DOI:10.31557/APJCB.2023.8.4.379

REVIEW

Oral Cancer at a Glance

Elham Saberian[1], Andrej Jenča[2], Adriána Petrášová[3], Janka Jenčová[3], Reza Atazadegan Jahromi[4], Rahman Seiffadini[5]

[1]MDDr., PhD and Specialty Student, Pavol Jozef Šafárik University, Klinika and Akadémia Košice Bacikova, Kosice, Slovakia. [2]MUDr., PhD., MBA, Assisstant Professor, Doctor of Klinika of Stomatology and Maxillofacial Surgery Akadémia Košice Bacikova, UPJS LF, Kosice, Slovakia. [3]MUDr., PhD., Assisstant Professor, Doctor of Klinika of Stomatology and Maxillofacial Surgery Akadémia Košice Bacikova, UPJS LF, Kosice, Slovakia. [4]General Medicine Student, Pavol Jozef safarik University, Kosice, Slovakia. [5]Dental Medicine Student, Pavol Jozef Safarik University, Kosice, Slovakia.

Abstract

Overview: This review aims to serve as a comprehensive resource for healthcare professionals, researchers, and students interested in oral cancer, providing them with up-to-date information and insights into the current state of knowledge and practice in the field. Oral cancer, also known as mouth cancer, is a type of cancer that affects the mouth, tongue, lips, or throat. It is a common form of cancer worldwide, and its incidence is increasing annually. Oral cancer can be life-threatening if not detected early and treated promptly. **Methods:** We searched the PubMed database, Web of Science (WOS), Google Scholar, Scopus, and selected studies by predefined eligibility criteria. This review aims to provide an overview of oral cancer, including its causes, risk factors, signs and symptoms, diagnosis, treatment options, and prevention strategies. **Result:** Oral cancer is a preventable disease, and ongoing research is providing valuable insights into its risk factors and development. With this increasing knowledge, healthcare professionals have the opportunity to improve clinical outcomes by developing better early detection and treatment strategies. By staying up-to-date with the latest advancements in biomedical sciences and dentistry, they can make a significant impact on patient outcomes and save lives. **Conclusion:** summarizing the key points discussed in the review and highlighting the significance of continued research and awareness efforts to combat this complex and aggressive disease.

Keywords: Oral cancer- Diagnosis- Treatment- Prevention strategies- Risk factors- Symptoms

Asian Pac J Cancer Biol, **8 (4)**, 379-386

Submission Date: 07/19/2023 Acceptance Date: 09/16/2023

Introduction

Oral cancer, also referred to as mouth cancer, is a type of malignancy that impacts the oral cavity, including the lips, tongue, cheeks, gums, floor of the mouth, and throat [1]. This form of cancer can arise in various regions of the mouth, manifesting as a painless white lesion that gradually thickens, develops red spots, and eventually evolves into an ulcerative lesion. On the lips, it often appears as a chronic non-healing ulcer that steadily enlarges over time [2]. Additional indicators of oral cancer may consist of dysphagia, odynophagia, neck swelling, and sensations of numbness in the lips. Awareness of these symptoms is crucial for early detection and optimal treatment outcomes [3,4]. The World Health Organization (WHO) introduced a paradigm shift in 2005 by recommending a change in the classification of precancerous lesions to "potentially malignant disorders" (PMDs). This move was motivated by the observation that the majority of oral squamous cell carcinoma (OSCC) cases had evolved from preceding precancerous lesions. The PMDs encompass a spectrum of conditions, including leukoplakia, erythroplakia, oral lichen planus, oral submucosal fibrosis, actinic keratosis, discoid lupus erythematosus, and palatal lesions potentially induced by smoking. These disorders are characterized by their heightened propensity for malignant transformation relative to other oral pathologies [5]. Oral cancer has a poor

Corresponding Author:
Dr. Elham Saberian
MDDr., PhD and Specialty Student, Pavol Jozef Šafárik University, Klinika and Akadémia Košice Bacikova, Kosice, Slovakia.
Email: El_saberian@yahoo.com

prognosis, with a five-year survival rate of approximately 40%. However, if detected early (stages I and II), the survival rate can exceed 80% [6,7]. Unfortunately, up to 50% of oral cancers are diagnosed at an advanced stage (stages III and IV) due to a lack of symptoms in the early stages, leading to delayed medical attention. Patients often present with obvious symptoms like pain, bleeding, or a mass in the mouth or neck only when lymphatic spread has already occurred [8]. A diagnostic delay of over one month significantly increases the likelihood of advanced-stage oral cancer [9]. While patients are primarily responsible for delays, misdiagnosis or inadequate treatment by healthcare providers can also contribute to the problem [9-11]. The prognosis worsens as the disease advances and the tumor location becomes less accessible, with lip cancer having better survival rates than oropharyngeal cancer. The clinical and pathological stage at diagnosis remains the most critical factor affecting prognosis [12]. Early detection and anticipation of diagnosis lead to improved survival rates, better prognosis, and reduced treatment-related morbidity [13]. More than 90% of malignant tumors in the oral region are squamous cell carcinomas that arise from the mucosal epithelium. However, it's important to recognize that these tumors can differ significantly based on their location, etiology, prognosis, and treatment options. Specifically, oral cancer affecting the mouth differs from carcinoma in the oropharynx in several ways. For instance, oropharyngeal cancer is predominantly linked to human papillomavirus (HPV) infection, whereas oral cancer is typically associated with exposure to tobacco and alcohol. As such, it's essential to assess each type of mucosal tumor individually and tailor our approach to diagnosis, staging, and treatment accordingly [14]. Globally, there are an estimated 400,000 new cases of oral cancer diagnosed annually, with a disproportionate number occurring in Asian countries. According to the World Health Organization (WHO), approximately two-thirds of these cases are found in South and Southeast Asia, specifically in countries such as Sri Lanka, Indonesia, India, Pakistan, and Bangladesh [15]. Oral squamous cell carcinoma (OSCC) typically occurs on the lateral border of the tongue (40%) or the floor of the mouth (30%). It can also affect the lower lip (30%) [16]. The objective of this article is to provide a comprehensive overview of the existing literature on oral squamous cell carcinoma (OSCC) for both the general public and healthcare professionals. This review aims to summarize the current knowledge of OSCC, including its definition, risk factors, symptoms, diagnosis, treatment options, and prognosis. By providing an up-to-date and accessible summary of the latest research in the field, we hope to increase awareness and understanding of OSCC among the general population and assist healthcare practitioners in their efforts to prevent, diagnose, and treat this disease.

Definition and risk factors

Oral squamous cell carcinoma (OSCC) is a preventable disease that is primarily caused by environmental factors, with tobacco being the leading culprit. The development of OSCC is directly related to the dose, frequency, and mode of exposure to carcinogens, which are substances that have the potential to cause cancer. In addition to tobacco smoke, other known carcinogens that can contribute to the development of OSCC include excessive alcohol consumption, certain viruses such as human papillomavirus types 16 and 18, and prolonged exposure to ultraviolet (UV) light. By avoiding these carcinogens and adopting healthy lifestyle habits, individuals can significantly reduce their risk of developing this disease [2,17].

Tobacco

Tobacco usage is a primary contributor to the development of oral cancer, as it triggers genetic alterations in the buccal cells that can culminate in malignancy. The carcinogenic properties of tobacco are attributed to the chemical compounds present in cigarette smoke and other tobacco products, which instigate mutations in the cellular DNA, thereby increasing the likelihood of cancerous growth in the oral cavity [3,18-20].

Alcohol

Heavy alcohol consumption has been linked to an elevated risk of developing oral cancer. The reason for this association is that excessive alcohol consumption can cause damage to the cells in the mouth, making them more vulnerable to the effects of cancer-causing viruses. When these damaged cells are infected with certain viruses, such as human papillomavirus (HPV), they can become cancerous and lead to the development of oral cancer. Additionally, heavy drinking can weaken the immune system, which can further increase the likelihood of developing oral cancer. Therefore, it's important to be mindful of alcohol consumption habits and take steps to reduce the risk of oral cancer, such as limiting alcohol intake, practicing good oral hygiene, and getting regular dental check-ups [3, 12, 20].

Human papillomavirus

Infection with human papillomavirus (HPV), specifically type 16, is a recognized risk factor and causative agent for oral cancer. However, there is a growing subset of patients diagnosed with oral cancer who do not fit the traditional demographic profile. Unlike the historically high-risk groups - people over 50, African Americans, males, and tobacco users - this new population is primarily made up of non-smoking, white individuals between the ages of 30 and 50, with males slightly outnumbering females. Research suggests that HPV16 is the main risk factor for this new population. The virus is also responsible for most cervical cancers and is the most common sexually transmitted infection in the US. Oral cancer in this group typically affects the tonsils, tonsillar pillars, base of the tongue, and oropharynx. Notably, individuals who develop oral cancer from this cause tend to respond better to radiation treatment than those whose disease is caused by tobacco use [20-24].

Table 1. Staging System

Stage	Number Staging System	TNM System	Description
0	Pre-cancerous condition	-	High risk of developing into invasive cancer if left untreated
1	Early invasive cancer	T1N0M0	Tumor ≤2cm, no spread to nearby tissues, lymph nodes, or organs
2		T1N1M0	Tumor >2cm but ≤4cm, may have spread to nearby tissues, but not to lymph nodes or organs
3		T2N0M0	Tumor >4cm, may have spread to lymph nodes or nearby tissues, but not to other organs
4a	Advanced cancer	T3N0M0	Cancer has grown into surrounding structures or spread to one lymph node ≤3cm
4b		T3N1M0	Cancer has spread to nearby areas like the base of the skull or surroundings of the neck arteries or has spread to a lymph node >6cm
4c		T4N0M0	Cancer has spread to other parts of the body like the lungs or bones
		T4N1M0	Same as above, plus cancer has spread to at least one lymph node
		T4N2M0	Same as above, plus the cancer has spread to at least two lymph nodes
		T4N3M0	Same as above, plus the cancer has spread to at least three lymph nodes
		M1	Cancer has spread to other parts of the body, such as the liver, brain, or distant lymph nodes

Nutritional factors

Historically, clinicians have noted a connection between iron deficiency and oral squamous cell carcinoma (OSCC), and subsequent research has consistently supported this association. Iron is essential for maintaining the health and integrity of epithelial tissues, and deficiencies can result in atrophic changes in the oral epithelium, rendering it more vulnerable to chemical carcinogens. Moreover, a diet low in fruits and vegetables has been associated with an elevated risk of OSCC, whereas a higher intake of these foods seems to decrease the risk. Encouragingly, interventional trials employing β-carotene and vitamin A have yielded promising outcomes in mitigating the severity of oral precancerous lesions. It is worth noting that riboflavin deficiency, commonly encountered in individuals who consume excessive alcohol, may also play a role in the development of OSCC. In summary, addressing nutritional deficits and advocating for a well-balanced diet could significantly contribute to both the prevention and treatment of OSCC [25].

Edentulous patients

Edentulous patients and poor oral hygiene are known risk factors for cancer of the oral cavity. Additionally, some studies suggest that the use of mouthwashes with high alcohol content may increase the risk of developing tongue and oral cavity squamous cell carcinoma (SCC), although this association remains unproven. Furthermore, research has linked the consumption of the traditional South American beverage, mate, to an elevated risk of oral cavity cancer [26].

Ultraviolet (UV) light

The oral microbiome, mucosal inflammation, and oral mucosal trauma caused by teeth and prosthetic devices have been gaining attention as potential contributors to the development of oral cancer. In addition, exposure to actinic ultraviolet radiation (UV), particularly UV-B, has been implicated in the development of lip cancer. Genetic predispositions, such as xeroderma pigmentosum, Fanconi's anemia, and ataxia-telangiectasia, also increase the risk of developing oral cancer due to defects in DNA repair mechanisms [26].

Prevention

Oral cancer can be considered a largely preventable disease, given that most risk factors can be eliminated. However, it can still occur in individuals who do not belong to known risk categories. Therefore, primary prevention through education on limiting behavioral risk factors, such as tobacco use and excessive alcohol consumption, is crucial. Additionally, HPV vaccination may also play a role in prevention, although its effectiveness in preventing oral cancer is not as well established as it is for anogenital and cervical cancer. Early detection and treatment of oral premalignancies and early-stage cancers are critical components of secondary prevention. Unfortunately, despite increased public awareness, the proportion of patients presenting with advanced disease has remained relatively unchanged over the past four decades [6,8,12,22].

Unlike other common cancers such as colorectal or cervical cancer, implementing a standardized population-based screening program for oral cancer is not cost-effective and therefore cannot be recommended. This is because the incidence of oral cancer is relatively low compared to other cancers, and the cost of screening the entire population would outweigh the benefits. However, targeted screening programs in high-risk populations, such as heavy smokers and drinkers, or individuals with a history of cancer outside the head and neck region, may be worth considering. Studies have shown that such targeted approaches can help identify early-stage cancer or precancerous lesions, potentially improving treatment outcomes. For example, a randomized controlled trial conducted in India demonstrated the effectiveness of a screening program in high-risk individuals. Additionally,

Table 2. Oral Cancer Statistics

Global
Oral cancer is the 11th most common cancer worldwide.
There were approximately 300,000 new cases of oral cancer diagnosed and 145,000 deaths due to oral cancer in 2012.
The age-standardized incidence rate (ASIR) for oral cancer is 6.4 per 100,000 population, while the age-standardized mortality rate (ASMR) is 2.4 per 100,000 population.
Regional
Europe: The ASIR for oral cancer in European men is 12.1 per 100,000 population, while it is 7.4 per 100,000 population in women. The ASMR for oral cancer in European men is 2.5 per 100,000 population, while it is 1.6 per 100,000 population in women.
North America: The ASIR for oral cancer in North American men is 4.2 per 100,000 population, while it is 3.1 per 100,000 population in women.
South America: The ASIR for oral cancer in South American men is 7.2 per 100,000 population, while it is 5.4 per 100,000 population in women.
Asia: The ASIR for oral cancer in Asian men is 10.4 per 100,000 population, while it is 7.4 per 100,000 population in women.
Australia: The ASIR for oral cancer in Australian men is 6.8 per 100,000 population, while it is 3.9 per 100,000 population in women.
Country-specific
United States: The ASIR for oral cancer in US men is 4.4 per 100,000 population, while it is 3.1 per 100,000 population in women.
Canada: The ASIR for oral cancer in Canadian men is 4.2 per 100,000 population, while it is 3.1 per 100,000 population in women.
Mexico: The ASIR for oral cancer in Mexican men is 3.1 per 100,000 population, while it is 2.1 per 100,000 population in women.
India: The ASIR for oral cancer in Indian men is 9.4 per 100,000 population, while it is 5.5 per 100,000 population in women.
Brazil: The ASIR for oral cancer in Brazilian men is 7.2 per 100,000 population, while it is 5.4 per 100,000 population in women.

Note that this table combines the information from both systems, so it's not strictly following either system, but rather providing an overview of the different stages and their corresponding characteristics.

opportunistic screening for oral mucosal lesions during routine dental check-ups in countries with good dental healthcare infrastructure could also contribute to reducing diagnostic delays and improving outcomes [27-30].

Staging System

According to the TNM staging system by the American Joint Committee on Cancer, there are four stages of oral cancer based on the tumor size, lymph nodes involved, and metastasis (Table 1) [16,31,32].

Oral Carcinogenesis

Oral carcinogenesis is a multifocal process involving genetic alterations in squamous epithelial cells, which can be detected through various molecular biology techniques. High-throughput methods are being used to search for oral cancer biomarkers in biofluids like saliva and serum. The concept of "field cancerization" suggests that cancer can develop at multiple sites, and research has shown that mutations in the p53 gene are linked to smoking and increase the risk of oral carcinoma. Long-term exposure to environmental and exogenous factors may lead to multi-focal presentations and mutational expressions of tumor suppressor genes, making it difficult to surgically remove premalignant lesions [33].

Epidemiology

It's worth noting that these statistics are based on data from 2012, so they may not reflect current trends. Additionally, the incidence and mortality rates vary widely depending on the specific type of oral cancer, with some types having much higher incidence and mortality rates than others [34-53] (Table 2).

Oral screening

According to recent statistics, only a minority of oral and pharyngeal cancers, approximately 30%, are detected at an early stage, whereas 50% are diagnosed at a more advanced stage (stage III or IV) when they have already spread to other parts of the body. This delay in detection is attributed to several factors such as patients seeking medical attention too late, diagnostic delays, and the absence of well-defined guidelines for referring patients from dentists to physicians. Consequently, incorporating oral cancer screenings into regular head and neck examinations performed by primary dental care providers is crucial [54-57]. The primary screening test for oral cancer involves a thorough clinical examination of the oral cavity. As recommended by the World Health Organization and the National Institute of Dental and Craniofacial Research, this examination should consist of

a systematic visual inspection of the face, neck, lips, labial mucosa, buccal mucosa, gingiva, floor of the mouth, tongue, and palate. A mouth mirror can be used to aid in visualizing all surfaces. In addition to the visual inspection, the examination should also include palpation of the regional lymph nodes, tongue, and floor of the mouth. Any abnormality that persists for more than two weeks should be re-evaluated and referred for biopsy. Early detection through regular screening can significantly improve treatment outcomes and survival rates for patients with oral cancer [58].

Early diagnosis

Oral cancer, which includes cancer of the lips, tongue, floor of the mouth, and other parts of the mouth, is a common type of cancer worldwide. Early detection is crucial in reducing oral cancer mortality. Most oral cancers occur in visible or palpable areas, making early diagnosis possible. Key indicators of oral cancer include ulceration, induration, infiltration, bleeding, and lymphadenopathy [55,59]. Oral cancer, which affects the mouth, tongue, lips, or throat, can be detected early through opportunistic oral cancer screening exams performed by oral health professionals (OHPs). During these exams, OHPs check for signs of cancer or precancerous changes in the mouth, and if they find anything suspicious, they refer the patient to a specialist for further evaluation. To diagnose oral cancer, a combination of clinical evaluation and biopsy is used. The biopsy is the most reliable method, involving the removal of a small tissue sample from the affected area for examination under a microscope. Imaging tests like CT scans, MRI scans, or PET scans help determine the cancer's extent, which guides treatment decisions. For early-stage oral cancer, surgery or radiation therapy may be enough. Advanced cancers might require a combination of surgery, radiation therapy, and chemotherapy. Targeted therapy could also be combined with radiation therapy for more aggressive cases. Managing oral cancer patients requires a multidisciplinary approach to address various side effects, including infections, mucositis, oral ulceration, xerostomia, bleeding, pain, osteoradionecrosis, taste loss, trismus, and dental caries. A team of healthcare professionals can help mitigate these issues and enhance the patient's quality of life. Early detection and prompt treatment are crucial for improving oral cancer outcomes. By performing regular opportunistic oral cancer screening exams, OHPs can identify cancer early, leading to better patient outcomes. A collaborative effort among healthcare professionals is essential for managing the diverse needs of oral cancer patients [60,61].

Before treatment

It is crucial for dentists to perform a thorough dental assessment and develop an oral care program before beginning cancer treatment to enhance treatment compliance and reduce infection risk. Most patients have underlying dental problems such as cavities and gum disease, so dentists must provide proper oral rehabilitation, non-invasive treatments, fluoride dental trays, and maxillofacial prosthetics when necessary. Additionally, radiation therapy can cause oral complications, and surgery may require removing infected teeth and bone resection. To prevent osteoradionecrosis, dentists should extract at-risk teeth seven to ten days before radiation therapy begins and ensure all sources of mucosal trauma are eliminated. A personalized oral hygiene regimen should also be implemented, including brushing, flossing, scaling, professional tooth cleaning, and denture cleaning [62]. Depending on the area being irradiated, provisions should be made for customized dental fluoridation trays. By following these guidelines, dentists can help protect their patients' oral health during cancer treatment. And other diseases, such as types of cancer, respiratory diseases and Alzheimer's, it is important to check the condition of the disease [63-67].

Treatment

Treatment for mouth cancer is tailored to the specific characteristics of the cancer, including its location, stage, and aggressiveness, as well as the patient's overall health and personal preferences. Patients may receive a single type of treatment or a combination of different therapies, such as surgery, radiation, and chemotherapy. It's essential to discuss the various options with a doctor to determine the best course of action for each individual case.

Surgery

Surgery has been the cornerstone of treatment for oral cancer for over a century, with a rich history dating back to the late 19th century. The advent of ionizing radiation therapy in the early 20th century revolutionized the treatment landscape, offering a non-invasive alternative to surgery. While radiation therapy remains an essential component of treatment for many patients, it is often used in combination with surgery, particularly in cases of advanced cancer. In these instances, postoperative radiation therapy is typically employed to ensure that any remaining cancer cells are eliminated and reduce the risk of recurrence [68].

Chemotherapy

In the past, chemotherapy was primarily used as a palliative treatment for oral carcinoma in the 1950s, 60s, and 70s. However, with the advent of cisplatin, clinical trials on induction chemotherapy showed promising results, with a considerable number of patients exhibiting responses to the treatment. Unfortunately, despite these initial positive outcomes, the use of induction chemotherapy did not lead to long-term control of primary oral squamous cell carcinomas, unlike its effectiveness in other head and neck tumors [69].

Targeted drug therapy and Immunotherapy

Researchers are actively exploring targeted therapies that focus on inhibiting epidermal growth factor receptor (EGFR) as a potential treatment for non-small cell lung cancer. In addition, immunotherapy and gene therapy are other promising areas of study that require further investigation. These approaches have shown encouraging results in early clinical trials, and scientists are working to

optimize their use in combination with existing treatments or as standalone therapies. The ultimate goal is to develop more effective and personalized treatments that can improve patient outcomes and quality of life [68,70].

In conclusion, early detection of oral cancer is crucial for improving treatment outcomes and saving lives. With advancements in technology and medical research, various diagnostic tools and techniques are available to aid clinicians in identifying and diagnosing oral cancer at its earliest stages. These include visual examination devices, salivary biomarker tests, and other point-of-care testing methods that can help identify potential cancerous lesions before they progress to advanced stages. While surgical biopsy and histology remain the gold standard for definitive diagnosis, these auxiliary methods can provide valuable information to support clinical decision-making. The scientific community continues to make strides in developing novel approaches to prevention, screening, and early detection of oral cancer. By staying up-to-date with the latest research and incorporating cutting-edge technologies into their practice, healthcare professionals can significantly reduce diagnostic delays and improve patient outcomes. In turn, this will lead to better management of oral cancer and improved quality of life for patients.

Acknowledgements

None.

Data availability

Not applicable as we used information from previously published articles.

Approved by any scientific Body

Not applicable as the manuscript is not a part of any student thesis or study.

Ethical issue and approval

Not applicable as we used information from previously published articles.

Consent for publication

All authors have given consent for publication.

Conflict of interest

The authors declare no potential conflict of interest.

References

1. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Annals of Surgical Oncology. 2010 06;17(6):1471-1474. https://doi.org/10.1245/s10434-010-0985-4
2. Marx, Stern D. Oral and maxillofacial pathology: a rationale for diagnosis and treatment. Stern, Diane. Chicago: Quintessence Pub. Co. ISBN 978-0867153903. OCLC 49566229. 2023;.
3. Rivera C. Essentials of oral cancer. International Journal of Clinical and Experimental Pathology. 2015;8(9):11884-11894.
4. Ettinger KS, Ganry L, Fernandes RP. Oral Cavity Cancer. Oral and Maxillofacial Surgery Clinics of North America. 2019 02;31(1):13-29. https://doi.org/10.1016/j.coms.2018.08.002
5. Liu D, Zhao X, Zeng X, Dan H, Chen Q. Non-Invasive Techniques for Detection and Diagnosis of Oral Potentially Malignant Disorders. The Tohoku Journal of Experimental Medicine. 2016 02;238(2):165-177. https://doi.org/10.1620/tjem.238.165
6. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncology. 2009;45(4-5):309-316. https://doi.org/10.1016/j.oraloncology.2008.06.002
7. Silverman S, Kerr AR, Epstein JB. Oral and pharyngeal cancer control and early detection. Journal of Cancer Education: The Official Journal of the American Association for Cancer Education. 2010 09;25(3):279-281. https://doi.org/10.1007/s13187-010-0045-6
8. McCullough MJ, Prasad G, Farah CS. Oral mucosal malignancy and potentially malignant lesions: an update on the epidemiology, risk factors, diagnosis and management. Australian Dental Journal. 2010 06;55 Suppl 1:61-65. https://doi.org/10.1111/j.1834-7819.2010.01200.x
9. Gómez I, Seoane J, Varela-Centelles P, Diz P, Takkouche B. Is diagnostic delay related to advanced-stage oral cancer? A meta-analysis. European Journal of Oral Sciences. 2009 Oct;117(5):541-546. https://doi.org/10.1111/j.1600-0722.2009.00672.x
10. McGurk M, Chan C, Jones J, O'regan E, Sherriff M. Delay in diagnosis and its effect on outcome in head and neck cancer. The British Journal of Oral & Maxillofacial Surgery. 2005 08;43(4):281-284. https://doi.org/10.1016/j.bjoms.2004.01.016
11. Groome PA, Rohland SL, Hall SF, Irish J, Mackillop WJ, O'Sullivan B. A population-based study of factors associated with early versus late stage oral cavity cancer diagnoses. Oral Oncology. 2011 07;47(7):642-647. https://doi.org/10.1016/j.oraloncology.2011.04.018
12. Chow LQM. Head and Neck Cancer. The New England Journal of Medicine. 2020 01 02;382(1):60-72. https://doi.org/10.1056/NEJMra1715715
13. Ford PJ, Farah CS. Early detection and diagnosis of oral cancer: Strategies for improvement. Journal of Cancer Policy. 2013 03 01;1(1):e2-e7. https://doi.org/10.1016/j.jcpo.2013.04.002
14. Speight PM, Farthing PM. The pathology of oral cancer. British Dental Journal. 2018 Nov 09;225(9):841-847. https://doi.org/10.1038/sj.bdj.2018.926
15. Abati S, Bramati C, Bondi S, Lissoni A, Trimarchi M. Oral Cancer and Precancer: A Narrative Review on the Relevance of Early Diagnosis. International Journal of Environmental Research and Public Health. 2020 Dec 08;17(24):9160. https://doi.org/10.3390/ijerph17249160
16. Givony S. Oral squamous cell carcinoma (OSCC) an overview / Shahaf Givony. Medicinos mokslai. Medical sciences. Kėdainiai : VšĮ Lietuvos sveikatos mokslinių tyrimų centras, 2020, vol. 8, no. 13, Mar 23.. 2020 03 30;.
17. Ravikiran Ongole, Praveen B N, ed. Textbook of Oral Medicine, Oral Diagnosis and Oral Radiology. Elsevier India. 2014;:p. 387. ISBN 978-8131230916.
18. Society AC. Cancer Facts and Figures 2018. Atlanta: American Cancer Society. 2018;.
19. Shapiro JA, Jacobs EJ, Thun MJ. Cigar smoking in men and risk of death from tobacco-related cancers. Journal of the National Cancer Institute. 2000 02 16;92(4):333-337. https://doi.org/10.1093/jnci/92.4.333
20. Znaor A, Brennan P, Gajalakshmi V, Mathew A, Shanta V,

Varghese C, Boffetta P. Independent and combined effects of tobacco smoking, chewing and alcohol drinking on the risk of oral, pharyngeal and esophageal cancers in Indian men. International Journal of Cancer. 2003 07 10;105(5):681-686. https://doi.org/10.1002/ijc.11114
21. Wong T, Wiesenfeld D. Oral Cancer. Australian Dental Journal. 2018 03;63 Suppl 1:S91-S99. https://doi.org/10.1111/adj.12594
22. Joseph BK. Oral cancer: prevention and detection. Medical Principles and Practice: International Journal of the Kuwait University, Health Science Centre. 2002;11 Suppl 1:32-35. https://doi.org/10.1159/000057776
23. Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C. Epidemiology of Human Papillomavirus-Positive Head and Neck Squamous Cell Carcinoma. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2015 Oct 10;33(29):3235-3242. https://doi.org/10.1200/JCO.2015.61.6995
24. Martín-Hernán F, Sánchez-Hernández JG, Cano J, Campo J, Romero J. Oral cancer, HPV infection and evidence of sexual transmission. Medicina Oral, Patologia Oral Y Cirugia Bucal. 2013 05 01;18(3):e439-444. https://doi.org/10.4317/medoral.18419
25. Kalu UE. Ogbureke1, Christopher Bingham. Overview of Oral Cancer. Published: March 14th, 2012 Overview of Oral Cancer | IntechOpen.. https://doi.org/10.5772/30520
26. Arrangoiz R, Cordera F, Caba D, Moreno E, Leon EL, Munoz M. Oral Tongue Cancer: Literature Review and Current Management. Cancer Reports and Reviews. 2018;2(3).
27. Lingen MW, Kalmar JR, Karrison T, Speight PM P. Critical evaluation of diagnostic aids for the detection of oral cancer. Oral Oncology. 2008 01;44(1):10-22. https://doi.org/10.1016/j.oraloncology.2007.06.011
28. Waal I, Bree R, Brakenhoff R, Coebergh JW. Early diagnosis in primary oral cancer: is it possible?. Medicina Oral, Patologia Oral Y Cirugia Bucal. 2011 05 01;16(3):e300-305. https://doi.org/10.4317/medoral.16.e300
29. Sankaranarayanan R, Ramadas K, Thomas G, Muwonge R, Thara S, Mathew B, Rajan B. Effect of screening on oral cancer mortality in Kerala, India: a cluster-randomised controlled trial. Lancet (London, England). 2005 06 04;365(9475):1927-1933. https://doi.org/10.1016/S0140-6736(05)66658-5
30. Lim K, Moles DR, Downer MC, Speight PM. Opportunistic screening for oral cancer and precancer in general dental practice: results of a demonstration study. British Dental Journal. 2003 05 10;194(9):497-502; discussion 493. https://doi.org/10.1038/sj.bdj.4810069
31. Kato MG, Baek CH, Chaturvedi P, Gallagher R, Kowalski LP, Leemans CR, Warnakulasuriya S, et al. Update on oral and oropharyngeal cancer staging - International perspectives. World Journal of Otorhinolaryngology - Head and Neck Surgery. 2020 03;6(1):66-75. https://doi.org/10.1016/j.wjorl.2019.06.001
32. Ghantous Y, Nashef A, Sidransky D, Abdelraziq M, Alkeesh K, Araidy S, Koch W, Brait M, Abu El-Naaj I. Clinical and Prognostic Significance of the Eighth Edition Oral Cancer Staging System. Cancers. 2022 09 23;14(19):4632. https://doi.org/10.3390/cancers14194632
33. Tanaka T, Ishigamori R. Understanding carcinogenesis for fighting oral cancer. Journal of Oncology. 2011;2011:603740. https://doi.org/10.1155/2011/603740
34. Listl S, Jansen L, Stenzinger A, Freier K, Emrich K, Holleczek B, Katalinic A, Gondos A, Brenner H. Survival of patients with oral cavity cancer in Germany. PloS One. 2013;8(1):e53415. https://doi.org/10.1371/journal.pone.0053415
35. Naghavi M, Wang H, Lozano R, Davis A, Liang X, Zhou M, et al. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet (London, England). 2015 01 10;385(9963):117-171. https://doi.org/10.1016/S0140-6736(14)61682-2
36. Sacker A, Bartley M. Social inequalities in oral health: from evidence to action (PDF). UCL Research Department of Epidemiology and Public Health. 2015;:p. 9. ISBN 9780952737766.
37. Jump up to:a b c d e f "Cancer of lip, oral cavity and pharynx. [online]". EUCAN. Archived from the original on 23 December 2017. Retrieved 14 November 2017..
38. Jump up to:a b "oral cancer statistics". CancerresearchUK. Retrieved 28 October 2014...
39. Annertz K, Anderson H, Biörklund A, Möller T, Kantola S, Mork J, Olsen JH, Wennerberg J. Incidence and survival of squamous cell carcinoma of the tongue in Scandinavia, with special reference to young adults. International Journal of Cancer. 2002 09 01;101(1):95-99. https://doi.org/10.1002/ijc.10577
40. Diz Dios P, Meleti M, Diniz-Freitas M, Vescovi P, Warnakulasuriya S, Johnson N, Kerr A. Oral and pharyngeal cancer in Europe: Incidence, mortality and trends as presented to the Global Oral Cancer Forum. Translational Research in Oral Oncology. 2017 06 01;2:2057178X1770151. https://doi.org/10.1177/2057178X17701517
41. Nemes J, Redl P, Boda R, Kiss C, Ildikó M. Oral Cancer Report from Northeastern Hungary. Pathology oncology research : POR. 2008 02 01;14:85-92. https://doi.org/10.1007/s12253-008-9021-4
42. Suba Z, Mihályi S, Takács D, Gyulai-Gaál S. [Oral cancer: morbus Hungaricus in the 21st century]. Fogorvosi Szemle. 2009 04;102(2):63-68.
43. Moore SR, Johnson NW, Pierce AM, Wilson DF. The epidemiology of mouth cancer: a review of global incidence. Oral Diseases. 2000 03;6(2):65-74. https://doi.org/10.1111/j.1601-0825.2000.tb00104.x
44. Gupta N, Gupta R, Acharya AK, Patthi B, Goud V, Reddy S, Garg A, Singla A. Changing Trends in oral cancer - a global scenario. Nepal Journal of Epidemiology. 2016 Dec;6(4):613-619. https://doi.org/10.3126/nje.v6i4.17255
45. Krishna Rao SV, Mejia G, Roberts-Thomson K, Logan R. Epidemiology of oral cancer in Asia in the past decade--an update (2000-2012). Asian Pacific journal of cancer prevention: APJCP. 2013;14(10):5567-5577. https://doi.org/10.7314/apjcp.2013.14.10.5567
46. Cheong SC, Vatanasapt P, Yi-Hsin Y, Zain RB, Kerr AR, Johnson NW. Oral cancer in South East Asia: Current status and future directions. Translational Research in Oral Oncology. 2017 01 01;2:2057178X17702921. https://doi.org/10.1177/2057178X17702921
47. Al-Jaber A, Al-Nasser L, El-Metwally A. Epidemiology of oral cancer in Arab countries. Saudi Medical Journal. 2016 03;37(3):249-255. https://doi.org/10.15537/smj.2016.3.11388
48. Jump up to:a b c d "All Cancers (excluding non-melanoma skin cancer) Estimated Incidence, Mortality and Prevalence Worldwide in 2012". International Agency for Research on Cancer. 2012...
49. Mallath MK, Taylor DG, Badwe RA, Rath GK, Shanta V, Pramesh CS, Digumarti R, et al. The growing burden of cancer in India: epidemiology and social context. The Lancet. Oncology. 2014 05;15(6):e205-212. https://doi.

org/10.1016/S1470-2045(14)70115-9
50. Varshitha A. Prevalence of Oral Cancer in India. Journal of Pharmaceutical Sciences and Research. 2015;7(10):e845-48.
51. Chapman DH, Garsa A. "Cancer of the Lip and Oral Cavity". In Hansen E, Roach III M (eds.). Handbook of Evidence-Based Radiation Oncology. Springer International Publishing. 2018;:193–207. https://doi.org/10.1007/978-3-319-62642-0_8
52. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, Curado MP, Ferlay J, Franceschi S, Rosenberg PS, Bray F, Gillison ML. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2013 Dec 20;31(36):4550-4559. https://doi.org/10.1200/JCO.2013.50.3870
53. Farah CS, Simanovic B, Dost F. Oral cancer in Australia 1982-2008: a growing need for opportunistic screening and prevention. Australian Dental Journal. 2014 09;59(3):349-359. https://doi.org/10.1111/adj.12198
54. Burket LW, Greenberg MS, Glick M, et al. Burket's oral medicine. 11th ed. Hamilton, Ont: BC Decker, 2008..
55. Oral Cavity and Oropharyngeal Cancer Prevention. National Cancer Institute, https://www.cancer.gov/types/head-andneck/patient/oral-prevention-pdq#section/ all (accessed 23 March 2018)..
56. DeSantis CE, Lin CC, Mariotto AB, Siegel RL, Stein KD, Kramer JL, Alteri R, Robbins AS, Jemal A. Cancer treatment and survivorship statistics, 2014. CA: a cancer journal for clinicians. 2014;64(4):252-271. https://doi.org/10.3322/caac.21235
57. Onizawa K, Nishihara K, Yamagata K, Yusa H, Yanagawa T, Yoshida H. Factors associated with diagnostic delay of oral squamous cell carcinoma. Oral Oncology. 2003 Dec;39(8):781-788. https://doi.org/10.1016/s1368-8375(03)00075-7
58. Manrow RE, Beckwith M, Johnson LE. NCI's Physician Data Query (PDQ®) cancer information summaries: history, editorial processes, influence, and reach. Journal of Cancer Education: The Official Journal of the American Association for Cancer Education. 2014 03;29(1):198-205. https://doi.org/10.1007/s13187-013-0536-3
59. Clinical Statistical Study of exfoliative Cytology Performed During Oral Cancer Screening in Chiba City in the past 11 years. http://ir.tdc.ac.jp/irucaa/ bitstream/10130/3988/1/8_33.pdf (accessed 17 May 2018..
60. Mupparapu M, Shanti RM. Evaluation and Staging of Oral Cancer. Dental Clinics of North America. 2018 01;62(1):47-58. https://doi.org/10.1016/j.cden.2017.08.003
61. Street W. Cancer Facts & Figures. 1930;1930:76.
62. Osterlind A. Cancer and UV-radiation. Pharmacology & Toxicology. 1993;72 Suppl 1:67-68. https://doi.org/10.1111/j.1600-0773.1993.tb01672.x
63. Taghavirashidizadeh A, Sharifi F, Vahabi SA, Hejazi A, SaghabTorbati M, Mohammed AS. WTD-PSD: Presentation of Novel Feature Extraction Method Based on Discrete Wavelet Transformation and Time-Dependent Power Spectrum Descriptors for Diagnosis of Alzheimer's Disease. Computational Intelligence and Neuroscience. 2022;2022:9554768. https://doi.org/10.1155/2022/9554768
64. Kalani N, Zare MR, Safniyat S, Hatami N, Razavizadegan SA. The First Case of the Subretinal Abscess After Sars-CoV2 Infection. Acta Medica Iranica. 2022 02 23;:132-134. https://doi.org/10.18502/acta.v60i2.8826
65. Mahmoudreza Moghimhanjani AT. 'Analysis of liver cancer detection based on image processing', 7th International Conference On Modern Finding In Sciences And Technology With A Focused On Science In Development Services. 2020;:p. 99/222.
66. Akbar D, Mohammad S, Alireza EP, et al. The effect of multiple intravitreal bevacizumab injection on the human corneal endothelial cells. International Journal of Pharmaceutical Research. 2021;13(1):5883-7. https://doi.org/10.31838/ijpr/2021.13.01.766.
67. Khajeh S, Ganjavi M, Panahi G, Zare M, Zare M, Tahami SM, Razban V. D-allose: Molecular Pathways and Therapeutic Capacity in Cancer. Current Molecular Pharmacology. 2023;16(8):801-810. https://doi.org/10.2174/1874467216666221227105011
68. Shah JP, Gil Z. Current concepts in management of oral cancer--surgery. Oral Oncology. 2009;45(4-5):394-401. https://doi.org/10.1016/j.oraloncology.2008.05.017
69. Endicott N, Jensen R, Lyman G, et al. Adjuvant chemotherapy for advanced head and neck squamous carcinoma. Final report of the Head and Neck Contracts Program. Cancer. 1987 08 01;60(3):301-311. https://doi.org/10.1002/1097-0142(19870801)60:3<301::aid-cncr2820600306>3.0.co;2-v
70. Singh H, Patel V. Role of Molecular Targeted Therapeutic Drugs in Treatment of Oral Squamous Cell Carcinoma: Development and Current Strategies-A Review Article. Global Medical Genetics. 2022 09;9(3):242-246. https://