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Side effects of cancer treatments in the oral cavity - a narrative review

Fernando Pessoa University

Faculty of Health Sciences

Porto, 5th July 2021

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ABSTRACT

According to the latest GLOBOCAN 2020 (Sung *et al.*, 2021) publication, more the 19 million people worldwide discovered that had to fight cancer in the last year, making cancer a leading cause of death and having damaging impact in quality of life. It is a fact that the load of cancer incidence and associated death is growing quickly worldwide, reflecting the population growth, aging and changes in main risk factors associated, mainly with socioeconomic growth. Cancer of the oral cavity is a challenging disease with high mortality rates; dentists and dental specialists play a key role in all phases of oral patient care.

Cancer treatments include local treatments such as surgery and radiotherapy, and systemic treatments such as chemotherapy, immunotherapy and hematopoietic stem cell transfusions. Although they have undergone a great deal of development over the years, they continue to cause adverse effects that cannot be ignored and most often result in a diminished quality of life for patients, which can even lead to death.

As a general dentist, understanding the different cancer treatments and their impact on the oral cavity is mandatory, to anticipate complications and helping to manage them.

Keywords: cancer treatments, oral cancer, chemotherapy, radiotherapy, oral cancer surgery, immunotherapy, oral manifestations, hematopoietic cell transplant.

DEDICATION

"If man does not hope for the unexpected, he will not find it because it is nowhere to be found and inaccessible"

Heraclitus

ACKNOWLEDGMENT

"A special thank you goes to my parents, who gave me the opportunity to embark on this fantastic journey, believing in me and for always giving me the strength and courage to carry on through the good times and the bad."

To my entire family, who despite the distance have always had a thought for me.

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Finally, to all the people I have met over the years, for making me understand what I need in life and who I need to surround myself with.

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ABBREVIATION

ANC Absolute neutrophil count

CBC Complete blood count

CT Chemotherapy

CIA Chemotherapy-induced anemia

CIT Chemotherapy-induced thrombocytopenia

CRT Chemoradiotherapy

GVHD Graft versus host disease

Hb Blood hemoglobin

HBO Hyperbaric oxygen

HNC Head and neck cancer

HSCT Hematopoietic stem cell transplantation

HSV Herpes simplex virus

IDSA Infectious Disease Society of America

FDA Food and Drug Administration

FN Febrile neutropenia

Gy Gray

ONJ Osteonecrosis of the jaw

MABs Monoclonal antibodies

MRONJ Medication related osteonecrosis of the jaw

OM Oral mucositis

ONJ Osteonecrosis of the jaws

ORN Osteoradionecrosis

QoL Quality of life

RT Radiotherapy

TMJ Temporo-mandibular joint

XRT Radiation therapy

I. INTRODUCTION

Worldwide it is expected that 1 in 5 people will develop cancer during their lifetime, according to the international agency for cancer research. It is impossible to deny that in the past decades, cancer management has been having encouraging evolution, allowing patients to live longer. Nevertheless, the current treatment modalities still have the potential to result in adverse side effects, that on one hand can sometimes be life-threatening, and on the other have an impact on patient's quality of life.

Cancer treatments can be divided into local therapies as radiotherapy or surgery and the so called "systemic" (drug treatments as chemotherapy, immunotherapy or target therapy).

Cancer is a complex disease and the treatment is usually multidisciplinary. The oral cavity due to its physiology is one of the sites that often suffer collateral damage, that can be directly done to the head and neck structures or indirectly by systemic toxicity. Understanding these side effects can help to prevent or manage oral complications at the appropriate time.

Aim

The aim of this work is to expose, list and explain to the general dentist the different types of cancer treatments and the oral complications associated with them. First, the diverse modalities of cancer treatments will be exposed, then the related oral side effects and some strategies to prevent and treat the most common oral complications related to dentistry.

1. Materials e methods

The literature review was conducted using the online search engines *PubMed, Google, EndNote and Mendeley*. The consultation of the online database took place from November 2020 to May 2021, using the keywords "cancer treatments, oral cancer, chemotherapy, radiotherapy, oral cancer surgery, immunotherapy, oral manifestations, hematopoietic cell transplant". Only articles published after 2010 were included, due to the advances in therapeutics for cancer and only the ones that had references to oral manifestations of cancer treatments; after reading the abstracts, 52 articles were selected in order to meet the objectives of this review and other 48 articles were excluded for not having met the pre-requisites set.

II. DEVELOPMENT

2. Cancer therapies

2.1 Chemotherapy: Chemotherapy is a systemic therapy and can be part of the curative treatment for locally advanced cancers and is used in various clinical scenarios for neoplasms. The purpose is to achieve long-term survival without evidence of recurrence (Girard *et al.*, 2011). Chemotherapy can be used with different objectives, normally as the primary treatment modality or in combination with radiation, where it is used as a radiation sensitizer. Induction chemotherapy refers to initial chemotherapy treatment before definitive local therapy (radiotherapy or surgery). The combination of different treatment modalities has some putative advantages that include, potentially reducing the risk of metastatic recurrence and downsizing of the primary tumor to improve locoregional control. (Hartner, 2018)

2.2 Radiotherapy: Radiotherapy is defined as 'the use of high-energy radiation from X-rays, gamma rays and other sources to kill cancer cells and 'shrink tumors'. Only has oral side effects when it is used for cancer in the head and neck region. It is often used with concomitant chemotherapy for managing head and neck cancers and has a significant role in achieving "cure". Radiotherapy-induced adverse events include oral mucositis, hyposalivation, loss of taste, dental caries, osteoradionecrosis, and trismus, which have a negative impact on patients' quality of life (Kawashita et al., 2020)

A positive impact in radiation treatment of head and neck cancer (HNC) was accomplished with the introduction of intensity-modulated radiation therapy (IMRT). (Schuurhuis *et al.*, 2018). Is a highly targeted, computer-planned treatment that is delivered by a linear accelerator to solid tumour. IMRT delivers a therapeutic dose to the tumour and protects nearby dose-limiting structures such as the eyes and orbital regions, cervical spinal cord and parotid glands. By sparing the salivary glands helps in reducing xerostomia when compared with conventional radiotherapy. An improvement in QoL was reported by patients using IMRT to treat head and neck cancers. (Brennan, Bradley and Brands, 2017)

2.3 Surgery: When the cancer is located in the oral cavity, surgery has consistently played an upfront role in the treatment of head and neck and oral cancers, alone or in combination with other treatment options. As said before to radiotherapy, surgical cancer treatment only has

adverse effects in the site of the body where it is performed. The decision of surgical treatment depends on tumor size, localization, proximity to bone, and depth of infiltration. When bone is involved is necessary a segmental resection with microvascular reconstruction using fibular free flaps to restore mastication and facial contour, and allow for the placement of osteointegrated implants for orofacial and dental rehabilitation, whenever possible. (Epstein et al., 2012)

2.4 Hematopoietic stem cell transplantation: This treatment refers to any procedure where hematopoietic stem cells of any donor type and any source are given to a recipient with the intention to repopulate and replace the hematopoietic system in total or in part. Stem cells for HSCT can be derived from bone marrow, peripheral blood or cord blood. (Duarte *et al.*, 2019). HSCT is an intensive multifaceted regimen and the treatment includes long inpatient stays, frequent outpatient clinic visits, and extensive supportive therapies including frequent blood product transfusions, nutrition therapy, symptom management, and strict infection control (Morrison et al., 2017).

2.5 Immunotherapy: Immunotherapy is one of the most promising developmental directions in the field of tumor therapy, and the breakthrough effect has become a new hope for many tumor patients. However, the effective rate of tumor immunotherapy now is only 10 %–30 %, and its side effects cannot be overlooked. Long years of clinical research have led to an evolution of this treatment by targeting the tumor only, eliminating the tumor cell population effectively and with milder side effects, but then again in some cases can be serious. (Li *et al.*, 2020)

Local immunotherapy delivers treatment directly into the tumor while systemic immunotherapy targets the whole body, and may be useful in preventing recurrence and metastasis. Oral side effects are primarily related to mucositis and myelosuppression but independently of the type of the immunotherapy can develop side effects that cannot be overlooked such as nausea, emesis, hair loss, as well as “bad blood counts”. (Kroschinsky *et al.*, 2017)

3. Oral manifestations of chemotherapy: Chemotherapeutic drugs are associated with a wide spectrum of hematologic toxicities that include anemia, neutropenia, and

thrombocytopenia that could result in treatment delay and dose reduction. (Villa and Akintoye, 2018); (Razzaghdoust, Mofid and Peyghambarlou, 2020). Chemotherapy-induced myelosuppression leads to the development of these complications may present as oropharyngeal and gastrointestinal mucositis that can lead to odontogenic infections, hemorrhage, periodontal changes, hyposalivation, pain, trismus, medication related osteoradionecrosis of the jaws (MRONJ). All of these alterations in the oral cavity make the maintenance of oral hygiene more complicated, altering the oral microbial flora, increasing microbial load and making patients susceptible to opportunistic bacterial, viral, and fungal infections (Villa and Akintoye, 2018).

3.1 Anemia: Chemotherapy-induced anemia (CIA) is a common complication in patients receiving myelosuppressive chemotherapy. Blood hemoglobin (Hb) level of less than 12 g / dL is frequently defined as anemia, but many individuals may not feel much difference until the hemoglobin level falls below 11 g/dL. (Mohamady, Elsisi and Aneis, 2017)

In the mouth, anemia may manifest as pallor of the oral mucosa or loss of tongue papillation, that patients may describe tongue soreness, burning, or tingling sensation. Anemia may also trigger the development of aphthous ulcerations, a lesion that have a round/elliptical shape, with a central fibrinous pseudomembrane and an erythematous border. (Image 1) (Napeñas, Brennan and Elad, 2020)

The prediction of chemotherapy-induced severe anemia may improve the supportive care and individual management of patients at risk for this serious toxicity. Furthermore, selective use of prophylactic erythropoiesis-stimulating agents (ESAs) in these patients may maximize the patients' QoL and optimize the healthcare costs.(Razzaghdoust, Mofid and Peyghambarlou, 2020)

3.2 Neutropenia: Neutropenia is one of the most common side effects of chemotherapy; is a common dose-limiting toxicity for cytotoxic agents leading to treatment delays and/or dose reductions.(Kasi and Grothey, 2018) It is diagnosed by a routine complete blood count (CBC), with the differential count yielding a decrease in the absolute number of neutrophils. By definition mild neutropenia is an absolute neutrophil count (ANC) less than 1,500 cells/mm3. When neutrophils go below 1,000 cells/mm3 is considered moderate; when the count is lower

than 500 cells/mm3 represent a severe degree of neutropenia. Pancytopenia is when the neutropenia is associated with thrombocytopenia and anemia, patients will have clinical manifestations of the three cellular lines. (Lustberg, 2012)

Neutrophil nadir is usually reached 8-14 days after each chemotherapy cycle and returns to normal levels after 3-4 weeks, and represents the lowest value, or nadir, of the absolute neutrophil count (ANC) and absolute lymphocyte count (ALC), this is the when the risk of oral side effects is higher affecting the periodontium, the dentition, and salivary glands. (Palozzo, 2011)(Zecha *et al.*, 2019)

Infections occur frequently in neutropenic patients and are associated with considerable morbidity and mortality, and account for 25–50% of the total infections, affecting areas that include teeth, gingiva, salivary glands, and mucosa (Wong, 2014). Bacterial infections are common in the early stages of neutropenia, with fungal infections emerging if neutropenia persists beyond 7–10 days (Nesher and Rolston, 2014). There are much common oral flora and opportunistic microorganisms, but the most dangerous complication in the realm of infections are related to fungal species, like Candida ssp. (Wong, 2014). Candida albicans is a commensal fungus that colonizes oral mucosal surfaces and that is normally harmless in healthy individuals as it is maintained at low levels by specific and non-specific salivary and mucosal defense mechanisms (Veilleux and Grenier, 2019). Candidiasis is one of the most frequent oral infections during therapy for oropharyngeal cancer, which usually presents as a removable white pseudomembrane or erythematous patch on the tongue, palate, and labial commissures, causing alterations in taste, mucosal soreness, and oral burning sensation. (Sanjaya *et al.*, 2011) (Nesher and Rolston, 2014) (Kawashita et al., 2020)

Viral infection can appear in immunocompromised patients during cancer treatments. HSV is the most common, and oral presentations may be primary herpetic gingivostomatitis, an initial infection with HSV type I, characterized by erythematous, swollen, and painful gingiva or of recurrent HSV infection, a single or multiple vesicles on the keratinized mucosa that quickly rupture into ulcers. (Napeñas, Brennan and Elad, 2020) Varicella-zoster virus, when it causes shingles (herpes zoster), presents similarly to HSV with vesicular eruptions, with the distinction that its distribution is usually unilateral, correlating with a single trigeminal dermatome, but lesions can occur along with the distribution of all 3 branches of the trigeminal nerve, both intraorally and extra orally. Oral lesions are typically raised papules that may form a shallow yellow or gray ulceration and are less painful than zoster lesions. Cytomegalovirus may

manifest as a nonspecific ulcer in immunosuppressed patients. (Napeñas, Brennan and Elad, 2020)

Bacterial infections of the oral mucosa are seen primarily in immunocompromised or immunosuppressed individuals. They often present as painful erosions or ulcerations, sometimes covered in a whitish fibrinous layer. The most common bacteria involved in infections in this patient population are enterococci, but Pseudomonas aeruginosa, Neisseria species, and Escherichia coli, remain of concern. (Napeñas, Brennan and Elad, 2020)

The general dental practitioner is responsible to ease the patient's suffering, and that entails morbidity reduction and systemic infection prevention. Despite although topical antifungal agents are commonly prescribed for their lower risk of side effects and drug interactions, literature support of their efficacy is inconsistent. According to the guidelines provided by the Infectious Disease Society of America (IDSA), the first line drugs for mild oropharyngeal candidiasis are clotrimazole troches and nystatin pastilles. (Wong, 2014)

3.3 Thrombocytopenia: Thrombocytopenia is another common side effect of myelosuppressive chemotherapy and is characterized by an abnormally low blood platelet count (Shaw *et al.*, 2021) occurring in approximately 15-25% of patients receiving platinum, taxane, and/or gemcitabine-based regimens. Currently there is no Food and Drug Administration management (FDA) for chemotherapy-induced thrombocytopenia (CIT) and platelet transfusion offers only temporary, unreliable improvement that is often impractical or impossible to continue for extended periods. Therefore, the current standard of care for the management of CIT are chemotherapy dose reductions and treatment delays, allowing platelet count to recover to the desired count for subsequent administration of cancer-directed treatment. (Al-Samkari *et al.*, 2021) Oral bleeding may be inadvertently triggered by normal oral function, and may require pharmacologic or surgical intervention to control it. The oral manifestations include submucosal bleeding or fresh bleeding into the oral cavity, petechiae on mucosal surfaces or the deposit of dried or clotted blood. Sites most prone to trauma are adjacent to the teeth on the occlusal plane, such as the buccal mucosa and labial mucosa. (Napeñas, Brennan and Elad, 2020)

3.4 Mucositis: Cytotoxic chemotherapy also causes an inflammatory form of oral and gastrointestinal injury known as mucositis. Combined with myelosuppressive effects of chemotherapy, promote bacterial and fungal translocation through mucosal barriers leading to bloodstream infections, a major cause of morbidity and mortality in patients undergoing cancer treatments. (Bertolini et al., 2019). Oral mucositis (OM) can be defined as the inflammation of the mucosa in the oral cavity, and it occurs when cancer treatments (chemotherapy, radiotherapy) collapse the epithelial cells. Some of the most frequent symptoms of this condition are atrophy, erythema, ulceration, and swelling of the mucosa, which can cause several problems, including pain, increased risk of local and systemic infections, bleeding, nutritional problems associated with the difficulty of eating, among others. (Razmara and Khayamzadeh, 2019).

Clinically, the earliest sign may be characterized by leukoedema, appearing as a diffuse, poorly defined area of milky-white opalescence most noticeable on the buccal mucosa, which will disappear upon stretching. Followed by a loss of epithelial structure and integrity is observed, and severe ulceration develops, usually after 1-2 weeks. The World Health Organization (WHO) has provided a useful grading scale that combines both objective and subjective elements of diagnosis (Table 1: Modified from WHO oral mucositis scale (Wong, 2014))

Many commonly cause OM, like doxorubicin, bleomycin, fluorouracil or methotrexate. Risk factors can be divided into two categories, related to the drug, showing that the higher the dose and frequency of the drug, the greater the risk of developing OM and risk factors related to patient, age, malnutrition, pre-existing medical problems, poor oral health, trauma, liver disease and functional status of the kidneys are also associated with the severity of the disease. (Poulopoulos, Papadopoulos and Andreadis, 2017)

These manifestations usually lead to a significant decrease in QoL because they can prolong hospital stay, affect the nutritional status of the patient, increase the risk of infections, and increase opioids prescription. (Curra *et al.*, 2018)

3.5 Medication related osteonecrosis of the Jaws (MRONJ): Osteonecrosis of the jaws (ONJ) associated with medications is defined as the presence of exposed necrotic bone or the presence of a fistula, in the maxillofacial territory, which is maintained for a minimum period of 8 weeks, with no history of radiotherapy in the area. (Image 2) The diagnosis of MRONJ is made by the clinical identification of one or more ulcers with exposed bone with a necrotic

appearance in the region of the jaws, followed by the development of a mucosal lesion in the oral cavity which tends not to heal. (Image 1) (Lungu *et al.*, 2018) (Foncea *et al.*, 2020)

Bisphosphonates are mainly responsible for the development of osteonecrosis of the jaws (ONJ). They are used as chemotherapy agents against bone metastases, malignant hypercalcemia, or malignant melanoma, and for the treatment of osteoporosis. The presence of ONJ can be intense in patients receiving sunitinib and bisphosphonates, because they both increase the risk. (Poulopoulos, Papadopoulos and Andreadis, 2017)(Patel, Walshaw and Aranha, 2020)

4. Oral manifestations of radiotherapy: Radiotherapy to the head and neck region may cause undesirable radiotherapy-induced changes in the surrounding tissues, impacting on patient's QoL. These adverse events include: osteoradionecrosis, oral mucositis, hyposalivation, loss of taste, dental caries, periodontal changes, and trismus. (Kawashita *et al.*, 2020)

4.1 Osteoradionecrosis: Osteoradionecrosis (ORN) is a severe complication of radiotherapy for malignancies affecting the head and neck, defined as "a potentially severe, delayed radiation-induced injury, characterized by bone tissue necrosis, failure to heal, and exposed bone for at least three months". The incidence of ORN in the head and neck region varies from 2% to 22% in subjects with a history of radiotherapy. Various mechanisms have been proposed to explain the occurrence of ORN. The most recent theory of ORN is the fibroatrophic theory, which states that vascular changes in the bone lead to endothelial changes along with an inflammatory response. This is followed by abnormal fibroblastic activity and altered bone healing which is more susceptible to infection. (Ajila and Hegde, 2020) .

Patients who receive radiation doses greater than 50 Gy to the head and neck region are highly susceptible to ORN. (Villa and Akintoye, 2018) The local risks factors include tumor site and stage, proximity or localization in the bone, radiation field, dose of radiation, oral health status, and associated trauma (i.e. extractions just before or after radiation therapy). (Decker *et al.*, 2018)

Diagnosis and management of ORN are based on patient's history and clinical presentation combined with radiological and histopathologic tests. (Villa and Akintoye, 2018) The incidence

of ORN is decreasing through the use of new RT protocols such as IMRT, which can deliver maximum radiation to the affected area while sparing the normal surrounding tissue as far as possible. The use of IMRT in combination with good oral hygiene measures and decreased radiation to the mandible and parotid salivary glands, is showing a decrease incidence of ORN in the jaws. (Villa and Akintoye, 2018) (Ajila and Hegde, 2020)

4.2 Trismus: By definition is the inability to normally open the mouth, with mouth opening of less than or equal to 35 mm (Agarwal, Shiva Kumar and Rai, 2016), that can result from high-dose RT exposure to the TMJ region, including the masseter/pterygoid muscles, and can also occur following head and neck surgery in combination with RT or CRT (chemoradiotherapy). (Image 3A and B) (Epstein et al., 2012). The prevalence of trismus in patients with oral cancer has been reported to vary from 0% to 69%, and the wide range is thought to be due to method of trismus assessment, position and size of the tumor, and type of cancer treatment. Patients with head and neck cancer manifest symptoms of radiation fibrosis syndrome that include muscle tenderness, trismus, dysarthria, dysphagia, cervical dystonia, trigeminal neuralgia, lymphedema. (Levi & Lalla, 2018)

Difficulty in daily activities such as biting, chewing, swallowing and speaking are probable to arise and may in the future lead to poor oral hygiene, pain, weight loss and even depression. It causes a detrimental impact on QoL and oral function and should be a focus in the post-operative management of patients with oral cancer. (Agarwal, Shiva Kumar and Rai, 2016)

Patients should be informed that radiation fibrosis syndrome is a late side effect of radiotherapy, and thus they should be encouraged to perform at home exercises during and after the completion of radiation therapy. These prophylactic exercises should be reviewed with patients before commencement of radiation therapy, and clinicians should encourage patients to complete these exercises daily throughout their lives and in addition should encourage patients to visit speech pathologists for swallowing therapy and physical therapists for prophylactic physical therapy. (Epstein *et al.*, 2012)

4.3 Dental and periodontal problems: Dentition integrity is influenced by tooth-level radiation dose, reduced salivary flow rate, topical fluoride use, oral hygiene status and radiation dose. Cariogenesis is predominantly associated with hyposalivation and its related

consequences, particularly altered composition of saliva and change in oral microflora to a highly cariogenic bacteria flora. Radiation-related caries are indirect complications of dentition, with a rapid onset and progression, but clinically are not related to severe pain. Alteration starts mainly on the labial surface due to low pH saliva and loss of remineralization capacity, the minerals of enamel and dentin are easily dissolved; then carious lesion progresses to affect the entire crown and results in increased friability and breakdown of tooth. (De Felice *et al.*, 2014) Radiation-associated dental caries may require dental extractions and consequently result in an increased risk of developing osteoradionecrosis (ORN) of the jaw. (Schuurhuis *et al.*, 2018). Radiotherapy treatments also involve the risk of developing periodontal disease, an inflammatory disease affecting the tissues surrounding the teeth resulting in inflammation of the gums and loss of bone adjacent to the affect teeth. Preventive periodontal and dental therapies are particularly important aspects in treating the cancer patient. Diagnosis, treatment, and establishment of regular maintenance protocols are essential in treatment of periodontal disease to prevent excessive oral bacterial shift changes. Further, is also important to extract teeth with untreatable periodontal problems, before starting cancer treatments to minimize risks of ONJ. (Decker *et al.*, 2018)

4.4 Glossodynia: Loss of taste occurs rapidly early in the course of radiation therapy to the oral cavity. Most patients report that the sense of taste is essentially nonexistent by the third or fourth week of treatment and, after the completion of radiation therapy; most patients report some taste improvement within 1 to 2 months. Full recovery of taste usually requires 2 to 4 months but, in some patients, taste never returns to normal, at least in part because of xerostomia. (Sideras, Hallemeier and Loprinzi, 2013)

Taste change during RT, typically occurs concurrent with mucosal damage, damaging taste receptor cells in epithelial taste buds. Persisting change in taste may reflect decreased turnover rates of taste receptor cells, lack of connectivity between receptor cells and neurons, and possible neuronal damage. Physiological changes in the oral environment and loss of taste progenitor cells may result in decreased recovery of damaged or lost taste buds over time. Evaluation of recovery of taste function should be based upon taste testing, as it is unpredictable, and may never fully recover. (Epstein *et al.*, 2020)

4.5 Xerostomia: Presents an acute and late side effect when treating head and neck cancer (HNC) patients with curative intended radiotherapy in the oral region. Is defined as the subjective feeling of oral dryness, with hyposalivation (physiological reduction in salivary flow) (Kaae, Stenfeldt and Eriksen, 2016); is perhaps the most commonly reported oral sequela among patients receiving radiotherapy for head and neck cancers. (Wong, 2014)

Saliva plays a central role in dental and oral care, in lubricating mucosa, in contributing to antimicrobial activity. Saliva daily volume is produced by submandibular glands (about 70%; serous and mucous secretion), parotid gland (about 20%; serous secretion) and minor salivary glands (less than 10%). Damage to major and minor salivary glands causes alteration in quantity, quality and consistency of saliva that turns into a white and viscous fluid. (De Felice *et al.*, 2014) Clinically, the condition becomes apparent as saliva becomes "scant, sticky, and viscous." (Wong, 2014)

The diagnosis of xerostomia requires a detailed medical history, which includes a detailed description of the symptoms, diseases and the use of medicines. The measurement of salivary flow is the basis for the diagnosis of xerostomia but it can be a problem to determine the amount of saliva that is indicative of the dysfunction of the salivary glands (Łysik et al., 2019). Hyposalivation is defined when whole saliva flow is of ≤0.2 mL/min, and symptoms of xerostomia often become evident when saliva flow is below 0.1–0.2 mL/min. (Kaae, Stenfeldt and Eriksen, 2016)

Frequent complaints of patients with xerostomia are the sensation of dry and burning mouth. Dry mouth impairs basic oral functions and increase the risk of caries, periodontal disease and opportunistic infections, directly influencing patients' QoL. (Łysik et al., 2019) (BARBIERI, COSTA and GUERRA, 2020).

5. Surgery of head and neck cancer: Today, most head and neck cancer subsites, such as the larynx, hypopharynx, nasopharynx, and oropharynx, are treated with radiation therapy (XRT) with or without chemotherapy as a primary treatment modality. Surgery is reserved for the salvage of recurrent tumors that occur within the head and neck in the absence of distant metastasis (lung, liver). (Shanti and O'Malley, 2018) Regarding oral cancer patients, the general treatment timeline consists on surgical treatment followed by postoperative chemo or radiation therapy depending on the surgical margins and specific tumor properties. Removal of

tumors that abut or invade the mandible or maxilla will require partial or complete removal of a small or large segment of bone in order to obtain clear surgical margins. Curative surgery consists of wide excision of the lesion with 1.0 to 1.5 cm mucosal and deep free margins.

5.1 Aesthetics and oral function modifications: The main complications after oncosurgery of the oral cavity, involve the remotion of large tumors in the mandible and maxilla that can lead to aesthetics alterations and/or loss of oral function. (Alberga *et al.*, 2021)

Over the years a number of classifications have been proposed to maxillectomies and mandibulectomies. Regarding the mandibula is still, accepted the classification proposed by Laney in 1979, that in a simplistic way divides in marginal (when the continuity of the bone is preserved) or segmental (lose of mandibular continuity). Recently, in 2016 Brown and his colleges published a new classification for mandibulectomies taking into account the reconstruction and/or rehabilitation. Based on the principle that the mandible has four corners: two vertical corners that make the angles of the mandible, and two horizontal corners that are centred at the canine teeth on each side in the dentate mandible and are roughly 7 mm anterior from the mental foramen in the edentulous jaw. These corners show the points of change in the form of the mandible and the increasing need to shape a graft with osteotomies. The anterior or horizontal corners are essential to maintain function and aesthetic (Figure 1). (Brown *et al.*, 2016)

Classification of maxillectomies and midface defects have always been controverse because of the complexity of the defect. The first ever classification for maxillectomies was publish by Aramany in 1978 based on the maxillary defects that patients from the university hospital of Pittsburg had, diving into classes from the most to the less common (Nunez and Kenyon, 2010). Brown et al, in 2010 projected a new classification of maxillary defects, taking into account, vertical and horizontal extent of the bony defect of the maxilla and the involvement of the nasal cavity or orbit and reconstruction and/or oral rehabilitation (Figure 2) (Image 4A). (Shanti and O'Malley, 2018)

The main complications after oncosurgery of the oral cavity, involve the remotion of large tumors in the mandible and the maxilla that lead to aesthetics alterations and/or loss of oral function as the patient knew. The anatomical changes, associated with bone or tissue loss conduct to restricted movement or loss of function in the case of neck dissections, leading to

cosmetic disfigurement and compromised oral function (difficulty in swallowing, eating, speaking, trismus), xerostomia, taste and neurological alterations. (Image 4 B and C) (Nandini *et al.*, 2020) If maxilla and mandible-sparing interventions are possible (partial thickness mandibular surgery, marginal mandibulectomy or subtotal maxillectomy) should be performed, associated with the reconstruction of the defect may involve the use of vascularized or no vascularized autogenous material, prosthetic devices with dental and/or zygomatic implants or obturative oral and facial prosthetics. (Image 5) (Ozaki et al., 2018).

6. Hematopoietic stem cell transplantation: Allogenic hematopoietic cell transplantation (AlloHCT) is used to replace diseased hematopoiesis and as a form of immunotherapy to induce a graft-versus-tumor or immune response in patients with hematologic malignancies. Candidates for alloHCT are prepared for transplantation using preoperative regimens described as chemotherapy, total body irradiation, or total lymphoid irradiation. These conditioning regimens depend largely on the grafted donor cells to eradicate cancer. Donor grafts can be obtained from a human leukocyte antigen (HLA)-matched sibling, an HLA-matched unrelated donor, umbilical cord blood, or an HLA-haploidenticale-related donor. In cases with persistence or recurrence of hematologic cancers, donor lymphocyte infusions can be provided a booster anticancer (Haverman *et al.*, 2020)

6.1 Graft versus host disease: Graft-versus-host disease (GVHD) is a complication of certain types of transplants in which the graft contains a large number of donor immune cells. Can be life threating side effect in some patients that have undergone hematopoietic stem cell transplantation. GVHD is triggered by the reactivity of donor-derived immune cells against allogeneic recipient tissues. Typically, this process affects the skin, liver, eyes, gastrointestinal tract, lungs and joints. GVHD usually occurs following allogeneic haematopoietic stem cell transplantation (HSCT), although the condition may occur following a blood transfusion, intestine transplant or face transplant (Elad, Aljitawi and Zadik, 2021).

There are two types of GVHD, acute or chronic: acute form usually occurs within a few weeks of the transplantation. Typical signs and symptoms may include nausea, vomiting, abdominal pain, diarrhea, bloody stool, and jaundice. The main risk factor is the major histocompatibility antigens (HLA) mismatch. Chronic GVHD may immediately follow the acute stage or may

occur several months later. The oral manifestation of GVHD varies with the severity of the condition and is associated with a spectrum of presentations, mild oral mucosal erythema, desquamative gingivitis, loss of lingual papillae, lichenoid hyperkeratosis, angular cheilitis, lichenoid-like changes and Sjogren's like syndrome, whereas acute GVHD patients may encounter painful desquamation and ulcerative-pseudomembranous reactions among all the oral cavity, particularly in the buccal mucosa (Wong, 2014).

7. **Immunotherapy:** The treatment is commonly given intravenously in a cyclic schedule and causes side effects such as nausea, emesis, hair loss, as well as "bad blood counts". Inhibitory drugs as monoclonal antibodies (MABs) such as rituximab or cetuximab, tyrosine kinase inhibitors, imatinib have been which have been developed and approved for various hematological and solid tumors in recent years, have been associated with the side effects above. Nevertheless, these new classes of immune therapeutics may induce overwhelming inflammatory responses and autoimmunity. Unspecific side effects relating to constitutional diseases, gastrointestinal symptoms, mucositis, and myelosuppression are commonly mild or lacking, but life-threatening complications often result from infections, inhibition of angiogenetic pathways, severe inflammatory syndromes, and autoimmune disorders. (Kroschinsky *et al.*, 2017) Oral side effects are primarily related with mucositis and myelosuppression. (Li *et al.*, 2020)

IV. DISCUSSION

The number of new cancers has been increasing worldwide in the past years but different treatment options (new therapies and new drugs) and new treatment combinations have been approved and being used. The handling of this group of diseases is still challenging in many aspects of all, the diseases themselves, the treatment options and their impact on patient's quality of life. The importance of promoting preventive measures, regular examinations in patients with risk factors and look for potentially malignant signs and symptoms of cancer is unquestionable, but is also essential to know the different types of cancer therapies and understand their unpleasant impact, as healthy cells suffer from aggressive treatments like the cancer ones. The direct and indirect toxicity to the mucosal lining of the mouth is due to is rapidly cell turnover, and is major target of cancer treatment related side effects. To these is

added a complex microbiological flora and possibility of trauma, that can be minor, during the normal function shows why the oral cavity is affected so easily by cancer management therapies. Dentists and dental specialists play a key role in all phases of patient care. Prevention through education, on how to stop smoking and safe alcohol consumption is critical, early detection and referral of premalignant lesions and oral cancer and ongoing surveillance, monitoring and preservation of oral health are just a few of the dentist's many roles in patients with cancer.

V. CONCLUSION

The oral cavity as discussed before, due to its specific physiopathology tends to be one of the areas of the body that suffers from adverse side effects of oncological treatments, directly throw to their tissue, as radiotherapy or surgery when the cancer is located in the oral cavity or systemically when patients go throw chemotherapy, hematopoietic stem cell transplantation or immunotherapy. Understanding the basic mechanisms of action of these therapies permits dental practitioner to anticipate complications during treatment and perform dental treatments, if needed with the safety that is required. Each patient should be cared for by a multidisciplinary team specialized in the treatment of head and neck tumors such as surgeons, oncologists, radiologists, dentists, nutritionists, rehabilitation and reconstructive specialists. This is to support the overall oral and systemic health and improve QoL during oncotreatment and in cancer survivors. A careful watch on patients is also necessary to prevent the risk of recurrences and development of secondary tumors.

IMAGE INDEX

Image 1: Oral ulceration due to anemia.

Provided by Professor Filipa Pinto de Oliveira

Image 2: Medication related osteonecrosis of the jaw in a patient being treated for Non Hodgkin Lymphoma

Provided by Professor Filipa Pinto de Oliveira

Image 3A: Trismus in an 18 year old patient treated with radiotherapy for rhabdomyosarcoma in the zygomatic region at the age of 10 years old.

Provided by Professor Filipa Pinto de Oliveira

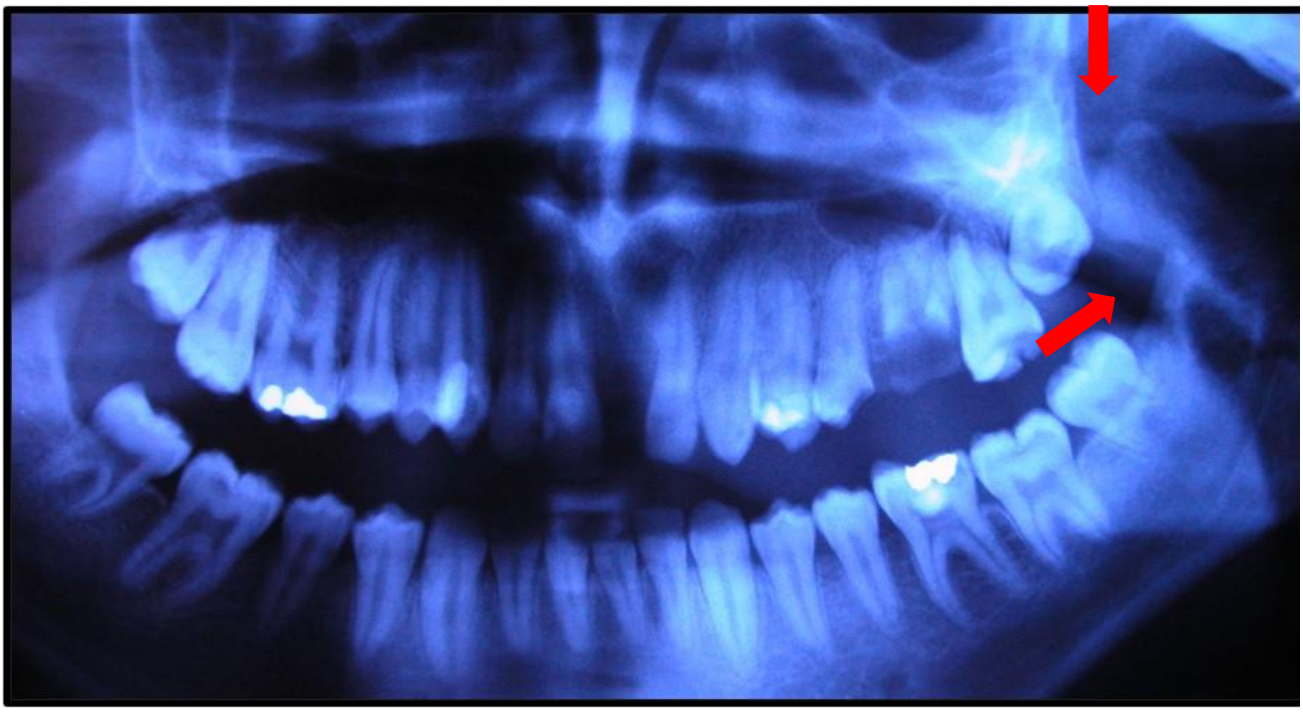


Image 3B: Old panoramic Rx showing left TMJ alteration (red arrow) in a 18 year old patient, treated with radiotherapy for rhabdomyosarcoma in the zygomatic region at the age of 10 years old. Provided by Professor Filipa Pinto de Oliveira

Image 4A: Aesthetics alterations and oral function changes in a patient treated for a squamous cell carcinoma in the maxilla with surgery.

Provided by Professor Filipa Pinto de Oliveira

Image 4B: Aesthetics alterations and oral function changes in a patient treated for a squamous cell carcinoma in the maxilla with surgery.

Provided by Professor Filipa Pinto de Oliveira

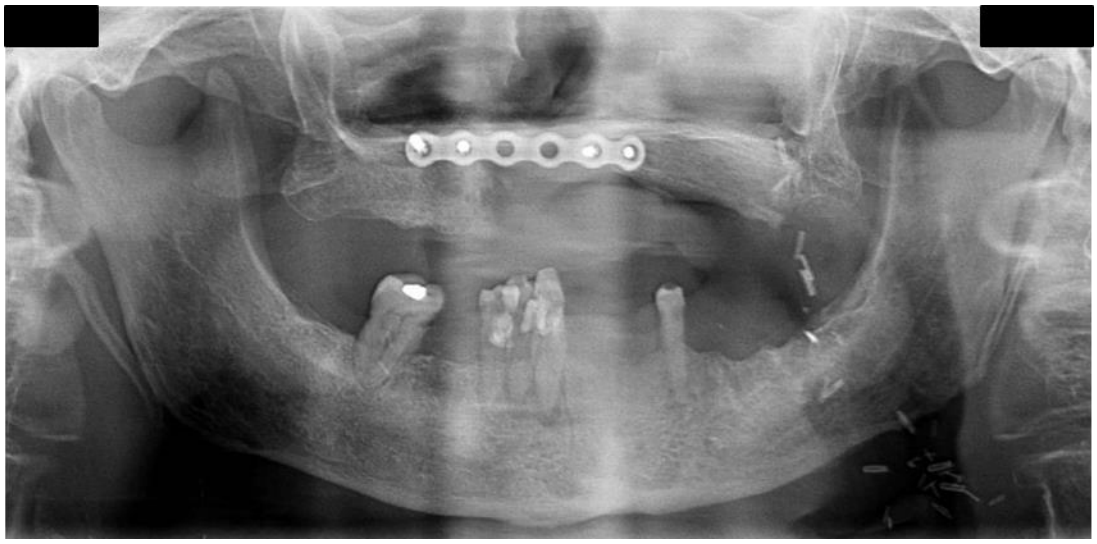


Image 4C: Aesthetics alterations and oral function changes in a patient treated for a squamous cell carcinoma in the maxilla with surgery and facial reconstruction. Provided by Professor Filipa Pinto de Oliveira

Image 5: Patient treated with marginal mandibulectomy and reconstruction of the defect with a flap. Provided by Professor Filipa Pinto de Oliveira

TABLE INDEX

Table 1: Modified from WHO oral mucositis scale (Wong., 2014)

GRADE	CLINICAL PRESENTATION
0	Normal
1	Soreness with/without erythema
2	Ulceration and erythema
3	Ulceration and extensive erythema, patient cannot swallow solid food
4	Mucositis of such severity that feeding is not possible

Table2: Modified from medications used in the treatment of various cancers that are antiangiogenic or targets of the Vascular Endothelial Growth Factor (VEGF) pathway that have been associated with jaw necrosis. (Patel, Walshaw and Aranha, 2020)

DRUG	MECAHNISM OF ACTION	PRIMARY INDICATION
Sunitinib (Sutent®)	Tyrosine kinase inhibitor	GIST, RCC, pNET
Sorafenib (Nexavar®)	Tyrosine kinase inhibitor	HCC, RCC
Bevacizumab (Avastin®)	Humanized monoclonal antibody	mCRC, NSCLC, Glio, mRCC
Sirolimus (Rapamune®)	Mammalian target of rapamycin pathway	Organ rejection in renal transplant

GIST gastrointestinal stromal tumor; RCC renal cell carcinoma; pNET pancreatic neuroendocrine tumor, HCC hepatocellular carcinoma; mCRC metastatic colorectal carcinoma; NSCLC non-squamous non-small cell lung carcinoma; Glio Glioblastoma; mRCC metastatic renal cell carcinoma.

FIGURE INDEX

Figure 1: Proposed classification of mandibular defects (Brown *et al.*, 2016)

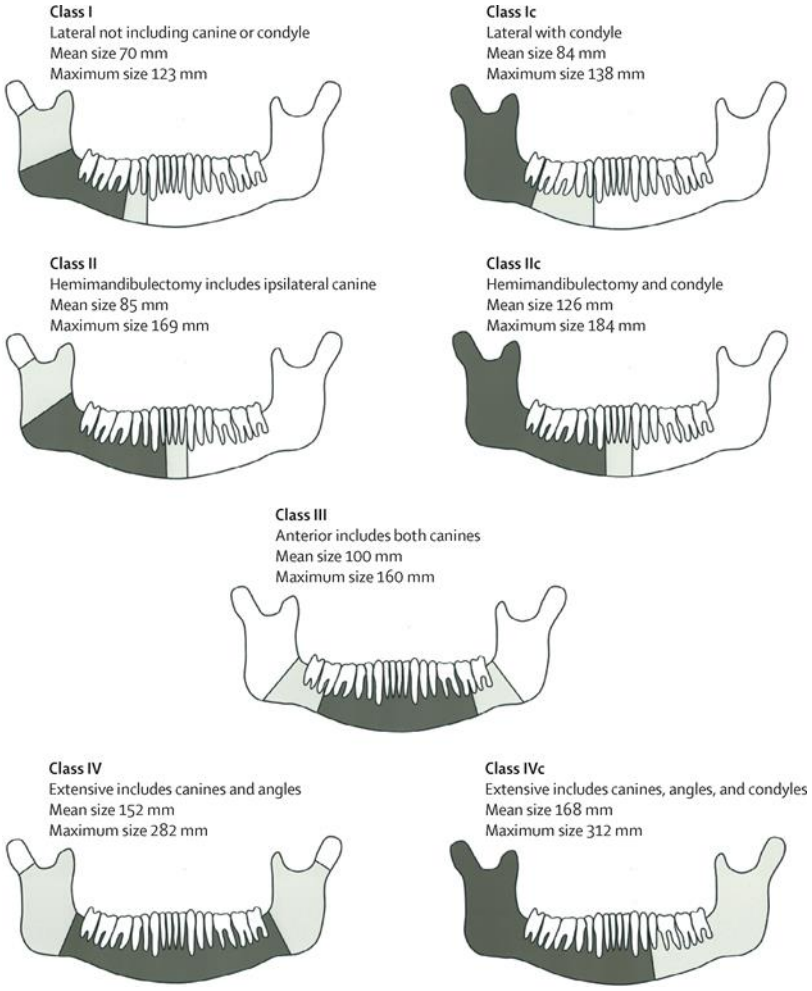
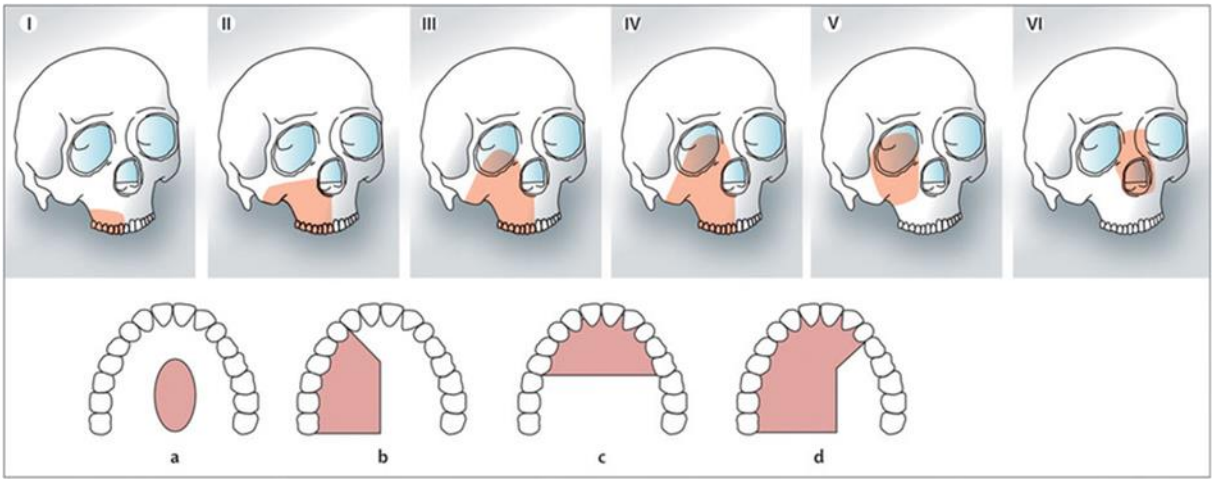


Figure 2: Classification of the maxillary and midface defects (Ragbir, Brown and Mehanna, 2016)



Classification of the maxillary and midface defects. Classes I–VI relate to the vertical component of the defect including orbitomaxillary (class V) nasomaxillary (class VI) when often the palate and dental alveolus are intact. Classes a–d relate to the increasing size of the palatal and dento-alveolar part of the defect indicating increasing difficulty in obtaining good results with obturation.

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