

Metabolic biomarker in oral squamous cell carcinoma – a comprehensive review

Stoffwechselbiomarker beim oralen Plattenepithelkarzinom – ein umfassender Review

Abstract

Oral squamous cell carcinoma (OSCC) is one of the most common malignant tumors worldwide with an increasing incidence. The surgical treatment is challenging and often requires the entire repertoire of plastic surgery. Diagnostically only a few crucial parameters are in use and even less for an individual and specific drug targeting. An individualised prognostic calculation is unavoidable to be able to adapt very complex surgical processes to an acceptable level. Unfortunately, the classic TNM system and grading are no longer sufficient, especially for individualized prognosis. Moreover, despite advances in treatment, studies have shown that the prognosis of patients with OSCC in terms of survival rate has not improved significantly, which is mainly due to the presence of treatment-resistant OSCC. Therefore, the identification of new, reliable biomarkers for early diagnosis and drug targets of OSCC is urgently needed. Meanwhile, the abundance of potential biomarkers for OSCC is difficult to keep track of. Therefore, the aim of the article was to provide an overview of articles listed in Pubmed® that deal with the topic of biomarkers in oral squamous cell carcinoma, focusing in particular on the topic metabolism. Another question of this study was to set the focus on essential additive metabolic biomarkers, which can also be easily used in clinical routine.

Keywords: metabolic biomarker, OSCC, prognosis, survival

Zusammenfassung

Das orale Plattenepithelkarzinom (OSCC) ist einer der häufigsten bösartigen Tumoren weltweit mit steigender Inzidenz. Die chirurgische Behandlung ist anspruchsvoll und erfordert oft das gesamte Repertoire der plastischen Chirurgie.

Diagnostisch sind nur wenige entscheidende Parameter relevant und noch weniger für eine individuelle und spezifische Medikamenten-Zielgruppenansprache. Um sehr komplexe chirurgische Prozesse auf ein akzeptables Maß anpassen zu können, ist eine individualisierte Prognoseberechnung unumgänglich.

Leider reichen das klassische TNM-System und die Einstufung insbesondere für eine individualisierte Prognose nicht mehr aus. Darüber hinaus haben Studien trotz Fortschritten in der Behandlung gezeigt, dass sich die Prognose von Patienten mit oralen Plattenepithelkarzinom im Hinblick auf die Überlebensrate nicht wesentlich verbessert hat, was hauptsächlich auf das Vorhandensein von behandlungsresistentem oralen Plattenepithelkarzinomen zurückzuführen ist.

Daher ist die Identifizierung neuer, zuverlässiger Biomarker für die Frühdiagnose und Wirkstoffziele von OSCC dringend erforderlich. Mittlerweile ist es schwierig, den Überblick über die Fülle an potenziellen Biomarkern für OSCC zu behalten.

Ziel des Artikels war es daher, einen Überblick über in Pubmed® gelistete Artikel zu geben, die sich mit dem Thema Biomarker beim oralen Plat-

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tenepithelkarzinom beschäftigen und dabei insbesondere auf das Thema Stoffwechsel eingehen. Eine weitere Fragestellung dieser Studie bestand darin, den Fokus auf essenzielle additive metabolische Biomarker zu legen, die auch im klinischen Alltag problemlos eingesetzt werden können.

Schlüsselwörter: metabolische Biomarker, orales Plattenepithelkarzinom, Prognose, Überleben

1 Introduction

Oral squamous cell carcinomas (OSCC) are among the twenty most frequent human malignancies worldwide (Global Cancer Observatory, <https://gco.iarc.fr/> [accessed 2024 Jun 25]). Treatment is usually surgical with resection of the tumor and neck dissection. The resulting defects are often not insignificant and require complex reconstruction procedures. From a plastic surgery perspective, it would often be desirable to minimize the extent of surgical methods, taking into account various risk factors [1]. This brings biomarkers into focus in order to be able to calculate the individual prognosis in detail. According to GLOBOCAN estimates, there is an overall increase in the incidence and mortality of this type of cancer in Europe [2]. Moreover, the 5-year survival rate has stagnated at around 50% for over four decades. This indicates that TNM and grading alone are not sufficient for an individualized prognosis [3], [4]. Consequently, there is an urgent need to establish new, additional prognostic factors ("biomarker") to characterize the individual aggressive potential of the OSCC in detail on the one hand, and on the other hand individualize the therapeutic strategy. In an earlier analysis, we were able to certify the excellent quality of head and neck tumor centers in Germany [5]. However, our results showed that biomarkers have not yet been used primarily in clinical routine in the majority of tumor centers. One of the first promising initial additive biomarkers is Epithelial Growth Factor Receptor (EGFR) [6]. However, on the one hand EGFR is not uniformly expressed on all OSCC tumor cells. Moreover, mutations in various domains of the EGFR gene not only alter drug binding dynamics giving rise to resistance have been described [7]. On the other hand and especially emphasized, the molecular pathogenesis of OSCC is very complex and results from a multitude of events that include the interplay between genetic mutations and altered transcript, protein and metabolite levels [8]. Intriguingly, of particular interest are biomarkers that are involved in tumor metabolism. This is due to the astonishing metabolic adaptation of many tumors, which was first demonstrated by Otto Warburg and colleagues at the beginning of the 20th century [9]. The Warburg effect characterizes an alteration of the glucose metabolism of tumor cells that leads to the production of large amounts of lactate. This requires a modulation of the expression of various biomarkers that influence this adaptive metabolism, which then become of course detectable. For a better understanding, the complexity of the glucose metabolism in the tumor cell should be emphasized more in detail.

Therefore, an overview of glycolysis in tumors is presented in Figure 1.

The aim of the present study was to analyze and develop a comprehensive analytical review to determine additive prognostic factors in oral squamous cell carcinoma, especially for metabolic parameters.

2 Material and methods

We reviewed Pubmed® within two and a half years from January 2022 to June 2024. All articles related to biomarkers in oral squamous cell carcinoma were checked fundamentally. "Oral squamous cell carcinoma, biomarkers and prognosis" (Boolean operators only AND), these were the keywords of our search.

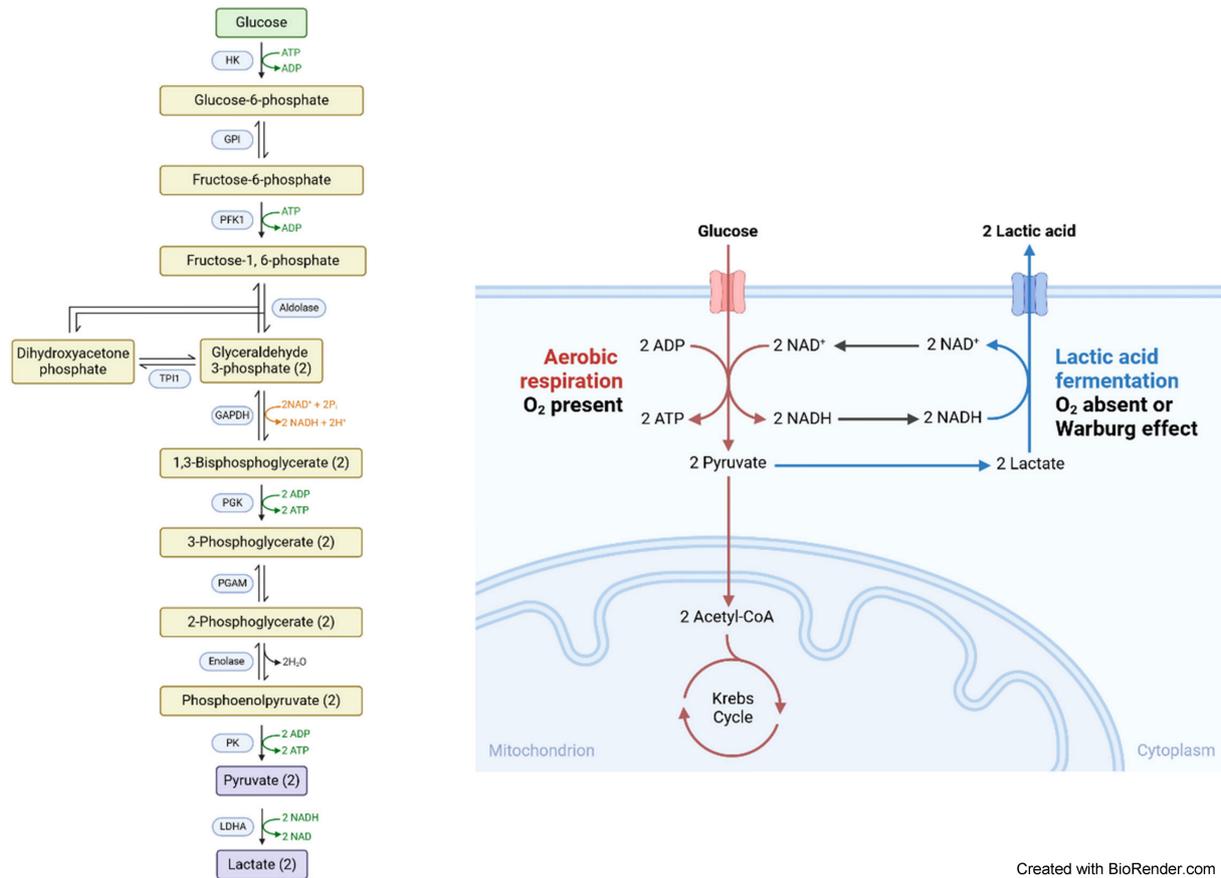
We set the following exclusion criteria: no review articles, no case reports, no paper written in a language other than English, no duplications, only pathways and no genetics (Figure 2).

In addition, all papers that were review articles or case reports were filtered out. Moreover, the articles that existed twice (described the same biomarker, only one article on the specific biomarker was reported here and was included in our study) were also eliminated. Furthermore, we were only interested in the pathways and not the genetic route (Boolean operators only NOT). In addition, the articles that were not written in English were excluded. All articles were successively assigned to these criteria using the NIH® (National Library of Medicine) algorithm. All inclusion and exclusion criteria are listed as flow diagram and shown graphically in Figure 2.

3 Results

The Pubmed search with the keywords "oral squamous cell carcinoma AND biomarkers AND prognosis" resulted in 6,004 articles found. Applying the exclusion criteria no review articles, no case reports, all articles in English, no duplications, only pathways and no genetics 2.517 publications remained. However, applying all exclusion criteria (see Figure 2) only 312 (5.2%) articles remained for further systematic analysis.

The publications were classified according to the different points as follows into 4 large groups: i) cell cycle, ii) metabolic, iii) immunological relevant proteins as well as iv) proteins involved in apoptosis. Figure 3 provides an overview of all 312 relevant proteins in accordance to their classification of the different pathways.



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Figure 1: Glycolysis pathway

Normally, the glucose metabolism ends in mitochondrial respiratory chain and TCA (citric acid cycle). In tumors, among them OSCC, it is limited at lactate!

Abbreviations: GAPDH – glyceraldehyde-3-phosphate dehydrogenase; HK – hexokinase; LDHA – lactate-dehydrogenase A; PFK1 – phosphofruktokinase; PGAM1 – phosphoglycerate mutase 1; PGK1 – phosphoglycerate kinase 1; TPI1 – triosephosphate-isomerase

i) The first and largest group summarizes all aspects acting directly on the cell cycle, 177 articles were identified (Figure 4). These were tumor suppressors (n=9), micro-RNA (n=41), long-RNA (n=16), and others (n=111). These 'others' mentioned include cell membrane structure, adhesion of the cells to each other like intermediate filaments, cyclin dependent kinase or mitosis-associated pathways.

The pathway that directly affects the cell cycle has been published most frequently (177 articles (57%)). Of these, 50 of the 177 articles described the structure of the cell membrane and the adhesion of cells, which corresponds to around 28%. Moreover, 41 of 177 articles (23%), had micro-RNA (for example: [10], [11], [12], [13], [14], [15], [16], [17]) as topic. In addition, mitosis-associated pathways were related to only 46 of the 177 articles (26%). In comparison, tumor suppressor genes (9 publications of the 177, 5%), cyclin dependent kinase markers (15 publications of the 177, 8%) and lncRNA (16 publications of the 177, 9%) (publishing examples: [18], [19], [20], [21]) were less studied.

ii) The second very interesting and quite homogeneous group (57 publications in total) can be subdivided into a metabolic-enzymatic pathway of which 28 articles were assigned to metabolism and 29 articles to enzymatic classified (Figure 5). Comparing these investigated pathways, it is noticeable that the metabolic-enzymatic pathway is published in 57 (18%) of the 312 articles which corresponds to one fifth of the articles found, according to our criteria. As this group appears to be the most promising for the establishment of biomarkers at the OSCC, all relevant and respective articles are also discussed in more detail in Table 1 and Table 2.

iii) The immunological pathway was the subject in a further 56 articles and iv) there were apoptotic mechanisms found in 22 publications (is equivalent to 7% of all relevant articles).

Figure 5 shows the respective distribution of the articles with metabolic and enzymatic accordance. The articles dealing with the metabolic pathway are summarized in Table 2.

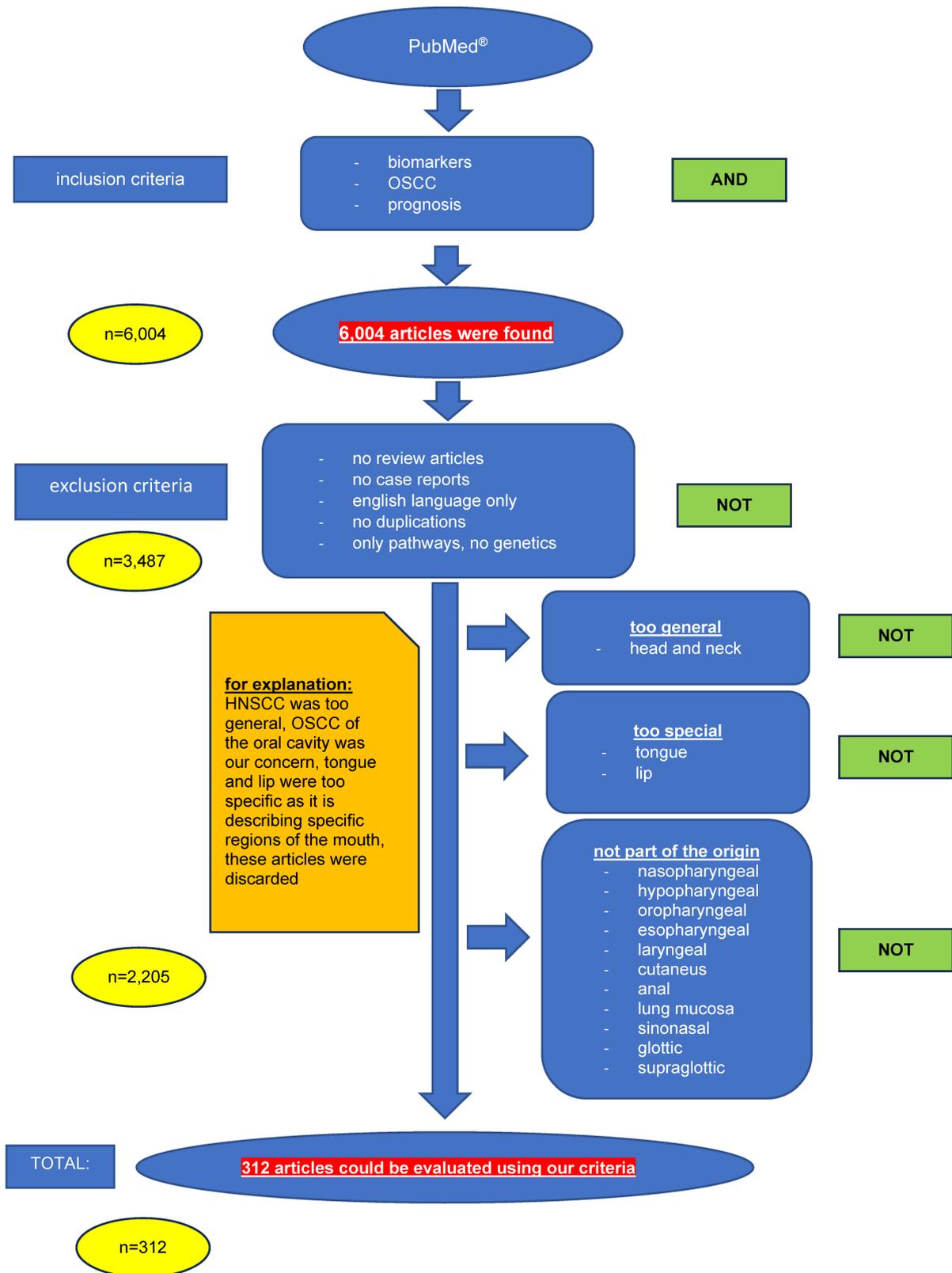


Figure 2: Graphic of inclusion and exclusion criteria in the PubMed® search

Classification according to investigated pathways
(total 312 articles)

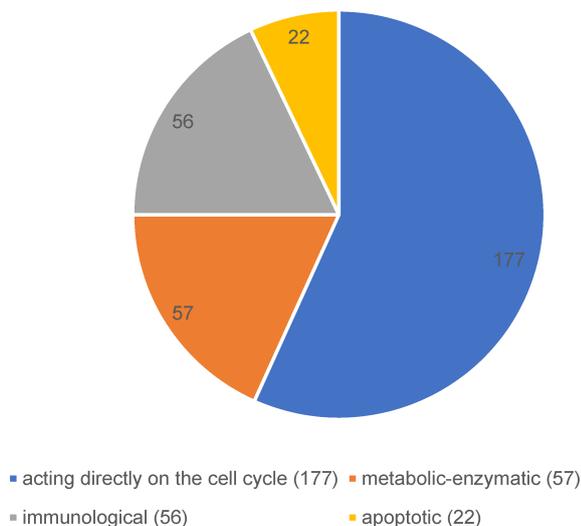


Figure 3: Classification according to investigated pathways

Classification of the cell cycle-related pathways
(total 177 articles)

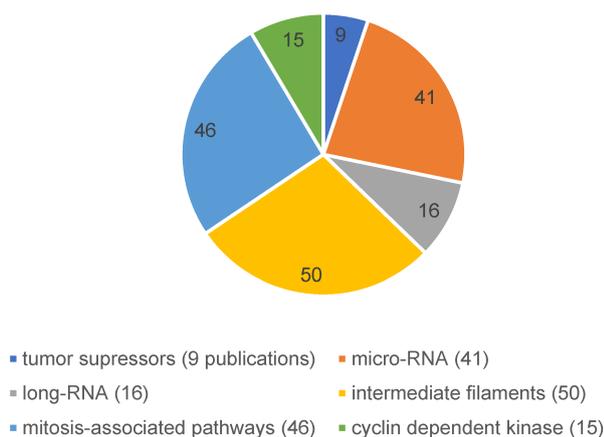


Figure 4: Classification of the cell cycle-related pathway

Distribution of articles with metabolic and enzymatic targets
(total 57 articles)

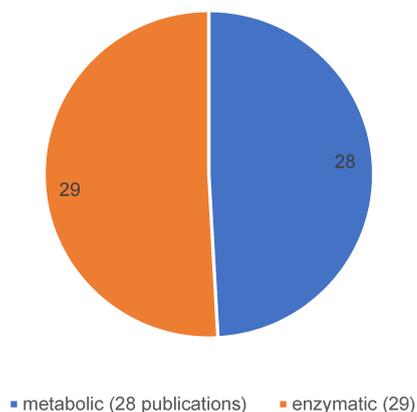


Figure 5: Articles with metabolic and enzymatic targets

4 Discussion

4.1 Study design and general aspects

Intensive research into the establishment of additive biomarkers in OSCC has now been ongoing for more than 20 years. The first groundbreaking review of biomarkers in OSCC was published in 2003 by Schliephake [22] as a systematic review of 169 articles. However, these 169 articles did not exclusively focus on tumor metabolism. Nevertheless, the conclusion of this review was sobering, as only 12 out of 23 articles dealing with of cell cycle acceleration and proliferation markers showed a significant association with the prognosis of OSCC. Three years later, Lothaire and colleagues provided an updated overview of the critical role of various prognostic factors in OSCC [23]. The author encouraged clinicians and scientists to push ahead with the establishment of additive biomarkers for more precise diagnosis as quickly as possible.

Other reviews on the subject are the articles by Cervino et al. [24], da Silva et al. [25], Dolens et al. [26] and Blatt et al. [27]. In the meantime, various attempts have been made to comprehensively analyze the topic of biomarkers at the OSCC. However, it is not uncommon for the investigations to be rather coarsely focused and each of the investigators had different criteria to filter the articles. Each investigator focused on different aspects of the article search, resulting in a different number of sources to which the investigator referred. For example, it should be mentioned that Cervino et al. [24] summarized 1,884 papers and finally focused on only 8 articles. Dolens et al. [26], on the other hand, included 172 articles and Blatt et al. [27] used 128 studies that met their specific inclusion criteria, among them were proliferative indicators like Ki-67, Cox-2, Cdc7 or ABCB5 [28], [29], [30], [31], [32].

All these excellent review articles are broadly based on the topic of biomarkers at the OSCC. However, the focus of our current survey was on energetic as well as metabolic biomarkers. Therefore, the present investigation would complement these analyses.

4.2 Metabolic aspects, glycolysis in OSCC and its benefit as additive biomarker

Whereas the metabolic-enzymatic pathway for OSCC has already been described quite well by many publications, which is why it should be discussed in more detail in this review. Since Otto Warburg's groundbreaking experiments on tumor metabolism and the discovery of increased glucose uptake by tumors, many attempts have been made to find valuable additive biomarkers describing this mechanism [9]. Since this major metabolic pathway of glycolysis, which is also significant in OSCC, is very diverse and very complex, so we focused our analysis on metabolic adaptations of gene activity in oral carcinogenesis.

Table 1: Relevant papers dealing with enzymatic biomarkers in OSCC

Authors	Year of publication	Study design	Results	Prognostic effects
Hu et al. Changsha, China [62]	2021	normal oral mucosa (n=17), oral squamous cell carcinoma tissues (n=61), paired adjacent tissues (n=47)	G3BP1 as potential biomarker	high G3BP1 mRNA levels associated with survival rates in patients with OSCC
Marconi et al. Chieti, Italy [63]	2022	Microscopic analysis on expression of MMP-9	e.g. MMP-9 as marker	MMP-9 is over-expressed in a cellular model of OSCC
Zhang et al. Luzhou, China [64]	2021	compared with healthy control group, were five proteins (I309, GDF15, AXL, MMP3, and CTACK) in the serum of in situ oral cancer group	e.g. MMP-3 as potential novel biomarker	p=0,04 proteins (I309, GDF15, AXL, MMP3, CTACK, and MCSF) had diagnostic value for OSCC
Liu et al. Kaohsiung, Taiwan [65]	2021	353 OSCC patients including 117 BMSCC, 187 TSCC, and 49 lip squamous cell carcinoma patients	GBP5 as potential biomarker and therapeutic target for OSCC	high gene expression levels of GBP5 were associated with poor overall survival
Sulkshane et al. Maharashtra, India [66]	2021	USP9X was assessed by immunoblotting and immunohistochemistry in OC lines and tissues	USP9X potential as a prognostic biomarker and therapeutic target in oral cancers	p=0,0197 expression correlated with poor prognosis in OSCC patients
Zeng et al. Shaanxi, China [67]	2021	SELENBP1 expression and its clinical significance in OSCC were analyzed from TCGA database	downregulation of SELENBP1 enhances oral squamous cell carcinoma chemoresistance	SELENBP1 knockdown enhances resistance of OSCC cells, over-expression → opposite effect
Starzyńska et al. Gdansk, Poland [68]	2020	92 patients, PIK3CA encoded on PTEN expression by IHC	PTEN as potential prognostic factor	inverse correlation with the T stage of the primary tumor
Bhanu et al. Mangalore, India [69]	2020	40 cases, immunohistochemical expression of lysyl oxidase using LOX2 primary antibody	lysyl oxidase as a potential predictive biomarker for OSCC	LOX expression was elevated in OSCC patients who had lymph node metastasis and in those who died of disease
Fang et al. Taipei, Taiwan [70]	2019	107 patients with OSCC, analyzed by immunohistochemistry	AKR1B10 is a valuable biomarker for prognostic prediction of recurrence and survival in OSCC.	p=0.043 tumor size, perineural invasion (p=0.012), recurrence (p=0.001)
Shimomura et al. Kashihara, Japan [71]	2018	98 OSCC patients, reduced DHRS9 expression in 68 of 98 patients (69.4%)	downregulation of DHRS9 → poor prognosis in OSCC	p=0.0135 low DHRS9 expression had a significantly poorer prognosis than high DHRS9 expression (p=0.0443)
Eckert et al. Halle, Germany [46]	2019	tumor samples from 72 OSCC patients and 24 samples of normal tissue, 158 OSCC samples: immunohistochemistry, 89 blood serum samples: ELISA	CAIX as prognostic factor	p<0.001 higher mRNA-level of CA9 in OSCC samples than in adjacent normal tissue
Pathiyil et al. Karnataka, India [72]	2017	20 patients, compared with 20 age and gender matched controls	Salivary lactate dehydrogenase as a prognostic marker in OSCC	p=0,001 lactate dehydrogenase levels → could be used not only as a diagnostic marker → could also be a valuable prognostic biomarker in surgically for OSCC

(Continued)

Table 1: Relevant papers dealing with enzymatic biomarkers in OSCC

Authors	Year of publication	Study design	Results	Prognostic effects
Lee et al. Seoul, Republic of Korea [73]	2017	233 patients → underwent curative surgery for previously untreated OSCC between 2000 and 2012 → immunohistochemistry	glutathione peroxidase 1 predicts poor prognosis OSC, useful biomarker	p<0,05 GPX1 overexpression → significantly correlated with nodal metastasis, advanced overall stage, depth of invasion of >10 mm, high grade, perineural invasion
Kelgandre et al. Ahmednagar, India [74]	2016	100 histopathologically proven cases of OSCC (study group) and 100 normal healthy individuals (control group)	adenosine deaminase as prognostic and diagnostic biomarker	ADA levels → in OSCC cases compared to the control group, also with histopathological grade
Harada et al. Kitakyushu, Japan [75]	2016	110 paraffin-embedded tumor samples → patients with surgically resected ESOSCC (T1-2N0). Recurrence was recognized in 37 of 110 (33.6%) patients, strong expression in 40 patients (36.4%)	N-acetylgalactosaminyl-transferase 3 as useful parameter in early stage	p<0.001 univariate and multivariate analyses demonstrated: strong GalNAc-T3+ status → markedly lower disease-free survival rates
Vincent-Chong et al. Kuala Lumpur, Malaysia [76]	2014	real-time quantitative PCR and immunohistochemistry methods in OSCC samples	MMP13, poor prognosis in OSCC	p<0.05 high level of MMP13 associated with poor prognosis, lymph node metastasis p=0.011, tumor staging p=0.002
Zhu et al. Shanghai, China [77]	2014	PLCG1: performed on the biopsies of 232 out of 256 OSCC patients at clinical stage III/IVA, PLCG1 positive score was determined by immunoreactive scoring system	phospholipase C gamma 1 is a potential prognostic biomarker	low PLCG1 expression: significantly better overall survival (p=0.022), disease-free survival (p=0.087)
Seto et al. Ibaraki, Japan [78]	2013	68 patients → immunohistochemistry using antibodies against GnT-V	Negative expression of N-acetylglucosaminyl-transferase V = poor prognosis	p=0.048 negative GnT-V expression was associated with mode of invasion by multiple logistic regression analysis
Pérez-Sayáns et al. Santiago de Compostela, Spain [79]	2010	patients with OSCC + control group of healthy individuals included age, sex, smoking, tumor location and tumor stage; brush cytology samples, analyzed by real-time quantitative polymerase chain reaction.	ATP6V1C1 expression levels: highly sensitive and specific diagnostic method	p<0.001: ATP6V1C1 expression (Mann-Whitney U test)
Begum et al. Tokyo, Japan [80]	2009	50 cases of OSCC demonstrated the overexpression of PAK4 to be significantly associated with a poorer prognosis	PAK4 = a good diagnostic and/or therapeutic target	immunohistochemical analysis of primary tumors from 105 cases of head and neck SCC including 50 cases of OSCC
Rao et al. Bangalore, India [81]	2020	40 cases each of OED and OSCC were retrieved from departmental archives, IHC → correlated with clinicopathological parameters	ALDH1 used as individual prognostic markers	p=0.05 expression increased from OED through OSCC

(Continued)

Table 1: Relevant papers dealing with enzymatic biomarkers in OSCC

Authors	Year of publication	Study design	Results	Prognostic effects
Da Silva et al. Sao Paulo, Brazil [25]	2009	qRT-PCR in laser capture microdissected OSCC samples	FASN+USP2a in OSCC → associated with tumor progression and poor prognosis	p=0,001 by qRT-PCR in laser capture microdissected OSCC samples
Søland et al. Oslo, Norway [82]	2008	Investigation of COX-2 at the invasive front and in central/superficial parts of OSCC, immunohistochemistry of 53 early stage OSCCs	in early stage: most tumours did not express COX-2 at the invasive front, COX-2: histomorphological grading systems and TNM stage were of no prognostic value	most tumours were COX-2 negative at the invasive front, lowest P-value in survival analyses was P=0.06 for p-ERK1/2 at the invasive front
Shen et al. Harbin, China [83]	2020	62 cases of OSCC and 18 normal tissues, pathological alterations were assessed by immunohistochemistry, NUDT1 in 31 cases of OSCC and normal tissues	NUDT1 potential independent predictor for the prognosis of patients with OSCC	p<0.0001 NUDT1 were statistically increased in OSCC tissue, had a significant association with histopathologic grades of OSCC
Sun et al. Nanjing, China [84]	2021	28 patients: mass spectrometry, 18 patients: public databases, 100 patients: immunohistochemistry	PLOD2: poor prognostic biomarker for OSCC	p<0.001 highly increased in HNSCC an OSCC
Kurokawa et al. Kitakyushu, Japan [85]	1998	43 patients, relationships among the various clinicopathologic parameters and clinical course	Manganese superoxide dismutase correlates with prognosis of OSCC	Mn-SOD activity in cancerous tissues / healthy controls, no significant difference patients with O-SCC / healthy controls, no significant difference tissue Mn-SOD activities / clinical stage
Hu et al. Taiwan [54]	2023	2 OSCC cell lines were grown + 30 tumor-adjacent normal tissues and 315 tumor tissues from oral cancer patients were downloaded from TCGA	<i>PFKFB3</i> and <i>PFKFB4</i> might be potential prognostic biomarkers and therapeutic targets for OSCC	significant differences between the scrambled control and knocked down cells were indicated as p<0.05, p<0.01, and p<0.001
Zhang et al. China [55]	2022	40 OSCC → recruited to the study for untargeted analysis → cell culture, PCR, western blot, IHC	NNMT may be a critical regulator of EMT in OSCC and may serve as a prognostic biomarker for OSCC	analyses: two-sided tests + considered statistically significant at p<0.05.
Tseng et al. Taiwan [56]	2022	tissue samples: collected from 133 patients with OSCC	level of HDAC6 may be a useful prognostic biomarker and offer a novel immune cell-related therapeutic strategy of targeting IL-13 in OSCC	significance of differences between 2 independent groups was analyzed with a two-tailed Student's t-test: p<0.05 was considered to indicate a significant difference in all statistical analyses

AXL – AXL protein; CAIX – Carbonic Anhydrase 9; CTACK – cutaneous T cell-attracting chemokine; COX-2 – cyclooxygenase-2; G3BP1 – Ras-GTPase activating protein binding protein 1; GBP5 – guanylate binding protein 5; GDF15 – growth/differentiation factor 15; I309 – human cytokine I-309; IHC – immunohistochemistry; MCSF – macrophage colony-stimulating factor; MMP – Matrix Metalloproteinase; PAK4 – p21-activated kinase 4; PIK3CA – phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; PLCG1 – phospholipase C gamma 1; PTEN – phosphatase and tensin homolog; SELENBP1 – selenium-binding protein 1

Table 2: Overview to relevant investigations with respect to metabolic pathways in OSCC

Authors	Year of publication	Study design	Results	Comments
Zuo et al. Zhengzhou, China [86]	2021	103 patients of OSCC before and after the operation	serum metabolomics (hypoxanthine)analysis could be used to prognosis of OSCC	p<0.001 14 differential metabolites and five disturbed pathways were identified, Succinic acid change-low, hypoxanthine change-high tumor grade, and tumor stage indicated a trend towards improved recurrence-free survival
Ishikawa et al. Iida-nishi, Japan [53]	2022	72 OSCC patients, training group: n=35, validation group n=37, comprehensive metabolomic analyses, unstimulated saliva samples	3-Methylhistidine and 5-Hydroxylysine as prognostic factors as metabolic product	p=0.009 concentrations of 5-hydroxylysine in training group, overall survival, 3-methylhistidine (p=0.0048) as prognostic factors for OS in the validation group
Zhou et al. Nachang, China [87]	2022	Glycolytic enzymes/ proteins	Several glycolytic proteins as biomarkers; LDH, GLUT-1, GLUT-3	Glycolytic proteins potential targets
Tzeng et al. Taipei, Taiwan [51]	2021	Human tongue carcinoma cell lines + 48 OSCC samples	Endothelin 1 (ET-1) involved in Epithelial-mesenchymal-transition	Knockdown of ET-1 remarkably reduced Epithelial-mesenchymal-transition signals
Zhu et al. Shandong, China [39]	2020	applying with quantitative real-time polymerase chain reaction (qRT-PCR)	HK2 level is consequently regulating cellular behaviors in OSCC as a tumor promoter	HK2 = a target of miR-106a-5p and miR-106a-5p played an anti-tumor role in OSCC by inhibiting HK2
Li et al. Xinjiang, China [33]	2016	1301 subjects were included for meta-analysis	GLUT-1 = prognostic biomarker for OSCC	p<0.001 high GLUT-1 expression was associated with advanced tumor stages, higher tumor grade (p=0.0031)
Sugiura et al. Fukuota, Japan [52]	2009	160 OSCC patients, IHC	increased levels of VEGF-C/-D are associated with lymph node metastasis	independent prognostic factors, enhanced VEGF-C ~ lymph node metastasis (p>0.001)
Chuang et al. Kaohsiung, Taiwan [88]	2009	25 cases of human buccal SCCs without bony invasion, 15 cases of gingival SCCs with mandibular bony invasion	RANK pathway as biomarkers for OSCC	strong cytoplasmic staining of RANKL proteins is detected in cancer cells of both buccal and gingival SCCs
Zhao et al. Tianjin, China [38]	2021	TCGA+GEO: mRNA expression of OSCC patients	ALDOA, PGK1 = poor prognosis in OSCC, potential markers in OSCC	two hypoxia-related genes = significantly associated with prognosis of OSCC

(Continued)

Table 2: Overview to relevant investigations with respect to metabolic pathways in OSCC

Authors	Year of publication	Study design	Results	Comments
Yu et al. Shandong, China [89]	2020	3 OSCC sufferers → 229 DEGs	SPRR3 diagnostic+ prognostic marker	diagnostic and prognostic values of the candidate genes were analyzed → provided evidence for new tumor markers
Wang et al. Chiayi, Taiwan [90]	2021	306 patients (2008–2017), Kaplan-Meier analysis	preoperative AGR → prognostic biomarker	p<0.001 = low AGR, TNM staging p=0.656 → 0.783 with inclusion AGR
Zheng et al. Tianjin, China [91]	2020	Glycolytic enzymes/proteins circMDM2/miR-532- 3p/HK2 axis	glycolysis of OSCC = diagnostic biomarker + therapeutic target	Glycolytic proteins potential targets
Tomasovic- Loncaric et al. Zagreb, Croatia [92]	2019	101 non-metastatic and 95 metastatic OSCC patients were analyzed by IHC	AR as potential biomarker in OSCC	AR-positive staining of OSCC epithelium → more than 20%
Xu et al. Chongqing, China [83]	2018	IHC of 72 OSCC specimens	CLIC1 = diagnostic marker and therapeutic target for OSCC	patients with high CLIC1 expression had remarkably poorer overall survival rate than low CLIC1 expression
Mankapure et. al. Aurangabad, India [94]	2015	40 OSCC cases → compared with control group	Endothelin-1 = prognostic marker	p<0.0001 independent t-test revealed significant higher big ET-1 concentration of OSCC cases when compared to controls
Koyama et al. Chiba, Japan [95]	2015	ANGPTL3 mRNA +protein in OSCC-derived cell lines (n=8) and primary OSCCs (n=109)→ assessed the effect of ANGPTL3 on the biology and function of OSCCs	ANGPTL3= biomarker	p<0.05: ANGPTL3 upregulation was detected in the cell lines and most primary OSCCs (60%) compared with the normal counterparts
Lv et al. Shanghai, China [96]	2014	9 OSCC cell lines + 36 paired OSCC specimens → real-time PCR and western blotting	PTHLH/PTHrP = role in the pathogenesis of OSCC	p<0.0001 PTHLH mRNA + pro- tein levels in 9 OSCC cell lines were much higher than that in normal epithelial cells
Huang et al. Wuhan, China [97]	2013	tissue microarrays containing 17 normal oral mucosa, 7 oral epithelial dysplasia,43 OSCC cases were studied by immunohistochemistry	Keap1 = potential therapeutic target and prognostic value	p=0.0969 Keap1, Nrf2, PPIA, Prdx6, CD147 expres- sion in OSCC were significantly higher → to normal oral mucosa
Cheng et al. Taipei, Taiwan [98]	2012	72 OSCC patients before and 3 months after surgical cancer excision and from 30 normal controls	PIGF = biomarker for therapeutic effect, progression, recurrence, prognosis	p<0.001 pre-surgery, tumor- size p=0.015, pos. lymph node p=0.001

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Table 2: Overview to relevant investigations with respect to metabolic pathways in OSCC

Authors	Year of publication	Study design	Results	Comments
Tripathi et al. New Delhi, India [99]	2012	IHC: OSCC n=214, dysplasia n=51, hyperplastic squamous mucosa n=45, normal tissue n=80	loss of DLC1 = independent prognostic factor in patients with OSCC	P<0.001 → with dysplasia, poor prognosis p=0.023, histopathological grade p=0.015
Li et al. Seoul, South Korea [100]	2011	IHC + Western blotting	Insulin-like growth factor II = prognostic factor in OSCC	IMP3 overexpression in OSCC, correlation with high histologic grade, lymph node metastasis, advanced tumor, clinical stages
Ayala et al. Sao Paulo, Brasilien [34]	2010	142 OSCC patients, IHC	GLUT-1 and GLUT-3 as metabolic parameters/ biomarkers	both independent prognostic factors, OS GLUT-1 RR 2.066 (p=0.006) GLUT-3 RR 1.933 (p=0.018)
Chuang et. al Kaohsiung, Taiwan [88]	2009	25 cases of human buccal SCCs without bony invasion, 15 cases of gingival SCCs with mandibular bony invasion	RANKL and OPG pathway as biomarkers for OSCC	strong cytoplasmic staining of RANKL proteins is detected in cancer cells of both buccal and gingival SCCs
Zhang et al. Shanghai, China [40]	2017	122 OSCC patients immunohistochemistry, correlation between clinicopathological expression	PGAM1 predicts the poor prognosis of OSCC	PGAM1 expression correlated with age, lymphatic metastasis and tumor recurrence, is closely associated with poor overall survival + disease-free survival
Sugiura et al. Fukuoka, Japan [52]	2009	160 cases for LVD + expression of VEGF-C and D → IHC	VEGF-D as marker in OSCC	p<0.001 expression VEGF-C/D and LVD → Lymph node metastasis
Song et al. China [57]	2024	OSCC + adjacent normal fresh tissues collected, period of 2022–2023	IGF2BP3 = upregulated in OSCC	significance level of p<0.05
Huang et al. China [59]	2023	329 tumor tissues and 32 adjacent non-cancerous tissues from TCGA	high expression of GGPS1 in OSCC = poor prognosis	correlation analysis between clinical information and gene expression was implemented by Cox regression (p<0.05)
Krishna et al. India [60]	2022	65 OSCC tissues: 41 tissues (63.1%) exhibited high expression for β2-AR protein → immunohistochemistry, western blot, PCR	β2-AR protein level: identified as an independent significant prognostic factor in patients	Cox:proportional hazards model, β2-AR was identified as a prognostic biomarker of OSCC (p=0.047).

AGR – albumin/globulin ratio; ANGPTL3 – angiopoietin-like protein 3; AR – Androgen receptor; CLIC 1 – chloride intracellular channel 1; CD147 – cluster of differentiation 147, Basigin; DEGs – differentially expressed genes; ET-1 – endothelin-1; GEO – Gene Expression Omnibus; GLUT-1/3 – Glucose Transport Molecule 1/3; IHC – Immunohistochemistry; IMP3 – Insulin-like growth factor II mRNA-binding protein 3; Keap1 – Kelch Like ECH Associated Protein 1; LVD – lymphatic vessel density; LDH – Lactate Dehydrogenase; Nrf2 – nuclear factor erythroid 2-related factor 2; OPG – osteoprotegerin; OS – overall survival; PIGF – placental growth factor; PPIA – peptidylprolyl isomerase A; Prdx6 – Peroxiredoxin 6; RANKL – Receptor Activator of NF-κB Ligand; TCGA – The Cancer Genome Atlas; VEGF-C/D – vascular endothelial growth factor C/D

Therefore, the metabolic pathway will be the focus of our work in this paper and will be presented in detail in accordance with Figure 1.

The metabolic process of glycolysis and associated genes – an early key step in oral carcinogenesis – has been described in many articles. It has been shown that overexpression of different glycolytic enzymes results in a worse prognosis. The most informative and promising markers are GLUT-1 (glucose-transporter type 1), GLUT-3 (glucose-transporter type 3) and HK2 (hexokinase 2), ALDOA (aldolase A, fructose-bisphosphate A), PGK1 (phosphoglycerate kinase 1) or PGAM1 (phosphoglycerate mutase 1). Some representative articles and proteins deserve to be discussed in more detail.

The glycolytic pathway starts with the uptake of glucose into the cells, for which transporters are responsible e.g. GLUTs. GLUTs are part of a carrier family consisting of 13 members. Among these members, GLUT-1 and GLUT-3 are relevant in OSCC. Consequently, GLUTs has been studied quite frequently and it's not surprising that GLUTs in general are among the most well-studied groups of biomarkers in OSCC [33]. Both GLUT-1 and GLUT-3 [34] can be considered as significant markers of poor prognosis in OSCC. An important meta-analysis regarding GLUT-1 summarized 13 studies with 1,301 subjects published by Li et al. [33].

The authors found that an increased expression of GLUT-1 is associated with higher tumor grade ($P=0.031$), tumor size ($P<0.001$), and lymph node metastasis ($P<0.001$) as well as with shorter overall survival in OSCC [33].

The article highlights GLUT-1 as a key enzyme in OSCC prognosis and aggressiveness.

Moreover, some other studies confirm this association in distinguishing between premalignant types and invasive cancer [35]. Beyond that, this general statement about the association between GLUT-1 transporter and OSCC has been reported in several articles [36], [37]. Although GLUT-1 is the main enzyme for the intake of glucose into the cells, there are other important enzymes involved in this pathway downstream of GLUTs. A study regarding ALDOA and PGK1 by [38] shows that a high expression of ALDOA and PGK1 is associated with poor prognosis in OSCC patients and that they can be used as potential markers for predict prognosis and hypoxia in OSCC patients. Both markers are important enzymes in glycolysis. HK2 [39], as well as PGAM1 [40] were found to be relevant OSCC-associated biomarkers. HK2 catalyzes the initial step in the conversion of glucose to glucose-6-phosphate (see Figure 1) [41].

Most analyses focused on the development of the primary tumor. Metastasis itself represents a complex cascade in tumor progression that should be characterized in detail in a further review article but is essential for the discussion. The pathway of metastasis must be strictly distinguished from our work. Blatt et al. focused on glycolysis in metastasis in their article [27], which indicates metabolism in OSCC progression/metastasis.

Our analysis supports the results of Blatt et al., but we focus on the metabolism of glycolysis and the enzymes involved in glucose metabolism in primary tumors.

4.3 Tumor microenvironment and pH stability

A second metabolic-related and tumor-specific characteristic is the tumor microenvironment. This required factors that affect the pH value e.g. carbonic anhydrase. One crucial enzyme is carbonic anhydrase, a membrane-spanning tumor-associated cell surface glycoprotein that is induced by hypoxia is involved in adaptation to acidosis and in cancer progression [42]. This is because glycolysis itself is able to decrease the extracellular pH value caused by the release of the product of tumor-specific glucose metabolism, namely lactate. This must be fixed by enzymes, produced by the tumor cells.

Intriguingly, all described tumor-related mechanisms required a key regulator protein. The best-investigated one is the hypoxia-induced factor 1 with its alpha subunit (HIF-1 α) [43]. HIF itself provides a short half-time of only a few minutes. Therefore, there is an urgent need to establish surrogate markers that have the capacity to reliably describe the content of HIF activation [44]. In this context, the next promising protein that is associated with hypoxia and tumor microenvironment is the prolyl 4-hydroxylase subunit α 1 (P4HA1), which encodes the active catalytic component of prolyl 4-hydroxylase (P4H). It is noteworthy to state, this is initially considered as a key enzyme for collagen processing and therefore for the structure of extracellular matrix [38]. On closer inspection, however P4HA1 is involved in HIF stabilization and has earned the term surrogate marker for tumor hypoxia.

The high metabolic glucose turnover into lactate causes further risks even for the tumor cell. Intracellular acidification is an essential issue, which is an obstacle to tumor DNA replication. At this point, further metabolic proteins are required that contribute to intracellular pH stabilization. The key protein carbonic anhydrase 9 (CAIX), a membrane-spanning tumor-associated cell surface glycoprotein that is induced by hypoxia is involved in adaptation to acidosis and in cancer progression [45]. The interesting GLUT1-CAIX axis has been described in several articles in PubMed® related to OSCC [46], [47], [48].

In addition to glucose, malignant tumors also require other substances to sustain their complex energy utilization. One of these is glutamine, which is needed both as a source of nitrogen to support tumor biomass and additionally for energy production [49], as a consequence, tumor-related increase in glutaminolysis should be discussed and further studies must be analyzed (one study, for example, is that of [50]).

4.4 Other metabolic proteins involved in oral carcinogenesis

Remembering the complex network and difficult structure of oral carcinogenesis there is also many peptides that can make metabolic-enzymatic predictions about tumor expression. This very interesting area that is also being investigated and highlighted as follows. In addition to energy supply at the cellular level, the development of a tumor's own vascular system also plays a decisive role. Whether they intervene in the vascular area such as ET-1, HIF-1 or VEGF, integrated in collagen metabolism like P4HA1, hexoses phosphorylate (hexokinase 2) or cell-surface associated (CAIX), require separate investigations and are only briefly explained and listed here. For example, endothelin (ET-1), a glycolytic enzyme-independent peptide that is involved in microvascular imaging of several organs.

It plays a central role in oral carcinogenesis due to its regulatory axis via miRNA 4893p and TWIST [51]. This phenomenon, together with the fact of increased energy expenditure, leads to the emergence of the epithelial-mesenchymal junction (EMT), another cornerstone of carcinogenesis. On the other hand, the HIF-1 regulated expression of vascular endothelial growth factor A (VEGFA) is a well-known and intensively described process in early oral carcinogenesis.

The next critical hallmark of OSCC is the development of lymphatic metastases. Reliable biomarkers are the vascular endothelial growth factors C and (VEGF-C/-D). In multivariate analysis, overexpression of VEGF-C and VEGF-D correlated with increased lymphatic vessel density (LVD) and increased lymph node metastasis in OSCC [52].

In addition, biomarkers that can be detected in saliva are also playing an increasingly important role. It's about studying biomarkers and another promising approach is to establish salivary biomarkers, as described by [53] for example. This study identified salivary metabolic biomarkers to predict the prognosis of OSCC based on comprehensive metabolomic analyses. Quantified metabolomics data from unstimulated saliva samples from patients with OSCC were randomly divided into the training and validation groups in Ishikawa et al.'s study [53]. The training data was used to develop a Cox proportional hazards regression model to identify significant metabolites as prognostic factors for overall survival and disease-free survival. Additionally, the validation set was used to develop another Cox proportional hazards regression model using the previously identified metabolites. There were no significant differences between groups in participant characteristics. The concentrations of 5-hydroxylysine ($p=0.009$) and 3-methylhistidine ($p=0.012$) were identified as significant prognostic factors for overall survival in the training group. Among them, the concentration of 3-methylhistidine was a significant prognostic factor for overall survival in the validation group ($p=0.048$). Ishikawa et al.'s results showed that salivary

3-methylhistidine is a prognostic factor for OS in patients with OSCC.

4.5 Crosstalk metabolism in immune oncology

Hu et al. underline the key role of both glycolytic relevant enzymes Phosphofructokinase-fructose biphosphatases PFKFB3 and PFKFB4 with different effects on the prognosis of oral cancer patients with different clinicopathological outcomes [54]. Moreover, PFKFB4 expression was significantly higher in the tumour tissues and may be helpful to discriminate tumours from normal and/or premalignant tissue. The research group among Zhang analysed the role of Nicotinamide N-methyltransferase (NNMT) as a metabolic enzyme catalysing the methylation of nicotinamide (NAM) to generate 1-methyl nicotinamide (MNAM). In addition, NNMT promoted OSCC tumour cell proliferation and migration in vitro [55]. In addition, NNMT was involved in OSCC tumour cell proliferation and migration in vitro and may be considered as critical regulator of EMT in OSCC as well as a prognostic biomarker in OSCC.

Another interesting aspect is the pivotal function of Histone deacetylase proteins (HDACs) – a family of enzymes that remove acetyl functional groups from histone proteins on DNA. One of them, HDAC6, is located in the cytoplasm and involved in many biological and pathological processes. These are cell migration, the DNA damage response and carcinogenesis, by regulating its substrates. As a consequence, patients, whose tumour intensively expressed HDAC6 showed a 3.248-fold increase mortality risk compared with the low HDAC6 expression group ($P=0.003$, [56]). Interestingly, levels of HDAC6 may be also a useful prognostic biomarker and offer a novel immune cell-related therapeutic strategy of targeting IL-13 in OSCC. Some investigations into the enzymatic role of carcinogenesis in OSCC is more complex. Song et al. demonstrated the influence of IGF2BP3, encoding for the insulin-like growth factor 2 mRNA-binding protein 3. Their results indicated that OSCC specimen with greater expression levels of IGF2BP3 exhibited significantly shorter overall survival compared to those with lower expression levels ($p=0.029$). Thus, IGF2BP3 is one possible additional gene/protein in facilitating tumour development and metastasis in vivo [57].

The discovery of the enzyme GGPS1 (geranylgeranyl diphosphate synthase 1) that has so far received little attention is also highly interesting. GGPS1 is a member of the prenyltransferase family and acts as an enzyme for the posttranslational modification of proteins [58], has key roles in signalling pathways like cytoskeletal regulation and intracellular transport and can serve as a biomarker in Hepatocellular carcinoma. Related to OSCC, the authors found significantly higher expressions of GGPS1 in tumour tissues compared to normal oral tissues [59]. Moreover, it is interesting to note that the GGPS1 expressions were very closely negatively linked to overall survival (OS) and disease-free survival (DSS) of the pa-

tients of OSCC. Of course, this moves away from classical tumour metabolism but shows the diversity of adaptation mechanisms in oral cancer.

A similar approach is pursued by Krishna and coworkers. They analysed the prognostic role of Beta 2-Adrenergic Receptor (β 2-AR) in OSCC. They have key functions in cAMP-pathway [60]. In Cox proportional hazards model, β 2-AR was identified as a prognostic biomarker of OSCC patients.

A trend can be observed over the entire observation period: while classical biomarkers for energy production and metabolism were still favoured in the first period, other proteins/enzymes that play a supportive role in the complex metabolism of energy production have now followed in recent months. In addition, the cross-linkage to immunologically biologically relevant key proteins has become apparent. This crystallizes that the current research initiatives take into account two relevant Nobel Prizes – on the one hand the one on HIF-1 system and on the other hand the one on immune checkpoint blockade.

5 Conclusion

To sum up, our results show that the current approaches in biomarker research in the OSCC are satisfactory compared to 20 years ago. However, if one compares all the pathways we have classified, it turns out that the cell cycle pathway, and here in particular the micro-RNA and the intermediate filaments, have been best studied. Overall, the long-noncoding RNA, the mitosis-associated pathway, the cyclin-dependent kinase, and tumor suppressors have been less described.

Most of the articles also show the fundamental role that glycolysis plays in OSCC prognosis and support Otto Warburg's pioneering idea in the early 20th century. In our opinion, the specific use of biomarkers in OSCC for an individualized diagnosis and prognosis calculation can be considered as a new milestone in cancer treatment in great accordance with Schilsky's excellent review [61]. Altogether, considering the multiple research initiatives in the establishment of metabolic and enzymatic biomarkers in OSCC, some key enzymes are crystallizing for use in addition to TNM and grading. These are GLUT-1, CAIX and HK2 – all enzymes that play an essential role in glucose metabolism. As key enzymes, they all excellently characterize the glucose metabolism and thus the energetic situation of the tumor cell: GLUT-1 as the gateway into the cell, HK2 as the initiator of tumor-related metabolism and CAIX for pH stability as well as and for elimination of toxic waste products. The latter can also be described as the gatekeeper of epithelial-mesenchymal transition. An upregulation of these proteins characterizes an increased metabolism and a more aggressive tumor subtype; possible therapeutic options would be targeted strategies against the expression of, for example, the surface enzyme GLUT-1. From a clinical transnational perspective, it can nevertheless be formulated that, at

the present time, the most promising additive (metabolic/enzymatic) biomarkers in the form of GLUT-1, HK2 and CAIX can complement the classic TNM system and the grading sufficiency and should support the clinical setting.

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Competing interests

The authors declare that they have no competing interests.

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