Journal of Dental Sciences and Education

Review

DOI: 10.51271/JDSE-0028

Dental caries and demineralization in head and neck cancer patients undergoing radiotherapy

Mehmet Salık, Elif Pınar Bakır

Department of Restorative Dentistry, Faculty of Dentistry, Dicle University, Diyarbakır, Turkiye

Cite this article: Salık M, Bakır EP. Dental caries and demineralization in head and neck cancer patients undergoing radiotherapy. *J Dent Sci Educ*. 2024;2(1): 24-29.

Corresponding Author: Mehmet Salık, mhmetsalik@gmail.com

Received: 06/03/2024 ◆ **Accepted**: 23/03/2024 ◆ **Published**: 30/03/2024

ABSTRACT

The number of head and neck cancer patients is steadily increasing, and the use of radiotherapy for treatment in this patient group has been associated with side effects such as mucositis, trismus, xerostomia, dental caries, periodontal disease, and osteoradionecrosis. Radiation caries can be atypical, and their treatment can be challenging. Preventing and treating RC become crucial as post-radiotherapy tooth extraction can pave the way for osteoradionecrosis. The aim of this review is to evaluate the restorative dental treatment for head and neck cancer patients before, during, and after radiotherapy. This includes examining the impact of radiotherapy on tooth decay and demineralization, and providing solutions to address these effects.

Keywords: Radiation caries, head and neck cancers, osteoradionecrosis, oral hygiene, saliva

INTRODUCTION

Head and neck cancers (HNC) encompass a broad term that includes epithelial malignancies affecting the oral cavity, nasal cavity, paranasal sinuses, salivary glands, pharynx, and larynx localized in the head and neck region.[1,2] These epithelial malignancies are predominantly identified as head and neck squamous cell carcinomas. Tobacco and alcohol consumption have been identified as the most significant risk factors.[2,3] HNC are reported to represent 6% of all malignancies.[4] Globally, it is estimated that over 550,000 individuals are diagnosed with HNC each year.[5,6] In 2020, it was reported as the sixth most common cancer worldwide, with over 870,000 new cases and 440,000 deaths.[7]

Treatment options for HNC patients involve surgical, radiotherapeutic, chemotherapeutic, or combined approaches, considering the condition of malignant tumors at the time of diagnosis, whether they are local, regional, or advanced.[8-10] Although surgical treatment is generally considered the primary choice, the selection depends on factors such as the location, size, and depth of infiltration of the cancer.[11] The most commonly used method is a combination of radiotherapy and surgery; however, for malignancies that cannot be removed surgically, simultaneous chemoradiotherapy has become a standard treatment, demonstrating higher survival rates compared to either radiotherapy or chemotherapy alone.[1,12]

Unfortunately, radiotherapy not only affects cancer cells but also damages normal cells in the irradiated area.[10,13] Side effects such as mucositis, trismus, SGD, dental caries, periodontal disease, and ORN are commonly documented outcomes of radiotherapy in HNC patients.[14-19]

To ensure individuals diagnosed with HNC receive the most effective treatment, a multidisciplinary approach is adopted. Scientific studies highlight the importance of consulting the restorative dental treatment clinic for HNC patients undergoing treatment to identify and address dental problems that may interrupt or jeopardize HNC treatment and maximize oral rehabilitation opportunities, thereby improving the quality of life during cancer treatment.[20]

Radiation caries (RC) are atypical and can be challenging to treat. Preventing and treating RC become crucial as post-radiotherapy tooth extraction can pave the way for ORN. Our aim in this review is to evaluate HNC patients undergoing radiotherapy before, during, and after treatment from the perspective of restorative dental treatment. We seek to provide solutions by examining the direct and indirect effects of radiotherapy on tooth decay and demineralization.

PRINCIPLE OF RADIOTHERAPY

Radiation is a physical agent used to destroy cancer cells, known as ionizing radiation, as it generates ions upon interaction and deposits energy in the cells of the traversed tissues. This accumulated energy can kill cancer cells or induce a series of genetic changes leading to their demise. High-energy radiation damages the genetic material (deoxyribonucleic acid, DNA) of cells.

Radiation can cause this damage in two ways:[21]

1. Direct effect of radiation: Radiation can directly interact with cellular DNA, causing damage.

2. Indirect effects of radiation: Indirect DNA damage caused by free radicals resulting from the ionization or excitation of cellular water components.

Fractionated radiation treatment is based on the differing radiobiological characteristics of cancer and normal tissues. These regimens are applied to advantageously enhance the survival rate of healthy cells compared to cancer cells. While aiming to maximize the destruction of tumor cells, radiotherapy also seeks to minimize damage to normal cells.[10,13] After radiation application, healthy cells can often repair themselves and maintain normal activity levels more rapidly than cancer cells. However, differentiated cancer cells are not as effective in repairing radiation-induced damage as normal cells, making radiotherapy more effective in causing the death of cancer cells.[21]

Radiation therapy does not immediately kill cancer cells. Cancer cells begin to die hours, days, or weeks after the start of treatment, and the process of cancer cell death can continue for weeks or months after the completion of radiotherapy.[22]

ORAL SIDE EFFECTS OF RADIOTHERAPY

Typically, radiation for the treatment of HNCs is administered in fractions, with a total dose ranging between 50 and 70 Gray (Gy) over a period of 4-7 weeks. Despite advancements in radiation techniques, high doses of radiation can lead to various undesirable reactions in large areas, including the oral cavity, maxilla, mandible, and salivary glands. Common complications of radiotherapy include mucositis, candidiasis, taste alterations, RC, ORN, soft tissue necrosis, and xerostomia.[10]

SALIVARY GLAND DYSFUNCTION

Salivary glands produce and channel saliva, a secretion called "saliva", into the oral cavity mucosa and surrounding areas. Salivary gland dysfunction (SGD) is defined as "any alteration in the qualitative (qualitative) and quantitative (quantitative) structure of saliva due to hypersalivation (increase) or hyposalivation (decrease) resulting from salivary gland secretion".[23-25] In HNC treatment, SGD is commonly observed as a side effect.[26] In HNC patients, SGD manifests as xerostomia (dry mouth) and hyposalivation (low saliva flow).[24]

Saliva, a complex and dynamic biological fluid, consists of approximately 99.5% water, 0.3% protein, and 0.2% inorganic matter. Inorganic elements in saliva include sodium, chloride, calcium, potassium, bicarbonate, phosphate, fluoride, iodine, and magnesium. The majority of proteins in saliva are glycoproteins, including mucoproteins, immunoglobulins, lactoferrin, peroxidases, and agglutinins, contributing to the structure of saliva. Mucoproteins provide lubrication, while other glycoproteins have antimicrobial properties. Proteins rich in statherin and proline contribute to calcium balance in saliva, while defensins play a role in the natural immune response. Sialins are protease inhibitor proteins with antimicrobial and immunomodulatory properties.[27-29]

Saliva composition, both qualitatively and quantitatively, is affected by the pathophysiological conditions of the body. Thus, changes in saliva reflect not only alterations in the oral cavity but also systemic changes occurring throughout the body.[30]

In cancer patients, hyposalivation and xerostomia can lead to functional problems such as eating, speaking, and swallowing, increase the risk of dental caries and oral candidiasis, contribute to the emergence of psychological issues, and worsen existing problems.[31] Causes of hyposalivation and xerostomia in cancer patients may include chemotherapy, radiotherapy applied to the head and neck region, and dehydration.[32]

Studies conducted among HNC patients have reported irreversible damage to salivary glands in approximately 63% to 93% of cases when radiation is applied to the gland's location.[33] Saliva serves various functions, including oral cavity and tooth protection as a natural defense system with its antimicrobial activity.[34-35] In cases of xerostomia and hyposalivation, affecting these functions may lead to complications.[36]

While the enamel surface continually reshapes through demineralization and remineralization processes, if demineralization becomes dominant in this dynamic process, mineral loss can occur, leading to cavitation through the breakdown of matrix components.[37-38] The remineralization process relies on two main substrates found in saliva, calcium, and phosphate. Changes in saliva flow and content in HNC patients can disrupt the remineralization process and promote demineralization, as an adequate supply of calcium and phosphate is crucial for remineralization.[23,38-39]

Additionally, a study by Valstar et al.[40], published in September 2020, demonstrated the presence of bilateral seromucous-secreting glands located on the posterolateral nasopharyngeal wall. These glands, named tubarial glands, are positioned above the Torus tubarius and have been proposed as a new organ. Since the macroscopic glandular structure in the posterior pars nasalis pharyngis was previously unknown, it has not been included in the structures to be protected during radiotherapy. Based on these findings, researchers suggested that the detection of previously unnoticed salivary glands residing in the posterior pars nasalis pharyngis could help avoid side effects of radiotherapy in patients.[41]

CHANGES IN ORAL MICROBIOME

The microbiome is an ecological community composed of symbiotic, commensal, and pathogenic microorganisms, including all genes and genomes, along with their metabolites and protein products. In other words, it is a system that encompasses the microbiota and its metabolic and protein products.[42,43] The oral microbial flora includes viruses, protozoa, archaea, fungi, bacteria, and is considered one of the most complex bacterial populations associated with the human body after the intestines.[44-45] Understanding the relationship between the microbiome and the oral environment is crucial to comprehend the cause of diseases developing in the oral cavity. There are two regions in the oral cavity where bacteria can reside: the hard surfaces of teeth and the soft tissues that make up the oral mucosa.[46]

A decrease in saliva flow can alter the ecological environment, leading to an increase in bacterial sequences associated with tooth decay. In patients exposed to severe radiation, an increase in cariogenic oral bacteria of the streptococcus and lactobacillus types associated with tooth decay has been observed.[47] In patients with HNC, the transition to cariogenic microorganisms has been clearly documented

during and after radiotherapy. These bacteria have effects that increase the risk of tooth decay through acid production.[48] Additionally, candida infection can be observed in 17-29% of patients exposed to radiotherapy. The increased risk of oral candidiasis may be attributed to the decrease in saliva flow as a result of radiotherapy.[10]

Radiation Caries and Demineralization

The oral cavity is highly sensitive to the negative effects of radiation. This sensitivity may be attributed to the rapid renewal rate of cells in the oral mucosa, a complex oral microbiota, and constant trauma to tissues even during normal function. One of the problems arising in the oral cavity due to radiotherapy is radiation-induced caries. Radiotherapy is a significant risk factor for the rapid development of rampant caries, known as RC.[13]

RC is one of the chronic oral complications of radiotherapy with a multifactorial etiology.[48,50] Studies have shown that approximately 29% of HNC patients experience tooth decay after radiotherapy. Furthermore, the probability of developing tooth decay within two years after radiotherapy in the head and neck region is reported to be approximately 37%.[51] Unfortunately, the risk of tooth decay continues persistently after radiotherapy.[52] RC negatively impacts the quality of life of patients, leading to reduced chewing efficiency, pain, chronic oral infections, increased risk of ORN, and adverse effects on diet, speech, and aesthetics.[53] Clinically, radiation-induced tooth decay typically starts with superficial enamel demineralization and progresses to lesions that turn brown or black over time. As demineralization advances, enamel dissolves, exposing the dentin underneath, which becomes highly susceptible to the cariogenic oral environment.[54]

The clinical features of RC differ from those of bacterial caries and are commonly found in the lingual surfaces of mandibular anterior teeth, tubercle peaks, incisal parts of incisors, and most frequently in the cervical portions of teeth, where traditional dental caries are rarely encountered.[50] RC, progressing rapidly from the cervical part of the tooth, can lead to a decrease in the support of the dental crown, its fracture and loss, leaving an infection-prone dental root behind in the oral cavity.[50,55]

Three different types have been defined in the progression process of carious lesions clinically.[13]

- **Type 1:** The most common lesion type that affects the cervical surfaces of teeth. The development of circumferential caries extending up to the cement-enamel junction occurs, and crown fracture is common in this type.
- **Type 2:** Demineralization occurs on all surfaces of the teeth. Widespread erosion is observed along with wear on incisal and occlusal surfaces.
- **Type 3:** A condition with changes in dentin color. Dark brown or black lesions occur in the crown with incisal or occlusal wear.

The treatment of RC should include appropriate treatment, oral prophylaxis, and restorative procedures. Tooth extractions should be avoided to prevent the risk of ORN after radiotherapy.

Osteoradionecrosis

ORN is a serious pathological condition that occurs as a side effect of radiotherapy, where non-healing exposed necrotic bone persists in the jaw for at least three months, leading to an opening in the oral cavity or skin.[56] Situations that increase the risk of ORN in patients who have undergone radiotherapy include:[20]

- When the total radiation dose exceeds 60 Gy
- When the patient's immune system is compromised
- In case of inadequate nutrition
- Poor oral hygiene
- Local trauma caused by tooth extraction or inappropriate prosthesis
- Tumor proximity to bone
- Periodontal diseases
- Presence of a tumor in the posterior mandible due to compact and dense bone structure

A strong relationship has been shown between tooth extraction after radiotherapy and the development of ORN.[57] The incidence of ORN due to tooth extraction and infection resulting from periodontal disease is three times higher in patients who have undergone radiotherapy compared to edentulous patients. Therefore, it is recommended to extract decayed and periodontally compromised teeth before radiotherapy.[56]

Conditions requiring tooth extraction include:[20,58]

- Teeth with extensive periapical lesions
- Unrestorable deep and extensive caries
- Moderate to advanced periodontal disease, especially with advanced bone loss and mobile or furcation-involved teeth
- Roots
- Impacted third molars and unerupted teeth associated with the oral environment

Teeth with a poor prognosis should be extracted at least two to three weeks before radiotherapy.[57]

PREVENTING THE ORAL SIDE EFFECTS OF RADIOTHERAPY

Before Radiotherapy

The purpose of evaluating patients by a dentist before starting radiotherapy for HNC treatment is to enhance the quality of life, preserve necessary teeth for function, aesthetics, and speech during treatment, and prevent the occurrence of ORN due to tooth extraction after radiotherapy.[20] ORN, characterized by exposed and necrotic bone, has been reported to be predisposed by untreated dental caries before, during, and after radiotherapy.[53] Considering this, eliminating dental pathologies and providing patients with oral hygiene education to maintain these practices become crucial.

Surgical treatment of advanced lesions can result in aesthetic, functional, and psychological outcomes. Depending on the

type and location of the lesion, maxillary cancer surgery often includes the hard palate, maxillary sinus, and nasal cavity.[59] After surgical procedures, some patients may need to use maxillofacial prostheses. The main objectives of using maxillofacial prostheses are to restore oral functions and enhance facial aesthetics and the patient's quality of life. To minimize the risk of dental and periodontal problems due to difficulty in maintaining oral hygiene, good hygiene education is essential.[59]

Patients should pay attention to the following for maintaining oral hygiene:[60]

- Use a soft-bristled toothbrush with an atraumatic brushing technique.
- Use fluoride-containing toothpaste.
- Rinse with alcohol-free 0.12% chlorhexidine mouthwash.
- Use dental floss or interdental brushes for interproximal cleaning.
- Apply fluoride gel for 5 minutes daily using patient-specific appliances (twice daily during radiotherapy).
- Clean the tongue with a soft toothbrush or gauze.
- Perform saltwater gargles.

Radiotherapy and chemotherapy can make soft tissues highly sensitive to trauma, so irregularities in restorations and sharp areas of teeth should be smoothed out, and adaptations should be made to prevent trauma if patients have prostheses in their mouths.[20,57-58]

During Radiotherapy

The goal of oral treatment during radiotherapy is to prevent secondary infection associated with severe mucositis, control pain, and support the patient's nutrition. Changes in the diet of HNC patients during BBK treatment can increase the risk of tooth decay. Due to the risk of weight loss during cancer treatment, patients are often advised to consume frequent small meals with high-calorie foods. Increased meal frequency can complicate brushing between meals, and patients may be compelled to use liquid supplements containing refined carbohydrates that adhere easily to tooth surfaces and promote decay.

Pain arising from mucositis can make it challenging to mechanically remove plaque.[61] While maintaining oral hygiene does not prevent the onset of mucositis, it can reduce the risk of oral infections. If using a toothbrush is painful due to the presence of mucositis, mouth rinsing can be a good alternative. The use of 0.2% chlorhexidine gluconate is recommended three to four times a day. Differentiating between mucositis caused by fungi and that resulting from radiotherapy is crucial, with candidiasis being one of the most common oral infections during radiotherapy.[63]

After Radiotherapy

After completing cancer treatment, restorative dental treatment can be performed normally. Effective restoration of tooth decay should be done to prevent the progression of lesions and eliminate the need for extraction, reducing the risk of ORN development.[64] Access to RC can be extremely challenging due to trismus and surgical defects, and the restoration can be difficult due to the presence of decay in cervical and root lesions, providing minimal mechanical retention in the prepared cavity. Given these technical issues, the development of protective and therapeutic strategies is crucial for the early treatment of radiation-induced dental caries.[48]

The selected material for restoration should provide proper adhesion to the tooth, prevent secondary caries, and be resistant to acid erosion.[65] McComb and colleagues have stated that fluoride-releasing materials are effective in preventing secondary caries in patients who have undergone radiotherapy.[66] Glass ionomer cements, despite having shorter oral retention and a higher incidence of secondary caries compared to composites in the cervical area in a healthy population, have been found to be more effective in preventing secondary caries than composites in radiotherapy patients with a high risk of dry mouth.[67] In radiotherapy patients who do not routinely receive fluoride, glass ionomer cements may be a better option compared to other materials.[51] Composite materials and resin-modified glass ionomer cements can be considered as applied options over traditional glass ionomers (sandwich technique) due to their adhesive potentials and sealing capabilities.[62]

For patients with reduced mouth opening, post-treatment xerostomia, or those with a high intake of cariogenic diets, an increased risk of tooth decay should be considered, and a more intense fluoride regimen should be contemplated. High-concentration fluoride toothpaste can be prescribed with the recommendation for the patient not to rinse their mouth after brushing. Additionally, using a fluoride mouthwash at times other than toothbrushing may be advised.[68]

Application of tropical fluoride can increase resistance to tooth decay. Fluoride toothpaste has been shown to provide significant benefits in preventing and remineralizing root caries in patients who have undergone radiotherapy.[69] However, preventing tooth decay in HNC patients is not easy. In these patients, the effect of fluoride may be limited due to decreased calcium and phosphate in the oral cavity as a result of hyposalivation.[70] Since remineralization does not occur if there is not enough calcium and phosphate in saliva in relation to the tooth, cancer patients with SGD should be called for regular check-ups by dentists to reduce the risk of widespread caries, and the use of 1.1% sodium fluoride gel or fluoride toothpaste should be recommended.[23]

For preventing tooth decay in HNC patients, regular dental care, maintaining oral hygiene, applying sodium fluoride to teeth for 3-4 minutes daily using custom-made appliances (with instructions for the patient not to eat or rinse their mouth for the next half hour), and minimizing the intake of cariogenic and acidic foods are recommended.[31]

SALIVARY GLAND DYSFUNCTION AND ARTIFICIAL SALIVA

The use of artificial saliva should be considered to alleviate the negative effects caused by xerostomia. Substitutes for artificial saliva should closely resemble the composition of human saliva, exhibiting biophysical properties such as lubrication and mucoadhesive function, similar to natural saliva.[71] There are numerous commercially available substitutes for artificial saliva, with the essential characteristics of these products summarized in Figure.[72]

Sample	Main components	Instruction for daily use
Biotene® Oral Rinse	Hydroxyethyl-cellulose (HEC), xylitol and sorbitol.	With approximately 15 mL rinse for 30 seconds and then expel.
Biotene® Spray	Xanthan gum, glycerin and xylitol.	Administer as required.
Bioxtra Spray®	Hydroxyethyl-cellulose (HEC), lactoperoxidase, citric acid, xylitol and sorbitol.	Administer 3 or 4 times a day to the mouth cavity.
Xeros®	Hydroxyethyl-cellulose (HEC), sodium phosphate, xylitol and sorbitol.	With approximately 15 mL rinse for 30 seconds and then expel.
Glandosane®	Carboxymethyl-cellulose (CMC) and xylitol.	Administer 1 or 2 times a day to the mouth cavity.
GUM®	Xanthan gum, carrageenan and xylitol.	Administer as required.
Oralis®	Xanthan gum, benzoic acid lactoperoxidase, the dispenser. Rinse for 30-45 seconds and then expel.	Use the amount corresponding to lysozyme, lactoferrin and xylitol.
Saliva Natura®	Yerba Santa extract, citric acid, xylitol and sorbitol.	Administer as required.
Saliva Orthana®	Porcine gastric mucin (PGM) and xylitol.	Administer 3 or 4 times a day to the mouth cavity.
Saliveze®	Carboxymethyl-cellulose (CMC) and potassium phosphate.	Administer 2 or 3 times a day to the mouth cavity.
Xerostom®	Xylitol, PEG-40 Hydrogenated Castor Oil, Betaine, Glycerin, Olea Europaea	Administer 1 or 2 times a day to the mouth cavity.
Xerotin®	Carboxymethyl-cellulose (CMC), potassium phosphate and sorbitol.	Spray the product several times a day

Figure. Artificial saliva and the essential characteristics.[72]

SALIVARY GLAND DYSFUNCTION AND PHARMACOLOGICAL INTERVENTIONS

The literature discusses variety of pharmacological approaches to prevent radiation-induced salivary gland dysfunction.[77] Some examples of these interventions are:

1. Parasympathomimetic drugs, including choline esters and cholinesterase inhibitors, induce salivary secretion by activating the parasympathetic nervous system. This system, responsible for increasing bodily secretions like tears, gastric juices, mucus, and saliva, aids in defending the body and facilitating digestion. Pilocarpine hydrochloride, classified as a choline ester, stands out as the most commonly prescribed parasympathomimetic for treating radiation-induced salivary gland dysfunction, with licensing in numerous countries.[73,77]

2. Parasympatholytic medications exert effects contrary to those of parasympathomimetic drugs; they act as anticholinergics, thereby suppressing saliva secretion.[74,75,77] Findings from animal experiments and research conducted by Rode et al.[75] propose that inhibiting saliva secretion during radiotherapy could potentially safeguard against subsequent damage to the salivary glands and enhance saliva production post-treatment.

3. Cytoprotective agents are administered prior to, during, or following cancer therapy to reduce or prevent harm or toxicity to normal cells and tissues while maintaining therapeutic effectiveness. Amifostine serves as one such cytoprotective agent and has demonstrated accumulation in the salivary glands. Reports suggest that this accumulation may potentially decrease parotid parenchymal damage caused by radiotherapy and reduce the occurrence of radiation-induced xerostomia.[76,77]

CONCLUSION

Adhesive materials that prevent secondary caries should be used for the restoration of RC. Resistance to tooth decay can be increased by applying topical fluoride. Ensuring and maintaining oral hygiene during and after radiotherapy is essential.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Paleri V, Roland N. Introduction to the United Kingdom national multidisciplinary guidelines for head and neck cancer. *J Laryngol Otol*. 2016;130(S2):S3-S4.
2. Kawashita Y, Soutome S, Umeda M, Saito T. Oral management strategies for radiotherapy of head and neck cancer. *Jpn Dent Sci Rev*. 2020;56(1):62-67.
3. Argiris A, Eng C. Epidemiology, staging, and screening of head and neck cancer. *Cancer Treat Res*. 2003;114:15-60.
4. Chow LQM. Head and neck cancer. *N Engl J Med*. 2020;382:60-72.
5. Fitzmaurice C, Allen C, Barber RM, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted lifeyears for 32 cancer groups, 1990 to 2015. *JAMA Oncol*. 2017;3(4):524-548.
6. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424.
7. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209-249.
8. De Felice F, Polimeni A, Valentini V et al. Radiotherapy controversies and prospective in head and neck cancer: a literature-based critical review. *Neoplasia*. 2018;20(3):227-232.
9. Specht L. Oral complications in the head and neck radiation patient. Introduction and scope of the problem. *Supp Care Cancer*. 2002;10(1):36-39.
10. Jham B C, da Silva Freire AR. Oral complications of radiotherapy in the head and neck. *Braz J Otorhinolaryngol*. 2006;72(5):704-708.
11. Shah JP, Gil Z. Current concepts in management of oral cancer-surgery. *Oral Oncol*. 2009;45(4-5):394-401.
12. Lin SS, Massa ST, Varvares MA. Improved overall survival and mortality in head and neck cancer with adjuvant concurrent chemoradiotherapy in national databases. *Head Neck*. 2016;38(2)208-215.
13. Gupta N, Pal M, Rawat S, et al. Radiation-induced dental caries, prevention and treatment– a systematic review. *Natl J Maxillofac Surg*. 2015;6(2):160-166.
14. Naidu MUR, Ramana GV, Rani PU, Mohan Iyyapu K, Suman A, Roy P. Chemotherapy-induced and/or radiation therapy-induced oral mucositis-complicating the treatment of cancer. *Neoplasia*. 2004;6(5):423-431.
15. Bensadoun RJ, Riesenbeck D, Lockhart PB, et al. A systematic review of trismus induced by cancer therapies in head and neck cancer patients. *Support Care Cancer*. 2010;18(8):1033-1038.
16. Jensen SB, Pedersen AML, Vissink A, et al. A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: prevalence, severity and impact on quality of life. *Support Care Cancer*. 2010;18(8):1039-1060.
17. Hong CH, Napeñas JJ, Hodgson BD, et al. A systematic review of dental disease in patients undergoing cancer therapy. *Support Care Cancer*. 2010;18(8):1007-1021.
18. Epstein JB, Stevenson-Moore P. Periodontal disease and periodontal management in patients with cancer. *Oral Oncol*. 2001;37(8):613-619.
19. Nabil S, Samman N. Incidence and prevention of osteoradionecrosis after dental extraction in irradiated patients: a systematic review. *Int J Oral Maxillofac Surg*. 2011;40(3):229-243.
20. Jawad H, Hodson NA, Nixon PJ. A review of dental treatment of head and neck cancer patients, before, during and after radiotherapy: part 1. *Br Dent J*. 2015;218(2):65-68.
21. Begg AC, Stewart FA, Vens C. Strategies to improve radiotherapy with targeted drugs. *Nat Rev Cancer*. 2011;11(4):239-253.
22. Baskar R, Lee KA, Yeo R, Yeoh KW. Cancer and radiation therapy: current advances and future directions. *Int J Med Sci*. 2012;9(3):193-199.

23. Wolff A, Joshi RK, Ekström J, et al. A guide to medications inducing salivary gland dysfunction, xerostomia, and subjective sialorrhea: a systematic review sponsored by the world workshop on oral medicine VI. *Drugs R&D*. 2017;17(1):1-28.
24. Mercadante S, Aielli F, Adile C, et al. Prevalence of oral mucositis, dry mouth, and dysphagia in advanced cancer patients. *Support Care Cancer*. 2015;23(11):3249-3255.
25. Buzalaf MAR, Ortiz AC, Carvalho TS, et al. Saliva as a diagnostic tool for dental caries, periodontal disease and cancer: is there a need for more biomarkers? *Expert Rev Mol Diagn*. 2020;20(5):543-555.
26. Papale F, Santonocito S, Polizzi A, et al. The new era of salivaomics in dentistry: frontiers and facts in the early diagnosis and prevention of oral diseases and cancer. *Metabolites*. 2022;12(7):638.
27. Chiappin S, Antonelli G, Gatti R, Elio F. Saliva specimen: a new laboratory tool for diagnostic and basic investigation. *Clin Chim Acta*. 2007;383(1-2):30-40.
28. Ruhl S. The scientific exploration of saliva in the post-proteomic era: from database back to basic function. E*xpert Rev Proteomics*. 2012;9(1):85-96.
29. Podzimek S, Vondrackova L, Duskova J, Janatova T, Broukal Z. Salivary markers for periodontal and general diseases. *Dis Markers*. 2016;9179632.
30. Kaczor-Urbanowicz KE, Martin Carreras-Presas C, Aro K, et al. Saliva diagnostics – current views and directions. *Exp Biol Med*. 2017;242(5):459-472.
31. Vistoso Monreal A, Polonsky G, Shiboski C, Sankar V, Villa A. Salivary gland dysfunction secondary to cancer treatment. *Front Oral Health*. 2022;3:907778.
32. Dawes C, Pedersen AM, Villa A, et al. The functions of human saliva: a review sponsored by the world workshop on oral medicine VI. *Arch Oral Biol*. 2015;60(6):863-874.
33. Mercadante V, Al Hamad A, Lodi G, Porter S, Fedele S. Interventions for the management of radiotherapy-induced xerostomia and hyposalivation: a systematic review and meta-analysis. *Oral Oncol*. 2017;66:64-74.
34. Levine N. Outfitting your practice for safety and efficiency. *Dent Prod Rep*. 2020;54:41-44.
35. Hegde M, Bhat R, Punja A, Shetty C. Correlation between dental caries and salivary albumin in adult Indian population—an in vivo study. *Br J Med Med Res*. 2014;4(25):4238-4244.
36. Lalla RV, Latortue MC, Hong CH, et al. A systematic review of oral fungal infections in patients receiving cancer therapy. *Support Care Cancer*. 2010;18(8):985-992.
37. Brosky ME. The role of saliva in oral health: strategies for prevention and management of xerostomia. *J Support Oncol*. 2007;5(5):215-225.
38. Da Silva JD, Mitchell DA, Mitchell L. Oxford American Handbook of Clinical Dentistry (Oxford American Handbooks of Medicine). Oxford University Press: 2007.
39. Walsh LJ. Contemporary technologies for remineralisation therapies: a review. *Int Dent SA*. 2009;11(6):6-16.
40. Valstar MH, de Bakker BS, Steenbakkers RJ, et al. The tubarial salivary glands: a potential new organ at risk for radiotherapy. *Radiother Oncol*. 2021;154:292-298.
41. Polat SÖ. Tükürük bezlerine güncel bakış: yeni bir organ tartışması. *Arch Med Rev J*. 2021;30(2):59-67.
42. Kilian M, Chapple IL, Hannig M, et al. The oral microbiome – an update for oral healthcare professionals. *Br Dent J*. 2016;221(10):657-666.
43. Whiteside SA, Razvi H, Dave S, Reid G, Burton JP. The microbiome of the urinary tract-a role beyond infection. *Nat Rev Urol*. 2015;12(2):81-90.
44. Willis JR, Gabaldón T. The human oral microbiome in health and disease: from sequences to ecosystems. *Microorganisms*. 2020;8(2):308.
45. Dominguez-Bello MG, Godoy-Vitorino F, Knight R, Blaser MJ. Role of the microbiome in human development. *Gut*. 2019;68(6):1108-1114.
46. Deo PN, Deshmukh R. Oral microbiome: unveiling the fundamentals. *J Oral Maxillofac Pathol*. 2019;23(1):122-128.
47. Epstein JB, Thariat J, Bensadoun RJ, et al. Oral complications of cancer and cancer therapy: from cancer treatment to survivorship. *CA Cancer J Clin*. 2012;62(6):400-422.
48. Kielbassa AM, Hinkelbein W, Hellwig E, Meyer-Lückel H. Radiation-related damage to dentition. *Lancet Oncol*. 2006;7(4):326-335.
49. Vissink A, Jansma J, Spijkervet FKL, Burlage FR, Coppes RP. Oral sequelae of head and neck radiotherapy. *Crit Rev Oral Biol Med*. 2003;14(3):199-212.
50. Palmier NR, Ribeiro ACP, Fonsêca JM, et al. Radiation-related caries assessment through the international caries detection and assessment system and the post-radiation dental index. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2017;124(6):542-547.
51. Moore C, McLister C, Cardwell C, O'Neill C, Donnelly M, McKenna G. Dental caries following radiotherapy for head and neck cancer: a systematic review. *Oral Oncol*. 2020;100:104484.
52. Siala W, Mnejja W, Elloumi F, et al. Late toxicities after conventional radiotherapy for nasopharyngeal carcinoma: incidence and risk factors. *J Radiother*. 2014;2014:268340.
53. Palmier NR, Migliorati CA, Prado-Ribeiro AC, et al. Radiation-related caries: current diagnostic, prognostic, and management paradigms. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2020;130(1):52-62.
54. Santos-Silva AR, Feio Pdo S, Vargas PA, Correa ME, Lopes MA. cGVHD-related caries and its shared features with other 'dry-mouth'-related caries. *Braz Dent J*. 2015;26(4):435-440.
55. Madrid CC, Paglioni MP, Line SR, et al. Structural analysis of enamel in teeth of head-and-neck cancer patients who underwent radiotherapy. *Caries Res*. 2017;51(2):119-128.
56. Madrid C, Abarca M, Bouferrache K. Osteoradionecrosis: an update. *Oral Oncol*. 2010;46(6):471-474.
57. Irie MS, Mendes EM, Borges JS, Osuna LG, Rabelo GD, Soares PB. Periodontal therapy for patients before and after radiotherapy: a review of the literature and topics of interest for clinicians. *Med Oral Patol Oral Cir Bucal*. 2018;23(5):e524-e530.
58. Schiødt M, Hermund NU. Management of oral disease prior to radiation therapy. *Supp Care Cancer*. 2002;10(1):40-43.
59. Lanzetti J, Finotti F, Savarino M, Gassino G, Dell'Acqua A, Erovigni FM. Management of oral hygiene in head-neck cancer patients undergoing oncological surgery and radiotherapy: a systematic review. *Dent J*. 2023;11(3):83.
60. Jones JA, Chavarri-Guerra Y, Corrêa LBC, et al. MASCC/ISOO expert opinion on the management of oral problems in patients with advanced cancer. *Supp Care Cancer*. 2022;30(11):8761-8773.
61. McCaul LK. Oral and dental management for head and neck cancer patients treated by chemotherapy and radiotherapy. *Dent Update*. 2012;39(2):135-138.
62. Yokota T, Tachibana H, Konishi T, et al. Multicenter phase II study of an oral care program for patients with head and neckcancer receiving chemoradiotherapy. *Supp Care Cancer*. 2016;24(7):3029-3036.
63. Turner L, Mupparapu M, Akintoye SO. Review of the complications associated with treatment of oropharyngeal cancer: a guide for the dental practitioner. *Quintessence Int*. 2013;44(3):267-279.
64. Kumar N. The oral management of oncology patients requiring radiotherapy, chemotherapy and/or bone marrow transplantation – clinical guidelines. *R Coll Surg Engl/Br Soc Disabil Oral Heal*. 2019.
65. Gupta N, Pal M, Rawat S, et al. Radiation-induced dental caries, prevention and treatment – a systematic review. *Natl J Maxillofac Surg*. 2015;6(2):160-166.
66. McComb D, Erickson RL, Maxymiw WG, Wood RE. A clinical comparison of glass ionomer, resinmodified glass ionomer and resin composite restorations in the treatment of cervical caries in xerostomic head and neck radiation patients. *Oper Dent*. 2002;27(5):430-437.
67. De Moor RJ, Stassen IG, van't Veldt Y, Torbeyns D, Hommez GM. Two-year clinical performance of glass ionomer and resin composite restorations in xerostomic head and neck irradiated cancer patients. *Clin Oral Investig*. 2011;15(1):31-38.
68. Kalsi H, McCaul LK, Rodriguez JM. The role of primary dental care practitioners in the long-term management of patients treated for head and neck cancer. *Br Dent J*. 2022;233(9):765-768.
69. Papas A, Russell D, Singh M, Kent R, Triol C, Winston A. Caries clinical trial of a remineralising toothpaste in radiation patients. *Gerodontol*. 2008;25(2):76-88.
70. Cochrane NJ, Cai F, Huq NL, Burrow MF, Reynolds EC. New approaches to enhanced remineralization of tooth enamel. *J Dent Res*. 2010;89(11):1187-1197.
71. Preetha A, Banerjee R. Comparison of artificial saliva substitutes. *Trends Biomaterials Artificial Organs*. 2005;18(2):178-187.
72. Foglio-Bonda A, Foglio-Bonda PL, Bottini M, Pezzotti F, Migliario M. Chemical-physical characteristics of artificial saliva substitutes: rheological evaluation. *Eur Rev Med Pharmacol Sci*. 2022;26(21):7833-7839.
73. Wiseman LR, Faulds D. Oral pilocarpine: a review of its pharmacological properties and clinical potential in xerostomia. *Drugs*. 1995;49(1):143-155.
74. Ahlner BH, Hagelqvist E, Lind MG. Influence on rabbit submandibular gland injury by stimulation or inhibition of gland function during irradiation. Histology and morphometry after 15 gray. *Ann Otol Rhinol Laryngol*. 1994;103(2):125-134.
75. Rode M, Smid L, Budihna M, Gassperssic D, Rode M, Soba E. The influence of pilocarpine and biperiden on pH value and calcium, phosphate, and bicarbonate concentrations in saliva during and after radiotherapy for head and neck cancer. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2001;92(5):509-514.
76. Brizel DM, Murphy BA, Rosenthal DI, et al. Phase II study of palifermin and concurrent chemoradiation in head and neck squamous cell carcinoma. *J Clin Oncol*. 2008;26(15):2489-2496.
77. Riley P, Glenny AM, Hua F, Worthington HV. Pharmacological interventions for preventing dry mouth and salivary gland dysfunction following radiotherapy. *Cochrane Database Syst Rev*. 2017;7(7):CD012744.