Int. J. Odontostomat.,
17(3):356-371, 2023.

Current Insights on Neoplasms and Adequate Dental Care for Patients with Oral Cancer

Actualización sobre Neoplasmas y su Correcta Atención Odontológica en Pacientes con Cancer Oral

Jefferson David Melo de Matos[1,2]; Leonardo Jiro Nomura Nakano[1]; Guilherme da Rocha Scalzer Lopes[1]; Sérgio Eberson Da Silva Mais[3]; Adriano Baldotto Barbosa[5]; Marco Antonio Bottino[1] & Valdir Cabral Andrade[4]

MATOS, J. D. M.; NAKANO, L. J. N.; LOPES, G. R. S.; MAIS, S. E. S.; BARBOSA, A. B.; BOTTINO, M. A. & ANDRADE, V. C. Current insights on neoplasms and adequate dental care for patients with oral cancer. *Int. J. odontostomat., 17(3)*:356-371, 2023.

ABSTRACT: The present study aimed to review the literature on the main complications of antineoplastic therapies and the degree of knowledge of dental surgeons about these complications. A bibliographic search was conducted in the main health databases PUBMED (www.pubmed.gov) and Scholar Google (www.scholar.google.com.br), in which studies published from 1987 to 2023 were collected. Laboratory studies, case reports, systematic and literature reviews, which were developed in living individuals, about the main neoplastic genes and their relationship with the cells of individuals affected by neoplasms in the head and neck region, and studies on the care with this group of patients, were included. Therefore, articles that did not deal with neoplasm and the main complications of antineoplastic therapies were excluded. Neoplasm is a clonal disorder, caused by mutations, resulting from changes in the genetic structure of cells. Each healthy cell has instructions on how to grow and divide. In the presence of any error in these instructions (mutation), it can result in a diseased cell that, when proliferating, may cause a tumor. Countless knowledge has been accumulated over the years on the main characteristics of neoplasms, whether they are cancer cell biology, carcinogenesis mechanism, neoplasms of the maxillofacial system and sequels of antineoplastic treatments. In this context, methods have been developed that offer a better quality of life for patients diagnosed with this pathology, as well as preventive vaccine models that may, in the not too distant future, contribute to this goal to be successfully achieved.

KEY WORDS: genes, neoplasm, head and neck neoplasms, early detection of cancer, pathology, oral, dental research.

INTRODUCTION

Neoplasm is a name given to a set of more than 100 different diseases, which in turn, have in common the disorderly growth of cells (WHO, 2002). Dividing rapidly, these cells group together to form tumors, which invade tissues and can invade neighboring and even distant organs (metastases) (Neville & Day, 2002).

Neoplasm is a clonal disorder, caused by mutations, resulting from changes in the genetic structure (DNA) of cells (Hills & Diflley, 2014). Each healthy cell has instructions on how to grow and divide. In the presence of any error in these instructions (mutation), it can result in a diseased cell that, when proliferating, may cause a tumor (Gaillard *et al*., 2015). Most neoplasms arise from a single cell that has been disturbed in its mechanism of regulation of proliferation and apoptosis (Golemis *et al*, 2018). It can appear in any part of the body, however, some organs are more

[1] Department of Dental Materials and Prosthodontics, São Paulo State University (Unesp), Institute of Science and Technology, São José dos Campos - SP, Brazil.
[2] Department of Restorative Dental Sciences, Center for Dental Biomaterials, University of Florida (UF Health), Gainesville, Florida, 32611, USA.
[3] Departament of Physiology, Graduate Program in Rehabilitation Sciences, Hospital for Rehabilitation of Craniofacial Anomalies, University of São Paulo, Bauru, Brazil.
[4] Department of Oral and Maxillofacial Surgery, Universidade Federal de Juiz de Fora UFJF, Governador Valadares - MG, Brazil.
[5] Midwest Dental Arts Inc., Palm Bay, FL 32909, USA.

Received: 2023-03-23 Accepted: 2023-05-23

affected than others and each organ, in turn, can be affected by different types of tumor, more or less aggressive (Kitao *et al*, 2018).

The World Cancer Report, published by the International Association for Research on Cancer (IARC), linked to the World Health Organization (WHO), showed an expressive growth in the number of new cases per year, from 10 million in 2000 to 15 million in 2022, the majority of cases occurring in underdeveloped countries (WHO, 2002). In more developed countries, neoplasms are also an important cause of death; this is due to the increase in the elderly population and their new lifestyles associated with cancer, which is considered the third largest cause of death in the world (Jemal *et al*., 2011).

There are many factors involved in the origin of the neoplasms, among these factors, the genetic predisposition stands out, in addition to social conditions, eating habits, alcohol and tobacco consumption as aggravating factors, infections, hygiene deficiencies, poor care, occupational factors, sexual habits and solar radiation (Caccelli & Rapoport, 2008; Oliveira *et al*., 2008; Colombo & Rahal, 2009). It is worth mentioning that the nomenclatures used for tumors are not common, but a special one gains notoriety, which is carcinoma, when the tumors start in epithelial cells (skin and mucous membranes) (Alvarenga *et al*., 2008), and sarcoma, when they start in connective cells (bones, muscles, ligaments and cartilage) (Cardoso *et al*., 2005).

The locations of malignant tumors in the head and neck are varied, about 40 % affect the oral cavity, 25 % the larynx, 15 % the pharynx, 7 % the salivary glands and 13 % other regions of the maxillofacial complex. The disease has a greater predilection for males, in the fourth decade of life (Cardoso *et al*., 2005; Alvarenga *et al*., 2008). The histological type of squamous cell carcinoma (SCC) is the most prevalent, representing 90 % of all cases of head-neck cancer (Alvarenga *et al*., 2008; Colombo & Rahal, 2009). According to the National Cancer Institute, it is estimated that 4,010 new cases of oral cancer in women and 11,280 in men occured in Brazil in 2008. These estimated values correspond to a risk of 3.92 new cases per 100 thousand women and 11.54 for every 100 thousand men (Instituto Nacional de Câncer, 2008).

There is a tireless search for the best treatment for individuals with neoplasm, enabling the development of several studies regarding the best conduct of neoplasms (Shenoy *et al*., 2007). Healing is still a distant reality, in this context, professionals seek a better quality of life for affected individuals. Thus, cancer treatment remains a major challenge, with a poor prognosis in more advanced cases (Epstein *et al*., 2004). In general, the recommended antineoplastic therapies are surgical resection with a safety margin of the tumor and its extensions, radiotherapy (RTx), chemotherapy (CTx) and even organ transplants, which can be used alone or together (Shenoy *et al*., 2007; Caccelli & Rapoport, 2008).

RTx is a therapeutic approach, in which it uses ionizing radiation to destroy tumor cells, in turn, promoting tissue ionization, making them electrically unstable (Jham & Freire, 2006; Rocha *et al*., 2008). This instability damages cellular deoxyribonucleic acid, preventing neoplastic cell replication (Salazar *et al*., 2008) and has three distinct objectives: curative, remissive and symptomatic. When the main objective of treatment is to eliminate all neoplastic cells, the therapeutic approach has a curative character, whereas when the objective is to complement surgical or chemotherapy treatment, or to reduce part of the tumor, it is remissive. The symptomatic purpose of radiation is to reduce localized pain from non-operable tumors (Rodrigues *et al*, 2006). As it is a non-selective treatment, RTx does not have the ability to differentiate between malignant and healthy cells, which make it toxic to the body (Salazar *et al*., 2008). The cells that are present in the mucosa of the oral cavity, larynx or pharynx, have high mitotic capacity and low radioresistance. For these reasons, they are easy targets for the development of adverse reactions due to radiation exposure (Neville & Day, 2002; Day *et al*., 2003). It is worth mentioning that the adverse consequences resulting from radiotherapy treatment depend on the volume and area that will be irradiated, whether the exposure will be unilateral or bilateral, the fractionation of doses, the total dose, age, social habits such as smoking and alcoholism, clinical conditions of the patient, in addition to other associated treatments (Rocha *et al*., 2008; Sassi & Machado, 2009).

CTx is another antineoplastic therapeutic approach, where chemical substances are used alone or in combination, with the objective of decreasing the population of malignant cells (Hartner, 2018). As in RTx, the performance is nonspecific, being able to harm both healthy and malignant cells, generating, in many cases, an unacceptable toxicity that causes periodic interruption of treatment for the patient to

recover (Carneiro-Neto *et al*., 2017). CTx can be classified as curative, when the objective is to eradicate evidence of the neoplasm; palliative, when it aims to improve the symptoms resulting from cancer, improving the quality of life for the incurable patient; enhancer, when used in conjunction with RTx for a better result in the therapeutic dose / toxic dose ratio; adjuvant, when performed after surgical or radiotherapy treatment; neoadjuvant, when it is performed before surgical or radiotherapy (Instituto Nacional de Câncer, 2008;Specenier & Vermorken, 2009; Carneiro-Neto *et al*, 2017; Hartner, 2018). For CTx start, it is important that there is a prior assessment of the patient, in order to ensure that his body is in a position to overcome its toxic effects, such as, for example, the immunosuppression caused by bone marrow suppression (Instituto Nacional de Câncer, 2008; Specenier & Vermorken, 2009; Carneiro-Neto *et al*, 2017; Hartner, 2018).

Since RTx and CTx cause several sequelae that affect the oral cavity, the dental surgeon has a fundamental role in supporting these patients, acting in an important way in the prevention, cure and oral rehabilitation (Wong & Wiesenfeld, 2018; Migliorati & Migliorati, 2000). Among the oral complications of antineoplastic therapies, it is possible to highlight some more prevalent and important ones, such as radio and chemo-induced mucositis, osteoradionecrosis (ORN), xerostomia, accompanied or not by candidiasis, and radiation caries (Epstein *et al*., 2004; Cardoso *et al*., 2005).

In order to reduce the consequences of these sequelae, dental evaluation should be performed, preferably, before the beginning of cancer treatment and remain during and after therapy (Migliorati & Migliorati, 2000). The patient should be instructed on the importance of maintaining oral health during antineoplastic therapies, on non-cariogenic diet habits, flossing and tooth brushing after meals (Joyston-Bechal, 1992; Marques, 2000). The procedures performed before cancer treatment by the dental surgeon mainly include preventive and curative procedures, which aim to improve the oral condition of patients who will be irradiated, that is, to avoid or mitigate the sequelae resulting from the treatment (Ragghianti *et al*., 2002).

The present study aimed to review the literature on the main complications of antineoplastic therapies and the degree of knowledge of dental surgeons about these complications.

Evidence Acquisition

Source Selection. A bibliographic search was conducted in the main health databases PUBMED (www.pubmed.gov) and Scholar Google (www.scholar.google.com.br), in which studies published from 1987 to 2023 were collected. In the first stage, the list of retrieved articles was examined by reading the titles and abstracts. In the second stage, the studies were selected by reading the full contents. Two authors (JDMM and LJNN) performed stages 1 and 2. Experimental, clinical, case-control, randomized controlled and laboratory cohort studies, case reports, systematic reviews and literature reviews, which were developed in living individuals, were included. Therefore, articles that did not deal with the subject in question, letters to the editor, opinion article, duplicated literature in databases and literature that did not address the variables under study, were excluded.

Data Source. Through bibliographic search 120 articles were selected, which 80 articles were extracted from PUBMED (www.pubmed.gov) and 40 Scholar Google (www.scholar.google.com.br). The following specific medical subject titles and keywords were used: Genes, Neoplasm (DeCS/MeSH Terms); Head and Neck Neoplasms (DeCS/MeSH Terms); Early Detection of Cancer (DeCS/MeSH Terms); Pathology, Oral (DeCS/MeSH Terms); Dental Research (DeCS/MeSH Terms) (Fig. 1).

According to Table I, it can be seen that the average publication of articles in the period from 1987 to 2023 from the Pubmed database was 2.96 and with a standard deviation of 2.42. While at Scholar Google, the average was 1.48 and the standard deviation 1.84 (Fig. 2). Thus, it was possible to verify that there was a significant variation in the number of articles in both databases (Fig. 3).

Evidence Synthesis. In a context where radiotherapy and chemotherapy cause several sequelae that affect the oral cavity, the dental surgeon needs to have prior knowledge regarding the biology of cancer, behavior of oral neoplasms and the main care that should be taken with this group of patients; whether acting in prevention, rehabilitation, cure or improvement in quality of life (Migliorati & Migliorati, 2000). Among the oral complications of antineoplastic therapies, it is possible to highlight some in particular that their manifestation is more prevalent, such as radio and chemo-induced mucositis, osteoradionecrosis, xerostomia, accompanied or not by candidiasis and radiation caries (Epstein *et al*., 2004; Cardoso *et al*., 2005).

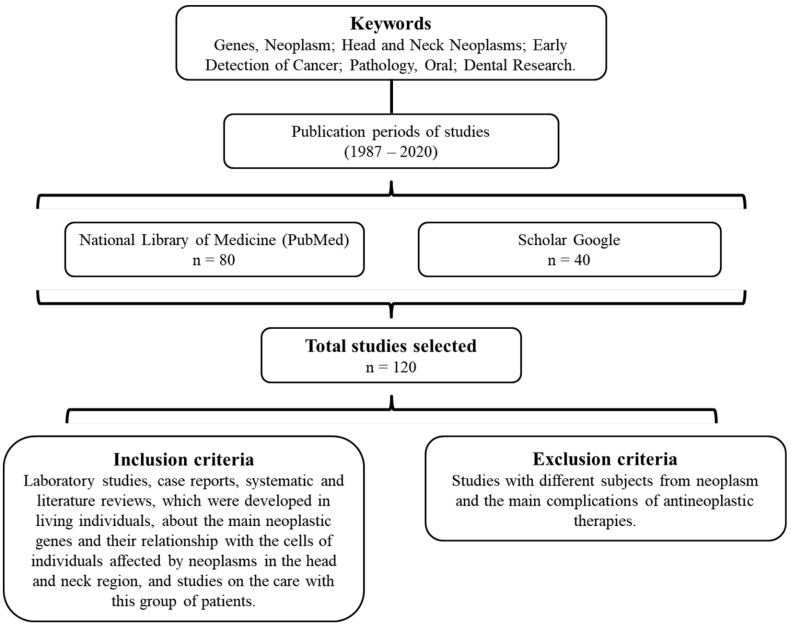

Fig. 1. Articles selection flowchart.

Table I. Mean ± standard deviation of the number of studies in the main health databases.

Database	Mean ± Stardard Deviation	Total Studies (1987-2023)
Pubmed	2.96 ± 2.42	80
Google Scholar	1.48 ± 1.84	40

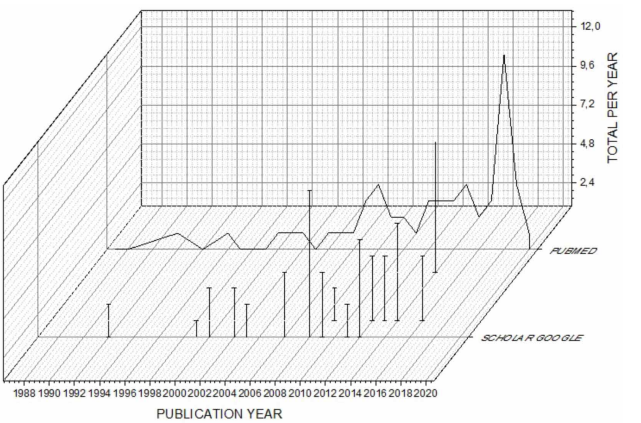

Fig. 3. Total articles published per year in the two main health databases.

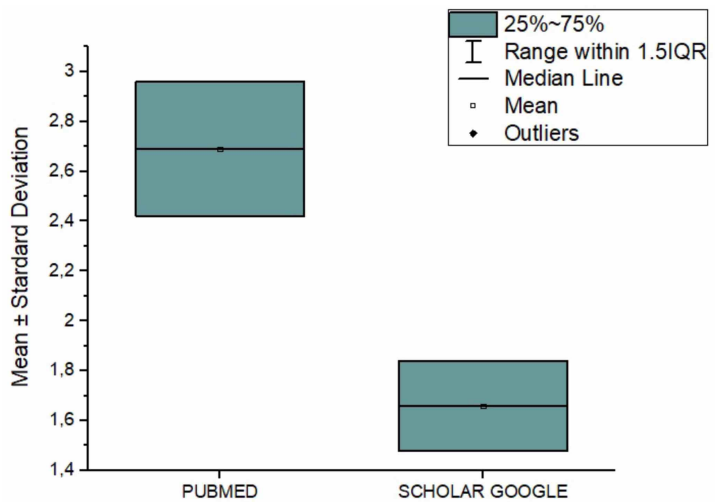

Fig. 2. Mean and standard deviation of total articles published per year in the two main health databases.

Cancer Biology. Neoplasm is a clonal disorder, caused by mutations, resulting from changes in the genetic structure (DNA) of cells. Each healthy cell has instructions on how to grow and divide (Tsantoulis *et al*., 2007) (Fig. 4). In the presence of any error in these instructions (mutation), it can result in a diseased cell that, when proliferating, may cause a tumor (Das & Nagpal, 2002; Kirita *et al*., 2014).

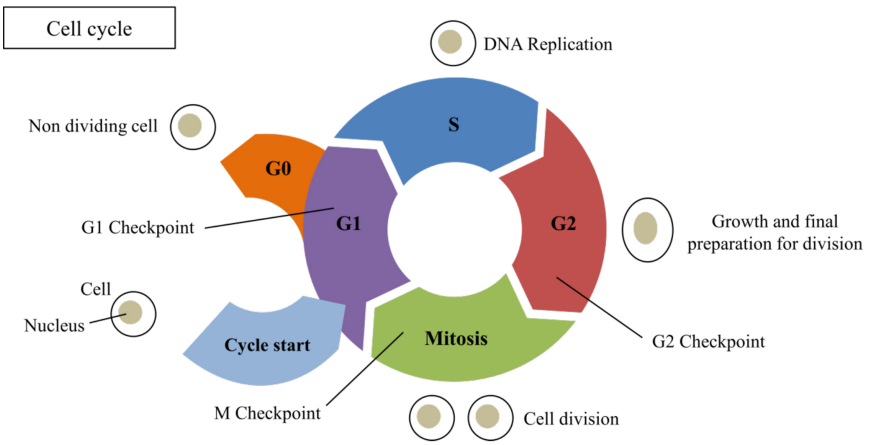

Fig. 4. Phases of the cell cycle.

A neoplastic cell presents a variation in its phenotype, when compared to the normal cell (Das & Nagpal, 2002). It is worth noting that the phenotype is the result of multiple non-linear interactions between the genes of this cell. Thus, neoplastic cells simultaneously exhibit six phenotypes that allow for a proliferative advantage. These being, self-sufficiency in proliferative signs, regardless of growth factors, insensitivity to antiproliferative signs, with insensitivity to growth inhibitors, avoidance of apoptosis, unlimited replicative potential, in turn offering immortality to the neoplastic cell; sustained angiogenesis, that is, the ability to form its own vascularization, regardless of the condition of the organism; and cell invasion, followed by metastasis (Das & Nagpal, 2002; Tsantoulis *et al*., 2007; Kirita, 2014) (Fig. 5).

Normal cells can exhibit any of these phenotypes, but they are no longer normal when they exhibit them simultaneously (Tsantoulis *et al*., 2007). For example, macrophages are capable of invasion, that is, migration to sites with inflammation; stem cells have unlimited replicative potential and some cells require low amounts of growth factors for proliferation (Das & Nagpal, 2002; Kirita, 2014). Thus, the phenotype only becomes malignant when there are specific interactions between the genes, which ends up resulting in the appearance of the six phenotypes presented; therefore, all

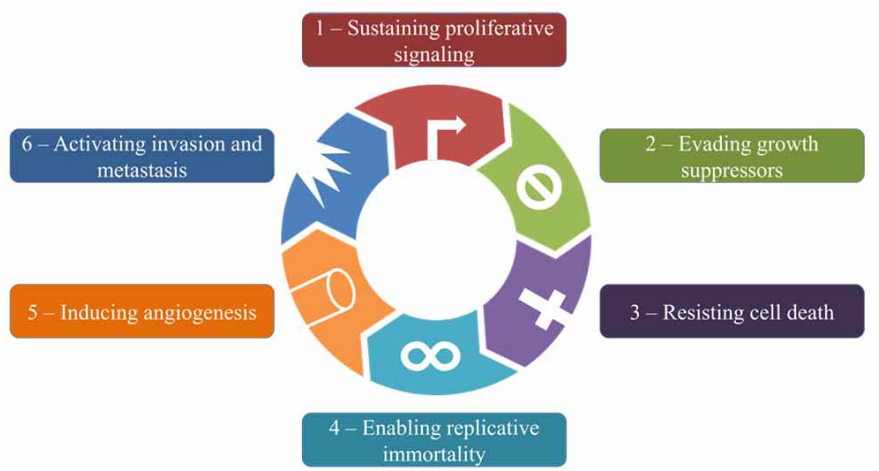

Fig. 5. The hallmarks of cancer.

of these phenotypes appear gradually, but without a defined order (Das & Nagpal, 2002; Tsantoulis *et al*., 2007; Kirita, 2014; Lambert *et al*., 2017; Irimie *et al*., 2018; Boras *et al*., 2018).

The characteristics resulting from the rearrangement of interactions between genes for the formation of the malignant phenotype occur through biochemical changes in proteins and metabolites, without occurring genetic alterations (Das & Nagpal, 2002; Tsantoulis *et al*., 2007; Kirita, 2014; Lambert *et al*., 2017; Irimie *et al*., 2018; Boras *et al*., 2018). On the other hand, there may be possible changes in important genes in the network of gene interaction, either through somatic mutations, chromosomal translocations, chromosomal deletions or inversions (Das & Nagpal, 2002). These changes are related to the presence of carcinogens, which promote the formation of cancer, be it chemical substances, for example, the benzopyrene that is present in cigarettes or ionizing radiation, which allows the inactivation of genes responsible for the integrity of the genome and the presence of viruses, such as HPV (Harden & Munger, 2017; Irimie *et al*., 2018) (Fig. 6). In this context, when the integration of the HPV genome into the cell's DNA occurs, there is a rupture of the E2 gene. In turn, this gene inhibits the expression of the E6 and E7 genes (Herber *et al*., 1996). The E6 protein acts by degrading the tumor suppressor cell protein, p53, while E7 binds to the pRB protein (retinoblastoma susceptibility protein), which negatively regulates the cell cycle from G1 to S (Cheah & Looi, 1998; Lambert *et al*., 2017; Harden & Munger, 2017; Shillitoe, 2018) (Fig. 7).

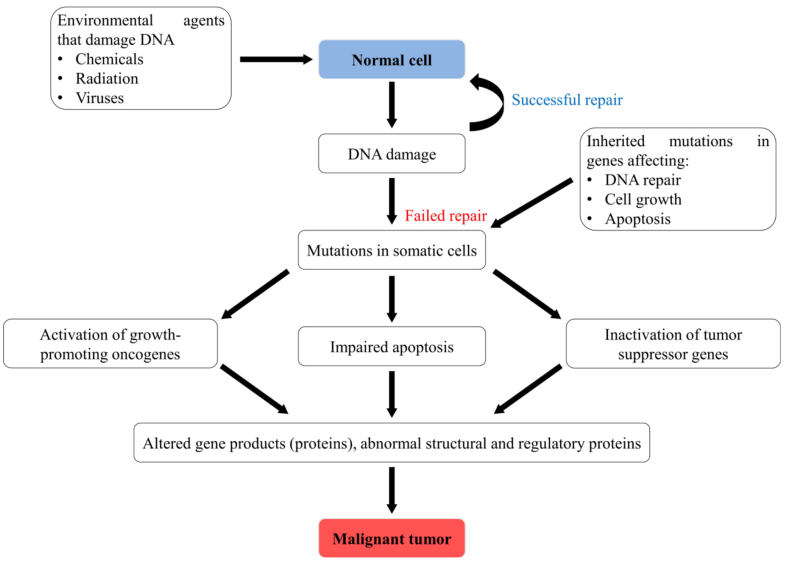

Fig. 6 Overview of Carcinogenesis.

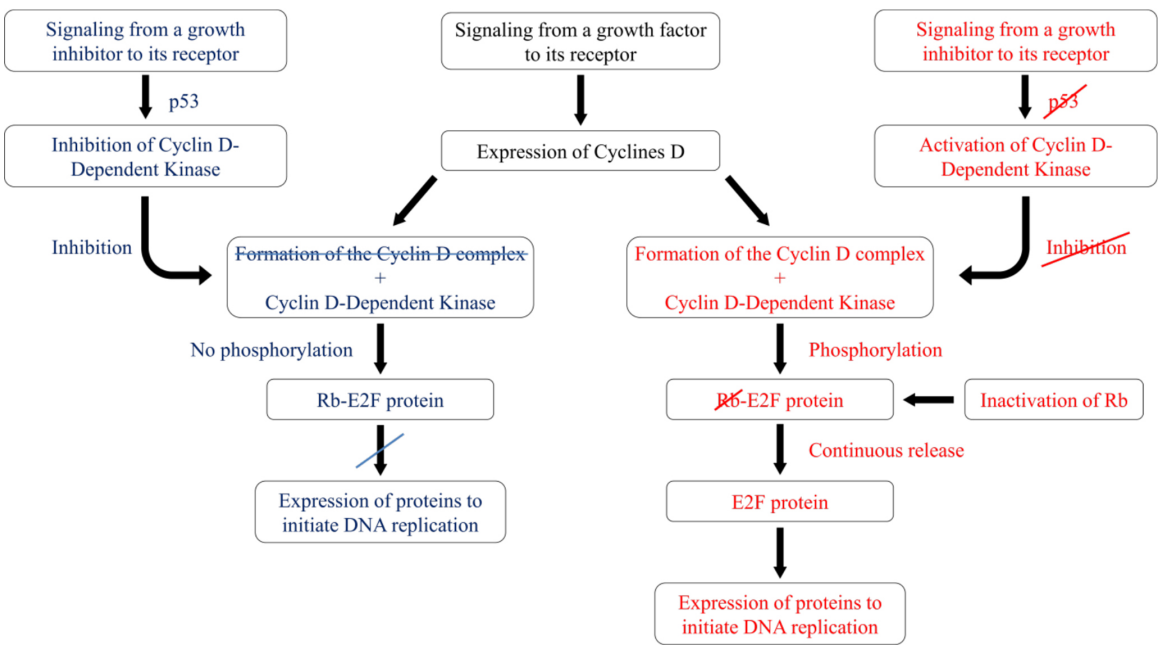

Fig. 7. Mechanisms that influence protein expression to initiate DNA replication.

Numerous are the genes that are present in the network of gene interaction, thus contributing to the emergence of neoplasms (Huang *et al*., 2019). Among the various types of genes, three in particular gain notoriety, namely: oncogenes, tumor suppressor genes and genes encoding DNA repair proteins (Khurshid *et al*., 2018). Oncogenes are normal genes involved in the positive control of cell proliferation, which when overexpressed promote the malignant phenotype (Kurman, 2013). Tumors arise when processes that control cell division, location and mortality, fail (Han *et al*., 2015). The loss of control of these mechanisms may be related to mutations in three categories of genes: proto-oncogenes, genes responsible for signaling the pathways that regulate the cell cycle and that, when mutable or present in many copies, turn into oncogens; tumor suppressor genes, which normally prevent deregulation of the cycle, repair division errors and control the apoptosis process and which, when changeable, lose that function; genes that encode DNA repair enzymes,

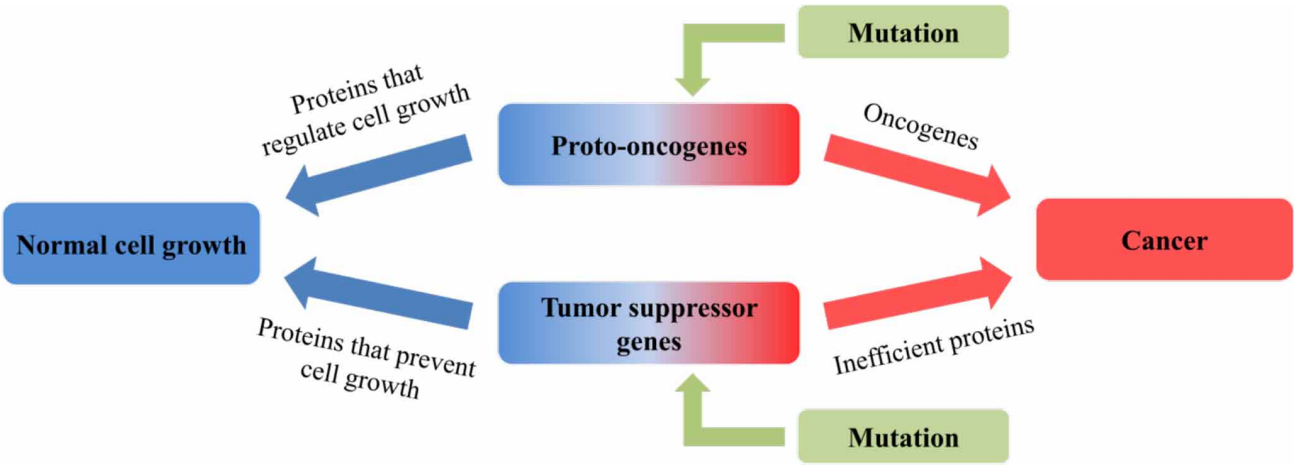

Fig. 8. Mechanism of proto-oncogenes and tumor suppressor genes.

Table II. Most well-known oncogenes, the main types of cancer caused and the role of genes on cells.

Gene	Type of cancer caused	Function
MYC	Chronic lymphocytic leukemia and lymphoma.	It encodes the pro-proliferative nuclear transcription factor. Therefore, the mutation process can increase the expression of this gene and cell proliferation (Yu *et al.,* 2018).
RET	Paraganglioma, lung cancer, papillary carcinoma, medullary thyroid carcinoma.	It encodes a cellular receptor that can mutate and become active without binding the respective growth factor (Weinreb *et al.,* 2018).
RAS	Countless types of cancer.	It encodes a proliferative signal transduction protein that can become active even without receiving a p revious signal (continuously producing signal) (Ali *et al.,* 2017).

which when mutable promote genetic instability (Das & Nagpal, 2002; Kirita, 2014; Irimie *et al*., 2018; Boras *et al*., 2018; Weinreb *et al*., 2018). When mentioning about oncogens and their related genes, three in special are highlighted because they are present in most individuals who have some neoplasia (Lambert *et al*., 2017; Kurman, 2013; Weinreb *et al*., 2018) (Fig. 8) (Table II).

Overexpression of oncogenes may result from a mutation of the RAS gene, which is present in most colon tumors or a chromosomal rearrangement, where a gene is positioned next to a promoter, increasing its expression (Mazumder *et al*., 2019; Katoh, 2012). Even in the formation of a new gene, as in chronic myeloid leukemia, a fusion of the ABR and BCL genes occurs, triggering a proliferation45,53 (Herber *et al*., 1996; Weinreb *et al*., 2018). Finally, there is no less important gene amplification, which is related to the generation of new copies of the oncogene, increasing its expression, this process commonly occurs with the MYC gene. It is worth mentioning that about 100 oncogenes have already been discovered; all of which have a dominant effect on the individual's phenotype. Thus, it is enough to overexpress one of the copies of an oncogene for the production of the malignant phenotype, even in the presence of a normal copy.

Tumor Suppressor Genes (TSGs) are normal genes involved in the negative control of cell proliferation that, when not expressed, promote the malignant phenotype (Senapati *et al*., 2018). For a TSG not to be fully expressed, it is necessary that both copies of these genes are mutated, lost or have mutilated promoter regions, that is, with a recessive effect, and its underexpression or lack of expression can be caused mainly by loss of heterozygosity (Sellers *et al*., 2019) (Table III).

For the establishment of a cancer, six stages or mutations are necessary, this according to the appearance of each characteristic of the malignant phenotype (Rivera, 2015). Therefore, to occur these steps, the genome must be unstable due to the malfunctioning of DNA repair genes, otherwise, such events are rare (Speight *et al*., 2018). Defects in DNA repair genes lead to carcinogenesis63. Thus, these six stages of carcinogenesis are distributed regularly (Fukuda *et al*., 2012; Rivera, 2015) (Figs. 5 and 6).

Table III. Main tumor suppressor genes and their functions.

Tumor Suppressor Genes (TSG)	Function
TGFBR	Receptor that inhibits cell growth in response to the TGF beta cytokine (inhibits lymphocyte proliferation, and macrophage functions) (Kim & Minna, 2018).
Rb	Regulates the cell cycle (Weinreb *et al.,* 2018; Kim & Minna, 2018).
NF1	Inhibition of proliferative signal transduction by RAS (Ali *et al*., 2017; Kim & Minna, 2018).
APC	Inhibits proliferative signal transduction (Ali *et al.,* 2017; Kim & Minna, 2018).
P53	Inhibits cell growth and multiplication if it detects DNA damage. It promotes damage repair and, if this is not possible, it triggers programmed cell death - apoptosis (Senapati *et al.,* 2018; Kim & Minna, 2018)
P16	Inhibits cell multiplication similar to p53 (Kim & Minna, 2018; Sritippho *et al.,* 2015).

The first stage of carcinogenesis is self-sufficiency, where the production of the growth factors themselves occurs (autocrine action), followed by activation of growth factor receptors without binding these factors (mutation or increase in expression). Consecutively, there is a lack of signaling after activation of growth receptors (also by mutation or increased expression) (Tanaka & Ishigamori, 2011; Fukuda *et al*., 2012). The second stage is insensitivity to growth inhibitors, which corresponds to the disturbance of the control of the cell cycle in the transition from G1 to S phase. The main targets are Rb (retinoblastoma protein) and inhibitors of Cyclin-Dependent Kinases (CDKs), which control the cell cycle in G1 / S, thus activating cell proliferation in a normal cell (Fukuda *et al*., 2012; Curry *et al*., 2014). In contrast, in a diseased or neoplastic cell, there is inhibition of proliferation, so the control of the cell cycle in G1 / S is compromised (Tanaka & Ishigamori, 2011; Fukuda *et al*., 2012). The third stage involves evasion of apoptosis, that is, there is an inactivation of the tumor suppressor gene p53, this gene triggering apoptosis when DNA repair is not possible. In some cases, overexpression of oncogenes can also contribute to the inhibition of apoptosis (Fukuda *et al*., 2012; Feller *et al*., 2013). The fourth stage is related to an activation of telomerase or immortality of cancer cells, allowing the DNA telomerases ribonucleoproteins to bind to the complementary telomeric sequence of RNA, using it as a template to catalyze the repeated addition of a specific sequence rich in G at the three end of a DNA molecule, forming the telomer (Fukuda *et al*., 2012). That is, the increase in telomeric activity can allow replication and uncontrolled cell growth. It is interesting to clarify that the telomere is presented as an end of a linear chromosome, in which it consists of consecutive repetitions of a small sequence rich in G in the terminal portion three, in which it complements the sequence of the portion five (Fukuda *et al*., 2012). This is all because the ends of the chromosomes present a problem for the replication sequence (Tanaka & Ishigamori, 2011; Fukuda *et al*., 2012; Feller *et al*., 2013; Curry *et al*., 2014). In this context, the absence of telomerase would result in the chromosome shortening at each replicative stage (Fukuda *et al*., 2012). The fifth stage refers to an invasive angiogenesis, in this sense a formation of new blood vessels from the existing vessels, so these new vessels can contribute to the proliferation of tumor cells (Merlo *et al*., 2006; Fukuda *et al*., 2012). Finally, the sixth and last stage the invasion capacity is reported, thus the cells of the first generation or progeny, proliferate excessively (Hanahan & Weinberg, 2000; Fukuda *et al*., 2012). However, it remains united in a single mass, thus forming a benign tumor, which can be removed completely (Fukuda *et al*., 2012; Pickup *et al*., 2014). On the other hand, a tumor is only malignant when its cells have the capacity to invade neighboring tissues, consecutively these tumor cells falls into the bloodstream or lymphatic vessels, forming secondary tumors in different regions of the organism (Hanahan & Weinberg, 2000; Merlo *et al*., 2006; Neville, 2009; Tanaka & Ishigamori, 2011; Fukuda *et al*., 2012; Feller *et al*., 2013; Curry *et al*., 2014; Pickup *et al*., 2014).

Radio-induced and chemo-induced oral mucositis. Labbate *et al*. (2003), studied 21 patients with head and neck cancer, treated with RTx, investigating the presence of mucositis. Patients were divided into a placebo group (n = 11) and a medication group (n = 10). In the first group, patients underwent 2 mouthwashes daily with distilled water. In the second group, two mouthwashes were performed daily with 0.12 % chlorhexidine gluconate. Patients were followed up weekly by filling out a quality of life questionnaire, taking into account aspects of pain, appetite, taste and eating habits. Local examinations were also carried out to detect changes in the mucosa, according to the protocol established by the WHO and the Group of Radiation Therapy in Oncology (grades 0 to 4). The results were more significant for the Placebo group, which had the most intense mucositis grading in 6 of

the 10 weeks of evaluation. The difference between the groups decreased over the weeks and all patients in the study had mucositis at the end of the study. It was also observed that the frequency and intensity of pain were worse in the 4th week of RTx and that in the 7th week they had a great change in taste. All patients undergoing RTx had changes in eating habits, and changes in appetite were more common in the placebo group. Regarding the other parameters of life, there was no significant difference between groups.

Redding (2005), when reviewing the pertinent literature on oral mucositis, observed that one of the main side effects caused by cancer therapy is oral mucositis, mainly caused by RTx in the head and neck. This frequent complication of RTx causes severe pain in the mouth, which can compromise the time and effectiveness of the treatment. According to the authors, in the past, the primary objective of the dental surgeon in these cases was to treat mucositis and to ease oral pain, making treatment less uncomfortable. Currently, the main objective would be to prevent the appearance of mucositis. The authors reported multiple strategies to prevent oral mucositis. Among them, topical therapies with the use of glutamine stand out, which provide nutrients necessary for cancer therapy. Another approach would be to prevent oral infection with proper oral hygiene, which can help prevent mucositis and also prevent infections of the cavity from spreading to the systemic circulation. In a damaged mucosa, the risk of secondary infection would be higher. They also explained the pathogenesis of oral mucositis, which occurs due to the loss of epithelial cells, caused by the death of proliferative stem cells from the mucosa. In a period of 7 to 14 days, the cells of the oral mucosa undergo a renewal, which can be observed in the healing of chemo-induced mucositis (QTx is usually performed every 21 days). However, in RTx, which is continuous and daily, the damage to the mucosa is constant and there is no time for adequate recovery. The authors conclude that it is necessary to have a specific staff of professionals in the field of dentistry, with the objective of accompanying oncologists in oral treatment in patients undergoing cancer therapies.

Cardoso *et al*. (2005), followed-up 12 patients with head and neck neoplasms, who underwent RTx at the Head and Neck Surgery Service of the Federal University of São Paulo (Unifesp / EPM). All patients received dental treatment before, during and at least six months after RTx. Three weeks before RTx, the pre-radiotherapy phase included analysis of decayed teeth with endodontic needs, residual roots, mobility, gingival and periodontal changes and oral hygiene guidance. During RTx, weekly observations were made to view the changes caused in the oral cavity. The patient's general condition, presence of dermatitis, dry mouth, changes in taste, caries, dysphagia, mucositis, candidiasis, ORN and trismus were observed. After the end of RTx, patients continued to be evaluated, at intervals, at 7, 15, 30, 60, 90, 120 and 180 days. The observation results showed that dermatitis occurred in all patients after the second week of RTx, mucositis started in the first week, all had candidiasis and dysphagia was present in 11 patients. There was general weakness and decreased quality of life, aggravated by mucositis and other sequelae such as changes in taste, dysphagia, dry mouth, poor appetite and opportunistic infections. The authors concluded that during the period of radiotherapy treatment, a multidisciplinary relationship is essential, involving the dentist with the medical team and other health professionals, thus providing an improvement in the patients' quality of life, offering better conditions for recovery, focusing not only on tumor remission, but also on its reintegration into the family and social environment.

Llonch *et al*. (2006), analyzed 50 patients submitted to RTx in megavoltage with doses between 66 and 70 Gy and also QTx with the use of cisplatin or carboplatin. The degrees of mucositis were assessed weekly according to the CTC (common toxicity criteria), on a 4-degree scale. Between the 3rd and 6th weeks of treatment, it was observed that the highest incidence of mucositis grades 1 and 2 was in the oropharynx region. Approximately 86 % of the patients had their treatment interrupted at some stage of the therapy, and 36 % of the interruptions were caused by mucositis, with an average stopping time of between 5 to 9 days for mucosal recovery. All patients with diabetes mellitus had their treatment interrupted by oral mucositis, and diabetic patients with oral cavity and oropharynx cancer had a higher risk of developing more aggressive mucositis (grades 3 and 4). According to the authors, diabetes is associated with a higher risk and greater severity of mucositis in RTx, and this pathology must be taken into account in patients irradiated in the head and neck. The study also showed the importance of oral mucositis in interrupting antineoplastic treatments, with the potential to decrease the effectiveness of these treatments. It also demonstrated that diabetes mellitus is an isolated factor that favored the appearance of severe mucositis, generating the need for special monitoring.

Kumar *et al*. (2016), carried out a study to evaluate the treatment of radio-induced oral mucositis. The study was carried out in the RTx and oral medicine departments of the Regional Cancer Center in Trivandrum, India. Twenty-four patients with oral mucositis were randomly divided into two groups of 12 patients each. In Group I (control group), mouthwashes were administered three times a day with 2g of powdered sodium bicarbonate, dissolved in warm water. In group II (study group), mouthwashes were administered with 0.03 % triclosan (Colgate Palmolive India Ltd, Colgate Plax), also three times a day. In both groups, patients were made aware of the main signs and symptoms of mucositis and a detailed clinical examination of the oral mucosa was carried out. Guidance was given to rinse the mouthwash during the entire RTx period and continue 45 days after the end of the treatment. On the first day of RTx, as well as every Monday and Thursday during the treatment, notes were made about food consumption (solid, semi-solid or liquid foods), the patients' body weight and the graduation of oral mucositis was performed through clinical examination. Group II patients had easier feeding and the mucositis index was significantly lower, resulting in less weight loss. The authors emphasize the importance of controlling radio-induced oral mucositis, taking into account its severity and duration, and that triclosan is more effective than sodium bicarbonate in this respect.

Hespanhol *et al*. (2010), analyzed the occurrence of oral manifestations in patients undergoing QTx, considering the sex, age and type of tumor. 97 medical records of patients undergoing chemotherapy treatment, collected at an oncology hospital in the city of Juiz de Fora (MG), which serves patients in the Unified Health System (SUS) in the region from 2000 to 2007, were analyzed. The results showed a large age range, ranging from 3 to 93 years. The main oral manifestations of QTx were mucositis, xerostomia, fungal and viral infections. Mucositis was the most prevalent lesion in both sexes, in all age groups, with prevalence in males aged 0-10 years (37.5 %). Xerostomia, or dry mouth, was the second most incident oral manifestation, accompanied by candidiasis and was verified only in women (average of 33.3 %). Patients aged between 71 and 80 years were the ones who most presented oral manifestations in both sexes. The authors concluded that both in the preliminary phase and during QTx, the presence of the dental surgeon in the multidisciplinary team is extremely important, given the high incidence of oral complications.

Suresh *et al*. (2010), evaluated the clinical consequences of interruptions in radiotherapy and the relationship with ulcerative mucositis, looking for strategies to reduce the mucositis index during treatment of head and neck cancer. 218 patients with head and neck cancer participated in this study, all of them middle-aged men, most of them with advanced disease (half with tumors in clinical stage III and 10 % in stage IV). Patients were treated with concomitant RTx and QTx and mucositis was assessed clinically. The results showed an increased incidence of mucositis related to poor oral hygiene and the use of tobacco, as well as higher doses of radiation. Patients with advanced disease had a higher rate of mucositis, possibly due to the need for more aggressive treatment. It was also observed that older patients had a higher risk of developing mucositis, possibly because they had less healing capacity. However, according to the authors, this report contrasts with other studies, in which young patients had a higher risk of developing mucositis, taking into account that young people have a greater number of cells in the proliferative phase. It was concluded that it is possible to predict the evolution of mucositis in a patient who undergo RTx in head and neck and concomitant QTx. Avoiding treatment interruptions by decreasing the duration of therapy improves patients' chances of healing, according to the authors.

Panghal *et al*. (2012), evaluated 186 patients with SCC of the oral cavity in order to assess the prevalence of mucositis. The study was carried out at the RTx unit of the Regional Cancer Institute, Haryana, India, from January 2007 to October 2009. The patients were divided into 3 groups, according to the chosen form of treatment: Group I - treated with RTx; Group II-treated with QTx; Group III - treated with concomitant QTx and RTx. The degree of mucositis was measured according to the scale: grade 0, without changes; grade 1, pain and erythema; grade 2, erythema and ulcers, managing to feed on solids; grade 3, ulcers, using only liquid diet; grade 4, patient cannot eat. The results demonstrated that mucositis was the most significant factor in group I. In group II, there were cases of neutropenia, febrile episodes, and the most prevalent factor was grade 3 oral mucositis. In group III, neutropenic cases, oral infection were reported, and the most common risk factor was mucositis grade 4. The authors concluded that both RTx and QTx are associated with severe mucositis and other undesirable effects, affecting the patient's quality of life. Taking into account that the occurrences of oral cancer are likely to increase in the future, it is very important that

healthcare professionals become familiar with the complications of antineoplastic treatments.

Osteoradionecrosis. Epstein *et al*. (1987), carried out a case study, where they analyzed approximately 1000 medical records of patients affected by head and neck cancer who received RTx between 1977 and 1984, seeking to evaluate the installation of Osteoradionecrosis (ORN) in these patients. According to the authors, of the 1000 cases evaluated, 2.6 % developed these sequelae, of which, 23% suffered pathological jaw fracture and 19 % continued to suffer signs and symptoms of the active and progressive sequelae until the study date. The authors reported ORN as a serious complication, which has a difficult and prolonged treatment. The low incidence of ORN found in the study by Epstein *et al*. (1987), may be related to dental prevention, planning and dental care after radiation. According to the authors, all patients evaluated received complete dental care prior to RTx and after receiving radiation. All individuals had their oral condition assessed, and those who required dental surgical therapy after RTx, were referred to specialists who performed minimally traumatic surgeries, with tension-free primary closure of the surgical wound tissues. In addition, all were followed up with antibiotic therapy. Epstein *et al*. (1987), concluded that ORN is a serious complication of ionizing radiation, and that the dose and fractionation of radiation received are related to the development of the sequel, as patients who receive high doses of radiation are more likely to appear ORN. They also added that dental prevention and maintenance of oral hygiene after cancer treatment are crucial in preventing this complication.

Curi & Dib (1997) carried out a retrospective study, in which 104 patients with ORN were evaluated, who were treated in the Oral Surgery department of Hospital AC Camargo between 1972 and 1992. All 104 cases had a history of ORN for one minimum period of 3 months, and were followed for at least 1 year. The authors evaluated the possible relationship between the appearance of the sequel and some variables: chosen treatment, patient's oral hygiene and dental conditions, anatomical location of the tumor, total daily dose of radiation received, duration of treatment, time during which the patient received radiation until the appearance of the sequel, and if there was dental trauma after radiotherapy treatment. Of the 104 individuals evaluated, 89.4 % had ORN related to induced trauma, and 10.6 % suffered the spontaneous appearance of this sequel. Trauma-induced ORN developed on average 18 months after RTx, with two peaks of incidence being identified: the first in the first 12 months after RTx and the second between 24 and 60 months. In the first peak, there was no difference between patients who received and patients who did not receive treatment prior to cancer treatment. The surgery to remove the tumor and tumor necrosis were the main factors for the appearance of this complication in the initial phase, being only 16 % of cases related to oral infections during this phase. The second peak had dental and oral factors involved in 60% of the cases, mainly the surgical trauma of extractions. Of the cases that did not receive dental care before irradiation, 9.6% of the incidence of ORN was due to tooth extractions. Oral hygiene before cancer treatment appeared to have played an important role in preventing trauma-induced sequelae in this second phase. Cases of acute ORN were observed in 25.1% of the patients of which 9.6% suffered pathological mandible fracture. Chronic and stable ORN were observed in 32.6%. The prevalence was higher in the mandible (95.2 %) than the maxilla (4.8 %). In this study, a positive relationship was identified between the location of the tumor and the incidence of ORN, as there was a high incidence of ORN related to oral tumors, especially lingual, of the retromolar region and oral floor. For the authors, it is possible that the incidence of the sequel is directly related to the involvement of the mandibular bone in the radiation field, and also, due to the removal of arteries important for the maintenance of blood flow in the mandible during the removal of cancer in these regions. The daily radiation dose received by the patients was also related to the appearance of the complication, only 5 patients (4.8 %), who received a total dose below 5,000 Gy developed ORN. In this study, patients who needed to undergo oral surgery after RTx, underwent a minimally traumatic procedure, with tension-free primary closure of the surgical wound tissues, in an attempt to reduce the chances of ORN.

Curi & Kowaslki (2003) reviewed the pathogenesis and pathophysiology of ORN, in order to describe the main risk factors for this sequel. The authors referred to ORN as the most severe and serious complication arising from RTx, which is characterized by the loss of lining mucosa, or cutaneous tissue of the oral cavity and consequent exposure of necrotic bone tissue for a certain time. Its clinical behavior can vary from small asymptomatic bone exposures, to more severe and acute processes that evolve to pathological fractures of the affected bone. These sequelae can occur spontaneously, when

related to the total and / or daily dose of radiation received by the tissues, being more frequently identified in cases where the dose is greater than 65 Gy, and less identified in cases where the dose is less than 50 Gy. And it can also be induced by some trauma, which represents approximately 90 % of all cases. According to the authors, late trauma-induced ORN, triggered mainly by dental procedures, can and should be avoided from a dental evaluation prior to cancer treatment. This assessment must judge not only the dental conditions, but also the patient's socioeconomic and cultural conditions, prognosis, planning and physical structure of care, in order to determine the dental conduct for each patient. They also reviewed the clinical aspects of ORN, which, radiographically, presents itself as a poorly defined radiolucent image without sclerotic margins, often accompanied by radiopaque areas, due to the formation of bone sequestrations. As for the time required for the healing of the surgical wound before the beginning of RTx, the authors reported that only the initial healing of the oral mucosa, which occurs from 7 to 14 days, is enough for the patient to be able to start radiotherapy treatment. In addition, time varies from patient to patient, and postoperative clinical evaluation is essential for all patients, as the literature reports periods ranging from 5 to 30 days.

Grimaldi *et al*. (2005) carried out a literature review on the behavior of the dental surgeon in the prevention and treatment of ORN. Based on the reviewed literature, they concluded that, among the side effects of head and neck cancer treatment, ORN is one of the worst complications. The dental surgeon, as a member of the oncology team, must act before, during and after RTx, with prevention always being the best approach. The dental team must prepare the patient for the cancer treatment, taking the appropriate preventive measures, performing the adequacy of the oral environment, and monitoring it during the treatment period in order to improve oral hygiene conditions during and at the end of the RTx.

Pereira *et al*. (2012) reviewed the literature about RTx, ORN and mandible. Through the reviewed articles, they stated that ORN is a serious late complication that can occur as a result of therapy with primary or adjuvant radiation, and internal (brachytherapy) or external (teletherapy) radiation. The authors defined the sequela as being a condition in which the bone that received radiation becomes exposed to the oral environment and without vitality, persisting without healing for a period of at least three months. They also state that ORN does not necessarily affect dentate patients and has spontaneous development percentages in the jaws of edentulous patients. They concluded, based on the studies reviewed, that the type of tumor, the patient and the treatment chosen are factors that influence the risk of developing this complication. Considering this, there are a number of preventive ways that can be taken to prevent the emergence of ORN, such as extractions and healing of surgical wounds in the time necessary before the start of RTx. The dental surgeon should leave the oral cavity of the cancer patient in ideal conditions to initiate anti-neoplastic treatment and thus reduce ORN rates.

The authors Koga *et al*. (2008a,b) reviewed the literature on tooth extractions and RTx on the head and neck, and concluded that complications after cancer treatment can be reduced through clinical examination preceding irradiation. The prior examination should assess the patient's individual characteristics, the type of tumor and the treatment the patient will receive. They reported that in cases where extraction after radiotherapy treatment is unavoidable, surgery should be performed by a specialist, who will use appropriate surgical techniques, along with therapy and strict post-surgical follow-up, always in a multidisciplinary approach.

Rolim *et al*. (2011) carried out a review of the scientific literature on the repercussions of RTx in the orofacial region and its treatment, in the following databases: Bireme, Medline, Cancerlit, Scirus, Portal Capes, SciELO, Medscape, PubMed, between the years of 1985 and 2011. 100 scientific articles were analyzed for study, with exploratory reading and critical analysis. Of these, 59 articles were not considered, as they had limitations in their methods. In total, 41 studies were analyzed. They stated that ORN is the most severe type of complication that affects patients irradiated in the head and neck, that its highest incidence is in elderly patients (10 % to 37 %), and that it occurs seven times more in the mandible due to less vascularization and high bone density in relation to the maxilla.

Knowledge of dental surgeons about the consequences of antineoplastic treatments. Recently, studies have been carried out to assess the degree of knowledge of dental surgeons and undergraduate dentistry students about the complications of antineoplastic therapies, given the importance of the topic.

Ragghianti *et al*. (2002) described the general clinical conduct that should be applied to patients before, during and after cancer treatment, emphasizing the importance of multidisciplinary treatment. Dental treatment, according to the authors, is the main way to prevent ORN and other complications, and the patient's oral health conditions are directly related to the development of sequelae after radiotherapy treatment.

Güneri *et al*. (2008) interviewed 204 individuals to determine the level of knowledge about oral complications of cancer therapy, its prevention and management. 37 dentistry students participated, 113 general clinical dental surgeons and 54 specialists from Turkey. Among the specialists, 18% were radiologists, 17 % periodontists and 15 % prostheses. The questionnaire consisted of 15 items, and contained information about the sequelae of cancer treatment. The total of correct answers ranged from 14.71 % to 99.5 %. When asked about the behavior of the dental surgeon during a previous oral evaluation, only 14.71% of the interviewees answered that patients should be instructed on the importance of maintaining adequate oral hygiene throughout cancer treatment and that the dental surgeon should promote elimination any future infection sites. Regarding the importance of time for dental procedures before RTx, only 39.30% answered the question correctly. Gender, age and training time were not significant in the rate of errors and correct answers regarding the questionnaire. The authors concluded that changes in the dental curriculum should be made, as well as the reorganization of graduate courses. Also, the founding of new national councils, with the objective of encouraging dentists to keep up to date with their practical knowledge and alerting to keep up to date for improving the quality of life of their patients.

Patel *et al*. (2012) carried out an investigative study in order to discover what difficulties are encountered in the prevention and management of oral complications of cancer treatment of patients with head and neck cancer. A questionnaire was developed to assess the knowledge and interest of dental surgeons in receiving education on this subject. The questionnaires were distributed to dentists at the Michigan Dental Association, and a modified questionnaire was distributed to members of the American RTx Society. Of the dental surgeons who answered, 81 % reported that the lack of time between the initial dental appointment and the start of cancer treatment are the main difficulties encountered, according to them, this factor is caused by the failure of communication between health professionals. The lack of adequate training was reported as the lack of adequate treatment for patients by 10 % of dental surgeons and 25% of radiotherapists. Of the interviewed dental surgeons, 55% of those said that the undergraduate courses were not effective in providing this training.

Ramaswamy *et al*. (2014) interviewed 450 postgraduate students from all specialties and from various dental schools in India. The questionnaire contained 10 questions about oral cancer, its risk factors, main symptoms, treatment plan and complications after treatment, and aimed to assess the knowledge of postgraduate students on the topics previously mentioned. The students were asked about the waiting time required to perform extractions in irradiated patients and 58 % answered correctly, according to the authors. Regarding the treatment of oral complications, 58 % of students would refer patients with oral sequelae to a dental surgeon and 28% to an oncologist. The results obtained showed that 94 % of postgraduate students were aware that habits are the main risk factors for cancer, 50 % knew the clinical presentation of cancer, and 67% were confident about treatment protocols. On the other hand, cancer treatment protocols and post-treatment complications would need to be better understood. The conclusions were that dentistry education on cancer should be improved, so that postgraduate students have an improvement in their knowledge.

FINAL CONSIDERATIONS

It can be concluded from this study that: Countless knowledge has been accumulated over the years on the main characteristics of neoplasms, whether they are cancer cell biology, carcinogenesis mechanism, neoplasms of the maxillofacial system and sequels of antineoplastic treatments. In this context, methods have been developed that offer a better quality of life for patients diagnosed with this pathology, as well as preventive vaccine models that may, in the not too distant future, contribute to this goal to be successfully achieved. However, even with broad knowledge on the subject, the early diagnosis of neoplasms presents itself as an excellent alternative to prevent a possible formation of cancer. In addition, there is a need for more clinical and laboratory studies for a better understanding of this topic, allowing the formulation of specific strategies for diagnosis and treatment.

MATOS, J. D. M.; NAKANO, L. J. N.; LOPES, G. R. S.; MAIS, S. E. S.; BARBOSA, A. B.; BOTTINO, M. A. & ANDRADE, V. C. Actualización sobre neoplasmas y su correcta atención odontológica en pacientes con cáncer. *Int. J. Odontostomat., 17(3)*:356-371, 2023.

RESUMEN: El presente estudio tuvo como objetivo revisar la literatura sobre las principales complicaciones de las terapias antineoplásicas y el grado de conocimiento de los odontólogos sobre este abordaje. Se realizó una búsqueda bibliográfica en las principales bases de datos de salud PUBMED (www.pubmed.gov) y Scholar Google (www.scholar.google.com.br), en la que se recopilaron estudios publicados entre 1987 y 2023. Fueron incluidos estudios de laboratorio, relatos de casos, revisiones de la literatura y revisiones sistemáticas, desarrolladas en individuos vivos, que incluyeran los principales genes neoplásicos y su relación con las células de individuos afectados por neoplasias en la cabeza y el cuello. También, se tuvieron en cuenta estudios relacionados con la atención a este grupo de pacientes. La neoplasia es un trastorno clonal, causado por mutaciones, como resultado de cambios en la estructura genética de las células. Cada célula sana tiene instrucciones sobre cómo crecer y dividirse. En presencia de cualquier error en estas instrucciones (mutación), puede provocar una célula alterada que, al proliferar, puede causar un tumor. Se han acumulado innumerables conocimientos a lo largo de los años sobre las principales características de las neoplasias, ya sea sobre biología de células cancerosas, el mecanismo de la carcinogénesis, la neoplasias del sistema maxilofacial y las diferentes secuelas de tratamientos antineoplásicos. En este contexto, se han desarrollado métodos que ofrecen una mejor calidad de vida para los pacientes diagnosticados con esta patología, así como modelos de vacunas preventivas que, en un futuro no muy lejano, pueden contribuir a alcanzar este objetivo con éxito.

PALABRAS CLAVE: genes relacionados con las neoplasias, neoplasias de cabeza y cuello, detección precoz del cáncer, patología oral, investigación dental.

REFERENCES

Ali, J.; Sabiha, B.; Jan, R. U.; Haider, S. A.; Khan, A. A. & Ali, S. S. Genetic etiology of oral cancer. *Oral Oncol., 70*:23-8, 2017.

Alvarenga, L. D. M.; Ruiz, M. T.; Pavarino-Bertelli, É. C.; Ruback, M. J. C.; Maniglia, J. V. & Goloni-Bertollo M. Avaliação epidemiológica de pacientes com câncer de cabeça e pescoço em um hospital universitário do noroeste do estado de São Paulo. *Rev. Bras. Otorrinolaringol., 74(1)*:68-73, 2008.

Boras, V. V.; Fucic, A.; Virag, M.; Gabric, D.; Blivajs, I.; Tomasovic-Loncaric, C.; Rakusic, Z.; Bisof, V.; Le Novere, N. & Vrdoljak, D. V. Significance of stroma in biology of oral squamous cell carcinoma. *Tumori J., 104(1)*:9-14, 2018.

Caccelli, É. M. N. & Rapoport, A. Para-efeitos das irradiações nas neoplasias de boca e orofaringe. *Rev. Bras. Cir. Cabeça Pescoço, 37(4)*:198-201, 2008.

Cardoso, M. D. F. A.; Novikoff, S.; Tresso, A.; Segreto, R. A. & Cervantes, O. Prevenção e controle das seqüelas bucais em pacientes irradiados por tumores de cabeça e pescoço. *Radiol. Bras., 38(2)*:107-15, 2005.

Carneiro-Neto, J. N.; de-Menezes, J. D.; Moura, L. B.; Massucato, E. M. & de-Andrade, C. R. Protocols for management of oral complications of chemotherapy and/or radiotherapy for oral cancer: Systematic review and meta-analysis current. *Med. Oral Patolol. Oral Cir. Bucal., 22(1)*:15-23, 2017.

Cheah, P. L. & Looi, L. M. Biology and pathological associations of the human papillomaviruses: a review. *Malays. J. Pathol., 20(1)*:1-10, 1998.

Colombo, J. & Rahal, P. Alterações genéticas em câncer de cabeça e pescoço. *Rev. Bras. Cancerol., 55(2)*:165-74, 2009.

Curi, M. M. & Dib, L. L. Osteoradionecrosis of the jaws: a retrospective study of the background factors and treatment in 104 cases. *J. Oral Maxillofac. Surg., 55(6)*:540-4, 1997.

Curi, M. M. & Kowaslki, L. P. Osteorradionecrose de mandíbula e maxila. *Rev. Bras. Cir. Cabeça Pescoço, 31(1)*:49-53, 2003.

Curry, J. M.; Sprandio, J.; Cognetti, D.; Luginbuhl, A.; Bar-ad, V.; Pribitkin, E. & Tuluc, M. Tumor microenvironment in head and neck squamous cell carcinoma. *Semin. Oncol., 41*:217-34, 2014.

Das, B. R. & Nagpal, J. K. Understanding the biology of oral cancer. *Med. Sci. Monit., 8(11)*:258-67, 2002.

Epstein, J. B.; Parker, I. R.; Epstein, M. S. & Stevenson-Moore, P. Cancer-related oral health care services and resources: a survey of oral and dental care in Canadian cancer centres. *J. Can. Dent. Assoc., 70(5)*:302-4, 2004.

Epstein, J. B.; Wong, F. L. & Stevenson-Moore, P. Osteoradionecrosis: clinical experience and a proposal for classification. *J. Oral Maxillofac. Surg., 45(2)*:104-10, 1987.

Feller, L. L.; Khammissa, R. R.; Kramer, B. B. & Lemmer, J. J. Oral squamous cell carcinoma in relation to field precancerisation: pathobiology. *Cancer Cell Int., 13*:31, 2013.

Fukuda, M.; Ohmori, Y. & Sakashita, H. *The Role of Tumor Microenvironment in Oral Cancer*. In: Biswas, S. (Ed.). Tumor Microenvironment and Myelomonocytic Cells. InTech, 2012.

Gaillard, H.; García-Muse, T. & Aguilera, A. Replication stress and cancer. *Nat. Rev. Cancer, 15(5)*:276-89, 2015.

Golemis, E. A.; Scheet, P.; Beck, T. N.; Scolnick E. M.; Hunter, D. J; Hawk E. & Hopkins N. Molecular mechanisms of the preventable causes of cancer in the United States. *Genes Dev., 32(13-14)*:868-902, 2018.

Grimaldi, N.; Sarmento, V.; Provedel, L; Almeida, D. D. & Cunha, S. D. Conduta do cirurgião-dentista na prevenção e tratamento da osteorradionecrose: revisão de literatura. *Rev. Bras. Cancerol., 51(4)*:319-24, 2005.

Güneri, P.; Cankaya, H.; Kaya, A. & Boyaciog˘lu, H. Turkish dentists' knowledge of head and neck cancer therapy-related complications: implications for the future. *Eur. J. Cancer Care, 17(1)*:84-92, 2008.

Han, Y.; Zhang, Y.; Jia, T. & Sun, Y. Molecular mechanism underlying the tumor-promoting functions of carcinoma-associated fibroblasts. Tumour Biol., 36(3):1385-94, 2015.

Hanahan, D. & Weinberg, R. A. The hallmarks of cancer. *Cell Press, 100(1)*:57-70, 2000.

Harden, M. E. & Munger, K. Human papillomavirus molecular biology. *Mutat. Res. Rev. Mutat. Res., 772*:3-12, 2017.

Hartner, L. Chemotherapy for oral cancer. *Dent. Clin. North Am., 62(1)*:87-97, 2018.

Herber, R.; Liem, A.; Pitot, H. & Lambert, P. F. Squamous epithelial hyperplasia and carcinoma in mice transgenic for the human papillomavirus type 16 E7 oncogene. *J. Virol., 70(3)*:1873-81, 1996.

Hespanhol, F. L.; Tinoco, E. M. B.; Teixeira, H. G. D. C.; Falabella, M. E. V. & Assis, N. M. D. S. P. Manifestações bucais em pacientes submetidos à quimioterapia. *Ciênc. Saúde Colet., 15(1)*:1085-94, 2010.

Hills, S. A. & Diffley, J. F. DNA replication and oncogene-induced replicative stress. *Curr. Biol., 24(10)*:435-44, 2014.

Huang, Q. W.; He, L. J.; Zheng, S.; Liu, T. & Peng, B. N. An overview of molecular mechanism, clinicopathological factors, and treatment in NUT carcinoma. *Biomed Res. Int., 2019*:1018439, 2019.

Instituto Nacional de Câncer (INCA). *Ações de enfermagem para o controle do câncer: uma proposta de integração ensino-serviço*. 3th ed. Rio de Janeiro, Instituto Nacional de Câncer, 2008.

Irimie, A. I.; Ciocan, C.; Gulei, D.; Mehterov, N.; Atanasov A. G.; Dudea, D. & Neagoe, I. B. Current Insights into Oral Cancer Epigenetics. *Int. J. Mol. Sci., 19(3)*:670, 2018.

Jemal, A.; Bray, F.; Center, M. M.; Ferlay, J.; Ward, E. & Forman, D. Global cancer statistics. *CA Cancer J. Clin., 61(2)*:69-90, 2011.

Jham, B. C. & Freire, A. R. D. S. Complicações bucais da radioterapia em cabeça e pescoço. *Rev. Bras. Otorrinolaringol., 72(5)*:704-8, 2006.

Joyston-Bechal, S. Management of oral complications following radiotherapy. *Dent. Update, 19(6)*:232-4, 236-8, 1992.

Katoh, M. Function and cancer genomics of FAT family genes (review). *Int. J. Oncol., 41(6)*:1913-8, 2012.

Khurshid, Z.; Zafar, M. S.; Khan, R. S.; Najeeb, S.; Slowey, P. D. & Rehman, I. U. Role of salivary biomarkers in oral cancer detection. *Adv. Clin. Chem., 86*:23-70, 2018.

Kim, J. & Minna, J. D. Evaluating tumor-suppressor gene combinations. *Nat. Genet., 50(4)*:480-2, 2018.

Kirita, T. Oral cancer: current status of molecular biology and treatment strategy. *Int. J. Clin. Oncol., 19(3)*:421-2, 2014.

Kitao, H.; Limori, M.; Kataoka, Y.; Wakasa, T.; Tokunaga, E.; Saeki, H.; Oki, E. & Maehara Y. DNA replication stress and cancer chemotherapy. *Cancer Sci., 109(2)*:264-71, 2018.

Koga, D. H.; Salvajoli, J. V. & Alves, F. A. Dental extractions and radiotherapy in head and neck oncology: review of the literature. *Oral Dis., 14(1)*:40-4, 2008a.

Koga, D. H.; Salvajoli, J. V.; Kowalski, L. P.; Nishimoto, I. N. & Alves, F. A. Dental extractions related to head and neck radiotherapy: ten-year experience of a single institution. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Oral Endodod., 105(5)*:1-6, 2008b.

Kumar, M.; Nanavati, R.; Modi, T. G. & Dobariya, C. Oral cancer: Etiology and risk factors: A review. *J. Cancer Res. Ther., 12(2)*:458-63; 2016.

Labbate, R.; Lehn, C. N. & Denardin, O. V. P. Efeito da clorexidina na mucosite induzida por radioterapia em câncer de cabeça e pescoço. *Rev. Bras. Otorrinolaringol., 69(3)*:349-54, 2003.

Lambert, A. W.; Pattabiraman, D. R. & Weinberg, R. A. Emerging biological principles of metastasis. *Cell Press, 168(4)*:670-91, 2017.

Migliorati, C. A. & Migliorati, E. K. J. *Preparo Odontológico*. In: Parise Junior, O. (Ed.). Câncer de Boca: Aspectos Básicos e Terapêuticos. São Paulo, Sarvier, 2000.

Neville, B. W. & Day, T. A. Oral cancer and precancerous lesions. *CA Cancer J. Clin., 52(4)*:195-215, 2002.

Neville, B. W. *Oral and Maxillofacial Pathology.* 3th ed. Philadelphia, Saunders/Elsevier, 2009.

Oliveira, L. C. S. D.; Vieira, C. A.; Mota, M. H. M; Salles, P. V.; Salles, J. M. P.; Di Ninno, C. Q. D. M. & Britto, A. T. B. D. O. Identificação das mudanças na mastigação e deglutição de indivíduos submetidos à glossectoma parcial. *Rev. Soc. Bras. Fonoaudiol., 13(4)*:338-43, 2008.

Panghal, M.; Kaushal, V.; Kadayan, S. & Yadav, J. P. Incidence and risk factors for infection in oral cancer patients undergoing different treatments protocols. *BMC Oral Health, 12*:22, 2012.

Patel, Y.; Bahlhorn, H.; Zafar, S.; Zwetchkenbaum, S.; Eisbruch, A. & Murdoch-Kinch, C. A. Survey of Michigan dentists and radiation oncologists on oral care of patients undergoing head and neck radiation therapy. *J. Mich. Dent. Assoc., 94(7)*:34-45, 2012.

Pereira, A. C. L.; Dewiette, F. G.; Paulisch, E. S. & Oliveira, M. G. Osteorradionecrose em mandíbula. *Rev. Cienc. Med., 16(4-6)*:251-6, 2012.

Pickup, M. W.; Mouw, J. K. & Weaver, V. M. The extracellular matrix modulates the hallmarks of cancer. *EMBO Rep., 15*:1243-53, 2014.

Ragghianti, M. S.; Greghi, S. L. A.; Capelozza, A. L. A. & Resende, D. R. B. D. Tratamento radioterápico: Parte II–Estratégias de atendimento clínico. *Rev. Salusvita, 21(1)*:87-96, 2002.

Ramaswamy, P.; Uday, G.; Sreenivasulu, P.; Kumar, B. P.; Khaitan, T. & Geethika, V. R. Awareness about oral cancer among dental postgraduate students in the State of Andhra Pradesh, India. *J. Cancer Educ., 29(4)*:665-8, 2014.

Redding, S. W. Cancer therapy-related oral mucositis. *J. Dent. Educ., 69(8)*:919-29, 2005.

Rivera, *C. Essentials of oral cancer.* Int. J. Clin. Exp. Pathol., 8(9):11884-94, 2015.

Rocha, R. D. C. A.; Lehn, C. N.; Oliveira, J. X. D. & Marcucci, M. Incidência de osteorradionecrose em pacientes com câncer de boca tratados com radioterapia exclusiva ou em associação com cirurgia. *Rev. Bras. Cir. Cabeça Pescoço, 37(2)*:91-4, 2008.

Rodrigues, H. M.; Franzi, E. A. & Dedivitis, R. A. A radioterapia e suas implicações nos tratamentos endodônticos. *Rev. Bras. Cir. Cabeça Pescoço, 35(1)*:57-60, 2006.

Rolim, A. E. H.; Costa, L. J. D. & Ramalho, L. M. P. Repercussões da radioterapia na região orofacial e seu tratamento. *Radiol. Bras., 44(6)*:388-95, 2011.

Salazar, M.; Victorino, F. R.; Paranhos, L. R.; Ricci, I. D.; Gaetti, W. P & Caçador, N. P. Efeitos e tratamento da radioterapia de cabeça e pescoço de interesse ao cirurgião dentista-Revisão da literatura. *Rev. Odonto, 16(31)*:62-8, 2008.

Sassi, L. M. & Machado, R. A. Protocolo pré-radioterapia de cabeça e pescoço. *Rev. Bras. Cir. Cabeça Pescoço, 38(3)*:208-10, 2009.

Sellers, K.; Allen, T. D.; Bousamra 2nd, M.; Tan, J.; Lucas, A. M.; Lin, W.; Bah, N.; Chernyavskaya, Y.; MacRae, J. I.; Higashi, R. M.; *et al*. Metabolic reprogramming and Notch activity distinguish between non-small cell lung cancer subtypes. *Br. J. Cancer, 121(1)*:51-64, 2019.

Senapati, P.; Dey, S.; Sudarshan, D.; Deepthi, S.; Das, S.; Kumar, M.; Kaypee, S.; Mohiyuddin, A.; Kodaganur, G. S. & Kundu, T. K. Oncogene c-fos and mutant R175H p53 regulate expression of Nucleophosmin implicating cancer manifestation. *FEBS J., 285(18)*:3503-24, 2018.

Shenoy, V. K.; Shenoy, K. K.; Rodrigues, S. & Shetty, P. Management of oral health in patients irradiated for head and neck cancer: a review. *Kathmandu Univ. Med. J., 5(1)*:117-20, 2007.

Shillitoe, E. J. The Microbiome of Oral Cancer. *Crit. Rev. Oncog., 23(3-4)*:153-60, 2018.

Specenier, P. M. & Vermorken, J. B. Current concepts for the management of head and neck cancer: chemotherapy. *Oral Oncol., 45(4-5)*:409-15, 2009.

Speight, P. M.; Khurram, S. A. & Kujan, O. Oral potentially malignant disorders: risk of progression to malignancy. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol., 125(6)*:612-27, 2018.

Sritippho, T.; Chotjumlong, P. & Iamaroon, A. Roles of human papillomaviruses and p16 in oral cancer. *Asian Pac. J. Cancer Prev., 16(15)*:6193-200, 2015.

Suresh, A. V.; Varma, P. P.; Sinha, S.; Deepika, S.; Raman, R.; Srinivasan, M.; Mandapal, T.; Reddy, C. O. & Anand, B. B. Risk-scoring system for predicting mucositis in patients of head and neck cancer receiving concurrent chemoradiotherapy [rssm-hn]. *J. Cancer Res. Ther., 6(4)*:448-51, 2010.

Tanaka, T & Ishigamori, R. Understanding carcinogenesis for fighting oral cancer. *J. Oncol., 2011*:603740, 2011.

Tsantoulis, P. K.; Kastrinakis, N. G.; Tourvas, A. D.; Laskaris, G. & Gorgoulis, V. G. Advances in the biology of oral cancer. *Oral Oncol., 43(6)*:523-34, 2007.

Weinreb, I.; Bishop, J. A.; Chiosea, S. I.; Seethala, R. R.; Ordonez, B. P.; Zhang, L.; Sung, Y. S.; Chen, C. L.; Assaad, A.; Oliai, B. R.; *et al*. Recurrent RET Gene Rearrangements in Intraductal Carcinomas of Salivary Gland. *Am. J. Surg. Pathol., 42(4)*:442-52, 2018.

Wong, T. & Wiesenfeld, D. Oral cancer. *Aust. Dent. J., 63(1)*:91-9, 2018.

World Health Organization (WHO). Policies and managerial guidelines for national cancer control programs. *Rev. Panam. Saúde Pública, 12(5)*:366-70, 2002.

Yu, F.; Shi, G.; Cheng, S.; Chen J.; Wu, S. Y.; Wang, Z.; Xia, N.; Zhai, Y.; Wang, Z.; Peng, Y.; *et al*. SUMO suppresses and MYC amplifies transcription globally by regulating CDK9 sumoylation. *Cell Res., 28(6)*:670-85, 2018.

Corresponding author:
Jefferson David Melo de Matos D.D.S.; M.D.; Ph.D. Student.
Post Graduate Student - Ph.D Program
Department of Dental Materials and Prosthodontics
São Paulo State University (Unesp)
Institute of Science and Technology
São José dos Campos - SP.
Avenida Engenheiro Francisco José Longo, 777/778
Jardim São Dimas
São José dos Campos – SP
CEP: 12245000
BRAZIL

E-mail: matosjefferson19@gmail.com

ORCID: https://orcid.org/0000-0003-4507-0785