Original Article

Glucose transporter 1 expression in ameloblastoma and odontogenic keratocyst – A comparative immunohistochemical study

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Abstract

Introduction: Facilitative glucose transporters (GLUTs), which mediate glucose transport across the cell membrane, differ in their tissue distribution and affinity for glucose. GLUT1 is ubiquitously present and help in the basal uptake of glucose into the cells. Its expression is known to be elevated in conditions that induce hypoxia and by growth factors. GLUT1 is known to be increased in many malignant tumors to meet the metabolic requirements, but its role in odontogenic tumors is not known.

Objective: The objective of this study is to evaluate and compare the immunohistochemical expression of GLUT1 in ameloblastoma (AM) and odontogenic keratocyst (OKC).

Materials and Methodology: Thirty cases each of AM and OKCs were immunohistochemically stained using anti-GLUT1 antibody according to the standard protocol. Qualitative assessment of GLUT1 expression was done under the categories of distribution, intensity and localization of staining. Quantitative assessment was done using Image J software. The results were tabulated and statistically analyzed.

Results: GLUT1 positivity was observed in 25 (83.3%) cases of OKC and 26 (86.7%) of AM cases. The majority of cells in the suprabasal layer of OKC showed positivity, whereas the equal distribution of staining was observed in the central and peripheral cells of AM.

Conclusion: GLUT1 expression in these tumors is suggestive of an increased glucose uptake and probably increased utilization of energy, which may be correlated with their aggressive behavior.

Keywords: Ameloblastoma, glucose transporters 1, odontogenic keratocyst, odontogenic tumors, remmele score

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INTRODUCTION

Glucose is the major substrate for energy supply in mammalian cells and is a precursor for other macromolecules such as glycoproteins, triglycerides, glycogen and riboses. The transport of this essential hydrophilic glucose molecule across the hydrophobic plasma membrane is mediated by a group of membrane-associated carrier proteins called glucose transporters (GLUT1s). There are two types of GLUT, sodium-dependent GLUTs, and facilitative GLUTs, which are present in a tissue-specific pattern with substrate

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specificity and their expression depends on cellular demand. Among these GLUT1 is ubiquitously present in all tissues of the body and help in the basal uptake of glucose. These transporters catalyze the translocation of glucose down its concentration gradient across the membrane.[1-3] Studies related to GLUT1 in both physiological and pathological conditions revealed its role in cell proliferation and survival. Its expression can be induced by growth factors, oncogenes, local hypoxia and inflammation.[4] Its expression is known to be increased in benign and malignant lesions, which is essential for acquiring more glucose into cells, thereby help in supplying the energy necessary for tumor cell proliferation and also reflects adaptation to adverse conditions of tumor environment. It is considered as one of the important factors for the local aggressiveness, resistance to chemotherapy and radiotherapy, activation of matrix metalloproteases, tumor invasiveness and metastasis, especially in malignant tumors. Increased GLUT1 may play a role in inhibiting the mitochondrial apoptotic pathway that leads to increased cell survival. GLUT1 alone may not predict the aggressiveness of a lesion but instead, should be correlated with either basic markers or clinical and histological grading.[5-7]

Odontogenic tumors are lesions derived from epithelial and/or ectomesenchymal elements of the tooth forming apparatus. They comprise a heterogeneous group of lesions demonstrating diverse clinical and histopathological features ranging from hamartomatous proliferations to malignant neoplasms with varying metastatic capabilities.[8,9] Clinically, these lesions are usually asymptomatic, although they may cause jaw expansion, displacement of teeth, root resorption and bone loss. Ameloblastoma (AM) belongs to the category of odontogenic tumors that are derived from the odontogenic epithelium with mature fibrous stroma without odontogenic ectomesenchyme. The other lesion considered in this study was odontogenic keratocyst (OKC) which was regarded as benign odontogenic tumor in the WHO 2005 classification based on its aggressive growth, high recurrence rate, occurrence of a solid variant, and presence of PTCH mutation is now again renamed as OKC and placed under cysts category because of the lack of evidence to justify the neoplastic nature of this lesion.[10]

The present study was designed to evaluate the expression of GLUT1 in AM and OKC, which may provide further scope in understanding the metabolic role and bring new insights into the molecular nature of these lesions. The study was approved by the institutional review board, Vishnu Dental College IEC/IRB No: VDC/IEC/2014-14.

MATERIALS AND METHODOLOGY

The present study included neutral-buffered formalin fixed paraffin-embedded blocks of previously diagnosed cases of 30 AM and 30 OKC that were retrieved from the archives of the department of oral pathology, Vishnu Dental College. H&E-stained slides of all the cases were observed for confirmation of diagnosis. Immunohistochemical (IHC) staining procedure was done using the manufacturer standard protocol with the anti-GLUT1 primary antibody (Biocare CM408A). Moderately and poorly differentiated oral squamous cell carcinomas were taken as external positive control and red blood cells as internal positive controls. In scanner view, whole tissue section was evaluated by two observers on a visual monitor screen and was marked as positive if brown staining was seen in epithelial tumor cells and as negative if there is no staining in neoplastic epithelial cells but the internal control showed positive staining. The positive staining was further evaluated both qualitatively and quantitatively in the photomicrographs taken at ×40 in 10 random high-power fields. Quantitative analysis was done using Image J software (Antibody was bought from Biocare, Delhi, India). The protocol followed for the evaluation of immunostaining is summarized in Figure 1. The obtained results were statistically analyzed using SPSS software and $P < 0.05$ was taken as statistically significant.

RESULTS

Out of the 30 cases of AM included in the study, 17 solid/multicystic variant (follicular – 4, plexiform – 9, acanthomatous – 3 and granular cell – 1), 3 were desmoplastic variant and 10 were unicystic variant (luminal type – 5 and mural type – 5). Due to the presence of an unequal number of cases within subgroups of AM, all the variants have been considered as a single entity.

Analysis of immunostaining

Odontogenic keratocyst

GLUT1 expression was observed in 25 out of 30 cases of OKC [Table 1]. The majority of cases in OKC showed predominant diffuse staining pattern with few cases showing focal pattern. The majority of cells in the supra basal layer showed positivity when compared to basal layer. The intensity of staining in each case varied from mild to intense, mild staining was predominantly seen in the basal layer, whereas moderate to intense staining was seen in the supra basal layer. None of the cells in the superficial layer showed immunopositivity [Figure 2a]. Focal clusters of cells in the supra basal layer of 14 cases showed intense positivity. Intense staining was also

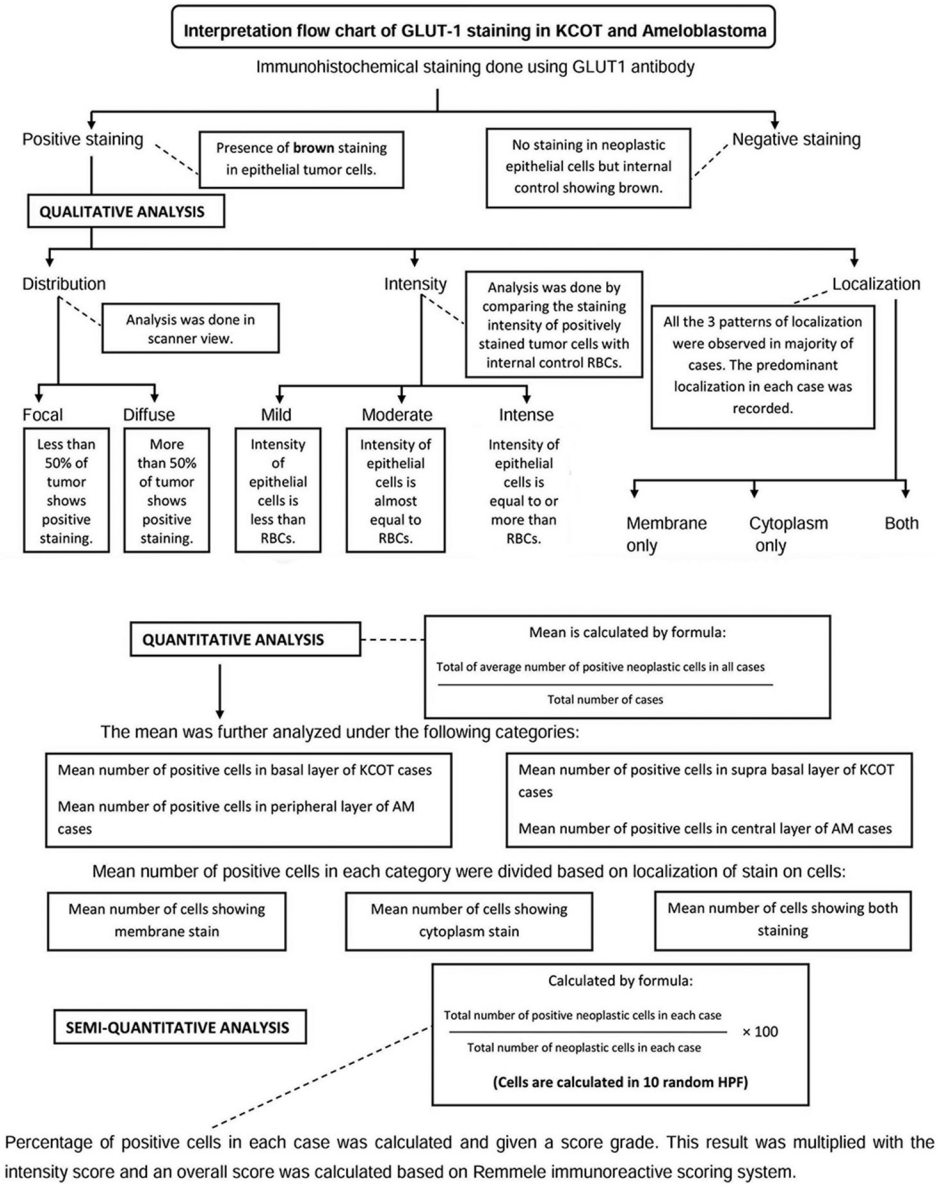

Figure 1: Protocol followed for qualitative and quantitative evaluation of glucose transporters 1 immunostaining

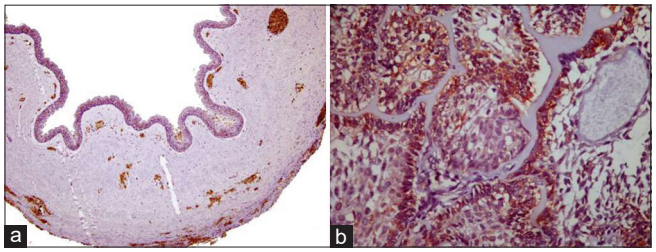

Figure 2: (a) Intensely stained cells localized predominantly in the supra basal layers of odontogenic keratocyst. Cytoplasmic staining is seen in the basal layer and membrane staining is seen in suprabasal layers (×10). (b) Equal staining distribution between central and peripheral cells of follicular ameloblastoma (×40)

observed in basal layer, in areas of basal cell hyperplasia and inflammatory component within the connective tissue wall [Figure 3a]. In areas of orthokeratinization, only the basal cells showed positivity for GLUT1. Mild staining was observed in daughter cysts present within the connective tissue wall of two cases. The localization of stain on a cell varied from membrane only, cytoplasm only to both membrane and cytoplasm. The majority of cells in basal layer showed cytoplasm staining, whereas in suprabasal layer, all the three patterns of localization were observed.

Ameloblastoma

Immunostaining of GLUT1 was seen in 26 out of 30 cases of AM [Table 1]. Diffuse staining pattern was seen predominantly with few cases showing focal

positivity. The staining intensity and localization of staining was variable. In follicular AM [Figure 2b] and granular AM cases, uniform staining pattern was observed in peripheral and central group of cells. Plexiform variant showed predominant staining in peripheral cells with only few areas showing positivity in central area. In acanthomatous type predominantly, the central cells showed positivity. Luminal variant of UA showed uniform staining pattern from basal to superficial layers, whereas in mural variant, basal layer showed more staining when compared to suprabasal layer. The intensity of staining did not show much variation within the lesion. Focal clusters of cells in nine cases showed intense staining [Figure 3b].

Qualitative analysis

The comparison of distribution of staining ($P = 0.684$), staining intensity ($P = 0.797$), and localization of staining ($P = 0.185$) in OKC and AM did not show any statistically significant differences [Table 2].

Quantitative analysis

The comparison between the mean number of positive cells in OKC and AM did not showed statistically significant difference ($P = 0.145$). The comparison between the mean number of positive cells in basal and suprabasal layers of OKC showed statistically significant difference ($P \leq 0.001$) but not between central and peripheral cells in AM ($P = 0.667$) [Table 3].

Semi-quantitative analysis

The comparison of percentage score grade ($P = 0.753$) and overall score ($P = 0.933$) in OKC and AM did not show statistically significant difference [Table 4].

DISCUSSION

In the present study, neoplastic epithelial cells were evaluated with GLUT1 marker in 30 cases each of OKC and AM and positivity was seen in 83.3% (25 cases) and 86.7% (26 cases), respectively. Otsuru *et al.*[11] and Sánchez-Romero *et al.*[12] in their GLUT1 IHC study on 4 cases and 55 cases of AM, respectively, found 100% positivity. The negative staining in our study (five cases of OKC and four cases of AM) may be due to the presence of other transporter proteins or presence of too low proteins to be detected by IHC.

The comparison of staining distribution in OKC and AM did not show any statistically significant difference. The possible explanation for these focal and diffuse distribution patterns of GLUT1 expression has not been discussed earlier. However, the results of our study showed that this distribution pattern appeared to be nonspecific in their presentation in OKC and also within the subgroups of AM. The differential distribution patterns observed here may be due to altered functional demands present in the epithelium which reflects the unequal growth activity present in these tumors, but this should be further evaluated.

Table 1: Number of positively and negatively stained cases observed in odontogenic keratocyst and ameloblastoma

	Positive	Negative
OKC (*n*=30)	25	5
AM (*n*=30)	26	4
SMA (*n*=17)		
Follicular (*n*=4)	4	0
Plexiform (*n*=9)	9	0
Acanthomatous (*n*=3)	3	0
Granular cell (*n*=1)	1	0
DA (*n*=3)	2	1
UA (*n*=10)		
Luminal (*n*=5)	2	3
Mural (*n*=5)	5	0

OKC: Odontogenic keratocyst, AM: Ameloblastoma, SMA: Solid Ameloblastoma, DA: Desmoplastic Ameloblastoma, UA: Unicystic Ameloblastoma

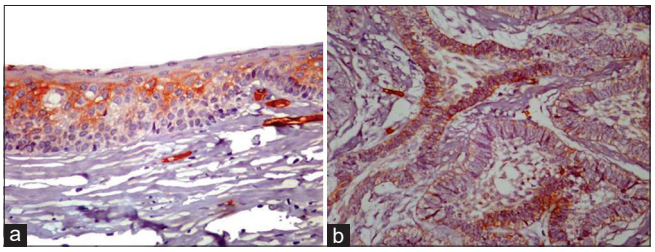

Figure 3: (a) Odontogenic keratocyst and (b) ameloblastoma lining showing focal clusters of intensely stained cells with predominant membrane staining (×40)

Table 2: Qualitative assessment of glucose transporter 1 staining

Lesion	Diffuse	Focal	χ^2	*P*		
KCOT	18	7	0.758	0.684		
AM	16	10				
Lesion	**Mild**	**Moderate**	**Intense**	**Mann-Whitney U-test value**	**Two-tailed *P***	
KCOT	10	9	6	433.0	0.797	
AM	10	10	6			
Lesion	**Membrane only**	**Cytoplasm only**	**Membrane and cytoplasm**	χ^2	***P***	
KCOT	4	11	10	4.821	0.185	
AM	0	12	14			

AM: Ameloblastoma, KCOT: Keratocystic odontogenic tumor

The staining intensity ranged from mild to intense in both OKC and AM. This variation in staining intensity may be due to the difference in the amount of protein and differences in the functionally active state of the proteins. Comparison of staining intensity between AM and OKC did not show any statistically significant difference $P = 0.797$. Focal clusters of neoplastic cells showed intense staining in 14 cases of OKC and nine cases of AM suggestive of focal localization of highly active cells with increased functional demands. The majority of OKC cases showed diffuse staining pattern with moderate to intense staining which infers that most of the epithelial cells are active with more amount of GLUT1 suggesting increased functional demands. In AM, also diffuse staining pattern was predominantly seen but the intensity of staining did not show any variation between diffuse and focal staining pattern. This variation in pattern and intensity of GLUT1 expression in AM and OKC may explain its differential growth pattern of OKC and its development in short duration.

Quantitative evaluation of GLUT1 expression, which was analyzed by comparing the mean number of positively stained cells, in OKC and AM showed a difference but was not statistically significant ($P = 0.145$). When the mean number of cells in basal and supra basal layers of OKC were compared a significant difference was observed, whereas such difference was not observed when peripheral and central cells of AM were compared [Table 3]. Similar finding was seen by Vera-Sirera *et al.* study which states that high intensity and pronounced membrane staining of GLUT1 in parabasal cells of OKCs.[13] Previous studies on OKC using proliferative markers such as Ki67, PCNA and AgNOR and cell cycle regulatory factor cyclin D1 showed increased expression in the supra basal layers of OKC when compared to basal and superficial layers.[14-16] This suggests that the cells in the supra basal cells are in the proliferative pool which reinforces the fact that OKC epithelial lining presents a different pattern of cell proliferation.[17] Hence, the high expression of GLUT1 in supra basal layer could be related to increased energy requirements for the proliferating cells. The decreased expression of GLUT1 in the basal layer, when compared to that of supra basal layer, reflects their low proliferative index observed in the previously mentioned proliferation studies. Superficial and parakeratin layers did not show GLUT1 expression as these were regarded as terminally differentiated cells. This was supported by the presence of intense expression of involucrin, a marker for terminally differentiated cells, in these layers.[18]

Table 3: Comparison between mean number of positive cells in odontogenic keratocyst and ameloblastoma and in basal and suprabasal layers of odontogenic keratocyst and central and peripheral cells in ameloblastoma using unpaired *t*-test

	Mean±SD	Range	Test value	*P*
OKC	51.32±43.117	0.0-182.5	−1.478	0.145
AM	71.717±62.052	0.0-269.4		
OKC - basal cells	9.29±9.044	0-32.4	−4.442	<0.001
OKC - suprabasal cells	42.03±39.348	0-169.9		(significant)
AM - peripheral cells	33.79±39.947	0-174.6	−0.433	0.667
AM - central cells	37.927±33.775	0-131.1		

OKC: Odontogenic keratocyst, AM: Ameloblastoma, SD: Standard deviation

Comparison of the mean number of positive cells between peripheral and central cells of AM did not have a significant difference in GLUT1 expression [Table 3]. Earlier studies using proliferative markers in AM showed higher proliferative index in the peripheral cells when compared with that of central cells. If the GLUT1 expression is to be correlated with the proliferative index of a lesion, then the GLUT1 positivity of the central cells should be less than peripheral cells but instead, it is more. The possible reason for increased expression of GLUT1 in central cells may be due to the presence of hypoxia. The IHC expression of vascular endothelial growth factor (VEGF), CD34 and CD 105, markers for hypoxia and vascularity, respectively, were studied by Dineshkumar *et al.*[19] and Jamshidi *et al.*[20] and observed high mean vascular density and stronger expression of VEGF in the stroma and peripheral cells of AM, whereas similar markers revealed decreased expression in OKC when compared to AM. Sánchez-Romero *et al.* observed 3 GLUT1 staining patterns such as prostromal, antistromal and full stromal in both solid and unicystic AM cases. In solid AM cases, the values for prostromal, antistromal, and full patterns were 38.5%, 20.5% and 41%, respectively. In unicystic AM cases, 75% were prostromal; antistromal and full patterns represented 12.5% each. They stated that the antistromal pattern of GLUT1 was related to hypoxic induction and prostromal expression pattern

Table 4: Semi-quantitative assessment of glucose transporter1 staining

Lesion	1 point (1%-10%)	2 points (11%-50%)	3 points (51%-80%)	4 points (>80%)	Mann-Whitney U-test value	Two-tailed *P*
KCOT	2	19	4	0	430.5	0.753
AM	3	21	2	0		
Lesion	**Weakly positive (1-5 points)**		**Strongly positive (6-12 points)**		χ^2	***P***
KCOT	18		7		0.138	0.933
AM	19		7			

AM: Ameloblastoma, KCOT: Keratocystic odontogenic tumor

in spite of having capillary oxygen supply might be due to induction of nonhypoxic mechanisms.[12]

The localization of GLUT1 protein in a cell depends on the duration of various stimuli acting on a cell such as growth factors, conditions such as hypoglycemia and hypoxia.[21] In our study, localization of GLUT1 immunostaining was observed as membrane only, cytoplasm only and/or both membrane and cytoplasm. In each case, all the three patterns of staining were observed. Qualitative analysis was done based on the predominant localization pattern observed in each case, whereas the quantitative analysis was performed by taking the mean of cells showing a particular type of localization in basal and supra basal layer. Qualitative analysis of the localization pattern showed predominant cytoplasm only and membrane and cytoplasm staining in OKC whereas in AM predominant membrane and cytoplasm staining followed by cytoplasm was observed. Comparison of localization of staining in OKC and AM did not show any statistically significant difference. The immunoreactive scoring system for semi-quantitative analysis was developed by Remmele and Stegner for the IHC detection of estrogen receptors in mammary carcinomas.[22] Later, it was adopted for many other malignancies because of its reliability in attaining a uniform score in routine diagnostics. This method opted for OKC and AM, the benign aggressive lesions, in this study to find any possible correlations. The score for the percentage of positive cells ranged from 0 to 3 points in this study. The comparison of percentage of positive cells between OKC and AM is not statistically significant. Based on the overall score, the majority of cases fall into the weakly positive group. Comparison of the overall score between AM and OKC did not show any significance. It can be hypothesized that malignant tumors show strong positivity when compared to that of benign tumors. The possible explanation for this type of scoring pattern in odontogenic tumors has not been discussed earlier. In this study, 18 cases of OKC and 19 cases of AM were in the weakly positive category and remaining 7 cases of AM and OKC were in the strongly positive category. This difference has not been significantly correlated to the clinical or histological features of these lesions. In this study, 5 squamous cell carcinoma cases (3 poorly differentiated and 2 moderately differentiated) which are taken as external controls showed more than 80% of positive cells in 3 cases of poorly differentiated cases and 70%–80% in moderately differentiated cases. Ohba *et al.* in their study on squamous cell carcinomas found a positive correlation between the GLUT1 expression and the depth of invasion of the tumor.[23]

The overall score in OKC and AM has been positively correlated with diffuse and focal staining pattern and intensity of staining (mild, moderate and intense). The possible inference from these positive correlations can be stated as more the functional demands in the tumors more the intensity of staining and more number of cells showing functionally active protein.

Additional features were observed in OKC which were not included in the evaluation of these lesions in this study. A single case of OKC which showed orthokeratinization in a part of the lining was evaluated to know whether any difference in staining was present. In areas of orthokeratinization, GLUT1 expression was confined to the basal layer. These are regarded as less aggressive variants and show low proliferative index when compared to OKC and the staining of proliferative markers is confined to the basal layer. Vera-Sirera *et al.* also found low and inconspious expression of GLUT1 in orthokeratinized OKCs.[13] As findings from single case do not help in giving any conclusion this has to be further evaluated.

The lining epithelium show changes such as loss of surface keratinization, thickening of epithelium, development of rete processes or ulcerations in the presence of chronic inflammation. Few of the OKC cases in this study showed areas of chronic inflammation.[24] Care has been taken to avoid such areas during evaluation, but they have been studied separately to find any difference in GLUT1 expression. Its expression in epithelium opposed by areas of inflammation revealed predominant staining in the basal layer when compared to that of supra basal layer. This finding was in accordance with the proliferative index in inflammatory OKCs where high proliferative index is seen in basal layer when compared to suprabasal layer.[14]

Over expression of GLUT1 is seen in a variety of tumors and their level of expression often correlated with the metastatic potential and poor prognosis of tumors.[25] Hence, GLUT1 is regarded as a potential target in oncology. WZB117, STF-31, Fasentin, Apigenin, Genistein, oxime-based inhibitors and pyrrolidine-derived GLUT1 inhibitors are various anti-GLUT1 agents developed till date and are in various phases of clinical trials.[26]

CONCLUSION

The present study showed a predominant diffuse distribution of GLUT1 staining with increased expression in suprabasal layers of OKC and central cells of AM. This highlights its expression in AM and OKC and suggests that altered glucose metabolism might be one of the

factors responsible for tumor growth. GLUT1 is a known marker for hypoxia in tissues and has a role in cell growth, proliferation, survival and resistance to chemo therapy and radiotherapy. Increased expression of GLUT1 is associated with increased utilization of energy and correlates with the aggressive behavior of these tumors. However, GLUT1 alone may not predict the aggressiveness of a lesion, but instead, it should be correlated with other basic markers or histological grading. The full biological significance of GLUT1 in odontogenic tumors has to be explored. Further studies with more number of samples and more sophisticated techniques such as cell culture studies and molecular analysis are necessary to ascertain the role of GLUT1 in the pathogenesis of the odontogenic cysts and tumors.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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