

Advances in Prognostic Ability for High-Risk Oral Cancers

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Squamous cell carcinomas of the oral cavity and oropharynx (OSCCs) include different types of cancers, some of which are associated with human papillomavirus (HPV). HPV status is an important and independent prognostic factor for oropharyngeal cancer, and it is associated with better prognosis and treatment response. For oral cavity cancers, in which HPV is relatively uncommon, studies to date indicate that HPV status is unlikely to be useful as a prognostic marker, and there are no other prognostic markers that can reliably predict the survival of these patients. Currently, the classification of oral cavity cancer to inform treatment and prognosis is heavily dependent on American Joint Committee on Cancer (AJCC) stage. Yet, the ability of staging to predict outcomes in oral cavity cancer is limited; patients with tumors of the same clinical and pathologic staging have heterogeneous response to clinical treatment. In other types of cancer, gene expression profiling is now being used to predict disease progression, such as predicting the risk of recurrence. For example, gene expression tests such as MammaPrint and Oncotype DX are now being used in breast and colon cancer. However, this has not been an option for patients diagnosed with HPV-negative oral cancer.

Drs. Pawadee Lohavanichbutr, Eduardo Méndez, Chu Chen and colleagues from the Public Health Sciences and Clinical Research Divisions investigated whether gene expression profiling could be used to predict survival specifically among HPV-negative OSCC patients. This project developed from an earlier study, in which these investigators identified and validated a set of 131 genes which could differentiate between normal oral epithelium, oral dysplasia, and OSCC. The same gene signature also was predictive of survival in OSCC patients. In order to develop a tool to predict survival specifically in patients with HPV-negative OSCC, authors used two datasets: one to develop the predictive model (FHCRC), and another, from MD Anderson Cancer Center (MDACC), for model validation. Statistical methods were used to identify a subset of 13 genes (from 131 genes) which most effectively predicted survival among 97 patients with HPV-negative OSCC. To assess the effectiveness of this 13-gene signature in predicting survival in populations other than the original dataset, validation was performed using the second (MDACC) dataset. To do this, each oral cancer case in the second dataset (n=71) was assigned a “risk score” based on expression profiles of the

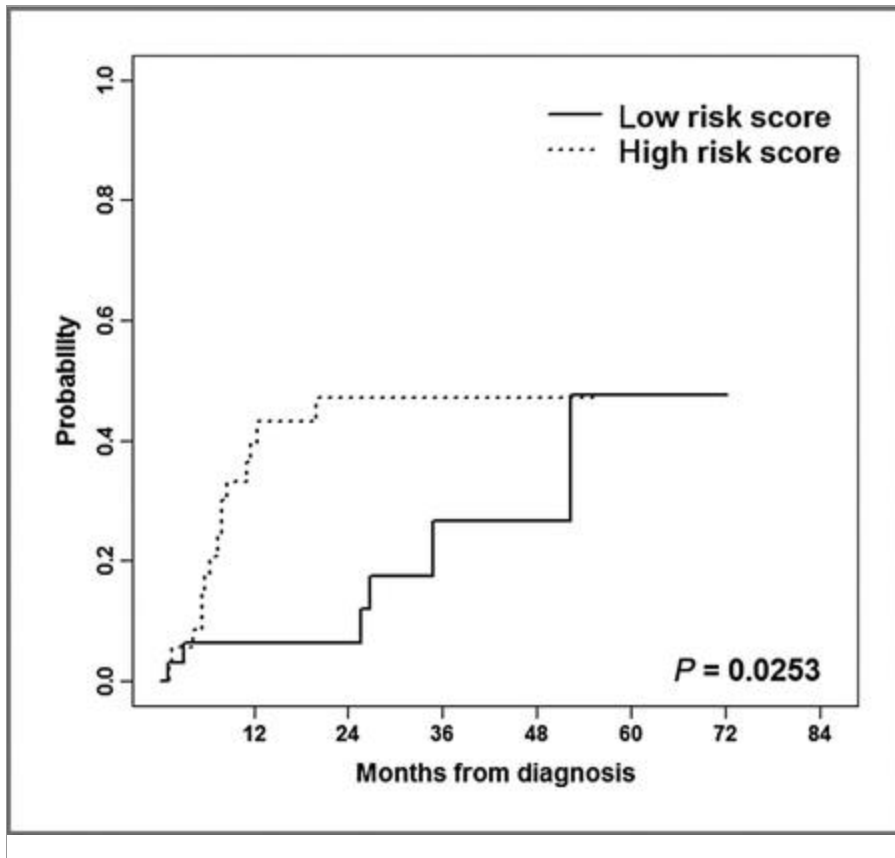
13 genes within the tumor samples. This risk score was used to categorize cases as “high” or “low” risk and to predict two-year survival.

Investigators found that patients predicted to be “high risk” were in fact much more likely to die from OSCC after two years (47% vs. 6%). After accounting for differences in age, gender, stage, and treatment, patients with a high-risk score, based on genetic characteristics of tumor tissue at diagnosis, were 3.7 times as likely to die from OSCC within two years compared to “low risk” patients (hazard ratio 3.7, 95% confidence interval 1.4-10.1). Moreover, the 13-gene signature had a much greater ability to predict 2-year survival than AJCC tumor stage (respective area under of Receiver Operating Curve: 0.78 vs. 0.54).

The gene set identified in this study is the first gene signature shown to be more effective at predicting survival for patients with HPV-negative OSCCs than AJCC stage. According to Dr. Chu Chen, “until now, the promise of gene signature for prognostication has only been realized for certain tumors such as those of the breast, colon and lung. This study represents a thirteen year effort to bring this promise to oral cancers.”

HPV-positive OSCCs have better treatment response and survival than HPV-negative OSCCs. Prognostic molecular markers might ultimately be able to guide treatment and improve survival in this group of patients. Further study is needed, however. “Before this gene signature can be used as a clinical test among HPV-negative oral cancer patients, it needs to be tested in trials involving a large number of patients to gauge the impact of its use on patient outcomes.” According to Dr. Chen, investigators have already begun efforts to initiate such a trial.

[Lohavanichbutr P, Méndez E, Holsinger FC, Rue TC, Zhang Y, Houck J, Upton MP, Futran N, Schwartz SM, Wang P, Chen C.](#) 2013. A 13-Gene Signature Prognostic of HPV-Negative OSCC: Discovery and External Validation. *Clinical Cancer Research*. March 19:1197-203.



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Cumulative incidence curves for oral cavity cancer-specific mortality of the 71 patients with oral cavity cancer in the MDACC dataset by group dichotomized by median of the risk score.