ASSESSING PROLIFERATIVE ACTIVITY AND GLUCOSE METABOLISM IN CELLS OF SALIVARY GLAND MUCOEPIDERMOID CARCINOMA USING DIFFERENT GRADING SYSTEMS

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Mucoepidermoid carcinoma (MEC) is the most common malignant tumor of the salivary gland consisting of three main histological components: mucocytes, intermediate and epidermoid cells. Various grading systems (AFIP, Brandwein, modified Healy, MSKCC) are difficult to use. The Ki-67 and GLUT1 markers associated with tumor aggressiveness can improve MEC diagnosis and classification. The study aimed to assess the correlation of the cell proliferative activity and glucose metabolism with the MEC grading systems. Tumors of a total of 40 patients with MEC were analyzed and determined in accordance with the following grading systems: AFIP, Brandwein, modified Healy, and MSKCC. Immunohistochemistry (IHC) was used to estimate Ki-67 proliferation indices and GLUT1 expression intensity. IHC showed high Ki-67 indices and GLUT1 values in epidermoid and intermediate cells, while mucocytes showed low or no expression. There were significant differences in Ki-67 and GLUT1 expression between epidermoid ($p < 0.005$) and intermediate cells ($p < 0.01$). Comparison revealed the increase between grades 1 and 2, 1 and 3, but no differences between grades 2 and 3. Spearman's rank correlation test revealed moderate positive correlations with tumor grades for GLUT1 and Ki-67, and the AFIP system showed the highest correlation (Ki-67: $rs = 0.55$; GLUT1: $rs = 0.50$). Thus, GLUT1 and Ki-67 are most intensely expressed in epidermoid and intermediate cells showing a strong correlation with the tumor grade and aggressiveness, especially in low-grade and intermediate-grade MEC. These markers can improve the diagnosis of MEC malignancy degree. The AFIP system most closely matches these markers in epidermoid and intermediate cells.

Keywords: GLUT-1, Ki-67, MEC grading, AFIP, Brandwein, Modified Healy, MSKCC

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ОЦЕНКА ПРОЛИФЕРАТИВНОЙ АКТИВНОСТИ И МЕТАБОЛИЗМА ГЛЮКОЗЫ В КЛЕТКАХ МУКОЭПИДЕРМОИДНОЙ КАРЦИНОМЫ СЛЮННЫХ ЖЕЛЕЗ ПРИ РАЗЛИЧНЫХ СИСТЕМАХ ГРАДАЦИИ

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Мукоэпидермоидная карцинома (МЭК) является наиболее распространенной злокачественной опухолью слюнных желез и состоит из трех основных гистологических компонентов: мукоцитов, промежуточных и эпидермоидных клеток. Различные системы градации (AFIP, Brandwein, Modified Healy, MSKCC) сложны в применении. Маркеры Ki-67 и GLUT1, связанные с агрессивностью опухоли, могут улучшить диагностику и классификацию МЭК. Целью исследования было провести оценку корреляции пролиферативной активности и метаболизма глюкозы клеток с системами градации МЭК. Были проанализированы опухоли 40 пациентов с МЭК и определены по системам градации: AFIP, Brandwein, Modified Healy и MSKCC. Для оценки индексов пролиферации Ki-67 и интенсивности экспрессии GLUT1 использовали иммуногистохимическое исследование (ИГХ). ИГХ показало высокие индексы Ki-67 и GLUT1 у эпидермоидных и промежуточных клеток, при этом в мукоцитах выявлена низкая или отсутствующая экспрессия. Статистически значимые различия в экспрессии Ki-67 и GLUT1 обнаружены между эпидермоидными ($p < 0,005$) и промежуточными клетками ($p < 0,01$). Сравнения показали увеличение между степенями 1 и 2, 1 и 3, но без различий между степенями 2 и 3. Корреляция Спирмена выявила умеренные положительные связи для GLUT1 и Ki-67 с градацией опухоли, причем система AFIP показала наибольшую корреляцию (Ki-67: $rs = 0,55$; GLUT1: $rs = 0,50$). Таким образом, GLUT1 и Ki-67 наиболее интенсивно экспрессируются в эпидермоидных и промежуточных клетках, сильно коррелируя со степенью и агрессивностью опухоли, особенно при низкой и средней степени МЭК. Эти маркеры могут улучшить точность диагностики степени злокачественности МЭК. Система AFIP наиболее точно соответствует этим маркерам в эпидермоидных и промежуточных клетках.

Ключевые слова: GLUT-1, Ki-67, градация МЭК, AFIP, Brandwein, Modified Healy, MSKCC

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Mucoepidermoid carcinoma (MEC) is the most common malignant tumor of the salivary gland and occurs in 30% of cases of malignant tumors salivary glands [1]. MEC most often affects large salivary glands, specifically the parotid gland (60% of cases), but can also affect minor salivary glands [2, 3].

As for MEC histopathological structure, mucocytes, intermediate and epidermoid cells are distinguished as the main components, but there can also be cylindrical, clear cells, and oncocytes, which leads to diagnostic difficulties for pathologists [4–6]. These components form various histological structures, such as cystic (the most common and well differentiated), solid (rare, with necrosis and considerable cellular and nuclear atypia) or solid cystic structures more typical for tumors that are more prone to invasive growth and metastasis [7, 8].

MEC can be diagnosed based on its histological features only, without any additional testing, such as immunohistochemistry (IHC) or genetic testing, however it is often difficult to establish the final diagnosis [1]. To date, many grading systems have been created for MEC classification. However, there is no universally acknowledged unified system [9]. MEC is classified as low-grade (G1), intermediate-grade (G2) or high-grade (G3) tumor based on four different grading systems, such as Goode, Auclair, and Ellis AFIP (Armed Forces Institute of Pathology), as well as the Brandwein system used in routine histopathology practice [1, 4, 6], along with the modified Healy and MSKCC grading systems of qualitative nature (Table 1). The AFIP and Brandwein methods are not always consistent when used to classify the same tumor, especially when it comes down to determination of certain differences between G2 and G3 tumors. Comparative studies of grading systems have revealed differences when describing major and minor salivary glands [7, 10].

Carcinogenesis is a multi-step process, in which glucose metabolism disturbances can play an important role due to rapid cell proliferation typical for malignant growth [11]. Modern studies have revealed high energy metabolism of malignant tumors and glucose involvement in their growth. Glucose is the main energy source for mammalian cells, and glucose transporters (GLUT) on the cytoplasmic membrane promote glucose cell entry. Thus, GLUT represents the important enzymes mediating glucose metabolism during carcinogenesis [12]. High GLUT1 expression in malignant tumors is associated with invasion and metastasis, including head and neck cancer [13]. The Ki-67 proliferation marker represents a gold standard of assessing the salivary gland malignancies. The role of Ki-67 in the diagnosis and classification of salivary gland tumors is huge: it is directly correlated to the cell proliferation rate being a key indicator of tumor aggressiveness [14].

The study aimed to estimate various MEC grading systems based on proliferative activity and glucose metabolism of the MEC cells in order to determine the grade.

METHODS

Retrospective analysis of the paraffin blocks of tumors of 40 patients (female and male) diagnosed with mucoepidermoid carcinoma from the archive of the Pathology Laboratory of the Central Research Institute of Dental and Maxillofacial Surgery of the Ministry of Health of the Russian Federation for the period 2014–2023 was conducted.

Table 1. Mucoepidermoid carcinoma grading systems

Criteria	AFIP	Brandwein	Modified Healey	MSKCC
Cystic component	(< 20%) 2	(< 25%) 2	L: macro + microcysts I: microcysts + solid H: solid ± microcysts	L: prediminantly cystic (> 80%) I: prediminantly solid H: any (usually solid)
Perineural invasion (PI)	2	3	H: present	n/a*
Necrosis (N)	3	3	n/a	L: absent I: absent H: present
Mitoses	3 (≥ 4/10 HPF)	3 (≥ 4/10 HPF)	L: rare I: rare H: many	L: 0–1/10 HPF I: 2–3/10 HPF H: 4+ /10 HPF
Nuclear anaplasia / pleomorphism	4	2	L: absent/minimal I: minimal/moderate H: prominent (including nucleoli)	L: negligible I: negligible H: any
Border / invasion front	n/a	2	L: broad/ circumscribed I: uncircumscribed H: soft tissue / perineural / vascular invasion	L: well-defined I: well-defined or infiltrative H: any (usually infiltrative)
Lymphovascular invasion	n/a	3	H: present	n/a
Bone invasion	n/a	3	n/a	n/a
Intermediate cells	n/a	n/a	L: rare I: more frequent H: predominant	n/a
Stroma	n/a	n/a	L: extravasated mucin + fibrosis + CI I: fibrosis separating nests + CI H: desmoplasia, minimal CI	n/a
Architecture	n/a	n/a	L: daughter cysts from larger ones I: larger canals are less prominent H: variable architectural pattern/cell morphology	n/a
Grading	L — 0–4 I — 5–6 H — 7–14	L — 0 I — 2, 3 H — ≥ 4	L — low grade I — intermediate grade H — high grade	

Note: n/a — not applicable.

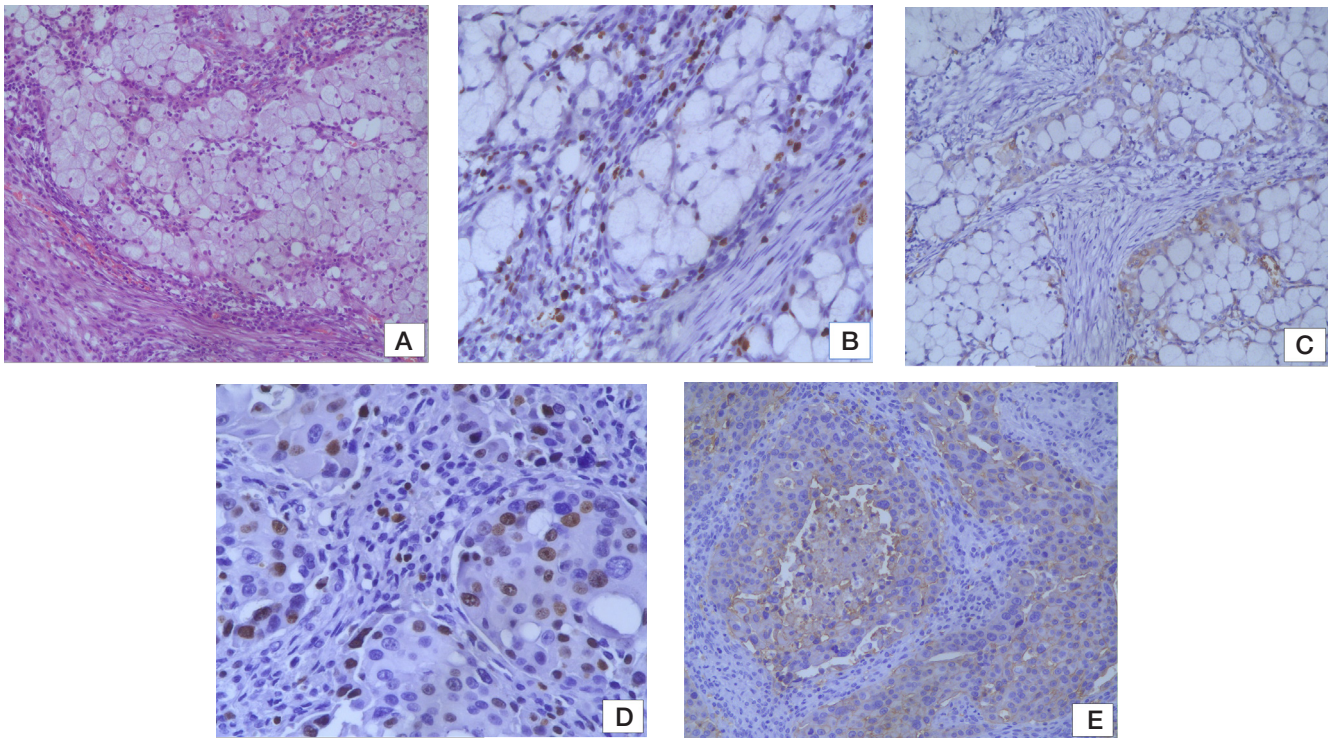

Fig. 1. MEC, hematoxylin and eosin stain ×100 **(A)**. Immunohistochemical reaction with antibody against Ki-67 ×200 **(B)**. GLUT1 cytoplasm staining in epidermoid and intermediate cells, weak response in mucin-producing cells ×100 **(C)**. High proliferative activity based on Ki-67 in epidermoid cells ×400 **(D)**. Intense GLUT1 cytoplasmic membrane staining in epidermoid cells ×200 **(E)**. IHC reaction with the background Mayer's hematoxylin DAB stain

Morphology assessment was performed in accordance with the standard hematoxylin and eosin stain protocols. Histological specimens were assessed using the following four grading systems: modified Healy grading, MSKCC grading, AFIP grading, and Brandwein grading. These systems were compared with the final estimates for each case and correlated to IHC assessment.

Histological and IHC assessment was conducted in accordance with the standard protocol. All biopsy specimens were stained with the Thermo Scientific anti-Ki-67 rabbit monoclonal antibody (USA, clone SP6), Thermo Scientific anti-GLUT1 rabbit polyclonal antibody (USA). The material collected was assessed using the Axioplan 2 Imaging microscope (Karl Zeiss, Germany), and the AxioCam ERc5s camera was used to take images of specimens (Karl Zeiss, Germany). IHC imaging was accomplished using the UltraVision Quanto Detection System HRP DAB (USA) system. The Ki-67 proliferation protein expression was estimated based on proliferation activity index (percentage of cells with the intensely stained nuclei per 300 nuclei of each MEC cell type). GLUT1 expression was assessed based on the cytoplasm and/or cytoplasmic membrane stain and scored based on conditional criteria: no expression — 0, weak expression — 1, moderate expression — 2, strong expression — 3.

MEC was graded using four grading systems, and correlations between the marker, cellular components, and grades were analyzed using the Kruskal–Wallis test, Dunn–Bonferroni test for pairwise comparison, and Spearman's rank correlation. Statistical analysis was conducted using the SPSS Statistics 23 software package for Windows 10 (IBM Corporation, USA).

RESULTS

Histological grading

The AFIP grading system showed a more conservative approach, allowing one to classify the largest number of tumors considered to be low-grade (G1) (40%) compared to other systems. Tumors classified as intermediate-grade accounted for 35%, while high-grade tumors (G3) accounted for only 25%. Such distribution suggests that tumors are assigned lower grades based on the AFIP system, which results in potential underestimation of tumor aggressiveness relative to other systems.

The Brandwein grading system is characterized by the more aggressive approach: the smallest number of tumors are assigned low grade (G1) (20%), while the largest number are classified as high-grade tumors (G3) (45%). Tumors assessed as intermediate-grade ones (G2) account for 35%, which is similar to the results of using AFIP. This suggests that in the Brandwein system preference is given to classification of higher grades, more tumors are assessed as potentially aggressive, but in some cases there is a risk to overestimate the disease severity.

The Modified Healy grading system presents a more balanced grade distribution: 25% of tumors were classified as low-grade ones (G1), 50% as intermediate-grade (G2) (the largest share among all systems), and 25% as high-grade ones (G3). This grading system focuses on the intermediate category, which makes it potentially more useful for identification of borderline or moderately aggressive tumors.

The MSKCC grading system showed the conservative approach similar to that of AFIP: 35% of tumors were classified as low-grade ones (G1) and 45% as intermediate-grade ones (G2). However, the lowest number of tumors were assigned high grade (G3) (20%), which reflects the trend towards the decrease in the number of cases of higher grade MEC. In some cases, this can result in underestimation of tumor aggressiveness.

Immunohistochemistry assessment

Assessment of the hematoxylin and eosin stained MEC slides revealed mucocytes, intermediate and epidermoid cells (Fig. 1A).

Table 2. Pairwise comparison (Dunn–Bonferroni test)

Cellular component	Comparison	Significance ($p < 0,05$)
Epidermoid	G1–G2	0.003
	G1–G3	0.0003
	G2–G3	0.067
Intermediate	G1–G2	0.036
	G1–G3	0.003
	G2–G3	0.23
Mucocytes	G1–G2	0.12
	G1–G3	0.12
	G2–G3	0.12

IHC assessment effectively complements the diagnosis of the hematoxylin and eosin stained slides. In this study, detection of the Ki-67 nuclear antigens associated with the cell cycle made it possible to estimate cell proliferation intensity, and GLUT1 was used as an indicator of glucose metabolism in MEC.

In all the MEC cellular components, Ki-67 protein was found in the cell nuclei (Fig. 1C, D) and GLUT1 was found in the cytoplasm and on the cytoplasmic membrane (Fig. 1C, E). There were considerable differences in distribution of the Ki-67 proliferation indices between three MEC components (epidermoid, intermediate, mucoid). In-depth statistical analysis showed high proliferation rate of epidermoid cells based on Ki-67, for which the median was 13.3% (9.3; 20.0). Intermediate cells demonstrated lower proliferation rates compared to epidermoid cells, and the median was 6.7% (3.5; 10.7), while mucocytes showed minimal Ki-67 expression, and the median was 1.3% (0.0; 2.7).

The Kruskal–Wallis test and pairwise comparison were applied to assess the correlation between Ki-67 indices and the tumor grade. Significant differences in Ki-67 indices between tumor grades were reported for epidermoid ($H = 16.25$, $p = 0.0003$) and intermediate cells ($H = 10.85$, $p = 0.0045$), but not for mucocytes ($H = 4.12$, $p = 0.12$).

Pairwise comparison performed using the Dunn–Bonferroni test revealed significant differences for epidermoid and intermediate cells (Table 2). Mucocytes showed no considerable differences based on grades.

The use of the statistical Spearman's rank correlation test revealed a significant correlation between the Ki-67-based proliferation indices and the MEC grade for three studied components. The strongest correlation was reported for epidermoid cells (0.53, $p = 0.0005$). This indicator suggests that the Ki-67 proliferation index in epidermoid cells increases incrementally with increasing tumor grade, which makes it valuable for assessment of the neoplastic process aggressiveness and makes it possible to use it as a marker of tumor aggressiveness. A moderate positive correlation has been also reported for intermediate cells ($rs = 0.47$, $p = 0.0025$), which confirms their contribution to tumor progression, although lesser than that of epidermoid cells. In contrast, mucocytes have shown a weak non-significant correlation ($rs = 0.25$, $p = 0.12$), which reflects their minimal proliferative activity and limited importance for tumor grading (Fig. 1D).

MEC grading based on calculating proliferative activity of epidermoid and intermediate cells suggests low grade (G1) with the activity below 10%, intermediate grade (G2) with the activity between 10% and 15%, and high grade (G3) with the activity exceeding 15–20%. These grades based on the Ki-67 labeling provide important information about the MEC biological behavior allowing one to determine tumor grade using quantitative indicators of proliferation of various cell populations within the tumor.

The analysis of GLUT1 staining intensity in all specimens revealed considerable differences between three components. Intermediate and epidermoid cells showed the highest staining intensity with the median score of 2 points (1; 3), which suggested moderate variability, while mucocytes showed the lowest intensity with the median score of 0 points (0; 0), suggesting consistently low or no GLUT1 expression in this component (Fig. 1E).

The Kruskal–Wallis test allowed us to reveal considerable differences in GLUT1 staining intensity by tumor grades for epidermoid ($p = 0.005$) and intermediate cells ($p = 0.01$), but not for mucocytes ($p = 0.15$). Pairwise comparison involving the use of the Dunn–Bonferroni test showed that in epidermoid and intermediate cells the staining intensity increased considerably between grade 1 and grade 2, as well as between grade 1 and grade 3. However, no significant differences between grades 2 and 3 were reported for both components, which suggested the GLUT1 expression plateau in higher grade tumors. Mucoid cells showed low staining intensity and uniformity, regardless of the salivary gland neoplasm malignancy degree; no significant differences were also revealed.

In addition to statistical analysis, we applied Spearman's rank correlation test to determine the correlation between the GLUT1 staining intensity and the tumor grade. The following results were obtained: epidermoid cells — $rs = 0.48$ ($p = 0.003$), intermediate cells — $rs = 0.42$ ($p = 0.008$). These data indicate a moderate positive correlation with the tumor grade and suggest a progressive GLUT1 expression increase with increasing tumor aggressiveness. In contrast, mucocytes showed a weak non-significant correlation ($rs = 0.15$, $p = 0.36$), which reflected their minor contribution to tumor grading.

In MEC, GLUT1 staining intensity in various cellular components allows one to achieve critical understanding of metabolic activity associated with various tumor grades. Epidermoid and intermediate cells demonstrate a progressive increase in GLUT1 expression. Such progression demonstrates a considerable increase in metabolic activity with increasing tumor grade: from low grade with minimal GLUT1 expression indicating the decreased metabolic demands to high grade, in which the staining intensity is close to maximum suggesting high metabolic activity that is necessary for rapid tumor growth and tumor aggressiveness.

Correlation between GLUT1 and Ki-67 in various MEC components

Spearman's rank correlation test allowed us to reveal a strong positive correlation between the GLUT1 and Ki-67 staining

Table 3. Correlation between GLUT1 and Ki-67 and tumor grades

Correlation between GLUT1 and tumor grades		
Grading system	Correlation coefficient (*rs*)	*p*-value
AFIP	0.5	0.001
Brandwein	0.45	0.003
Modified Healy	0.48	0.002
MSKCC	0.4	0.01
Correlation between Ki-67 and tumor grades		
Grading system	Correlation coefficient (*rs*)	*p*-value
AFIP	0.55	0.0005
Brandwein	0.48	0.002
Modified Healy	0.52	0.001
MSKCC	0.45	0.003

intensity in epidermoid cells ($rs = 0.68$, $p < 0.001$). This suggests that higher GLUT1 expression is stably associated with the increased proliferative activity for this component. A moderate positive correlation was reported for intermediate cells ($rs = 0.52$, $p = 0.004$), which suggested a significant, but less strong, association between two markers. In contrast, mucocytes showed a weak non-significant correlation ($rs = 0.20$, $p = 0.18$), which reflected a minimal interplay between the GLUT1 expression and Ki-67 proliferation in this component.

Both markers, GLUT1 and Ki-67, showed high correlation and strong relationship in epidermoid and intermediate cells. In epidermoid cells, the following values were obtained for GLUT1 and Ki-67: $rs = 0.48$ ($p = 0.003$) and $rs = 0.53$ ($p = 0.0005$). Similar values were reported for intermediate cells: GLUT1 — $rs = 0.42$ ($p = 0.008$) and Ki-67 — $rs = 0.47$ ($p = 0.0025$). This indicates moderate correlation with the malignancy degree, which makes the markers selected important for tumor progression assessment. When assessing the correlation with the malignancy degree, in contrast to epidermoid and intermediate cells, mucocytes showed weak correlations for both GLUT1, where $rs = 0.15$ at $p = 0.36$, and Ki-67, where $rs = 0.25$ at $p = 0.12$, which once more emphasized their limited contribution to tumor grading.

GLUT1 correlation with tumor grading systems

GLUT1 staining intensity showed a moderate positive correlation with tumor grades for all grading systems. The strongest correlation was reported for the AFIP system ($rs = 0.50$, $p = 0.001$), which suggests that GLUT1 agrees well with the tumor aggressiveness determined by the AFIP criteria. The modified Healy system ($rs = 0.48$, $p = 0.002$) also showed a comparable correlation. The Brandwein ($rs = 0.45$, $p = 0.003$) and MSKCC ($rs = 0.40$, $p = 0.01$) systems showed weaker correlation, which suggests less full GLUT1 compliance with the grading ctiteria.

Ki-67 correlation with tumor grading systems

Ki-67 proliferation indices showed stronger correlation with tumor grades, than GLUT1, for all grading systems. The highest correlation was reported for the AFIP system ($rs = 0.55$, $p = 0.0005$) that was followed by the modified Healy system ($rs = 0.52$, $p = 0.001$). These findings emphasize the effectiveness of Ki-67 as a reliable tumor progression marker, especially within the limits of these grading systems. The Brandwein ($rs = 0.48$, $p = 0.002$) and MSKCC ($rs = 0.45$, $p = 0.003$) also showed moderate correlations, but weaker, than the AFIP and modified Healy systems.

Comparison of grading systems

Among four grading systems assessed, AFIP consistently showed the strongest correlation with both GLUT1 and Ki-67 expression, which suggests being most close to tumor biology reflected by these markers. The modified Healy system showed almost the same results, especially for Ki-67, which makes it one more reliable basis for tumor aggressiveness assessment. The Brandwein and MSKCC systems showed a slightly weaker correlation, especially for GLUT1, which indicates lower coordination with metabolic and proliferative activity (Table 3).

DISCUSSION

In this study we assessed proliferative activity (Ki-67) and activity of the glucose transporter protein (GLUT1) in various MEC components, which were found in all cellular components. High expression of the selected proteins was revealed in the MEC epidermoid and intermediate cells, which indicates growth and neoplastic process aggressiveness. The findings are similar to the earlier reported data [15, 16], according to which GLUT1 expression was higher in the epidermoid component and high-grade tumors, respectively.

The Ki-67 index serves as the most important biomarker to determine the MEC grade that complements conventional histological assessment. Thus, in 46 patients, low Ki-67 index was correlated to favorable outcomes, while higher index values indicated the increased risk of aggressive disease course [17]. In contrast to more subjective histological assessment involving indirect measurement of proliferative activity based on the share of solid areas, the Ki-67 index allows one to directly determine proliferation through enumeration of the actively dividing cells. Such a direct approach makes it a more objective and reliable marker allowing one to clearly distinguish indolent and aggressive MEC forms [14, 17]. Thus, using the Ki-67 index along with histological assessment can considerably improve accuracy of predicting the clinical course of such tumors, ensuring invaluable guidance for targeted therapeutic strategies.

Mostly, such grading systems, as AFIP and MSKCC, are prone to conservative grading, which highlights low and intermediate classification, while the Brandwein system is characterized by the more aggressive approach and higher effectiveness when dealing with high-grade tumors. The modified Healy system is more effective when dealing with intermediate-grade tumors. Such variation emphasizes the impact of grading criteria on tumor classification and the importance of matching the grading system to clinical goals, such as risk stratification or treatment planning.

CONCLUSIONS

The study emphasizes the key role of GLUT1 and Ki-67 in assessing metabolic and proliferative activity of salivary gland MEC. High expression of these markers revealed in epidermoid and intermediate cells corresponded to the following values: low grade — Ki-67 below 10%, GLUT1 intensity 1–2; intermediate grade — Ki-67 between 10 and 15%, GLUT1 intensity 2; high grade — Ki-67 >15%, GLUT1 intensity 3. The data obtained were correlated to tumor grade, while mucocytes demonstrated the lowest activity. GLUT1 and Ki-67 help effectively distinguish low-grade tumors (G1) from intermediate-grade (G2) and high-grade (G3) ones, and the plateau effect is observed between grades 2 and 3. Among four grading systems assessed, AFIP has shown the strongest correlation with these biomarkers, which suggests that it agrees with the MEC biological behavior. The modified Healy system has also shown good results, it is suitable for medium-grade tumors, while the Brandwein system is better suited for dealing with highly aggressive poorly differentiated tumors; the MSKCC seems to be more conservative. These findings highlight potential value of integrating IHC markers, such as GLUT1 and Ki-67, into MEC grading protocols in order to improve accuracy of the diagnosis and prognostic evaluation. However, mismatch between grading systems emphasizes the need for standardized approaches. Further large-scale studies are necessary to confirm these results and assess the effectiveness of additional markers for improvement of the MEC diagnosis, grading, and treatment planning.

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