

DENTAL COMPLICATIONS OF RADIOTHERAPY: CLINICAL PICTURE, DIAGNOSTICS, TREATMENT. A REVIEW OF THE LITERATURE

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ABSTRACT

The use of radiotherapy in the treatment of head and neck cancers leads to complications in tooth tissues and caries progression caused by changes in the amount and composition of saliva and bacterial microflora. The aim of this article was to review and summarise knowledge about dental complications of radiotherapy among oncological patients with head and neck cancer (HNC). A search of the literature was performed using the keywords radiotherapy, tumours of the head and neck, and radiation caries in the PubMed database and epidemiological data from the Polish National Cancer Register. The selection of the most comprehensive papers published until October 2018 was analysed. According to the analysis of the reviewed literature dentists did not have clear recommendations for treatment and follow-up of patients after radiotherapy. A complex approach may prevent irreversible changes in the oral cavity, e.g. teeth damage. Radiation-induced caries have multifactorial aetiology; thus oncological patients require constant, careful and comprehensive dental care before, during and after irradiation. Various conflicting results of many studies were obtained. Studies were conducted in different conditions (in vivo, in vitro) that led to creation of different protocols of proceedings. The best practice is to follow the guidelines to ensure the best patient care and standardisation of treatment. There is a need to reach an international consensus.

KEY WORDS: radiotherapy, head and neck cancer, radiation caries.

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INTRODUCTION

Head and neck cancers (HNCs), depending on geographical region, are among the most frequently diagnosed cancers. It has been stated that about 2/3 of cases are diagnosed in developing countries such as Sri Lanka, India, Pakistan, Brazil, Uruguay, Cuba, and the countries of Oceania [1]. The highest incidence rates in the countries of the European Union have been noted in Hungary, Slovakia, Slovenia and France. The diagnosis is most often

noted after the age of 50 in an advanced stage of development in the form of squamous cell carcinoma (90%). The risk of developing oral cancer in men is estimated at 1.85%, in women about 0.37%.

In Poland, the number of cases of malignant cancer of the lips, mouth, and throat in 2010 was 3,669, of which 2,709 involved men, 960 women. In 2010, the incidence of cancer in men was 1.4 times higher than the average for EU countries, while among women this difference was smaller at approximately 1.2. The average survival rate

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with confirmed oral cancer after 5 years is approximately 50-60% [2].

Among the treatments for cancer is radiotherapy (RTH), used alone or in combination with other methods, e.g. surgery or chemotherapy. Radiation leads to the destruction of cancer cells along with surrounding tissues. The applied radiation dose is usually 65-72 Gy in daily doses of 1.8-2.0 Gy, 5 days a week, for a period of 7 weeks. Among the most common destructive changes in the teeth of patients undergoing irradiation are damage to enamel, dentine and the dentine-enamel junction (DEJ), as well as the studied and discussed changes within dental pulp. In addition, severe carious changes caused by changes in the amount and composition of saliva and microflora have been observed [3]. Recurring carious lesions with a characteristic distribution are caused by a loss in the amount and quality of secreted saliva, increased consumption of carbohydrates, shift in bacterial microflora, lack of proper oral hygiene and the direct effects of radiation on tooth tissue (Table 1). The consequences of irradiation in the head and neck region affect the whole oral cavity and are related to its functions. Dental sequelae, that are observed in the enamel, dentine and pulp, are closely associated with the other adverse effects of RTH such as altered function of the salivary glands, digestive disorders and oral microbial shift.

OBJECTIVES

The aim of this article was to summarise knowledge about dental complications of radiotherapy among oncological patients with HNC, to assess the risk of developing radiation-induced caries and evaluate treatment methods.

MATERIAL AND METHODS

A search of the literature was performed using the keywords radiotherapy, tumours of the head and neck, and radiation caries in the PubMed database and reviewing the selection of the most comprehensive papers published until October 2018. Additionally, the authors looked into epidemiological data from the Polish National Cancer Register. The literature searched includ-

ed original papers, cases based on *in vivo* and *in vitro* studies, review papers and epidemiological databases. The total number of references was 43.

CHANGES IN SALIVARY GLANDS

Studies by Kiellbassa showed changes in the parameters of saliva responsible for its immunological properties and a drop in pH to 5.0, which is below the critical level [4]. As a result, conditions for remineralisation are lacking in the oral environment of patients following RTH. At the same time, studies by Sim (2018, nasopharyngeal carcinoma) indicate that after 2 years the pH and buffer capacity of stimulated saliva exhibit a return to pre-radiotherapy values, as compared to the parameters of resting saliva, which remain below normal values [5]. Many publications indicate the irreversibility of damage to the salivary glands following irradiation at a dose exceeding 30 Gy [5, 6]. Studies by Franzén present a drastic decline in resting salivation below 0.5 ml/min within the first 2 weeks after initiating treatment [6].

CHANGES IN ORAL MICROFLORA

Treatment of the basic disease in patients with HNC results in a change in bacterial microflora, with a shift towards acid-resistant forms [7-9]. Within the oral cavity and the initial part of the digestive tract, detailed studies have shown:

- an increase in numbers of *Streptococcus sobrinus* in resting saliva [7];
- an increase in *Lactobacillus* and *Candida*, with a decrease in *Streptococcus* and *Neisseria*, and, after two years, a further decrease in *Neisseria* and *Prevotella* as well as increased *Candida* on the tongue;
- an increase in *Lactobacillus* and *Staphylococcus aureus* on the cheeks [8];
- an increase in numbers of *Lactobacillus* and *Candida albicans* in subgingival plaque,
- an increase in numbers of *Enterococcus* in the oral vestibule in the area of molars and on the mucosa of the tongue,
- a decrease in *Streptococcus salivarius* and *Fusobacterium nucleatum* [9].

TABLE 1. Direct and indirect influence of radiation on post-radiation induction of caries

Direct	Indirect
Changes in crystalline structure	Reduction in and changes in the composition of saliva
Reconstruction of dentine-enamel junction	Difficulty in maintenance of good hygiene
Change in the resistance of enamel to solubility under the influence of acids	Difficulty chewing and swallowing, changes in diet to a softer, more liquid, high-carbohydrate diet
Changes in the microhardness and biomechanical immunity of enamel and dentine	Changes in the composition of the oral microflora



FIGURE 1. Mouth of a patient 2 years after radiotherapy due to cancer of the tongue; characteristic clinical picture of cavities following radiation in the cervical area



FIGURE 2. Mouth of a patient after radiotherapy due to lymphoma: cavities due to post-radiation caries located within the incisal edges

CHANGES IN DIGESTION

Patients with HNC also present eating, chewing, and swallowing disorders, as the result of scarring caused by surgical procedures, radiotherapy, or infiltration by the primary tumour leading to contractures. What is more, sometimes radio- and chemotherapy themselves, along with the stress accompanying the entire stage of diagnosis and treatment of the patient, lead to significant weight loss and wasting of the body due to malnutrition. In order to prevent such situations, patients, independently or on the advice of doctors, adopt a pulpy, easily digestible, high-carbohydrate diet. Difficulty in maintaining proper hygiene and systemically developed prophylaxis against oral diseases intensifies the destruction of tooth tissues. Studies by Kraaijeng indicate that patients requiring assistance in swallowing using a tube are limited in their rehabilitation. For patients who have not regained their ability to chew or swallow independently up to 5 years after radiotherapy, further rehabilitation is ineffective [10].

POST-RADIATION CARIES

Post-radiation caries is a violent and highly destructive process. The risk of its occurrence varies, depending

on the type of research: 24%, according to Jie Deng [11], or 12 in 200 cases, according to Liang (nasopharyngeal carcinoma) [12]. Studies conducted by Siala showed that the risk of complications in teeth during the first year was assessed at 16%; after 3 years, 36%; after 5 years, 55%; after 7 years, 74% (nonmetastatic nasopharyngeal carcinoma) [13]. The first symptoms appear approximately 3 months after the end of the therapy cycle but some studies report that this occurs after 17 days of therapy, at the time a dose of 35.8 Gy is exceeded, which damages the salivary glands [12]. Other research estimates the number of decay-missing-filled teeth (DMFT) in patients following radiotherapy at 17.01, compared to patients constituting a healthy control group: 4.4 [11].

Changes occurring within hard tissues are observable even with a minimum dose of 0.5 Gy, whereas a single therapeutic dose is usually around 2 Gy. No effects of an increase in a single dose on the rate of onset and severity of changes were observed. However, a relationship was found between the total dose absorbed by the patient in the course of therapy and the severity of the clinical picture. Radiation of 0-30 Gy leads to insignificant changes, while a 30-60 Gy dose causes a threefold increase in changes. Exposure to doses above 60 Gy causes a tenfold increase in changes. This is explained by the overlapping effect inducing remodelling of the internal structure of hard tissues, leading to the deterioration of biomechanical parameters [14].

Post-radiation caries is the destruction of hard tissues within the enamel from more or less extensive loss of translucency, through cavities confined to enamel, or total loss, with less caries-resistant dentine becoming visible. Brown, dark colour of dentin is considered the result of the direct action of radiation on exposed dentine, not the presence of bacteria. Loss of enamel, destruction of the dentine-enamel junction, uncovering of surface layers of dentine, and stresses and strains in the chewing process all increase the risk of bacterial colonisation and caries progression.

The changes occur on surfaces that are classically free from caries, such as areas adjacent to the gums, the tops of cusps, and incisal edges (Figures 1 and 2). In studies by Nishtha Gupta [15], occurrence of caries following radiation was classified according to location and degree of severity. Type 1 applies to the area around the neck and widens along the dentine-enamel junction; type 2 describes changes on all surfaces, mainly chewing surfaces and incisal edges; type 3 is the rarest form, associated with changes in the colour of dentine, i.e. dark brown discolorations of chewing surfaces.

The Post-Radiation Dental Index is recommended for identification of the relevant type of the postradiotherapy complications in clinical images, as well as assessment of the rate of progression. The index consists of the MSS (mean surface score) and the MRS (mean restoration score), which are evaluated on the basis of various indications concerning the front and lateral teeth, using

the attached tables. Using this indicator, we can monitor patients' treatment by many specialists [16].

ULTRASTRUCTURAL CHANGES IN HARD TISSUES

Demineralisation of enamel in radiotherapy patients differs from that found in non-irradiated patients. Some studies indicate greater sensitivity to the action of acids and greater loss of biomechanical resistance [17-19], as opposed to other indications that there is no increase in the sensitivity of enamel to the effects of acids (*in vitro*) [20, 21].

Studies by Gonçalves indicate the direct effect of radiation on the structure of enamel and dentine. Changes caused by radiotherapy are reflected in the microscopic structure, and consequently in the physical parameters as well. The use of ionising radiation over 60 Gy (the overall therapeutic dose applied most frequently) causes no changes in the microhardness of the enamel. Interestingly, at dosages over 40 Gy, the superficial layer presents an increase in microhardness, which may be associated with an increase in the brittleness of this enamel layer as well as with the tendency to form cracks. All of these symptoms may contribute to hypersensitivity and promote marginal leakage of the materials used. No changes in prismatic construction were observed following the application of radiation, as opposed to the restructuring of the interprismatic substance [22]. It is believed that the remodelling of enamel induced by radiotherapy is the result of changes within the organic matrix rather than the inorganic structure. This is confirmed by transformations within the interprismatic structure corresponding to the organic matrix, due to the formation of free radicals and reactive oxygen forms. Studies by Ping Qing in *in vitro* conditions demonstrated an increase in the coefficient of friction leading to the formation of cavities in enamel characterised by greater delamination. In addition, some crystals were shown to be enlarged, along with simultaneous reduction of the inorganic component, potentially leading to reduced resistance on the part of the enamel to abrasion (*in vitro*) [22].

Dentine behaves differently, exhibiting decreased microhardness, especially in the middle layer. Changes in its microscopic structure with regard to reconstruction, as well as obliteration and cracks within the dentinal tubules and defragmentation of collagen fibres, are probably caused by dehydration. Reduced activity of odontoblasts and obliteration of dentinal tubules are direct effects of radiotherapy on cells, leading to vascularisation and metabolic disorders [23]. Radiation causes changes in the secondary and tertiary structures of proteins, impeding the hydration of collagen (*in vitro*) [24].

Decarboxylation occurs, along with the growth of crystals, leading to increased porosity and deterioration of the parameters of hardness and elasticity in enamel and dentine (*in vitro*) [14, 25, 26].

CHANGES IN PULP

There are many conflicting studies on the effect of RTH on pulp vitality. Some of them, assessing the vitality of pulp on the basis of bleeding during endodontic treatment, showed significant impairment of vitality. Others, however, indicated no differences between the pulp of healthy patients and that of patients following radiotherapy [27].

Studies conducted by Knowles (*in vivo*) in 1986 assessing pulp reactivity to stimuli using Pulp Tester and microscopically evaluating changes in pulp following RTH showed a number of complications: reduced reactivity to stimuli was found for as long as 5 years following RTH; it was additionally emphasised that teeth of the mandible showed less sensitivity than teeth of the upper jaw.

Electron microscope imaging revealed a lack of ordering of the internal structure, numerous instances of fibrosis, and changes in the vascular structure. Thinning of endothelium and thickening of muscularis were observed within their walls, with a reduction in vascular flow as well as a change in the construction of the collagen coat surrounding the capillary in the form of intense fibrosis impairing the proper nutrition of surrounding tissues (in the control group, the coat was characterised by a lace-like structure, whereas in the RTH group there were numerous instances of fibrosis) [28]. Similar results indicating possible pulp necrosis were obtained in studies by Kalnis [29]. The authors of these studies presented the negative impact of radiation therapy on the pulp of the teeth of dogs in the form of endothelial cell growth and thickening of the collagen layer around the vessels. Research conducted by Meyer presented the possibility of pulp necrosis, severe bleeding, and calcification in various areas, as well as inflammatory infiltration and radiation damage to fibroblasts [30].

Research published in recent years assessing the status of the dental pulp of patients following RTH using pulse oximetry analysis indicated that radiotherapy may not have a long-term effect on pulp vitality; however, it may cause temporary circulatory disorders. In studies by Kataoka, saturation was restored 5 months after the end of radiotherapy to values close to those at the initial stage, suggesting that pulp is able to regenerate and re-establish a proper supply of blood. The decrease in oxygen saturation observed initially may be associated with inflammation in the pulp, partial necrosis, or reduction of microcirculation due to radiation damage to the vessels. The observed low level of reaction in thermal tests is probably related to limitations in ion transport or to congestion (*in vivo*) [31, 32]. The restoration of a proper blood supply depends on the presence of stem cells and the capacity of the pulp to maintain vasculogenesis, due to the presence, confirmed by research, of transmembrane glycoprotein CD34 and its participation in haematopoiesis. Rabbani additionally states that tissue hypoxia is a factor in inducing the secretion of HIF-1 α

(a hypoxia-inducing agent), which is responsible for the promotion of angiogenesis. The presence of the markers S-100 and NCAM/CD56 and of neurofilaments in immunohistochemical studies indicates the potential for maintaining innervation [32, 33].

Tooth pulp subjected to centrifugation exhibits a significant increase in the number of HP (hydroxylsilylpyridinoline) and LP (lysylpyridinoline) bonds within the collagen samples. Since pulp is responsible for the proper metabolism of odontoblasts, and thus for the proper elasticity and biomechanical resistance of teeth, it is believed that the likelihood of injury and broken crowns in patients undergoing radiation therapy is comparable with the likelihood of these conditions in teeth of non-RTH patients which have undergone root canal therapy (*in vitro*) [34].

The response of dental pulp to radiotherapy is directly associated with understanding of the mechanisms of inflammation, ischaemia, and hypoxia, which affect not only the pulp but also tumour tissue. When analysing patients following RTH in terms of diseases of pulp in the early period following the end of therapy, one should bear in mind potential congestion and disturbances in oxidation; a lack of reaction is not always evidence of irreversible pulp inflammation.

CARIES TREATMENT

Changes in the structure of hard tissues, problems with maintaining oral hygiene, and persistent dryness cause problems in the treatment of post-radiation caries. In addition, the results of some studies indicate that patients with HNC are often characterised by low social status and are uninsured [11].

In treating cavities in this group of patients, many factors that may have an impact on the quality and duration of the applied fillings should be borne in mind. The use of glass ionomer (GI) cements is recommended, due to the reduced risk of development of secondary caries. In the case of partial or total loss of GI fillings, which can occur due to erosion and dehydration caused by xerostomia, the material can be replaced.

Research indicates that the source of failure in post-RTH patients in whom GI cements are used is loss of surface integrity, not secondary caries. In patients with good oral hygiene for whom 2 years have passed since the completion of radiotherapy, the 'sandwich' technique of restoration can be considered (*in vivo*) [35].

Standing in contrast to the above recommendations are the results of research conducted by Mjor, in which it was found that the main cause of replacement of GI fillings is secondary caries, with a frequency of occurrence similar to cases of composite fillings (*in vivo*) [36-38]. Moreover, studies by Randall and Wilson showed no significant evidence of a reduced risk of secondary caries around GI fillings in relation to others [39].

When composite materials are used, studies indicate that radiotherapy does not cause clinically important changes in the binding parameters of existing fillings; however, it may have an impact on reducing the binding strength of adhesive materials used following radiotherapy [40]. It has been observed that self-etch adhesive systems used in patients following RTH show better clinical parameters due to the 10 MDP monomers (10-methacryloyloxydecyl dihydrogen phosphate) contained therein, which show greater binding strength with regard to calcium ions from hydroxyapatite [40].

Restorative treatment of radiation-induced caries is difficult and often not effective. That is why comprehensive preventive measures should be undertaken. Fluoride prophylaxis before, during and after RTH is recommended as well as patients' education and motivation. In the group of patients treated by radiotherapy the fluoride helps to maintain the outer morphology of irradiated and cycled enamel by reducing mineral loss. However, it was not as effective in preserving the mechanical properties of enamel. Radiotherapy altered the enamel's elastic modulus and its chemical composition [41]. Additional use of CPP-ACP with stannous fluoride gel in irradiated nasopharyngeal carcinoma (NPC) patients gave similar results compared to stannous fluoride gel alone in reducing caries progression [42]. Hygienic procedures, plaque control and daily use of remineralizing preparations may help to avoid further decay [15].

The use of radiotherapy involving gamma radiation in the treatment of cancer of the head and neck, apart from the expected therapeutic effects, leads to many complications, including in tooth tissues. These complications have an influence on the patient's deteriorating quality of life (QoL) and present a challenge for dentists during outpatient therapy. Based on an analysis of the reviewed literature, there were no clear recommendations regarding the treatment of oncological patients in the dental surgery. However, there has been a recent update (2018) of clinical guidelines on oral management of oncology patients requiring radiotherapy, chemotherapy and/or bone marrow transplantation by the Royal College of Surgeons of England/British Society of Disability and Oral Health [43]. Due to the existence of various conflicting results of many studies, conducted in different conditions (*in vivo*, *in vitro*), it led to the creation of different protocols.

CONCLUSIONS

Radiation-induced caries has multifactorial aetiology, and thus oncological patients require constant, careful and comprehensive dental care before, during and after irradiation. Invasive treatment of this RTH sequela is not efficient enough; preventive measures should be undertaken as soon as possible. A complex approach may prevent irreversible changes in the oral cavity, e.g. teeth damage.

In summary, it needs to be noted that because of the complexity and severity of cancers, the patient should not be burdened with additional suffering from dental treatment. The best practice will be to use the clear guidelines based on the newest research. Guidelines should be introduced and recognised as a gold standard by national consultants. By using them we will be able to follow up patients treated in different medical centres by different doctors.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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