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Spinocellular Carcinoma: diagnosis, clinical presentation and treatment

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Resumo: O cancro oral é o sexto tipo de cancro mais prevalente a nível global. Dentro do cancro oral, destaca-se o carcinoma espinocelular (CEC), também denominado por carcinoma das células escamosas, pela sua prevalência, sendo a neoplasia oral mais comum. O CEC é mais prevalente no sexo masculino, verificando-se uma proporção de 3:2 em relação ao sexo feminino, e afeta maioritariamente indivíduos apos os 45 anos. Os principais fatores de risco do Carcinoma Espinocelular estão intimamente relacionados com hábitos, estilos de vida e comportamentos, tais como são exemplos o consumo de tabaco e de álcool. Dadas as suas elevadas taxas de mortalidade, promover um diagnóstico precoce é de extrema importância sendo um fator crucial para aumentar as hipóteses de sobrevivência. Os profissionais de saúde devem estar sempre alerta para lesões pré-malignas ou malignas, analisando a mucosa oral de forma minuciosa, sistematizada, atenta e regular. Várias técnicas têm sido desenvolvidas no sentido de auxiliar no processo de diagnóstico, tais como o azul de toluidina e a avaliação da autofluorescência. O tratamento cirúrgico permanece a primeira escolha de abordagem, não sendo a terapêutica cirúrgica considerada apenas em casos de tumores irressecáveis, ou quando o doente não quer ser submetido a esta. A escolha da terapia deve considerar os aspetos macroscópicos da lesão, ao mesmo tempo que tenta responder às vontades e necessidades do doente. O planeamento terapêutico deve almejar a ser o mais eficaz possível, otimizando a qualidade de vida, a função e os compromissos estéticos que podem resultar. É expectável que, num futuro próximo, ferramentas como marcadores salivares ajudem a promover um diagnóstico ainda mais precoce.

Keywords: Carcinoma espinocelular, carcinoma das células escamosas, patologia oral, cancro oral, tratamento, fatores de risco.

Abstract: Oral cancer is the sixth most prevalent type of cancer worldwide. Among these, oral squamous cell carcinoma (OSCC) is the most common oral neoplasia. OSCC's has a higher incidence rate in men, rather than in women (3:2), and most commonly affects individuals after the age of 45. OSCC risk factors are intimately linked to behavior and lifestyle, such as tobacco and alcohol consumption. Given its high mortality, early diagnosis is of the utmost importance. Early diagnosis is an important factor in achieving the best chances of survival. Healthcare professionals should always be on the lookout for premalignant and malignant lesions, by systematically, thoroughly, and carefully examining the oral mucosa. To assist clinicians in the diagnostic process, adjunctive tools have been developed and studied, such as toluidine blue staining and autofluorescence imaging. Surgery remains the mainstay of the OSCC approach and is the first choice, except in cases where a tumor is considered unresectable or in cases where the patient prefers not to undergo surgery. The choice of treatment should be based not only on the macroscopic features of the cancer, but also on the patient's wants and needs. Treatment planning should aim to be as effective as possible, achieving the highest possible curative effect while optimizing quality of life, function, and esthetic afterwards. It is expected that, in the near future, salivary markers also promote an earlier diagnosis.

Keywords: Spinocellular carcinoma, squamous cell carcinoma, oral pathology, oral cancer, treatment, risk factors.

1. Introduction

Cancer is one of the leading causes of mortality and morbidity worldwide, with oral cancer being the sixth most prevalent cancer worldwide.[1] The entity “head and neck squamous cell carcinoma” (HNSCC) is one of the most common cancer entities, within the large and heterogeneous group of head and neck cancers.[2] Among these, Oral Spinocellular Carcinoma, also known as Oral Squamous Cell Carcinoma (OSCC) is the most prevalent oral carcinoma, corresponding to 90% of all oral neoplasias.[3–6]

The localization of OSCC is variable. This carcinoma can occur in many sites, including the tongue, which is the most common site, gingiva, buccal mucosa, floor of the mouth and lips. Small tongue tumors (stage I and II) can be treated by partial glossectomy. Large tongue tumors may require hemiglossectomy, subtotal glossectomy or total glossectomy. Small tumors arising on the anterior floor of the mouth are usually excised together with the ventral surface of the tongue.[6]

The diagnosis of OSCC, when associated with an older age, may be justified by a continuous accumulation of exposure to the risk factors. However, alterations in pathways involved in DNA repair, genetic stability and regulation of cell growth are thought to have an impact in the likelihood of developing any type of cancer, including head and neck cancer, and, therefore, SCC.[7]

Some OSCCs arise in apparently normal and healthy mucosa, while others may be preceded by premalignant lesions.[8]

Clinical signs and symptoms of Head and Neck tumors are often non-specific and may be misinterpreted, confused, or even downplayed.[9] Timely diagnosis and treatment are associated with improved perceived quality of care and reduced patient anxiety.[10] Although it is generally accepted that the prognosis is best in early stages of OSCC, with an estimated 92% 3-year survival rate[11], especially for those that are well-differentiated and not metastatic [5,8], these stages often present as asymptomatic and may go unnoticed, reason why most diagnoses are established in advanced stages.[5]

Oncological awareness is essential.[3] Regular screening, early detection and diagnosis significantly reduce morbidity, treatment duration and complexity, and promote a better prognosis for our patients. Prognosis depends on patient-related factors, tumor-related factors, and the choice of treatment.[8]

In the primary stages, I and II, the treatment of choice is surgery and/or radiotherapy, which usually results in permanent resolution. However, when it comes to advanced stages, III and IV, the therapeutic approach is usually a combination of surgery, radiotherapy, or

chemotherapy. When radiotherapy is administered, oral care is of extreme importance, as this treatment often leads to xerostomia, mucositis and osteonecrosis.

Recurrence rates have remained fairly constant over the last few decades, at around 10-25%[2]. However, in advanced disease, tumor recurrence is common, occurring in approximately 40-60% of all cases, and is associated with poor overall survival. Tumor staging and histopathological grading appear to be of extreme importance in predicting recurrence.[2] Despite advances in therapeutic approaches, morbidity and mortality rates have not improved significantly over the past 30 years, and remain low[12], at around 50-60% [8,13,14] at 5 years, and hovering around 12% in more advanced staged cancers.[8]

Population awareness of risk factors and a detailed, thorough, and systematic examination of the oral mucosa are essential to ensure an overall more optimistic clinical picture.[15]

Among the risk factors, tobacco (both smoked, and smokeless[16]) and alcohol are the most studied and are closely associated with OSCC occurrence. The incidence of oral cancer is strongly influenced by lifestyle, habits, and demographics[1].

This narrative review aims to review the literature on Oral Spinocellular Carcinoma in terms of diagnosis, clinical aspects, and current treatment guidelines.

Global guidelines and protocols were compared with Portuguese Institute of Oncology's (PIO) in order to better understand and to systematize the current diagnostic process, treatment, and overall approach that patients receive when referred to this center.

2. Materials and methods

PubMed and Google Scholar databases were searched using the terms "oral spinocellular carcinoma" and "oral squamous cell carcinoma", together with the terms "etiology", "risk factors", "clinical aspects", "diagnosis" and "treatment", within the period 2013-2023. Articles were selected by title, and posterior abstract reading. The search included articles in both Portuguese and English. Other articles were included by cross referencing.

3. Discussion

3.1 Prevalence and incidence

Cancer is a major cause of morbidity and mortality worldwide, with incidence rates varying widely according to geographic location, age, gender and race.[15] HNSCC is one of the most common types of human cancer, and is the sixth most common cancer worldwide, with 890,000 new cases and 450,000 deaths in 2018.[17] Oral cancer, alone, accounts for 2-4% of all cancer cases.[6,8]

Although most authors claim that the incidence is higher in developing countries[18,19], some claim that countries with better development indicators have higher rates.[20] There seems to be general agreement that people with lower socioeconomic status and education have a higher incidence, higher mortality, lower quality of life and lower survival.[19] It is consensual that mortality is higher in less developed areas.[20] Squamous cell carcinoma (SCC) of the upper aerodigestive tract mucosa is the most common histological subtype of head and neck cancer.[21] Among these, OSCC accounts for approximately 90-95% of all oral cancers.[3–6,22] The prevalence of OSCC is higher in males than females, with a 3:2 ratio, but this has been decreasing,[23] as the incidence of OSCC has been increasing in young women, aged 18-44 years.[8] The risk of developing OSCC increases significantly after the age of 45 years[3,18] , with only 5% of cases diagnosed before this age. The mean age at diagnosis is 66 years for HPV-negative patients and 53 years for HPV-positive patients.[17] Despite this, studies have shown an increase in incidence in the younger population.[19,24] The localization of OSCC is variable. This carcinoma can occur in many sites, of which the tongue stands out, due to its higher prevalence, accounting for 50%[19] of all OSCC cases, followed by the gingiva, buccal mucosa, floor of the mouth (35%) and the lips (1%).[19]

During 2018, 2019 and 2020, 187 patients were diagnosed with OSCC in the POI. From this sample group of 187, 133 were men and 54 were women. Of this group, only 6 (3.2%) patients were younger than 45 years. The mean age was 66 years.

The most common site was the tongue, with 78 patients (41.7%) presenting tongue SCC, followed by the lip, 46 patients (24.6%), floor of mouth, 14 patients (7.5%), gingival mucosa, 13 patients (6.95%), and palate, 9 patients (4.8%). The remaining 27 patients had lesions in other areas of the oral cavity (14.4%). The higher incidence of lip OSCC compared to global data may be explained by a possible bias. PIO is included in a very specific context: in addition to the very high levels of sun exposure in Portugal, Coimbra receives patients from areas closely linked to agriculture and fishing, which increases the effects of UV light.

3.2 Pathophysiology and Histopathology

OSCC originates from the mucosal epithelial cells that line the oral cavity, pharynx, larynx and sinonasal tract.

Histologically, OSCC follows a progression from epithelial cell hyperplasia to dysplasia, which can be mild, moderate or severe, to carcinoma in situ and, finally, to invasive carcinoma. However, most patients who are diagnosed with head and neck squamous cell carcinoma have no history of premalignant lesions.[17] This process usually begins in a normal adult stem or progenitor cell, which undergoes oncogenic transformation to become cancer stem cells with self-renewal and pluripotency properties.

HNSCC is characterized by genetic instability, associated with frequent loss or gain of chromosomal regions. Some stages of progression may be associated with specific chromosomal abnormalities.[17] The genetic alterations observed in head and neck cancers are mainly due to oncogene activation and tumor suppressor gene inactivation, leading to deregulation of cell proliferation and death.[4] For example, loss of the chromosome 9p21 (Ch9p21) locus, which contains tumor suppressor genes, occurs in normal epithelial mucosal hyperplasia; progression from hyperplasia to dysplasia is marked by loss of 3p21 and 17p13; the transition from dysplasia to carcinoma in situ involves loss of 11q13, 13q21 and 14q32, whereas loss of 6p, 8, 4q27 and 10q23 can be observed in progression to invasive carcinoma.[17] These studies show that multiple genetic alterations may be required for a carcinoma to progress to its invasive form. It's still unknown whether these alterations need to occur in a sequential temporal order or whether their co-occurrence is sufficient.

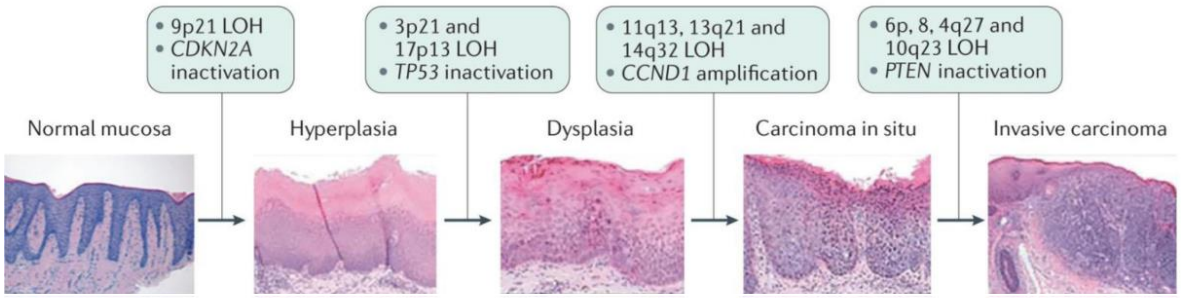

Figure 1. Progression of HNSCC and key genetic events; mucosal epithelial cell hyperplasia is followed by dysplasia, and carcinoma in situ precedes the development of invasive carcinoma. Specific genetic events have been shown to be more pronounced at each stage of progression.

In normal cells, there is a limited number of cycles of growth and division that a cell can go through before it reaches senescence, when this process ends. This is determined by telomeres, which shorten with successive cycles of cell division. Telomerase is a specialized DNA polymerase that elongates the telomeres, allowing further cell division by synthesizing additional telomere repeat sequences. While absent in most non-immortalized cells,

telomerase is functionally expressed in over 90% of immortalized cells, including cancer cells. In an immunohistochemical study, samples of OSCC and oral epithelial dysplasia, 81.48% and 77.06% of cells were observed to express telomerase, while only 62.91% activation was observed in normal oral mucosa controls.[11] The genetic component of HNSCC can be demonstrated by the apparent association between rare inherited syndromes, such as Fanconi anaemia, xeroderma pigmentosum, Bloom, ataxia telangiectasia, Li-Fraumeni and familial atypical multiple melanoma and a higher prevalence of head and neck cancer in general.[7,25] Suspicion of a genetic component should be based on a thorough family history that describes 1) a first-degree relative with the same tumor type and clinical presentation; 2) two or more first-degree relatives with a tumor at the same site; 3) two or more first-degree relatives affected by rare tumors.[7]

In tumor tissue, genetic changes often lead to the activation of angiogenesis to provide oxygen, nutrients, and the removal of metabolic waste. This new blood vessel formation often develops through dysregulation of a small subset of cytokines, upregulation of vascular endothelial growth factor (VEGF)-A and decreased expression of its inhibitor, thrombospondin-1 (TSP-1). Factors associated with angiogenesis, such as CD44, and blood microvessel density have been reported to be increased in oral cancer compared to normal epithelium.[11]

As the disease progresses and the tumor grows and develops, new blood vessels are formed. This process is called angiogenesis and it's a sine qua non for tumoral formation. In order to explain the process of oral carcinogenesis, the theory of field cancerization has been developed. According to field cancerization, as the oral epithelium is exposed to carcinogenic factors, the entire area of the oral cavity is at greater risk of developing malignant lesions. Multiple oral cancers may develop from independent cell clones. This theory is supported by chromosome X inactivation studies, microsatellite analysis, and p53 mutation analysis. Recent studies suggest that multiple cancers may be clonally related and arise from expansion of the same clone. These studies have modified the cancerization field theory, culminating in the patch field carcinoma model, in which a stem cell, located in the oral epithelium, acquires a genetic alteration, and produces daughter cells that share the genetic alteration. This patch of cells expands and invades the surrounding oral mucosa, but remains macroscopically undetectable. In some cases, however, it may be associated with the morphological features we associate with premalignant lesions: leukoplakia and erythroplakia.[8]

As epithelial cancers progress towards more severe stages, they develop morphological and molecular changes that allow them to further invade tissues, both locally and distally. One of the most important changes is the loss of E-cadherin, a cell-to-cell adhesion molecule, that assists in epithelial cells sheet formation and helps maintain cellular quiescence. Meta-analyses have reported a poorer overall prognosis in OSCC patients with reduced E-cadherin

expression compared to those with normal or increased expression. As cancer cells progress, dysregulation of additional transcription factors can lead to resistance to apoptosis, expression of matrix-degrading enzymes and increased motility.[11]

The cell cycle is the series of cellular events that results in the production of two genetically identical daughter cells from a parent cell and is a largely controlled by specialized groups of proteins known as cyclins and cyclin-dependent kinases (CDKs).

There is also growing interest in the oral microbiome and its relationship to oral cancer. Poor oral health is associated with oral cancer, and tobacco, alcohol and HPV can modulate the composition of the oral microbiota.[17]

As HNSCC derives from the stratified epithelium, the histopathological spectrum is characterized by the degree of cellular atypia and squamous differentiation. An advanced and well differentiated tumor resembles the stratified epithelium, with mature-appearing cells organized into layers with irregular keratinization; a poorly differentiated tumor is characterized by immature cells with nuclear pleomorphism and atypical mitosis, with minimal to no organized stratification or keratinization.[17] HPV-associated tumors are usually poorly differentiated, whereas HPV-negative patients often show a greater level of differentiation, with preservation of stratification and keratinization.

3.3 Etiology and risk factors

The etiology of OSCC remains complex as this disease presents multiple etiologic factors. Although the effect of some etiologic/risk factors for OSCC is well established in the literature, especially tobacco and alcohol consumption[17], with 25% of cases associated with smoking and 7-19% attributable to alcohol[5,19,26], 15-20% of all oral cancer cases occur in patients without a history of smoking or alcohol consumption, which means that there are numerous cases of OSCC, not related to tobacco or alcohol,[19] of unknown etiology. In an attempt to explain this percentage, several studies conducted have identified other factors that may influence cancer incidence and predisposition, of which HPV stands out.[19] Other factors that may promote the appearance of premalignant lesions, include: viral infections, oral lichen planus, iron deficiency, immunosuppression, as various levels of immune dysregulation have been shown to affect survival and recurrence rates in oral cancer[27], consumption of hot food and exposure to traumatic agents.[8,23] Nevertheless, the literature suggests that smoking increases the risk of developing oral cancer by almost 10 fold, rising to 17 times when it comes to heavy smokers (+80 cigarettes per day) [23] and that, although alcohol and tobacco are independent factors, there is evidence of a synergistic effect between them, with some authors suggesting that the

permeability of the buccal epithelium to other carcinogens is increased due to the previous effect of ethanol on its cells.[19]

Tobacco use is the major risk factor for HPV-negative head and neck cancer.[17] Tobacco products are associated with a wide range of cancers, including lung, nasal and oral cavity, stomach, liver, larynx, bladder, etc., as tobacco contains more than 60 carcinogens. In particular, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), N-nitrosonornicotine (NNN) and polycyclic aromatic (PAHs) are strongly associated with oral cancer.[19,26] The risk is thought to be lower in former smokers than in current smokers, and there is a tendency for the risk to decrease with the number of years since quitting.[19] It is also known that patients who have been treated for previous oral neoplasia have 2-6 times higher risk of developing a secondary tumor if tobacco use continues. The use of cigars and pipes has also been shown to be more aggressive. The risk of developing OSCC is tobacco dose-dependent.[23] However, it's worth noting that even among individuals with similar levels of exposure to tobacco carcinogens, only some will develop oral cancer, suggesting the important role of genetic factors in cancer development and predisposition. In the absence of coexisting risk factors, light smokers are not at increased risk of OSCC compared with non-smokers. The risk of head and neck cancer rises abruptly when smoking duration exceeds 20 years and consumption exceeds 20 cigarettes per day. [26] Heavy smokers are at a manifestly higher risk, and a strong association between long-term smoking and OSCC has been reported.[5]

In addition to tobacco chewing or smoking tobacco, alcohol consumption also increases the risk of oral cancer.[28] Abusive alcohol consumption has also been identified as one of the best-established cancer risk inducing factors. As with tobacco, the effects of alcohol are dependent on dose and duration of use, with very short-term exposure being insufficient to induce tumourigenesis [29], and 100 g of alcohol per day being associated with a 100-fold increased risk of developing suspicious lesions.[23] Three alcoholic drinks per day (considered as a high dose) in non-smokers can increase the risk of developing head and neck cancer by a factor of 2.04.[30,31] Overall, approximately 7-19% of oral cancer cases are attributable to heavy alcohol consumption.[26] More importantly, alcohol can act as a solvent and increase the penetration of carcinogens into target tissues. Acetaldehyde, the alcohol metabolite, has been identified as a tumor promoter.[4]

Viral infections are one of the most preventable causes of OSCC, namely, Human Papiloma Virus (HPV). More than 200 genotypes of HPV have been detected in human tissues.[32] HPV has been viewed as a possible risk factor, among others, because of HPV virus' specificity to epithelial cells, keratinocytes, as there is a morphological similarity between oropharyngeal and genital epithelium. Besides, studies have shown that HPV that infects genital area can also infect the oral cavity.[19] Infection with HPV is an increasingly common risk

factor for HNSCC. Dysplasia and subsequent oral carcinoma have been linked to various HPV types, with HPV-16 being the primary causative type [23,29], detected in more than 22% of all oral carcinomas[23], and other high-risk HPVs, including HPV-18 (14%[23]), HPV-31, HPV-33 and HPV-52, detected in a small percentage of patients.[17,23,33] Smoking and tobacco are also linked to HPV: tobacco exposure and consume seem to modify the survival and recurrence of HPV-positive HNSCC. HPV-positive tumors are characterized by the absence of P53 mutation and fewer chromosomal abnormalities. The P53 tumor suppressor gene is often mutated in HPV-negative cancers; in HPV-positive cells, intact p53 is present, making them sensitive to treatment and restoring apoptotic function.[29] The human immunodeficiency virus (HIV) should also be considered: a defective immune response may predispose to cancer. The most common oral malignancy in HIV-infected patients is Kaposi's sarcoma, for which human herpesvirus type 8 (HHV-8) has been implicated as the etiological agent. Lymphoma, most commonly non-Hodgkin's B-cell lymphoma in HIV-infected individuals, or other immunosuppressed individuals, is often associated with Epstein-Barr virus.[4] The role of HIV in OSCC is controversial. Although OSCC is more common in transplant recipients on immunosuppressive therapy, or seropositive individuals, some authors claim that HIV infection does not predispose to intra-oral squamous cell carcinoma[4,34], while others argue that these individuals have a higher susceptibility for developing spinocellular carcinoma.[23,35–37]

Approximately 30-40% of all cancers are related to unhealthy diet, sedentary lifestyle, and obesity. Fruit, vegetable, and carotenoid deficiencies appear to be associated with oral cancer: 10-15% of oral cancer cases are associated with low fruit and vegetable intake. This relation is yet to be explained. Some authors believe that these foods, because they contain substances with antioxidant and anticarcinogenic properties, such as vitamins A, C and E, carotenoids, flavonoids, folates, fiber and phytosterols, may play an important role in compensating and balancing the effects of carcinogenic activities.[26]

Another substance that may increase the risk of OSCC is betel, an evergreen vine whose leaves are commonly used in India and South East Asia for their refreshing and analgesic properties. Betel chewing often results in the progression of a premalignant lesion, oral submucosal fibrosis (OSMF), which consists of abnormal collagen deposition that can progress to malignancy.[23,38] Although frequent and prolonged exposure to betel increases the risk of oral cancer, recent data do not support an association between OSCC risk and low or moderate betel chewing in the absence of other risk factors such as tobacco and alcohol.[26]

3.3.1 Premalignant lesions as a risk factor

In order to promote early diagnosis, careful and thorough inspection of the mucosa is mandatory, in order to spot possible premalignant lesions. Premalignant lesions can have different clinical appearances, from exophytic to endophytic lesions, with different colors such as leukoplakia, erythroplakia or erythroleukoplakia[23], to a nodule or ulcer with fissured raised margins,[8] always suspicious for a diagnosis of OSCC whenever these features persist for more than two weeks. Biopsy should be performed in case of doubt to establish a definitive diagnosis. Leukoplakic, erythroplakic and erytroleucoplakic lesions often correspond to earlier stages, whereas exophytic and ulcerative lesions are more commonly associated with later, more advanced stages.[23] Both leukoplakia and erythroplakia are strongly associated with the presence of oral epithelial dysplasia (OED). Most premalignant lesions present clinically as leukoplakia or erythroplakia, but histologically, they can have a wide range of phenotypes including hyperkeratosis, dysplasia, or carcinoma.[9]

Potentially malignant disorders include leukoplakia, erythroplakia, erythroleukoplakia, OSMF, oral lichen planus (OLP), chronic inflammation, and oral bacteria related alterations.

3.3.1.1 Leukoplakia

Leucoplakia has a prevalence of 1-4% [39] and is described by the World Health Organization as a “clinical diagnosis that include any white lesion (plaque or patch) on the oral mucosa that cannot be considered clinically or pathologically as any other disease”.[18,40,41] The differential diagnosis must include oral candidiasis, oral lichen planus, leukoedema and hyperkeratosis.[23] Early detection of leukoplakia is key to preventing its transformation into aggressive malignant OSCC, far more violent and harder to treat.[5] The location of leucoplakia is of great importance and is strongly related to the prevalence of the development of dysplastic alterations. The annual malignant transformation rate of leukoplakia is 1%.[18] Lesions located on the lateral tongue margin are often more malignant: the tongue has been identified as a high-risk site with a malignant transformation rate of 24.2%.[36] Homogeneous leukoplakia is more common and usually benign; it is uniform and flat, with small superficial fissures. Non-homogeneous leukoplakias can have a range of different characteristics; they can either be flat and speckled, white and red (erythroleukoplakia), nodular, exophytic, or papillary/verrucous. The distinction between the two types is purely clinical and is extremely important as it is known that non-homogeneous leukoplakia carries a much higher risk of malignant transformation. Some authors consider the transformation rate of inhomogeneous lesions to be similar to that of erythroplakia. Another factor to consider is that proliferative verrucous leukoplakia (PVL) also has a higher prevalence of malignancy.[23] PVL is the most

destructive form of leukoplakia and presents clinically as multiple spreading white lesions with a high recurrence rate and high likelihood of malignant progression.[5] As leukoplakia progresses, the lesion becomes whiter and thicker, becoming fissured, irregular or even papillary (verrucous).[23] PVL is characterized by relentlessly progressive, multifocal leukoplakia, or a large leukoplakia in a single site or in contiguous sites.[39] Although leukoplakia is more common in males, females with these lesions are more likely to develop OSCC.

3.3.1.2 Erythroplakia

Erythroplakia is “any red lesion of the oral mucosa that cannot be clinically diagnosed as any other condition”.[42] This lesion is usually well defined with a velvety texture.[41] Erythroplakia occurs more commonly in men over 55 years of age and on the lateral border of the tongue and is usually asymptomatic[23], although some patients may report a burning sensation/soreness, most commonly when in the presence of erythroleukoplakia.[41] While both erythroplakia and leukoplakia are usually precursors of OSCC, a true erythroplakia is a more alarming clinical finding than leucoplakia.[5] This lesion enters into differential diagnosis with candidiasis, lichen planus, mucositis and systemic lupus erythematosus.[41] Erythroplakia is the rarest of the oral premalignant lesions, but over 90% of such lesions show OED, carcinoma in situ, or OSCC on initial biopsy[39] and surgical excision is, therefore, recommended.[18] The most common site for the occurrence of this lesion is the soft palate, followed by the ventral tongue, floor of the mouth, and tonsillar pillars. Most patients present with a single lesion.[41]

3.3.1.3 Erythroleukoplakia

Erythroleukoplakia, also denominated as speckled leukoplakia, is a mixed red and white lesion, usually with more advanced dysplastic changes than leucoplakia.[4] Erytholeukoplakia is not as common as leukoplakia. Its prevalence in the general population is not well known and has been reported to be between 0.02% and 0.2%.[41,43] Due to its irregular margins, Candida colonization of these lesions is very common. *Candida albicans* can induce epithelial proliferation and produce carcinogens. Chronic hyperplastic candidosis presents as a nodular or as spotted-white mucosal plaques, which are potentially malignant oral epithelial lesions.[4] The likelihood of malignant transformation of erythroleukoplakia ranges from 18 to 47%.[44]

3.3.1.4 Oral Submucous Fibrosis (OSMF)

OSMF, which often results from chronic areca nut chewing, is also likely to develop into a malignant tumor (1.5-15%[38] ; 9%[41]). It manifests with ulceration, xerostomia, burning sensation, and restricted mouth opening, which greatly affects the patient's quality of life.[38]

OSMF consists of a chronic fibrotic lesion of the oral mucosa, which probably represents the expression of an overhealing wound, responding to chronic insults to the mucosal lining, either mechanical or chemical. Submucosal fibrosis is characterized by a loss of fibroelasticity in the affected tissue, resulting in fibrous bands that affect the mobility of the tongue and limit mouth opening. This condition most commonly affects the buccal mucosa, followed by the tongue, lip, palate and gingiva, and has been found to be more prevalent in males.[41]

3.3.1.5 Oral Lichen Planus (OLP)

OLP is an immune-mediated chronic inflammatory disease which clinically presents as reticular white areas that may or may not be associated with erosive and ulcerative lesions.[39] OLP usually affects middle-aged patients, particularly women aged 30 to 60 years.[41] Histopathologically, OLP is characterized by the presence of a band-like lymphocytic infiltrate at the interface between the epithelium and connective tissue and by the destruction of the basal layer, often accompanied by colloid body formation. It may or may not be keratotic, acanthotic or atrophic, with or without intraepithelial inflammation and with or without sawtooth rete ridges.[39] It is still controversial whether oral lichen planus should be considered a premalignant disorder, as its malignancy rate is approximately 1%.[5,39] Some authors believe that when malignant transformation does occur, it's more likely to be associated with erosive and atrophic forms of OLP.[45,46] However, it has been reported that tumor recurrence rate of OSCC is higher in patients with previous OLP than in patients with primary OSCC.[47]

3.3.1.6 Chronic Inflammation

Chronic inflammation triggers the release of mediators such as cytokines, which induce oxidative stress and subsequent damage to cellular DNA, ultimately leading to a carcinogenic process. Chronic inflammation can be caused by traumatic agents such as ill-fitting dentures, sharp or broken teeth and parafunctional habits. Chronic irritation of the mucosa has been postulated as an etiological factor in oral cancer.[41]

3.3.1.7 Oral Bacteria

Recent evidence shows several intimate links between oral bacteria, mainly from periopathogenic biofilms, and oral carcinogenesis. Bacteria such as Fusobacterium nucleatum, Porphyromonas gingivalis,[41,48,49] Tannerella forsythia and Prevotella intermedia [50] and epithelial cells have been implicated in this association: some authors believe that these bacteria interfere with the production and use of E-cadherin and adhesins, subvert immune

defence mechanisms, extracellular signal-related kinases, suppress apoptosis and stimulate proliferation.[41]

Other potentially malignant lesions include discoid lupus erythematosus, actinic keratosis (limited to lip cancer), hereditary conditions such as dyskeratosis congenita and epidermolysis bullosa, and chronic Candida infections.[41]

3.4 Clinical presentation

Cancers of the oral cavity, such as the tongue, floor of the mouth, buccal mucosa and hard palate, usually present as a non-healing sore or ulcer that lasts more than two weeks and may or may not be accompanied by any pain or symptoms. Overall, the sites with higher risk of carcinogenesis are the lateral border of the tongue and the floor of the mouth, which can be explained by two motives. On the one hand, any carcinogen that comes into contact with the saliva mixes with it and ends up on the floor of the mouth, where it is in constant contact with the mucosa and the tongue. On the other hand, the mucous membrane in these areas is not keratinised and is, therefore, less protected from the carcinogenic factors and their effects.[9,51]

Although the oral cavity is accessible for a complete examination, OSCC is often diagnosed in the more advanced stages of the disease because early stages don't course with any signs or symptoms.[17] Either due to ignorance or inaccessibility to medical care, the disease is detected in later stages.[4] Patients usually don't contact their doctor until they are in pain or feel some kind of discomfort. Healthcare professional awareness also plays a fundamental role: physicians should be able to diagnose OSCC in its early stages, identify premalignant lesions, act accordingly, educate their patients and refer for biopsy whenever necessary. Later stages may present with dysphagia, dysarthria, pain when chewing or speaking, tooth loss and bleeding.[9,17,23] Clinical suspicion should be heightened whenever we're in the presence of risk factors such as tobacco or alcohol use.[17]

Ignorance of the potential cancerous etiology can lead to a delay in seeking medical attention because the patient is not in pain, experiences only mild discomfort, and tends to play down the lesion as long as it doesn't interfere with their functionality. In most cases, patients do not seek medical attention until they experience pain or difficulty speaking or eating. Late diagnosis can also be the fault of the healthcare professional, due to poor diagnosis or inability to recognize such lesions as cancerous or pre-malignant. Like patients, physicians are sometimes unable to associate the presenting signs and symptoms with a neoplastic etiology and make a poor diagnosis. Sometimes patients are subjected to long-term, ineffective antibiotic therapy or unnecessary endodontic, periodontal or surgical treatment.[3]

Late stages of OSCC may present with pain, tooth loss or mobility, bleeding, odynophagia, dysphagia, aphasia, dysphasia, otalgia, dysarthria, bone invasion and cervical lymphadenopathy.[9,23] Taste disorders represent the most common side effect of OSCC treatment; with, dysgeusia being noted by 70% of oral cancer patients. Although survival remains the primary endpoint for cancer patients, taste impairments can cause psychological distress.[52]

Staging is considered the most important and determinant factor for OSCC prognosis and nowadays, the most used system for staging is the Tumor-Nodes-Metastasis (TNM) system. TNM classification system has been outlined as having the following 6 objectives: (1) aid in treatment planning, (2) prognosis, (3) aid in the assessment of treatment results, (4) facilitate the exchange of information between institutions, (5) support cancer control activities, and (6) contribute to continuing investigation of human malignancies.[53]

The TMN classification is a reliable method for estimating a patient's prognosis based on the characteristics their tumor presents. This system is of great importance in oncology and is currently used globally to describe the extent of the tumor at presentation, clinically, prior to treatment (cTMN), after surgical treatment, pathological staging (pTMN), and at disease recurrence (rTMN).[54] In this system, T, M and N describe the extension of the cancer.

"T" score describes the growth of the primary tumor, and it's divided into 6 main scores. TX means the primary tumor could not be found – the tumor is restricted within the top layer of tissue. T1 means the tumor is ≤2cm and its invasion ≤5mm of depth of infiltration (DOI); T2 tumors are ≤2cm and 5mm>DOI ≤10mm; or tumor >2cm and ≤4 cm and DOI ≤10mm; T3 tumor >4cm or any tumor with 10mm>DOI ≤20mm; T4a moderately advanced local disease (tumor invades adjacent structures only, or extensive tumor with bilateral tongue involvement and/or DOI>20mm; T4b very advanced local disease (tumor invades masticatory space, pterygoid plates, or skull base and/or encases the internal carotid artery. The highest the score, the more serious the growth.

"N" describes the cancer status/presence of nearby lymph nodes. N is divided in 5 scores. NX means the nodes could not be assessed. N0 means the nodes are cancer-free. N1 through N3 is based on 1) number of nodes with cancer; 2) cancer on one or both sides of the neck; 3) nodal size; 4) cancer growth through the node. (Fig.4) The highest the score, the more serious the growth.

"M" refers to the tumor having, or not, spread into distant body parts. M0 means there are no distant metastases. M1 means one or more distant metastases are present.

Metastasis can be of two types: regional and/or distant metastasis.[5] At the time of the diagnosis, 40% of the cases exhibit metastases, and 6% exhibit distant metastases.[55]

In terms of regional metastasis, nodal metastasis occur when tumor cells from the primary site invade lymphatic channels and migrate to regional lymph nodes in the neck. Lymph node metastasis is an important prognostic indicator for oropharyngeal and oral cancer.[5] Cervical lymph node metastasis occurs in nearly 80% of patients[8] and reduces survival by 50%.[5,11] Cancer cells usually spread to the lymph nodes on the same side as the primary cancer. Therefore, a thorough inspection and palpation of the head and neck lymph nodes should be performed in first-time patients to promote early detection of cancer, which improves prognosis and the chance of successful treatment. The presence of disseminated tumor cells outside the lymph node capsule worsens prognosis and reduces patient survival.[5]

In order for distant metastasis to occur, carcinomas require specific biological events to spread from the primary tumour site to an anatomically distant site. This process begins at the primary tumour site, where cancer cells usually reach the basement membrane and invade the surrounding connective tissue. The tumour cells move into lymphatic or blood vessels and travel to distant metastatic sites.

3.5 Diagnosis

OSCC can be diagnosed in a variety of ways, depending on the location and characteristics of the tumor. OSCC is usually diagnosed by clinical oral examination followed by biopsy of suspicious tissue. Despite the diagnostic modality, biopsy and histopathological analysis remain fundamental to the definitive diagnosis of OSCC. Adequate biopsy technique includes the administration of local anesthesia, adequate width and depth (margins) of the tissue removed, proper handling of the tissue, and non-contamination of the tissue sample.[5]

Exfoliative cytology consists of the collection of exfoliated cells for microscopic examination, which allows early detection of oral cancer. However, cells exfoliate normally and in the presence of both benign and malignant tumors. This method does not allow tumor staging as it doesn't measure DOI; it only shows whether cancer cells are present. An accurate diagnosis of OSCC can only be made through biopsy.[5] Despite the advantages of low invasiveness, the smear taken does not have sufficient sensitivity and specificity to serve as a predictive diagnostic tool for squamous cell carcinoma, despite the low invasiveness of the sample collection. More modern diagnostic methods have been developed. Brush biopsy and microbiopsy have been proposed and shown to be useful in the follow-up of precancerous lesions, avoiding the need to repeat more invasive surgical biopsies.[41]

There are several other diagnostic adjuncts that have been developed to help us identify lesion margins and to help us differentiate between benign and potentially malignant lesions.

These methods include toluidine blue staining, light-based detection techniques, and salivary biomarkers assessed with point of care devices.

Toluidine Blue Staining is a simple, inexpensive and non-invasive technique used to aid diagnosis of malignant and premalignant lesions. Toluidine blue works by staining areas of the dysplastic epithelium. It is of very easy and quick application: first, a 1% acetic acid is used to remove salivary and bacterial pellicle; then, 1% toluidine blue aqueous solution is applied for 30s on the area of the suspect lesion; the staining pattern is then evaluated. The mechanism by which toluidine blue binds to high-risk and malignant cells is not fully understood.[41]

Autofluorescence Imaging is also used to aid diagnosis: autofluorescence imaging can provide additional information about the nature of the lesion, helping discern lesions that demand biopsy. When excited with light of a specific wavelength, tissues produce autofluorescence. Dysplasia and cancer cause changes in the fluorescence of the mucosa: they cause a loss of green fluorescence, making the affected mucosa appear darker. Besides being a non-invasive technique, autofluorescence imaging is highly sensitive (estimated 91%) but low in specificity (estimated 58%), as conditions such as inflammatory diseases can cause changes in tissue's fluorescence similar to those caused by malignant or premalignant lesions.[41]

There is growing interest in the role of salivary biomarkers in the detection of OSCC, as they could be used for its early diagnosis. It has been suggested by various researchers that a specific group of protein biomarkers are increased in saliva of individuals with OSCC.[41,56] In 2019, Shree et al. published a systematic review with meta analyses affirming that saliva can be used as a diagnostic tool with highly sensitive and specific markers (Matrix metalloproteinase (MMP-9), Chemerin) for early detection of Oral Squamous Cell Carcinoma.[57] Multiple authors have described that a specific group of protein biomarkers are increased in saliva of individuals with OSCC[58], and they could help diagnose OSCC and head and neck cancer: Franzmann et al. reported CD44 as a probable biomarker for oral cancer; Nagler et al. described Cyfra 21-1 and cancer antigen-25 to be potential biomarkers for oral cancer[14,58]; in a study, Elashoff et al. stated increased levels of IL-8 and subcutaneous adipose tissue in saliva, exhibiting higher sensitivity and specificity to diagnose of OSCC[21] ; authors claim there's an increased expression of IL-8 and IL1β in saliva of patients with OSCC as compared to control patients[59,60], which was also proved by a study in which Gleber-Netto et al. reported increased expression of IL8 and IL1β in saliva of patients with OSCC.[56]

Early detection and diagnosis of potentially malignant oral epithelial lesions is of extreme importance when it comes to improving survival and reducing mortality. Although the early stages of OSCC are usually asymptomatic, we should be concerned about the following: persistent mouth sores and/or pain; local changes in the appearance of the oral mucosa; local

changes in the consistency of the oral mucosa; persistent white or red or mixed white and red oral mucosal staining; raised oral mucosal staining or plaque; persistent oral mucosal lump or growth; and localized oral mucosal bleeding.

Any mucosal lesion persisting for two weeks or more, after removal of possible local irritants (broken teeth, ill-fitting dental prosthetic devices, and appliances, etc.), must be biopsied, as histological examination is the gold standard in diagnosis of OSCC.[41]

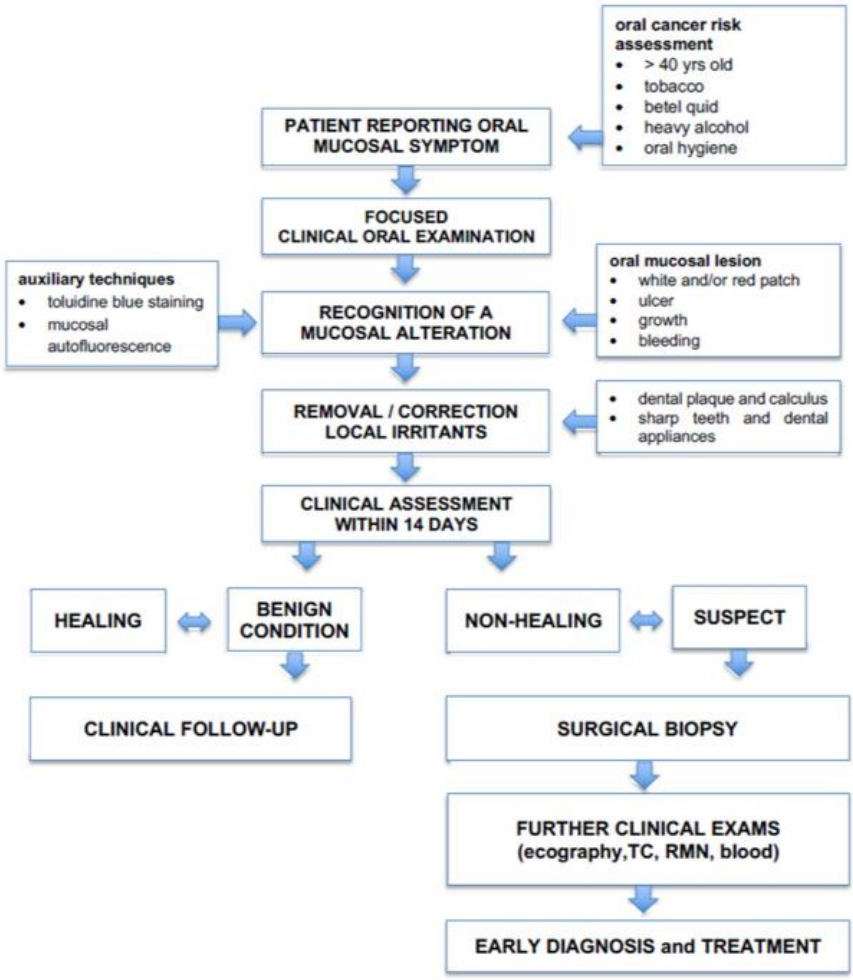

Figure 2. Clinical flow-chart to guide the clinician in anticipating the diagnosis of oral cancer and other mucosal diseases and conditions, adapted from Abati S. et al

In POI, the diagnosis begins with a clinical examination of the oral cavity and cervical region. The lesion is then biopsied. A computed tomography (CT) scan of the cervical and thoracic region is also ordered. Other complementary imaging studies may also be relevant and ordered for the patient: Magnetic resonance imaging (MRI) of the tongue and floor of the mouth, fluorodeoxyglucose (FDG) positron emission tomography (PET) if cervical lymph node involvement or pulmonary metastases are suspected. Dentition, nutrition and swallowing are also assessed. Pre-anesthesia assessment is also carried out if surgery is being considered

or is an option. The tumor is staged according to the TMN system, both clinically (c) and pathologically (p) and treated accordingly.

Lesion biopsy in PIO can be either incisional or excisional. Furthermore, in case of lymph node involvement, biopsy aspiration of cervical nodules is performed.

3.6 Treatment

Factors influencing the choice of treatment are both tumor and patient related.[1] The pivotal treatment decisions for OSCC patients (elective neck dissection yes/no; adjuvant radiation yes/no; chemotherapy yes/no, targeted therapy and/ or immunotherapy yes/no) are still mainly based on the macroscopic features of the primary OSCC[61], however, therapeutical approach should be tailored to the needs of the patient and individualized: varying according to the patient's wishes, needs, functionality and postoperative morbidity[6,17]. Treatment planning should aim to be the most effective, reaching the highest curative effect possible while optimizing quality of life, function, and esthetic afterwards.[11,17]

It is also important to take into account the primary site, location, size, stage, proximity to bone and depth of infiltration. The histological feature most decisive to treatment selection and eventual prognosis is the depth of infiltration (DOI).[1,62]

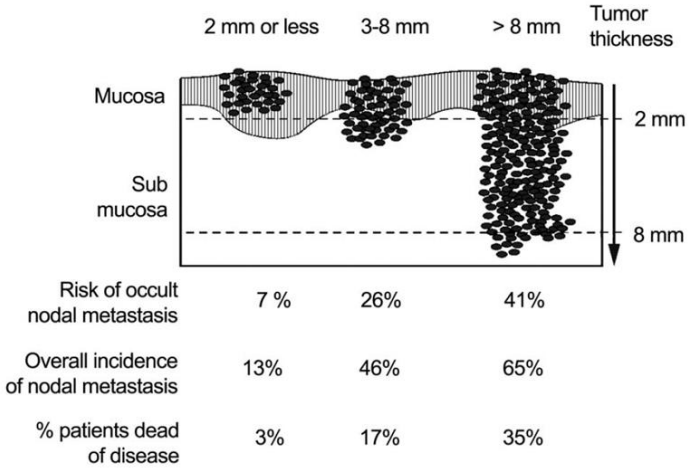

Figure 3. Risk of nodal metastases and death in relation to thickness of primary squamous cell carcinomas of the tongue and floor of the mouth. (adapted from Spiro et al)

Treatment options include surgery, radiotherapy, chemotherapy or a combination of these, often with postoperative follow-up and monitoring.[11]

Despite all these considerations, surgical treatment remains the foundation of multimodal therapy[1,63] consisting of surgery, followed by chemotherapy plus radiation[17] and plays a central role in the treatment of radiotherapy-naïve patients with recurrent OSCC. The ultimate goal of surgical resection is adequate clearance of tumor tissue as inadequate clearance of tumor

cells results in increased risks of local and regional recurrence and decreased long-term survival rates.[6] It is usually accompanied by adjuvant radiotherapy or radiochemotherapy depending on histopathological staging and presence of risk factors.[2] Patients who received surgically based therapy had a significantly better outcomes in terms of disease-free survival (DFS) and overall survival.[2] Oral cancer affects patients' quality of life by impairing chewing and speech functions, as well as facial aesthetics. If the tumor is at an advanced stage and treatment involves extensive surgery, we must consider that both function and aesthetics will be greatly altered and challenged[3] ; increasing the resection margins may result in increased esthetic and functional morbidities. After resection of the primary tumor, reconstructive surgery is usually required to restore oral function and cosmetic appearance.[6] In the event of treatment failure after single modality radiation or surgery, salvage with the alternative modality offers a high chance of cure.[17]

The most important factor influencing long-term outcomes is disease staging at the time of diagnosis and presentation. Early diagnosis, correct surgical approach, patient- and tumor-appropriate, selective management of regional lymph node metastases at risk, and multidisciplinary intervention to achieve the implementation of adjuvant radiotherapy or chemotherapy all contribute to improving the survival of patients with oral cancer. When patients present a small primary HNSCC without clinical node involvement, or involving a single node, cure rates of over 80% can be achieved with single modality intervention, such as resective surgery or radiotherapy. When we talk specifically about oral cancers, surgery is the most selected choice.[6,17] Patients with newly diagnosed oral squamous cell carcinoma (OSCC) are treated with surgical resection of the primary tumor with microscopically clear margins and prophylactic or therapeutic lymphadenectomy, followed by adjuvant radiotherapy with or without chemotherapy in advanced stages and in the presence of high-risk pathological features. During oral cancer surgery, the operating surgeon evaluates surgical margins through clinical examination, visual observation, and palpation.[64] Achieving clear margins is the main objective in the surgical management of OSCC as this is associated with reduced risk of recurrence and improved survival.[65] The surgeon’s goal is to achieve a 1[6,64]–2[64] cm gross visible margin routinely to assure adequate microscopic tumor-free clearance at final histopathology.[64] Currently, most regard a clear resection margin as being >5 mm, a close margin as more than 1 mm but <5mm and an involved margin <1mm. [65] Recent National Comprehensive Cancer Network (NCCN[66]) guidelines define a clear margin as invasive tumor that is at least 5 mm from the resected margin. A close margin is defined as invasive tumor that is located between 1-4mm [65] and 1-4.9 mm, from the resected margin and invasive tumor less than 1 mm from the margin of resection constitutes a positive margin.[64] An involved margin or one with inadequate adjacent normal tissue (a close margin) has negative prognostic implications and in such cases further resection or adjuvant treatment is often required.[65]

In POI's parameters, "adequate surgical margins" are defined as clean margins, consisting of 1-1.5 cm of normal visible and palpable mucosa; margins are considered "free"/ when there's a distance of, at least, 5 mm between the margin and the invasive tumor; a "close margin" indicates that the distance between the tumor and the surgical margin stands between 2-5 mm; a "positive margin" means that an *in situ* or invasive carcinoma is detected in the resection margin.

Despite the separate definitions of "close" and "positive" margins as distinct entities, they are typically grouped together when determining the need for adjuvant treatment. An involved margin necessitates the need for adjuvant treatment to reduce the likelihood of tumor recurrence at the primary site or more distant disease[65]: a positive or close margin on final histopathology is an indication for re-resection; however, this may not be possible for all patients. A close or positive margin, along with other adverse risk features such as extranodal extension (ENE), lymphovascular invasion (LVI), perineural invasion (PNI), inflammatory response and advanced T and N stages are considered as adverse risk factors and are indicators for postoperative adjuvant therapy and have been described as prognostic indicators. [64,65] Excision margins can potentially be increased at the time of surgery by including more normal tissue than the commonly accepted 1 cm resection distance from the macroscopic tumor edge; however, this can lead to poorer quality of life for patients. A positive margin following OSCC excision is associated with a poorer prognosis but should always be considered in relation to other pathological indicators of aggressive disease.[65] In primary tumor resection, vital staining with iodine solution is recommended to detect and delineate the dysplastic epithelium.[6]

In the presence of extra-nodal extension, involved margins or perineural invasion, concurrent chemotherapy with radiotherapy improves disease-free survival.[6,17] Surgical treatment may include neck dissection. This is associated with aesthetic and functional morbidity: scarring, shoulder pain, limited abduction and scapular winging, which drastically affect quality of life. This is the main reason why elective neck dissection (END) should be carefully considered, and why selective neck dissection evolved as a strategy to remove lymph node groups at greatest risk but was also intended to reduce morbidity.[67] Patients' preferences should be always considered. Elective Neck Dissection may be an option during surgical treatment. Surgical therapy, such as resection of the malignancy, combined with (END), is the most common modality for the primary treatment of OSCC.[2] Cervical lymph node status is one of the most important prognostic factors for OSCC. Neck dissection is the only accepted standard treatment for cervical node metastases.[6] Studies have pointed to a probability of occult metastasis of 20% to recommend elective treatment of the neck. This risk percentage is determined based on modern imagining techniques, such as computed tomography (CT),

magnetic resonance imaging (MRI), positron emission tomography (PET) and ultrasound, which are more reliable than palpation. When there is lower likelihood of occult lymph node metastases, the choice is between elective treatment and watchful waiting. his question certainly arises in the smaller, T1 and T2, OSCCs, for these tumors usually can be excised transorally and the neck is not entered surgically. END can be avoided in the majority of patients. However, in the few patients who need a (salvage) neck dissection for delayed metastases, treatment of the neck will probably be more extensive, such as modified radical neck dissection with or without (chemo-)radiotherapy as compared to upfront elective treatment, by a selective END (SND) followed by (chemo-) radiotherapy based on indication from pathology reports[67] Clinical N0 necks (cN0 neck), with no regional lymph node metastasis, have approximately 20–30% chance of occult node metastasis. The management of clinical N0 neck is controversial, with some clinicians advocating a 'wait and see' approach, while others favor elective neck dissection. Patients with delayed neck node metastases generally have a poorer prognosis. Elective neck dissection is also recommended when it's necessary to enter the neck, either to remove the primary tumor or for reconstruction. It may also be indicated if the patient is unlikely to return for close follow-up. For clinical N1–3 neck, it is generally recommended to perform a standard or modified radical neck dissection (RND).[6]

The co-joint administration of chemo and radiotherapy (CRT) following surgery usually leads to increased late toxicities of radiation, leading to a higher rate of non-cancer mortality in survivors. Therefore, it is extremely important to determine and predict the extent of the disease, correctly diagnosing and staging it, previous to treatment initiation. This prevents the possibility of needing to add chemo and radiotherapy after what was initially projected to be single modality surgical treatment. Multidisciplinary definitive treatment with CRT is recommended as non-surgical treatment for patients with advanced disease stages, T3 and T4, with more than one node involved, for function preservation. Standard chemotherapy consists of cisplastin, 100mg/m2 each three weeks.[17]

Presently there are no globally accepted treatment protocols for oral cancer. According to each center's experience, survival and success rates, each institution develops their own therapeutical approach. Portuguese Oncology Institute (POI) has their "Clinical Protocol for Head and Neck". Regarding oral cavity and after an initially division according to their staging (T1-2N0 or T3N0, T1-T3N1-3, T4aN0) the treatment protocol is distinguished. T1-2N0 cancers start with a local surgery and/or neck dissection. Another option for this kind of cancer is intensive RT (66Gy/6 weeks-70Gy/7weeks). Regarding T3N0, T1-T3N1-3, T4aN, local surgery complemented, or not, by ipsilateral or bilateral neck dissection is recommended for N0, N1 N2a-b and N3; for N2c, the approach is local surgery and bilateral neck dissection. When it comes to lip SCC, the approach is different for cancers staged T1-2N0 and T3, T4aN0, TN1-3. For T1-2N0, therapeutical approach consists of either local

surgery (preferential), or intensive RT (66Gy/6 weeks-70Gy/7weeks). Regarding T3, T4aN0, TN1-3, first choice treatment involves local surgery and, for N0, possible ipsilateral or bilateral neck dissection, for N1, N2a-b, N3 ipsilateral and possible contralateral neck dissection, and for N2c, bilateral neck dissection. Treatment of T3, T4aN0, TN1-3 can also be based on RT or ST (70Gy/7weeks). POI follow-up recommendations concern clinical, imagiological, laboratorial and rehabilitation aspects. Clinical follow-up should be performed every 1-3 months in the 1st year, every 2-6 months in the 2nd year, every 4-8months between 3rd and 5th year, and every 12 months after the 5th year. CT CT should be taken 6 months post treatment ending, and annually whenever there's suspicion of metastasis or relapse. Thyroid function should be examined every 6-12 months, in case of previous treatment with cervical irradiation, and patients should be accompanied in their rehabilitation process, after treatment, in order to reestablish speech, deglutition and nutritional and emotional appropriate scores.

Patients with recurrent disease have a poor life expectancy. The management of these patients is challenging and requires a multidisciplinary team approach. In the surgical management of recurrent OSCC, it is necessary to differentiate between heavily pretreated patients who have previously received adjuvant radio(chemo)therapy and those who have only received surgery as their primary treatment. Patients with a history of multimodal therapy are more difficult to treat and have a higher risk of early recurrence. Patients without prior radiotherapy (RT) have been shown to have a better outcome after tumor recurrence.[2]

Survival rates at 5-year are intimately related with tumor staging, being of 60-80% for stage I[9] and only around 30% for patients with stages III or IV.[58,68] A significant percentage of patients are diagnosed at late stages of the disease, which often qualifies the patient for only palliative treatment.[3] Most patients diagnosed with late staged OSCC won't survive 30 months into the disease.[8]

3.6.1 Adjuvant therapy

Post surgical treatment, RT is to be considered. Surgery and tumor remotion may be complicated by tissue characteristics such as fibrosed mucosa. Large primary tumors, positive or close surgical margins and signs of perineural, lymph, and or vascular invasion generally dictate the use of radiotherapy at the primary site. Radiotherapy is recommended to begin within 6 weeks after surgery, and, while radiation doses vary, a total dose of approximately 60 Gy is typical. The neck is also commonly treated, especially if there are positive nodes, in order to prevent potential metastasis and recurrence.[6] Regarding POI protocol in the presence of non clean (non free) cancer margins RT is used as an adjuvant with a dose of 66Gy/6,5 weeks.

Chemotherapy has also emerged as an important adjuvant modality for locoregional advanced oral OSCC. Although not considered a curative treatment in itself, chemotherapy can be used before surgery or in combination with radiotherapy, chemoradiotherapy, before or after surgery. Nowadays, adjuvant chemoradiotherapy is almost considered the standard of care for advanced cases.[17]

Targeted Therapeutic Stratagies mean “performing the right therapeutics, on the right patient, at the right time”. Targeted anticancer therapy gives rise to the concept of personalized cancer therapy, which can be explained as the delivery of specific targeted therapy to patients according to their specific molecular characterization of cancer cells and cancer microenvironment to promote clinical outcome. The urgent need for this type of therapy lies in the identification of biomarkers that are uniquely expressed or overexpressed in cancer and their use for early detection, prognostic prediction, clinical outcome assessment or personalized diagnostic and therapeutic planning. Two types of molecularly targeted therapy have been approved for OSCC. One of them is Epidermal Growth Factor Receptor (EGFR) targeted therapy. Studies have shown that EGFR activity is increased in a large majority of cancers, and that almost all premalignant lesions are characterized by EGFR overexpression. After being activated, by its ligands EGF or by transforming growth factor-α (TGF-α), EGFR becomes phosphorylated and subsequently activates signal transduction pathways that are crucial in cellular growth and migration. In 2006, the use of a drug called cetuximab, a chimeric monoclonal antibody that works by competitively inhibiting the binding of EGFR to its ligands, was approved. The clinical outcome of this strategy has, however, not been remarkably improved. Another recently approved targeted therapy approach in this area is anti-PD1 therapy based on immune checkpoint blockade. In the cancer immune microenvironment, the immune checkpoint receptor programmed cell death 1 (PD1), expressed on CD8+ T cells, and its ligand programmed cell death ligand 1 (PDL1), expressed on cancer cells and associated stromal cells, work together to dampen the anti-cancer effects of CD8+ T cells. Anti-PD1 therapy works by blocking the PD1-PDL1 interaction, thereby releasing the inhibition on CD8+ T cells and promoting immune normalization. For oral squamous cell carcinoma (OSCC), anti-PD1 therapy with pembrolizumab and nivolumab was approved in 2016. Although there was a statistically significant improvement in overall survival in patients with metastatic and recurrent head and neck squamous cell carcinoma (HNSCC) treated with pembrolizumab in combination with chemotherapy compared to those who received cetuximab plus chemotherapy, only a fraction of patients responded to anti-PD1 therapy and toxicities were observed in organs such as the lung, which also express PD-L1.[69]

3.7 Future Perspectives

In the next 5-10 years, it is expected that an inclusive strategy for the care of HNSCC survivors, encompassing early rehabilitation, psychosocial support, lifestyle interventions, and self-management, will be adopted.[17]

Future evaluations should consider the potential implementation of age-stratified treatment approaches.[70]

We now know enough about the causes of cancer to prevent about a third of all cases worldwide. In addition, we have sufficient information to facilitate early detection and timely treatment for another third of cases. Education of the general population as well as targeted education for individuals at specific risk, together with a solid theoretical foundation to address key aspects of oral cancer and continuous updating of oral pathology for healthcare providers, are critical to reducing the number of cases that have persisted over the past decades.[20]

The future goal of staging systems goes beyond TNM staging to create a dynamic, personalised and accurate prognostic tool that takes into account multiple variables, including tumour response to treatment and host characteristics. The ultimate goal is to develop an advanced staging system that incorporates these factors to provide an accurate and individualised assessment of prognosis.[54]

Studying the molecular biology of cancer cells to improve the efficacy of targeted therapies is an essential part of the fight against cancer. The identification of tumour-specific biomarkers remains a prerequisite for this approach. It is expected that in the foreseeable future targeted therapy will potentially replace traditional methods and become the primary option for treating tumours.[71]

Ongoing research into oral cancer is providing a clearer understanding of its molecular biology, although certain aspects remain elusive. In particular, the study of interacting pathways in oral tumors of different origins is of great interest to oral cancer researchers.[11] Currently, targeted therapies for patients with oral squamous cell carcinoma (OSCC) are limited and it is crucial to explore alternative targeting strategies. Several cell receptors in OSCC have been the focus of published research for targeted delivery of anticancer therapeutics, considering their biochemical characteristics, expression patterns and targeting strategies. Some of these receptors include urokinase-type plasminogen activator receptor, folate receptor, EGFR and PDL1, mesenchymal-epithelial transition factor, gastrin-releasing peptide receptor, podoplanin, sigma receptors, transferrin receptor 1, integrin αvβ3, and secreted protein acidic and rich in cysteine. Investigating the targeting potential of these receptors may lead to the development of novel and more effective therapeutic approaches for OSCC patients.[69]

4. Conclusion

OSCC is a current concern due to its high incidence rates. It is the most prevalent oral neoplasia and is still responsible for thousands of deaths each year. The main risk factors for OSCC are behavioral and lifestyle-related, and public awareness and education are essential.

Early diagnosis is crucial, and the most important factor concerning OSCC prognosis. Therefore, techniques have been increasingly investigated and developed, in order to address this issue.

In spite of being the preferential approach, surgical intervention is an invasive procedure and can be debilitating, impacting patients' quality of life. Targeted Therapeutic Strategies will, hopefully, help in this matter.

POI line of action is consistent with most consensus information in the literature, from surgery to neck dissection indications.

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