REVIEW

Role of Glut-1 in Tumor Progression and Prognosis in Oral Squamous Cell Carcinoma: A Systematic Review

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Abstract

Introduction: Oral cancer, one of the most common cancers worldwide constitutes a major public health problem and is one of the leading cancer sites among men and women in India. Increased uptake of glucose in cancer cells are mediated by glucose transporters. Among 14 isoforms of glucose transporters, Glucose transporter 1 (GLUT-1) isoform expression predominate Oral squamous cell carcinoma (OSCC).

Aim: To emphasize the expression of GLUT-1 in OSCC and to assess its role in tumor progression and prognosis.

Materials and Methods: Hand searching and electronic databases such as PubMed/Medline, Google scholar and Science-Direct were done for mesh terms such as OSCC, GLUT-1, prognosis, tumor markers, prognostic marker and risk predictor. Studies were pooled and relevant articles were evaluated.

Results: Final analysis identified thirteen articles after considering the inclusion and exclusion criteria. These studies evaluated 926 OSCC cases and 70 healthy controls for GLUT-1 immunoexpression. The data was extracted and evaluated manually. GLUT-1 expression was found to be elevated in OPMDs and OSCC than in healthy controls. The pattern of expression of GLUT-1, its correlation with clinico-pathological features, role in tumour progression and prognosis, expression in tumor invasive front, correlation with other markers and role in therapeutics are also discussed in detail.

Key Words: GLUT-1; Oral Squamous cell carcinoma; Prognosis; Tumor markers; Prognostic marker; Risk predictors

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Introduction

Oral carcinogenesis is a multistep process that often arises from a precancerous phenotype followed by uncontrolled cell proliferation associated with multistep genetic alterations and phenotypic progression to invasive malignancy.[1] Proliferation in tumor population is characterized by accelerated glucose metabolism that helps to maintain energy in hypoxic condition. A malignant cell shows high rate of anaerobic metabolism even in presence of oxygen (aerobic glycolysis) and is known as Warburg effect.[2]

Increased uptake of glucose in cancer cells are mediated by glucose transporters. They are the transmembrane proteins that transport glucose across plasma membrane of a cell. They include two families: Sodium glucose linked transporters (SGLTs) and the facilitative glucose transporters (GLUTs). Glucose transporter-1(GLUT-1), one of the 14 members of the mammalian facilitative glucose transporter family is detectable in normal tissues like erythrocytes, perineurium of the peripheral nerves; endothelial cells in the blood – brain barrier vessels etc.[3] GLUT-1 expression has been detected in various malignant tumors like cervical, ovarian, thyroid, esophageal, pancreatic, breast, gastrointestinal carcinoma and OSCC. Among 14 isoforms of glucose transporters, GLUT-1 isoform expression predominates in OSCC.[4]

The presence of hypoxia in tumors leads to resistance to radiotherapy & chemotherapy and is associated with an increased potential for metastasis. Therefore, pretreatment characterization of tumor hypoxia may be useful for predicting the prognosis and facilitate in establishing a risk adapted treatment strategy.[5] This systematic review is an attempt to reflect the findings of various authors on the role of GLUT-1 as a biomarker for tumor progression and prognosis in OSCC.

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Materias and Methods

An initial search using Pub Med/Medline database, Google scholar and Science direct was performed using the

MESH terms contained in the research title. The keywords included were oral squamous cell carcinoma, GLUT-1, Prognosis and tumor markers. Only articles published from 2003-2017 written in English were included. Two investigators independently extracted the information according to the determined criteria from acceptable studies. Articles were then selected for relevance upon reading titles and abstracts. Additional search with mesh terms like prognostic marker & risk predictors added 3 more articles. Removing duplication, 13 articles were selected finally for the systematic review. The last search was updated on July 2018 (Figure 1).

Inclusion criteria

Articles in English language which assessed expression of GLUT-1 to evaluate the prognosis of OSCC during 2003–2017 were included in the study.

Exclusion criteria

Animal studies and studies done in cancers other than oral squamous cell carcinoma were excluded from the study. Articles without full text available were also excluded. Applying this inclusion and the exclusion criteria, 50 articles were excluded as 32 of them were done on cancers other than oral squamous cell carcinoma, 5 of them did not assess prognosis of OSCC with GLUT-1 expression, 3 of them were animal studies, one of them was in Chinese language, and full text was not available for 9 articles.

Results

Thirteen research studies were shortlisted for the systematic review. These studies included 926OSCC cases and 70 healthy controls evaluated for GLUT-1 immunoexpression.

Data pooled was categorized using a table having all the characteristics of the included study [Table 1]. Studies were analyzed and inference drawn based on pattern of staining, correlation with clinico-pathological features, tumor progression & prognosis, invasion in tumor front, comparison with other immuno markers and as a marker of radio-resistance.

Only One study assessed GLUT-1 expression in tobacco and non-tobacco users which identified significant correlation between tobacco usage, alcohol consumption and GLUT-1 immunoexpression. Eight studies proved GLUT-1 to be a prognostic marker in OSCC significantly predicting the survival rate of patients. GLUT-1 expression in tumor invasive front of OSCC was assessed in two studies which concluded GLUT-1 along with depth of invasion could be used as risk predictors. In yet another study, GLUT-1 proved to be a better indicator of lymph node metastasis in comparison with markers like CA-9, ki-67 and P53. Another study establishing GLUT-1 as a marker of radio resistance in OSCC showed high expression associated with poor radiation response and unfavorable clinical outcome.

Discussion

Oral squamous cell carcinoma is a locally aggressive neoplasm with rapid progression & significantly reduced oxygen concentration.[6] GLUT-1 also called as erythrocyte brain or HepG 2- type glucose transporter is a Hypoxia induced factor (HIF-1) regulated protein validated as an intrinsic marker of tumor hypoxia.[7] GLUT-1 can thus alter glucose influx under certain conditions that have a higher metastatic requirement, such as cell division(mitosis & meiosis), malignant transformation and nutrient depletion.[8,9]

Mechanism of GLUT-1 Overexpression

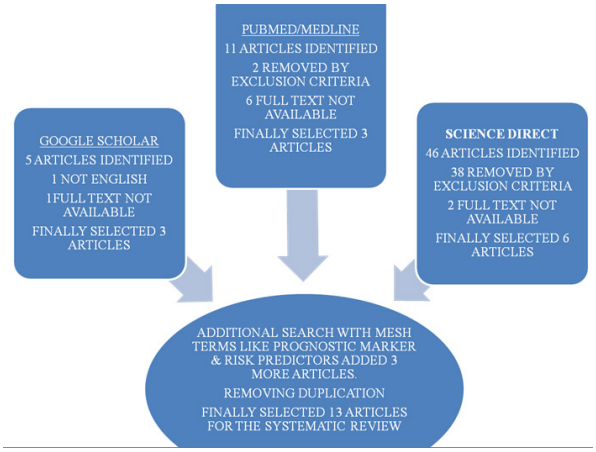
GLUT-1 induction following hypoxia involves a succession of changes to its intrinsic activity, kinetics and expression. Initially, there is "unmasking" of the protein that enhances its affinity for glucose. Further stimulation results in translocation of existing glucose transporters from cytoplasmic vesicles to the plasma membrane and an eventual increase in the synthesis of GLUT-1 m-RNA.[10]

Pattern of staining

The pattern of GLUT-1 expression in OSCC ranges from membranous to cytoplasmic and sometimes even combined.[14,20] Previous studies in the literature states that the presence of GLUT-1 expression in the basal compartment of NOE suggests proliferative activity associated with glucose transport from the basement membrane. With increased maturation, GLUT-1 expression decreases and total absence of GLUT-1 reflects complete maturation and degradation.[21] This implies that membrane staining could be an indicator of low proliferative potential, and thus favorable prognosis. Ariely et al. investigated whether cytoplasmic and membranous expression of GLUT-1 in tumors was related to the duration and extent of hypoxia present in different areas. They suggested that co-localization of GLUT-1 with the Golgi leads to combined membrane and cytoplasmic expression.[10] Angadi et al reported that location of GLUT-1 showed a progressive switch from a membranous to cytoplasmic location then to combination of both as the grade of OSCC increase.[20]

In the study by Angadi et al GLUT-1 expression increased with severity of dysplasia. In mild dysplasia, GLUT-1 expression was noted in the basal layer and demonstrated predominantly mild staining, whereas in moderate dysplasia, it was intense and extended to the spinous layer. In all cases of severe dysplasia (100%), the entire epithelium including the granular and corneal layers expressed GLUT-1 strongly.[20] This association of GLUT-1 expression with the grade of dysplasia has been previously documented by Ayala et al and has been linked to the glycogen content of the cells, being high in non-dysplastic areas of epithelium and decreased or absent in areas of dysplasia.[11]

In almost all studies analyzed GLUT-1 expression was



Systematic Review of 2018

Table 1

SI NO.	AUTHOUR & YEAR	JOURNAL NAME	METHOD	PARAMETERS MEASURED	CONCLUSION
1.	Kunkel et al, 2003	Cancer	IHC & FDG-PET	GLUT-1	Both glucose transport and glucose metabolism determine the glycolytic tumor phenotype, which is a significant negative biomarker of prognosis and overall survival in patients with OSCC.
2.	Oliver et al,2004	European journal of cancer	IHC	GLUT-1	Glut-1expession increased with disease progression
3.	Kunkel et al, 2007	Oral oncology	IHC	GLUT-1	GLUT-1 expression in the tumor is a marker of radioresistance in OSCC, with high expression being associated with poor radiation response and shorter survival.
4.	Li et al, 2007	British journal of oral and maxillofacial surgery	IHC & FDG-PET	GLUT-1	Glut-1 have a useful role as a predictor for poor prognosis in HNSCCAs. However, there was no significant correlation between FDG accumulation and Glut-1 expression.
5.	Roh et al, 2008	Oral oncology	IHC	HIF-1α, HIF-2α, CA-9, GLUT-1, EPOR	GLUT-1 could be used as a marker of nodal metastasis. EPOR expression is independent predictor of disease specific survival compared to GLUT-1.
6.	Eckert et al, 2008	Oncology reports	IHC	GLUT-1	Glut-1 expression is an independent prognostic marker for routine assessment of OSCC
7.	Ayala et al, 2010	Molecules	IHC	GLUT-1 & GLUT-3	GLUT-1 and GLUT3 protein expression are significantly indicators of poor prognosis outcome in OSCC, probably due to the enhanced glycolytic metabolism of more aggressive neoplastic cell.
8.	Ohba et al, 2010	Journal of Oral Pathology & Medicine	IHC	GLUT-1	GLUT-1 served as a marker indicating that tumors with deep invasion tended to result in a worse prognosis in patients due to either lymph node metastasis, a recurrence of the primary lesion or distant metastasis.
9.	Kondo et al, 2011	Oncology Reports	IHC	CA9, GLUT-1, Ki-67, p53	GLUT-1 expression was observed in 98% of subjects, similarly to CA9 expression, no significant correlation between its expression and the survival rate was seen. However, subjects with lymph node metastasis had significantly higher GLUT-1 expression, demonstrating that GLUT-1 could be an indicator of lymph node metastasis.
10.	Harshani et al, 2014	Journal of Oral & maxillofacial Pathology	IHC	GLUT-1	Higher IHC staining scores were obtained with increased clinical staging and histopathological grades of OSCC. High expression of Glut-1 may be related to poor prognosis in OSCC
11	Grimm et al, 2014	Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology (OOOO)	IHC & WESTERN BLOTTING	GLUT-1 & TKTL1	GLUT-1 expression alone cannot be an independent prognostic factor. Combined GLUT-1and TKTL1coexpression predicts shorter survival in OSCC.
12.	Azad N, 2016	Journal of Oral biology &Craniofacial reasearch	IHC	GLUT-1	GLUT-1 expression correlates with the histological grade and pTNMstaging of OSCC. Significant correlation with tobacco addiction also observed. Glut-1 expression may serve as a biomarker for OSCC patients.
13	Ganver SM, 2017	Translational research in oral oncology	IHC	Depth of invasion and GLUT-1	The correlation of these two parameters, that is, DOI with GLUT-1 over expression at the invasion front, used simultaneously in progressive histological grades of OSCC, might have a significant prognostic value by highlighting those cases that should be subjected to further lymph node assessment, thereby predicting their risk of occult metastasis, assisting in the selection of patients requiring more aggressive therapy.

predominantly evident at the periphery of well differentiated tumor islands and absent in the central keratin pearls, i.e. a "prostromal" pattern was observed.[11,14,20,21,22,23,24] In keratin pearls, increased accumulation of glycogen has been reported, correlating inversely with GLUT-1 immunoexpression, suggesting that differentiated and mature cells present in keratinized regions lack GLUT-1 expression.[11] In most of the PDSCC cases, GLUT-1 expression showed an "antistromal" pattern with higher expression in central and perinecrotic zones. This suggests hypoxia-driven GLUT-1 stimulation, which creates an antistromal staining pattern in areas devoid of squamous differentiation/keratinization.[20] Thus authors suggest that this protein might be able to predict the degree of histologic differentiation.[25] A few studies have suggested that the varying patterns of GLUT-1 expression could have prognostic value, such as the study of Smeland et al. on sarcomas.[26]

2. GLUT-1 and correlation with clinico-pathological features in OSCC

In a study by Ayala et al GLUT-1 expression with clinico-pathological features like gender, primary site, staging, vascular embolization, lymph node involvement and habits like alcohol & tobacco were assessed. Univariate statistical analysis showed a significant association of cases with a reported history of alcohol consumption with GLUT-1 staining nuclear pattern. In relation to the GLUT-1 frequency of cells stained, statistically significant results were found with: gender, alcohol consumption and clinic tumor stage and no significant association was found with primary site and lymph node involvement.[11] The observations of Ayala et al were similar to the clinical parameters observed in other malignancies such as esophageal carcinomas.[12,13]

A recent study by Azad et al on expression of GLUT-1 in oral squamous cell carcinoma in tobacco and non-tobacco users revealed tobacco addiction group showed more percentage of cells displaying GLUT-1 immunostaining in comparison to non-tobacco group. In non-tobacco group, pattern of staining was found to be membranous and combined (both nuclear & membranous) while in tobacco group it was predominantly combined pattern of staining. Contrary to the findings of Ayala et al, this recent study found no significant association of additional alcohol consumption and GLUT-1.[14]

3. GLUT-1 and correlation between tumor progression and prognosis

Kunkel et al performed a retrospective analysis of GLUT-1 expression by immunohistology in 118 patients with OSCC. In this study, the hypothesis was tested that Glut-1 expression and FDG-PET scans used together have a significant prognostic value in patients with OSCC and thus a GLUT-1 labeling index (LI) was established for each. The patients who had OSCC with a low LI for GLUT-1 survived significantly longer compared with patients who have OSCC with a high LI. It was found that GLUT-1 expression was an independent marker of prognosis in patients with OSCC.[15] The results agree with those described by Baer et al who reported that glucose transporter expression was associated with poor survival in 44 patients with laryngeal carcinoma who were evaluated by immunohistochemistry of tumor biopsies.[16] However Oliver et al states that the study did not state if this was disease related death or if there was any correlation with locoregional disease control. Oliver et al. investigated the relationship between GLUT-1 expression and clinical outcome in a series of OSCCs. There was a significant relationship between those tumors which demonstrated intense staining and recurrence overall. This relationship was strongest in relation to regional lymph node recurrence. A significant relationship between disease related death and intense GLUT-1 staining was also observed. The results of this study indicate a relationship between GLUT-1 expression and disease progression of oral cancer and could indicate a need for neoadjuvant chemoradiotherapy for those tumors demonstrating intense GLUT-1 expression.[2]

Eckert et al., studied on samples collected from 42 patients with a primary OSCC. Immunohistochemical staining for GLUT-1 was carried out and compared with clinicopathological data. In multivariate Cox's regression hazard analysis, moderate to strong GLUT-1 expression possessed a 4.9-fold increased risk of tumor related death compared to other patients. Results suggested that GLUT-1 expression can be used as an independent prognostic marker for routine assessment of OSCC. Eckert et al suggest that a moderate expression should be considered for prognostic statement additionally to the strongly stained tumors.[17] Whereas Kunkel et al considered strong expression vs. low expression of GLUT-1 and found a 2.65-fold increased risk of tumor related death for the patient group whose tumours showed a strong expression.[15] Yet another study was conducted by Li S assessing Glut-1 expression in primary and recurrent HNSCCAs. The study also documented that expression of Glut-1 in recurrent HNSCCAs was higher than that in primary HNSCCAs, and in poorly-differentiated HNSCCAs higher than in better-differentiated HNSCCAs, which indicated that Glut-1 may have a useful role as a predictor for poor prognosis in HNSCCAs.[31]

In a study by Kondo et al GLUT-1 expression was observed in 98% of subjects, similarly to CA9 expression but no significant correlation between its expression and the survival rate was seen. However, the study demonstrated that subjects with lymph node metastasis had significantly higher GLUT-1 expression, demonstrating that GLUT-1 could be an indicator of lymph node metastasis.[18]

Harshani et al conducted a study in thirty cases of OSCC where IHC was used to detect the expression of GLUT-1 in OSCC and the same was compared with the normal subjects. In this study, GLUT-1 expression was detected in all grades of OSCC. Higher immunohistochemical staining scores were obtained with increased clinical staging and histopathological grades of OSCC. It was concluded from the study that higher expression of GLUT-1 may be related to poor prognosis in OSCC.[19] But the study does not mention the assessment of survival rate of OSCC individuals nor stated any follow up being carried out.

Contrary to the above findings data provided by Grimm et al, indicate that GLUT-1 expression is associated with advanced tumor stage in OSCC and reduced tumor-specific survival among patients with positive GLUT-1 expression compared with the negative GLUT-1 subgroup. However, GLUT-1 expression cannot be considered an independent prognostic factor, as confirmed by multivariate analysis.[34]

Angadi VC recently conducted a study to evaluate GLUT-1 immunoexpression in OED, OSCC and verrucous carcinoma (VC). It is claimed to be the first study of GLUT-1 expression in VC. The study observed GLUT-1 expression increased with the degree of dysplasia and increasing grade of OSCC. The expression in VC was predominantly membranous and intense, resembling WDSCC. This study thus demonstrated that GLUT-1 has a consistent role in oral premalignant and malignant lesions and that its expression level and activity appear to be associated with malignant transformation and aggressiveness.[20] Study by Azad et al also goes consistent with the findings of Angadi VC and GLUT-1 expression correlated significantly with histological grade and PTNM staging of OSCC. Thus, the authors state that GLUT-1 may serve as a biomarker for patients of OSCC.[14]

4. Glut-1 and invasion:

Ohba et al studied GLUT-1 immuno staining invasion front on 24 OSCC. The analysis showed that in all OSCC patients GLUT-1 expression correlated the depth of the tumors. The survival of patients who had over expression of invasion front was significant shorter than that of patients with GLUT-1 immunostaining. GLUT-1 expression indicated that tumors with deep invasion result in a worse prognosis in patients due to either lymph node metastasis, a recurrence of primary lesion or distant metastasis.[3] A much more larger sample size of 90 OSCC patients was included in the study of Sindhu et al to evaluate the mechanisms linking GLUT-1 expression to depth of invasion in progressive grades of OSCC. In order to study the changes in GLUT-1 expression at tumor invasive front in combination with depth of invasion in the progressive histological grades of OSCC, mechanistic study, that is, receiver operating characteristic (ROC) curve analysis was done by the authors. It was observed that the staining index of GLUT-1 at the deep invasive front became stronger with the progressive histological grades of tumour, with corresponding increase in the depth of invasion. In other words, the expression of GLUT-1 became significantly stronger when the tumour demonstrated deep invasion.[27] This is because invasive tumour depth is associated with intense degree of hypoxia. GLUT-1, being an endogenous marker of hypoxia, is over expressed at the tumor invasive front, not only permit cancer cells to survive under adverse conditions such as hypoxia but enable their proliferation, progression, invasiveness, and subsequent distant metastasis.[28] According to the authors depth of invasion and GLUT-1 would probably help in removing the hurdle in the effective management of clinically negative neck in early SCC (T1–T2/NO) of oral cavity and could be a deciding factor for elective neck dissection which would further improve the survival rates of OSCC.[27]

5. Glut-1 and other markers:

Ayala et al associated clinical-pathological features of 142 OSCC with the expression pattern of GLUT-1 and GLUT3 in order to estimate their prognostic value by the IHC analysis of GLUT-1 and GLUT3. In contrast to GLUT-1 expression, the GLUT3 protein was positive in only 30/142 cases (21.1%). They concluded GLUT-1 is more specific compared to GLUT3 as significant indicators of poor prognosis outcome in OSCC.[11]

Kondo et al immunohistochemically observed the expression of antigens such as CA9, Ki-67, GLUT-1 and p53 in 107 subjects with OSCC, and examined their correlation with clinicopathological parameters. Among the markers CA9 had higher sensitivity compared to GLUT-1, Ki-67 and p53. Glut-1 expression was about 98% of CA-9. But considering antigen expression with lymph node metastasis GLUT-1 had a higher specificity over other markers.[18]

Roh et al evaluated whether hypoxia biomarkers like hypoxia-inducible factor (HIF)-1a, HIF-2a, CA-9, GLUT-1, and erythropoietin receptor (EPOR) and clinicopathologic variables were prognostic predictors in patients with T2-staged SCC of the oral tongue as it has a high propensity for regional metastasis and locoregional failure after radical surgery or radiotherapy, affecting patient survival. Authors states that, of these markers only EPOR expression may be an independent predictor for disease specific survival in patients with T2-staged SCC of the oral tongue. But however, GLUT-1 expression was associated with nodal metastases compared to other markers, suggesting that latter may be used as a potential predictor of nodal metastases in patients with oral tongue cancer.[32]

6. GLUT-1 as marker of radio-resistance:

Studies have confirmed the prognostic value of the GLUT-1 levels for OSCC of head and neck.[2,11,15,17] But yet another study by Kunkel et al has also established GLUT-1 as a marker of radio-resistance in OSCC, with the high GLUT-1 expression being associated with poor radiation response as well as with an unfavorable clinical outcome. The study also documents two fundamental drawbacks, first the expression of GLUT-1 in cancer cells reflect a hypoxia independent stimulation of glycolysis. The second is that the "true" efficacy of radiation therapy has not been verified in previous studies, because no complete or even representative histological controls were performed.[29] However, In vitro experiments and tumor xenograft studies reported by Pederson and coworkers argue that GLUT-1 expression plays a hypoxia independent role in the modulation of radiation susceptibility. These investigators demonstrated a linkage between GLUT-1 expression and radiation resistance in two cell sublines (CPH-54A and CPH-54B) derived from a single small cell carcinoma of the lung.[30] Study by Janssen et al also proved that hypoxia markers like GLUT-1 and EPOR can so be used to noninvasively identify tumors showing poor response to radiotherapy and chemotherapy.[33] This is further supported by a recent study stating that OSCCs are associated with combined enhanced glucose uptake (GLUT-1) and hypoxia-related glucose metabolism (TKTL1alpha). Therefore, targeting metabolism in cancer cells have the possibility to enhance the effect of adjuvant radiotherapy and chemotherapy.[34]

Conclusion

This systematic review is focused on the association of OSCC and GLUT-1 expression with special emphasis on its pattern of expression, correlation with clinico-pathological features, tumor progression and prognosis, depth of invasion, other markers and role of GLUT-1 in therapeutics. The literature search suggested pattern of expression of GLUT-1 changes from membranous to cytoplasmic with increasing grades of dysplasia and OSCC. GLUT-1 expression also showed significant correlation with tobacco and alcohol habits. GLUT-1 expression significantly could predict the survival rate of patient and could be used as a prognostic marker. Tumor invasive front

of OSCC expressed high amount of GLUT-1 expression and together could be used as risk predictors. GLUT-1 expression is found to be highest in OSCC among all other GLUT markers and also proved to be an indicator of lymph node metastasis as it had higher expression over markers like CA-9, ki-67 and P53. Its role in therapeutics has also been acknowledged by several authors stating it could also be considered as a marker of radioresistance. This could indeed help in increasing the efficiency of radiotherapy and chemotherapy. Since there is only one study in the literature review for assessing GLUT-1 expression in oral epithelial dysplasia we suggest more studies need to be carried out in oral potentially malignant disorders to establish GLUT-1 as an early diagnostic marker in OPMDs.

References

1. Perez-Ordon EZ B, Beauchemin M, Jordan R C K. Molecular biology of squamous cell carcinoma of the head and neck. J Clin Pathol 2006;59:445-453.
2. Olivera RJ, Woodwards RTM, Sloana P, Thakkera NS, Stratford IJ, Airley RJ. Prognostic value of facilitative glucose transporter Glut-1 in oral squamous cell carcinomas treated by surgical resection: results of EORTC Translational Research Fund studies. Eur J Cancer 2004;40(4):503-507
3. Ohba S, Fujii H, Ito S, Fujimaki M, Matsumoto M, Furukawa M, Yokoyama J et al. Over expression of GLUT-1 in the invasion front is associated with the depth of oral squamous cell carcinoma and prognosis. J Oral Pathol Med 2010;39:74-78
4. Augustin R. The protein family of glucose transport facilitators: it's not only about glucose after all. IUBMB Life 2010; 62(5):315-333.
5. Choi YS, Kim SJ, Kim DS, Park SJ, Park Y, Shin HJ et al. Glucose transporter 1 expression in squamous cell carcinoma of the tongue. Cancer Res T REAT 2007;39(3):109-115
6. Ryu MH, Park HM, Chung J, et al. Hypoxia–inducible factor-1 alpha mediates oral squamous cell carcinoma invasion via upregulation of alpha5 integrin and fibronectin. Biochem Biophys Res Commun.2010; 393:11-15.
7. Airley RE, Loncaster J, Raleigh JA, Harris AL, Davidson SE, Hunter RD, West CM and Sratford IJ: Glut-1 and CAIX as intrinsic markers of hypoxia in carcinomas of the cervix: relationship to pimonidazole binding. Int J Cancer 10: 85-91, 2003.
8. Jonathan RA, Wijffels KI, Peeters W, de Wilde PC, Marres HA, Merkx MA et al. (2006) The prognostic value of endogenous hypoxia-related markers for head and neck squamous cell carcinomas treated with ARCON. Radiother Oncol 79, 288-297
9. Mueckler M. Facilitative glucose transporters. Eur J Biochem 1994;219:713-25.
10. Airley R, Loncaster J, Davidson S, Bromley M, Roberts S, Patterson A et al. (2001) Glucose transporter Glut-1 expression correlates with tumor hypoxia and predicts metastasis-free survival in advanced carcinoma of the cervix. Clin Cancer Res 7, 928-934.
11. Ayala FR, Rocha RM, Carvalho KC, Carvalho AL, da Cunha IW, Lourenço SV, et al. GLUT-1 and Glut3 as potential prognostic markers for oral squamous cell carcinoma.Molecules 2010;15:2374-87
12. Tohma T, Okazumi S, Makino H, Cho A, Mochizuki R, Shuto K, Kudo H, Matsubara K, Gunji H, Matsubara H, Ochiai T. Over expression of glucose transporter 1 in esophageal squamous cell carcinomas: a marker for poor prognosis. Dis. Esophagus 2005; 18: 185–189. 18.
13. Zhou S, WangS, Wu Q, Fan J, Wang Q. Expression of glucose transporter-1 and -3 in the head and neck carcinoma—the correlation of the expression with the biological behaviors. ORL J 2008; 70:189–194.
14. Azad N, Kumari Maurya M, Kar M, et al. Expression of GLUT-1 in oral squamous cell carcinoma in tobacco and non-tobacco users. J Oral Biol Craniofac Res. 2016;6(1):24-30.
15. Kunkel M, Reichert TE, Benz P, Lehr HA, Jeong JH, Wieand S et al. Over expression of GLUT-1 and increased glucose metabolism in tumors are associated with a poor prognosis in patients with oral squamous cell carcinoma. Cancer 2003; 97(4):1015-1024.
16. Baer S, Casaubon L, Schwartz MR, Macrogliese A, Younes M. Glut-3 expression in biopsy specimens of laryngeal carcinoma is associated with poor survival. Laryngosope. 2002; 112:393–396.
17. Eckert AW, Lautner MHW, Taubert H, Schubert J, Bilkenroth U. Expression of GLUT-1 is a prognostic marker for oral squamous cell carcinoma patients. Oncology Reports 2008; 20:1381-1385
18. Kondo Y, Yoshikawa K, Omura Y, et al. Clinicopathological significance of carbonic anhydrase 9, glucose transporter-1, Ki-67 and p53 expression in oral squamous cell carcinoma. Oncol Rep. 2011;25(5):1227-1233.
19. Harshani JM, Yeluri S, Guttikonda VR. Glut-1 as a prognostic biomarker in oral squamous cell carcinoma. J Oral Maxillofac Pathol 2014;18:372-8.
20. Angadi VC, Angadi PV. GLUT-1 immunoexpression in oral epithelial dysplasia, oral squamous cell carcinoma & verrucous carcinoma. Jour of Oral Science 2015;57(2):115-122.
21. Rudlowski C, Becker AJ, Schroder W, Rath W, Büttner R, Moser M.GLUT-1 messenger RNA and protein induction relates to the malignant transformation of cervical cancer. Am J Clin Pathol 2003; 120: 691-698.
22. Mendez LE, Manci N, Cantuaria G, Gomez-Marin O, Penalver M, Braunschweiger P et al. Expression of glucose transporter-1 in cervical cancer and its precursors. Gynecol Oncol 2002; 86: 138-143.
23. Haber RS, Rathan A, Weiser KR, et al. GLUT1 glucose transporter expression in colorectal carcinoma: a marker for poor prognosis. Cancer. 1998; 83(1):34-40.
24. Brown RS, Goodman TM, Zasadny KR, Greenson JK, Wahl RL. Expression of hexokinase II and Glut-1 in untreated human breast cancer. Nucl Med Biol. 2002; 29:443-453.
25. Reisser C, Eichhorn K, Herold-Mende C, Born AI, Bannasch P (1999) Expression of facilitative glucose transport proteins during development of squamous cell carcinomas of the head and neck. Int J Cancer 80, 194-198.
26. Smeland E, Kilvaer TK, Sorbye S, Valkov A, Andersen S, Bremnes RM et al. (2012) Prognostic impacts of hypoxic markers in soft tissue sarcoma. Sarcoma 2012, 541650.
27. Ganvir SM, Swathi BA, Shashikant KP, Pratima KG, Vinay HP, Suchitra R. Depth of invasion and GLUT-1 as risk predictors in oral squamous cell carcinoma: An Immunohistochemical study. Translational research in Oral Oncology 2017; 2 :1-10.
28. Dakubo GD. The warburg phenomenon and other metabolic alterations of cancer cells. In: Mitochondrial genetics and cancer. Berlin Heidelberg: Springer-Verlag, 2010.
29. Kunkel M, Moergel M, Stockinger M et al. Over expression of GLUT-1 is associated with resistance to radiotherapy and adverse prognosis in squamous cell carcinoma of the oral cavity. Oral Oncol 2007; 43:796-803.
30. Pedersen MW, Holm S, Lund EL, Hojgaard L, Kristjansen PE. Coregulation of glucose uptake and vascular endothelial growth factor (VEGF) in two small-cell lung cancer (SCLC) sublines in vivo and in vitro. Neoplasia 2001; 3: 80–7.
31. Li SJ, Guo W, Ren GX, Huang G, Chen T, Song SL. Expression of Glut-1 in primary and recurrent head and neck squamous cell carcinomas, and compared with 2-[18F]fluoro-2-deoxy-D-glucose accumulation in positron emission tomography. Br J Oral Maxillofac Surg. 2008; 46:180-186.
32. Roh JI, Cho KJ, Kwon GY, Ryu CH, Chang HW, Choi SH, Nam SY and Kim SY: The prognostic value of hypoxia markers in T2-staged oral tongue cancer. Oral oncol 45: 63-68, 2008.
33. Janssen HL, Haustermans KM, Balm AJ, Begg AC. Hypoxia in head and neck cancer: how much, how important? Head Neck 2005;27(7):622–38.
34. Grimm M, Munz A, Teriete P, et al. GLUT-1þ/TKTL1þ coexpression predicts poor outcome in oral squamous cell carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol 2014; 117(6): 743–756