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Radiotherapy-induced salivary dysfunction: Structural changes, pathogenetic mechanisms and therapies

Monique Dossena Acauan[a], Maria Antonia Zancanaro Figueiredo[a], Karen Cherubini[a], Ana Paula Neutziling Gomes[b], Fernanda Gonçalves Salum[a,*]

[a] Oral Medicine Division, Pontifical Catholic University of Rio Grande do Sul-PUCRS, Brazil
[b] Oral Pathology Division, Federal University of Pelotas-UFPEL, Brazil

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ABSTRACT

Purpose: This review addressed the structural changes observed in salivary glands and pathogenic mechanisms resulting from oxidative stress caused by radiotherapy. The preventive and regenerative therapies for altered acinar morphology and glandular function were also reviewed. Among acute and late microscopic alterations in glandular tissue, there are particularly changes indicative of cell death, hypovascularization, formation of fibrous tissue and edema. A critical role was identified for the Akt–MDM2–p53 pathway in the suppression of DNA damage-induced apoptosis in acinar cells. Prophylactic treatment with pilocarpine, cevilemine, bethanechol and isoproterenol has shown a positive effect on salivary flow, but lasting results have not been observed. Growth factors, histamine and lidocaine, have also demonstrated radioprotective effects on the salivary glands. Stem cell preservation and transplantation may be an alternative to maintain tissue homeostasis and thus allow glandular regeneration.

Conclusion: Knowledge of the structural changes observed in the salivary glands contributes to proving the short- and long-term efficacy of the therapies investigated. It is important to know the mechanisms involved in radiation-induced damage, since the control of the pathogenic mechanisms can inhibit the initial process of tissue degeneration. The challenge for investigators is to protect normal cells selectively, without promoting tumor growth.

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* Corresponding author at: Pontifícia Universidade Católica do Rio Grande do Sul, PUCRS, Hospital São Lucas, Av. Ipiranga, 6690, Room 231, CEP: 90610-000 Porto Alegre, RS, Brazil. Fax: +55 51 3320 3254.
E-mail address: fernanda.salum@pucrs.br (F.G. Salum).

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1. Introduction

Although effective in treating malignant neoplasms of the head and neck, radiotherapy has side effects, where its action in tissues is not selective, affecting normal cells as well as tumors. The major salivary glands are often irradiated as they are close to the sites of primary tumors and lymph nodes (Bhide, Ahmed, Newbold, Harrington, & Nutting, 2012; Mossman, Shatzman, & Chencharick, 1982). Approximately 70% of patients receiving head and neck radiotherapy develop hyposalivation due to a progressive loss of salivary gland function (Mossman et al., 1982). The hyposalivation can be observed during the first weeks of treatment and often persists throughout the patient's life (Bhide et al., 2012; Epstein et al., 2012). Due to the quantitative and qualitative changes that occur in saliva, patients become vulnerable to complications that directly or indirectly affect their quality of life. These complications include loss of taste, painful and burning mouth, susceptibility to caries and other oral infectious diseases, dysphagia, dysphonia and even psychological disorders such as depression (Dirix, Nuyts, Vander Poorten, Delaere, & Van den Bogaert, 2008).

There are no studies that clearly show how radiotherapy acts on the function of the salivary glands. Although acinar cells do not have a high mitotic activity, they show an early response to radiation (Avila, Grundmann, Burd, & Limesand, 2009; Coppes, Zeilstra, Kampinga, & Konings, 2001; Limesand, Schwertfeger, & Anderson, 2006; Paardekooper, Cammelli, Zeilstra, Coppes, & Konings, 1998). Disrupted signal transduction as a result of radiation-induced damage to the plasma membrane has been suggested to be the cause of the decrease in salivary flow observed just after radiation (Konings, Coppes, & Vissink, 2005). However, this effect does not explain the persistence of hyposalivation for years. Macroscopic and microscopic changes in salivary glands resulting from radiation are also described in the literature; many studies indicate that there is a close relation between acinar loss and chronic glandular dysfunction (Avila et al., 2009; Feng, van der Zwaag, Stokman, van Os, & Coppes, 2009; Limesand, Said, & Anderson, 2009; Lombaert et al., 2008a).

Aiming to improve the quality of life of patients treated with radiotherapy, investigators have sought to develop treatments that reduce the effect of ionizing radiation on the salivary glands. However, many treatments produce a short-term improvement in salivary flow but have no effect on acinar morphology (Coppes et al., 2001). The aim of this review was to address the structural changes observed in the salivary glands resulting from oxidative stress caused by radiotherapy and to describe the pathogenic mechanisms involved. Preventive and regenerative therapies for altered acinar morphology and glandular function are also discussed.

2. Influence of radiation dose on the function and recovery of salivary glands

Different levels of hyposalivation have been observed in patients after completion of radiotherapy. The area of salivary tissue exposed and the dose of radiation are the main factors that influence the glandular changes as shown by some studies (Deasy et al., 2010; Li, Taylor, Ten Haken, & Eisbruch, 2007; Murdoch-Kinch, Kim, Vineberg, Ship, & Eisbruch, 2008). Buus et al. (2006) found a direct relationship between the decline in glandular function and increased radiation dose. Li et al. (2007) and Eisbruch, Ten Haken, Kim, Marsh and Ship (1999) reported that the recovery of parotid salivary flow can occur with doses <25–30 Gy. Murdoch-Kinch et al. (2008) evaluated salivary flow in submandibular glands and found that the recovery of salivary flow occurred at radiation doses up to 39 Gy. On average, recovery of gland function occurs within two years after the end of radiotherapy (Li et al., 2007; Murdoch-Kinch et al., 2008).

To limit the adverse effects of radiation therapy, intensity-modulated radiotherapy (IMRT) has been developed. This therapy focuses on a higher dose of radiation in the tumor tissue. However, in many cases of head and neck malignant neoplasms, a high dose of radiation still reaches the adjacent tissues, including the salivary glands, which are exposed to doses higher than 30 Gy (Braam, Terhaard, Roesink, & Raaijmakers, 2006).

3. Macroscopic glandular changes

Studies report a macroscopically detectable loss of the structure of the salivary glands as a consequence of radiotherapy (Fiorentino et al., 2012; Nagler, Baum, Miller, & Fox, 1998; Radfar & Sirois, 2003; Ricchetti et al., 2011). Ricchetti et al. (2011) measured the volume of the parotid and submandibular glands during radiotherapy and found that reduction in glandular size was significant in the first week. Fiorentino et al. (2012) observed a linear decrease in the volume of the parotid glands in patients undergoing IMRT. Radiation doses ranged from 24.9 to 37 Gy; and on the twentieth day of treatment, the glands had lost about 30% of their original volume.

Nagler et al. (1998) irradiated rats with doses between 2.5 and 15 Gy and found a decrease in weight of the parotid and submandibular glands. This decrease was proportional to radiation dose; weight of the parotid and submandibular glands decreased to 60 and 40% of the initial value, respectively. The decrease in the volume of parotid and submandibular glands of minipigs irradiated with 70 Gy also varied between 50 and 60% compared to the control group. Histological analysis confirmed the presence of acinar atrophy (Radfar & Sirois, 2003).

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