Oral Cancer

Genetics and the Role of Precision Medicine

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KEYWORDS

• Oral cancer • Oral squamous cell carcinoma • Malignant transformation
• Epigenetics • Omics technology • Big data • Personalized medicine
• Precision medicine

KEY POINTS

- Oral squamous cell carcinoma (OSCC), a distinct subtype of head and neck squamous cell carcinoma, is typically human papillomavirus-negative and harbors *TP53* loss-of-function mutations.
- OSCC is thought to begin with cancer initiating cells that are able to self-renew and generate heterogeneous clones of neoplastic cells to comprise the tumor (ie, tumor heterogeneity).
- Carcinogenesis is a multistep process, which involves an accumulation of both genetic and epigenetic alterations in oncogenes and/or tumor suppressor genes.
- Metastasis is one of the major prognostic indicators in OSCC. Both epithelial-to-mesenchymal transition and interactions between OSCC cells and the tumor microenvironment play significant roles in this complex process.
- The integration of omics technologies, bioinformatics, and molecular biology uncovers complex, clinically meaningful information that greatly improves our understanding of the disease process.

INTRODUCTION TO ORAL CANCER

Cancer is a major global health issue. According to the GLOBOCAN project of the International Agency for Research on Cancer, there were approximately 14.1 million newly

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Dent Clin N Am 62 (2018) 29–46
http://dx.doi.org/10.1016/j.cden.2017.08.002 **dental.theclinics.com**

diagnosed cancer cases with 8.2 million deaths worldwide in 2012.[1] Globally, oral cancer is one of the leading cancers, accounting for 2% of all cancer cases, with a nearly 50% mortality rate.[1] Internationally, the highest rates of oral cancer are seen in South Asian countries, such as Sri Lanka, India, and Taiwan, which are attributed to the high rates of cigarette smoking and areca nut use in these countries.[2] In the United States, 48,330 cases of oral and oropharyngeal cancer are diagnosed each year, comprising approximately 3% of all cancer cases.[3–8] It is the eighth leading cancer in men, with more than two-thirds of oral cancer cases occurring in male patients.[1,3]

Multiple factors contribute to the initiation of oral cancer. In addition to the well-established roles of tobacco, alcohol, and areca nut as risk factors for oral cancer, high-risk human papillomavirus infection (eg, HPV-16 and HPV-18) has been identified as a significant risk factor for oropharyngeal cancer.[9] Recent studies over the past decade have revealed an increasing incidence of HPV-positive oropharyngeal cancer in developed countries, which exhibits a better prognosis than HPV-negative oral cancer.[10,11] Specific germline mutations are also associated with a higher incidence of oral cancer. For example, patients with Li-Fraumeni syndrome (germline *TP53* mutation) are predisposed to early-onset oral cancer.[12] Additionally, patients with Fanconi anemia, a condition characterized by defects in the DNA repair process and consequent chromosomal instability, are associated with aggressive oral cancers that present at a young age.[13,14] Due to defective telomerase maintenance, patients with dyskeratosis congenita exhibit a thousand-fold increased risk for developing oral cancer.[15]

Squamous cell carcinoma (SCC) constitutes more than 90% of all cancer cases arising in the head and neck region, including the oral cavity and oropharynx.[16] Oral cancer and oropharyngeal cancer are two distinctive entities clinically, histopathologically, and genetically.[17] This article focuses on oral cancer. The most common sites of oral SCC (OSCC) are the tongue and floor of mouth, which account for more than 50% of all the cases, followed by the gingiva, palatal mucosa, and buccal and labial mucosa.[18] OSCC usually progresses rapidly, and the prognosis is closely associated with the tumor staging.[19] In the United States, approximately 50% of the OSCC patients present with regional or distant metastasis at the time of diagnosis.[20] OSCC tumors can double in size within three months, which clinically equates to a T1 tumor progressing to a T3 tumor in less than two years.[21] This accelerated progression corresponds to a dismal prognosis. The overall 5-year survival rate of OSCC is approximately 60%, varying between 80% for stage I cancers and 40% for stage IV cancers.[3]

Treatment strategies for OSCC vary based on the stage at time of diagnosis. Patients with localized disease typically receive surgery and/or radiotherapy, leading to a high probability of long-term survival but with considerable morbidity.[22] With metastatic OSCC, chemotherapy and radiotherapy are the mainstays of treatment.[22] Recently, targeted therapeutics have been introduced into treatment regimens or ongoing clinical trials to improve survival rate and reduce toxicity, such as cetuximab (monoclonal epidermal growth factor receptor [EGFR] antibody), bevacizumab (monoclonal vascular endothelial growth factor [VEGF] antibody), and mechanistic target of rapamycin (mTOR) inhibitors.[22] With the advancement of immunotherapy, monoclonal antibodies that target programmed cell death protein-1 (PD-1), a receptor of the immune escape pathway, such as nivolumab and pembrolizumab, have been approved by the Food and Drug Administration (FDA) for recurrent and/or metastatic head and neck SCC.[22]

Despite the progress in investigating the pathobiological mechanisms of OSCC, the prognosis has unfortunately not improved over the past few decades.[23] This is largely due to the frequent occurrence of local and regional OSCC recurrences as well as high morbidity and mortality rates.[23] The clinical challenge remains in accurately detecting regional metastasis and efficiently treating second primary OSCC and recurrent