Oral Cancer Prevention

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Preface

Dear Colleagues,

It is my pleasure to take part in announcing the Workshop on Prevention of Oral Cancer in Romania in March 2019.

This event organized under the auspices and with participation of renowned dental professionals, incl. dr Patrick Hescot, past FDI President and WHO expert, is another evidence of the growing importance of continuing medical education in dentistry.

Dentists play a significant role in the field of public health since they should not only deal with strictly dental conditions (e.g. caries or periodontal disease), but nowadays are also expected to act as primary care professionals in oncological prevention and diagnosing.

The patient is often unaware of the early symptoms of oral cancer, and during even a routine dental checkup the dentist is the one who may take notice of the first symptoms and provide adequate guidance to the patient. The dental practitioner's task is not limited to recognize signs of cancer, but also a number of other systemic diseases that may be visible in the oral area.

A dentist should also be prepared to teach the patient about the risk factors commonly recognized as carcinogenic, by encouraging to quit smoking, promoting healthy diet and lifestyle. Not without a good reason, the FDI World Dental Federation and the WHO World Health Organization commonly stress that:

Helping patients to stop smoking may be the single most important service dentists can provide for their patient's oral and general health.

I wish the organizers a successful event and all the participants an enjoyable and productive learning experience which will serve for the best interests of our patients.

Best regards,

Dr Anna Lella
ERO President

Preface

Nowadays, despite the advances in prevention, the oral cancers (lips, tongue, gingiva, buccal mucosa, floor of the mouth, soft and hard palate) and oropharyngeal cancers are still epidemic in Europe, especially in Central and Eastern areas.

This book was published with the intention of targeting a whole range of healthcare providers across Europe and in order to meet various needs for in-depth knowledge regarding epidemiology, prevention, or screening of oral cancers.

Considering the diagnosis of most oral cancers in severe stages, the book highlights Dental practitioners as one of the most important providers within the healthcare system that when implied in the early detection, becomes a vital key to patients' possibly surviving oral cancer.

Various preventive measures are presented, including the education to patients about high risk factors and behaviours, protocols for early detection as well as interdisciplinary management strategies for patients with suspected injuries or those diagnosed with oral cancer.

The text is also fully documented with multiple photographs promoting an early diagnosis of oral cancer

Finally, the objective of the book is to help the Dental Practioners apply the Primary, Secondary or Tertiary preventive strategies on oral cancer.

As a result of a number of dedicated specialists in the field of Oromaxillofacial Dentistry, this book aims to make the most pertinent information readily available for the Dental and Surgical Practitioners

Workshop committee

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1. ORAL CANCER

1.1. Definition

The term "head and neck cancer" encompasses a large number of neoplasms with diverse natural backgrounds, arising from a number of local anatomical regions. Oral cancers arise from the structures of the upper aerodigestive tract, primarily the oral cavity and its allied structures alone, whereas head and neck cancers may also include the (oro- & naso-) pharynx, tonsillar regions, the larynx and the paranasal sinuses. Occasionally, tumors of the salivary glands, thyroid, soft tissues, bones, and skin cancers are also included. Although in many publications, head and neck cancers are discussed together, it is now apparent that these mucosal tumors, mainly represented by carcinomas, comprise a number of different diseases and therefore must be considered separately, due to differences in location, aetiology, prognosis and management (1). This has traditionally made data assessment across publications very challenging, as definitions of anatomical areas included / excluded from studies varies considerably and has clouded overall understanding of incidence and prognosis accordingly.

The oral cavity and the oropharynx have historically been considered as a single anatomic compartment of the head and neck (1). Together, both constitute a single continuous chamber lined by an uninterrupted stratified squamous epithelium. However, they are dissimilar in many essential respects. Most important is the location and ascription of tonsillar tissue, i.e. lingual and palatine tonsils to the oropharynx, and their absence from inclusion in the oral cavity (1). These critical distinctions between squamous cell carcinoma of the oral cavity and of the oropharynx are reflected in the recently published 4th edition of the World Health Organization (WHO) Classification of Tumors of the Head and Neck (2), as well as in the 8th edition of the American Joint Committee on Cancer the Staging Manual (AJCC) (3) (4).

The oral cavity extends from the vermilion border of the lips to the circumvallate papillae of the tongue inferiorly and the junction of the hard and soft palate superiorly. Oral cavity cancer includes cancer of the inner lips, the floor of the mouth, the anterior two-thirds (ie, the oral) tongue, the buccal mucosa, the upper and lower gingivae, the hard palate, and the retromolar trigone (5) (6). In order of decreasing frequency within the oral cavity, the lower lip, oral tongue, and floor of mouth, are the main sites sites of a primary tumor in over 75% of patients with Oral Squamous Cell Carcinomas (OSCC) (7).

The oropharynx is the part of the pharynx that lies posterior to the oral cavity, between the nasopharynx and the hypopharynx. The oropharynx contains the base (posterior one-third) of the tongue, the palatine tonsils, soft palate, and oropharyngeal mucosa (7).

More than 90% of oral cancers have an epithelial origin and are called oral squamous cells carcinomas OSCCs (8) , this being the most common carcinoma of the head and neck (9). Other histopathological types include slow-growing verrucous carcinomas, salivary gland benign and malignant forms with several subtypes, and lymphomas and melanomas of the mouth and lips (10).

1.2. Epidemiology

Oral cancer represents the 11th most common form of cancer globally, although there are a wide global differences regarding oral cancer incidence and mortality rates (11). Cancers of the oral cavity were highly common in south-central Asia, especially in India (associated with smokeless tobacco, bidi, and betel-quid use) (12) . Recent available data from the World Health Organisation International Agency for Research on Cancer (WHO IARC) for 2012 reported 202,000 cases of oral cavity cancer and 100,500 cases of oropharyngeal cancer diagnosed per annum. The global estimated age-standardised rate of oral cavity cancer was 2.7 per 100,000 in 2012, with the largest proportion (48.7%) diagnosed in south-central Asia and occurrence being consistently higher in men than women (M:F rate ratio 2:1) (12) .While the incidence of oropharyngeal cancer is increasing rapidly, especially in high-income countries and especially in the United States, oral cancer incidence rates remain stable or decline in men worldwide and increase slightly in women (5)(13).

Regarding the European areas, in 2012, the estimated age-standardised incidence of oral cavity cancer (per 100,000 person-years) was 7.5 in males and 2.5 in females. Compared with the global values (5.5 in males, 2.5 in females), the age-standardised incidence is similar for females, but it is significantly higher for males (12) . The incidence rates are higher in eastern compared with western, northern or southern Europe, with the highest incidence rates in Hungary, Slovakia and Slovenia (14).

Variations of epidemiological data between different European areas can be explained by the prevalence of cancer risk factors (smoking, alcohol consumption, dietary habits) as well as comorbidities, medical treatment conditions and the accessibility to public and private health systems services.

New epidemiological studies are required to relate epidemiological data to specific features of local preventive policies as well as to social, economic and cultural peculiarities of each European geographic area, aiming to achieve prevention and urther significant decreases in incidence and mortality rates.

1.3 The importance of prevention in oral cancer and the role of the dental team

Reduction in consumption of the main risk factors including tobacco and alcohol products is effective for reducing the incidence of oral cancer (15).

Early detection (lesions <2 cm and < 5 mm of deepest invasion (DOI) with no regional node involvement) can improve treatment outcomes, increase survival and provide a better quality of life after treatment (16).

The FDI recognises that the oral health care team play an essential role in the fight against oral cancer through the following actions (17):

- Educating patients and the public about the main risks factors and high-risk behaviours.
- Encouraging all patients to minimise their exposure to risk factors that cause cancer.

- Offer specific counselling to quit smoking and advice on moderate alcohol intake and good nutrition, as part of routine oral health education and practice.
- Early detection of oral cancer through a thorough intra- and extra-oral examination of soft and hard tissues.
- Remaining current with reliable and valid diagnostic technologies.
- Establishing referral protocols for patients with suspected lesions or those diagnosed with oral cancer, as well as effective interdisciplinary management strategies including awareness of psychosocial support networks.

The dental profession therefore has a critical role in the fight against oral cancer, fulfilling an invaluable task across the three levels (Primary, Secondary and Tertiary) of prevention.

1.3.1 Primary Prevention

Primary prevention is aimed at reducing the incidence of the disease and protecting healthy people from developing oral cancer. The preventive approach is quite clear and dentists, along with other primary health care professionals, have excellent opportunities to contribute. Primary prevention is the most ideal approach and oral health professionals can contribute (18) by:

- Promoting healthy lifestyles (e.g. protection against sunlight exposure, physical exercise and healthy diet).
- Urge to avoid known major risk factors, such as tobacco and alcohol.
- Promote (where appropriate) immunisation against infectious agents such as Human Papilloma Viruses.

1.3.2. Secondary prevention

Secondary prevention focuses on the detection of the disease at an early stage of its natural history. An early action will lead to healing or minimisation of damage, ultimately reducing mortality. Early stage detection delivers not only an increase in survival rates, but also a better quality of post-intervention life, as a consequence of less aggressive and mutilating treatments. Secondary prevention also includes the appropriate management of potentially malignant disorders to reduce the malignant transformation rate.

1.3.3. Tertiary prevention

The goal of tertiary prevention is to reduce the possibility of the appearance of new oral cancer and help the patient to minimise the side effects of oncological therapy. Oral cancer and, in particular, its treatment can cause problems in the daily maintenance of oral health and reduce the quality of life for survivors.

The aim of the current book is to present an update on the performance of oral health professionals in the primary, secondary and tertiary prevention of oral cancer.

1.4. Key Points

- Oral cancer represents the 11th most common form of cancer globally and shows and heterogeneous worldwide distribution.
- In the geographical areas of the European Union, Eastern and Central European countries show the highest incidence and mortality rates.
- Main oral cancer concerns include the increasing rate among women and young patients.
- The dental team may have an essential role in all oral cancer prevention levels.

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2. Primary prevention

2.1. Introduction

Primary prevention of oral cancer is aimed at preventing the onset of oral cancer in healthy individuals, through reducing exposure to modifiable risk factors and increasing an individual's resistance (1,2). The main modifiable risk factors are tobacco smoking and alcohol consumption, which have been documented to be responsible for up to 75% of oral cancers (1). Primary prevention is clearly the most ideal approach to oral cancer prevention which all health care practitioners should be involved with. Furthermore, as primary oral cancer prevention essentially focuses on healthy lifestyle behaviours, it has wider positive health impacts (1).

Oral cancer is based on non-lethal genetic and epigenetic alterations whereby normal oral mucosa cells become transformed into a group of tumoral anaplastic cells (3). Most of these genetic errors are caused by environmental and acquired agents such as chemical, physical, or biological agents, making oral cancer pathogenesis a self-induced disease to a large extent. In fact, most of oral cancers are related to life-style; particularly the use of tobacco and excess alcohol consumption (1,3,4). Therefore, primary prevention holds the possibility of preventing oral cancer through eliminating these risk factors. Most oral cancers are preventable, however for this to be possible, it is fundamental to clearly identify it's risk factors.

In this chapter we will firstly discuss the etiologic and risk factors for oral cancer and then consider means of risk reduction.

2.2. Risk Factors

2.2.1.Tobacco

Over 75% of oral cancers are attributed to tobacco consumption (in smoked or smokeless presentations) and alcohol misuse and when used together they produce a synergistic effect. As an example, heavy drinkers and heavy smokers are 38 times more likely to develop oral cancer when compared with abstainers from both products (1). A large-scale epidemiological study by the "The International Head and Neck Cancer Epidemiology" (INHANCE) consortium who have pooled their data on 25 500 patients with head and neck cancer (i.e., cancers of the oral cavity, oropharynx, hypopharynx, and larynx) and 37 100 controls provides evidence on major risk factors for oral cancer. The INHANCE analyses have confirmed that tobacco use and alcohol intake are key risk factors of head and neck cancer and have provided precise estimates of risk, dose response, the benefit of quitting, and the hazard of smoking even a few cigarettes per day (5).

Tobacco, defined as any preparation derived from leaves belonging to the Nicotiana family, is the main risk factor for oral cancer in the world (2,6). Although nicotine is present in only 5% of tobacco leaves, is the main psychoactive substance responsible for effects such as tachycardia, vasoconstriction, and increased attention, by binding to nicotinic acetylcholine receptors. This substance has a dependency effect on genetically, mentally and socially predisposed individuals (2). Tobacco can be consumed in many ways, but smoked (cigarettes, cigars, or pipe) is the most frequently found in European countries. In India, bidi consumption,

tobacco that is manually wrapped in tendu leaves with higher risk than cigarette smoking, is very popular, not only because of the tradition implied, but also due to its lower price (7). Tobacco smoke has more than 6000 chemical substances' and over 60 are carcinogens including polycyclic aromatic hydrocarbons, such as benzopyrene and benzanthracene, as nicotine derived nitrosamines (TSNA), 4-(metilnitrosamin)-1-(3-pyridyl)-1-butanone (NNK) and N-nitrosonornicotine (NNN), aromatic amines and aldehydes such as formaldehyde or acetaldehyde in addition metals, like arsenic or lead (8). These major carcinogenic agents possess primary capacity to promote genetic alterations, especially when activated by enzymatic mechanisms. Polymorphisms that alter the function of the genes involved in the activation or detoxification of tobacco smoke carcinogens can potentially influence an individual's risk of developing a tobacco-related cancer (8).

It has been estimated that the relative risk of developing oral cancer for tobacco users is 2 to 13 times higher than for non-tobacco users. This depends on dose, increasing significantly with higher consumptions, habit duration and early commencement of tobacco use, especially when an individual starts to smoke under the age of 16 years (9-12). In a systematic review from Gandini et al. (13) the pooled risk estimate is 3.43 times higher in smokers when compared with non-tobacco users. Head and neck cancer risk markedly increases when habit duration is over 20 years and the number of cigarettes smoked per day is over 20 (13). However, the cessation of smoking diminishes the relative risk for oral cancer; an individual is able to reach risk levels comparable to that of non-smokers after 10 years of cessation (1).

All tobacco products are carcinogenic (IARC, 2012), and there is no evidence to suggest that replacing smoking with another tobacco product or smokeless tobacco is harmless (1,14).

2.2.2. Smokeless tobacco and betel quid

Tobacco can be directly applied over the mucosa without combustion (smokeless tobacco) and is consumed in some countries under various forms, including snuff, snus or chewing tobacco (1). The use of tobacco in snuff form is found in Northern America and several Scandinavian countries, being related with cancer of the oral mucosa. Snus, as used in Sweden has probably a lower nitrosamine content (14). Commercially packaged chewing tobacco used in the Indian subcontinent- referred to as Gutka - contributes to much of the burden of oral cancer in India (15).

The most popular form of chewing activity found in Southern Asia, Pacific regions and from migrants from these regions is the use of betel (areca) quid. It's probably the most ancient preparation with psychoactive substances in the World and the 4th most used nowadays. Betel quid consists of a mixture (paan) of components such as areca, a nut from the areca catechu tree, calcium hydroxide (lime) and sometimes tobacco, wrapped in betel leaves (7). This preparation is placed in the vestibule, next to buccal mucosa and then chewed for several minutes. The main objective is to obtain alkaloids like arecoline that, by activating muscarinic receptors, produces effects such as increased glandular secretion, increased attention and euphoria. There is a strong association between this habit and oral cancer, likely due to carcinogen production, as nitrosamines and generation of reactive oxygen species. Betel quid with and without tobacco are carcinogenic to man (16). The addition of tobacco to betel quid increases the risk of oral cancer by 15 times (1,2).

The evidence of this type of habit as an independent risk factor was confirmed by the "International Cancer Research Agency" and has been related with the high incidence of oral cancer in some countries e.g. Papua New Guinea, Guam and Taiwan, where it is often consumed without tobacco. On the other hand, its high consumption by the female gender in Asian countries might explain the high incidence of oral cancer in the buccal mucosa of women from these regions. Areca nut is also the major cause of oral submucous fibrosis, an oral potentially malignant disorder with a malignant transformation rate up to 7% over 10 years (1,14).

2.2.3 e-cigarretes

Electronic cigarettes, or e-cigarettes, consists in an electronic device that uses heat to transform a liquid (e-liquid) into a "vapour" that is then inhaled. The liquid can contain multiple substances including nicotine, creating an arterial nicotine concentration similar to that of a smoker without the physical combustion of tobacco (17). Recent reports have suggested that e-cigarettes can help improve the success of quitting attempts, showing they are effective in maintaining the aspect of psychological addiction, whilst weaning off the physical addiction (18), especially nicotine containing e-cigarettes (19). However, it seems that they are less likely to increase the likelihood of quitting, but often simply leads to a reduction of cigarette use, opposed to complete cessation (20). Conversely, other reports also suggest that, some non-smokers can start to smoke after using e-cigarettes. There are some additional negative aspects; some toxic substances in the e-liquid have been found in the e-cigarette's body and adverse effects, such as mucosal irritation and increase in blood pressure, are reported. However, the main concern is the lack of long follow-up studies on long term effect of these devices (19).

2.2.4. Alcohol

The main ingredient in alcoholic beverages is ethanol, which is metabolized into acetaldehyde by alcohol dehydrogenase (ADH), and is mainly responsible for alcohol's carcinogenic affects, besides others, such as nitrosamines (21).

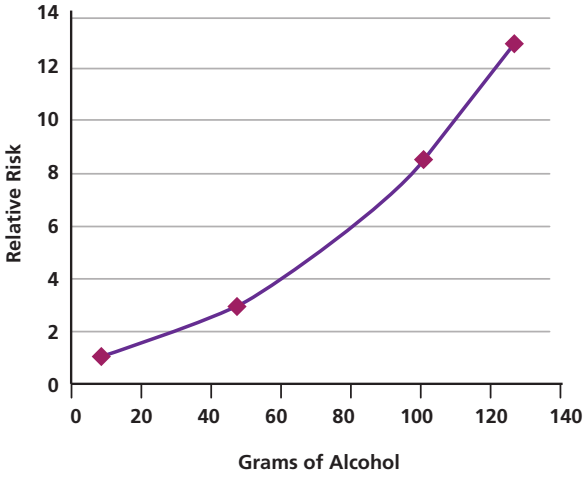
Excessive alcohol consumption (>14 units/week) is the second most important risk factor for oral cancer and is associated with a 3 to 5 times increased risk of oral cancer development (1, 21). This risk is dose-dependent as it has been demonstrated by Tramacere et al (22), who reported a relative risk increases:

- 1.29 for 10g of ethanol/day,
- 3.24 for 50g of ethanol/day,
- 8.61 for 100g ethanol/day,
- 13.02 for 125g of ethanol/day.

In contrast, a low consumption of red wine has demonstrated a protection effect in some studies (23).

Although some studies report an increased risk of oral cancer with the use of mouthwashes containing alcohol, systematic reviews and meta-analyses do not support such evidence (2,24,25). Nevertheless, it has been reported that the presence of alcohol in mouthwashes can

be broken down to acetaldehyde in the mouth by bacteria present in oral biofilms, which could potentiate the effect of acetaldehyde in these individuals. In view of this, it is possible that people with poor oral hygiene could be more susceptible if alcohol is retained in close contact with the oral mucosa (26).



As already stated for tobacco, although alcohol and tobacco consumption represent independent risk factors, when combined they have an exponential synergistic effect, being 38 times more likely to develop oral cancer when compared with abstainers from both products (9,27). Furthermore, an excessive alcohol intake leads to significant nutritional deficiencies that can also be risk factors for oral cancer (9).

2.2.5. Sunlight

Ultraviolet radiation, namely UVB, potentiates squamous cell carcinoma development, particularly on the lower lip. White-skinned individuals with chronic sun exposure as in some professions (for example, farmers or fishermen) are particularly affected by lip cancer. It is more frequent in elderly males and is often diagnosed at it's initial stages, probably due to its easy visualization, leading to a good prognosis in most cases (3).

2.2.6. Diet and other Nutritional Factors

Diet may have an aetiologic association with oral cancer in 10 to 15% of cases (3,28). In the last two centuries, after the Industrial Revolution, nutritional habits in developed countries have changed dramatically. Diet has become richer in saturated fats and refined carbohydrates, but poorer in vegetable and fruit intake. Un-diversified diets, poor in fresh vegetables and fruit and deficient in iron have been related to oral cancer (2,3,28). Red meat consumption has also been associated with an increased risk of oral cancer development. Diets rich in fruit, vegetables and folates have revealed to be protective against oral cancer development due to their production of anti-oxidant and anti-carcinogenic compounds, such as vitamins A, C and E, retinol, selenium, folic acid, carotene and other carotenoids, flavinoids and phytosterols. In some studies, coffee has revealed a protective effect (3,29).

2.2.7. Human papillomavirus (HPV)

Human papillomavirus (HPV), a member of papillomaviridae family, has been associated with the carcinogenesis of a group of oral cancers since 1983 (2,30). Since then, the frequency of HPV of in oro-pharyngeal cancers has been quoted in the literature with varying figures. More than 150 types of HPVs have been discovered, with approximately 15 of these having been associated with a high oncogenic potential and classified as high-risk types (e.g. types 16 and 18). HPV type 16 represents over 75% of all HPV found in oropharyngeal cancers, whilst types 18, 31 and 33 are noted in but a few (1,31).

HPV is present in more than 25% of all head and neck cancers and a particularly higher prevalence (~50%) is reported in oropharyngeal cancer (posterior tongue, tonsil, soft palate and the oropharynx), inevitably due to orogenital contact. However, IARC report a relatively low presence of HPV in oral cancers, with only 3.9% of oral cancers being associated with HPV. Studies demonstrated HR-HPV present in premalignant lesions, carcinomas in situ, invasive carcinomas and even in nodal metastasis (1,30-33).

HPV mediates its oncogenic influence thought the proteins E6 and E7 that have the capacity to block and inactivate the p53 tumor-suppressor gene and pRB respectively. Secondary to this, expression of p16 can be detected by immunohistochemistry (IHC) and is strongly expressed in HPV-associated tumors but absent in HPV negative tumors. In view of this, p16 expression is now generally considered to be a surrogate marker for HPV-induced SCCHN and is easily detected by immunochemistry (1,30-34).

Curiously, many neoplasms infected by HR-HPV in the oropharynx are diagnosed in younger individuals, non-smokers and lower alcohol consumers. Many cases are associated with certain sexual behaviors, such as multiple partners, early sexual activity and frequent orogenital contact history. Oral cancer is increasing in women with cervical cancer related to HPV, as well as among their partners (35). Histologically, they correspond to less differentiated tumors with a non-keratinizing, basaloid pattern, but no mutations of the TP53, a low p53, pRb and D1 cyclin cell expression and increased expression of p16. In the oropharynx, these tumours, especially HPV-HR positive with high p16 expression, have better prognosis and therapeutic responses (33-34).

This data lead to recognition of the existence of two distinct types of oropharyngeal carcinomas, related to two risk factors groups;

- those associated with the excessive consumption of tobacco and alcohol,
- those predominantly associated with HR-HPV infection.

With the emergence of anti-HPV vaccination, a decrease in cervical cancer and, probably oral cancer (mainly of the oropharynx), is therefore expected.

2.2.8. Other factors

The following are sporadically reported as risk factors for oral cancer, however are more rare or have less consistent scientific evidence supporting the association (1).

The existence of immunosuppression could be associated with an increased risk of oral cancer. It is known that following renal or other organ transplantation where immunosuppressive agents (azathioprine and cyclosporin) are routinely used. In some situations of prolonged immunosuppression therapy for conditions such as inflammatory bowel disorders (eg.Crohn's disease) there is an increased risk of oral cancer development, namely tongue cancer. The association of oral cancer with HIV infection is controversial. Although these patients present a high risk of developing Kaposi's Sarcoma and Non-Hodgkin's lymphomas, any association with squamous cell carcinomas is still unclear (1).

Some studies suggest a hereditary association in oral cancer development, where first-degree relatives of patients with oral cancer present an increased relative cancer risk, estimated at 1.1

to 3.8 (2, 37). Inherited genetic instability increases oral cancer susceptibility. Polymorphisms in the dehydrogenase enzymes (ADHB1 and ADH7) that metabolise alcohol into acetaldehyde might condition higher protection to upper aero-digestive tract cancers. Genetic syndromes or conditions may contribute to oral malignant transformation. In dyskeratosis congenita, a rare hereditary disease that involves oral leukoplakia and erythroplakia, skin pigmentation, onychodystrophy and hematologic disorders, malignant transformation may occur in the mouth. Also, in Xeroderma pigmentosum and Fanconi's anemia, an increased oral cancer incidence is reported. Autoimmune candidiasis-ectodermal-polyendocrinopathy dystrophy, an autosomal recessive condition, has shown to be associated with chronic oral candidiasis, which carries an increased risk of oral cancer development (2, 37).

Maté is an infusion of yerba-mate leaves (Ilex paraguariensis) characteristic of Southern America, namely, Argentina, Uruguay and Southern Brazil. It's drunk whilst very hot. Dassanayaka et al (38) initially registered the association of this drink to an increased risk of oral cancer and a recently published meta-analysis has reconfirmed the risk of maté drinking with upper aerodigestive tract cancers (39).

Study evidence associates tooth loss, chronic trauma, periodontal disease and lack of oral hygiene with oral cancer (2). Some bacterial species present in dental plaque (especially in patients with periodontal disease and poor oral hygiene) produce acetaldehyde which might have a genotoxic effect when distributed via saliva (26). The presence of chronic trauma induced by maladapted prosthesis or fractured teeth have also been associated with an increased risk of oral cancer (40,41).

A relation between oral cancer and lower socio-economic status (SES) has been reported (42). These underprivileged groups are likely to be more exposed to risk factors, including tobacco and alcohol consumption and are often less likely to seek regular dental care. However, Conway et al (42) provided evidence to support lower SES to be an independent risk factor for oral cancer.

Also infection by Candida albicans has been reported as a factor related to malignant transformation of the oral mucosa, primarily in cases of chronic hyperplastic candidiasis (candida leukoplakia). Nevertheless, the transformation frequency of these lesions is relatively low (1). It has long been postulated that oral keratosis harboring yeasts or hyphae of the fungus Candida albicans carry an increased risk of progressing to malignancy and where present appropriate anti-fungal therapy (local and/or systemic) should be prescribed.

2.3. Preventive measures – What to do?

As the major risk factors for oral cancer are related with lifestyles and personal habits of populations, preventive measures are possible and indicated. Since tobacco and/or betel quid (areca nut) use, alcohol misuse, the presence of HPV infection and dietary deficiencies are the main risk factors several actions could be implemented direct to eliminate these risk factors. It is reasonable to propose that more than 50% of oral cancers could be prevented by the elimination of tobacco smoking and a reduction in alcohol consumption, particularly in individuals where these habits co-exist.

This could be implemented with increased awareness and public education, and some with the help of political action and governmental policies towards reducing common risk factors in the communities.

2.3.1. Tobacco Cessation

It is well known that smoking cessation diminishes the relative risk for oral cancer after 10 years, being able to reach levels comparable to that of non-smokers. It can also reverse some oral potentially malignant disorders (see chapter 3) and therefore further reduce risks for oral cancer. In Gandini et al (13) meta-analysis, a pooled risk estimates for ex- smokers (OR 1.40 CI: 0.99-2.00) were significantly lower compared with current smokers (OR 3.43 CI:2.37- 4.94) (1,2,4,13,43).

Treatment of tobacco dependence is a major phase of primary preventive measures, especially among high risk patients. This should be developed with the help of primary care practitioners (including dentists and other oral health professionals) and where possible with assistance from specialist smoking cessation clinics.

Evidence-based protocols could be used in the diary of dental practices, to deal with smoking cessation to help our patients. Dental practitioners should give advice to their patients to stop smoking and refer cases (when available) to a smoker's clinic for additional assistance. Well researched protocols, include steps motivating people to stop smoking, known as the "5 A's" that stand for: Ask, Advise, Assess, Assist and Arrange. Some resources could be used by the dentist to improve the knowledge and to facilitate this process (http://smokingcessationtraining.com) (44).

2.3.2. Moderation of alcohol use

Other cancer prevention approaches relate to alcohol moderation advice. This includes not only the information and awareness of the harms of the alcohol misuse and also to identify and refer individuals with alcohol dependence disease to treatment centres. Following European guidelines, we could advise a limit of two drinks per day for men and one drink for women and discourage the binge drinking habits, especially prevalent among today's young people. I the UK, current guidance is a maximum of 14units per week for men and women, again avoiding binge consumption habits. Brief interventions on alcohol use by dental clinicians could help to reduce the incidence of oral cancer and oral potentially malignant disorders. There are some resources such as the tool "drinks meter" developed to measure up alcohol consumption for self-help (www.drinksmeter.com) (1,4,5,43).

2.3.3. Lip Protection

Awareness and education for protection of lips from the sun, is important particularly for white skinned individuals living in Southern Europe, Australia, Canada and Israel. Use of lip protection creams, wearing protective hats could reduce the exposure to UVB (1,4,43).

2.3.4. Diet Advice

Nutritional factors are perhaps the easily administered preventable agents against oral cancers. The adequate daily amount of fresh fruits and vegetables should be encouraged, as they

possess protective agents such as vitamins A, C and E, that work as antioxidants and scavenge mutagenic agents. They are best delivered naturally in red, yellow and green fruits and non-starchy vegetables, and we should encourage people to eat about five helpings of such foods a day. These health promotion messages on dietary interventions can be directed at whole communities or to individuals, particularly when opportunities arise in routine clinical practice (1,4,23,28,43).

2.3.5. Chemoprevention

Chemoprevention refers to the appropriate selection and regular consumption of diets rich in anti-cancer agents (as mentioned in 2.3.4) or the use of medical therapies - either natural or synthetic products - to arrest or reverse the process of cancer development. Chemopreventive agents may be applied as topical therapies to the sites of the oral cavity showing an increased risk of cancer or through systemic administration. Most chemoprevention trials to prevent oral cancer have been directed against subjects at risk of oral cancer development i.e those with oral leukoplakia or oral submucous fibrosis (see Chapter 3). The administration of chemopreventive agents aims to address the challenges associated with surgery for these potentially malignant disorders (45).

Different classes of agents have been evaluated so far, including some natural products listed below:

- Vitamin A and retinoids
- Beta carotene and carotenoids
- NSAIDs – ketorolac and celecoxib
- Tea components
- Chinese herbal mixtures
- Freeze dried black raspberries
- Bowerman –Birk inhibitor
- Curcumin
- Aloe vera

These agents may act through various mechanisms, mostly as anti-oxidants to reduce the oxidative DNA damage that has occurred due to specific carcinogenic agents, such as tobacco. One other mechanism of action of several retinoids is via inhibition of NFκB activation.

While many of these chemoprevention trials report significant rates of clinical resolution of premalignant lesions, compared with placebo or absence of treatment none have been subjected to long term use to demonstrate any benefit to prevent cancer development (45).

2.3.6. Prevention of HPV infection

Regarding the potential etiological role of HR-HPV, especially on oropharynx cancers, the existence of a vaccine against HPV´s is a goal for all young people specially before beginning of sexual activity. There are now vaccines against 9 types of HPV´s including the genotypes HPV16 and HPV18 and officially indicated for young girls with the aim of the prevention of cervical

cancer. In Australia and Portugal, boys are also given the benefit of vaccination against HPV and the case has been made for considering gender neutral vaccination programs (46). The UK government has recently announced free-vaccination for boys through the National Health Service to begin in 2020.

It is expected that this vaccine will also have an impact on the decrease of the incidence of oropharyngeal cancer in both females and males. In the view of this, prophylactic vaccination may in the future reduce the risk of HPV 16/18 infection and availability of HPV vaccination should be included in countries' strategic cancer control policies (1,4,43).

2.4 Key points

- Over 75% of oral cancers are attributed to tobacco consumption (in smoked or smokeless presentations) and alcohol misuse.
- Tobacco smoke has more than 6000 chemical substances' and over 60 are carcinogens including hydrocarbons, aromatic amines, formaldehyde or even arsenic or lead.
- Excessive alcohol consumption (>14 units/week) is the second most important risk factor for oral cancer
- Ultraviolet radiation, potentiates lip cancer particularly on the lower lip.
- Diets poor in fresh vegetables or rich in red meat has been associated to an increased risk of oral cancer development.
- HPV is present in more than 25% of all head and neck cancers specially in oropharyngeal cancer.
- At least 50% of oral cancers could be prevented by the elimination of tobacco smoking and a reduction in alcohol consumption.
- Brief interventions targetting tobacco cessation and alcohol use by dental clinicians could help to reduce the incidence of oral cancer.
- Use of lip protection creams, wearing protective hats could reduce the exposure to UVB.
- Rich diet (at least 5 portions) in red, yellow and green fruits and non-starchy vegetables should be encourage.
- Prophylactic vaccination against HPV´s is a goal for all young people especially before beginning of sexual activity.

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3. Secondary Prevention in Oral Cancer

Introduction

Head and neck cancer (HNC) is the sixth most common cancer in the world (1,2). The 2018 GLOBOCAN statistics reveal that worldwide in 2018, lip and oral cancer had:

- The 17th highest incidence of all cancers (3)
- 354,864 new cases (3)
- 177,384 deaths accounting for 2.01% of all cancer deaths (3)

The incidence of oral cancer in Western Europe has increased over the past two decades (1). A recent review of incidence and mortality of oral and pharyngeal cancer in Europe has shown a significant annual percentage increase between 2009-2013 in Denmark, Finland, Sweden and the Czech Republic (4). Over the last decade in the United Kingdom (UK), incidence rates of HNC have increased by 24% and by nearly a third since 1993 (5). Even with improved knowledge and treatment of oral cancer, the five year survival rate from diagnosis for most countries was approximately 50% for many decades, however promisingly in the past decade have improved to nearly 60% (1,6).

Secondary prevention of oral cancer is the early detection and management of oral cancer and potentially malignant disorders with the goal of slowing or stopping disease progression at an early stage (7-9). The Tumour-Node-Metastasis (TNM) stage at which an oral cancer is first diagnosed can make a significant impact on the morbidity and mortality rates (10,11). The 8th edition of the American Joint Committee on Cancer (AJCC) Tumour Node Metastasis (TNM) staging system was implemented in January of 2018 and introduced major modifications in the area of head and neck squamous cell cancer (HNSCC) staging (12), however, further validation of this new classification is needed (13). A 2009 UK study reported that the overall five year survival rate for p Stage 1 oral cancers is 76% (or 96% disease specific) compared to 37% (or 57% disease specific) for p Stage 4 oral cancers (10).

Methods of secondary prevention include extra-oral and intra-oral examination by general dental practitioners with the ability to recognise clinically suspicious features (7-9). Most oral cancers are preceded by clinically detectable potentially malignant disorders (PMDs) (14,15), for example oral leukoplakia (Fig 1), oral lichen planus (Fig 2) and erythroplakia, which opens a potential doorway for secondary prevention (9). General dental practitioners should be

Figure 1: Oral leukoplakia in the right buccal mucosa

Figure 2: Oral lichen planus in the left buccal mucosa with a central ulceration

able to identify potentially malignant disorders and refer promptly to specialist services who have access to early detection aids (16-18). Furthermore, secondary prevention also involves organised and opportunistic oral cancer screening and public education on self-examination for the signs and symptoms of oral cancer and oral potentially malignant disorders OMPD (19).

3.1. Public Education

3.1.1. Public awareness

In comparison to other types of cancer, awareness of oral cancer is relatively low (20-22). A UK study in 1999 revealed only 56% of participants were aware of oral cancer (20). This does appear to have improved with a study in 2006 revealing 95.6% of participants were aware of oral cancer (22). However, the same paper showed that recognition of signs of oral cancer was low and a further study in 2012 revealed that 77% of participants knew only 'little' or 'nothing at all' about oral cancer (21). Although there is increasing public awareness that tobacco and alcohol are risk factors for the development of oral cancer (22,23), the fact that patients have poor awareness of the signs of oral cancer, means that mouth self-examination (MSE) may be under-utilised. MSE is a secondary prevention opportunity that could potentially increase early oral cancer detection rates (19,24), although not all authors agree (25).

Breast self-examination, a screening method used in an attempt to detect early breast cancer, has been widely employed as a screening tool (26,27). In comparison, self-examination for oral cancer is less known. Of course, dental health care professionals are the most appropriate individuals to perform oral cancer screening, however, often it can be one or two years between patient's dental examinations, in addition to many patients being infrequent dental attenders.

3.1.2. Mouth-self examination (MSE)

MSE has been shown to be a potentially feasible and effective way of increasing oral cancer awareness and allowing for early detection of oral cancer and PMDs (24,26). In a 2015 Spanish study, 90 participants were enrolled in an oral cancer education programme which included face-to-face verbal instructions of how to carry out MSE and three months later were contacted by telephone and asked if they had carried out MSE at home. 80.2% of participants performed MSE, and people who perceived themselves at higher risk of oral cancer were more likely to perform MSE (28). Two Indian studies have evaluated the use of MSE for detecting oral cancer via distribution of brochures to households. One study showed a 36% compliance with MSE (24) whereas the other showed 87% compliance (26). One of the studies found that MSE resulted in an oral cancer detection rate of 87/100000 which compared favourably to detection rates by healthcare workers (24). The other study showed that MSE has a low sensitivity rate for detecting oral cancer or PMDs (18%) with white patches being the most undetected lesion by MSE, however specificity was almost 100% (26). A differently structured UK pilot study revealed MSE has a low sensitivity rate of 33% and a specificity rate of 54% (25). Although the accuracy of detection is low, what the studies do highlight is that MSE can be useful for early detection of oral cancers or PMDs which otherwise may not have been identified until a later stage. By analysis of published data, a Cochrane systematic review in 2013 concluded that there was "insufficient evidence to satisfactorily determine the diagnostic test accuracy of MSE

as part of an organised screening programme" (29). Appropriate visual charts or smart-phone applications may help to improve the performance of MSE in future studies (26).

3.1.3. The role of the General Dental Practitioner

General dental practitioners (GDP) have a role in educating their patients about oral cancer, routinely screening for oral cancer and being aware of the early signs. Studies have revealed that very few patients report having received information on oral cancer from a GDP or general medical practitioner (22,23), with one UK study revealing only 7.1% having ever been spoken to about oral cancer (22). The same study demonstrated patients have generally poor knowledge of what signs could be indicative of early oral cancer; only 24.5% were aware that a red patch could be an early sign (22), yet erythroplakia (Figure 3) has the highest malignant transformation risk of all PMDs (85%+) (16).

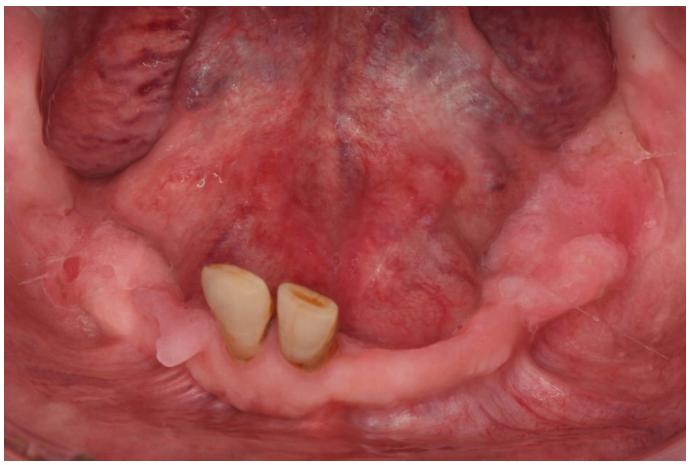

Fig 3. Oral Erythroplakia of the floor of the mouth

Furthermore, it has been shown that there is a lack of awareness amongst patients regarding a dentist's role in oral cancer screening. One study has shown that only 14% of participants were aware that their dentist routinely screens for oral cancer (21). With the increasing incidence of oral cancer (2) it may be advisable that GDPs should routinely be discussing oral cancer with their patients and informing them that oral cancer screening is taking place (17, 19). The British Dental Association (BDA) advocates this and advises that patients should be informed that oral cancer screening is taking place as this can improve patient satisfaction (30). This is supported by a study that showed that 92% of patients wish to be told that oral cancer screening is taking place (21).

Other oral healthcare professionals (OHPs) including dental hygienists, dental therapists and dental nurses also have an important role in public education of oral cancer. The WHO Global Oral Health Programme uses the following statement to lead its work for oral cancer control; 'To take steps to ensure that prevention of oral cancer is an integral part of national cancer-control programmes, and to involve oral-health professionals or primary health care personnel with relevant training in oral health in detection, early diagnosis and treatment.' (31). Dental hygienists and dental therapists are encouraged to screen for all cancer in the same manner as GDPs routinely at all routine assessments (32). The BDA released a management strategy for dental practice on opportunistic oral cancer screening in 2000 which outlines a dental

nurse's roles in oral cancer screening/education including making accurate notes of the dentist's observations during examination, confirming that oral cancer screening has been performed at every routine assessment and providing emotional support to patients (30). All OHPs can also be involved in advising patients in risk factors with oral cancer.

3.1.4. Raising awareness

So, how can public awareness be improved? As discussed, the GDP and other OHPs have a pivotal role, however other approaches may be utilised to further enhance this. General medical practitioners (GMPs) are also in a position to educate patients on the early signs and symptoms of oral cancer; in fact patients with symptoms of oral cancer more often seek advice of their GMPs rather than their GDPs (33), perhaps reflecting the popular misconception that dentistry concerns teeth whereas cancer is a medical specialty. Furthermore, those at high risk of oral cancer (tobacco and/or alcohol users) may be irregular dental attenders but regularly consult GMPs (34). Public awareness of oral cancer and attendance for screening has also shown to be increased by using various social marketing strategies including radio advertisements, newspaper advertisement and billboards (35). A Scottish media campaign utilising television advertisements was successful in improving people's knowledge of oral cancer symptoms and when to consult a GDP/GMP (36). The two studies just mentioned were published in 2010 and 2009 respectively. More modern-day approaches may include the use of websites and social media platforms such as Facebook, Twitter and Instagram; The Oral Cancer Foundation, for example, has utilised these networks to promote oral cancer awareness (37). Campaigns such as UK Mouth Cancer Action Month, an Awareness Campaign devoted to the cause have each year promoted increasing public awareness through media (3).

3.1.5. Key points

- Compared to other types of cancer, public awareness of oral cancer is low.
- Public education on
- Oral cancer is an essential part of secondary prevention.
- This includes increasing awareness of the early signs of oral cancer and how to perform MSE – the important message to the public should be "if in doubt get it checked out".
- Furthermore, increasing public awareness of a GDPs role in oral cancer screening and detection may assist in compliance with regular annual dental attendance.
- The cumulative effect of these public education programmes may result in successful early detection of oral cancer and OPMDs

3.2. Oral Potentially Malignant Disorders

A range of oral mucosal disorders with an increased risk of malignancy transformation has been described in the literature with the term oral potentially malignant disorders (OPMDs) (38). This was adopted by WHO embracing precancerous lesions and conditions that were included in the previous WHO classifications (39). Recently, it is proposed the new term "Potentially

Premalignant Oral Epithelial Lesions [PPOELs]" recognizing these disorders could become malignant so that before malignant transformation, they are still (potentially) premalignant (40). This embraces the inclusion of oral lichenoid lesions and oral lesions of GvHD as potentially malignant disorders (40). We present a list of multiple disorders with the potential malignant transformation highlighting the most common clinical conditions, risk factors as well some management options. The list selected embraced the work of Warnakulasuriya et al (2018) in which embraced the new term previously described (38).

3.2.1. Erythroplakia

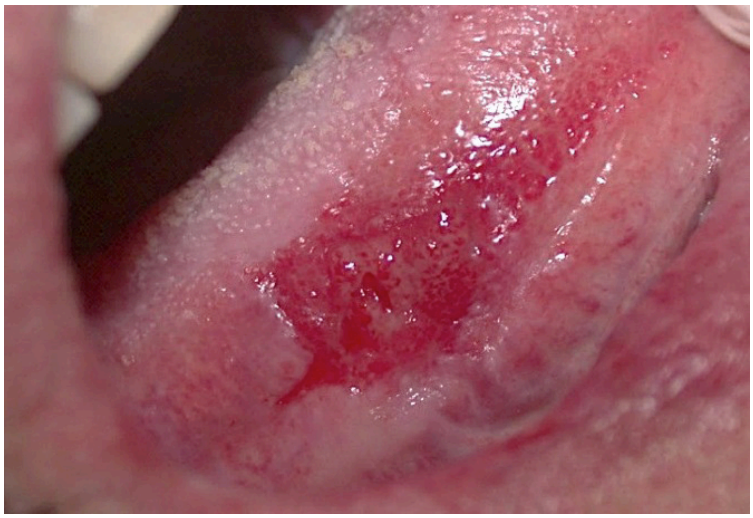

Fig. 4 Erythroplakia on the right border of the tongue

Oral erythroplakia is an erythematous precancerous lesion that presents as a red patch with high malignant potential, being more common among middle aged to elderly persons and, especially among men (41-43). The prevalence of these lesions range from 0.02-0.83% in different regions (43). It harbors carcinoma in about 51% of cases, severe dysplasia or carcinoma in situ in 40% and mild to moderate dysplasia in 9% (43). Erythroplakia is strongly associated with tobacco habits and alcohol consumption (54;55) (45).

Clinical presentation: The lesions of erythroplakia are usually irregular in outline, although well defined, and have a bright red velvety surface. Sometimes the surface is granular (40). The most frequently involved sites are soft palate, the floor of mouth, the ventral surface of tongue and the retromolar area (45). It is soft on palpation and can get indurated once it progresses to invasive carcinoma (43,46). It is usually, asymptomatic but some may complain of sore or burning sensations. Oral erythroplakia has the highest risk of malignant transformation compared to all other mucosal lesions (47,48).

An urgent diagnostic biopsy is essential to diagnose the condition and evaluate the dysplastic nature of the lesion which may harbour carcinoma in situ or even frank carcinomas (40).

A timely referral to a specialist centre is indicated. Management mainly emphasizes on prevention of malignant transformation by excision and early diagnosis of cancer. Individuals with erythroplakia should be encouraged about life style changes which includes- tobacco/

alcohol habits cessation and diet rich in vegetables and fruits. In view of the high malignant potential of these lesions the recommended treatment is surgical excision, including laser (43,49). The area of oral erythroplakia is a predictive factor for postoperative recurrence (41). In view of its high-risk nature, long term follow-up is recommended.

3.2.2. Leukoplakia

Leukoplakia is defined as 'white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer (38). They are commonly diagnosed after the 4th decade, predominantly seen in males (50) and are 6 times more common among smokers than among non-smokers. Use of causative agents like tobacco, alcohol and betel quid play a significant role in cases of leukoplakia (51).

Oral leukoplakia may remain asymptomatic or manifest a benign clinical appearance which can confuse clinicians while differentiating it from other reactive or inflammatory conditions of the oral mucosa (40). It can affect multiple sites in the oral mucosa with lateral margin of the tongue and floor of the mouth being the most prevalent site affected in the western population. But the most common sites affected among the Asian population tend to be buccal mucosa and buccal sulcus due to the widespread habit of betel quid chewing (40,52).

Fig.5 Leukoplakia on the right ventral surface of the tongue

According to clinical presentation, leukoplakia can be broadly classified as Homogenous and Non-homogenous type. The homogenous leukoplakia are uniformly flat and thin with a smooth surface, occasionally with shallow cracks. Non-homogenous leukoplakia are more commonly symptomatic and can be divided into 3 clinical types: speckled, nodular and verrucous/ exophytic (40).

Leukoplakia can be asymptomatic but usually symptomatic in cases of non-homogenous leukoplakia. The symptoms described by the patients ranges from a sense of discomfort, burning, tingling to soreness associated with sharp flavours (40).

Proliferative verrucous leukoplakia is characterized by thick keratosis and multiple squamous papillary nodules (45). Though rare, it is an aggressive form of oral leukoplakia, and majority of cases of proliferative verrucous leukoplakia has a tendency of malignant transformation at multiple sites (45).

Biopsy is recommended to diagnose the cause of a white patch. The primary reason for a biopsy is to confirm the diagnosis. This also helps to grade the lesion if dysplasia is identified which enables the clinician in assessment of any risk of malignant transformation, treatment plan and monitoring regime (53).

3.2.3. Erythro-leukoplakia

Erythroleukoplakia refers to a mixed red and white lesion usually associated with soreness and an irregular margin (54). Atrophic mucosa (thinning) or sometimes speckling contributes to the erythema and soreness could be as a result of colonization by candidal hyphae (40).
Its excision technique may vary depending mostly on size, location and histopathology with the potential to use CO2 laser or a scalpel. The OEL has a significantly higher risk of malignant transformation than oral leukoplakias (54).

Fig. 6 Erythroleukoplakia on the left border of the tongue extending to the ventral surface.

3.2.4. Submucous fibrosis

Oral submucous fibrosis (OSF) is a chronic, premalignant condition of the oral mucosa prevalent amongst the Asian population (55). This disease primarily affects the lamina propria. As the disease progresses, deeper tissues (eg. Muscles) are affected which results in loss of elasticity of the mucosa and eventually leads to a reduction of mouth opening (40). Research shows increased frequency and duration of consumption of areca nut and commercially packaged forms of areca nut poses a significant risk in the severity of OSF (55). The prevalence of OSF ranges from 0.2-1.2% in India (56). The frequency of malignant transformation in OSF has been reported to be in the range of 7–13% (57).

Clinical presentation: Early presentation of the disease includes a burning sensation of the mucosa on eating sharp flavors characterized by blanching of the mucosa and loss of normal pigmentation (58). A mottled, leathery texture of the mucosa with fibrous bands palpable across the blanched mucosa advances gradually leading to limitation of mouth opening (40). A patient with sunken cheeks out of proportion to age and limited mouth opening would be a typical presentation of this disease. Furthermore, reduction in the size of the tongue with reduced mobility, shrunken uvula, blanched floor of the mouth and a pale appearance of palate

with fibrous banding would be other features in advanced cases. The most common sites affected are the buccal mucosa, lips, soft palate and the tongue.

A biopsy is recommended to confirm the diagnosis and to rule out any epithelial dysplasia. Cessation of habits is strongly advisable and clinicians should be able to explain to the patients the risks associated with long term chewing as well as organise further referral to the appropriate clinics according to their National Policies. Multiple treatments have been discussed including mouth opening exercise, Oral lycopene, Submucosal injections of steroids, hyaluronidase, collagenase (59,60). However, the latest Cochrane review highlighted the lack of reliable evidence for the effectiveness of any specific interventions for the management of oral submucous fibrosis (39,61). More recently in several experimental studies published from India natural agents such as curcumin and aloe vera have been tried for the treatment of OSF.

Fig. 7 Orange staining affecting the right buccal mucosa and teeth are commonly seen in patients with long term betel quid habit consumption. On the posterior aspect, evidence of fibrous bands are visible.

3.2.5. Actinic keratosis

Actinic keratosis are hyperkeratotic lesions that represent focal abnormal proliferation of epidermal keratinocytes commonly affecting the lips, especially the lower (40). Those with a fairer skin are at an increased risk and may be predisposed to actinic keratosis. Solar exposure is the primary risk factor for actinic keratosis. Men in outdoor occupations show a stronger predisposition for Actinic keratosis compared with females (40).

Clinical presentations commonly comprise of white lesions along with crusting, flaking and dryness, or a mottled appearance which could be erythematous (40,63). With the progression of the disease, ulcerative lesions may develop, with inflammation, atrophy and loss of epithelium.

The development of Actinic keratosis is dependent on a variety of factors, namely- the length of patient's sun exposure, location, age, genetic predisposition, outdoor occupation and leisure activities (40). Actinic keratosis can transform into SCC and studies have shown that failure to apply sun screen can play a big role in the transformation.

Fig. 8 Actinic cheilitis affecting the lower lip

A biopsy is recommended to confirm the diagnosis and rule out dysplasia. Various treatment modalities have been discussed for by different authors from surgical interventions (excision, cryosurgery, curettage, laser surgery and vermilionectomy and non-surgical treatments including topical chemotherapy (fluorouracil or masoprocol cream), chemo-exfoliation and dermabrasion (64).

Picascia and Robinson (65) recommended use of Topical fluorouracil and laser ablation while McDonald et al. highlighted Imiquimod 5% has the potential to downgrade the degree of dysplasia in the lower lip with AC (66). The evidence is still limited with regards to which treatment is recommended.

Prevention of Actinic cheilitis to avoid prolonged exposure to direct sunlight as well as the use of lip sun blocker with the capacity to absorb the ultraviolet light (64).

3.2.6. Oral Lichen Planus

Oral Lichen Planus is an autoimmune inflammatory skin condition that can affect the mouth. This mostly affects middle aged people, especially women (67,68). The prevalence of this disease ranges from 0.5 to 2.6% (67,68).

Lichen planus lesions usually present bilaterally as keratotic lace-like network on the buccal mucosa and the lateral margins of the tongue.

The different types of Lichen planus are:

- Reticular - It is the most common type seen in clinical practice. These are mostly asymptomatic. The reticular lesions appear as interwoven, raised lacy lines forming a latticework. Reticular type can also be evident on the muco-buccal fold, gingiva, floor of mouth, labial mucosa, lips and rarely the palate.
- Annular - The keratotic striae may be in the form of annules (rings).
- Papular - The papular type presents as small, white, raised papules which can be mistaken as fordyce's spot.
- Plaque type - The plaque type is found commonly on the dorsal aspect of the tongue and

closely resembles leukoplakia; however, keratotic striae are found at the lesion periphery.

- Atrophic erosive and ulcerative- These present as erythematous or with distinct ulceration. The keratotic striae are seen most often at the margins. When the lesion is ulcerated, patients typically complain of soreness or a burning sensation while eating hot or spicy food. The features described as desquamative gingivitis is usually seen in atrophic oral lichen planus.
- Bullous type - It is rare but has tendency of recurrence. It is important to differentiate these lesions from other immunobullous conditions such as mucous membrane pemphigoid and pemphigus.

Fig. 9 Reticular Oral Lichen Planus

Fig. 10 Erosive Oral Lichen Planus

Some patients may develop cutaneous lichen planus. Their medical history may help to identify oral lichen planus cases. Other extraoral mucosal sites, such as the genitalia, may also be affected. Genital examination may help to identify persons with the vulvovaginal gingival variant of lichen planus (40). Several studies have shown its malignant potential, ranging from 0.4 to 5.6%; however, the highest rate is seen in erosive OLP and lichenoid lesions (67,69).

The diagnosis of OLP can be made from the clinical features if there are sufficient characteristics, but biopsy is recommended to confirm the diagnosis and to exclude dysplasia and malignancy.

With regards to treatment, maintenance of good oral hygiene and eliminating precipitating factors might help to reduce discomfort in symptomatic lichen planus. Multiple topical corticosteroids have been advocated on the erythematous and erosive form however previous Cochrane review found no research evidence to show that one type of topical corticosteroid steroid is better or worse than another (68).

Candida albicans are present in 37% of oral lichen planus and symptoms may be aggravated by this (67). Antifungal treatment of erosive lesions can be beneficial in changing these lesions to the reticular form. Miconazole gel is found to be useful in the treatment of oral lichen planus with candidiasis (67).

Systemic steroid therapy or long term immunosuppressants is reserved for severe exacerbations. Several other agents like topical or systemic retinoids, topical tacrolimus or cyclosporin and photodynamic therapy have also been tried in oral lichen planus with variable success (70).

3.2.7. Oral lichenoid reactions

Oral lichenoid lesions are intraoral keratotic and erythematous lesions with a reticular, striated appearance and clinical features similar to those of Oral lichen planus. But oral lichenoid reactions have an underlying causative agent. Oral lichenoid reactions can be classified into 3 types (40):

1. In topographic relationship to a dental restoration (71), often amalgam, also named oral lichenoid contact lesions (OLCRs),
2. Drug-related
3. In association to chronic graft-versus-host disease (cGvHD).

Oral lichenoid reactions to amalgams are recognized as hypersensitivity reactions to low-level mercury exposure (71,72). It is usually localised to the area of contact with the mucosa. If drug induced, patient's history and length of prescription will aid in diagnosis.

With regards to investigations, a combination of history, clinical examination, skin patch testing and a biopsy helps to diagnose oral lichenoid reaction. However, microscopically it is difficult to distinguish between oral lichenoid reaction and oral lichen planus (40).

Skin patch testing is a valuable tool to confirm clinically suspected oral lichenoid reactions however the evidence is still limited in which further prospective studies are needed to ascertain that a clinically suspected oral lichenoid reaction with a positive patch test result may resolve after the replacement of amalgam fillings (73).

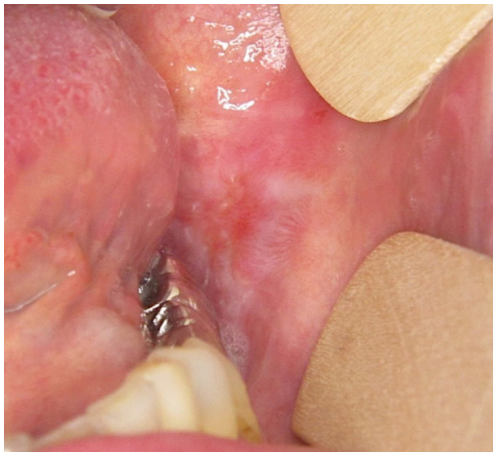

Fig. 11 Lichenoid reaction secondary to amalgam fillings

Fig 12. Lichenoid reaction secondary to amalgam filling

3.2.8. Discoid lupus erythematosus (DLE)

Lupus erythematosus is a chronic autoimmune disease that commonly affects skin and may involve the mucosal surface of the lips and the oral cavity. It can be subdivided into 3 forms: 1) systemic, 2) drug-induced and 3) discoid (40). Young women are more commonly affected (72). Oral lesions may also manifest in approximately 20% patients with systemic lupus (40). The discoid lupus erythematosus typically affects the areas of the face and neck exposed to sun and may present with the typical butterfly rash across the nasal bridge (5). Clinically, oral discoid lesions are characterized by central atrophy, small white keratinized plaques

with elevated borders, radiating white striae and telangiectasia (45) commonly affecting buccal mucosa, lips and palate. It has close resemblance to oral lichen planus in appearance. Immunofluorescence studies demonstrate subepithelial immunoglobulin and complement deposition (the lupus band) (75), which aid in differentiating DLE from lichen planus. Blood investigation may show positive ANA which is generally negative in OLP patients.
Though rare, there has been reports of malignant transformation of oral lesions of Discoid lupus erythematosus commonly affecting the labial mucosa and vermillion border (45,38). Treatment can vary from topical corticosteroids to long term immunosuppressants, depending on severity of oral clinical presentation (74).

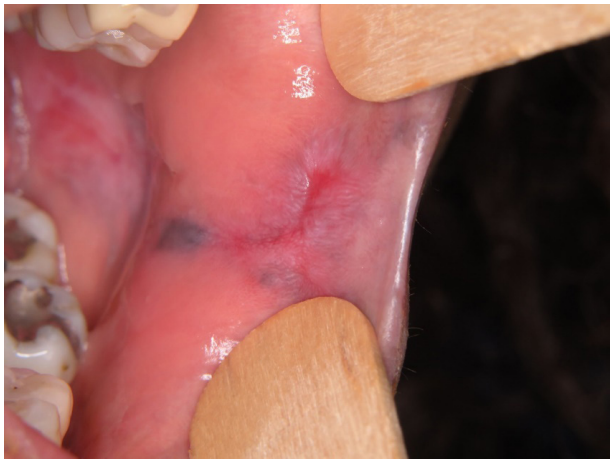

Fig. 13 Discoid Lupus with pigmentation affecting the left buccal mucosa

3.2.9. Graft-versus-host Disease

Haemopoietic-cell transplantation is a highly specialized therapy used to treat high-risk hematological malignant disorders and other life-threatening haematological and genetic diseases. The main complication of haemopoietic cell transplantation is graft-versus-host disease (GVHD), an immunological disorder that affects many organ systems, including the gastrointestinal tract, liver, skin and lungs and oral cavity (77).
Oral soreness is one of the main features of acute or chronic oral GvHD. It can spread to many surfaces in the mouth. The oral disease presents with keratotic striations and plaques, or erosive and ulcerative areas (40) and typically involves the buccal mucosa and the lateral tongue. The dorsum of the tongue may show papillary atrophy. Other clinical features include xerostomia (oral dryness), and patients may develop recurrent mucoceles on the labial and buccal mucosae, tongue, or soft palate (40).

The American Society for Blood and Marrow Transplantation defined a general diagnostic criteria and specific differential features of oral cGVHD (78). In their criteria it highlights the appearance of clinical lichenoid lesions, hyperkeratotic plaques and limited oral aperture secondary to sclerosis (48). Management can be complex and can involve multiple healthcare professionals from Haematology to Oral Medicine in which the severity of the condition will trailer treatment from topical to systemic immunosuppressant's (78).

Fig. 14. Severe lichenoid reaction affecting the dorsum of the tongue of a patient with GVHD

3.2.10. Palatal changes in reverse smoking

Reverse smoking is a habit that is endemic in many Indian, South American and Caribbean communities as well as Sardinia and Phillipines (40). This is an unusual way of smoking in which the lighted end of a cigar, cigarette or chutta (Indian smoking product) is held in the mouth. The mucosal changes associated with reverse smoking affects mostly the palate due to exposure to direct heat and smoke (40). The different changes noted in the mucosa ranged from some pigmentation and erythema only to various combination of leukoplakia, fissuring and thickening of palatal mucosa. Other features noted included nodularity, erythema, prominence and reddening of minor salivary gland duct openings (77). Gupta et al. followed up a cohort of 3000 patients over 6 years and demonstrated the potentially malignant nature of this condition as 6 patients developed palatal cancer (80). Palatal lesions associated with reverse smoking are more persistent than stomatitis nicotina found in regular cigarette smokers and, compared with leukoplakia, have a higher risk of developing into malignancies (40).

3.2.11. Epidermolysis Bullosa

Epidermolysis bullosa (EB) is a cutaneous disease characterized by fragile epithelium that may manifest as blistering and erosions of the oral mucosa. The disease is classified into 32 different subtypes. Intraoral soft tissue manifestations are found in all subtypes and include marked frequency of oral and perioral blistering that leads to ulceration, scaring, and obliteration of the oral vestibule and microstomia (81).

In a study involving 2745 patients with EB in the United States at least 1 SCC arose in 2.6% (73 of 2745) of the study population, almost all in sun-exposed areas (82). Multiple SCCs were found in the group with recessive dystrophic EB (RDEB). Based on this data, the authors have highlighted that in the recessive dystrophic type (i.e. RDEB) the life time risk of developing squamous epidermal cancers is greater than 90%. There has been only 1 reported oral SCC reported on the tongue among non-cutaneous cancers (82).

Fig 15. Superficial blister on a patient with Epidermolysis Bullosa.

3.2.12. Dyskeratosis Congenita

Dyskeratosis congenita (DKC) is a rare, inherited disorder classically known by the mucocutaneous triad of nail dystrophy, oral leukoplakia and lacy reticulated skin hyperpigmentation. Genetic mutations resulting in shortened telomeres have been shown as the cause of DKC (83). Patients with DKC have significantly increased risk of malignancy. Oral leukoplakia is the most common presentation in this condition, found in 65% to 80% of patients (40,84).

Leukoplakia on tongue and occasionally on buccal mucosa affects often young patients, and most reported cases with oral leukoplakia have occurred in children and adolescents under age 15 years (85). Keratotic oral lesions are rare in children, and the evidence of a white patch on the tongue of a child, in the absence of any other obvious cause (e.g., candidal infection or chronic trauma) must arouse suspicion of this rare condition (40).

3.3. Oral Cancer Screening

Oral cancer screening is a process whereby a practitioner evaluates if an asymptomatic patient has a potentially malignant or malignant oral lesion. This is most commonly performed through conventional oral examination (COE) although adjunctive techniques can be utilised (33). Therefore, oral cancer screening is a key aspect of secondary prevention, allowing the opportunity for early detection and management of oral cancer and PMDs, hence potentially slowing down or stopping disease progression at an early stage (7-9).

3.3.1. Definition

The definition of screening accepted by the World Health Organisation (WHO) originated from a Commission on Chronic Illness (CCI) conference in 1951; "screening is the presumptive identification of unrecognised disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably do not. A screening test is

not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment" (87). The table below outlines the main different types of screening in healthcare.

Applying the above definition to oral cancer, screening in this context implies oral examination or simple tests which can identify OPMDs or early cancers in patients who are generally asymptomatic. The identified patients would then be referred onto the appropriate specialist service. However, unlike screening for breast, cervical and bowel cancer, Speight et al in 2017 report that 'no national oral cancer screening programmes have been implemented' (93). In 1968, Wilson and Jungner first defined criteria that needed to be met for the implementation of a screening programme (36) which have been modified over time and the UK National Screening Committee (UK-NSC) now have 19 criteria for implementation of a screening programme (94). These encompass aspects of the condition (i.e. oral cancer), the test, the treatment and the screening programme. To date the UK-NSC considers that oral cancer screening does not satisfy the essential criteria to make it a screenable disease. (19,93).

Type of Screening	Explanation	Example
Mass screening	Large scale screening of major population groups eg. 'adults' 'men' etc (87,88)	Cervical cancer screening for women age 25-64 (90)
Selective/Targeted screening	Screening of a selected high-risk group eg. 'smokers' 'genetic history' etc (87,88)	Screening for familial cancers (91)
Multiphasic screening	Combining two or more screening tests (87,88)	Chest x-ray for tuberculosis, heart disease and lung cancer (88)
Opportunistic screening	Screening a person for a disease when they attend a clinic for another reason (87,88)	Alcohol Use Disorders Identification Test (AUDIT) (92)
Occupational screening	Screening employees for previously un-recognised diseases that are caused or influenced by work associated factors or which can influence work (89)	Blood test for blood-borne viruses for medical and dental professionals (89)
Surveillance	Long term monitoring of health of at risk patients (87,88)	Surveillance of communicable diseases (88)

Table 1: Types of Screening (87-92)

3.3.2. Conventional oral examination (COE)

Conventional oral examination (COE) is the main method of oral cancer screening (33,94,95). A 2013 Cochrane systematic review of oral cancer screening programmes described a visual screen as 'not surgically invasive, painless and socially acceptable' (15). Taking this concomitantly with the fact that most oral cancers are preceded by a clinically detectable PMD (9), an oral cancer screening programme would seem feasible, however difficulties and limiting factors exist. The main challenge has been that the natural history of OPMDs has not been well established based on carefully conducted follow-up studies and furthermore evidence-based management of OPMDs has not been tested (16,96).

There are both advantages and disadvantages to COE. As mentioned, it is non-invasive and painless, as well as being quick and simple if being performed by someone acceptably trained to do so. Multiple studies have revealed good specificity and sensitivity of COE (97-99). For example, a screening programme undertaken in a company headquarters in London, UK in 1995, revealed a sensitivity of 71% and specificity of 99% on a cohort of 292 participants (98). A more recent study in 2015 in Oporto, Portugal revealed a sensitivity of 96% and specificity of 98% on a cohort of 727 participants (97). Some of these studies also show that non-dental health care workers, for example health care workers or dental care professionals, are equally able to perform COE for the screening of oral cancer, providing they are adequately trained (99,100). Furthermore, as COE is so simple to perform, it can be undertaken opportunistically alongside other examinations and without the need for any specialised equipment (97,98). Further evidence for COE is discussed in 'Evidence for oral cancer screening.'

As COE is purely a visual test, in comparison to cervical smear for example, there is the risk of introducing subjectivity (95). The result may also vary depending on the quality and training of the examiner (93). Although there is reported good sensitivity and specificity, oral cancer screening through visual examination, as with other types of cancer screening, does also have the potential to produce false negatives and false positives (15,87,95). Potentially the biggest limitation to COE is the fact that it is often not possible to distinguish between benign lesions, PMDs and oral cancer (93,95). PMDs and early cancerous lesions may appear subtle and go undetected, whilst conversely not all clinically detectable PMDs will progress to oral cancer (93,95,96). The natural history of PMDs is not clear but a review of the literature by Napier and Speight in 2008 reported that approximately only 2% of PMDs per annum will transform into an oral squamous cell carcinoma (96).

A COE requires good quality white light and ideally two dental mouth mirrors. For patients with removal dentures, examination should be performed both with and without the dentures in situ. It should begin with thorough inspection and palpation of the neck for cervical lymphadenopathy, salivary gland enlargement, asymmetry or skin lesions. Observation of the neck is best performed standing in front of the patient, whereas palpation of the cervical lymph nodes is best performed standing behind the patient. Correct positioning of the neck is important, not to extend the neck during the examination and the dental chair should be upright and not inclined. The cervical lymph nodes should be examined systematically to include; preauricular and postauricular nodes, parotid node, occipital node, buccal node, facial node, submental and submandibular nodes, jugulodigastric node, deep cervical chain nodes, jugulo-omohyoid node, anterior supraclavicular node and posterior deep cervical nodes (see Fig 4). Information that should be documented regarding any palpable lymphadenopathy includes

location, size, shape, texture, mobility, induration and tenderness (104). If any abnormalities are detected, imaging, including an ultrasound scan, may be warranted. If abnormal lymph nodes are confirmed on the ultrasound scan then a fine needle aspiration (FNA) should follow (53).

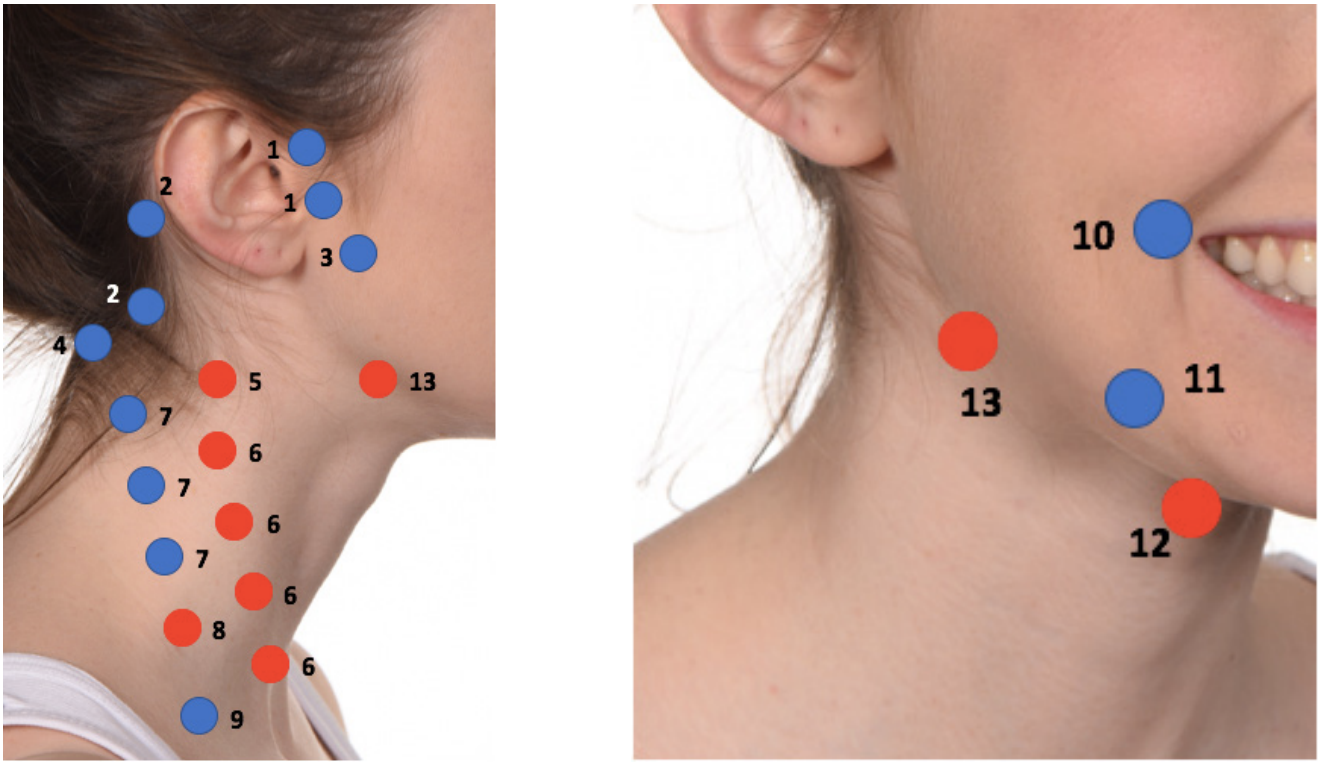

Fig 16. The lymphatic system of the head and neck with lymph nodes likely to positive in lip and oral cancer marked in red

1. Preauricular nodes
2. Postauricular nodes
3. Parotid node
4. Occipital node
5. Jugulodigastric node
6. Deep cervical chain
7. Posterior deep cervical nodes
8. Jugulo-omohyoid node
9. Supraclavicular node
10. Buccal node
11. Facial node
12. Submental node
13. Submandibular nodes

Following this, inspection of the oral cavity should include thorough visual and tactile examination of the following areas:

1. Examination of the outer lips including commissures and peri-oral area.
2. Examination of the upper and labial mucosa including vestibules and frenum.
3. Examination of the right and left buccal mucosa including commissures and upper and lower buccal sulci.
4. Examination of the labial, buccal, palatal and lingual gingivae. This should include examination of any edentulous alveolar ridges, retromolar pads and maxillary tuberosities.
5. Examination of the dorsum, right and left lateral borders and ventral aspect of the tongue. Use gauze to hold and move the tongue to ensure thorough examination.
6. Examination of the floor of the mouth.
7. Examination of the hard and soft palate.
8. Examination of the oropharynx – gently depress tongue and ask the patient to say ‘ah’ to allow for visualisation.

Fig 17.A systematic oral examination

3.3.4. Other oral cancer screening aids

Although COE is the current gold standard for oral cancer screening (102), other diagnostic aids that could potentially be involved in the oral cancer screening process include; visual staining (toluidine blue), light-based systems (chemiluminescence, tissue fluorescence imaging, tissue fluorescence spectroscopy), exfoliative cytology/brush biopsy and in vivo microscopy (15,95,102,103). Although there has been a lot of research into these adjuncts, all-be-it mostly conducted in secondary care facilities, currently there is insufficient evidence to support their use as screening tools (33,55). These early detection aids will be discussed in more detail in the next section of this chapter.

3.3.5. Evidence for oral cancer screening

In 2013, Brocklehurst et al. performed a Cochrane systematic review into screening programmes for oral cancer (15). The review included any randomised controlled trial (RCT) of screening programmes for the early detection of oral cancer or PMD with the primary outcome measure being oral cancer mortality. Any type of screening method was included. Only one study met the inclusion criteria; a cluster-RCT by Sankaranarayananin Kerala, India which began in 1995 with four rounds of screening over a 15-year period (104-107). The screening method used was COE performed by trained non-medical university graduates. For the intervention arm, screening was performed and screen-positive lesions were referred to a dentist for diagnosis; for the control arm, subjects did not receive screening. The results of the study showed an overall 12% reduction in oral cancer mortality between the intervention and the control arms, however this was not statistically significant. There was, however, a statistically significant reduction of 24% in oral cancer mortality between intervention and control arms in high-risk subjects that used tobacco and/or alcohol. Five-year survival rate was also found to be significantly higher in the intervention arm than the control arm. Only 20% of the eligible population attended all four rounds of screening, however of this cohort there was a very significant 79% reduction in oral cancer mortality (and 81% reduction in the high-risk subjects) in the intervention arm compared to the control arm (15,93,104). The systematic review (15) concluded that there was inadequate evidence from this study to suggest a national oral cancer screening programme and that the study had a high risk of bias (15). However targeted/selective screening using COE applied to high-risk groups may be cost-effective in reducing oral cancer mortality and opportunistic screening was also recommended (15,93).

Another Cochrane systematic review was carried out in 2013 by Walsh et al. to estimate the diagnostic accuracy of COE, vital rinsing, light-based detection, biomarkers and MSE in apparently healthy adults (29). The review included RCTs and cross-sectional studies with a primary objective of test accuracy. Thirteen studies met the inclusion criteria; ten assessed COE alone, two assessed MSE alone and one RCT compared COE alone to COE with toluidine blue staining. Results showed that COE has variable sensitivity values (0.50-0.99) but high specificity (>0.80). MSE had low sensitivity values (0.18 and 0.33) and higher but variable specificity (0.54 and 1.0). A RCT found a higher oral cancer detection rate when combining COE with toluidine blue staining compared with COE alone (29,93). This systematic review (29) concluded that the current evidence base for COE is limited but has shown good sensitivity and specificity in some studies and, as above, may reduce mortality in high risk populations (29). There was insufficient evidence on the test accuracy of MSE to recommend it as part of a national screening programme (29,93).

A more recent systematic review in 2015 by Warnakulasuriya et al. was undertaken to evaluate the effectiveness of PMD and oral cancer screening programmes in Europe (108). A total of sixteen European studies between the years of 1980 and 2014 were included. All of the studies used COE as the screening method. None of the studies were RCTs and nine of the studies were purely descriptive and had not analysed the outcome, therefore the validity of their data could not be evaluated. Only one European study had reported long-term follow up data after screening. This systematic review concluded that there were no consistent results across the studies reviewed and, as in line with other reviews, suggested that opportunistic screening in dental practices or selective screening of high-risk patients may be beneficial (93,108).

The Global Oral Cancer Forum recently published a review on the current international status on oral cancer screening in 2017 (93) that summarises much of the evidence that has been discussed in this section. In conclusion of the evidence, although there is plentiful research into oral cancer screening, there has only been one evaluation of a screening programme, which is the RCT by Sankaranarayanan (104-107) and that itself had a high risk of bias (15). Overall, it seems that oral cancer screening using COE is feasible, has been shown to have good validity in many studies, and may reduce mortality in high-risk groups. The evidence appears to be in general agreement that opportunistic and selective screening of high-risk groups has the potential to be a successful and cost-effective oral cancer screening method. Further research is needed into the natural history of oral cancer, different types of screening tests (see the next section) and ideally screening programme based RCTs (93).

3.3.6. Cost-effectiveness

Little is known about the cost-effectiveness of oral cancer screening (109). The one available RCT on oral cancer screening by Sankaranarayanan (104-107) which has been discussed, did undertake a costing analysis as part of their research (110). This showed that oral cancer screening using COE may be cost-effective in high-risk groups. The cost per life-year saved was US$835 for the whole population and US$156 for high-risk groups (93,110). This also shows that utilising non-dental or non-medical health care workers can be cost-effective. In 2006 Speight et al. used a decision-analysis model to determine incremental costs of alternative oral cancer screening programmes carried out in primary care environments in the UK (109). This showed that the cost per life-year saved for opportunistic selective high-risk oral cancer screening was £22,850, which is considered value for money by the National Health Service (NHS) in the UK, suggesting this type of screening may be cost-effective (109).

3.3.7. The role of the General Dental Practitioner (GDP)

As discussed, oral cancer screening can be an effective secondary prevention tool for early detection of oral cancer and PMDs, particularly in the form of opportunistic screening targeted at high-risk groups (15,93,108). Opportunistic screening is screening a person for a disease when they attend a clinic for another reason (87,88) and in the case of oral cancer screening, this is most likely to be carried out by a GDP or other OHPs when a patient attends the practice for a routine examination or treatment session. Unfortunately, a study by Netuveli et al. in 2006 showed that high-risk patients (tobacco and/or alcohol users) are less likely to be regular dental attenders than low-risk patients (111). Hence, "the greater the risk of oral cancer, the

lower the probability of regular dental check-ups" which has been described as the 'inverse screening law' (111). These patients may be more likely to attend only when in pain, therefore it is important that opportunistic screening is also undertaken at emergency appointments. A short review in the Journal of the American Dental Association (JADA) describes that a comprehensive oral cancer examination should take just 90 seconds, based on methods recommended by WHO (112), therefore can realistically be incorporated into every dental visit.

Oral cancer can take various forms, however typical clinical features to be aware of include (18):

- White lesion
- Red lesion (erythroplakia)
- Mixed red/white (speckled) lesion
- Granular ulcer with raised/rolled margins
- Lump/swelling
- Verrucous lesion
- Induration
- Abnormal vasculature
- Pain or numbness
- Non-healing extraction socket
- Unexplained mobile teeth
- Cervical lymphadenopathy
- Dysphagia
- Weight loss

The BDA released a management strategy for dental practice on opportunistic oral cancer screening in 2000 which outlines that a dentist's duty of care includes an obligation to examine the whole mouth (30). It highlights the ever-increasing medico-legal importance of this responsibility, but more importantly the unique opportunity that dentists have to reduce oral cancer mortality through opportunistic oral cancer screening (30). It is important to remember that the obligation of a GDP does not end at screening; the GDP must also refer suspicious lesions to the appropriate specialists for diagnosis in a timely manner (17,18). Most local areas will have specific referral forms for suspected oral cancers, however if there is no pro-forma and a traditional referral is being made, it must be stated that the referrer is suspicious of a diagnosis of oral cancer. In 2000, NHS England set out the 'NHS Cancer Plan' which outlined a national target for all suspected cancer referrals to be seen within two weeks (113). The National Institute for Health and Care Excellence (NICE) Guidelines in 2015 recommend guidelines for when a suspected oral cancer pathway referral should be made (114) (Table 2).

Guidelines for suspected oral cancer referral
Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for oral cancer in people with either: • unexplained ulceration in the oral cavity lasting for more than 3 weeks or • a persistent and unexplained lump in the neck
Consider an urgent referral (for an appointment within 2 weeks) for assessment for possible oral cancer by a dentist* in people who have either: • a lump on the lip or in the oral cavity or • a red or red and white patch in the oral cavity consistent with erythroplakia or erythroleukoplakia
Consider a suspected cancer pathway referral by the dentist (for an appointment within 2 weeks) for oral cancer in people when assessed by a dentist as having either: • a lump on the lip or in the oral cavity consistent with oral cancer or • a red or red and white patch in the oral cavity consistent with erythroplakia or erythroleukoplakia

Table 2. NICE Guidelines for suspected oral cancer referral (NG12) (114

**This guideline has been criticised that it could possibly lead to delayed oral cancer diagnosis as there is not a defined referral pathway between GMPs and GDPs. More prompt diagnosis could be achieved through direct referral from GMPs to specialists in secondary care. Grimes et al undertook a retrospective audit of suspected oral cancer referrals in a UK Oral and Maxillofacial Surgery department which found that out of nine referrals that met the criteria in NG12 guidance recommending initial referral to a dentist, one of these patients was subsequently diagnosed with oral cancer. Although a small sample size, these results show that potentially 1 in 9 patients may have their oral cancer diagnosis delayed. The authors also raised the issue that not all adults are registered with an NHS dentist (115).*

But what are dentist's opinions and perceptions on their role in oral cancer screening? A Spanish study in 2008 surveyed dentists and found that 95% felt dentists are qualified to perform oral cancer examination but only 50% felt their oral cancer knowledge was current (116). A more recent 2013 study in Malaysia promisingly showed approximately 85% of dentists' report performing oral cancer examination either always or occasionally and 82.5% described themselves as confident to do so (117). A different study in Northern-Germany, also in 2013, revealed slightly different opinions from dentists; although 71.3% felt dentists are qualified to perform oral cancer exams, only 37.2% felt that most dentists are adequately trained to do so, and only 49.1% described their knowledge of oral cancer as current. Disappointingly, only 32.4% reported always performing routine oral examination at initial appointment (118). Overall the evidence appears to show that although dentists feel they are qualified to perform opportunistic oral cancer screening, many do not feel confident in their own knowledge and abilities to do so. This highlights a need for further education in oral cancer screening aimed at both undergraduate and postgraduate dentists.

With regards to patients' perceptions of oral cancer screening in dental practice, a previously mentioned cross-sectional study in 2012 revealed that only 14% of patients were aware that their GDP routinely screens for oral cancer, yet 92% of patient wish to be told that oral cancer screening is taking place (21). This further supports the role of a GDP in oral cancer screening.

3.3.8. Educational resources aimed at GDPs/GPs on oral cancer detection/screening

As discussed, GDPs and other HCP's knowledge and confidence in oral cancer screening is often suboptimal (116-118). The Internet is an extremely widely used platform for accessing knowledge by both patients and HCPs (119). There are various web-based educational resources on oral cancer screening and these have been summarised and assessed for quality in a recent paper by Varela-Centelles et al. The authors found that the overall quality of the information in HCP-addressed websites was of a high standard, particularly in the following four websites (119):

- BC Cancer Agency: www.bccancer.bc.ca
- British Dental Association: www.bda.org
- Oral Cancer Foundation: www.oralcancerfoundation.com
- www.ocEdr.org: Oral Cancer Education and Research Centre (WHO C-C on Oral Cancer)

Selection of reliable websites for oral cancer screening education may improve the present gaps in knowledge of HCPs (119).

3.3.9. Key point

Oral cancer screening is a key aspect of secondary prevention and involves using oral examination or simple tests to clinically detect PMDs or oral early cancer in generally asymptomatic patients. The cumulative evidence shows that opportunistic screening of high-risk groups may be cost-effective and successful in reducing oral cancer mortality. GDPs therefore have an integral role in oral cancer screening however evidence has highlighted a need for further education in this area. Various educational web-based resources are available for both GDPs and GPs on oral cancer screening. Patients should be informed oral cancer screening is taking place in dental practices as this has been found to improve satisfaction and awareness.

3.4. Early detection aids

As discussed, COE is the main method and gold standard for oral cancer screening, however there are several adjunctive diagnostic aids that have potential to be utilised in oral cancer screening (33,93,102,103,120). The main adjunctive techniques are; visual staining (toluidine blue), light-based systems (chemiluminescence, tissue fluorescence imaging, tissue fluorescence spectroscopy) and exfoliative cytology/brush biopsy. These are summarised and described in Table 3.

3.4.1. Summary of main adjunctive techniques

Technique	Examples	Description
Vital tissue staining	Toluidine blue (TB)	• Also known as tolonium chloride, TB is believed to stain nucleic acids which are theoretically more abundant in dysplastic and malignant cells. • Positive staining is dark royal blue. • It has been used since the 1980s to highlight dysplastic and malignant lesions as well as to demarcate the extent of a lesion before surgery.
Light-based systems: Chemiluminescence	Vizilite and Vizilite Plus© Microlux/DL©	· Visual inspection of oral mucosa with chemiluminescent blue/white light after oral rinse with 1% acetic acid solution. · Normal epithelial cells will absorb the light and appear blue whereas abnormal epithelium will reflect light and appear bright white, or 'acetowhite.' · This is thought to be due to the higher nucleus/ cytoplasmic ratio in dysplastic and malignant epithelium.
Tissue fluorescence Imaging	VELscope© Vizilite Pro© Identafi©	· Exposure of tissues to a specific wavelength of light causing autofluorescence of cellular fluorophores. · VELscope© & Vizilite Pro© emit intense blue excitation light (400 to 460nm). · The presence of cellular atypia will change the concentration and distribution of fluorophores, which will affect how the tissue reacts to the light, hence changing the colour that is visualised. · In the oral mucosa, abnormal tissue will demonstrate loss of fluorescence and appear darker in comparison to healthy tissue.

Technique	Examples	Description
Tissue fluorescence Imaging (continued)		• IdentafiÒ has three light sources; traditional white light, violet light 405nm that detects autofluorescence similar to that in VELscopeÒ & Vizilite Pro® and a green-amber light (540-575nm) to demonstrate vascular changes by enhancing contrast and overall reflect light from multiple tissue planes, in similar fashion to the contrast enhancement in Narrow Band (NBI) imaging. • The value of visualising vasculature is based on the principle that increased angiogenesis is found in oral cancer.
Tissue Fluorescence Spectroscopy		• Exposure of tissues to various excitation wavelengths. • Spectrograph receives, records and analyses data eliminating any subjectivity. • Currently it's use is limited to evaluation of previously identified small mucosal lesions.
Brush cytology (brush biopsy)	OralCDxκ	• Collection of a trans-epithelial sample using a non-lacerational device. • Samples are fixed onto a glass slide or sent in liquid-based fixatives and stained with a modified Papanicolau test. • The cell block method can be used to prepare cytological material so that it can be processed and viewed as a histology section. Cell block increases the cellular yield and improves diagnostic accuracy (123) • If results come back as 'positive' or 'atypical' they must be referred for traditional scalpel biopsy. • Is not an alternative for scalpel biopsy.
In vivo confocal microscopy	Reflectance confocal microscopy: Vivascope 1500κ Vivascope 3000κ	• Non-invasive technique of imaging superficial soft tissues to approximate depths of 200-300 κm (124). • Offers opportunity for 'real-time' inspection at a microscopic level (125). • A light source is focused onto a small illuminated spot within the tissue called a 'voxel.' Light from this voxel is detected and forms a pixel. Multiple pixels form an image in a process known as 'optical sectioning' where tissue may be non-invasively sectioned, as in conventional light microscopy (124). • Currently, the main clinical applications are in the fields of dermatology and ophthalmology (124).

Table 3. Early detection aids (103,121-125)

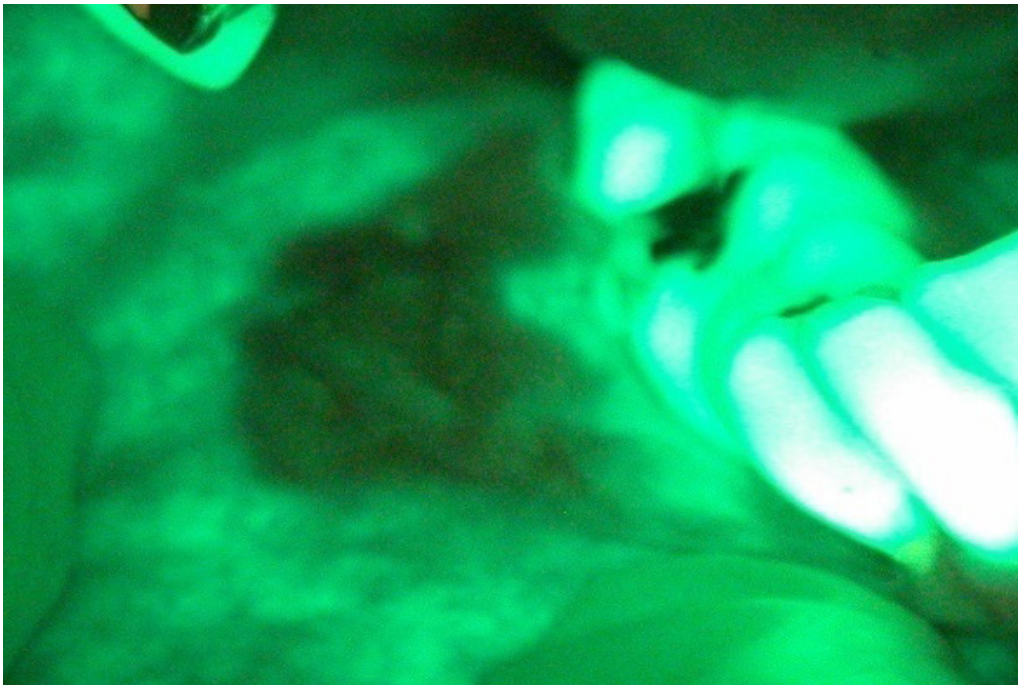

Fig. 18 Squamous cell carcinoma on the right buccal mucosa (dark zone due to loss of fluorescence of the lesion)

3.4.2 Evidence for adjunctive techniques

A systematic review of detection aids for oral cancer by Lingen et al. in 2008 concluded that none of the adjunctive techniques have sufficient evidence to support their use in oral cancer screening when compared to COE alone (103). Many of the studies evaluated the techniques in a diagnostic fashion in already identified oral lesions, rather than as screening tools (103). There was a further systematic review in 2008 carried out by Patton et al. into adjunctive techniques for detection of oral cancer and PMDs (120). This found that the largest evidence base was for TB and that this may be effective as a diagnostic tool in high-risk patients with identifiable oral lesions, however there was no evidence to support its use as a screening tool (92,120). There was lack of evidence of the adjunctive techniques use as detection tools in primary care and overall the review concluded that there is insufficient evidence to support their use (120). A 2017 review published in the British Dental Journal (BDJ) discussed diagnostic adjuncts for oral cancer and pre-cancer detection that can be utilised chairside in clinical practice and that may assist GDPs in earlier referral to specialists.
This highlighted that several systematic reviews into various adjunctive techniques in early detection in oral cancer have concluded that although sensitivity is moderately good, specificity is poor and false positives can cause unnecessary patient anxiety. ViziLite testing has been shown to have low sensitivity for the detection of high-risk lesions and various studies have revealed TB can identify high-risk oral premalignant lesions. However, sample sizes have been small and there are no long-term follow up studies (126).

Most studies have utilised single tools and therefore it is difficult to compare outcomes of different techniques. One study that examined several tools in a single cohort of patients and compared their efficacy is Awan et al. which reported improved specificity through combining autofluorescence, chemiluminescence and TB (127).

A recent Cochrane systematic review and meta-analysis in 2015 estimated the diagnostic accuracy of early detection aids for detection of oral cancer and PMDs of the lip and oral cavity, in people presenting with clinically evident lesions (128). 41 studies were included in the review, including vital staining, cytology and light-based detection. None of the studies were deemed as low risk of bias in all the domains assessed. The authors of the review concluded that none of the adjuncts to visual examination could be recommended as replacement for scalpel biopsy and histopathological examination (93,128). Cytology appeared to have the highest sensitivity and specificity therefore may offer the most potential, however further studies are warranted (93,128). As this review was estimating diagnostic accuracy, there was no evidence supporting adjunctive techniques as a screening tool for oral cancer.

A 2016 review by Maher et al. analysed the current scope and evidence for applications of in vivo confocal microscopy (CM) in diagnosing and managing patients with oral mucosal pathology. Of the 25 included papers, there was two case-control studies and one cross-sectional study, with the remainder being case reports or case series. Reflectance CM (RCM) was the most commonly used type of CM. Seven papers discussed the use of in vivo CM in oral malignancies and six papers discussed it's use in oral dysplasia, however sample sizes were small (124). A further 2016 systematic review by Lucchese et al. analysing the literature on RCM found three articles on oral precancerous lesions and oral cancer. A study by Maitland et al. found that the confocal images in normal tissue, oral dysplasia and oral cancer correlated well to the subsequent histology, however again, the sample size was small (125). Both reviews concluded that although there is promising potential for CM to be used for non-invasive detection of PMDs and oral cancer, the current evidence is limited and further research is required (124,125).

A more cost-effective alternative to CM is high-resolution microendoscopy. This uses a fiber-optic probe to obtain high-resolution fluorescence images of tissue without the need for complex scanning systems. It uses a low-cost light-emitting diode to provide illumination and a camera to capture high-resolution digital images on a computer. Muldoon et al. has published promising data for the use of microendoscopy in early detection of oral cancer (126,129).

3.5. Biopsy and histopathology

Despite continued research into adjunctive diagnostic aids for oral cancer, as we have described above, scalpel biopsy and histopathology remains the gold standard for oral cancer diagnosis (102,120,128,130). If an oral lesion is suspected to be malignant or premalignant, a biopsy should be carried out by an appropriate specialist in secondary care (130). An incisional biopsy is the biopsy of choice as it still allows for visualisation and definitive management of the lesion upon diagnosis (130-132). Excisional biopsies should be reserved for when the clinician is almost certain the lesion is completely benign (eg. Fibro-epithelial polyps, mucoceles) or if the lesion is so small that incisional biopsy would be almost impossible (131).

There are two types of incisional biopsy; traditional scalpel biopsy and punch biopsy. A traditional scalpel biopsy is usually performed using a number 15 blade to create an elliptical incision of adequate depth and of length to width ratio of 3:1. This ellipse is then excised by gently holding one end of the ellipse with tissue forceps and dissecting it out using the scalpel (130,132,133). Alternatively, a punch biopsy is a circular blade attached to plastic handle, which

comes in various sizes from 2-6mm diameter, mostly commonly used are 4 or 6mm. The circular blade is advanced into the oral tissue with continuous rotational pressure and the resultant cylinder of tissue is grasped at the base with tissue forceps and a scalpel used to excise it (130) Depending on the anatomical site of the biopsy, both techniques are completed by suturing the resultant wound using an appropriate resorbable suture. Table 4 outlines a stepwise approach to undertaking an incisional biopsy. There is debate as to the preferred technique; traditional elliptical biopsies have a larger area of epithelium for pathological assessment and are easier to embed during processing, however it has been shown that punch biopsies contain fewer artefacts that in traditional biopsies (134).

Stage	Procedure
1	Appropriate consent gained for biopsy procedure including possible risks and benefits
2	Identify appropriate area to biopsy (see below)
2	Administer appropriate local anaesthetic
3	Scalpel biopsy technique: • Number 15 blade is used to create an elliptical incision of adequate depth and of length to width ratio of 3:1. • This ellipse is then excised by gently holding one end of the ellipse with tissue forceps or suture and dissecting it out using the scalpel Punch biopsy technique: • The circular blade of the punch biopsy device is advanced into the oral tissue with continuous rotational pressure. (Consider deep tissue structures – nerves / vessels etc as the incision is blind) • The resultant cylinder of tissue is grasped at the base with tissue forceps and a scalpel used to excise it.
4	Immediately fix biopsy sample in a transport medium (10% phosphate buffered formalin)
5	Place appropriate resorbable sutures if anatomy allows, otherwise alternative haemostatic techniques such as bi-polar cauterisation or silver nitrate can be utilised.
6	Confirm haemostasis before the patient leaves the surgery.
7	Deliver post-operative instructions

Table 4. Step-wise approach to incisional biopsy

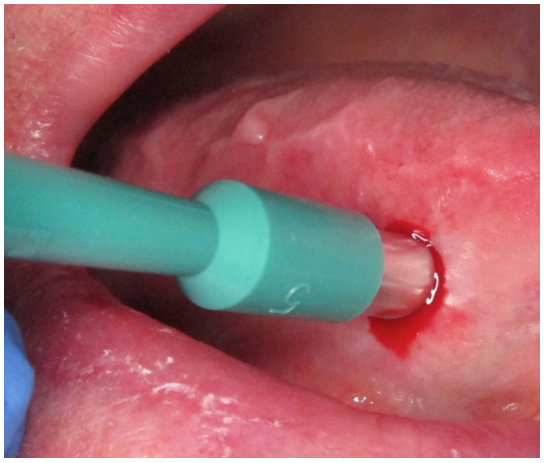

Fig 19. Punch biopsy on the right ventral surface of the tongue

For a suspected malignant lesion, an incisional biopsy should be taken from the margin of the lesion and should ideally include some clinically normal epithelium (Figure 5). If confirmed as malignancy, this allows for comparison and aids confirmation that the tumour is arising from the overlying the epithelium (130). In addition, it may allow visualisation of the invasive tumour front; there is increasing evidence that the cells are the invasive front are the most aggressive and are a major prognostic factor for oral cancer (130,135). The centre of the suspected tumour should be avoided as this may contain necrotic tissue or ulceration hence be of less diagnostic value (particularly as the primary invasive growth is at the advancing lesion margin) (130,131). For a suspected premalignant or dysplastic lesion, then an incisional biopsy should be taken from the most suspicious part of the lesion, for example an area of speckling, erythema, induration, or in the case of a leukoplakia, the densest or most verrucous area (Figure 6) (130,132) If TB is available to the operator, application of TB may help to indicate the optimal biopsy site ie. darkly stained region.

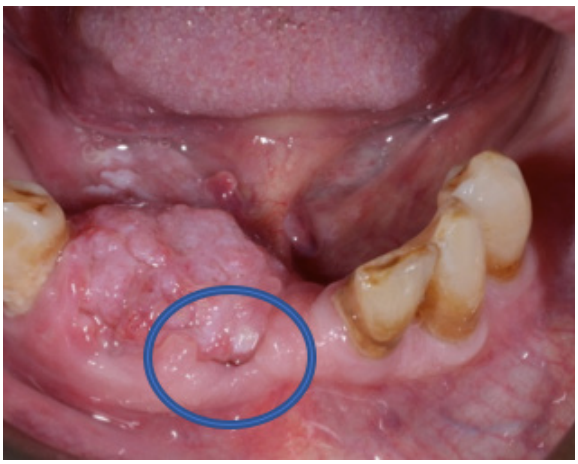

Fig 20. Example of location for incisional biopsy of suspected malignancy

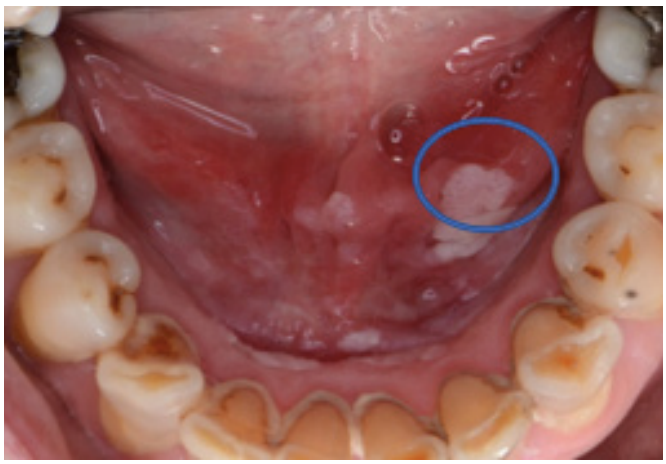

Fig 21. Example of location for incisional biopsy of suspected dysplastic lesion

Histopathological assessment with confirm or exclude the presence of malignancy. The most common malignancy of the oral cavity is oral squamous cell carcinoma (OSCC). An incisional biopsy can only give limited information on the tumour, such as degree of differentiation (136). A multi-disciplinary team approach will then be adopted to manage the patient appropriately, whether this be with curative or palliative intent. Imaging techniques including radiographs, CT (computed tomography) scans, MRI (Magnetic resonance imaging) scans and ultrasound scans are usually used to aid diagnosis, treatment and tumour staging (102). If the patient undergoes surgical excision of the tumour +/- neck dissection, this will also contribute to tumour staging. The universal classification of tumour staging is the TNM system first developed by the International Union Against Cancer 1988 (136).

The histopathology of PMDs is variable depending on the specific type of lesion. PMDs have an increased risk of malignant transformation however are not necessarily dysplastic. Oral epithelial dysplasia (OED) is defined by WHO as 'a spectrum of architectural and cytological epithelial changes, associated with an increased risk of progression to OSCC' (137).

Traditionally, OED is classified into three grades of severity; mild, moderate and severe. There are three main factors in determining the grade of dysplastic lesion; cytological atypia, architectural disturbance and the number of thirds of the epithelium in which atypia is found. Cytological changes include abnormal variation in nuclear and cell size and shape, increased nuclear to cytoplasmic ration, atypical mitotic figures and hyperchromatism. Architectural changes include drop-shaped rete ridges, irregular epithelial stratification, loss of basal cell polarity. Traditionally, mild dysplasia is confined to the lower one-third of the epithelium exhibiting cytologic and/or architectural atypia, moderate dysplasia exhibits atypia extending across the lower two-thirds of the epithelium and severe dysplasia/carcinoma in situ can exhibit atypia across entire thickness of the epithelium (138).

Dysplasia grading is at risk of subjectivity and the intra-rater and inter-observer reproducibility is poor, therefore a binary grading system has been suggested. This binary system is two-tiered; categorising oral epithelial dysplasia into low-grade and high-grade dysplasia. Table 4 outlines the overlap between the WHO grading system and the binary system. Kujan et al described the cut-off between low-grade lesions and high-grade lesions as 4 architectural changes and 5 cytological changes, with these features being associated with disease progression (138). Although the binary system is not officially validated; pathologists will now often state both systems on their reports.The most up to datehistological classification of OED as defined by WHO, is summarised below (137).

WHO grading system	Binary system
Mild dysplasia	Low-grade dysplasia
Moderate dysplasia	
Severe dysplasia	High-grade dysplasia

Table 5. Oral epithelial dysplasia grading systems (89)

There is no universal consensus on how to manage OED. A review on the management of OED by The World Workshop on Oral Medicine (WWOM IV) in 2007 concluded that due to a lack of randomised controlled trials, evidence-based recommendations could not be given for surgical management of oral dysplastic lesions (139). However, there is general opinion that mild OED can be monitored closely unless there is high suspicion with regards to clinical features or patient risk factors. Patients with severe OED should be offered complete excision of the lesion, unless the lesion is extensive and would compromise function when close monitoring should be undertaken. The management of moderate OED is more of a grey area for clinicians and the binary system is aimed to help address this. The literature generally suggests to offer excision of these lesions, although close monitoring of moderate OED is also acceptable depending on clinical and patient factors (140). The histology cannot be taken in isolation; clinicopathological correlation and patient preference are essential for all management decisions.

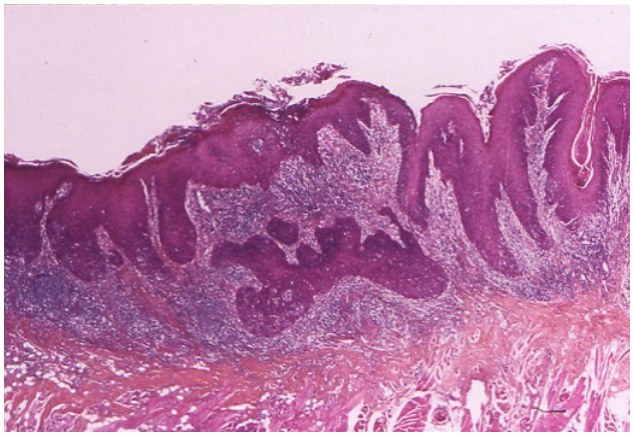

Fig. 22 Keratosis without dysplasia

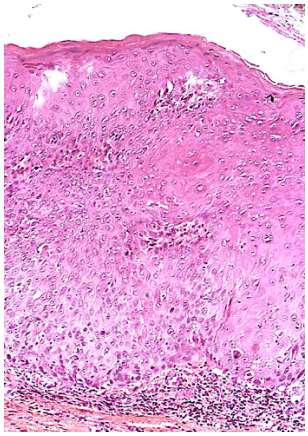

Fig. 23 Moderate dysplasia

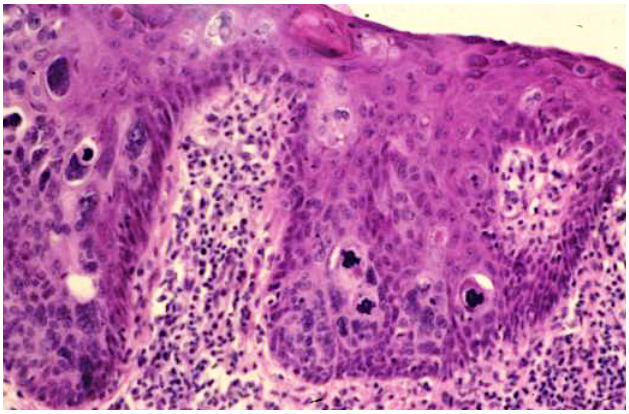

Fig. 24 Severe Dysplasia

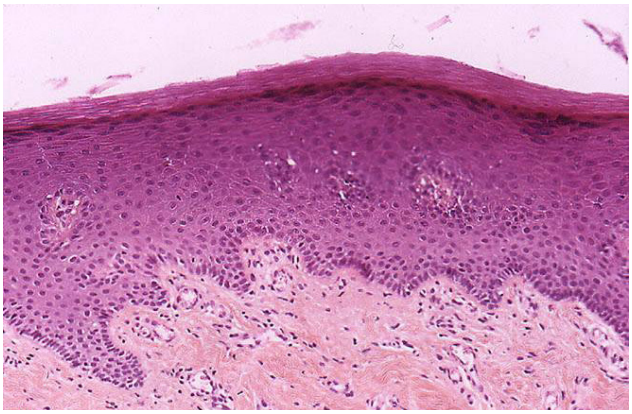

Fig. 25 Squamous Cell Carcinoma

3.6. Key points

- There is increasing research into the use of adjunctive detection aids for oral cancer including vital staining, chemiluminescence, tissue fluorescence and oral cytology.
- However, there is no evidence to support their use as screening tools and the current evidence base does not recommend them as a replacement for scalpel biopsy and histopathological examination.
- An incisional biopsy from the margin of the lesion is recommended for suspected malignant lesions or incisional biopsy from the most suspicious area of a suspected PMD.

The future?

As established, secondary prevention of oral cancer is the early detection and management of oral cancer and potentially malignant disorders, with the goal of slowing or stopping disease progression at an early stage (7-9). The fact that most oral cancers are preceded by a detectable PMD, gives an opportunity for this early detection. As discussed, the current evidence for oral cancer screening is limited, although supports the effectiveness of opportunistic screening of high risk groups using COE. Some studies have suggested that molecular markers could be used a screening tool for oral cancer; at present, there is no evidence to support this however there are implications for future research. (93,95).

Molecular markers hold the potential to act as objective predictors of PMDs and their risk of malignant transformation. This is an important and exciting prospect, as the reliability of the current clinical and histopathological methods to predict malignant change is low. There are various categories of molecular markers that have been implicated in oral cancer and PMDS, for example DNA ploidy status, loss of heterozygosity, proliferations markers such as Ki67, epigenetic events, markers of DNA damage and stem cells (9,136). There is evidence that the initiation and propagation of OSCC is related to a subpopulation of tumour cells known as cancer stem cells (CSC) (142,143). Therefore there is potential to develop CSC markers which may be used to predict malignant transformation. There are a number of studies into the presence of these CSC markers in PMDs and OSCC, for example the identification of Bmi1 (144,145). Although there is a plethora of research into molecular markers, the difficulty lies with translating this into our clinical patient care. The British Journal of Oral Cancer published guidelines in 2005 for the conduction of tumour marker prognostic studies (REMARK) which will help guide future research (146).

Secondary Prevention in Oral Cancer Key Points

- Secondary prevention of oral cancer is the early detection and management of oral cancer and potentially malignant disorders, with the goal of slowing or stopping disease progression at an early stage.
- Public education on oral cancer is an essential part of secondary prevention. This includes increasing awareness of the early signs of oral cancer and how to perform mouth self-examination.
- Increasing public awareness of a GDPs role in oral cancer screening and detection may assist in compliance with dental attendance and seeking the opinion of a dentist if there is any suspicion or doubt that something is wrong in the oral soft tissues such as a non-healing ulcer.
- Social media and advertising may also have a role in increasing public awareness.
- Oral cancer screening is a key aspect of secondary prevention and involves using oral examination or simple tests to clinically detect PMDs or oral early cancer in generally asymptomatic patients.
- Opportunistic screening of high-risk groups may be cost-effective and successful in reducing oral cancer mortality.
- GDPs have an integral role in oral cancer screening however further education is needed in this area.
- Adjunctive detection aids for oral cancer exist including vital staining, chemiluminescence, tissue fluorescence and oral cytology, although these need to be tested in primary care facilities.
- However, traditional scalpel biopsy and histopathological examination is still gold standard. An incisional biopsy from the margin of the lesion is recommended for suspected malignant lesions or incisional biopsy from the most suspicious area of a suspected PMD.
- Molecular markers hold the potential to act as objective predictors of PMDs and their risk of malignant transformation and hence a screening tool; although further research is needed.

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4. Tertiary prevention in oral cancer

4.1. Introduction

Tertiary prevention may be defined as the alleviation of disability or sequalae resulting from disease, in order to improve the final outcome of the illness, management and rehabilitation inputs, aiming to restore the patient to a functional, satisfying and where possible, self-sufficient role in society. Tertiary prevention is therefore aimed at improving the prognosis, quality of life and final outcome for affected individuals by providing the best available treatment and rehabilitation programmes available.

Moreover, for those who have already been treated for cancer, the prevention and early diagnosis of either recurrence or a later second primary malignant tumour is also considered as tertiary prevention (1).

Elimination of the main risk factors, tobacco and alcohol, at the point of diagnosis and treatment of oral cancer has been shown to:

- decrease the recurrence and second primary tumour risk
- improve survival after primary treatment (2).

Educational interventions and risk factor modifications (eg. smoking cessation for those who continue to smoke inspite of a malignant diagnosis), as well as diagnostic techniques that are also valid for tertiary prevention, were addressed in Chapters 1 and 2.

In this chapter, we will focus on the types of therapies available for the treatment of oral cancer, as well as dental management before, during and after cancer therapy. We are aiming to improve quality of life and prevent late complications linked to the cancer, its diagnosis and its short, medium and long term management.

4.2. Survival of oral cancer patients

Patient survival rates following oral cancer diagnosis have remained stable for many years at around 50% at 5 years, but in the last decade have improved to approximately 60% (3). This slight improvement in survival has been attributed: to early cancer identification and diagnosis, a better understanding of the biology of local progression, treatment of metastatic lymph nodes in the neck and the use of radiotherapy and / or adjuvant chemotherapy (3,4).

Other factors that have been suggested to have also contributed to improving survival rates include:

- improved pre-operative diagnostic information collection with computed tomography and magnetic resonance imaging studies,
- wider surgical resections due to the availability of free flap reconstructions,
- increased use of adjuvant radiotherapy and combination radio-chemotherapy regimens with or without additional cetuximab (epidermal growth factor receptor (EGFR) inhibitor) in addition to conventional chemotharapeutics, the usual use of imaging modalities during follow-up and the introduction of a multidisciplinary team approach (5).

4.3. Oral cancer treatment

The treatment of oral cancer requires management by a multidisciplinary team involving surgeons, radiation (& chemo-) oncologists, Speech & Language rehabilitation, Occupational Therapists, primary care oral specialists and others.

The ultimate goal of cancer treatment in the oral cavity is to eradicate the primary lesion, preserve or restore the anatomical structures and functions as far as possible, while minimizing the sequelae of treatment and finally, preventing any new primary or secondary cancer recurrence / formation. To achieve these objectives, current treatment modalities include surgery, radiotherapy, chemotherapy, combined modality treatments, along with primary and secondary prevention strategies around changes in lifestyle and chemoprevention (4,6,7).

After the initial diagnosis, complementary imaging studies will usually be conducted (including Computed Tomography, PET scans, Magnetic Resonance Imaging) and staging (progression of the cancer) using TNM Classification will be established. The 8th edition of the American Joint Comiteee on Cancer (AJCC) Tumour Node Metastasis (TNM) staging system was implemented in January of 2018 and introduced major modifications in the area of head and neck squamous cell cancer (HNSCC) staging (Table 1):

- important T and N modification for oral cavity cancer,
- the introduction of clinical and pathological stages for neck disease,
- a new HPV-16-positive HNSCC classification (8).

	7th edition AJCC		8th edition AJCC
T category		**T category**	
Tx	Primary tumor cannot be assessed	Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor	T0	
Tis	Carcinoma in situ	Tis	Carcinoma in situ
T1	Tumor ≤ 2 cm in greatest dimension	T1	Tumor : ≤2 cm, DOI : ≤5 mm
T2	Tumor >2 cm but ≤ 4 cm in greatest dimension	T2	Tumor : ≤2 cm, DOI >5 mm and ≤10 mm or tumor >2 cm but ≤4 cm and DOI ≤ 10 mm
T3	Tumor >4 cm in greatest dimension	T3	Tumor >4 cm or any tumor DOI >10 mm
T4a	Moderately advanced local disease Lip: tumor invades through cortical bone, inferior alveolar nerve, FOM, or skin of face (ie, chin or nose) Oral cavity: tumor invades adjacent structures only (ie, through cortical bone, [mandible or maxilla], into deep [extrinsic] muscles of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus] maxillary sinus, skin of face)	T4a	Moderately advanced local disease Lip: tumor invades through cortical bone or involves the inferior alveolar nerve, FOM, or skin of face (ie, chin or nose) Oral cavity: tumor invades adjacent structures only (that is, through cortical bone of mandible or maxilla, involves the maxillary sinus, or skin of the face)
T4b	Very advanced local disease Tumor invades masticator space, pterygoid plates, or skull base and/ or encases internal carotid artery	T4b	Very advanced local disease Tumor invades masticator space, pterygoid plates, or skull base and/ or encases internal carotid artery

	7th edition AJCC		8th edition AJCC
N category		**N category**	
Nx	Very advanced local disease	Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis	N0	No regional lymph node metastasis
N1	Metastasis in single ipsilateral lymph node ≤ 3 cm in greatest dimension	N1	Metastasis in single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE-negative
N2a	Metastasis in single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension	N2a	Metastasis in single ipsilateral or contralateral lymph node ≤3 cm in greatest dimension and ENE positive or metastasis in single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension and ENE-negative
N2b	Metastasis in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension	N2b	Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE-negative
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension	N2c	≤6 cm in greatest dimension and ENE-negative
N3	Metastasis in a lymph node >6 cm in greatest dimension	N3a	Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE-negative
		N3b	Metastasis in single ipsilateral lymph node, >3 cm in greatest dimension and ENE-positive or metastasis in multiple ipsilateral, contralateral or bilateral lymph nodes, with any ENE-positive

AJCC: American Joint Committee on Cancer; DOI: depth of invasión; ENE: extranodal extension

Table 1: T and N categories modifications from the 7th edition to the 8th edition of the AJCC Cancer Staging Manual. Adapted from Ettinger K et al., (2019)(10)

However, further validation of this new classification is needed (9).

Factors influencing the choice of initial treatment are influenced by 3 factors;

- the characteristics of the primary tumour,
- the general health status of the patient,
- medical/surgical experience and preferences of the oncological team.

In selecting the optimal therapy for oral carcinoma, these three sets of factors should be considered in the initial treatment planning. The tumour factors affecting the choice of initial treatment of oral cancer are the primary location, the size of the tumour (T stage), the proximity to the maxillary bones, the condition of the cervical lymph nodes (N stage), the presence of distant metastases (M Stage), the effects of any previous treatment and the histology of the tumour (histo-type, grade and depth of invasion) (4) .

In addition, several factors related to patient characteristics are crucial in the selection of initial treatment for oral cancer. These include: patient's age, general medical condition, tolerance to treatment, patient's occupation, acceptance and compliance regarding lifestyle modification (smoking and drinking) and other socioeconomic considerations (4).

Finally, the medical/surgical factors related to the multidisciplinary team that performs the treatment are also important for the selection of the oral cancer treatment modality. Experience, technical capabilities and support services of various disciplines, including maxillofacial surgery, radiotherapy, chemotherapy, rehabilitation services, dental support and psychosocial support are all crucial to achieving a successful therapeutic program outcome (4).

4.3.1. Surgery

Considering Oral squamous cells carcinomas (OSCC), surgery remains the gold-standard first-line treatment modality, possibly supplemented by radio and/or adjuvant chemotherapy (11). Current evidence indicates that, whenever possible from a medical-surgical perspective, earliest primary surgical treatment should be attempted to enable the best chance of a definitive cure (6) . However, although surgery is the ideal primary treatment modality for OSCC, there are risk (damage) / benefit (outcome) limitations of surgery in controlling disease, including;

- local (primary site) advanced neoplasms,
- spreading (cervical lymph nodes)
- invasion of critical structures, such as the carotid artery, base of skull, orbital walls & contents or the intracranial cavity, which significantly reduces the ability to achieve an adequate control of the disease through surgery and creates increasing recovery and rehabilitation challenges (11).

The removal of oral cancer can range from minimally invasive procedures that require brief hospitalization, anesthetic time and invasive surgery (in its most ideal form- the complete removal of the whole lesion at biopsy- often referred to as a curative biopsy) to procedures that may involve significant operations that span different parts of the body, mandating prolonged hospitalization, anaesthetics, rehabilitation and recovery process (11,12).

Surgery involves complete resection of the lesion ideally with a security margin of healthy adjacent tissue and when indicated, some or all of the ipsilateral cervical lymph nodes and in some cases, can also include the contralateral ones.

Although there are controversies regarding the definition of surgical margins, currently, they are considered:

- free or negative when the tumour cells are more than 5mm from the specimen margins,
- close when tumour is 1 to 5mm apart from the margins,
- positive when there is less than 1mm free of tumour (13).

In the case of lip cancer, the location which has a better prognosis, free margins are defined by whether 0.5cm to 1cm of tissue is free of tumour cells (8).

Achieving free surgical margins is essential for loco-regional control and survival (14). In early stages, if the surgical procedure achieves an adequate resection with free margins and cervical dissection shows negative lymph nodes, there is usually little need for additional treatment. Factors that may influence the obtaining of free margins include:

- tumour subsite,
- tumour size,
- depth of invasion,
- pattern of invasion,
- previous treatment.

Due to the complexity of these tumours, clear margins are achieved in only 50% to 80% of cases and some authors suggest an intraoperative histopathological analysis of the margin tissues to ensure obtaining adequate surgical margins and minimising the need for re-operation (15).

In advanced stages, when free margins are not achieved or if there is concern over more distant unresected metastasis risk, adjuvant treatment with chemoradiotherapy has been shown to reduce the risk of recurrence (16).

Positive surgical margins are considered as an indication for surgical reoperation or adjuvant chemotherapy and near margins are an indication for radiotherapy(11).

Cervical dissection is the systematic procedure of neck lymph node removal; presence and extent of lymph node involvement being a critical component of tumour staging, treatment planning and decision guidance for subsequent oncological therapy. At the time of diagnosis, approximately 40% of patients with oral cancer have metastases to the cervical lymph nodes.

Cervical dissection can be elective or therapeutic. Elective cervical dissection is performed when lymphadenopathy is neither clinically indicated and imaging did not detect involved tissue. The removal of cervical lymph nodes in this circumstance aims to reassure / rule out the presence of hidden metastases, crucial for decision making around adjuvant therapy. By contrast, a therapeutic dissection is performed when lymphadenopathy is detected clinically or by imaging, to determine the extent of dissemination as well as the presence of extracapsular extension (suggesting the metastases have spread out beyond the lymph nodes, which are significant indicators for adjuvant chemoradiotherapy.

The decisions around when to perform clinical monitoring or to treat the clinically negative neck, as well as when to use surgery or radiotherapy, continue to be controversial. Some authors have suggested elective cervical dissection could avoid regional recurrences, while others consider this approach to be too aggressive an approach, that can result in complications and co-morbidities such as:

- shoulder dysfunction,
- neck pain, lymphoedema swelling and stiffness,
- unaesthetic neck contour changes, pain, stiffness & scarring,

and therefore recommend a more conservative clinical monitoring protocol.

There is evidence that, among patients with early stage OSCC and negative necks, elective neck dissection reduces regional recurrences and results in higher survival rates, especially in the case of OSCC of the tongue and the floor of mouth, confirming the need for elective cervical dissection in these patients (17).

The use of sentinel lymph node biopsy (SLNB) in the treatment of oral cancer is beginning to be included in the treatment guidelines, although it still does not apply universally across international boundaries. However, there has been an increase in the number of published papers on this topic in recent years, which reflects the interest in its application (18).

The sentinel lymph node (SLN) is defined as the first lymph node to which a solid tumour metastasizes. The SLNB technique is based on the premise that lymphatic flow from a lesion site is sequential and predictably flows first to the SLN, then disseminating to the rest of adjacent regional lymph nodes in the direction of flow returning to the circulation at the supraclavicular fossae. In this way, the histological state of the SLN should reflect & predict that of the other regional nodes. If the SLN is free of metastatic infiltration, the remaining downstream regional lymph nodes could also be presumed free of disease. On the other hand, if there is metastatic disease in an SLN there is a greater probability that other nodes are affected, supporting the decision to electively treat the affected nodal area (19) .

It has been reported that SLNB offers a similar precision to elective neck dissection in the detection of cervical lymph node metastasis, with equivalent survival rates in stage I and II OSCC and with lower morbidity (20). Studies comparing SLNB versus elective neck dissection have shown that SLNB is associated with better functional results of the shoulder, reduction of dysfunction in swallowing, reduction of postoperative lymphoedema, reduction in risk of injury to the lingual and mandibular marginal nerves (21,22) and length of postoperative hospital stay is significantly shortened (20).

With the technical advances in surgical procedures, extensive intraoral lesions can be successfully removed with satisfactory functional results. In addition, reconstruction techniques allow achieving favorable aesthetic solutions.

Even so, surgical procedures that affect the hard and soft tissues of the oral cavity often change the physical appearance (23). Modern surgical and reconstructive techniques allow the replacement of lost tissues and cause fewer visible scars. It is common to use soft tissue and bone replacement grafts from other locations. The size and volume of the surgical defect will dictate the need for reconstruction (6).

4.3.2. Radiotherapy

Although surgery is usually the treatment of choice, since it is associated with an increase in survival when compared with non-surgical treatment, definitive radiotherapy is reserved for those patients who cannot undergo surgery (24). It is unknown why OSCC is so responsive to primary surgery in comparison to primary radiotherapy or primary chemotherapy, which is not necessarily the case for other head and neck subsites, such as the larynx, hypopharynx, or nasopharynx, and in certain cases, oropharyngeal SCC (11).

When radiotherapy is combined with surgery, there seems to be a preference for postoperative radiotherapy; irradiated tissues having a poorer (slower) healing capacity, radiation induced fibrosis also potentially making surgery far more difficult.

Radiotherapy is indicated as postsurgical treatment in locally advanced tumours or in the face of other poor prognosis tumour factors. Indications for postoperative radiotherapy include:

- margins status,
- the presence of peri-neural or perivascular invasion,
- tumour stage (25).

It has been shown that postoperative radiotherapy after the removal of lesions in advanced stages (stages III and IV) has improved loco-regional control and survival. It has also been shown that in the case of extracapsular extension and/or positive surgical margins, concurrent cisplatin chemotherapy improves regional control and survival when compared to radiotherapy alone (16).

Acute side effects associated with head and neck radiotherapy manifests as;

- mucositis,
- pharyngitis,
- dysphagia,
- odynophagia,
- xerostomia (26).

These side effects are common during the course of standard radiotherapy and are rarely life-threatening but can be some of the most bothersome side effects from the patient's perspective (27).

Late complications of particular importance include mucosal fragility and osteoradionecrosis, due to the proximity of the maxillary and mandibular bones to the path of the radiotherapy beam; affecting their vascularity and cellular function (28).

Previous studies have described rates of osteoradionecrosis ranging from 14-18%, but recently with intensity modulated radiotherapy (IMRT) protocols have described very low rates ranging 0-6.3% (29).

The introduction of IMRT approximately 15 years ago has become the standard of care for the administration of radiotherapy in patients with head and neck cancer. IMRT allows more precise administration of radiation to the tumour by reducing radiation doses to nearby anatomical structures, such as the salivary glands, resulting in the reduction of complications such as hyposalivation, but maintaining loco-regional recurrence rates and overall survival comparable to conventional radiotherapy (26).

4.3.3. Chemotherapy

Chemotherapy is not a curative treatment modality in Oral cancer care, but may improve the prognosis when used in combination with surgery and radiotherapy in locally advanced tumours (6).

Systemic chemotherapy, as part of the primary treatment, administered in combination with radiotherapy can be classified into: induction or neo-adjuvant chemotherapy, when administered before radiotherapy; concomitant chemotherapy when administered during radiotherapy and adjuvant when administered after radiotherapy (30).

There is evidence of the benefits of chemotherapy in all these scenarios at the expense of increased toxicity related to treatment. In tumours with advanced stages (stages III and IV) the protocols may include chemotherapy or biological treatments, usually with cisplatin and cetuximab, respectively. Other drugs used include fluorouracil (5-FU), carboplatin and paclitaxel (30).

Myelosuppression and immunosuppression are well recognised secondary haematological consequences of chemotherapy. Communication with the oncological team is fundamental to design a correct therapeutic strategy for these patients.

Chemotherapeutic agents are associated with a broad spectrum of haematological side effects that include:

- anaemia,
- leukopenia,
- neutropenia,
- pancytopenia (lowered levels of all white cells),
- thrombocytopenia.

In general, the cell count begins to decrease in the first days after the administration of chemotherapy. This reduction continues to around 10-14 days, when the cell count begins to rise again. This reduction has a significant impact on white blood cells, particularly neutrophils, and when levels are significantly reduced, dental procedures should not be performed without medical counselling (31). The impact of chemotherapy on the platelet count, although less frequent and less severe, may increase the risk of bleeding during surgical procedures. If a patient needs dental treatment during chemotherapy it is essential to understand which session in the cycle the patient is in and his/her concurrent haematological status. Surgical procedures should not be performed in patients with a platelet count below 50 x109 / l (32). If the patient presents an acute dental infection or febrile neutropenia, management in conjunction with the multidisciplinary team is essential and administration of antibiotics is required (31).

Although immunosuppression related to oral cancer treatment is transient, these patients are intermittently susceptible to bacterial, viral and fungal infections during treatment (7). Oral infections in immunosuppressed patients can also be aggravated, resulting in further increased morbidity and mortality.

4.3.4. Targeted Cancer Therapy

Current knowledge of the mechanisms involved in carcinogenesis has served as the basis for the development of new therapeutic strategies, such as Targeted cancer therapy; comprising the use of drugs - biological agents - developed to attack targets in cancer cells, mainly by altering specific cell signaling pathways, using monoclonal antibodies (mAb) and small molecules (SMs) (33). One of the most studied targets in head and neck cancer, including OSCC, is the overexpression of the epidermal growth factor receptor (EGFR) (34). Numerous strategies for inhibiting EGFR have been investigated and several are in clinical use already, including monoclonal antibodies (e.g. cetuximab), tyrosine kinase inhibitors (e.g. gefitinib, erlotinib), radio-labelled antibodies, ligand-toxin conjugates and immunoconjugates. They may be used in combination with other conventional therapies, as radio and chemotherapy (35). EGFR inhibitors affect signal transduction pathways, inhibiting cell proliferation. Cetuximab (Erbitux®) is a monoclonal antibody with high specificity for EGFR that blocks its activity by binding to the receptor, inhibiting tumour growth and making the tumour more sensitive to subsequent radiotherapy (30). Cetuximab is usually used in combination with standard radio and/or chemotherapy. There is evidence that adding monoclonal antibodies against EGFR to standard therapy can improve loco-regional control and overall survival of OSCC (36).

Adverse effects of cetuximab are usually moderate, with flu-like symptoms, headache, fever, chills or dizziness at the time of infusion. The other most common adverse effect is the transient cutaneous rash which usually appears/manifests two weeks after the start of treatment and resolves spontaneously (30).

In general terms, the adverse effects of targeted therapies are less severe compared to conventional chemotherapy, however, when combined with chemotherapy, these effects, such as oral mucositis, can be even more severe (30).

4.4. Oral cancer patient management

4.4.1. Assessment before starting oral cancer treatment

Proper dental management, before, during and after cancer therapy, can significantly reduce the complications associated with oral cancer therapy and consequently improve the patient's quality of life (26). Priority therefore should be given to dental care in the care path to patients diagnosed with oral cancer. Few Hospital Centres have the resources needed to provide integral dental care and often this care must be provided by the patient's dentist concurring with the advice of the patient's oncology team. There is a vital opportunity for dentists and their teams to play an essential role in their community, as patients generally prefer to be treated by their own dentist, thereby avoiding having to travel to the Hospital Head & Neck Oncology Centre, to receive oral treatment (27).

The need to start oncological treatment as soon as possible often requires modifications to an ideal dental treatment plan. The main objective of dental treatment is to eliminate or stabilise all oral disease and to minimize the occurrence of local and systemic complications during and after oral cancer treatment. The oncological team must provide information about the comprehensive treatment plan and the patient's prognosis. Patients often do not know or

understand the reasons for referral to and urgent treatment from the dentist. Therefore, it is important to explain the purpose of the pre-treatment oral evaluation and to inform the patient of the associated oral complications, both in the short, medium and the long term, highlighting the important role of maintenance of proper oral health.

The patient should be informed of the complications that we anticipate in the course of cancer therapy (e.g. mucositis, xerostomia, caries, etc.), and of the measures they can take to reduce the minimal adverse effects of therapy. The importance of the long-term follow-up must also be highlighted, especially with respect to the appearance of post-radiation caries and osteonecrosis. In addition, it is useful to provide written information to patients and their family.

The ideal time for a dental treatment plan in patients with oral cancer is before they initiate oncological therapy (28). Patients diagnosed with oral cancer tend to have poor oral health, and up to 97% of them usually have oral treatment needs (9). Advice on factors such as tobacco and alcohol, that may increase the risk of the appearance of adverse effects, is mandatory and it has been addressed in Chapter 1.

Before starting treatment, a systematic dental evaluation should be carried out and an oral care programme should be established to reduce the risk of complications during oncological treatment. At the time of diagnosis, most patients usually have associated dental pathologies (typically caries, periodontal and periapical disease) that must be treated before the start of therapy).

Obtaining a complete medical history is crucial for the preparation and development of the treatment plan. The clinician should review not only the patient's medical history but also previous surgeries, medications, family and social history, allergies, etc. The oncological history should include previous treatments for cancer, as these patients have a higher risk of developing secondary tumours and should be closely monitored for recurrences or new lesions in the oral cavity and loco-regionally (28).

It is important to know the diagnosis, including location, stage and grade, proposed treatment and prognosis. In those patients who are going to receive radiotherapy, the clinician must know the date of the first session as well as the simulation (a familiarisation and alignment visit for the patient without exposure to radiotherapy); ideally, all dental treatments must be completed before starting the simulation appointment (28).

The dental history and oral hygiene habits should be reviewed, including the date of the last revision for oral health maintenance. The dental evaluation should include a periodontal examination, diagnosis of caries, missing teeth, signs of odontogenic infection and previous restorations. Sensitivity to palpation and percussion and tooth mobility should also be noted. Radiological tests (panoramic, intraoral radiographic series and bitewings) may be necessary for diagnosis.

The intraoral examination should include not only a complete evaluation of the dentition but also of the soft tissues of the oral cavity and oropharynx, including the mucosa, palatine and lingual tonsils, soft palate, uvula, hard palate, gums, lips, tongue and floor of the mouth. The sublingual, submandibular and parotid glands should also be explored.

Obtaining sialometry and sialochemistry from patients, who are going to receive radiotherapy, may be useful as it can be compared with the salivary flow and composition during and after therapy. Salivary pH determination may also be useful (32), all aiding un understanding evolution of ongoing disease risk on a patient by patient basis.

Patients recently diagnosed with oral cancer need oncological treatment without delays (emergent) and treatment needs should be evaluated and prioritized (28). The priority dental treatment, before the onset of oncological therapy, should be to eliminate any conditions that could interfere with or interrupt the oncology therapy. It should focus on the elimination of possible foci of odontogenic and/or periodontal infection, through dental scaling and periodontal treatment, endodontics and dental extractions.

Maintenance of the natural dentition is always preferred option where feasible (37). Non-restorable decayed teeth, teeth with deep periodontal pockets (hopeless) or teeth with pulpal involvement with a poor prognosis that would otherwise require prolonged interventions (thereby delaying the cancer care) should be extracted. Ideally, all extractions should be performed / completed at least two weeks before starting radiotherapy, to allow re-epithelialisation and healing of the socket. The extractions should be carried out as atraumatically as possible and if feasible, with primary closure without tension, to maximise chances of clean (non-exposed) tissues for healing within the operative area. Priority should be given to those teeth included in the high doses radiation field (>50Gy) (32).

Restorable teeth with pulp involvement must be endodontically and definitively restored. Trauma sources must also be eliminated and failing restorations, fixed orthodontic appliances or removable prostheses should be adjusted or removed. A flexible mouth guard, with a thickness of approximately 6 mm, may be indicated in patients with metal restorations included in the radiation field to reduce the radiation dispersion effect, which increases the risk of mucositis (38).

It is also useful to take dental impressions just after the exodontia phase has been completed to manufacture custom trays for the topical application of fluoride, and the planning of the dental rehabilitation treatment after the oncological treatment (31).

Surgical bone resections may require the fabrication of maxillofacial prostheses, including palatal obturators, nasal, orbital or ocular prostheses. Maxillectomies typically result in oro-antral communications; to restore the floor of the nasal cavity and the roof of the oral cavity to improve swallowing and speech, surgical repair and maxillofacial prosthesis are usually needed. When prosthetic rehabilitation is planned pre-surgical diagnostic models may help.

4.4.2. Prevention and management of oral complications during oral oncologic therapy

Avoid elective treatments until the end of head and neck radiation therapy and chemotherapy. However, in the case of active infections, the oncology team should be asked for advice about the possibility of performing the dental procedure during therapy (32).

A complete blood analysis should be requested to evaluate the neutrophil and platelet counts. Treatment and be performed in those patients receiving chemotherapy without head and neck radiation, and with an absolute neutrophil count of at least 1000 cells/mL and platelets of at

least 50,000 cells/mL (32). The dentist should consult the chemotherapy calendar to schedule the dental treatment.

Non-restorable teeth included in the field of high doses of radiotherapy whenever possible should receive conservative treatment through endodontics and coronectomy. If extraction is needed, the doses administered in the radiation field must be known. Surgical trauma should be minimized and primary closure performed.

Treatments for oral cancer are associated with a series of complications including hyposalivation, increased risk of caries, mucositis, dysgeusia, dysphagia, mucosal lesions and infections (Table 1).

Oral complications related to oral cancer treatment	
Acute complications	Pain Functional impairment/disfigurement Mucositis Oral Infections (Fungal, Bacterial, Viral) Hyposalivation Dysgeusia
Late complications	Pain Functional impairment/disfigurement Oral Infections (Fungal, Bacterial, Viral) Hyposalivation Dysgeusia Soft tissue necrosis Trismus Dental Caries Osteoradionecrosis

Table 1: Oral complications related to oral cancer treatment

The design of a comprehensive treatment plan is essential to minimize the occurrence of these complications.

Early complications of oral cancer therapy result from the surgical procedures and the toxic effects of radio and chemotherapy, can affect different orofacial structures. Surgery may cause alterations in sensitivity in the oral, facial, neck or shoulder tissues. The common tingling around the scars can take months to recover (6). Some surgeries, especially in the posterior areas of the oral cavity, can produce trismus. Physical therapy (eg.Therabite) can prevent trismus from becoming permanent (6).

Although complications from chemotherapy are limited to a few weeks, the effects of radiotherapy tend to persist for months or years.

Early complications of radiotherapy include oral, oropharyngeal and gastrointestinal mucositis, hypofunction of the salivary glands, odontogenic infections, pain and neurotoxicity. Late complications may take months or years to appear and include orofascial soft tissue fibrosis,

trismus, osteoradionecrosis (39). These complications are associated with a significant loss of function and facial disfigurement, which leads to a loss of quality of life and undesired psychological effects.

Early diagnosis, treatment plan and implementation of dental treatment before, during and after radiotherapy are fundamental aspects that can improve the prognosis and improve the quality of life of patients (40) .

Oral Mucositis

Both radiotherapy and chemotherapy can result in oral mucositis (31), an acute adverse reaction that affects most patients receiving head and neck radiation therapy. In patients who receive a standard protocol of 6-7 weeks of radiotherapy, oral mucositis usually manifests 2-3 weeks after the start of treatment as an oral mucosa erythema and progresses to the development of ulcers and pseudomembranes as the radiation dose increases (41). (Figure 1) Chronic mucositis after finishing radiation therapy rarely occurs with modern regimes but remains a real possibility(42). Oral mucositis may appear earlier and can be more severe in patients receiving concomitant chemotherapy and/or treated with target therapies (41).

Fig 1: Oral mucositis during head and neck radiotherapy

Oral mucositis induced by radiotherapy is limited to areas in proximity to the path of the radiation bean (31). Although the anatomical distribution of mucositis varies according to the distribution and the radiation dose administered, non-keratinised tissues (buccal mucosa, lateral tongue, soft palate, floor of mouth) are more susceptible (41). On the contrary, oral mucositis induced by chemotherapy can affect the entire gastrointestinal tract (31) .

Oral mucositis results in severe discomfort and decreases patients' ability to eat, swallow and speak. Mucositis can also have an indirect effect on the prognosis since its presence can result in a modification or interruption of the oncological treatment protocols with radio or radio-chemotherapy (42).

Grade	Description
0	None
I (Mild)	Oral soreness, erythema
II (Moderate)	Oral erythema, ulcers, solid diet is tolerated
III (Severe)	Oral ulcers, only liquid diet is possible
IV (life-threatening)	Oral alimentation is impossible

Table 2 : Oral mucositis WHO assessment scale

The World Health Organization (WHO) classifies mucositis in 5 grades (0-IV):0 None; I (mild) Oral soreness, erythema; II (moderate) Oral erythema, ulcers, solid diet is tolerated; III (severe) Oral ulcers, only liquid diet is possible; and IV (life-threatening) Oral alimentation is impossible (Table 2).

The patient's education in oral hygiene habits is mandatory. The maintenance of good oral hygiene is one of the most effective strategies to reduce the severity and persistence of oral mucositis (38). The existence of oral pathology, e.g. caries, periodontal disease, pulp pathology and xerostomia before the start of cancer treatment has been associated with greater bacterial colonisation and severity of oral mucositis (43). Patients should also be advised to have a soft diet, avoiding irritants such as tobacco, alcohol and spicy foods (42).

Different strategies for the prevention and management of oral mucositis have been studied in oncological patients, including the use of barrier agents, chlorhexidine, aloe vera, granulocyte colony stimulating factor (GCSF), pure natural honey and combination of antibiotics and antifungals, although the scientific evidence in relation to these interventions is limited (31).

Oral cryotherapy (cooling of the mouth using ice, ice-cold water, ice cream or ice lollies/ popsicles during the drug infusion) has been shown to reduce the severity of oral mucositis in patients treated with 5-fluorouracil, however, its efficacy on mucositis induced by radiotherapy has not been proven(43,44).

Once established, the presence of oral mucositis lesions may require analgesic treatment with opiates, parenteral or enteral nutrition, and even hospitalization.

One of the most popular agents for the management of oral mucositis is benzidamine hydrochloride (Difflam or Tamtun), since it reduces the production of proinflammatory cytokines, eliminates reactive oxygen species, stabilizes the cell membrane and it has antimicrobial activity. However, its efficacy has not been conclusively demonstrated and its prescription has not been approved by the US-Food and Drug Administration (FDA) for this indication.

Within systemic therapies, palifermin, a recombinant derivative of human keratinocyte growth factor, is the only drug approved so far by the European Medicines Agency and the FDA to reduce the incidence and the severity of mucositis. The indication for prescribing palifermin is restricted to adults with hematologic malignancies who receive myelotoxic treatment and require the supply of hematopoietic stem cells. However, the FDA also proposes its application

as a complementary preventive measure in patients who are going to undergo therapeutic regimens in which the appearance of severe mucositis is very prevalent, as it happens in some radiotherapy and chemotherapy regimens involving the orofacial area. In summary, there are very few evidence-based tools to prevent and treat post-radio and chemotherapy induced mucositis in patients with oral cancer. In general, topical agents only provide symptomatic relief and there is no rigorous scientific support to recommend systemic medications or their indications are very strict (eg. palifermin).

The main recommendations for the prevention and management of the cancer patient with oral mucositis are shown in Table 3.

ORAL MUCOSITIS PREVENTION DURING ORAL CANCER TREATMENT
Routine oral hygiene care • Soft toothbrush (brushing 2-3 times a day) • Cleaning with dental floss and interproximal brushes (atraumatic technique) • Frequent rinses • Minimise denture use Avoiding irritants such as tobacco and alcohol Dietary Advice • Soft diet with low sugar and non-acidic food and drinks • Oral cryotherapy during chemotherapy (Cold fluids / solids intra orally to minimize local blood flow and thus mucosal drug exposure)
ORAL MUCOSITIS TREATMENT DURING ORAL CANCER TREATMENT*
Topical agents (eg. benzydamine hydrochloride rinses) Systemic agents (eg. palifermin)

*Low scientific evidence

Table 3: Oral mucositis prevention and treatment during oral cancer treatment.

Salivary gland dysfunction

Both radiotherapy and chemotherapy can cause salivary gland dysfunction and result in drier mouth in extreme cases xerostomia. Hyposalivation induced by radiotherapy can have a transitory or irreversible character depending on the dose of irradiation, while the hyposalivation induced by chemotherapy tends to have a more transitory character in some cases (31) .

This salivary gland dysfunction consists of a progressive reduction of the salivary flow, with both quantitative and qualitative alterations of the saliva, which becomes thicker and more

viscous, with a more acidic pH. The patient may then report xerostomia (the subjective sensation of dry mouth) and symptoms can include: discomfort, pain, difficulty in swallowing, phonation and dysphagia. The perception of dry mouth is sometimes, but not necessarily, accompanied by a reduction in the salivary flow.

Altered salivary flow may be temporary if radiation doses are low (e.g. 10 Gy); however, relatively low doses (30 Gy) can also cause irreversible changes in the salivary glands (32) . Xerostomia occurs when the dose exceeds 10 Gy and reaches its maximum expression 1-3 months after completing radiotherapy. Patients recover from xerostomia gradually (up to 1-2 years after the radiation therapy), although recovery is typically incomplete.

Saliva plays an important role in oral health. It functions by protecting against bacteria and fungi, transportation of nutrients and digestive enzymes, lubrication of the oral cavity, remineralisation of teeth, as well as aiding in chewing, swallowing and speech (45).

Generally, salivary gland hypofunction is defined as an unstimulated total saliva flow rate of less than 0.1 ml/min, and a stimulated total saliva flow of less than 0.7 ml / min. Although research in the field of hyposalivation and dry mouth is extensive, there are no established protocols for these patients based on scientific evidence (46). The management guidelines vary from the application of topical agents to the use of pharmacotherapy. It is therefore important to adapt these recommendations to each individual patient. In those who suffer from dry mouth, it is very important that they maintain a meticulous oral hygiene, as well as the application of fluoride. In addition, limited sugar intake should be advised, as well as avoiding the use of alcohol-based mouthwashes due to their dehydrating effects (38).

Intensity-modulated radiotherapy (IMRT) significantly reduces the incidence of xerostomia and leads to recovery of saliva secretion and improvements in associated quality of life (47).

Amifostine is the only cytoprotective agent approved to date by the FDA to prevent the dysfunction of the salivary glands secondary to head and neck radiotherapy; this organic thiophosphate increases unstimulated salivary flow and reduces the risk of moderate or severe xerostomia at the end of radiotherapy and up to 3 months later. The recommended dose is 200 mg / m2 administered intravenously 15-30 minutes before each radiotherapy session. The benefits of amifostine should be weighed against its high cost and side effects (i.e. vomiting, hypotension and allergic reactions) (38).

The management of salivary gland dysfunction is mainly based on two therapeutic strategies: the stimulation of the salivary glands when they are still functional, and the use of saliva substitutes (31).

There is a wide range of topical products on the market, with different forms of presentation (gels, rinses, sprays, pills), and the dentist must choose the most appropriate for each patient, however, the most important advice for the patient with dry mouth is the need to maintain hydration by drinking an adequate volume of water, approximately 1.5 L of water daily. When there is the possibility of stimulating the salivary glands, sialogogues can be used. In this case, pilocarpine is the drug of choice (5mg/ 3-4 times a day with a maximum doseof 30 mg/day); however, it is not indicated in all patients due to its adverse effects, mainly cardiovascular ones (hypotension, hypertension, bradycardia and tachycardia). In a recent systematic review and meta-analysis (48), the authors concluded that pilocarpine and cevimeline should represent

the first line of therapy in patients with hyposalivation and xerostomia induced by head and neck radiotherapy. There is very weak evidence that salivary substitutes provide some benefit. The frequent side effects of pilocarpine and cevimeline must be considered; these include nausea, sweating and increased urinary frequency, so a risk-benefit analysis should be carried out before prescribing them, as many of the patients may suffer additional morbidities and polypharmacy may interact or be influenced by sialogogues.

The main recommendations for the management of the oncologic patient with hyposalivation are shown in Table 4.

Treatment of hyposalivation following ORAL CANCER TREATMENT
• Pretreatment sialometry (comparison with post-treatment values)
• Regular consumption of water (1.5L of water daily)
• Chewing stimuli: chewing gums with xylitol (or sugar free)
• Salivary substitutes "artificial saliva"
• Solutions containing mucin, carboxymethyl cellulose, enzymes.
• Oral hygiene instructions
• Dietary advice
• Stimulants of saliva (partial loss of glandular parenchyma):
• Parasympathomimetic stimulants:
• Pilocarpine tablets 5mg / day 3-4 times a day, or drops at 2% concentration.

Table 4: Treatment of hyposalivation following therapy for oral cancer

Infections

The loss of protective functions of the oral mucosa, as well as the hyposalivation, the immunosuppression induced by the oncological treatment and the frequent use of antibiotics can lead to the appearance of opportunistic infections and superinfections, the most frequent being oral candidiasis (Figure 2). Oral candidiasis can result in dysphagia, dysgeusia, and in some cases, a burning sensation.

Fig 2. Pseudomembranous candidiasis

As prevention measures, oral hygiene instructions should be reinforced, as well as denture hygiene instructions particularly in those patients with removable prostheses; whether oral or oral and maxillofacial prostheses. The diagnosis of candidiasis must be confirmed through microbiological studies before prescribing antifungals. Oral candidiasis is preferably treated with topical antifungal agents, however, some severe cases require the use of systemic agents, even intravenously administered. The guidelines for prevention and treatment of oral candidiasis in cancer patients are shown in Table 5.

ORAL CANDIDIASIS PREVENTION DURING ORAL CANCER TREATMENT
Oral hygiene instructions - Removable denture cleaning at least twice a day - Rinses with 0.9% saline solution + sodium bicarbonate solution (1 tea spoon of bicarbonate + 1 tea spoon of salt diluted in 1 liter of water)
ORAL CANDIDIASIS TREATMENT DURING ORAL CANCER TREATMENT
• Diagnostic confirmation through culture • Preferably topical agents. e.g. Nystatin (100,000 IU) 3-4 times a day, 21 days. • Consider systemic treatment in more severe and resistant infections. e.g.: Fluconazole 50-150 mg, once a day, 7 days. • Mouthwashes with 0.12% chlorhexidine • Consider adjustment of removable prostheses

Table 5: Prevention and treatment of candidiasis secondary to oncological therapy.

Fibrosis/Trismus

Head and neck radiotherapy may produce fibrosis that presents as muscular sensibility and trismus. The prevalence of trismus in patients with oral cancer can vary from 0 to 69%. This wide variation can be explained due to factors such as trismus assessment method, tumour location and size, and oncological therapy. It should be reported that fibrosis and trismus is a potential late complication of radiotherapy and recommend daily home exercises during and after radiation therapy. At present, there is no standardized program for its management, which can be conservative with drugs (e.g. botulinum toxin) or with physical therapy (e.g. Therabite® type devices) or, in exceptional cases, surgery. None of these stretching techniques nor of the devices designed to mobilize the jaw has been clearly superior to the others nor in terms of prevention or treatment of trismus (49).

In some situations, the referral of patients to speech & language therapists may be indicated.

4.4.3. Management after oral cancer therapy

Post-radiation caries

Hyposalivation favours oral cavity colonization by cariogenic microflora. In addition, saliva loses its buffer capacity which predisposes the patient to the development of post-radiation dental caries. These tend to be aggressive cavities, rapidly evolving and are characterized by dental deterioration at the level of the cementoenamel junction (CEJ) causing tooth decoronation (Figure 3).

Fig 3: **Post**-radiation caries.

The prevention strategy of caries must begin before starting radiotherapy promoting oral hygiene. A healthy and balanced diet should be recommended, as well as avoiding cariogenic foods. Fluoridation is the method of choice to fight post-radiation caries in patients with oral cancer. Daily application of 1% sodium fluoride gel in individual trays is recommended (Figure 4) during radiation and until the acute effects of radiation on the oral mucosa disappear; then, daily fluoride rinses at 0.05% or 0.2% at weekly intervals have been suggested. Fluoride application can also be accomplished with professionally applied fluoride varnishes (e.g. 22,600 ppm) and high fluoride prescription toothpaste (eg: 5.000 ppm). The application of fluoride should continue as long as hyposalivation persists.

Fig 4: Individual trays for daily application of 1% sodium fluoride gel during radiotherapy.

The administration of antibacterial/antiplaque agents is another prevention strategy against radiotherapy induced caries. Some authors recommend the application of 1% chlorhexidine gel in patients with high salivary concentrations of streptococcus mutans(46).

A follow-up protocol must be established (e.g. every 3- 6 months), for the early detection of new or newly recurrent caries. In patients with hyposalivation and dental demineralization, the use of remineralising agents (Casein phosphopeptide-amorphous calcium phosphate) may be useful, although the evidence of its benefits in patients treated with radiotherapy is scarce and the high cost limits its application(31) .

In all cases, the risk of caries must be evaluated, based on the disease indicators, the risk: protective factor balance, the likely influence of therapy on protective factors (eg. salivary function) and an individualized treatment plan should be provided and regularly reviewed (to see if performance is adequate for case needs) for all cancer patients(50).

General recommendations for the prevention of post-radiation caries are shown in Table 6.

POST-RADIATION DENTAL CARIES PREVENTION
Routine oral hygiene care • Soft bristle brush (brushing 2-3 times a day) • Cleaning with dental floss and interproximal brushes (atraumatic technique) • Frequent rinses • Toothpaste (high fluoride content) e.g.5.000 ppm • Topical fluoridation: Neutral gel of 1% sodium fluoride in individual templates, for 5 minutes, daily (during radiotherapy) • Topical treatment of lesions with early decalcification (e.g. calcium and phosphate products) • Caries risk assessment: with Streptococcus mutans count (> 10 cfu/mL saliva), 1% gel chlorhexidine in individualized trays for 2 weeks, every 3 months. • Dietary advice: Reduce sugars and fermentable carbohydrates

Table 6 Prevention of dental caries after irradiation of the head and neck.

Osteoradionecrosis

Osteoradionecrosis (ORN) is probably the most severe oral complication following radiotherapy of the head and neck. It is defined as an area of bone exposure in a previously irradiated field, of at least 3 months of evolution and in the absence of persisting or recurrent tumour (28) .

The risk of developing ORN after receiving head and neck radiotherapy is estimated at around 7%. Although it seems that the maximum risk occurs after the first 2 years of the administration of radiotherapy, some risk still remains after years of treatment.

Clinical signs and symptoms of ORN include ulceration or necrosis of the mucosa with exposure of necrotic bone for longer than 3 months, severe pain, trismus and suppuration in the area (Figure 5). Progression of ORN may lead to pathological fractures, intra-oral or extra-oral fistulae and local or systemic infection (28). Risk factors for ONR are show in table 7.

RISK FACTORS FOR OSTEORADIONECROSIS
Moderate to high risk factors
• Preradiation and postradiation extractions or surgery
• Proximity to tumor
• Jaw location: posterior mandible > anterior mandible > posterior maxilla > anterior maxilla
• Dental disease
• Radiation dose >60 Gy
• Time lapse between preradiation extractions and commencement of radiation <14 days
• Low to negligible risk factors
• Tobacco and alcohol use
• Radiation dose <50 Gy

Table 7: Risk factors for osteoradionecrosis. Modified from Wahl MJ (2006) (51) .

The management of osteonecrosis frequently requires mutilating surgery, affecting the function and quality of life of patients. Therefore, the preventive approach is a priority. The incidence of ORN has decreased over the past 20 years because of greater awareness of dental health before treatment and the development of more targeted radiotherapy techniques including intensity-modulated radiation therapy (IMRT)(51).

Fig 5: Mandibular osteoradionecrosis following dental extractions.

The incidence of ORN can be minimized with adequate oral care prior to oncological therapy. Although it may appear spontaneously, most cases are associated with dental extractions and, therefore, extraction of all non-restorable teeth with poor prognosis (that can´t be root treated & managed as abutments) should be performed as far prior to radiotherapy as possible, to minimize the need for tooth extractions during and after radiotherapy (39). Preferably, these extractions will be carried out sufficiently in advance (approximately 15 days) to allow tissue repair before starting treatment. There are no unified criteria for tooth extraction prior to radiotherapy, and each patient must be evaluated individually. In those requiring extractions after radiotherapy, an atraumatic technique should be performed, with alveolectomy and primary closure being the gold standard modes of choice to minimize ONJ risk (52); some authors recommend antibiotic prophylaxis, although its beneficial effect in reducing the risk of osteonecrosis is not clear (53). Recommendations for tooth extraction before and after radiotherapy are shown in Table 8.

PRE-RADIATION TOOTH EXTRACTION
• Caries (non-restorable teeth)
• Active periapical disease (symptomatic teeth)
• Moderate and severe periodontal disease (with risks of progressing infections)
• Partial impaction or incomplete eruption
• Extensive periapical lesions (if not chronic or well localized)
POST-RADIATION TOOTH EXTRACTION
• Delay extractions 18 months if possible
• Anesthetic agents without vasoconstrictor
• Avoid intraligamentous anesthesia
• Alveolectomy and primary closure (mucoperiosteal flap)
• Limit the number of extractions per session
• Space the extractions in time
• Consider antibiotic prophylaxis prior to extraction
• In case of high-risk of ORN consider root canal therapy and restoration/crown amputation

Table 8 : Recommendations for exodontia before and after head and neck radiotherapy.

4.5. Rehabilitation

Reconstructive surgery after OSCC resection is considered when there is a functional or aesthetic loss of the remaining oral structures, such as: the loss of a significant part of the tongue, the floor of the mouth or buccal mucosa and the loss of a segment of the jaw. The resection of the primary tumour, would be indicators for reconstructive surgery. Superficial surgical defects of the mucosa and underlying soft tissue can be repaired adequately by using

a split-thickness skin graft. On the other hand, larger defects that exceed half of the tongue or large superficial areas of the floor of the mouth, gums and buccal mucosa may well require tissue transfer grafting – either pedicled (myocutaneous or osteomyocutaneous flaps based on a feeding vessel to muscle and perforators to the skin paddle) or free (a free transplant including muscle and soft tissues with blood supply). A free radial forearm flap provides excellent tissue to resurface mucosal defects and underlying soft tissue deficiencies. The radial flap of the forearm is also an excellent option for the reconstruction of any substantial resection of the tongue (4).

Complete rehabilitation of oral functions after treatment of OSCC is a desirable goal but difficult to achieve in some patients. While treatment of oral cancer in early stages provokes a minimum oral dysfunction, treatment of tumours in advanced stages alters the capacity of speech, chewing and swallowing (23).

Tumours that require bone resections of the maxillary bones result in aesthetic deformity and functional deterioration due to discontinuity of the mandibular arch and edentulism, as well as loss of sensitivity in the remaining teeth. The ideal rehabilitation after the treatment of tumours in advanced stages includes: the restoration of the external aesthetic appearance, the reconstruction of the mandibular arch and the facial contour, preserving or restoring oral competence, clarity of speech and stability of the dentition, in order to achieve the ability to chew all kinds of food and preserve or restore the ability to swallow (23).

If the immediate reconstruction of the post-surgical defect is not planned, the placement of an obturator is indicated (37) . In order to minimize postoperative trauma, an immediate obturator can be designed, which is adapted and fixed in the same surgical act. In any case, it is advisable to have a temporary obturator installed at 3-4 weeks after surgery and replace it with a definitive one at 4-6 months.

Surgical reconstruction of the jaw often achieves the goal of acceptably restoring external aesthetic appearance but does little to restore oral functions. Historically, tooth loss due to any cause was restored by making a removable denture. However, in patients treated for oral cancer, rehabilitation with a removable prosthesis rarely achieves satisfactory functional and aesthetics results due to the anatomical alterations of the oral cavity (23). Endosseous dental implants can be used to support fixed prostheses or as removable prosthetic retaining abutments providing improvement of retention, support, and stability of prosthetic devices. Studies have shown that dental implants can exhibit high survival rates in selected patients who received treatment for OSCC including radio and chemotherapy (54). The interval between the end of oral cancer therapy and the insertion of dental implants can influence the success or failure of osseointegration. Most authors suggest a minimum waiting time of six months, currently, there is no consensus on this matter in the literature (54).

Patients should be informed about the complications (increased risk of implant failure and osteoradionecrosis) associated with dental implant rehabilitation after radiotherapy (54) and a strict follow-up protocol should be established by the oral health team to prevent the onset of these complications and reduce failures. This protocol should include periodic reviews, instructions on hygiene techniques, making occlusal and contact point adjustments, and radiographic controls when necessary (55).

Some studies have described the appearance of OSCC, after dental implant therapy, in patients with a prevous history of oral cancer. These tumours can present as a red hyperplastic or ulcerated perimplant mucosa, with loss of alveolar bone and therefore can be misdiagnosed as periimplantitis. In such circumstances, a detailed clinical and radiological evaluation should be performed accompanied by biopsy and histopathological evaluation in case of suspicion of a malignant process (56).

4.6. Follow-up

Typically within the first 3 years of therapy approximately 20% of patients will develop a local recurrence, and approximately 25% will develop a regional metastasis at the cervical lymph nodes (57),. In addition, approximately 20% of patients with oral cancer will develop a second primary tumour in some other location of the upper aerodigestive tract, which is attributed to a process of field cancerization.

Therefore, during the first five years, after successful treatment, a strict follow-up is mandatory. The objectives of the follow-up protocol are the early diagnosis of recurrences, second primary tumours and cervical lymph node metastasis, as well as the monitoring of functional rehabilitation and psychological support (58,59). The techniques of screening (addressed in Chapter 2) are also useful for the early detection of recurrences.

There is no consensus around the interval and the optimal duration of follow-up appointments in patients treated for OSCC, which usually varies from three years after treatment, to a lifetime. Available evidence is insufficient to design the optimal follow-up schedule (59) . Most of the studies support a three years follow-up although this can be extended up to five years in high-risk patients (e.g. smokers and drinkers). During the first three years, this interval usually ranges from 1 to 2 months, and every 6 months during the 4th and the 5th year after cancer treatment.

There is a consensus that both the duration and the frequency of follow-up should be personalised based on risk factors such as the state of the surgical margins, the presence of lymph node metastasis, histological differentiation, the stage of the primary tumour and the ability of the patient to be able to self-detect relapses and second primary tumours (58,59). Sometimes recurrences are not visible or palpable and therefore the computed tomography and magnetic resonance imaging must also be part of the routine follow-up of patients treated for OSCC (60).

Recurrences are frequently diagnosed at a late stage, once symptoms appear and when treatment options are limited, with poor results. This delay is mainly caused by side effects related to the treatment (anatomical changes, fibrosis) that prevent the early detection of relapses. These difficulties make biomarkers attractive to optimise patient monitoring, since recurrences could be detected before the development of any clinical or radiological evidence (1).

4.7. Key points

- Tertiary prevention consists of offering the best available oncological treatment, rehabilitation and follow up programmes, as well as the prevention and early diagnosis of either recurrence or a second malignant tumour.
- Oral cancer treatment (surgery, radiotherapy and chemotherapy) affects oral health and results in functional impairment and disability. Proper dental management, before, during and after cancer therapy, can significantly reduce the complications associated with oral cancer therapy and consequently improve the patient's quality of life.
- Some of the complications derived from oncological treatment will remain over time and therefore the dentist has a continuous role in the prevention and treatment of new oral diseases.

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