Republic of Iraq
Ministry of Higher Education
And scientific Research
University of Baghdad
College of Dentistry

Reviewing the oropharyngeal cancer, besides the role of general dental practitioner in the treatment of oral complications in oropharyngeal cancer treatment

A Project Submitted to
The College of Dentistry, University of Baghdad, Department of oral surgery
in Partial Fulfillment for the Bachelor of Dental Surgery

By:
Hassan Ali Noori
Jumana Hesham Mohammed
Dania Abd-alhakim Abd-Alaziz

Supervised by:
Dr. Sarmad Al-Sahaf
BDS, MSc, NBDE1 (USA), PhD (UK)
May, 2022

Supervisor Certification

I certify that this project entitled "**Reviewing the oropharyngeal cancer, besides the role of general dental practitioner in the treatment in oropharyngeal cancer treatment**'' was prepared by fifth-year students Hassan Ali Noori, Jumana Hesham Mohammed, and Dania Abd-alhakim Abd-Alaziz under my supervision at College of Dentistry - University of Baghdad in partial fulfillment of the graduation requirement for the Bachelor Degree in Dentistry.

Sarmad Al-Sahaf

Supervisor

Dr. Sarmad Al-Sahaf

BDS, MSc, NBDE1 (USA), Ph.D (UK)

Collage of Dentistry, University of Baghdad

We dedication our work to God, without him nothing is possible. We also dedicate this project to our parents and friends. A special feeling of gratitude to our loving and supporting parents who always have our back, they are the ones who pushed us and made us what we are today.

Acknowledgement

First praise to Allah the lord of the universe, peace in upon our prophet Mohanmmed the messenger of Allah and upon his relatives. Grateful thanks are expressed to Professor Dr. Raghad Al-hashimi , the dean of college of dentistry, university of Baghdad. Grateful thanks are expressed to the head of the department of oral and maxillofacial surgery Assistant Professor Dr. Sahar Shaker Al-Adeli. Many thanks to Dr. Sarmad Al-Sahaf for his continuous guidance, and for being always ready to help me in my project. We want to thank our families for everyone from the youngest person to oldest person for their help in every step in our life. Special thanks to our spiritual parents for all of their help.

LIST OF CONTENTS

LIST OF TABLES

List of abbreviations

- 1. (AJCC) American Joint Committee on Cancer tumor
- 2. (CRT) chemoradiotherapy
- 3. (CT scan) Computed tomography
- 4. (GVHD) graft versus-host disease
- 5. (HBO) hyperbaric oxygen
- 6. (HIV) human immunodeficiency virus
- 7. (HNC) head and neck cancer
- 8. (HNSCC) head and neck squamous cell carcinoma
- 9. (HPV) human papillomavirus
- 10. (HSV) herpes simplex virus
- 11. (MRI) Magnetic resonance imaging
- 12. (OC) Oral cancer
- 13. (OPC) oropharyngeal cancer
- 14. (ORN) Osteoradionecrosis
- 15. (OPSCC) oropharyngeal squamous cell carcinoma
- 16. (SCC) squamous cell carcinoma
- 17. (TNM) Tumor, Node, Metastasis
- 18. (TMJ) Temporomandibular
- 19. (US) Ultrasound
- 20. (PET) Positron emission tomography

LIST OF FIGURES

Abstract

Oropharyngeal cancer (OPC) is the 6th most common cancer worldwide. Focus on risk factors, improved diagnostic methods and effective management strategies have made it possible to successfully treat OPC. However, the 5-year survival rate has not improved for several years due to multiple treatment complications, tissue morbidity, and loss of function and diminished quality of life. Survivors are faced with complications like oral mucositis, hyposalivation, osteoradionecrosis; tissue fibrosis, morbidity from jaw resection; disfigurement and loss of function that further diminish quality of life. The aim of this project is to review the OPC and its therapeutic modalities. Besides, highlighting the major oral complications associated with the treatment of OPC and management of these oral complications.

Chapter one:

1.1. Introduction:

Historically, head and neck cancer (HNC) treatment has represented an epitome of a multidisciplinary approach that generally includes surgery, chemoradiotherapy (CRT), and systemic therapy. Approximately two thirds of patients present with locoregionally advanced disease treated with some combination of these three therapeutic modalities. Several extrinsic and intrinsic risk factors contribute to development of oropharyngeal cancer (OPC) including age, ethnicity, gender, habitual use of tobacco and alcohol, and viral infections, (Ari J,*et al*., 2021),

Fifty potential carcinogens have been identified in tobacco, making smoking a significant risk factor for oral cancer. These carcinogens can alter cellular mechanisms through genetic mutations, cell cycle disruption and altered immune response making smokers 5 to 7 times more susceptible to oral carcinogenesis than non-smokers. Acetaldehyde, a metabolite of alcohol, interferes with DNA synthesis and repair, while alcohol itself acts as a solvent on the oral mucosa exposing it to potential carcinogens. Habitual use of tobacco and alcohol simultaneously has a synergistic effect resulting in 13-fold increased risk for developing oral cancer compared to either tobacco or alcohol use alone, (Ferraguti, *et al.*, 2022).

Over the past two decades, human papillomavirus (HPV) has emerged as an etiologic factor associated primarily with oropharyngeal squamous cell carcinoma (OPSCC). HPV associated disease results in higher rates of cure compared with non HPV disease with current treatment paradigms. The notably improved clinical outcomes in HPV associated HNC juxtaposed with significant treatment related morbidity and mortality has

led to interest in the development of deescalated therapeutic strategies with the goal of maintaining or further improving oncologic outcomes while reducing short and long term toxicity. HNC is one of the critical diseases that attack the organs and tissues of the upper aerodigestive tract, these regions are including: oral cavity, nasopharynx, oropharynx, larynx, salivary glands as well as nasal and paranasal sinuses (Figure 1.1.). World-wide, HNC occupies the rank sixth in between the other types of body cancers, the most common types of HNC is the squamous cell carcinoma (SCC), (Cláudia V. , *et al*., 2020)

Despite substantial efforts invested into therapeutic development of HNSCC, the 5-year survival rate of patients with HNSCC still remains dismal. The primary reason is being late diagnosis, recurrent metastasis, relapse and resistance to therapies. Currently surgery and radiotherapy represent the baseline treatment options for most initial stage HNSCC patients, but these treatments are associated with significant morbidity and poor prognosis. Moreover, the issue of resistance to both radiotherapy/chemotherapy and recurrent relapse are common in HNSCC. Elucidation of the genetic landscape, tumor microenvironment and aberrant signaling pathways have generated new insights into the molecular pathogenesis of this disease, (Advani, Sharma, Sudhanshu, et al. 2022).

The different types of the HNC region hold many dissimilarities in their clinical behavior and vary from anatomical site to site. (Taylor,*et al* ,.2004; TB. Steinbichleretal, 2020). Owing to the complex anatomical location and the vital tumour involved structures directed the objectives of treatment are not limited to improving survival, but also to conserving organ function, (Argiris *et al*, 2008). Oral cancer (OC) and oropharyngeal cancer (OPC) are the most prevalent HNCs and present a major health

public problem. Therefore, a thorough understanding to the tumour nature and its microenvironment is paramount for improved HNC management and early diagnosis, (Lechner, *et al*., 2022).

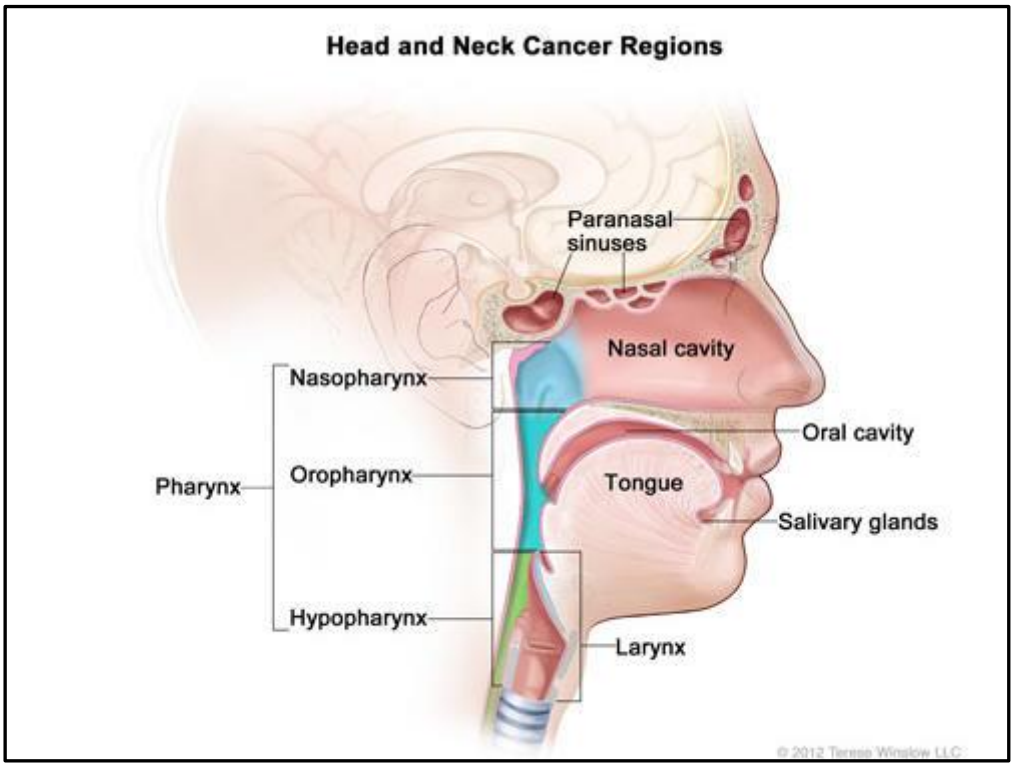

Figure (1.1) Anatomical sites for head and neck region. The most common anatomical sites for HNSCC development include the nasopharynx, oropharynx, larynx, and oral cavity. Adapted from, (Giampiero, *et al*., 2022).

1.2. Aim of the study:

1- The OPC and its therapeutic modalities.

2- Highlighting the major oral complications associated with treatment of OPC and management of these oral complications.

Review of Literature

1.3. The Oropharyngeal cancer:

Oropharyngeal squamous cell carcinoma (OPSCC) comprises cancers of the tonsils, base of tongue, soft palate and uvula; there is surge increase in the incidence of OPC especially in the developed countries, as shown in (Figurs. 1.2). Like other head and neck squamous cell carcinomas, OPSCC has historically been linked to alcohol and tobacco consumption. A reduction in the prevalence of smoking in most high-income countries over the past 20 years has led to a decline in the incidence of HNSCC; however, carcinogenic human papillomavirus infection has emerged as an important risk factor that has driven an increase in the incidence of OPSCC over the same period, (Matt , *et al.* 2022).

Symptoms of OPC include a sore throat that doesn't go away; a lump in the throat, mouth or neck; coughing up blood; white patch in the mouth and other symptoms. Treatments may include surgery, radiation therapy, chemotherapy, targeted drug therapy and immunotherapy**.**

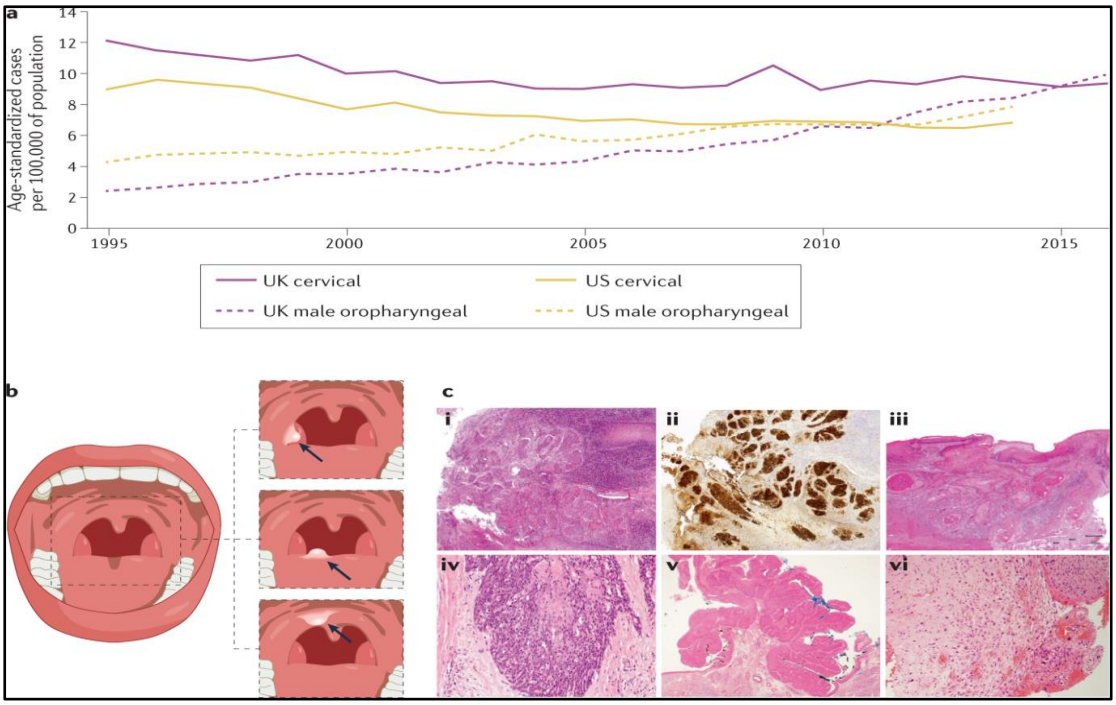

Figure (1.2): Incidence, anatomical locations and histological appearance of OPC, (Matt, et al., 2022).

1.4. Types of OPC according to HPV infection:

There are two types of OPC according to HPV-infection status:

1. HPV-positive OPC, which is caused by an oral human papillomavirus infection.
2. HPV-negative OPC, which is linked to use of alcohol, tobacco, or both, and any other causative factor other than the HPV, (S. Warnakulasuriya, *et al.* , 2009).

The general types of the OPC are SCC and approximately more than 90% of the cancers in the oral cavity and oropharyngeal area. These cancers start in early forms of squamous cells, which are flat, scale-like cells that form the lining of the mouth and throat. The earliest form of squamous cell cancer is called carcinoma in situ. This means that the cancer cells are only in the layer of cells called the epithelium. This is different from invasive squamous cell carcinoma, where the

cancer cells have grown into deeper layers of the oral cavity or oropharynx, (J.O. Kemnade *et al*, 2020).

About 70% to 80% of the cases happened in the tonsillar region because the lining epithelium for this site is different from the other sites. The incidence is increasing at nearly Epidemic rate. Particularly that is driven by the HPV-infection, However, the oropharyngeal sites and the other sites of the upper aerodigestive tract have the same incidence of carcinoma because they all shared common exposure to the same carcinogens in tobacco/alcohol and HPV, Patients with OPC have better survival rate after treated with chemoradiation therapy than patients with other types of HNC, and significantly better prognosis in OPC with HPV-positive. The Symptoms of OPC generally include, sore throat and painful and/or difficulty in swallowing if not caused by HPV, lump on the neck if it caused by HPV. OPC can be diagnosed by laryngoscopy, operative endoscopy, and imaging studies for staging, (Maciejewski B. et al, 1989), (Tahari , et al,. 2014).

The OPC can be treated by one or in combinations of the following therapeutic modalities, which are including surgical intervention, radiation, and chemotherapy, (Taylor, et al, 2004). However, surgery has begun to be used more often in HPV-negative OPC; and some cases of HPV-positive OPC radiotherapy could be the sufficient treatment. Survival rate is much higher in HPV-positive patients.

1.5. Oropharyngeal anatomy and natomical considerations:

The oropharynx is bounded proximally by the posterior edge of the hard palate and distally by the valleculae and hyoid bone as shown in the (figure 1.3.). The muscular pharyngeal wall defines the posterior/posterolateral limits of the oropharynx, and the circumvallate papillae and palatoglossal muscle mark the anterior borders. The lateral walls of the oropharynx are composed of the tonsils and tonsillar fossae. For the purposes of management of oropharyngeal tumors, the oropharynx should be understood to consist of four subsites: the posterior pharyngeal wall, the soft palate, the tonsillar complex (i.e. tonsil, tonsillar fossa, and pillars), and the base of the tongue, (Osborne .,*et al*. 2004) (Shah , *et al*. 2019).

The oropharynx is posterior to the oral cavity between the nasopharynx and hypopharynx (this part (hypopharynx) is separated from the oropharynx by superior aspect of the hyoid bone), (Harreus , *et al* ,.2005). The oropharynx is composed from walls which are:

1. Anterior wall (base of the tongue /lingual tonsils).

2. Lateral walls (palatine tonsils).

3. Superior wall (soft palate).

4. Posterior wall (is its posterior limit).

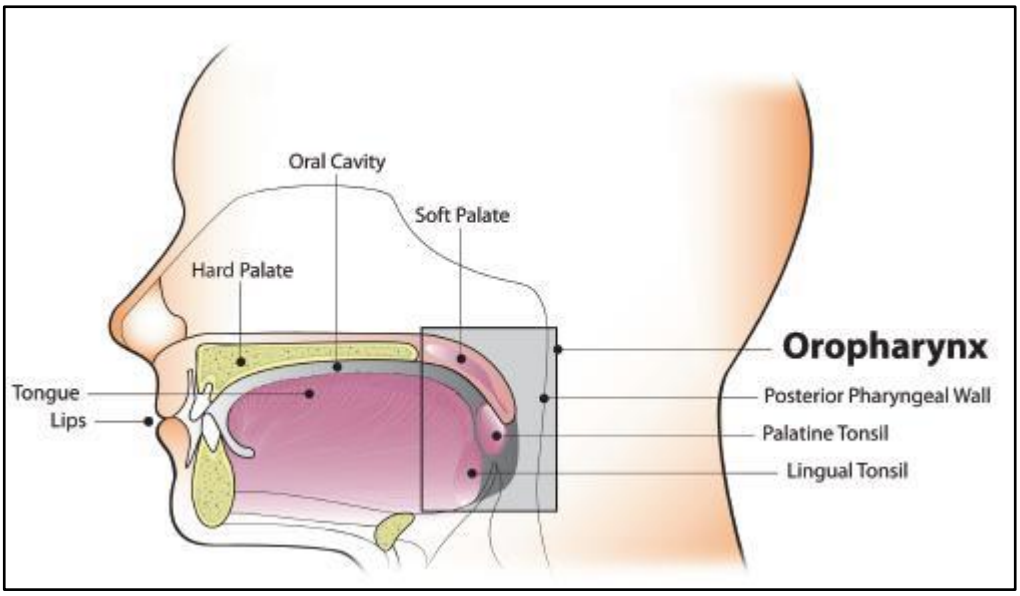

Figure 1.3.: The oropharyngeal anatomical subsite, subsite, (Christopolous , *et al*., 2018)

These subsites are very common locations for the development HNC, and a tumour present in any of these subsites can be largely classified as an oropharyngeal tumour, The tonsils (also referred to as palatine tonsils) are collections of lymphoid tissue located on each side of the oropharynx which participate in the immune function of the aerodigestive tract. Although tonsils may be quite large during childhood, they generally regress with age, and many adults have very little visible tonsillar tissue remaining. Enlargement or asymmetry of the tonsils in an adult may simply be an anatomic variant, but may also be an indication of tumour presence. However, removal of tonsils has not been found to compromise immune status.

The base of tongue (or tongue base) refers to the portion of the tongue which resides in the oropharynx (posterior 1/3 of the tongue). The base of tongue is functionally and anatomically distinct from the oral tongue, which is the portion of the tongue which resides in the oral cavity (anterior 2/3 of the tongue) and is most important for speech

and language. The muscles of the base of tongue are more involved with swallowing than speech, and play a critical role in controlling the passage of food and liquids from the mouth into the throat. Base of tongue dysfunction resulting from tumour, loss of tissue due to surgery, or radiation-related effects may result in difficulty swallowing or aspiration (spillage of liquids into the larynx or voice box), (Moore, *et al*., 2011).

The soft palate is a muscular soft tissue, which resides behind the hard palate, or roof of the mouth. The soft palate separates the nose and nasopharynx from the remainder of the pharynx and oral cavity during speech and swallowing. Inability to close the soft palate (Velopharyngeal insufficiency) due to tumour, resection, or scar may result in hyper-nasal speech as well as reflux of liquids into the nose during swallowing. The lateral and posterior walls of the oropharynx are comprised primarily of muscles which play a supporting role in the pharyngeal phase of swallowing, (Moore, *et al* ,. 2011).

1.6. Epidemiology:

It is anticipated that approximately 833,000 and 151,000 new cases of HNC will occur worldwide and in Europe, respectively, (Boscolo. *et al.*, 2018). OC and OPC represent a serious problem, reaching a global incidence of half million cases annually as shown in (Figure 1.4.),
(M Ustrell B., *et al*., 2020). The number of the OPC linked to HPV-infection has increased over the past few decades, and sufficient amounts of data has shown that these cancers are becoming more common in people with no history of alcohol abuse or tobacco use than they were in the past, the reason could be because of changes in sexual practices, in recent decade. In contrast to non-HPV- associated

OPC; HPV-associated OPC has excellent survival rates, ranging from 80% to 90% for early–stage disease.

Importantly, researchers note that the average age of patient with HPV-positive OPC has significantly increased in recent years, as the result of that the HPV positive OPC can no longer characterized as a disease of young individuals, (C. Fakhry, *et al*., 2020). Depending on recent finding, Europe has the most prevalent rate of OPC and lower in Africa, and there is an increase in the incidence and prevalence by 24%, and 12% respectively during the past three decades, whilst mortality has declined by around 5%, (R. Nocini, G. Mattiuzzi,et al. 2020). As already noted worldwide, the incidence of OC and OPC overall is higher for males than females (this may be because of their greater indulgence in the most important risk factors, such as heavy alcohol and tobacco consumption). In fact, 71.7% of all OPC patients were male although this trend has begun to decrease over the last few decades, (Tataru D. et al., 2017). OPC appears in about 90% over the age of 45 years, (Gao G.,*et al*. 2017).

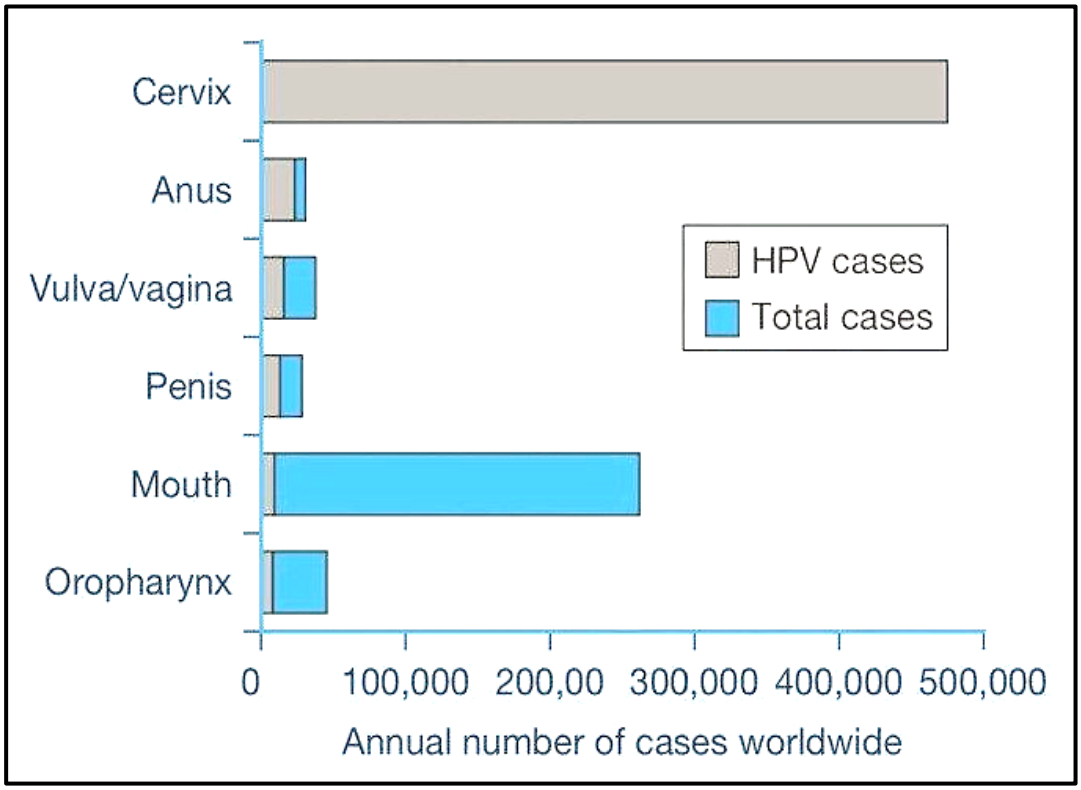

Figure 1.4.: Number of new cases of cancer in 2020, including cervical and ororpharyngeal cancer, worldwide in both sexes, all ages, (Data obtained from GLOBOCAN 2020).

1.7. Mechanism of carcinogenesis:

Cancer begins when healthy cells change and grow out of control, forming a mass called a tumour. A tumour can be cancerous or benign. A cancerous tumor is malignant, meaning it can grow and spread to other parts of the body. A benign tumor means the tumor can grow but will not spread. Human malignancy is one of the most complex groups of diseases, representing an intersection of pathophysiology, genetics, and environmental factors as well as immunology. Indeed, cancer represents not a single disease but a wide range of conditions with highly variable clinical course ranging from extremely inactive to highly aggressive. Doctors and scientists can’t say for sure what causes each case of OC or OPC, and it’s difficult to say why some people develop cancer and others don’t. But they do

know many of the risk factors and how some of them may lead to cells becoming cancerous, and increase a person's chances of getting OPC, (Tomasetti, *et al*,.2017).

Scientists believe that some risk factors, such as tobacco or heavy alcohol use, may cause these cancers by damaging the DNA of cells that line the inside of the mouth and throat. DNA makes up our genes and the instructions for how our cells function. Some genes called protooncogenes can help control when cells grow and divide. DNA changes can change these into genes that promote cell division that are called oncogenes. Some genes that slow down cell division or make cells die at the right time and are called tumour suppressor genes, (Daniel, *et al*,. 2022).

DNA changes can turn off tumour suppressor genes, and lead to cells growing out of control. Cancers can be caused by DNA changes that create oncogenes or turn off tumour suppressor genes. When tobacco and alcohol damage the cells in the epithelial lining the mouth and throat, the cells in this layer must grow more rapidly to repair this damage. The more often cells need to divide, the more chances there are for them to make mistakes when copying their DNA, which may increase their chances of becoming cancer. Many of the chemicals found in tobacco can damage DNA directly. Scientists are not sure whether alcohol directly damages DNA, but they have shown that alcohol helps many DNAdamaging chemicals get into cells more easily. This may be why the combination of tobacco and alcohol damages DNA far more than tobacco alone. This damage can cause certain genes for example, those in charge of starting or stopping cell growth to malfunction. Abnormal cells can begin to build up, forming

a tumour. With additional damage, the cells may begin to spread into nearby tissue and to distant organs, (Johnson, *et al*. 2020).

In HPV-infections, the virus causes cells to make 2 proteins known as E6 and E7. When these are made, they turn off some genes that normally help keep cell growth in check. Uncontrolled cell growth and divisions may in some cases lead to cancer. When HPV-DNA is found in the tumour cells, especially in nonsmokers who drink little or no alcohol, HPV is thought to be the likely cause of the cancer. Some people inherit DNA mutations from their parents that increase their risk for developing certain cancers. However, inherited oncogene or tumour suppressor gene mutations are not believed to cause very many cancers of the oral cavity or oropharynx. Some oral cavity and OPC have no clear cause. Some of these cancers may be linked to other, as of yet unknown risk factors. Others may have no external cause, they may just occur because of random DNA mutations inside a cell. OC most commonly begin in the squamous cells, (Li, *et al*,.2008) .

1.8. The risk factors

The risk factors are anything that increases the person's chance of developing cancer. Some people with several risk factors never develop cancer, while others with no known risk factors develop cancer, (Ana Casal-Mouriño, *et al*,.2020). Having one or more risk factors does not mean the subject will get OPC, Also having no risk factors does not mean will not develop OPC, (Ana Casal-Mouriño, *et al*,.2020). The main risk factors are alcohol and tobacco, in addition, oral HPV-infection, now recognized as major OPC risk factor.

There are well-established risk factors for HNC such as:

1- **Smoking:** One of the clearest causes is the consumption of the smoke. More specifically, the risk of oropharyngeal cancer increases the greatest when both alcohol and tobacco are used together, rather than either one alone, (Pfeifer G, 2002). Tobacco itself releases multiple carcinogens into the respiratory system when smoked, (La D, SwenbergJ, 1996). Organisms generally release cytochrome in the presence of carcinogens, an enzyme that will catalyze the addition of an oxygen atom to the compound to increase its hydrophilic nature and make it easy to eliminate from the system, (La D, SwenbergJ, 1996). However, if this process is not efficient enough (such as during heavy or prolonged exposure), the electrophilic intermediates formed by this process will be produced for longer periods of time, allowing them to react with DNA and form DNA adducts, (Gao G, Smith DI,2017).

   Adducts are simply segments of DNA bound to large carcinogenic molecules, preventing the proper replication of the DNA. This is usually the starting point for a mutation, which can produce damaged tumour cells.

   2. Alcohol consumption: Drinking alcohol is linked to throat cancer. The more alcohol a person drinks, and the more years they drink for, the higher the risk to getting cancer, about 7 out of 10 patients with OC are heavy drinkers, (Alaram, *et al*,. 2002).

   3. Poor oral hygiene and dentition: People with poor oral hygiene and poor dentition may have an increased risk of cancer especially in people who use alcohol and tobacco products, (Morshed, *et al*,. 2014).. It is likely that chronic irritation from dental factors may facilitate exposure to carcinogens, so this may

act as a co-factor in high-risk individuals only. Oral microbes (together with biofilms) may also be a factor in chronic alcohol users as some microbes facilitate the metabolism of ethanol to acetaldehyde (a potent carcinogen) in the oral cavity. This may contribute to acetaldehyde formation in the oral environment and acetaldehyde adducted to cancer cells among chronic alcoholics was recently demonstrated, (Ana Casal-Mouriño, *et al*,.2020).

4. **Immune system:** People with a weakened immune system may have a higher risk of developing OPC; the immunity may be suppressed in cases like unhealthy diet, immune-suppressive medications, and specific condition that suppress the immune system.

5. **The gender:** The OPC is twice common in men than women.

6. **The age:** This type of the cancer takes many years to develop so it's not common in young patient.

7. **Poor nutrition:** Several studies have found that a diet low in fruits and vegetables is linked with an increased risk of OPC.

8. **Previous cancer:** People who previously have had an OC or OPC have an increased risk of getting recurrence, (Ana Casal-Mouriño, *et al*,.2020).

9. **Family history:** Although many studies show a definitive link between family history and OPC, however the explanation is derived from gene mutations caused by behaviours such as heavy tobacco smoking and alcohol intake, (Gillison ML, 2007).

10. **Genetic conditions:** People with certain conditions caused by inherited cell mutations have an increased risk of OPC, (Ana Casal-Mouriño, *et al*,.2020).

11. HIV infection: Anti-retroviral therapy that lead to the immunosuppression in HIV disease could increase the risk for OPC, but there is no strong epidemiological evidence to confirm an association of HIV infection or AIDS with these cancers, in addition to that OPC with a known infective disease cause HPV may be moderately increased in people with HIV.

12. Socio-economic status: OPC is seen more often in people from lower socio-economic groups. A higher prevalence of smoking, alcohol use and poor diet in these groups was thought to account for this unequal distribution. However, new research suggests that lower socio-economic status is a significant risk factor for OPC, (Ana Casal-Mouriño, *et al*,.2020).

13. Precancerous conditions: These conditions include Leukoplakia and Erythroplakia. These are white or red patches in the mouth that are often linked to tobacco use and poorly fitting dentures that rub against the tongue or inside of the cheeks. A biopsy is the only way to know for certain if an area of leukoplakia or erythroplakia contains dysplastic (precancerous) cells or cancer cells. Most cases of leukoplakia do not turn into cancer. But can progress to cancer if not properly treated. Erythroplakia and erythroleukoplakia are less common, but are usually more serious. Most of these red lesions turn out to be cancer. Still, it's important to note that most OC do not develop from pre-existing lesions (either leukoplakia or erythroplakia), (Ana Casal-Mouriño, *et al*,. 2020).

14. HPV: HPV is group of more than 180 types of viruses. They are called papillomaviruses because some of them cause a type of growth called papilloma and these are not cancer. Exposure of the

oral cavity and oropharynx to HPV often results in an asymptomatic, transient infection that is cleared by the body's immune system; however a small percentage of these infections can persist in a dormant state. Depending on the HPV genotype, a persistent oral infection may lead to benign or malignant disease, (Sedghizadeh, *et al*, 2016).. Certain types of HPV cause some types of cancer including the mouth and throat, the type that linked to the OPC is HPV-16, and less often is HPV-18, these types also cause most cervical and anal cancers.

Most sexually active people will get it during their life time HPV-infection, it is estimated that 80 - 90% of individuals who contract it are able to clear it through a cell mediated immune response without symptoms arising, (Doorbar , *et al*,. 2019).

1.9. Signs and Symptoms:

Some oral squamous cell carcinomas (SCCs) arise in apparently normal mucosa, but many are preceded by clinically obvious potentially malignant disorders, especially erythroplakia (red patch), leukoplakia (white patch), erythroleukoplakia (red and white patch), or verrucous leukoplakia, and lichenoid lesions. Many others are associated with such lesions (especially in Southeast Asia), **(Scully C.2014)**. In most cases, a biopsy with histologic examination is required because dysplasia may precede malignant changes. The rate of malignant changes can be as high as 36% when moderate or severe dysplasia is present. Be aware that single ulcers, lumps, red patches, or white patches (particularly if they persist >3 wk) may be manifestations of malignancy, **(Saman; Daniel M. 2012)** .

1. Most commonly presents as a neck mass or sore throat.
2. Might also present as dysphagia
3. A visualized mass.
4. Globus sensation.
5. Odynophagia or otalgia.
6. A sore in the mouth that doesn't heal, for more than 2 weeks (very common).
7. Persistent pain in the mouth (very common).
8. A lump or thickening in the cheek.
9. A white or red patch on the gingiva, tongue, tonsil, or lining of the mouth. 10. A sore throat or a feeling that something is caught in the throat that doesn’t go away.
11. Trouble moving the jaw or tongue.
12. Numbness of the tongue or other area of the mouth.
13. Swelling of the jaw that causes dentures to fit poorly or become uncomfortable.
14. Loosening of the teeth or pain around the teeth or jaw.
15. Voice changes.
16. A lump or mass in the neck.
17. Constant bad breath, (Cohan DM et al, 2009).

Many of these signs and symptoms can also be caused by other than cancer, or even by other cancers. If any of these conditions lasts more than two weeks so that the cause can be found and treated, if needed. Some people with early stages of OPC don’t have any symptoms at all. The Signs and Symptoms are depending on the potential cause of the cancer. For example, individuals with OPC linked to HPV are more likely to notice a neck mass as the first sign of cancer, whereas those with cases linked to carcinogens like tobacco are more likely to first experience a

sore throat, trouble swallowing, (Pitchers M, Martin C, 2006; Tim M *et al.*, 2013).

1.10. Evaluation and staging of oral pharyngeal tumors:

The first step in evaluating a potential oropharyngeal tumor is a comprehensive history and physical examination. Typically, this is followed by panendoscopy with biopsies of suspicious areas. Particularly important points to elicit in taking a history include the presence/absence of trismus, dysphagia, odynophagia, altered tongue mobility, otalgia, or all. On physical examination and endoscopy, size and gross characteristics (e.g. ulceration) of lesions, as well as anatomic subsite(s), should be carefully documented. A detailed examination of the lymph node bearing regions of the neck is crucial for accurate staging. Attention should also be paid to the supra and infraclavicular fossae, (Lin, *et al*,. 2005).

Several recent articles have reviewed the roles of screening and various screening modalities in the diagnosis of oral cancers. Unfortunately, none of these articles separates oropharyngeal lesions from oral cavity lesions. Moreover, although toluidine blue and autofluorescence appear to be useful in the early diagnosis of malignant and premalignant lesions, no consensus has been reached on the applications of these techniques. Annual detailed physical examinations of the oral cavity, oropharynx, and neck should be performed by primary care providers on patients at high risk for the development of oral cancers, including smokers, heavy drinkers, and patients with a prior history of head and neck cancer, (Monk and Tewari,. 2007) number of oral premalignant lesions have been identified, including leukoplakia, erythroplakia, mixed red and white lesions, lichen planus, and verrucous lesions. The potential for malignant transformation of these lesions appears to correlate with the degree of

dysplasia exhibited. Topical application of toluidine blue appears to assist in the identification of oral premalignant lesions, in the delineation of the borders of malignant and dysplastic lesions, and in predicting the malignant potential of various oral mucosal lesions (on the basis of degree of dye retention), (Epstein, *et al*,. 2008).

1.11. Diagnosis:

The following tests may be used to diagnose oral or oropharyngeal cancer:

Physical examination: Dentists and doctors often find lip and oral cavity cancers during routine checkups. If a person shows signs of oral or oropharyngeal cancer, then complete medical history, asking about the patient's symptoms and risk factors. Any lumps on the neck, lips, gums, and cheeks, related to people with oral or OPC have a higher risk of other cancers elsewhere in the head and neck region, the area behind the nose, the larynx, and the lymph nodes of the neck must be examined as well, (Jamal Z, Anjum F., 2022)

Endoscopy: An endoscopy allows the doctor to examine the oral cavity and throat. Typically, a thin, flexible tube is inserted through the nose to examine the head and neck areas. Sometimes, a rigid endoscope, which is a hollow tube with a light and view lens, is used to examine the throat, (Jamal Z, Anjum F., 2022).

Biopsy: Other tests can suggest that cancer is present, but only a biopsy can make a definite diagnosis. The type of biopsy performed will depend on the location of the cancer. During a fine needle aspiration biopsy, cells are removed using a thin needle inserted directly into the suspicious area. Oral brush biopsy can be used during routine dental examinations. The specimen is then sent to a laboratory for analysis. This procedure can be done in the dentist's chair with very little or no pain. If cancer is found using this method, a traditional biopsy is recommended to confirm the diagnosis, (Joshi, Poonam et al., 2014).

HPV-testing: HPV-testing may be done on a sample of the tumour removed during the biopsy. Finding if a person has HPV-infection can

help to determine the cancer's stage and the treatment options that are likely to be most effective, (Scully C. 2014).

X-ray: Radiological test may be recommended to examine any abnormal findings in the oropharyngeal area.

Barium swallow/modified barium swallow: There are 2 barium swallow tests that are generally used to look at the oropharynx and to check a patient's swallowing. The first is a traditional barium swallow, which is used during an x-ray exam, to check any changes in the structure of the oropharyngeal area. A modified barium swallow, or videofluoroscopy, may be used to evaluate difficulties with swallowing, (Lewis-Jones H, Colley S, Gibson D. 2016).

Computed tomography (CT scan): A CT scan can be used to measure the tumour's size, deciding the whether the tumor can be surgically removed, and show whether the cancer has metastasis to lymph nodes in the neck or mandible, (Joshi, Poonam et al. 2014).

Magnetic resonance imaging (MRI): An MRI uses magnetic fields, not x-rays, to produce detailed images of the body, especially images of soft tissue, such as the tonsils and the base of the tongue. MRI can be used to measure the tumor's size. A special dye called a contrast medium is given before the scan to create a clearer picture, (PDQ Adult Treatment Editorial Board. 2021).

Ultrasound: This test can detect the spread of cancer to cervical lymph nodes, (Saman, Daniel M. 2012).

Positron emission tomography (PET) or PET-CT scan: A PET scan is usually combined with a CT scan, called a PET-CT scan. A small amount of a radioactive sugar substance is injected into the patient's body. This radioactive substance is taken up by cells that use the most energy. Because cancer tends to use energy actively, it absorbs more of the radioactive substance. However, the amount of radiation in the substance is too low to be harmful. A scanner then detects this substance to produce images, (Joshi, Poonam et al. 2008).

1.12. Staging:

In 2018 the American Joint Committee on Cancer tumor (AJCC) upgraded the tumor, node, metastasis (TNM) as follows

Classification

Primary tumor, as follows:

- Tis - Carcinoma in situ
- T1 - Tumor 2 cm or smaller
- T2 - Tumor 4 cm or smaller
- T3 - Tumor larger than 4 cm
- T4 - Tumor larger than 4 cm and deep invasion to muscle, bone, or deep structures (eg, antrum)

Lymphatic node involvement, as follows:

- N0 - No nodes
- N1 - Single ipsilateral node smaller than 3 cm
- N2 - Nodes(s) ipsilateral smaller than 6 cm
- N3 - Nodes(s) larger than 6 cm and/or bilateral

Tumor metastasis, as follows:

- M0 - No metastasis
- M1 - Metastasis noted

Staging

Stage I is T1, N0, M0.

Stage II is T2, N0, M0.

Stage III is as follows:

- T3, N0, M0
- T1-T3, N1, M0

Stage IVa is as follows:

- T4a, N0-N1, M0 or
- T1-T4a, N2, M0

Stage IVb is as follows:

- Any T, N3, M0 or
- T4b, N0-N1, M0

Stage IVc is as follows: Any T, Any N, M1, (Lydiatt WM et al. 2017) .

1.13. Treatment of OPC

Treatment of OPC depends on the stage of disease at diagnosis. For stage I or II disease, surgery is the treatment of choice, and complete resection of the tumor with a margin of non-involved tissue is usually possible. The status of the resection margins can be verified microscopically during surgery using frozen sections, and if margins are not tumor free, the resection can be further extended. In addition to the primary tumour mass, cervical lymph nodes may be removed during surgery for stage I or II OPC. Neck dissection is performed to remove the involved nodes and to prevent lymphatic spread. The 5-year survival rate of patients with early disease varies by site from 91.5% for the lip, to 71.4% for the oral cavity and 58.4% for the oropharynx, (Palmer CE, Gullane PJ, Gilbert RW, *et al.*, 2004).

Radiotherapy is added even in patients with early disease if the surgical margins are microscopically involved by tumour cells, because the rate of failure in locoregional control (local recurrence or regional lymph node

metastasis) is significantly increased if the surgical margins are not free of disease, (Kovacs AF. *et al.*, 2004).

In advanced disease (stage III and IV), it may not be possible to achieve tumour-free margins. In tumours considered resectable, a bimodal approach is used, consisting of surgical resection and radiotherapy to the tumour bed and the neck. The prognosis, depending on the site and the stage, is significantly lower in advanced than in early disease. In the lip, 5-year survival ranges from 82.6% to 52.2%, decreasing to 45.8% to 21.8% in the oral cavity and 41.2% to 20.3% in the oraopharynx.

Most of the cancer types in the oral cavity and oropharynx are less sensitive to chemotherapy than to radiotherapy. Therefore, chemotherapy alone has been used only in patients with metastatic or unresectable recurrent disease, with previous radiotherapy. Multiple-agent chemotherapy protocols are more effective than single-agent ones. In recent years, several clinical trials have proved that in advanced disease, combination therapy (radiochemotherapy) is superior to radiation alone in terms of survival rates, (Hanna E, Alexiou M, Morgan J, et al., 2004). Severe short-term treatment toxicity from the therapy is significantly increased with the combined protocol, although long-term toxicity is not significantly higher than with radio- therapy alone, (Denis F, Garaud P, Bardet E, *et al.*, 2004).

1.14. Complications Associated with Treatment of OPC

Radiation and chemotherapeutic agents induce significant cellular changes on oral tissues with consequent loss of function, (Myers RA, Marx RE.1990; Marx RE 1990). These changes may be transient or permanent but often result in long-term repercussions (Table 1). Acute reactions from direct toxicity of treatment persist throughout the duration of treatment but gradually resolve within the first few weeks after completing treatment. Chronic complications, however, may be protracted for a significant period resulting in lifelong morbidity.

Successful management of these complications often improves the patients' quality of life.

Table 1.1: Complications of Oral Cancer treatment, (Marx RE, 1990)

Organs affected	**Chemotherapy**	**Radiation therapy**
Oral mucosa	Infections: fungal, viral, bacterial	Mucositis
Skin		Dermatitis
Teeth	Caries: secondary to hyposalivation	Radiation caries
Jaws/bone	Chemotoxicity Secondary infections Mastication difficulties	Osteoradionecrosis Mastication difficulties
Muscles and soft tissues	Mastication and speech difficulties	Fibrosis, mastication and speech difficulties
TMJ		Fibrosis and trismus
Tongue and taste buds	Taste dysfunction	Taste dysfunction
Salivary glands	Hyposalivation/xerostomia	Hyposalivation/xerostomia (if glands are not-spared)
Others	Pain	Pain Dentofacial abnormalities

Oral complications after chemotherapy, in general, are of shorter duration, usually from a few weeks to a couple of months. After cessation of the radiation therapy, the oral complications tend to be more severe and quite often lead to permanent tissue changes that might lead to more serious chronic complications.

Oral mucositis

Oral mucositis is an acute reaction associated with radiotherapy, chemotherapy or a combination of both treatments. It is characterized by erythema, mucosal ulceration, oropharyngeal pain, and speech difficulties (Figures 1.5. A and B). Etiologically, it is a direct result of injury to the oral epithelium by several free radicals released by the therapeutic agents; hence limiting the dose and rate of administration can control it, (Fischer DJ, Epstein JB 2008; Sonis ST 1998). Oral mucositis usually develops within 2 weeks of starting either radiotherapy or chemotherapy.

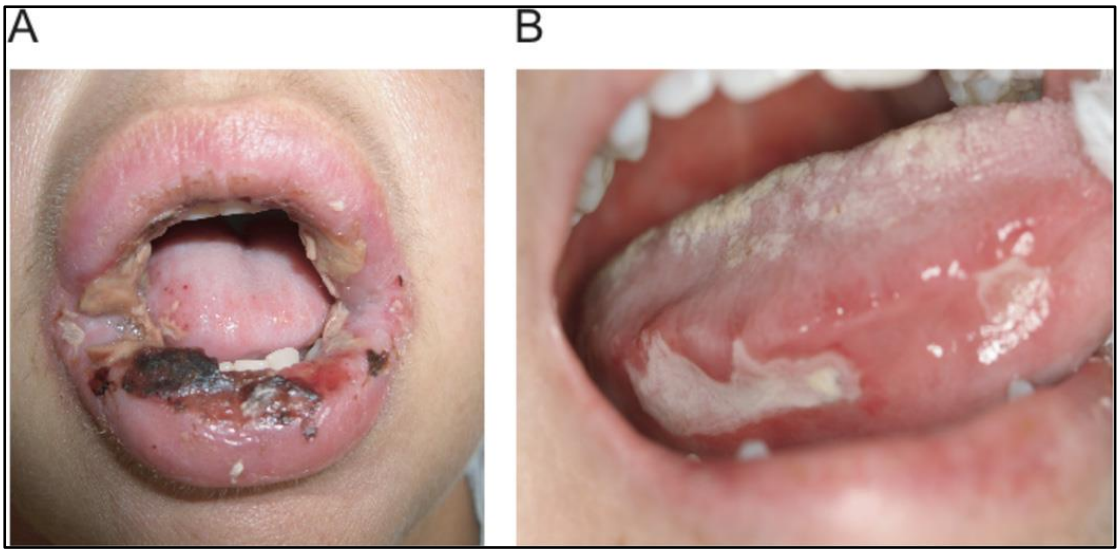

Figure 1.5. : Oral mucositis: (A) severe generalized oral mucositis, (B) moderate on the lateral border of the tongue, (Fischer DJ, Epstein JB 2008).

Infections

The risk for oral infections increases during and after OPC therapy because the oral microbial flora is altered by myelosuppression and the oral cleansing property of saliva is diminished by reduced salivary flow. In addition dormant viral, odontogenic and periodontal infections usually become reactivated to further complicate OPC therapy, (Akintoye SO *etal* 2008; Lerman MA, Laudenbach J, Marty FM, Baden LR, Treister NS 2008).

Fungal Infections

Candida is a normal oral commensal in 34–68% of healthy individuals; hence, candidiasis is one of the most frequent oral infections during OPC therapy, (Fischer DJ, Epstein JB 2008; Ship JA, Vissink A, Challacombe SJ., 2007). Oral candidiasis presents as a removable white pseudomembrane or erythematous patch on the tongue, palate and labial

commissures (Figures 1.6. A – C). Topical antifungal therapy is very effective in reducing oral candidiasis, (Epstein JB, Gorsky M, Caldwell J. Fluconazole 2002). Persistent or systemic spread of fungal infections can be controlled with systemic antifungal treatment.

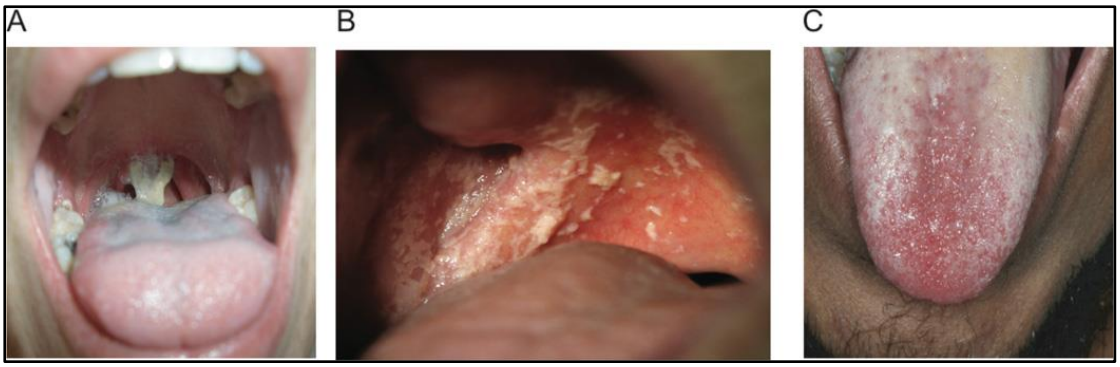

Figure 1.6.: **Candidiasis:** Heavy accumulation of pseudomembranous candidiasis on the oropharynx and buccal mucosa while another patient developed erythematous candidiasis on the dorsum of the tongue, (Fischer DJ, Epstein JB 2008)..

Viral Infections

Reactivation of latent herpes simplex virus type-1 (HSV) is one of the most common causes of viral infection in OPC patients receiving radiotherapy and chemotherapy (Figures 3A and B), (Mosel DD, Bauer RL, Lynch DP; Hwang ST 2011; Schubert MM. 1991). In healthy individuals, herpetic lesions are self-limiting, usually resolving within 2 weeks. However, in OPC patients receiving therapy, HSV infections have atypical appearance, disseminate throughout the oral cavity and may become life threatening. Viral cultures are the most useful diagnostic tools for HSV infections. OPC patients usually receive prophylactic treatment with acyclovir, an inhibitor of viral thymidine kinase, (Lerman MA, Laudenbach J, Marty FM, Baden LR, Treister NS.2008; Epstein JB, Stevenson-Moore P., 2001). Valacyclovir and famciclovir are alternative

drugs with better bioavailability than acyclovir. In cases of acyclovir-resistant HSV infections, other therapeutic options like foscarnet or cidofovir should be considered, (Lerman MA, Laudenbach J, Marty FM, Baden LR, Treister NS, 2008).

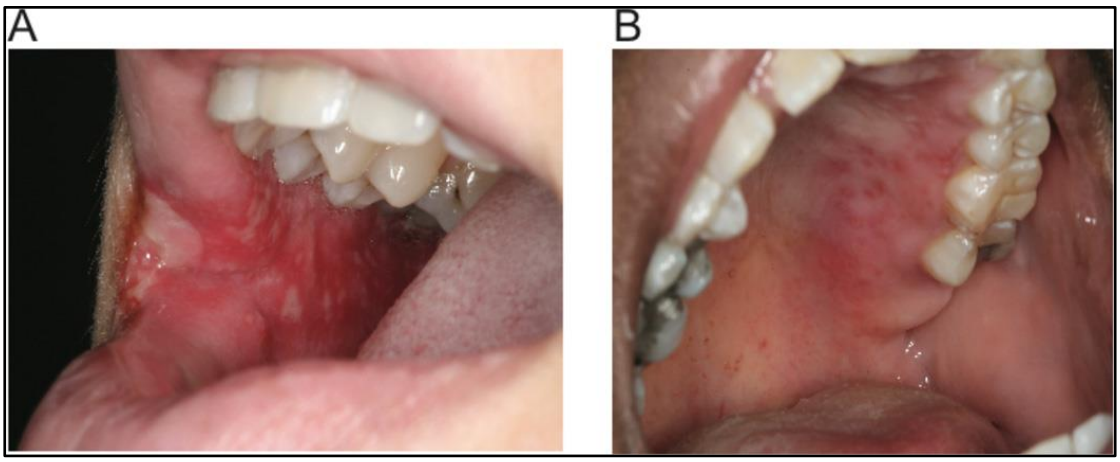

Figure 1.7. Herpes simplex virus (HSV) infection. Chemotherapy caused reactivation of HSV infection on the labial and buccal mucosa (A) and hard palate (B) of these patients , (Mosel DD, Bauer RL, Lynch DP,Hwang ST 2011; Schubert MM. 1991).

Bacterial Infections, Dental Caries and Periodontal Diseases

Bacterial infections often arise from mucosal, gingival or odontogenic sources. Poor oral hygiene and hyposalivation increase the oral microbial load thereby disrupting balance of the oral flora, (Mosel DD, Bauer RL, Lynch DP, Hwang ST. 2011; Lee MK, Nalliah RP, Kim MK, Elangovan S, Allareddy V, Kumar-Gajendrareddy P.,2011). Therefore, it is important to eliminate potential sources of dental infection prior to OPC therapy . The teeth should be protected by use of topical fluorides. The use of fluoride rinses, gels and construction of custom-made trays for

fluoride application should be established during and following radiotherapy until normal salivary functions return, (Kielbassa AM, Hinkelbein W, Hellwig E, Meyer-Luckel H., 2006). Teeth with periodontitis and bone loss may become exacerbated during OPC therapy resulting in local and systemic complications, (Epstein JB, Stevenson-Moore P., 2001). Direct radiation injury to periodontal structures will compromise vascular supply, cause destruction of more periodontal tissues and promote bacterial invasion, (Fujita M, Tanimoto K, Wada T.1986; Chambers MS, Posner M, Jones CU, Biel MA, Hodge KM, Vitti R, *et al.*, 2007). Chemotherapy causes further delay tissue healing and consequent loss of more periodontal tissues, (Galler C, Epstein JB, Guze KA, Buckles D, Stevenson-Moore P., 1992; Epstein JB, Lunn R, Le N, Stevenson-Moore P., 1998). Due to significant long-term effects of periodontal disease, it is important to assess the periodontal status of teeth and tissues within the field of radiation prior to therapy, (Epstein JB, Stevenson-Moore P., 2001). Teeth with advanced periodontal bone loss should be extracted before treatment to reduce the risk of osteoradionecrosis (ORN) that often develops if the extraction is performed after radiotherapy, (Reuther T, Schuster T, Mende U, Kubler A., 2003).

Osteoradionecrosis

ORN, the most significant oral complication of OPC radiotherapy presenting as prolong soft tissue dehiscence with exposure of underlying necrotic bone (Figure 1.8). It was originally associated with the triad of trauma, infection, and radiation, (Marx RE.,1983), but its etiology is linked more to radiation-induced hypoxic, hypocellular, hypovascular tissue and defective wound healing rather than infection. There is a higher

incidence of ORN in the mandible than the maxilla purportedly due to lower vascular network and more cortical bone in the mandible. ORN can develop within 2 weeks of radiotherapy but it is usually a late complication occurring within the first year of treatment. Dentate patients are at higher risks of ORN than edentulous patients; so dental evaluation before OPC therapy is a standard protocol to eliminate potential sources of infections, (Fischer DJ, Epstein JB., 2008; Reuther T, Schuster T, Mende U, Kubler A. 2003 ; Marx RE, Johnson RP., 1987).

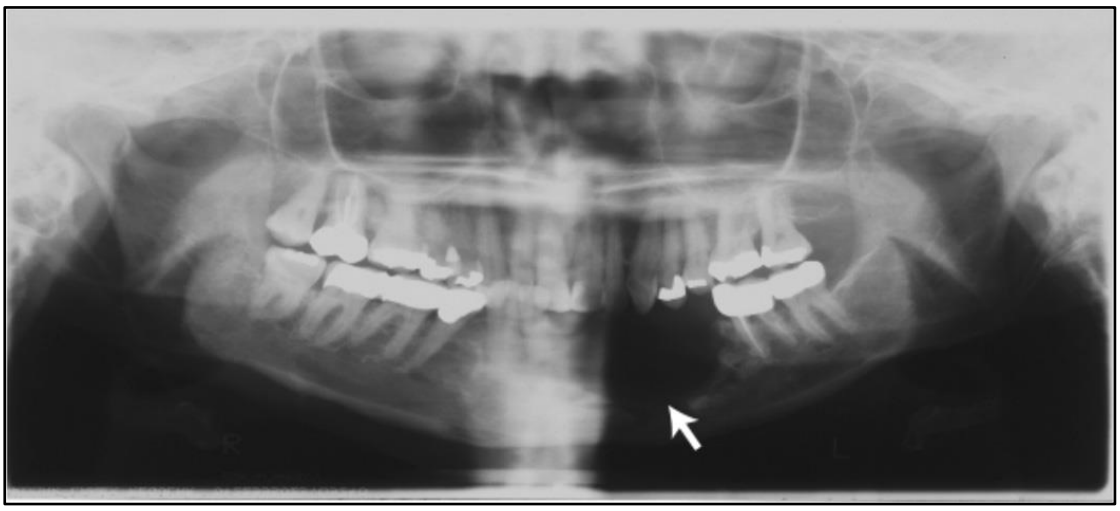

Figure 1.8. Osteoradionecrosis: Panoramic radiograph shows osteoradionecrosis that developed in the left mandible (white arrow) within the first year of oral cancer radiotherapy, (Marx RE.1983).

In most cases of ORN, healing occurs after conservative therapy consisting of local debridement, antibiotic therapy, and saline irrigation. In severe cases, healing may be prolonged for up to 6 months and more aggressive use of surgical debridement and hyperbaric oxygen (HBO) therapy are warranted. Different protocols combining surgery and HBO therapy have shown variable success rates ranging from 15–90% recovery. Recent advances have also demonstrated successful

mobilization of stem cells to the damaged bone to promote healing, (Thom SR, *et al.*, 2006).

Pain and loss of function

Neuropathic pain and neurosensory abnormalities can also complicate OPC therapy. Neuropathic pain occurs in 25% of OPC cases due to tumour invasion of peripheral or central nervous system or as a sequela of treatment. A wide range of pharmacologic agents such as anticonvulsants, antidepressants, local anesthetics, and N-methyl-D-aspartate receptor blockers are usually used to manage peripheral neuropathy and neuropathic pain, (Baron R, Binder A, Wasner G. Neuropathic2010).

Post-surgical tissue fibrosis, orofacial muscle contracture and trismus significantly affect jaw function. Patients have difficulty speaking, swallowing and chewing which ultimately affect long-term quality of life after OPC treatment, (Buchbinder D, Currivan RB, Kaplan AJ, Urken ML1993). The practice of stretching exercises to maintain maximum jaw opening and mobility will prevent long-term disability. Passive stretching with tongue depressors or extra-oral devices will help prevent muscle contracture and gradually increase mandibular opening. Spastic reactions that cause abnormal jaw muscle closure can be controlled with botulinum toxin injections, (Stubblefield MD, Manfield L, Riedel ER., 2010; Clark GT., 2003). As the oral and pharyngeal mucosa are exposed to radiation, taste perception and taste discrimination will become progressively compromised, (Nelson GM.1998). Extensive degeneration of the taste buds might occur following radiation therapy. If there is enough salivary flow to dissolve the tastants, the taste sensation returns within 60–120 days after completion of radiotherapy. While zinc sulfate has been used to

improve taste alterations, its effectiveness after OPC radiotherapy is still inconclusive, (Nelson GM., 1998; Halyard MY *etal* 2007)

Radiation caries

The developing tooth buds are destroyed if irradiated prior to mineralization. Also radiation therapy can increase the severity of dental developmental disturbances induced by chemotherapy, (Cubukcu CE, Sevinir B, Ercan I.2012). Therefore, tooth agenesis and retarded root development often occur in younger patients (Figure 1.8). In adults, the teeth are resistant to direct effects. Radiation caries has been categorized based on clinical and radiographic features. Type 1 radiation caries is widespread superficial caries, type 2 is caries of the cementum and dentin at the cervical region and type 3 is dark pigmentation of the entire crown; however, any combinations of these features may occur, (Aguiar GP,et al 2009). The risk of radiation caries is mainly secondary to a number of factors that include a shift to a more cariogenic oral microbial flora, xerostomia and a reduction in the antimicrobial and mineralization properties of saliva. The dental care provider should motivate the patient to follow stringent plaque control. In addition, prescribing medications that stimulate salivary flow and nutritional counseling to limit cariogenic diet are essential aspects of reducing radiation caries to improve quality of life of OPC survivors.

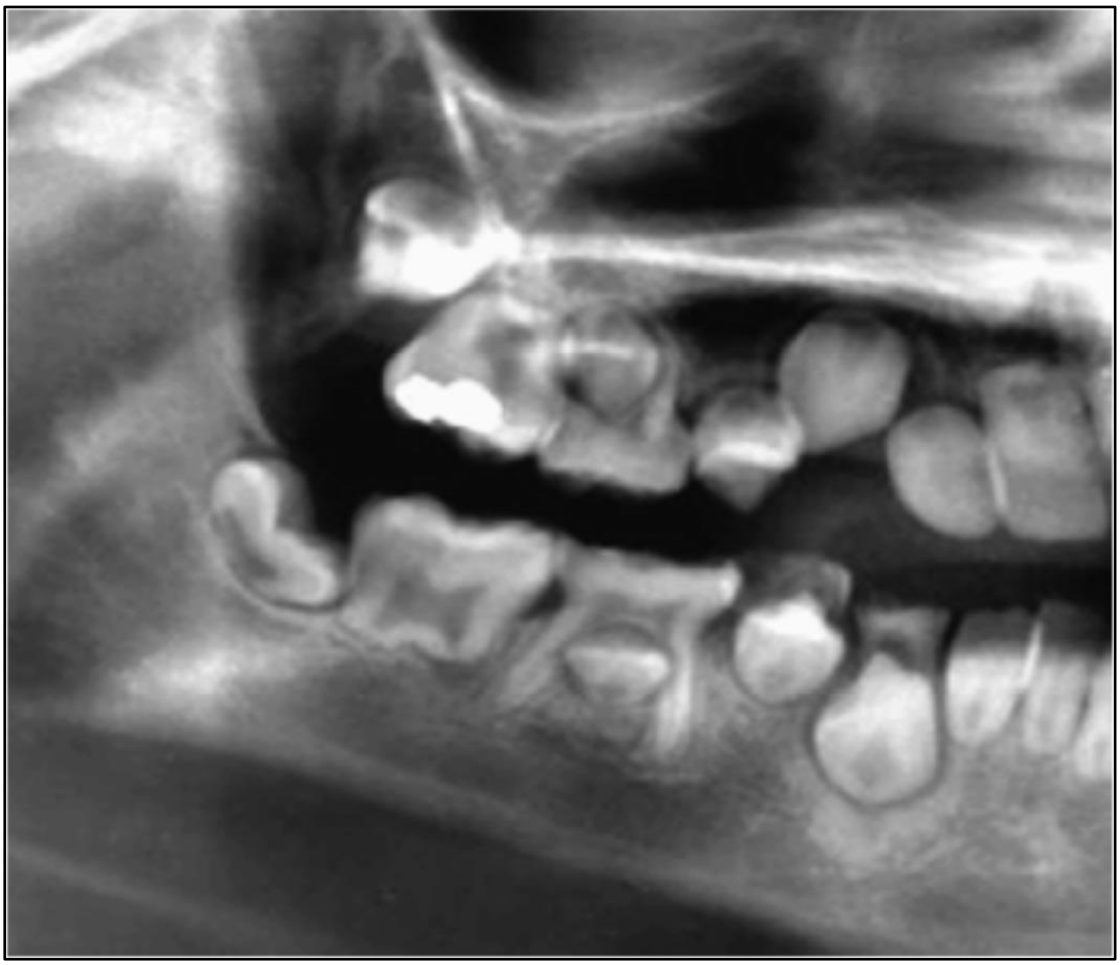

Figure 1.9: Delayed dental development. This 13-yr-old patient received radiation therapy before development of the permanent teeth. This has been complicated by delayed shedding of the deciduous molars, stunted development of the premolars and permanent molars as a result of radiation damage to the developing tooth buds, (Cubukcu CE., 2012).

1.15. Dental management strategies for the general dental practitioner

The general dental practitioner can readily manage most oral complications of OPC radiotherapy. In addition to the management issues discussed under each complication, the following specific dental health guidelines are highly recommended.

Tooth brushing and dentifrice

Although, it is recommended the use of soft nylon-bristled toothbrushes with two or three rows, the use of electric and ultrasonic toothbrushes are also acceptable if the patients can use them without causing trauma to the oral mucosa. The general dental practitioner should emphasize that the patient should perform the correct tooth brushing technique (bass sulcular scrub method) at least 2 or 3 times daily with frequent rinsing. Any fluoride-containing dentifrice can be used by most patients that received radiotherapy. However, non-mint flavored dentifrices are better tolerated than the mint-flavored dentifrices when there is co-existing graft versus-host disease (GVHD). The patients should be also being instructed to air-dry brushes between uses.

Mouth rinsing and flossing

Post mucositis dental management should include frequent mouth rinses with 0.9% saline, sodium bicarbonate solution or a combination of both solutions. The patient should rinse with at least 8–12 fluid ounces in mouthful portions with expectoration until finished.

Fluoride supplementation

Typically, the dental practitioner should recommend to the patients the use of a 1.1% neutral sodium fluoride gel or a 0.4% stannous fluoride gel. The gel should be used to brush gently on the teeth followed by expectoration and rinsing the mouth gently. The fluoride should be applied at least once a day.

Topical antimicrobial rinses

The practitioner should recommend either 0.12 – 0.2% Chlorhexidine or providence iodine oral rinse for management of acute gingival lesions. The patient can be advised to hold the rinse in the mouth for 1 to 2 minutes before expectoration. This can be repeated up to four times a day depending on severity of the gingival and periodontal inflammation.

Care of dentures during and after radiation therapy

Wearing dentures should be discontinued during radiotherapy and for a few weeks after completion of radiotherapy to promote healing of radiation mucositis. The patient should be instructed to wear the dentures only when eating and discontinue their use at other times. When the dentures are not being used, they should be soaked in antimicrobial solutions. If necessary, a denture can be used a carrier to keep medications such as antifungals needed for oral care in close contact with the oral mucosa.

Care of lips and mouth

Preventing lip dryness will reduce risks of tissue injury. Patients should be advised to use lip care products containing petroleum based oils and waxes. Lanolin-based creams and ointments may be more effective in moisturizing and lubricating the lips and thereby protect the lips from trauma.

These recommendations indicate that the general dental practitioner can be the caregiver immediately after radiotherapy and during the follow up months or years of routine maintenance. Since dental caries secondary to xerostomia is a big complication, appropriate instructions to prevent the

radiation caries along with methods to increase salivation will ensure the highest quality of patient lifestyle during the post-radiotherapy period. The dental practitioner plays a vital role in the overall management of the dental patient after radiotherapy and an even more significant role during the extended follow-up period, (Schubert MM, Peterson DE.2009).

Chapter two:

Conclusion

More advanced knowledge about OPC and improved screening methods have undoubtedly improved survival. OPC therapy is aimed at complete elimination of the tumour, reduction of morbidity and preservation of tissue functions. Similarly, the goal of rehabilitation should be to improve quality of life OPC survivors and resumption of normal day-to-day activities. These can be better achieved by seamless multidisciplinary interactions and teamwork. It is important to understand potential complications of OPC therapy and harness the resources necessary to prevent or minimize them. Oral care is an integral component of both OPC chemotherapy and radiotherapy. A well-informed dental practitioner can become an effective caregiver for a debilitated patient during the recovery phase and later when the patient resumes normal day-to-day activities.

Reference

1- Advani, Dia; Sharma, Sudhanshu; Kumari, Smita; Ambasta, Rashmi K.; Kumar, Pravir , Anti-Cancer Agents in Medicinal Chemistry , 2022 , Formerly Current Medicinal Chemistry - Anti-Cancer Agents, Volume 22, Issue 3, pp. 433-468. Available at : https://doi.org/10.2174/1871520621666210308101029(Accessed:2021).

2- Aguiar GP, Jham BC, Magalhaes CS, Sensi LG, Freire AR. A review of the biological and clinical aspects of radiation caries. J Contemp Dent Pract. 2009;10:83–89.

3- Akintoye SO, Brennan MT, Graber CJ, McKinney BE, Rams TE, Barrett AJ, et al. A retrospective investigation of advanced periodontal disease as a risk factor for septicemia in hematopoietic stem cell and bone marrow transplant recipients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002;94:581–588.

4- alaram P, Sridhar H, Rajkumar T, Vaccarella S, Herrero R, Nandakumar A, Ravichandran K, Ramdas K, Sankaranarayanan R, Gajalakshmi V, Muñoz N, Franceschi S (2002) Oral cancer in southern India: the influence of smoking, drinking, paan-chewing and oral hygiene. Int J Cancer 98(3):440–445

5- Ana Casal-Mouriño, Alberto Ruano-Ravina, María Torres-Durán, Isaura Parente-Lamelas, Mariano Provencio-Pulla, Olalla Castro-Añón, Iria Vidal-García, Carolina Pena-Álvarez, José Abal-Arca, María Piñeiro-Lamas, Ismael Fuente-Merino, Alberto Fernández-Villar, Ihab Abdulkader, Luis Valdés-Cuadrado, Juan Miguel Barros-Dios, Mónica Pérez-Río. (22 may 2020) https://doi.org/10.1016/j.canlet.2020.05.022.

6- Ari J. Rosenberg, Everett E. Vokes,(January 2021),The Oncologist, Volume 26, Issue 1, pp. 40–48). Available at: https://doi.org/10.1634/theoncologist.2020-0303 (Accessed : 21 September 2020).

7- Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol. 2010;9:807–819.

8- Boscolo-Rizzo P, Schroeder L, Romeo S, Pawlita M.(2015). The prevalence of human papillomavirus in squamous cell carcinoma

Reference

of unknown primary site metastatic to neck lymph nodes: a systematic review. Clin Exp Metastasis;Volume32,pp. 835–845.

9- Buchbinder D, Currivan RB, Kaplan AJ, Urken ML. Mobilization regimens for the prevention of jaw hypomobility in the radiated patient: a comparison of three techniques. J Oral Maxillofac Surg. 1993;51:863–867.

10- C Fakhry, WH Westra, S Li, A Cmelak, JA Ridge, H Pinto, A Forastiere,(2020) . Journal of the National Cancer Institute Volume100 Issue4, pp.261-269.

11- Christopolous C, Moubayed SP, Nader ME, Ayed T, Ghannoum JE Mouth Anatomy: Overview. Medscape. Available at: http://emedicine.medscape.com/article/1899122-overview". Accessed December 14, 2018.

12- Christopolous C, Moubayed SP, Nader ME, Ayed T, Ghannoum JE. Mouth Anatomy: Overview. Available at : http://emedicine.medscape.com/article/1899122-overview. (Accessed December 14, 2018)

13- Cláudia Viegas, ORCID,Daniela S. M. Pereira and Pedro Fonte et.al Insights into Nanomedicine for Head and Neck Cancer Diagnosis and Treatment, (11 March 2022), Nanomedicine for Head and Neck Cancer , Volume 15, Issue 6, pp.85-109) . Available at: https://doi.org/10.3390/ma15062086(Accessed: 30 December 2021).

14- Cubukcu CE, Sevinir B, Ercan I. Disturbed dental development of permanent teeth in children with solid tumors and lymphomas. Pediatr Blood Cancer. 2012;58:80–84.

15- Daniel CR, McQuade JL. (2019) Nutrition and cancer in the microbiome era. Trends Cancer.;5:521–4.

16- Daniel N. Frank, Yue Qiu, Yu Cao, Shuguang Zhang, Ling Lu, Jennifer M. Kofonow, Charles E. Robertson, Yanqiu Liu, Haibo Wang, Cassandra L. Levens, Kristine A. Kuhn, John Song, Vijay R. Ramakrishnan, Shi-Long Lu,(2022). A dysbiotic microbiome promotes head and neck squamous cell carcinoma,

Reference

Oncogene, ,Volume: 41, Issue 9, pp.1269-1280, Available at : https://doi.org/10.1002/hed.21140(Accessed 2009).

17- Doorbar, J., and Griffin, H. (2019). Refining our understanding of cervical neoplasia and its cellular origins. Papillomavirus Res. 7, 176–179. doi: 10.1016/j.pvr.2019.04.005.

18- Epstein JB, Gorsky M, Cabay RJ, et al. (2008) Screening for and diagnosis of oral premalignant lesions and oropharyngeal squamous cell carcinoma. Can Fam Physician; 54:870–875.

19- Epstein JB, Stevenson-Moore P. Periodontal disease and periodontal management in patients with cancer. Oral Oncol. 2001;37:613–619.

20- Ferraguti, G.; Terracina, S.; Petrella, C.; Greco, A.; Minni, A.; Lucarelli, M.; Agostinelli, E.; Ralli, M.; de Vincentiis, M.; Raponi, G.; et al. Alcohol and Head and Neck Cancer,(2022), Antioxidants, volume 11, Issue145, pp. 4–24) . Available at: https://doi.org/10.3390/antiox11010145 (Accessed: 27 October 2021).

21- Fujita M, Tanimoto K, Wada T. Early radiographic changes in radiation bone injury. Oral Surg Oral Med Oral Pathol. 1986;61:641–644.

22- . Fischer DJ, Epstein JB. Management of patients who have undergone head and neck cancer therapy. Dent Clin North Am. 2008;52:39–60. viii.

23- Galler C, Epstein JB, Guze KA, Buckles D, Stevenson-Moore P. The development of osteoradionecrosis from sites of periodontal disease activity: report of 3 cases. J Periodontol. 1992;63:310–316.

24- Gao G, Smith DI.(2017). Human Papillomavirus and the Development of Different Cancers. Cytogenet Genome Res. March. doi:10.1159/000458166.

25- Gao G, Smith DI.(2017). Human Papillomavirus and the Development of Different Cancers. Cytogenet Genome Res. Available at : https://doi:10.1159/000458166

Reference

26- Gillison ML. (2007).Current topics in the epidemiology of oral cavity and oropharyngeal cancers. Head Neck.;29(8):779-792. doi:10.1002/hed.20573.

27- Giampiero Ferraguti, Sergio Terracina, Carla Petrella, Antonio Greco,et al. Alcohol and Head and Neck Cancer,, January 2022, Antioxidants,Volume11,Issue145,pp.48-71,Available at:http://doi:10.3390/antiox11010145(Accessed (2021).

28- Halyard MY, Jatoi A, Sloan JA, Bearden JD, 3rd, Vora SA, Atherton PJ, et al. Does zinc sulfate prevent therapy-induced taste alterations in head and neck cancer patients? Results of phase III double-blind, placebo-controlled trial from the North Central Cancer Treatment Group (N01C4) Int J Radiat Oncol Biol Phys. 2007;67:1318–1322.

29- Harreus U. (2005). Cummings otolaryngology: head & neck surgery. 5th ed. Philadelphia: Mosby, Inc.Volume16,pp.63-68.

30- J.O ,Kemnade, Elhalawani, H., Castro, P. et al. CD8 infiltration is associated with disease control and tobacco exposure in intermediate-risk oropharyngeal cancer(2020). Sci Rep Volume10, pp.243. Available at: https://doi.org/10.1038/s41598-019-57111-5(Accessed 2020).

31- Jamal Z, Anjum F. Oropharyngeal Squamous Cell Carcinoma. In: StatPearls. Treasure Island (FL): StatPearls Publishing; January 24, 2022

32- Johnson, D. E., O'Keefe, R. A. & Grandis, J. R.(2018) Targeting the IL-6/JAK/STAT3 signalling axis in cancer. Nat. Rev. Clin. Oncol. 15, 234–248.

33- Johnson, D.E., Burtness, B., Leemans, C.R. et al. Head and neck squamous cell carcinoma.(November 2020). Nat Rev Dis Primers ,Volume: 6,Issue: 92, Available at: https://doi.org/10.1038/s41572-020-00224-3(Accessed October 2020).

Reference

34- Joshi, Poonam et al. “Head and neck cancers in developing countries.” Rambam Maimonides medical journal vol. 5,2 e0009. 28 Apr. 2014, doi:10.5041/RMMJ.10143

35- Kielbassa AM, Hinkelbein W, Hellwig E, Meyer-Luckel H. Radiation-related damage to dentition. Lancet Oncol. 2006;7:326–335.

36- La D, Swenberg J.(1996). DNA adducts: biological markers of exposure and potential applications to risk assessment. Mutat Res Genet Toxicol.;365(1-3):129-146. doi:10.1016/S0165-1110(96)90017-2.

37- Lechner, M., Liu, J., Masterson, L. et al. HPV-associated oropharyngeal cancer: epidemiology, molecular biology and clinical management.(01 February 2022) Nat Rev Clin Oncol , Volume19,Issue1, pp.306–327 . Available at:https://doi.org/10.1038/s41571-022-00603-7(Accessed: 13 January 2022).

38- Lechner, M., Liu, J., Masterson, L. et al. HPV-associated oropharyngeal cancer: epidemiology, molecular biology and clinical management, (2022). Nat Rev Clin Oncol, Volume 19, pp. 306–327. Available at: https://doi.org/10.1038/s41571-022-00603-7(Accessed 2021).

39- Lerman MA, Laudenbach J, Marty FM, Baden LR, Treister NS. Management of oral infections in cancer patients. Dent Clin North Am. 2008;52:129–153. Ix

40- Lewis-Jones H, Colley S, Gibson D. Imaging in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol. 2016 May;130(S2):S28-S31

41- Li SC, Loudon WG.(2008) A novel and generalizable organotypic slice platform to evaluate stem cell potential for targeting pediatric brain tumors. Cancer Cell Int.;8:9.

42- Lin DT, Cohen SM, Coppit GL, Burkey BB. (2005) Squamous cell carcinoma of the oropharynx and hypopharynx. Otolaryngol Clin North Am ; 38:59–74.

Reference

43- . Lee MK, Nalliah RP, Kim MK, Elangovan S, Allareddy V, Kumar-Gajendrareddy P. Prevalence and impact of complications on outcomes in patients hospitalized for oral and oropharyngeal cancer treatment. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011;112:581–591.

44- Lydiatt WM, Patel SG, O'Sullivan B, Brandwein MS, Ridge JA, Migliacci JC, Loomis AM, Shah JP. Head and Neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017 Mar;67(2):122-137.

45- Maciejewski B, Withers H, Taylor J, Hliniak A. Dose Fractionation and Regeneration in Radiotherapyfor Cancer of the Oral Cavity and Oropharynx - Tumor Dose-Response and Repopulation. Int J RadiatOncol Biol Phys. 1989Volume 16Issue 3,pp. 831-843.

46- Monk BJ, Tewari KS. (2007) The spectrum and clinical sequelae of human papillomavirus infection. Gynecol Oncol; 107:6–13.

47- Morshed K, Polz-Gruszka D, Szymański M, Polz-Dacewicz M.(2014),. Human papillomavirus (HPV)—structure, epidemiology and pathogenesis. Otolaryngol Pol.;68(5):213–219.

48- Mosel DD, Bauer RL, Lynch DP, Hwang ST. Oral complications in the treatment of cancer patients. Oral diseases. 2011;17:550–559.

49- Myers RA, Marx RE. Use of hyperbaric oxygen in postradiation head and neck surgery. NCI Monogr. 1990:151–157.

50- Nelson GM. Biology of taste buds and the clinical problem of taste loss. Anat Rec. 1998;253:70–78.

51- Osborne RF, Brown JJ. (2004). Carcinoma of the oral pharynx: an analysis of subsite treatment heterogeneity. Surg Oncol Clin N Am; 13:71–80.

52- Osborne RF, Brown JJ. (2004). Carcinoma of the oral pharynx: an analysis of subsite treatment heterogeneity. Surg Oncol Clin N Am; Volume13,pp.71–80.

Reference

53- Osborne RF, Brown JJ. (2004). Carcinoma of the oral pharynx: an analysis of subsite treatment heterogeneity. Surg Oncol Clin N Am,Volume13,pp.71–80.

54- PDQ Adult Treatment Editorial Board. Oropharyngeal Cancer Treatment (Adult) (PDQ®): Patient Version. In: PDQ Cancer Information Summaries. Bethesda (MD): National Cancer Institute (US); October 14, 2021.

55- Pfeifer G, Denissenko M, Olivier M, Tretyakova N, Hecht S, Hainaut P(.2002) . Tobacco smoke carcinogens, DNA damage and p53 mutations in smoking-associated cancers. MF . 1998 Environ. Mol. Mutagen. 31: 197–205.

56- Reuther T, Schuster T, Mende U, Kubler A. Osteoradionecrosis of the jaws as a side effect of radiotherapy of head and neck tumour patients--a report of a thirty year retrospective review. Int J Oral Maxillofac Surg. 2003;32:289–295.

57- Saman Warnakulasuriya et al. Global epidemiology of oral and oropharyngeal cancer , April–May 2009, Oral Oncology, Volume 45, Issues 4–5, Pages 309-316 . Available at : https://doi.org/10.1016/j.oraloncology.2008.06.002(Accessed 2009).

58- Saman, Daniel M. “A review of the epidemiology of oral and pharyngeal carcinoma: update.” Head & neck oncology vol. 4 1. 13 Jan. 2012, doi:10.1186/1758-3284-4-1

59- Schubert MM, Peterson DE. Oral complications of hematopoitic cell transplantation. In: Appelbaum FR, Forman SJ, Negrin RS, Blume KG, editors. Thomas' Hematopoietic cell transplantation: Stem cell transplantation. Oxford, UK: Wiley-Blackwell; 2009. pp. 1589–1607.

60- Scully C. Challenges in predicting which oral mucosal potentially malignant disease will progress to neoplasia. Oral Dis. 2014 Jan. 20(1):1-5.

61- Shah KV, Westra WH. (2007) Genital HPVs in the aerodigestive tract: etiologic association with a subset of oropharyngeal/tonsillar cancers and with recurrent respiratory papillomatosis. Dis Markers;Volume 23,pp.235–245.

Reference

62- Ship JA, Vissink A, Challacombe SJ. Use of prophylactic antifungals in the immunocompromised host. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;103(Suppl:S6):e1–e14.

63- Sonis ST, Sonis AL, Lieberman A. Oral complications in patients receiving treatment for malignancies other than of the head and neck. J Am Dent Assoc. 1978;97:468–472.

64- Steven M. , OlsenEric J. , MooreCody A. , KochJan L. , KasperbauerKerry D.Olsen, Oral cavity and oropharynx squamous cell carcinoma with metastasis to the parotid lymph nodes 2011, Oral Oncology, Volume 47, Issue 2, pp. 142-144, Available at : https://doi.org/10.1016/j.oraloncology.2010.11.010(Accessed February 2011).

65- Stubblefield MD, Manfield L, Riedel ER. A preliminary report on the efficacy of a dynamic jaw opening device (dynasplint trismus system) as part of the multimodal treatment of trismus in patients with head and neck cancer. Arch Phys Med Rehabil. 2010;91:1278–1282.

66- Tahari AK, Alluri KC, Quon H, Koch W, Wahl RL, Subramaniam RM. FDG PET/CT imaging of oropharyngeal squamous cell carcinoma: characteristics of human papillomavirus-positive and - negative tumors. Clin Nucl Med. 2014,Volume39 , Issue3),pp.225-231. Available at: https://doi:10.1097/RLU.0000000000000255 (Accessed 2014.(

67- Tataru D, Mak V, Simo R, Davies E a., Gallagher J e. (2017). Trends in the epidemiology of head and neck cancer in London. Clin Otolaryngol.Volume 42.Issue1,pp.104-114. Available at : https://doi:10.1111/coa.12673.(Accessed:2017).

68- Taylor , M E B Powell et al. ,2004, Intensity-modulated radiotherapy , Volume 4,Issue2,pp 68–73. Available at: https: doi: 10.1102/1470-7330.2004.0003(Accessed:2004).

69- Thom SR, Bhopale VM, Velazquez OC, Goldstein LJ, Thom LH, Buerk DG. Stem cell mobilization by hyperbaric oxygen. Am J Physiol Heart Circ Physiol. 2006;290:H1378–H1386.

70- Tomasetti C, Vogelstein B, Parmigiani G.(2013) Proc. Natl. Acad. Sci. U.S.A.;110:1999–2004.