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Oral Side Effects of Head and Neck Irradiation

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Abstract

Head and neck irradiation is the standard treatment of advanced oral/oropharyngeal cancer. The treatment has severe side effects such as mucositis, xerostomia, irradiation caries, trismus, and osteoradionecrosis. Side effects can lead to treatment discontinuation, infection, increased drug consumption, and increased duration of hospital admission and can have negative impact on the quality of life and overall survival. Furthermore, some of them (mucositis and xerostomia) affect almost every (>90%) patient. Since nearly two-thirds of oral/oropharyngeal cancers are diagnosed in advanced stage, one might conclude that the great majority of patients will be affected. However, these side effects can be prevented or at least reduced by proper oral/dental care. Therefore, every patient planned for head and neck irradiation should undergo dental evaluation before beginning of the treatment.

Keywords: oral cancer, radiotherapy, mucositis, xerostomia, osteoradionecrosis, radiation caries

1. Introduction

Head and neck irradiation is the standard treatment of advanced oral/oropharyngeal cancer. Most often, radiotherapy (RT) is delivered after surgery, alone or in combination with chemotherapy to assure better locoregional control. Indication for postoperative radio-/chemoradiotherapy includes: T3 or T4 tumor, close (<5 mm) or positive surgical margin, positive cervical lymph nodes with or without extracapsular spread, lymphovascular and/or perineural invasion. RT can be delivered as a primary treatment in cases of unresectable disease, compromised patient's health, unfavorable cosmetic, or functional outcome of anticipated surgery and recurrent disease with multiple previous surgeries [1].

Head and neck cancer patients usually receive the total dose of 60–70 Gy divided into 2 Gy daily fractions (5 days a week) over 6–7 weeks. Along with therapeutic action on tumor cells, ionizing radiation causes damage to surrounding healthy tissues located in the radiation field. Radiation induced damage to surrounding healthy tissues is responsible for complications that arise during and after radiotherapy. There are several reasons why these complications are very frequent in the oral cavity:

- fast turnover rate of oral mucosal cells
- rich and complex oral microflora
- mucosal microtrauma during mastication [2]

Most orofacial complications are dose-dependent and side effects occur when doses greater than 45 Gy are delivered. Apart from the total dose, intensity of oral side effects depends on the fraction size and scheduling, field size/affected tissue volume, and concomitant use of chemotherapy. In order to minimize the irradiation damage to surrounding tissue, novel techniques such as 3D (three-dimensional) conformal radiotherapy and intensity-modulated radiotherapy (IMRT) are introduced. These techniques allow more precise design of radiation field enabling delivery of high doses to the target tissue while reducing doses to surrounding structures [3].

Radiation-related oral side effects can be acute or chronic. Acute side effects begin during the RT and last several weeks after the therapy cessation. Acute side effects include

- oral mucositis
- taste disorder
- xerostomia

Chronic oral side effects begin several weeks, months, or even years after the RT. Chronic side effects are as follows:

- trismus
- radiation-induced dental caries
- osteoradionecrosis [4]

Patients undergoing RT demand a multidisciplinary approach in order to reduce the intensity of radiation-induced oral side effects and understand the role of dentist and themselves in their prevention and therapy.

2. Acute side effects of head and neck irradiation

2.1. Oral mucositis

Oral mucositis (OM) is the most common complication of head and neck irradiation affecting 80–90% of the patients. Oral mucositis is defined as reactive inflammation of oral mucosa due

to radiation-induced damage of cellular DNA and subsequent cellular death of basal keratinocytes. Mucositis manifests as ulcerative inflammation of the oral mucosa (**Figure 1**) which can cause severe pain, deteriorated oral function, increased drug consumption, and can lead to temporary treatment interruption with consequent reduction in therapeutic effect [4].

Pathogenesis of oral mucositis can be divided into five stages: initiation, upregulation/activation, signal amplification, ulceration, and healing. First step, initiation is characterized by radiation-induced DNA damage and generation of reactive oxygen species (ROS). In the next step, ROS activate nuclear factor- κ B (NF- κ B) transcription factor, which further upregulates genes responsible for the synthesis of pro-inflammatory cytokines like interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF- α). As the RT continues, generated pro-inflammatory cytokines further amplify inflammatory mucosal damage by providing positive feedback on NF- κ B activation. In the next stage, patients develop ulcerations which are colonized by oral microorganisms that further promote epithelial damage. Last stage characterized by healing of the ulcers occurs when radiation-induced DNA damage stops [5].

First clinical sign of oral mucositis is whitish appearance of oral mucosa which begins at the end of the first week of irradiation. In the third week, patients usually develop ulcerations covered with fibrinous pseudomembranes that are prone to secondary infection. Mucositis persists throughout the radiotherapy with a peak at the end of irradiation and lasts for 2–4 weeks after treatment cessation. Intensity of mucositis is strongly dependent on the total dose, fraction size, field size, number and frequency of fraction delivery, and type of ionizing irradiation [4, 5].

Even though there are numerous scales for the assessment/classification of mucositis available, most commonly used scoring system is the one established by the World Health Organization [6–9]. The scoring system is very simple to apply and based on patient's ability to eat solid food. According to WHO, oral mucositis can be divided into four stages as follows [9]:



Figure 1. Oral mucositis.

- stage 0 = no pain
- stage 1 = erythema and mild edema
- stage 2 = erythema and ulcers, patient is able to eat solid food
- stage 3 = erythema and ulcers, patient is unable to eat solid food
- stage 4 = peroral alimentation is not possible

There is still no effective agent that could prevent the development of oral mucositis in patients undergoing head and neck irradiation [10]. The treatment of oral mucositis therefore remains symptomatic, aimed at relieving pain, preventing infection of oral lesions, and maintaining normal functioning of oral cavity.

2.2. Xerostomia

Xerostomia is one of the most frequent and debilitating side effects of head and neck RT. It develops acutely (early in the course of irradiation), but frequently remains chronic (permanent) complication (**Figure 2**). Lack of saliva affects the health of the entire oral cavity and favors the occurrence of other oral complications, which impair patient's quality of life, such as development of dental caries, oral infections, dysgeusia, dysphagia, oral discomfort, and pain [11]. Major salivary glands produce 70–80% of the total salivary flow. Parotid gland predominantly produces stimulated, watery saliva, and its serous acinar cells are more radiosensitive than mucous cells of submandibular and sublingual glands [12]. It seems that the extent of parotid irradiation is a major contributing factor for the development of xerostomia, as well as a total dose of received irradiation [3]. Xerostomia often remains permanent if radiation dose is greater than 40 Gy. Head and neck tumors are usually treated with a total dose greater than 60 Gy, during 6 weeks, which can lead to decrease in salivary production by 80% [2].



Figure 2. Xerostomia.

Together with quantitative effect on salivary flow, RT also changes the composition of saliva. Concentration of different ions and proteins in saliva rises, while the bicarbonate concentration decreases, causing a low salivary pH and a low buffering capacity [13, 14]. Quantitative and qualitative changes in saliva seriously impair patient's quality of life. Sparing salivary glands during irradiation, if possible, can reduce the long-term reduction in salivary flow [11].

2.3. Taste disorder

During the RT, majority of patients experience complete or partial taste loss. According to a recent literature review, taste disorder affects 66.5% of patients undergoing RT alone and 76% of patients undergoing combined chemoradiotherapy [15].

Taste disorder is a result of two factors: (i) a direct radiation effect on the taste buds and (ii) changes in salivary flow and composition. Taste buds are very sensitive to irradiation and demonstrate signs of degeneration and atrophy at doses of 10 Gy [4]. Decreased salivary flow disrupts transport of flavor molecules to taste buds while changed ionic composition of saliva further impairs taste perception. Most patients report their taste disorder as mild. Impact of taste disorder on the quality of life is difficult to assess because patients often report taste disorder along with other, more severe side effects of head and neck irradiation like xerostomia, sticky saliva, and difficulty swallowing [15].

In majority of cases, taste gradually returns to normal or near-normal levels within 1 year after RT. Because of this transitory aspect, there is usually no need for treatment. However, in around 15% of patients, taste disorder can last longer. There have been cases of patients whose taste disorder lasted 5–7 years after RT. To date, no universally recommended preventive or management strategies are available [15].

3. Chronic side effects of head and neck irradiation

3.1. Radiation-induced dental caries

The primary cause of radiation-induced dental caries is change in quality and quantity of saliva, due to radiation-induced salivary gland damage. After RT, salivary viscosity is increased and its buffering capacity and pH are reduced. Salivary pH becomes cariogenic, decreasing from 7.0 to 5.0 and making minerals of enamel and dentin dissolve easily [16]. A defensive role of saliva is impaired, which leads to changes in oral flora of these patients. Within 3 months of completing RT, oral flora becomes more acidogenic and cariogenic because of increased concentration of *Streptococcus mutans*, *Lactobacillus*, and *Candida* species [17, 18]. If the teeth are located in the irradiation field, irradiation also has a direct destructive effect on dental hard tissue, causing decreased circulation through pulp, secondary fibrosis, and degeneration of the odontoblast processes. As shown from the literature, the effect of irradiation on tooth structure is dose-dependent. Doses lower than 30 Gy cause minimal tooth damage, doses 30–60 Gy increase risk of tooth breakdown two to three times while doses greater than 60 Gy increase risk of tooth damage 10 times [19]. Radiation-induced caries characteristically has a

quick progress and affects smooth tooth surfaces where caries in nonradiated patients seldom occurs. The affected teeth become discolored and demineralized, with erosions in the cervical region, which makes them fracture easily (**Figure 3**). Despite advanced clinical presentation, the lesions are painless [16]. The risk of occurrence of radiation caries is lifelong so patients should be instructed to maintain adequate oral hygiene and to come to regular dental check-ups every 1–3 months.

3.2. Osteoradionecrosis

Osteoradionecrosis (ORN) is the most serious complication of head and neck RT, which affects the bone in irradiated area. RT alters collagen synthesis and induces inflammation and obliteration of the blood vessels that provide blood supply to the bone. Irradiated bone becomes hypovascularized and hypoxic, with impaired healing capacity [20]. The process is irreversible and progressive, and the risk of osteonecrosis is lifelong. The most commonly used definition of ORN implies exposed bone without healing for 3 months, without recurrence of the tumor [2], although there is no universally accepted definition in the literature. Due to the disagreement about the definition, there are no accurate data about the prevalence and incidence of ORN in the jaws. The reported relative frequency of ORN is between 0 and 7.1%, but patients with tumors localized in the oral cavity have higher relative frequency of ORN, up to 13.6% [21]. Results from one literature review report a weighed ORN prevalence of 7.4% for conventional radiotherapy, 5.1% for IMRT, 6.8% for chemoradiotherapy, and 5.3% for brachytherapy [22]. The literature shows that two-thirds of ORN in the orofacial region appear after a traumatic event, such as tooth extractions, ill-fitting dentures, biopsies, or periodontal dental procedures, while one-third can appear spontaneously. The most frequently affected bone in the head and neck region is the mandible [21, 22].



Figure 3. Radiation caries.

Risk factors for the development of ORN include therapeutic dose and mode of irradiation or combined chemotherapy and radiotherapy. Doses greater than 60 Gy, use of brachytherapy, or combined chemo- and radiotherapy increases the risk of development of ORN, while hyperfractionated RT or moderately accelerated fractionated RT, even in greater doses, decrease the risk of its occurrence [23]. Other risk factors include poor oral hygiene, malnutrition, chronic trauma from ill-fitting dentures, or acute trauma from surgical procedures in the jaw, especially in posterior mandible [24].

ORN manifests as an area of exposed bone in the oral cavity (**Figure 4**). Symptoms of ORN include pain, dysgeusia, dysesthesia, halitosis, or food impaction in the area of exposed bone, although in early stages it can be asymptomatic. Untreated, it can lead to fistulas and pathological fractures of the bone (**Figure 5**) [20–24]. Still, there is no universally accepted classification system for ORN, which makes comparison of different studies difficult [25].

3.3. Trismus

Trismus can occur if temporomandibular joint and masticatory muscles are located in irradiated area during head and neck cancer therapy. Irradiation causes spasm and fibrosis of masticatory muscles, which limits mouth opening [26, 27]. Trismus is often defined as reduced mouth opening with interincisal space less than 35 mm, but there is no universally accepted definition in the literature which is the reason for a wide range of reported prevalence of trismus after head and neck RT, ranging from 5 to 38% of patients [28, 29]. Trismus is often underreported as RT side effect, although it seriously impairs quality of life, resulting with difficulties in patient's social life, affecting speech, food intake, and oral hygiene maintaining and even leading to depression [30]. Risk factors for the occurrence of the trismus are similar as for other late oral side effects of RT and include the total dose of radiation, fractionation



Figure 4. Osteoradionecrosis.



Figure 5. Osteoradionecrosis progressing to pathological fracture of the mandible (*Courtesy of Prof. Alajbeg*).

regimen (mode of irradiation), treatment modality (conventional RT vs. intensity-modulated radiotherapy (IMRT)), overall duration of RT, tumor location, and poor physical condition [26, 27, 31, 32]. Some results show that a total dose of RT greater than 55 Gy increases the incidence of trismus up to 47%, while treatment modality as conventional RT compared to IMRT decreases the mean incidence of trismus from 25.4 to 5% [27, 33]. Patients receiving RT to head and neck area should be instructed in rehabilitative exercises during and after RT to prevent the trismus development.

4. Dentist's role in head and neck cancer team

As early as 1995, experts of the health system of the United Kingdom concluded that health policy in addition to acting on the length of survival of patients with head and neck tumors (PwHNTs) must take all measures to increase their quality of life [34].

Over decades, modern treatment modalities have increased the survival rate of these patients, owing to the great efforts invested. However, it is obvious that the quality of life to which PwHNTs are destined is far below the level of being comfortable and functional [35]. The function of the upper aerodigestive tract is impaired following the treatment in PwHNT, especially of structures related to the oral tissues. The function of the mouth is a very important aspect of the quality of life of cancer patients in general [36]. While significant developments occur in the field of treatment, especially in terms of procurement of modern equipment for RT, as well as in education of radiation oncologists and medical physicists, which improves the survival rate of patients, we have to ask ourselves: what about the quality of life of our PwHNT following RT?

Oral toxicities related to RT are discussed in detail elsewhere in the text. Although oral mucositis does not last longer than a few weeks after completion of RT, its most serious consequence is interruption of RT [37]. The practice in which oncologists would temporarily interrupt radiation in case of severe form of mucositis “until the PwHNT gets his oral situation improved”

might still exist. This practice reduces the cure rate by 1–2% per each day of interruption [38]. Therefore, the dentists must take all measures to help PwHNT withstand the uninterrupted treatment, no matter how uncomfortable it gets.

Although it might require a lot of effort in continuous communication with oncology surgeons and oncologists, our profession must strive to provide arguments against interruption of radiation. Dentists need to convince oncologists that good preparation of PwHNT and close monitoring during RT at 2-week intervals can effectively prevent the need for interruption of RT, and this practice should be ever so rarer. Centers that include collaborative dentist would not normally interrupt radiation in cases of severe mucositis.

As discussed elsewhere in the chapter, there are also lifelong complications of head and neck RT, which ultimately can cause pathological fractures of the jaw and, indirectly, death. It is a cascade process with connected temporal occurrences. Briefly described, it begins with the destruction of acini of the salivary glands by radiation. The teeth, as there is no saliva, cannot defend demineralization, which leads to the inevitable radiation caries. The destruction of tooth leads toward the need for extraction, which is a high-risk procedure in the irradiated bone, because of RT-induced hypovascularity, ultimately leading toward ORN [39]. ORN can be so extensive that it may cause pathological fracture of the mandible (**Figure 5**). This “domino effect” could be prevented if dental profession is included into multidisciplinary approach.

Good protocols for an interdisciplinary approach to PwHNT clearly emphasize that the dentist is a part of the oncology team [40]. Unfortunately, is not usually so. There are exceptions in most developed countries, but it really is not a part of standard of care, especially in developing countries such as Croatia. The causes of such inappropriate practices lay on both sides of the bridge: medical doctor (head and neck surgeon) generally is not aware of the true significance and is not easily bothered to spend his limited energy on oral complications. A dentist, on the other hand, often has “better things to do” than to deal with a handful of neglected people of low socioeconomic status, who seem hopelessly ill. It could be due to personal ignorance on the subject, and due to a fear to treat PwHNT. And so, our task is twofold: as representatives of the profession called “oral medicine” to build a bridge between our fellow dentists and fellow medical doctors, and to strive to persuade them how important it is to cooperate. In addition, we have to introduce an educational intervention among fellow dentists to foster their engagement in this important activity. What we still do not know is how to motivate fellow dentists to enthusiastically participate in the care of PwHNT. Until then, only few institutions in Croatia, such as ours, will remain one of the few places that provide this type of care.

Dentists’ activities are directed to adherence to guidelines for oral care, which improve the quality of life in PwHNT, especially those who are treated with RT. Those include the reduction of the inevitable side effects of treatment, as well as the prevention of long-term complications of treatment.

Oral care needs to be based on the good practices from developed countries. The US National Comprehensive Cancer Network (“National Comprehensive Cancer Network,” NCCN) brings

together 26 of the top cancer centers in the United States and publishes guidelines for good clinical practice of treating head and neck tumors [41]. According to their guidelines, it is clearly stated that patients should be referred to dental evaluation before the treatment of any head and neck cancer site: lip cancer, oral cavity, oropharynx, hypopharynx, nasopharynx, glottic, and supraglottic larynx, paranasal sinuses (pp. 11–59). With the obligatory oral and dental evaluation and treatment before cancer treatment, NCCN guidelines emphasize the necessary oral evaluation and care during and after radiotherapy, stating that dental evaluation is recommended for oral cavity and all sites exposed to significant radiotherapy (p. 83) [41]. As a mandatory postulate, the NCCN approach describes the integration of treatment, stating that it is critically important that a multidisciplinary evaluation and treatment are prospectively coordinated and integrated by all disciplines involved in the care before starting any treatment (p. 84) [41].

Timing of RT as the part of multimodal treatment is important. It is well established that time elapsed between surgery and RT inversely affects the prognosis [42]. There are, however, papers questioning this concept, but today it is considered the best to start RT 6 weeks following the surgery [43]. This leaves enough time for dental treatment to be completed before the RT.

However, it is not unusual that dentists see PwHNT scheduled for RT, who comes at their first dental appointment only several days before the actual start of RT. If a dentist extracts their teeth, he would be causing further postponing of RT, which may be disastrous for the patient. Today, thanks to better planning in health care, waiting for RT is not so long anymore (at least in the institutions we work with), but the PwHNTs also come to point of oral care soon after discharge after surgery, which is early enough so that all dental procedures can be performed at a normal pace prior to the RT. This minimizes the risk of toxicities, eliminating the need for extractions after radiation. During and after RT, specific procedures are followed, as discussed elsewhere in the chapter.

Guidelines of the British Society for Disability and Oral Health, by Kumar et al., offer an elaborate approach to pathways of oral care in PwHNT [44]. Their basic postulate, without which we will certainly fail, is that clear pathway of care is necessary if we want to prevent or minimize oral complications. Regardless of how simple this may look, the lack of “clear pathway of care” was what caused the previous absence of this specific care. It requires strong dedication, exceptional effort, time, and preparedness for countless disappointments along the journey our profession takes in order to foster this type of oral care.

One should be aware that most of PwHNTs are not easy to motivate for compliance to oral care. It is very difficult to explain PwHNT how important the preventative effect of fluoridation is, when combined with good oral hygiene. A typical PwHNT has a history of consuming large amounts of alcohol and tobacco products, and is not easily motivated to suddenly start adhering to very strict oral hygiene measures. However, the efforts lead to success in a considerable number of patients.

Dentists should be aware of obstacles inherent in most health systems. One of them is that primary care dentists usually are unprepared and uninterested to participate in oral care.

The probable reason is the lack of specific knowledge and skills. These patients should be continuously motivated, closely followed up, and helped to obtain good adherence to our recommendations. If their primary care dentist is not collaborating with specialists, PwHNT most certainly will not comply.

Specialists should write very extensive medical histories, explaining the primary care dentist what and why certain dental procedures must be done in their offices and the therapeutic rationale behind these procedures. These are written dental recommendations with an educational component. Secondary and tertiary care professionals who coordinate oral care should always clearly emphasize that they would be available for telephone or other types of consultation. Furthermore, it has been noted that the advice on oral and dental complications of head and neck RT treatment communicated by head and neck surgeon had much more impact on patients than if that same advice was communicated by the responsible dentist. It is therefore of utmost importance that head and neck surgeon possesses basic knowledge of the subject matter and that is willing to firmly insist that PwHNT complies with oral health measures. Regardless of how disappointing this might be for oral care professionals, this discovery is very important and should help guiding efforts to change oral behavior in our PwHNT. Head and neck surgeons who assume a role of “oral health advocates” can help dentists to significantly increase patients’ compliance. We have observed that if surgeons also motivate patients for good oral care, a significant increase in compliance with the recommendations will be achieved [45]. The ideal would be that the oral assessment is introduced as a legal requirement before the radiation of the head and neck. Listed experiences should be of practical help to readers who plan to start this service [46].

5. Dental management prior radiation therapy for head and neck cancers

Prior to the head and neck RT, all patients without exception should be referred for oral/dental care. There are no generally accepted evidence-based clinical guidelines for dentists how to prepare patients for RT; however, it is rational to follow effective strategies from the relevant literature [47].

The main purposes of pretreatment dental evaluation are as follows:

- to prevent or minimize acute and chronic oral side effects associated with RT
- to facilitate submission of RT and radiation-induced sequelae

(1) The task of the dentist, as a member of the oncology team preparing the patients for head and neck RT, is to perform the following procedures:

- (a) treatment of oral and dental diseases
- (b) implementation of preventive procedures
- (c) education of the patients

5.1. Treatment of oral and dental diseases

Since treating diseased oral tissues prior to RT prevents or minimizes the development of many radiation-induced complications, a thorough oral examination before RT is essential. The fact that some patients are edentulous does not mean that for them dental management before, during, and after radiotherapy is not or is less important.

In order to reveal the presence of periapical lesions, impacted teeth, general bone conditions, and tumor rarefactions, a panoramic radiograph is performed [48]. Dental caries with or without root canal infection, necrotic pulps, periodontitis, periodontal abscesses, diseases of oral mucosa are additionally assessed through clinical dental evaluation. Oral status is evaluated and recorded: present teeth, clinical and radiographic findings (carious lesions, oral mucosa status, periodontal status, salivary gland functional assessment, interincisal opening), presence of orthodontic devices, and denture use.

Prophylactic dental clearance includes restorative treatments, periodontal scaling, fluoride therapy, and dental extractions. The following teeth need to be extracted [49]:

- Teeth with advanced caries lesions with questionable pulpal status or pulpal involvement
- Teeth with extensive periapical lesions
- Teeth with signs of severe periodontal disease (advanced bone loss and mobility or furcation involvement)
- Residual root tips not fully covered with bone or showing radiolucency
- Impacted or incompletely erupted teeth, particularly third molars that are not fully covered by alveolar bone or that are in contact with the oral environment

Three weeks before radiation therapy begins, all dental treatments should be completed. In the case there is less than 10 days to the beginning of the RT, teeth extractions are delayed for the “window” period after radiation (within 5–6 months after completion of RT) [50].

5.2. Implementation of preventive procedures

The elimination of all potential causes of local trauma is mandatory. It is known that ORN can develop also in edentulous patients [45] and therefore the adjustment of ill-fitting dentures is necessary. It is important to remove sharp edges and protruding teeth fillings. Orthodontic braces should be removed before the beginning of the RT.

5.3. Education of the patients

Besides teeth preservation and elimination of potential trauma, it is necessary that dentist educates the patient prior to RT. The dentist should explain the expected and possible RT-induced complications. Patients must be aware that the salivary glands may be affected by irradiation, which can result in severe decrease of salivary function [51]. Radiation-induced xerostomia is an important chronic side effect of RT that can lead to many oral diseases and patients should be warned on the rapid occurrence of dental caries [52]. Untreated on time, it results in the

extraction of teeth and the possible development of ORN. During preirradiation, dental management dentist should strongly emphasize to the patients that postirradiation caries and following oral diseases are avoidable through the regular and meticulous dental hygiene, daily fluoridation, and regular dental checkups.

Regrettably, in addition to poor oral health, before RT in many head and neck squamous cell carcinoma patients, even from developed countries and regardless of their dental status, poor oral hygiene is common [45]. Patients should therefore receive optimal mouth care before RT begins. During the preirradiation treatment, it is important that the dentist provides patients with instructions for oral hygiene during and after radiation therapy.

It is useful to provide the patient with the Fact Sheets created by the Oral Care Study Group of the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO) [53]. These are available online, multilingual, and written in plain language and the notable parts of the Fact Sheets are provided below along with their original section numbers.

1.3.1. Oral care advices that dentist should give to the patient before RT include instructions about [53]

1.3.1.1. proper toothbrushing: "Use a soft toothbrush. Brush before bed. Gently brush tongue. Brush within 30 minutes of eating."

1.3.1.2. dental floss use: "Floss at least once daily with waxed floss."

1.3.1.3. rinsing: "Rinse, swish and spit rinse several times after brushing or flossing. Ensure medicated rinses are done 20 minutes apart.

HOW TO MAKE YOUR MOUTH RINSE 1. Mix 1 teaspoon of baking soda and 1 teaspoon of salt with 4 cups of water. 2. Put the mouthwash in a container with a lid. 3. The mouthwash should be kept at room temperature. 4. Discard at the end of each day and make a new batch.

HOW TO USE YOUR MOUTH RINSE Shake well before using. • Rinse and gargle with one tablespoon (15 mL) and then spit out. • Repeat 2 or 3 times at each use. • Use mouthwash every 2 hours during the day."

1.3.1.4. oral moisturizing: "Moisturize nasal passages through the night with a steam vaporizer in your room. Moisturize with mouth rinse and water based lubricants often. Avoid petroleum jelly and glycerin products."

1.3.1.5. lip care: "Use water-soluble, wax-based, or oil-based lubricants. • Apply after cleaning, at bedtime and as needed. Do not apply petroleum Jelly."

1.3.3.6. fluoridation

"INSTRUCTIONS FOR USE OF FLUORIDE TRAYS 1. Brush and floss before wearing trays. 2. Fill the grooves of the trays 1/3 full with gel. 3. Insert tray and spit out any excess gel. 4. Leave the tray in for 5 minutes. • Use at bedtime for longer lasting results. • Brush trays and air dry after each use. • Do not use hot water to clean trays (hot water will distort the tray). • Do not eat, drink or rinse for 30 minutes after tray use."

Besides explaining how to perform fluoridation, dentist should emphasize the importance of fluoridation in preventing post-radiation dental caries.

1.3.1.7. Denture care instructions

“• Keep your dentures out as much as possible. • Remove dentures, plates and prostheses before brushing. • Brush and rinse dentures after meals and before bed. • Soak dentures in cleansing solution for at least 8 hours. • If you are on antifungal therapy, soak in anti-fungal solution.” [53]

Edentulous patient should also be instructed to remove dentures during RT. [48]

As a member of oncology team, the dentist should also explain to the patients:

1.3.2. The necessity of avoiding the consumption of cigarettes and alcohol

1.3.3. The necessity of regular dental visits during and after RT.

Dental consultation should always be in order prior to RT. During the first pre irradiation dental visit, patient should become aware that the dentist plays very important role in the management of head and neck cancer. They should realize that dental treatment before, during, and after head and neck RT is mandatory part of the more successful oncological therapy, which reduces the morbidity and mortality associated with RT.

6. Oral care during head and neck radiotherapy

Oral care during head and neck RT is directed to the treatment of acute complications—oral mucositis, xerostomia and taste alterations.

6.1. Oral mucositis

Most pronounced symptom of oral mucositis is pain associated with dysphagia, odynophagia, and difficulty speaking. Symptoms usually begin in the third week of RT. Sometimes pain can be so intense that it can prevent oral food intake resulting in the need for parenteral nutrition, and in some cases discontinuation of RT. During this period, regular checkups at dental office every 7–10 days are recommended [54]. Up to now, a lot of treatment modalities for OM have been tested, but most of them with varying success.

The treatment of OM is symptomatic, and it mainly consists of pain management and infection control. For the pain management, mouthwash containing topical anesthetic agent such as lidocaine is usually prescribed. Tetracaine, amethocaine, dyclonine, and benzocaine are also used for pain relief. The use of topical anesthetics allows patients to do regular daily activities such as eating and tooth brushing. Most of the studies, aimed at pain relief, reported less frequent interruption of RT, when topical anesthetic is used [55–57]. Administration of systemic analgesics, including opioids, is used in most patients with moderate or severe OM [58]. Except topical anesthetic, mouthwash can contain anti-inflammatory and antimicrobial agents. A nonsteroidal anti-inflammatory drug, benzydamine hydrochloride, is effective in reducing

the intensity and duration of mucosal damage [10, 59]. Plaque control and oral hygiene is very important in controlling OM. Even though chlorhexidine (CHX) is not recommended in the prevention or management of oral mucositis, its administration may provide indirect benefits like plaque control and gingivitis prevention, as well as oral candidosis prevention [10]. In the case of oral candidosis, local antifungal drugs such as miconazole or nystatin are prescribed [54]. Cytoprotective drug amifostine and biological response modifiers (interleukin 1, interleukin 11, and transforming growth factor β) have also been introduced for management of OM, but with varying success and are not recommended [10]. From all of the above mentioned, it can be concluded that there is still no effective therapy for the prevention and treatment of OM. However, it is important to emphasize that dentist can significantly contribute to the implementation of RT in its entirety, without interrupting it.

6.2. Taste disorder

The prevalence of taste alterations in patients receiving RT is 66.5%, and approximately 15% of them continue to experience this problem after cessation of the treatment [15]. Taste disorder has a negative impact on quality of life and may cause malnutrition, weight loss, and in severe cases, significant morbidity. However, it is important to note that this problem is reversible, and in most of the patients spontaneous return of taste occurs within a year and therefore no specific treatment is necessary [15]. Additionally, up to now no efficient agent for treating or preventing RT related taste disorder exists [15]. Zinc gluconate, amifostine, and dietary counseling have been studied for that purpose. Studies that tested administration of zinc gluconate reported variable results [60, 61]. Zinc gluconate is therefore not recommended for taste disorder prevention in head and neck cancer patients, even though it was found to be beneficial in a noncancer idiopathic dysgeusia [15]. It has been shown that use of amifostine only modestly helps in reducing the severity of taste disorder, without affecting the incidence [62, 63]. Because of conflicting results of the studies which examined the use of amifostine in the prevention and/or management of taste disorder, recommendation is not to use it in head and neck cancer patients [15]. Use of dietary and educational counseling on the incidence and severity of dysgeusia in cancer patients has shown a minor impact on early-onset taste disorder (30% vs. 40%), but with a greater effect on long-term taste disorder (5% vs. 25%) [64].

6.3. Xerostomia

It is well known that salivary gland hypofunction and xerostomia are significant morbidities during and following head and neck RT, resulting in decrease of salivary flow rates. Treatment goals for salivary gland hypofunction are stimulation of residual salivary gland tissue, relief of oral dryness, prevention of tooth demineralization, caries, and oral infection [11]. Pilocarpine, cevimeline, bethanechol HCl, and amifostine have been tested for the prevention of salivary gland hypofunction in cancer patient undergoing RT. Due to conflicting results their use is not recommended [11]. On the other hand, recent systematic review suggested that both pilocarpine and cevimeline can reduce xerostomia symptoms and increase salivary flow compared to placebo *after* RT but “some aspects of the relevant effect size, duration of the benefit, and clinical meaningfulness remain unclear” [65].

Intensity-modulated radiation therapy (IMRT) can reduce the radiation dose to salivary glands, thus helping in decrease of salivary gland hypofunction and symptoms of xerostomia [66, 67]. Surgical transfer of submandibular gland to the submental space can contribute to preservation of salivary gland function and reducing xerostomia symptoms. However, this method applies only to patients with clinically negative cervical lymph nodes [11]. Despite their short-term effect, it has been shown that use of saliva substitutes is more effective in the treatment of dry mouth than placebo. The saliva substitutes are mainly based on carboxymethylcellulose,

Oral care during head and neck radiotherapy

- regular checkups every 7–10 days during RT
 - for the pain management prescribe topical anesthetics and/or analgesics
 - use a soft toothbrush with a fluoride toothpaste for brushing after meals and before bed. Floss at least once a day (use xylocaine anesthetic rinse prior to brushing and flossing)
 - if brushing is too painful, use a clean moist gauze or foam swab soaked in baking soda mouth rinse
 - rinse the mouth with a baking soda and salt solution (mix 1 teaspoon of baking soda and 1 teaspoon of sat with four cups of water) several times a day. Avoid salt during mucositis
 - management of dry mouth (sip water frequently, use saliva substitutes, use sugar-free candies, and gums)
 - keep dentures out of the mouth as much as possible; soak it in cleansing solution for at least 8 hours
 - exercises for the jaw muscles at least three times a day to avoid trismus
 - avoid spicy or acidic foods, tobacco, and alcohol
-

Table 1. Oral care during head and neck radiotherapy (modified from Refs. [68–70]).

hydroxypropylmethylcellulose, hydroxyethylcellulose, and polyglycerylmethacrylate. Some of them contain electrolytes and fluoride for preventing teeth demineralization. Artificial saliva substitutes come in the form of gel, spray, and solution. Because its lubricating effect lasts longer, saliva substitute gel is recommended, especially during the night or other periods of severe oral dryness [11].

Points to remember for the oral care during head and neck RT are presented in **Table 1** [68–70].

7. Oral care after head and neck radiotherapy

After completion of RT, frequent follow-up appointments at dental office and good oral hygiene are of utmost importance. Initially, follow-up appointments are carried out once a month, and subsequently their dynamics is determined individually. Xerostomia and salivary gland dysfunction as acute complication of RT continues in the posttreatment period, thereby becoming chronic, which greatly increases the risk of dental caries and its sequelae. Radiation caries is extremely progressive and highly destructive type of caries, which certainly increases the risk of ORN by increasing risk for tooth extraction. Therefore, every effort

should be focused on caries prevention. In order to avoid difficulties in maintaining oral hygiene and the implementation of necessary dental procedure, early signs of trismus should be recognized.

7.1. Radiation caries

Radiation caries is primarily a consequence of salivary hypofunction, saliva composition changes, and increase in acidogenic bacteria number. Furthermore, direct damage on the hard dental tissues frequently occurs from RT. For caries prevention good preoperative dental treatment, frequent dental evaluation and treatment after RT, consistent home care that includes brushing after meals and before bed, daily flossing, plaque control, self-applied fluoride products, and restricted intake of cariogenic foods are required [54].

It is considered that the fluoride therapy is the best option for the prevention and treatment of radiation caries. The use of fluoride products significantly reduces caries activity in postRT patients. High concentrated fluorides (≥ 5000 ppm) directly applied on tooth surfaces or with custom-made carriers should be maintained every day. Literature data have demonstrated no significant difference on caries activity related to the type of fluoride gel or fluoride delivery system [71].

Chlorhexidine (CHX) as a bisguanide with bactericidal activity reduces plaque accumulation and helps in reducing mainly Gram-positive and bit less Gram-negative bacteria. It is interesting that use of CHX has shown decrease in oral *Streptococcus mutans*, with no influence on oral lactobacillus counts [72, 73]. Generally, CHX is recommended for maintaining oral health, although potential side effects such as tooth staining, taste changes, and increased calculus deposits should be taken into account. CHX mouthwashes should be administered daily after tooth brushing [71].

In cases where radiation caries is not possible to prevent, restoration with a proper dental material is required. Lack of salivary buffering, reduction of normal plaque pH, and formation of the hydrofluoric acid in patients with xerostomia lead to erosion of glass ionomer restorations [74]. Hence, conventional glass ionomer restorations are not recommended in patients who have been treated with RT. For the dental restoration in patients who have been treated with RT, the use of resin-modified glass ionomer, composite resin, and amalgam restorations are recommended [71].

7.2. Trismus

Reduced mouth opening is a result of the damaging effects of RT on the masticatory muscles. It is very important to identify early signs of trismus considering the fact that early treatment can significantly affect its prevention. For the prevention as well as for the treatment of reduced mouth opening, passive and active physiotherapy from the commencement of RT can be performed. Active physiotherapy is carried out with the muscles placed around the joint, while passive motion includes use of various devices [33]. Passive physiotherapy implies the use of tongue depressors, a hand operated device "Therabite Jaw Motion Rehabilitation System," and forced mouth opening with finger pressure several times a day [75]. Except of the aforementioned therapeutic options, pentoxifylline and botulinum toxins have shown efficacy in reducing

radiation-induced trismus [76, 77]. However, the latter needs to be confirmed by randomized controlled studies. Whenever possible, sophisticated multiple-field techniques should be used to reduce the dose of radiation to the mastication muscles and temporomandibular joint [2].

7.3. Osteoradionecrosis

Head and neck cancer patients undergoing RT are at lifelong risk of developing ORN. Therefore, dental extractions after RT should be avoided if possible. Furthermore, every local trauma must be avoided, and endodontic therapy, instead of extractions, should be the treatment of choice. Otherwise, if there is a need for extractions in postradiation period, they should be performed during first 5–6 months after RT with minimal trauma and primary closure [25]. Obliteration of the blood vessels and hypovascularity of the bone that occurs after RT is not an overnight process and it takes 5–6 months to develop [20, 50]. This “window” period should therefore be used for necessary extractions if possible. Literature results on the incidence of ORN after tooth extraction support this as significantly lower incidence of ORN was reported when extractions were performed within 1 year postRT compared to extractions performed 2–5 years postRT (7.5% vs. 22.6%) [78]. Use of antibiotic prophylaxis for the prevention of ORN is widespread in the literature, but there is no consensus on the type and dose of application. Their administration is empirical [23]. Hyperbaric oxygen therapy (HBO) is not strongly recommended for the prevention of ORN prior dental extractions, due to unclear clinical efficacy and cost-effectiveness. No specific and universally accepted guideline for the administration of HBO therapy exists [22]. Most of the protocols propose 20–30 dives before and 10 dives after dental extraction at 2.0–2.5 atmosphere pressure [22, 23]. Despite that, recent Cochrane systematic review concluded that HBO therapy “appears to reduce the chance of ORN following tooth extraction in an irradiated field” and that “the application of HBOT to selected participants and tissues may be justified” [79].

Management of ORN includes conservative treatment, surgical debridement with the use of adjunctive antibiotics and reconstructive surgery. Conservative treatment should be the first line therapy for ORN because surgical procedure may enhance the necrotic process [23]. Treatment consists of local wound care and good oral hygiene using 0.2% chlorhexidine mouthwashes and course of systemic antibiotics in acute episodes [80, 81]. If a conservative

Oral care after head and neck radiotherapy

- regular checkups every 4–8 weeks for the first 6 months (afterwards based on the patient's needs)
 - avoid invasive surgical procedures including dental extractions (if necessary, the use of antibiotics and HBO therapy before and after surgery should be considered)
 - daily fluoride application (using a tray or brush-on method), flossing and meticulous oral hygiene (use a soft toothbrush and 0.02% CHX mouthwash) must be performed
 - management of dry mouth (sip water frequently, use saliva substitutes, sugar-free candies, and gums)
 - exercises for the jaw muscles at least three times a day (minimum first 6 months postRT)
 - a new removable denture can be made 3–6 months postRT (avoid any tissue irritation/trauma)
-

Table 2. Oral care after head and neck radiotherapy (modified from Refs. [68–70]).

approach does not achieve wound healing, surgical removal of necrotic bone is indicated. Indications for reconstructive surgery include advanced cases with oral and/or cutaneous fistula, radiographically visible osteolysis, and pathologic fracture [81, 82]. The use of anti-oxidant agent pentoxifylline and tocopherol (vitamin E) for the treatment of ORN has shown promising results but more clinical trials are needed to confirm their efficacy [82].

Points to remember for the oral care after head and neck RT are presented in **Table 2** [68–70].

8. Conclusion

Efforts of dental professionals will have a significant clinical and financial impact on the treatment of PwHNT. The dentist must be a member of the oncology team and must have knowledge on the specific complications of head and neck RT. Dentist should make a plan of treatment and prevention before the start of RT. Surgeons, radiation oncologists, and medical oncologists can find valuable partners in dental profession, with the aim of improving patients' overall quality of life. Such care can greatly prevent and reduce side effects of treatment, resulting in a significant reduction in the cost of treatment, and some of those aspects facilitate implementation of radiation therapy without interruption, which increases the chances of cure.

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