishi et al., 2020; Narayan et al., 2022).

Our study showed a significant relationship between the incidence of membranous ALCAM and lymph node involvement, so that the incidence of membranous ALCAM was 64% lower in people who were positive for lymph node involvement, which was in line with similar studies conducted in the field (Darvishi et al., 2020; van den Brand et al., 2010). For example, a study by van den Brand et al., (2010) using immunohistochemistry on OSCC specimens and application of polyclonal antibodies against ALCAM extracellular regions showed that membranous ALCAM expression is significantly associated with lymph node involvement. Another study by Piao et al., (2012) in order to evaluate ALCAM and its relationship with pathological and clinical features of breast cancer in 150 women showed the high levels of membranous ALCAM expression may lead to decreased adhesion ability and metastasis. In contrast, high levels of cytoplasmic ALCAM expression enhance the invasive power of malignant cells and lead to further tumor development.

The results of the study on SCC of esophageal and colorectal cancers did not show a significant relationship between the incidence of ALCAM and the pathological tissue differentiation of the samples which our study also confirms this finding (Verma et al., 2005; Weichert et al., 2004). However, in other studies on endometrial carcinoma, OSCC, colorectal cancer, and breast carcinoma, the incidence of ALCAM has been associated with worse differentiation and, consequently, more malignant course of the tumor (Darvishi et al., 2020; Piao et al., 2012; Sawhney et al., 2009; Tachezy et al., 2012). In general, in all cancers, the cells must be attached to each other during malignant mass formation. The tumor can metastasize directly to surrounding structures or indirectly to distant tissues through proliferation. For metastasis, malignant cells must be able to leave the primary tumor and reach distant areas by connecting to blood and lymph vessels. For metastasis, malignant cells must be able to leave the primary tumor and reach distant areas by connecting to blood and lymph vessels. ALCAM play a role in these connections, both before, during, and after the invasion. Studies have shown that ALCAM is associated with increased metastatic strength and increased tumor thickness and ultimately worse patient prognosis, however there are discrepancies in the incidence and role of ALCAM in other carcinomas (Darvishi et al., 2020; Verma

et al., 2005; Zhang et al., 2020). Certainly more and more specialized studies can clarify the role of ALCAM in the prognosis and its relationship with different stages of tumor progression.

Limitation

In interpreting the results of the present study, the limitations of a retrospective cross-sectional study should be noted. These limitations include biases resulting from the use of data recorded in files and also the lack of accurate information, especially about the exact status of patients in terms of stage and metastasis. OSCC tumors include heterogeneous cell populations that simultaneously have different biological properties and varying degrees of differentiation. Therefore, to determine tumor prognosis, methods based on integrated and comprehensive cell evaluation should be used to provide more valuable information about tumor growth potential and behavior. This suggests the need for further research to understand the behavior and pathogenesis of this disease, especially at the molecular level (Aminnejad et al., 2020). Therefore, cohort studies are suggested in order to analyze the survival of patients or their therapeutic response, taking into account the ALCAM incidence along with other important molecular indicators in patients with OSCC.

In conclusion, the overall incidence of ALCAM in OSCC was high and size and tumor location were the most important predictors of overall ALCAM occurrence. The results of our study suggest preliminary evidence for the potential clinical application of ALCAM as a prognostic biomarker for OSCC which may be the basis for future clinical application, however further studies are recommended.

Author Contribution Statement

All authors contributed to the study. PM and OM designed and conducted the research. OM and AGH carried out the assays. MM and KM contributed to data collection and analysis, and prepared the manuscript. PM, MM, and AGH provided the samples. PM, AGH, MM, KM and OM prepared the manuscript. All authors read and approved the final manuscript.

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Ethics approval

This study was performed according to the principles expressed in the Declaration of Helsinki and was approved by the Deputy of Research and Ethics Committee of Tehran University of Medical Sciences (Iran).

Availability of data

The data that supported the findings of this study are available on request from the corresponding author, OM.

Conflict of Interests

The authors declare that they have no competing interests.

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