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Policy Brief

# A Policy Brief on Improving the Prognosis of Patients With Oral Squamous Cell Carcinoma

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## Background

Oral cancer is the most malignancy in the head and neck region (1), and oral squamous cell carcinoma (OSCC) accounts for the most significant proportion of cancers in the oral cavity (2). OSCC is the sixth most common carcinoma worldwide, affecting 350 000 patients across the globe each year, leading to approximately 50% of individual deaths. The most risk factors of OSCC are smoking tobacco, consuming alcoholic drinks, and human papillomavirus infections (3,4). Currently, tumor excision, radiotherapy, chemoradiation therapy, and immunotherapy using cetuximab/PD-1 are gold standard approaches for OSCC treatment (5).

## Significance of the Subject/Study

Despite developments in therapeutic approaches, the 5-year survival rate of patients with OSCC has remained at ~ 50%, demonstrating the poor outcome of patients affected by the disease. Several reasons have been reported for poor prognosis and the high morbidity rate of patients with OSCC, including patients' common diagnosis in the late stage of the disease, drug resistance, distant metastasis, and tumor recurrence (6-22). Therefore, it is necessary to predict the outcome of patients with OSCC, probably resulting in the most appropriate treatment decision.

## Policy Options

Cancer biomarkers are molecules that are either produced by cancer cells or secreted in response to tumor cells. Three main classes have been introduced for biomarkers, including diagnostic, predictive, and prognostic markers. Prognostic markers inform the overall survival of patients (23,24). Thus, identifying critical markers for predicting the development of tumors and outcome could lead to the most suitable treatment of a disease. Due to the significant role of prognostic markers in the pathogenesis of conditions, they could also be assigned drug targets for therapeutic goals in future studies (19,25-28).

Previous reports have introduced several genes as prognostic markers in patients with OSCC (29,30). Biomarkers could either be used as a single gene (Table 1) or a combination of features (Table 2), each of which has its benefits and limitations. A prognosis with a single gene is less costly than a combination of genes. However, a combined panel might produce a more reliable, accurate, and specific result (31).

Bayat et al (29) identified potential biomarkers associated with the prognosis of OSCC patients with poor prognosis and discovered differentially expressed miRNAs (DEMs) in OSCC patients with a poor prognosis compared to OSCC patients with a favorable prognosis. Subsequently, they constructed a protein interaction map (PIM) based on DEM targets. Finally, they identified hub markers within the PIM and evaluated their possible prognostic role in OSCC.

Likewise, Taherkhani et al (30) executed an integrated bioinformatics study to unravel potential biomarkers linked to primary OSCC compared to the healthy oral mucosa following the methods of Bayat et al (29). They indicated several prognostic markers and combined panels related to a dismal prognosis in OSCC patients.

## Recommendation

It has been demonstrated that two genes called cytochrome c (CYCS) and Myc proto-oncogene protein (MYC) are more dysregulated in primary OSCC than in the healthy oral mucosa. They are also affected in OSCC patients with dismal prognoses compared to good prognoses. The hazard ratio (HZ) value for CYCS and MYC in patients with OSCC was calculated as 1.4 and 1.3, respectively.

In this respect, the HZ value of the combination of these two genes was evaluated using the GEPIA2 web server (32), available at http://gepia2.cancer-pku.cn/#index. Interestingly, the combination of the genes elevated the HZ value to 1.5. Further, the log-rank test *P* value reached a more significant result of 0.0055 (Figure 1). Therefore, it is recommended that a combination of CYCS and MYC be used as a prognostic panel in patients with OSCC due to several reasons; CYCS and MYC are affected in primary OSCC and OSCC with a dismal prognosis, suggesting their critical role in the etiology of OSCC at any stage. Moreover, combining these genes leads to more accurate and reliable results than a single gene. Additionally, the HZ value is considerable.

**Table 1.** Prognostic Biomarkers in OSCC

| Gene Symbol | *P* (Log-Rank Test) | HR (High) | *P* (HR) | Description of the Study Identifying the Markers | Reference |
|---|---|---|---|---|---|
| EGF | 0.00078 | 1.6 | 0.0009 | Poor prognosis OSCC vs. favorable prognosis OSCC | (29) |
| CALM1 | 0.001 | 1.6 | 0.0011 | Primary OSCC vs. healthy control | (30) |
| RTN4 | 0.0014 | 1.5 | 0.0015 | Poor prognosis OSCC vs. favorable prognosis OSCC | (29) |
| RAN | 0.0019 | 1.5 | 0.0021 | Poor prognosis OSCC vs. favorable prognosis OSCC | (29 |
| ACTB | 0.0054 | 1.5 | 0.0057 | Poor prognosis OSCC vs. favorable prognosis OSCC | (29) |
| CYCS | 0.009 | 1.4 | 0.0096 | Primary OSCC vs. healthy control & poor prognosis OSCC vs. favorable prognosis OSCC | (29,30) |
| H2AFZ | 0.013 | 1.4 | 0.013 | Poor prognosis OSCC vs. favorable prognosis OSCC | (29) |
| RPL9 | 0.015 | 1.4 | 0.016 | Poor prognosis OSCC vs. favorable prognosis OSCC | (29) |
| CCT6A | 0.018 | 1.4 | 0.019 | Primary OSCC vs. healthy control | (30) |
| CDC27 | 0.02 | 1.4 | 0.02 | Poor prognosis OSCC vs. favorable prognosis OSCC | |
| THBS1 | 0.0099 | 1.4 | 0.01 | Primary OSCC vs. healthy control | (30) |
| MYC | 0.028 | 1.3 | 0.029 | Primary OSCC vs. healthy control & poor prognosis OSCC vs. favorable prognosis OSCC | (29,30) |
| HSP90AA1 | 0.028 | 1.3 | 0.029 | Poor prognosis OSCC vs. favorable prognosis OSCC | (29) |
| PKM | 0.035 | 1.3 | 0.036 | Poor prognosis OSCC vs. favorable prognosis OSCC | (29) |
| NPM1 | 0.039 | 1.3 | 0.04 | Poor prognosis OSCC vs. favorable prognosis OSCC | (29) |
| CCT2 | 0.044 | 1.3 | 0.044 | Poor prognosis OSCC vs. favorable prognosis OSCC | (29) |
| FASN | 0.044 | 1.3 | 0.045 | Poor prognosis OSCC vs. favorable prognosis OSCC | (29) |
| PRMT5 | 0.047 | 1.3 | 0.048 | Poor prognosis OSCC vs. favorable prognosis OSCC | (29) |
| GATA6 | 0.047 | 1.3 | 0.049 | Poor prognosis OSCC vs. favorable prognosis OSCC | (29) |
| SPRED3 | 0.049 | 1.3 | 0.049 | Primary OSCC vs. healthy control | (30) |
| BCL2L11 | 0.041 | 0.76 | 0.042 | Primary OSCC vs. healthy control | (30) |
| KAT2B | 0.034 | 0.75 | 0.035 | Poor prognosis OSCC vs. favorable prognosis OSCC | (29) |
| DDX6 | 0.037 | 0.75 | 0.037 | Poor prognosis OSCC vs. favorable prognosis OSCC | (29) |
| ESR1 | 0.024 | 0.74 | 0.025 | Poor prognosis OSCC vs. favorable prognosis OSCC | (29) |
| GAK | 0.03 | 0.74 | 0.031 | Poor prognosis OSCC vs. favorable prognosis OSCC | (29) |
| XRN1 | 0.021 | 0.73 | 0.021 | Poor prognosis OSCC vs. favorable prognosis OSCC | (29) |
| ARRB1 | 0.011 | 0.71 | 0.011 | Poor prognosis OSCC vs. favorable prognosis OSCC | (29) |
| GIGYF1 | 0.0041 | 0.68 | 0.0042 | Primary OSCC vs. healthy control | (30) |
| PIK3R3 | 0.00073 | 0.63 | 0.0008 | Primary OSCC vs. healthy control | (30) |

*Note*. HR: Hazard ratio; OSCC: Oral squamous cell carcinoma.

**Table 2.** Prognostic Panels in OSCC

| Prognostic Panel | *P* (Log-Rank Test) | HR (High) | *P* (HR) | Description of the Study Identifying which the Markers | Reference |
|---|---|---|---|---|---|
| CALM1 + CYCS | 0.000033 | 1.8 | 0.000042 | Primary OSCC vs. healthy control | (30) |
| CALM1 + CYCS + THBS1 | 0.0015 | 1.5 | 0.0017 | Primary OSCC vs. healthy control | (30) |
| CALM1 + CYCS + THBS1 + MYC | 0.002 | 1.5 | 0.0022 | Primary OSCC vs. healthy control | (30) |
| CALM1 + CYCS + THBS1 + MYC + GATA6 | 0.0069 | 1.4 | 0.0072 | Primary OSCC vs. healthy control | (30) |
| CALM1 + CYCS + THBS1 + MYC + GATA6 + SPRED3 | 0.0011 | 1.6 | 0.0012 | Primary OSCC vs. healthy control | (30) |
| PIK3R3 + GIGYF1 | 0.021 | 0.73 | 0.022 | Primary OSCC vs. healthy control | (30) |
| PIK3R3 + GIGYF1 + BCL2L11 | 0.033 | 0.75 | 0.033 | Primary OSCC vs. healthy control | (30) |

*Note*. HR: Hazard ratio; OSCC: Oral squamous cell carcinoma.

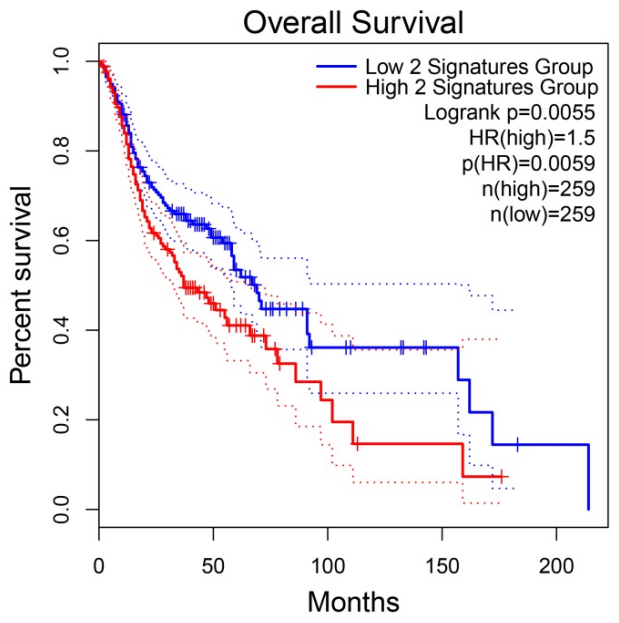


**Figure 1.** Prognostic Roles of the Genes' Signature, including CYCS and MYC, in Patients with OSCC. *Note*. CYCS: Cytochrome c; MYC: Myc proto-oncogene protein; OSCC, oral squamous cell carcinoma; HZ, hazard ratio. The X and Y axes demonstrate the survival time and probability in OSCC patients, respectively. The dotted lines represent 95% confidence intervals.

The mitochondrial release of CYCS results in the caspase-3/caspase-9 signaling activation, leading to apoptosis process hyperactivation (32,33). It is hypothesized that the enhanced CYCS tissue expression is due to the elevated tumor mass in late OSCC compared to primary OSCC.

MYC (a well-known proto-oncogene) is an important transcription factor in signaling pathways, mediating cell growth and proliferation. This gene plays a critical role in tumor development and drug resistance in cancer therapy (34). In addition, it is upregulated in 80% of OSCC cases (35).


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### Availability of Data and Materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

### Competing Interests
The authors declare that they have no competing interests.

### Consent for Publication
Not applicable.

### Ethical Approval
The current study was approved by the Ethics Committee of Hamadan University of Medical Sciences, Hamadan, Iran (Ethics No. IR.UMSHA.REC.1400.315 and IR.UMSHA.REC.1399.983).


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