Cancers of the Oral Mucosa

- Author: Crispian Scully, MD, MRCS, PhD, MDS, CBE, FDSRCS(Eng), FDSRCPS, FFDRCSI, FDSRCSE, FRCPath, FMedSci, FHEA, FUCL, FSB, DSc, DChD, DMed(HC), Dr(HC); Chief Editor: Dirk M Elston, MD more...

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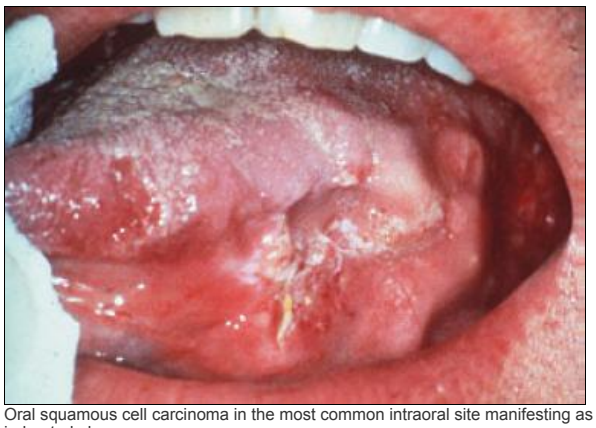
Background

Mouth (oral) cancer is a major neoplasm worldwide and accounts for most head and neck cancers. It theoretically should be largely preventable or detectable at an early stage.[1] Approximately 90% of oral cancers are squamous cell carcinoma (SCC), which is seen typically on the lip or lateral part of the tongue usually as a lump or ulcer that is white, red, or mixed white and red. Note the image below. Any single lesion persisting for more than 3 weeks should be regarded with suspicion. The mnemonic RULE (Red, Ulcerated, Lump, Extending for 3 or more weeks) is an aid to diagnosis.[2]



Oral squamous cell carcinoma in the most common intraoral site manifesting as a chronic, indurated ulcer.

Oral SCC (OSCC) is particularly common in the developing world, mostly in older males. There is concern about an ongoing increase in younger patients and in women, as well as in the oropharynx. The etiology of SCC appears to be multifactorial and strongly related to lifestyle, mostly habits and diet (particularly tobacco alone or in betel, and alcohol use).Other factors such as infective agents may also be implicated, particularly in oropharyngeal cancer. Immune defects or immunosuppression, defects of carcinogen metabolism, or defects in DNA-repair enzymes underlie some cases of SCC. Sunlight exposure predisposes to lip cancer.

Findings from the history and clinical examination by a trained diagnostician are the primary indicators of OSCC, but the diagnosis must always be confirmed histologically with repeated biopsies if the clinical picture is consistent with SCC.

Pathophysiology

In oral squamous cell carcinoma (OSCC), modern DNA technology, especially allelic imbalance (loss of heterozygosity) studies, have identified chromosomal changes suggestive of the involvement of tumor suppressor genes (TSGs), particularly in chromosomes 3, 9, 11, and 17. Functional TSGs seem to assist growth control, while their mutation can unbridle these control mechanisms.

The regions most commonly identified thus far have included some on the short arm of chromosome 3, a TSG termed *P16* on chromosome 9, and the TSG termed *TP53* on chromosome 17, but multiple other genes are being discovered.

As well as damage to TSGs, cancer may also involve damage to other genes involved in growth control, mainly those involved in cell signaling (oncogenes), especially some on chromosome 11 (*PRAD1* in particular) and chromosome 17 (Harvey ras [H-*ras*]). Changes in these and other oncogenes can disrupt cell growth control, ultimately leading to the uncontrolled growth of cancer. H-*ras* was one of the oncogenes that first caught the attention of molecular biologists interested in cell signaling, cell growth control, and cancer. It and the gene for epidermal growth factor receptor (*EGFR*) are involved in cell signaling.

The genetic aberrations involve, in order of decreasing frequency, chromosomes 9, 3, 17, 13, and 11 in particular, and probably other chromosomes, and involve inactivated TSGs, especially *P16,* and *TP53* and overexpressed oncogenes, especially *PRAD1*.

The molecular changes found in OSCC from Western countries (eg, United Kingdom, United States, Australia), particularly *TP53* mutations, are infrequent in Eastern countries (eg, India, Southeast Asia), where the involvement of *ras* oncogenes is more common, suggesting genetic differences that might be involved in explaining the susceptibility of certain groups to OSCC.

The rare Li-Fraumeni syndrome is associated with defects in *TP53*.

Carcinogen-metabolizing enzymes are implicated in some patients. Alcohol dehydrogenase oxidizes ethanol to acetaldehyde, which is cytotoxic and results in the production of free radicals and DNA hydroxylated bases; alcohol dehydrogenase type 3 genotypes appear predisposed to OSCC. Cytochrome P450 can activate many environmental procarcinogens. Ethanol is also metabolized to some extent by cytochrome P450 IIEI (CYP2E1) to acetaldehyde. Mutations in some TSGs may be related to cytochrome P450 genotypes and predispose to OSCC. Glutathione S transferase (GST) genotypes may have impaired activity; for example, the null genotype of GSTM1 has a decreased capacity to detoxify tobacco carcinogens. Some GSTM1 and GSTP1 polymorphic genotypes and GSTM1 and GSTT1 null genotypes have been shown to predispose to OSCC. *N* -acetyltransferases NAT1 and NAT2 acetylate procarcinogens. *N* -acetyl transferase NAT1*10 genotypes may be a genetic determinant of OSCC, at least in some populations.

Tobacco is a potent risk factor for oral cancer. An interaction occurs between redox-active metals in saliva and the low reactive free radicals in cigarette smoke. The result may be that saliva loses its antioxidant capacity and instead becomes a potent pro-oxidant milieu.[3]

DNA repair genes are clearly involved in the pathogenesis of some rare cancers, such as those that occur in association with xeroderma pigmentosum, but, more recently, evidence of defective DNA repair has also been found to underlie some OSCCs.

Immune defects may predispose to OSCC, especially lip cancer. OSCC is also now being reported with increased frequency in association with diabetes and systemic sclerosis.

Intraoral OSCC primarily affects the posterior lateral part of the tongue. Spread is local, especially through muscle and bone, and metastasis initially is to the anterior cervical lymph nodes and later to the liver and skeleton.

Epidemiology

Frequency

The oral cavity is 1 of the 10 most frequent sites of cancer internationally, with three quarters of cases affecting people in the developing world, where, overall, oral cancer is the third most common cancer after stomach and cervical cancer. An estimated 378,500 new cases of intraoral cancer are diagnosed annually worldwide.

Unfortunately, the parts of the world where oral cancer is most common are also those where descriptive information (ie, incidence, mortality, prevalence) is least available. In certain countries, such as Sri Lanka, India, Pakistan, and Bangladesh, oral cancer is the most common cancer. In parts of India, oral cancer can represent more than 50% of all cancers. OSCC is also common in Brazil.

In developed countries, oral cancer is less common but is the eighth most common form of cancer overall; however, the ranking varies a great deal among countries. For example, in areas of northern France, oral cancer is the most common form of cancer in men. Estimates show that in 1980, more than 32,000 new cases of oral cancer were diagnosed throughout the European community. The prevalence of lip cancer appears to be decreasing, but the prevalence of intraoral cancer appears to be rising in many countries, especially in younger people. This is especially true in Central and Eastern Europe, especially Hungary and Northern France.

Race

The prevalence of tongue cancer is consistently found to be higher (by approximately 50%) in blacks compared with whites within the same regions of the United States.[4] The prevalence of oral cancer is also generally higher in ethnic minorities in other developed countries.[5]

Sex

Oral cancer affects males more frequently than females, although the ratio is equalizing.

Age

Oral cancer is predominantly found in middle-aged and older persons.

Clinical Presentation

Contributor Information and Disclosures

Author
Crispian Scully, MD, MRCS, PhD, MDS, CBE, FDSRCS(Eng), FDSRCPS, FFDRCSI, FDSRCSE, FRCPath, FMedSci, FHEA, FUCL, FSB, DSc, DChD, DMed(HC), Dr(HC) Emeritus Professor, University College London; Visiting Professor, Universities of Athens, BPP, Edinburgh, Granada, Helsinki and Plymouth

Crispian Scully, MD, MRCS, PhD, MDS, CBE, FDSRCS(Eng), FDSRCPS, FFDRCSI, FDSRCSE, FRCPath, FMedSci, FHEA, FUCL, FSB, DSc, DChD, DMed(HC), Dr(HC) is a member of the following medical societies: Academy of Medical Sciences, British Society for Oral Medicine, European Association for Oral Medicine, International Academy of Oral Oncology, International Association for Dental Research, International Association for Oral and Maxillofacial Pathology

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Specialty Editor Board
David F Butler, MD Section Chief of Dermatology, Central Texas Veterans Healthcare System; Professor of Dermatology, Texas A&M University College of Medicine; Founding Chair, Department of Dermatology, Scott and White Clinic

David F Butler, MD is a member of the following medical societies: American Medical Association, Alpha Omega Alpha, Association of Military Dermatologists, American Academy of Dermatology, American Society for Dermatologic Surgery, American Society for MOHS Surgery, Phi Beta Kappa

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John G Albertini, MD Private Practice, The Skin Surgery Center; Clinical Associate Professor (Volunteer), Department of Plastic and Reconstructive Surgery, Wake Forest University School of Medicine; President-Elect, American College of Mohs Surgery

John G Albertini, MD is a member of the following medical societies: American Academy of Dermatology, American College of Mohs Surgery

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Chief Editor
Dirk M Elston, MD Professor and Chairman, Department of Dermatology and Dermatologic Surgery, Medical University of South Carolina College of Medicine

Dirk M Elston, MD is a member of the following medical societies: American Academy of Dermatology

Disclosure: Nothing to disclose.

Additional Contributors
Kelly M Cordoro, MD Assistant Professor of Clinical Dermatology and Pediatrics, Department of Dermatology, University of California, San Francisco School of Medicine

Kelly M Cordoro, MD is a member of the following medical societies: Alpha Omega Alpha, American Academy of Dermatology, American Medical Association, Medical Society of Virginia, Society for Pediatric Dermatology, Women's Dermatologic Society, Association of Professors of Dermatology, National Psoriasis Foundation, Dermatology Foundation

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