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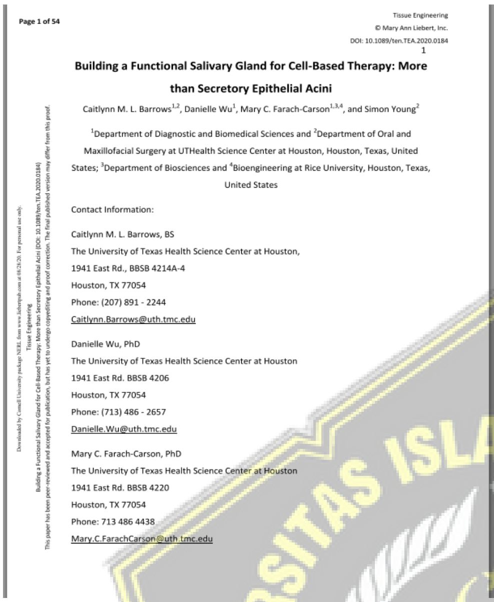

Tissue Engineering
© Mary Ann Liebert, Inc.
DOI: 10.1089/ten.TEA.2020.0184

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Building a Functional Salivary Gland for Cell-Based Therapy: More than Secretory Epithelial Acini

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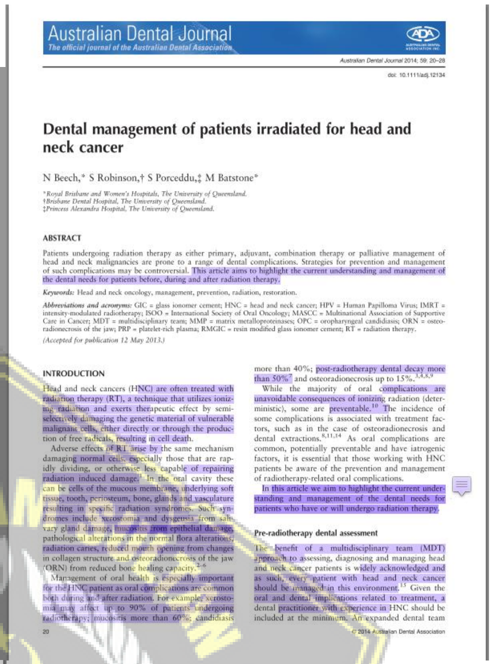

Australian Dental Journal
The official journal of the Australian Dental Association
Australian Dental Journal 2014; 59: 20–28
doi: 10.1111/adj.12134

Dental management of patients irradiated for head and neck cancer

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ABSTRACT

Patients undergoing radiation therapy as either primary, adjuvant, combination therapy or palliative management of head and neck malignancies are prone to a range of dental complications. Strategies for prevention and management of such complications may be controversial. This article aims to highlight the current understanding and management of the dental needs for patients before, during and after radiation therapy.

Keywords: Head and neck oncology, management, prevention, radiation, restoration.

Abbreviations and acronyms: GIC = glass ionomer cement; HNC = head and neck cancer; HPV = Human Papilloma Virus; IMRT = intensity-modulated radiotherapy; ISOO = International Society of Oral Oncology; MASCC = Multinational Association of Supportive Care in Cancer; MDT = multidisciplinary team; MMP = matrix metalloproteinases; OPC = oropharyngeal candidiasis; ORN = osteoradionecrosis of the jaw; PRP = platelet-rich plasma; RMGIC = resin modified glass ionomer cement; RT = radiation therapy.

(Accepted for publication 12 May 2013.)

INTRODUCTION

Head and neck cancers (HNC) are often treated with radiation therapy (RT), a technique that utilizes ionizing radiation and exerts therapeutic effect by semi-selectively damaging the genetic material of vulnerable malignant cells, either directly or through the production of free radicals, resulting in cell death.

Adverse effects of RT arise by the same mechanism damaging normal cells, especially those that are rapidly dividing, or otherwise less capable of repairing radiation induced damage.[1] In the oral cavity these can be cells of the mucous membrane, underlying soft tissue, tooth, periosteum, bone, glands and vasculature resulting in specific radiation syndromes. Such syndromes include xerostomia and dysgeusia from salivary gland damage, mucositis from epithelial damage, pathological alterations in the normal flora alterations, radiation caries, reduced mouth opening from changes in collagen structure and osteoradionecrosis of the jaw (ORN) from reduced bone healing capacity.[2–6]

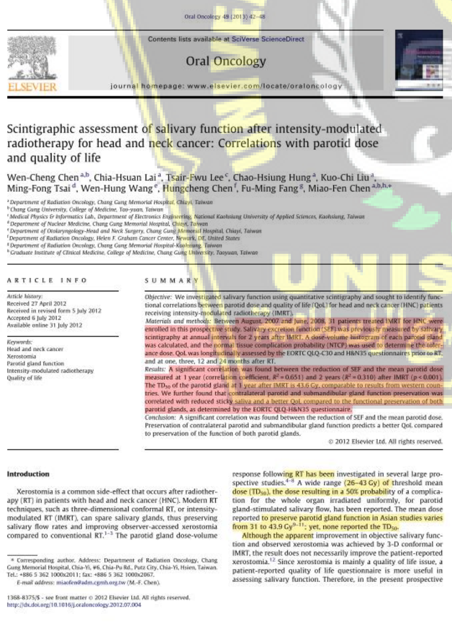
Management of oral health is especially important for the HNC patient as oral complications are common both during and after radiation. For example, xerostomia may affect up to 90% of patients undergoing radiotherapy; mucositis more than 60%; candidiasis more than 40%; post-radiotherapy dental decay more than 50%[7] and osteoradionecrosis up to 15%.[3,4,8,9]

While the majority of oral complications are unavoidable consequences of ionizing radiation (deterministic), some are preventable.[10] The incidence of some complications is associated with treatment factors, such as in the case of osteoradionecrosis and dental extractions.[8,11,14] As oral complications are common, potentially preventable and have iatrogenic factors, it is essential that those working with HNC patients be aware of the prevention and management of radiotherapy-related oral complications.

In this article we aim to highlight the current understanding and management of the dental needs for patients who have or will undergo radiation therapy.

Pre-radiotherapy dental assessment

The benefit of a multidisciplinary team (MDT) approach to assessing, diagnosing and managing head and neck cancer patients is widely acknowledged and as such, every patient with head and neck cancer should be managed in this environment.[15] Given the oral and dental implications related to treatment, a dental practitioner with experience in HNC should be included at the minimum. An expanded dental team



Oral Oncology 49 (2013) 42–48
Contents lists available at SciVerse ScienceDirect
Oral Oncology
journal homepage: www.elsevier.com/locate/oraloncology
ELSEVIER

Scintigraphic assessment of salivary function after intensity-modulated radiotherapy for head and neck cancer: Correlations with parotid dose and quality of life

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ARTICLE INFO

Article history:
Received 27 April 2012
Received in revised form 5 July 2012
Accepted 6 July 2012
Available online 31 July 2012

Keywords:
Head and neck cancer
Xerostomia
Parotid gland function
Intensity-modulated radiotherapy
Quality of life

SUMMARY

Objective: We investigated salivary function using quantitative scintigraphy and sought to identify functional correlations between parotid dose and quality of life (QoL) for head and neck cancer (HNC) patients receiving intensity-modulated radiotherapy (IMRT).
Materials and methods: Between August, 2007 and June, 2008, 31 patients treated IMRT for HNC were enrolled in this prospective study. Salivary excretion function (SEF) was previously measured by salivary scintigraphy at annual intervals for 2 years after IMRT. A dose-volume histogram of each parotid gland was calculated, and the normal tissue complication probability (NTCP) was used to determine the tolerance dose. QoL was longitudinally assessed by the EORTC QLQ-C30 and H&N35 questionnaires prior to RT, and at one, three, 12 and 24 months after RT.
Results: A significant correlation was found between the reduction of SEF and the mean parotid dose measured at 1 year (correlation coefficient, $R^2 = 0.651$) and 2 years ($R^2 = 0.310$) after IMRT ($p < 0.001$). The TD_{50} of the parotid gland at 1 year after IMRT is 43.6 Gy, comparable to results from western countries. We further found that contralateral parotid and submandibular gland function preservation was correlated with reduced sticky saliva and a better QoL compared to the functional preservation of both parotid glands, as determined by the EORTC QLQ-H&N35 questionnaire.
Conclusion: A significant correlation was found between the reduction of SEF and the mean parotid dose. Preservation of contralateral parotid and submandibular gland function predicts a better QoL compared to preservation of the function of both parotid glands.

Introduction

Xerostomia is a common side-effect that occurs after radiotherapy (RT) in patients with head and neck cancer (HNC). Modern RT techniques, such as three-dimensional conformal RT, or intensity-modulated RT (IMRT), can spare salivary glands, thus preserving salivary flow rates and improving observer-accessed xerostomia compared to conventional RT.[1–3] The parotid gland dose-volume response following RT has been investigated in several large prospective studies.[4–8] A wide range (26–43 Gy) of threshold mean dose (TD_{50}), the dose resulting in a 50% probability of a complication for the whole organ irradiated uniformly, for parotid gland-stimulated salivary flow, has been reported. The mean dose reported to preserve parotid gland function in Asian studies varies from 31 to 43.9 Gy[9–11]; yet, none reported the TD_{50}.

Although the apparent improvement in objective salivary function and observed xerostomia was achieved by 3-D conformal or IMRT, the result does not necessarily improve the patient-reported xerostomia.[12] Since xerostomia is mainly a quality of life issue, a patient-reported quality of life questionnaire is more useful in assessing salivary function. Therefore, in the present prospective

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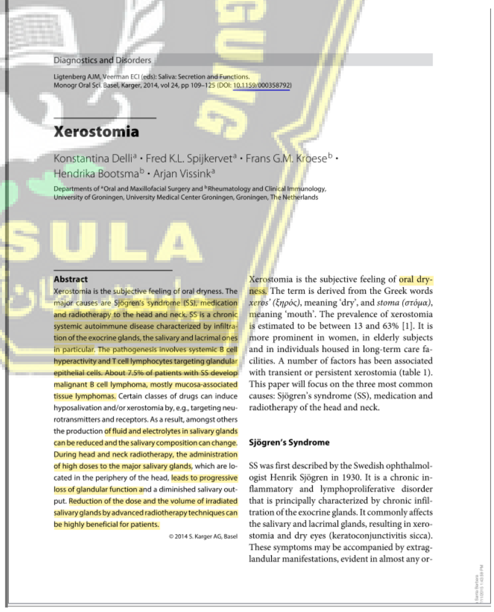
http://dx.doi.org/10.1016/j.oraloncology.2012.07.004



Diagnostics and Disorders

Ligtenberg AJM, Veerman ECI (eds): Saliva: Secretion and Functions.
Monogr Oral Sci. Basel, Karger, 2014, vol 24, pp 109–125 (DOI: 10.1159/000358792)

Xerostomia

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Abstract

Xerostomia is the subjective feeling of oral dryness. The major causes are Sjögren's syndrome (SS), medication and radiotherapy to the head and neck. SS is a chronic systemic autoimmune disease characterized by infiltration of the exocrine glands, the salivary and lacrimal ones in particular. The pathogenesis involves systemic B cell hyperactivity and T cell lymphocytes targeting glandular epithelial cells. About 7.5% of patients with SS develop malignant B cell lymphoma, mostly mucosa-associated tissue lymphomas. Certain classes of drugs can induce hyposalivation and/or xerostomia by, e.g., targeting neurotransmitters and receptors. As a result, amongst others the production of fluid and electrolytes in salivary glands can be reduced and the salivary composition can change. During head and neck radiotherapy, the administration of high doses to the major salivary glands, which are located in the periphery of the head, leads to progressive loss of glandular function and a diminished salivary output. Reduction of the dose and the volume of irradiated salivary glands by advanced radiotherapy techniques can be highly beneficial for patients.

Xerostomia is the subjective feeling of oral dryness. The term is derived from the Greek words *xeros' (ξηρός)*, meaning 'dry', and *stoma (στόμα)*, meaning 'mouth'. The prevalence of xerostomia is estimated to be between 13 and 63% [1]. It is more prominent in women, in elderly subjects and in individuals housed in long-term care facilities. A number of factors has been associated with transient or persistent xerostomia (table 1). This paper will focus on the three most common causes: Sjögren's syndrome (SS), medication and radiotherapy of the head and neck.

Sjögren's Syndrome

SS was first described by the Swedish ophthalmologist Henrik Sjögren in 1930. It is a chronic inflammatory and lymphoproliferative disorder that is principally characterized by chronic infiltration of the exocrine glands. It commonly affects the salivary and lacrimal glands, resulting in xerostomia and dry eyes (keratoconjunctivitis sicca). These symptoms may be accompanied by extraglandular manifestations, evident in almost any or-

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Oral Oncology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Review

Dental demineralization and caries in patients with head and neck cancer

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ARTICLE INFO

Article history:
Received 16 March 2015
Received in revised form 23 June 2015
Accepted 24 June 2015
Available online xxxx

Keywords:
Head and neck cancer
Dental demineralization
Dental caries
Decay
Radiation caries
Radiation therapy
Prevention
Review

SUMMARY

Concurrent chemoradiation (CCR) therapy is a standard treatment for patients with locally advanced head and neck cancer (HNC). It is well documented that CCR causes profound acute and late toxicities. Xerostomia (the symptom of dry mouth) and hyposalivation (decreased salivary flow) are among the most common treatment side effects in this cohort of patients during and following treatment. They are the result of radiation-induced damage to the salivary glands. Patients with chronic hyposalivation are at risk for demineralization and dental cavitation (dental caries), often presenting as a severe form of rapidly developing decay that results in loss of dentition. Usual post-radiation oral care which includes the use of fluoride, may decrease, but does not eliminate dental caries associated with radiation-induced hyposalivation. The authors conducted a narrative literature review regarding dental caries in HNC population based on MEDLINE, PubMed, CINAHL, Cochrane database, EMBASE, and PsycINFO from 1985 to 2014. Primary search terms included *head and/or neck cancer, dental caries, dental decay, risk factor, physical symptom, physical sequelles, body image, quality of life, measurement, assessment, cost, prevention, and treatment*. The authors also reviewed information from National Institute of Dental and Craniofacial Research (NIDCR), American Dental Association (ADA), and other related healthcare professional association web sites. This literature review focuses on critical issues related to dental caries in patients with HNC: potential mechanisms and contributing factors, clinical assessment, physical sequelea, negative impact on body image and quality of life, potential preventative strategies, and recommendations for practice and research in this area.

Introduction

Treatment paradigms for head and neck cancer (HNC) have shifted dramatically over the past two decades. Increased use of chemoradiation for patients with locally advanced HNC has improved local disease control and overall survival [1]. Unfortunately, chemoradiation is associated with increased acute and late effects that result in substantial symptom burden and decrements in quality of life (QoL) [2–5]. A second major paradigm shift results from the epidemic of human papillomavirus (HPV)-associated HNCs [6,7]. These tumors are biologically and epidemiologically distinct. Of note, the literature provides evidence of improved survival in patients with HPV-positive HNC [8]. Patients with HPV-associated HNC are younger, thus long-term functional outcomes are of critical importance as these patients are likely to live for protracted periods with the late effects of therapy. The treatment and epidemiologic shifts noted above have resulted in an increased number of HNC survivors. There are more than half a million HNC survivors in the United States [9]. Prevention and treatment of long-term effects of HNC therapy have therefore become a priority issue. Among common but under-addressed long-term effects of radiation therapy are oral complications such as, xerostomia and hyposalivation, dental demineralization and caries, trismus, and osteonecrosis [10] (see Figs. 1 and 2).

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http://dx.doi.org/10.1016/j.oraloncology.2015.06.009
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Please cite this article in press as: Deng J et al. Dental demineralization and caries in patients with head and neck cancer. Oral Oncol (2015), http://dx.doi.org/10.1016/j.oraloncology.2015.06.009

Methods

The authors conducted a narrative literature review regarding dental caries in HNC population based on MEDLINE, PubMed,

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Head and Neck Cancer

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N Engl J Med 2020;382:60-72.
DOI: 10.1056/NEJMra1715715

ALTHOUGH HEAD AND NECK CANCER IS ASSOCIATED WITH PAIN, DISFIGURation, dysfunction, psychosocial distress, and death, recent advances have brought substantial improvements in outcomes. The introduction of immune-checkpoint inhibitors for treatment of recurrent or metastatic head and neck cancer led to a remarkable benefit for some patients. In parallel, improvements in standard therapy, such as minimally invasive, organ-sparing surgical techniques; advances in radiotherapy, and curative multimodal approaches, have enhanced preservation of function and reduced morbidity and mortality. Increased awareness and diagnosis of human papillomavirus (HPV)–associated oropharyngeal carcinoma, alongside decreases in tobacco-related head and neck cancers, are similarly changing the understanding of this disease, its treatment, and the prognosis for affected patients.

DEFINITION

The prognosis and multimodal therapeutic options for patients with head and neck cancer vary depending on epidemiologic factors, anatomical location, and stage. There is marked heterogeneity of tumors arising in the head and neck region (Fig. 1). The focus here is on squamous-cell carcinomas arising from mucosal surfaces of four major anatomical sites: the oral cavity, sinonasal cavity, pharynx, and larynx. (Nasopharyngeal cancer is not discussed because of differences in epidemiology, pathology, natural history, and treatments that are beyond the scope of this review.)

EPIDEMIOLOGY

Head and neck cancer was the seventh most common cancer worldwide in 2018 (890,000 new cases and 450,000 deaths),[1] accounting for 3% of all cancers (51,540 new cases) and just over 1.5% of all cancer deaths (10,030 deaths) in the United States.[2] Typically diagnosed in older patients in association with heavy use of tobacco and alcohol, head and neck cancers are slowly declining globally, in part because of decreased use of tobacco.[3,4]

Conversely, cases of HPV-associated oropharyngeal cancer, induced primarily by HPV type 16, are increasing, predominantly among younger people in North America and northern Europe, reflecting a latency of 10 to 30 years after oral-sex exposure.[4,5] The fraction of head and neck cancers diagnosed as HPV-positive oropharyngeal cancers in the United States rose from 16.3% in the 1980s to more than 72.7% in the 2000s as a result of increased awareness, identification of the association between HPV and cancers of the head and neck, and enhanced diagnostic evaluation for HPV.[3] The effectiveness of prophylactic HPV vaccination is less well defined for oropharyngeal cancer than for anogenital and cervical can-

Saliva and the Control of Its Secretion

Jörgen Ekström, Nina Khosravani, Massimo Castagnola, and Irene Messana

Contents

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Med Radiol Diagn Imaging (2017)
DOI 10.1007/174_2017_143, © Springer International Publishing AG

Journal of Oral Microbiology

REVIEW ARTICLE

Salivary mucins in host defense and disease prevention

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Mucus forms a protective coating on wet epithelial surfaces throughout the body that houses the microbiota and plays a key role in host defense. Mucins, the primary structural components of mucus that creates its viscoelastic properties are critical components of the gel layer that protect against invading pathogens. Altered mucin production has been implicated in diseases such as ulcerative colitis, asthma, and cystic fibrosis, which highlights the importance of mucins in maintaining homeostasis. Different types of mucins exist throughout the body in various locations such as the gastrointestinal tract, lungs, and female genital tract, but this review will focus on mucins in the oral cavity. Salivary mucin structure, localization within the oral cavity, and defense mechanisms will be discussed. These concepts will then be applied to present what is known about the protective function of mucins in oral diseases such as HIV/AIDS, oral candidiasis, and dental caries.

Keywords: saliva; mucin; oral health; MUC5B; MUC7

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Received: 15 September 2015; Revised: 16 November 2015; Accepted: 17 November 2015; Published: 22 December 2015

Mucins, the primary gel-forming components of mucus, provide a critical layer of protection on wet epithelial surfaces in the body including the gastrointestinal tract, female genital tract, and respiratory tract. Unregulated mucin production can greatly affect the health of the host. For example, mice spontaneously develop ulcerative colitis when intestinal mucin is artificially downregulated (1). In a separate study where lung mucin was downregulated in mice, there were significantly more bacteria in their lungs, which greatly reduced long-term survival (2). In the oral cavity, decreased salivary flow is linked to the increased incidence of candidiasis and dental caries, which could be caused by reduced levels of salivary mucins (3–6). These findings highlight the importance of regulated mucin production, but our understanding of the precise mechanisms by which mucins provide protection in the oral cavity is continually being revised. One of the primary questions that still remains unanswered is how the mucus layer protects the oral cavity from pathogenic microbes and harmful substances while also providing a home for the beneficial oral microbiota. This review will provide an overview of what is known about the structural features of salivary mucins, potential mechanisms by which salivary mucins protect the oral cavity without widespread bacterial killing, and how they play a role in the prevention of specific oral diseases.

Introduction to salivary mucins

There are at least 20 identified mucins throughout the human body that cover wet epithelial surfaces such as the gastrointestinal tract, respiratory tract, and eyes. A summary of areas where mucins can be found in the body is given in Fig. 1a. Each of these mucins has a unique structure that can influence its localization and function. This section will address structural aspects of the mucins found in the oral cavity, MUC5B, MUC7, MUC19, MUC1, and MUC4 (7).

Mucins in the oral cavity

Each of the salivary mucins MUC5B, MUC7, MUC19, MUC1, and MUC4 are composed of a unique domain structure that influences the mucins' physical properties and localization in the oral cavity (Fig. 1b). MUC5B is the primary gel-forming mucin in the mouth that is secreted by mucous cells in the submandibular, sublingual, palatine, and labial salivary glands (8, 9). Transcripts and glycoproteins of MUC19, another gel-forming salivary mucin, have been identified, but MUC5B is still thought to be the predominate gel-forming mucin in the oral cavity (10–12).

Citation: Journal of Oral Microbiology 2015, **7**: 29759 - http://dx.doi.org/10.3402/jom.v7.29759

- Journal List
- Natl J Maxillofac Surg
- v.6(2); Jul-Dec 2015
- PMC4922225

National Journal of Maxillofacial Surgery
Official Publication of Maxillofacial Society of India

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Natl J Maxillofac Surg. 2015 Jul-Dec; 6(2): 160–166.

doi: 10.4103/0975-5950.183870

PMCID: PMC4922225

PMID: 27390489

Radiation-induced dental caries, prevention and treatment - A systematic review

Nishtha Gupta, Manoj Pal,[1] Sheh Rawat,[1] Mandeep S. Grewal, Himani Garg, Deepika Chauhan,[1] Parveen Ahlawat,[1] Sarthak Tandon,[1] Ruparna Khurana,[1] Anjali K. Pahuja,[1] Mayur Mayank,[1] and Bharti Devnani[2]

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Abstract

Go to:

Introduction

Head and neck squamous cell carcinoma is the sixth most common form of cancer worldwide and represents approximately 5% of all cancers diagnosed annually in the United States.[1] India continues to report the highest prevalence of oral cancers with 75,000–80,000 new cases of such cancers reported every year. There are about 700,000 new cases of cancers every year in India out of which tobacco-related cancers are 300,000. According to WHO 8.2 million people worldwide died from cancer in 2012, 60% of world's total new annual cases occur in Africa, Asia, and Central and South America.

Head and neck cancers (HNCs) are often treated with radiation therapy (RT), a technique that utilizes ionizing radiation and semi-selectively damages the genetic material of vulnerable malignant cells, directly or through the production of free radicals, leading to cell death. Beech *et al.*, mentioned in a study that RT damages normal cells also,

Hadley *et al. Medical Gas Research* 2013, **3**:15
http://www.medicalgasresearch.com/content/3/1/15

MEDICAL GAS RESEARCH

STUDY PROTOCOL Open Access

Does hyperbaric oxygen therapy have the potential to improve salivary gland function in irradiated head and neck cancer patients?

Tiffany Hadley[1], Cassaundra Song[2], Lauren Wells[3], Jennifer Lehnhardt[3], Marcy Wells Rogers[3], Jeffery Anderson[4], Michael Terry[5], Brian Novy[6] and Takkin Lo[7*]

Abstract

Following radiotherapy, many patients with osteoradionecrosis suffer from xerostomia, thereby decreasing their quality of life. Patients can develop problems with speech, eating, increased dental caries, dysphagia, fractured dentition, chronic refractory osteomyelitis and osteoradionecrosis. Symptoms associated with salivary gland dysfunction can be severe enough that patients terminate the course of their radiotherapy prematurely due to the decrease in their quality of life. Currently, the only treatments available to patients are palliative. A definitive treatment has yet to be discovered. Head and neck cancers, which comprise 5% of overall cancer treatments, rank 8th most expensive to treat in the United States today. Hyperbaric oxygen is being considered for the therapy of radiated salivary glands because it has been shown to stimulate capillary angiogenesis and fibroplasia in radiation treated tissues. It has been hypothesized that salivary acinar cells undergo apoptosis following radiation therapy. The purpose of this paper is to discuss the mechanisms of salivary gland injury and evaluate whether hyperbaric oxygen therapy improves salivary gland function in patients who develop xerostomia and osteoradionecrosis following head and neck radiation.

Keywords: Osteoradionecrosis, Xerostomia, Saliva, Hyperbaric Oxygen Therapy

Background

Head and neck cancers account for approximately 5% of the overall cancers treated in the United States and ranked the 8th most expensive cancer in the United States today [1]. There are five primary sites that make up this group of cancers: larynx, pharynx, oral cavity, salivary glands, and paranasal sinuses [2]. Of these patients who undergo standard head and neck radiotherapy, significant damage to the salivary glands can occur and result in hyposalivation and xerostomia, which is the condition of dry mouth caused by decreased salivation. In addition, hyposalivation is among the most widely recognized causes of dental caries, and oral discomfort, which includes oral sores, changes in taste, difficulty chewing, swallowing, and difficulty with speech [3]. This condition place patients at risk for dental caries and tooth decay because saliva normally bathes the oral cavity and acts as a clearing agent [4]. Xerostomia is one of the most common complications of head and neck irradiation, and essentially all patients that undergo radiotherapy will develop some form of xerostomia as a result of damage to their major and minor salivary glands [5]. End-stage complications of hyposalivation include fractured dentition, osteonecrosis, and chronic refractory osteomyelitis. Patients affected by salivary gland dysfunction often terminate their radiotherapy course prematurely because they become malnourished and experience a significant decrease in their quality of life [5]. Intensity-modulated radiation therapy as opposed to traditional radiation therapy, acupuncture, other masticatory or gustatory stimulatory therapies, administration of cytoprotective agents (i.e. amifostine), stimulation of residual tissue with cholinergic muscarinic agents (i.e. pilocarpine and bethanecol), and various lubricating agents are some options to aid with symptom control

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Original Article

Relationship between Physicochemical Properties of Saliva and Dental Caries and Periodontal Status among Female Teachers Living in Central Iran

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ABSTRACT

Objectives: There are inconsistent data about the association between saliva properties, dental caries, and periodontal status. In this study, we tried to examine the association between dental caries and periodontal status with salivary viscosity, flow rate, pH, and buffering capacity in adults.

Methods: In the present cross-sectional study, 450 female teachers were randomly selected from schools located in Yazd, Iran. Oral examinations were conducted, and unstimulated saliva samples were collected. Salivary viscosity, flow rate, pH, and buffering capacity were assessed. The salivary physicochemical properties were compared among teachers with different types of oral health. Analyses were done using the Statistical Package for the Social Sciences version 16.

Results: In total, 431 female teachers aged 40.45 ± 8.18 years were included in the study. Salivary flow rate, buffering capacity, pH, and viscosity, community periodontal index status were not significantly different in participants with and without tooth caries. There was a reverse linear association between salivary pH and flow rate with the decayed, missed, and filled teeth index ($P < 0.05$). The saliva buffering capacity was not significantly related to dental properties. Those with bleeding on probing had lower salivary pH, and buffering capacity compared to those with healthy gum. However, the salivary resting flow rate was not different in participants with bleeding on probing and healthy participants.

Conclusion: Based on our results, saliva properties might be important predictors in oral health status. This means that any change in saliva combination might affect periodontal and dental diseases. Future prospective studies are recommended to confirm these results.

Received : 30-10-17.
Accepted : 18-12-17.
Published : 22-02-18.

KEYWORDS: *Dental caries, periodontal index, physicochemical properties, saliva*

Introduction

Saliva is a body fluid secreted by salivary glands which essentially contains water, proteins, glycoproteins, electrolytes, small organic molecules, and compounds that is transported from the bloodstream.[1-3] It plays an important role in maintaining oral health due to its biological functions such as food swallowing, lubrication of oral tissues, and washing off food debris.[1] Saliva also helps maintaining the integrity of dental tissues and especially helps in prevention of dental caries.[2] Furthermore, it has three specific roles in the oral cavity. First, it protects the enamel against demineralization caused by the acids. Second, it facilitates the remineralization of incipient caries and then the last one it has some antimicrobial functions.[1,4]

Saliva can be assessed by some characteristics, such as flow rate, buffering capacity, hydrogen-ion

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How to cite this article: Hosseini-Tekani A, Nadjarzadeh A, Vossoughi M, Reza JZ, Golkari A. Relationship between physicochemical properties of saliva and dental caries and periodontal status among female teachers living in Central Iran. J Int Soc Prevent Communit Dent 2018;8:48-55.

Access this article online
Quick Response Code:
Website: www.jispcd.org
DOI: 10.4103/jispcd.JISPCD_391_17

Accepted Article

Dry mouth diagnosis and saliva substitutes — A review from a textural perspective

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Signal Transduction and Targeted Therapy www.nature.com/sigtrans

REVIEW ARTICLE OPEN

DNA damage response signaling pathways and targets for radiotherapy sensitization in cancer

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Radiotherapy is one of the most common countermeasures for treating a wide range of tumors. However, the radioresistance of cancer cells is still a major limitation for radiotherapy applications. Efforts are continuously ongoing to explore sensitizing targets and develop radiosensitizers for improving the outcomes of radiotherapy. DNA double-strand breaks are the most lethal lesions induced by ionizing radiation and can trigger a series of cellular DNA damage responses (DDRs), including those helping cells recover from radiation injuries, such as the activation of DNA damage sensing and early transduction pathways, cell cycle arrest, and DNA repair. Obviously, these protective DDRs confer tumor radioresistance. Targeting DDR signaling pathways has become an attractive strategy for overcoming tumor radioresistance, and some important advances and breakthroughs have already been achieved in recent years. On the basis of comprehensively reviewing the DDR signal pathways, we provide an update on the novel and promising druggable targets emerging from DDR pathways that can be exploited for radiosensitization. We further discuss recent advances identified from preclinical studies, current clinical trials, and clinical application of chemical inhibitors targeting key DDR proteins, including DNA-PKcs (DNA-dependent protein kinase, catalytic subunit), ATM/ATR (ataxia–telangiectasia mutated and Rad3-related), the MRN (MRE11-RAD50-NBS1) complex, the PARP (poly(ADP-ribose) polymerase) family, MDC1, Wee1, LIG4 (ligase IV), CDK1, BRCA1 (BRCA1 C terminal), CHK1, and HIF-1 (hypoxia-inducible factor-1). Challenges for ionizing radiation-induced signal transduction and targeted therapy are also discussed based on recent achievements in the biological field of radiotherapy.

Signal Transduction and Targeted Therapy (2020)5:60 ; https://doi.org/10.1038/s41392-020-0150-x

INTRODUCTION

The increasing prevalence of cancer worldwide is a major challenge to the improvement of quality and length of life. According to reports, 975,396 patients were newly diagnosed with cancer in 2012, and there were 358,392 deaths due to cancer in youth globally[1]. In 2015, the number of identified cancer cases increased to ~17.5 million, and the deaths from cancers increased to 8.7 million globally. Notably, from 2005 to 2015 (an 11-year span), the number of patients with cancer increased by 33%[2]. In 2016, ~9 million deaths were attributed to cancer, an increase of almost 18% over one decade[3]. Moreover, in the United States in 2017, there were 1,688,780 newly diagnosed cancer patients and almost 600,920 deaths due to cancer[4]. These numbers have increased rapidly annually, and in 2018, ~18.1 million newly diagnosed cancer patients and 9.6 million cancer deaths were reported worldwide[5]. In China, in 2014, there were 3.804 million newly diagnosed cancer patients and 2.296 million cancer deaths, and the statistical results showed that the crude incidence rate and the crude mortality rate were 278.07 per 100,000 people and 167.89 per 100,000 people, respectively[6]. Furthermore, it is estimated that by 2035, the number of annual cancer deaths will reach 14.5 million because worldwide cancer cases are expected to dramatically increase from 15 million at present to 24 million in the next 20 years[7]. Moreover, in parallel with the increasing rates of cancer diagnosis and death, the global burden of cancer has gradually increased over the past decade. Based on the Global Burden of Disease Cancer Collaboration announcement, 208.3 million disability-adjusted life-years (DALYs) were attributed to cancer globally in 2015. Lung cancer was the top cause of death among males, accounting for 25.9 million DALYs, while in females, breast cancer-attributable deaths were the top cause, accounting for 15.1 million DALYs[8]. Significant advances in the war against cancer have been achieved over the past decade. For instance, deaths from Hodgkin lymphoma declined significantly between 2005 and 2015 (−6.1%; 95% uncertainty interval: −10.6% to −1.3%), and other cancer deaths, such as deaths from esophageal cancer and stomach cancer, have also significantly decreased over the past decade[8]. Additionally, through large-action control of tobacco use and human papillomavirus vaccination in females, the burden of cancer in the female population has been substantially decreased in both economically developed and economically developing areas[7]. Although large-scale implementation of prevention and treatment methods has made these improvements possible, there is still a long way to go in the fight against cancer.

The management of cancer mainly involves surgery, radiotherapy, chemotherapy, and the rapidly evolving field immunotherapy[9]. The most commonly used cancer therapies over the past century include chemotherapy and radiotherapy methods[10–12]; among these, radiotherapy is widely and predominantly used prior to surgery and other treatment methods[13–15]. Radiotherapy is

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Received: 24 January 2020 Revised: 20 February 2020 Accepted: 16 March 2020
Published online: 01 May 2020

J Natl Cancer Inst Monogr (2019) 2019(53): lgz016
doi: 10.1093/jncimonographs/lgz016
Article

ARTICLE

Salivary Gland Hypofunction and Xerostomia in Head and Neck Radiation Patients

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Abstract

Background: The most manifest long-term consequences of radiation therapy in the head and neck cancer patient are salivary gland hypofunction and a sensation of oral dryness (xerostomia).
Methods: This critical review addresses the consequences of radiation injury to salivary gland tissue, the clinical management of salivary gland hypofunction and xerostomia, and current and potential strategies to prevent or reduce radiation injury to salivary gland tissue or restore the function of radiation-injured salivary gland tissue.
Results: Salivary gland hypofunction and xerostomia have severe implications for oral functioning, maintenance of oral and general health, and quality of life. Significant progress has been made to spare salivary gland function chiefly due to advances in radiation techniques. Other strategies have also been developed, e.g., radioprotectors, identification and preservation/expansion of salivary stem cells by stimulation with cholinergic muscarinic agonists, and application of new lubricating or stimulatory agents, surgical transfer of submandibular glands, and acupuncture.
Conclusion: Many advances to manage salivary gland hypofunction and xerostomia induced by radiation therapy still only offer partial protection since they are often of short duration, lack the protective effects of saliva, or potentially have significant adverse effects. Intensity-modulated radiation therapy (IMRT), and its next step, proton therapy, have the greatest potential as a management strategy for permanently preserving salivary gland function in head and neck cancer patients. Presently, gene transfer to supplement fluid formation and stem cell transfer to increase the regenerative potential in radiation-damaged salivary glands are promising approaches for regaining function and/or regeneration of radiation-damaged salivary gland tissue.

It is well documented that head and neck radiotherapy, in addition to its antitumor effects, inevitably induces severe adverse effects to normal oral tissues surrounding the tumor tissue. Adverse effects include mucositis, pain, salivary gland hypofunction (objectively decreased saliva secretion), and xerostomia (subjective feeling of dry mouth), fungal infection, taste disturbances and muscular fibrosis. Depending on the cumulative radiation dose to the gland tissue, permanent salivary gland hypofunction may occur, impeding oral functioning, compromising oral and general health, and diminishing the quality of life following radiation therapy in head and neck cancer patients (1–4). In addition, the head and neck cancer patient may also experience a heavy economic burden due to the extensive need for oral preventive measures and dental treatment after radiation therapy. It should be noted that salivary gland hypofunction and xerostomia may also be sequelae of other radiation regimes, although to a much lesser extent, that is, radioiodine treatment of thyroid cancer and preconditioning total body irradiation in hematopoietic stem cell transplantation for the treatment of hematologic malignancies (4–6).

The National Institutes of Health (NIH) Consensus Conference

In 1989, the NIH sponsored the first Development Consensus Conference on Oral Complications of Cancer Therapies (7). No

Received: May 21, 2019; Revised: May 21, 2019; Accepted: May 26, 2019

Exp Biol Med (Maywood) OnlineFirst, published on November 29, 2016 as doi:10.1177/1535370216681550

Minireview

Saliva diagnostics – Current views and directions

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Impact statement

The purpose of this mini-review is to make an update about the present and future applications of saliva as a diagnostic biofluid in many fields of science such as dentistry, medicine and pharmacotherapy. Using saliva as a fluid for diagnostic purposes would be a huge breakthrough for both patients and healthcare providers since saliva collection is easy, non-invasive and inexpensive. We will go through the current main diagnostic applications of saliva, and provide a highlight on the emerging, newly developing technologies and tools for cancer screening, detection and monitoring.

Abstract

In this review, we provide an update on the current and future applications of saliva for diagnostic purposes. There are many advantages of using saliva as a biofluid. Its collection is fast, easy, inexpensive, and non-invasive. In addition, saliva, as a "mirror of the body," can reflect the physiological and pathological state of the body. Therefore, it serves as a diagnostic and monitoring tool in many fields of science such as medicine, dentistry, and pharmacotherapy. Introduced in 2008, the term "Salivaomics" aimed to highlight the rapid development of knowledge about various "omics" constituents of saliva, including: proteome, transcriptome, micro-RNA, metabolome, and microbiome. In the last few years, researchers have developed new technologies and validated a wide range of salivary biomarkers that will soon make the use of saliva a clinical reality. However, a great need still exists for convenient and accurate point-of-care devices that can serve as a non-invasive diagnostic tool. In addition, there is an urgent need to decipher the scientific rationale and mechanisms at convey systemic diseases to saliva. Another promising technology called liquid biopsy enables detection of circulating tumor cells (CTCs) and fragments of tumor DNA in saliva, thus enabling non-invasive early detection of various cancers. The newly developed technology – electric field-induced release and measurement (EFIRM) provides near perfect detection of actionable mutations in lung cancer patients. These recent advances widened the salivary diagnostic approach from the oral cavity to the whole physiological system, and thus point towards a promising future of salivary diagnostics for personalized individual medicine applications including clinical decisions and post-treatment outcome predictions.

Keywords: Saliva, diagnostics, trancriptomics, point-of-care, liquid biopsy, biomarkers

***Experimental Biology and Medicine* 2016; 0: 1–14. DOI: 10.1177/1535370216681550**

Introduction

Saliva (whole saliva [WS], oral fluids [OFs]) is an acidic (pH = 6–7) biological fluid composed of secretions from the three major salivary glands (parotid, submandibular, sublingual) and from minor glands (i.e. labial, buccal, lingual, and palatal tissues), gingival crevicular fluid, cell debris, plaque, bacteria, nasal and bronchial secretions, lining cells, blood and exogenous substances.[1,2] It contains 99% water, 0.3% proteins and both 0.2% inorganic and organic substances.[3] The most prevalent inorganic components include: sodium, potassium, calcium, magnesium, chloride, and carbonates, while the organic components comprise amylases, peroxidase, lipase, mucins, lysozyme, lactoferrins, kallikreins, cystatins, hormones, and growth factors.[4] In a healthy individual, the daily salivary secretion is estimated to be between 0.5 and 1.5 L.[3]

Saliva plays an important role in many biological functions such as perception of oral sensations (i.e. taste, temperature and touch), lubrication, chewing, swallowing, and digestion. In addition, it enhances remineralization of tooth enamel and prevents demineralization due to its buffering capacity.[4–7]

Saliva also protects oral mucosa against biological, mechanical, and chemical factors, as well as against bacterial, viral, and fungal infections, thus maintaining the oral cavity ecosystem remain in balance.[8,9]

ISSN: 1535-3702 *Experimental Biology and Medicine* 2016; 0: 1–14

Review Article DOI: 10.18231/2455-6750.2017.0004

Radiotherapy for Head and Neck cancers-a review

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Abstract

Radiotherapy still remains an enigma in the treatment of Head and Neck cancers. Radiotherapy treatment planning of Head and Neck cancers pose a challenge due to its proximity to critical adjacent organs. This article briefs the various types, uses, techniques of Radiotherapy.

Keywords: Radiotherapy, Van de Graff Generator, Linearaccelerator, Brachytherapy, Teletherapy.
Key Messages: Radiotherapy still remains an enigma in the treatment of Head and Neck cancers. Radiotherapy treatment planning of Head and Neck cancers pose a challenge due to its proximity to critical adjacent organs. This article briefs the evolution, various types, uses, techniques of Radiotherapy.

Introduction

The invention of xray by Wilhelm Conrad Roentgen and radioactivity by Henry Becquerel marked a history in the evolution of radiotherapy.[1,2] The various rays used in radiotherapy consists of electromagnetic (x rays and Gamma rays) and Particulate radiation (Electrons, Protons, Neutrons).

The first application of Radiotherapy in the field of Medicine was done by Emile Grubbe on 29th January, 1896[3] in Chicago for the treatment of breast carcinoma.[4,5] The evolution of radiotherapy machines is shown in Table 1.

Table 1: Evolution of radiotherapy machines

Year	Evolution of radiotherapy machines
1900	Low voltage Teletherapy <150 KV
1919	Radium Teletherapy Machines
1920	Orthovoltage Xray Machines 200-500 KV
1922	Radium Howitzer
1939	Megavoltage Xray Machines > 1MV
1956	First Cobalt therapy machine (Eldorado A) at W.I.A cancer Institute, Chennai
1953	Linear Accelerator (LINAC) 8MV
1968	Gamma Knife
1976	First Linear Accelerator at Cancer Institute, Chennai
1980	Linac Based- Stereotactic Radiotherapy(SRT)
1993	Tomotherapy
1994	MiMIC Tomotherapy
1995	MLC Dynamic
1997	MLC Step and Shoot or MSF(Multi static field) First LINAC based Stereotactic Radiotherapy started in AIIMS(All India Institute of Medical sciences)
2002	Helical Tomotherapy
2013	Hybrid Linac MRI (linac-MR)

Radiotherapy has a wide range of applications in the treatment of tumors like Lymphoma, seminoma, Myeloma, Ewings sarcoma, Wilms tumor, Medulloblastoma-an exquisitely radiosensitive tumor and Kaposi Sarcoma occurring in AIDS, to palliate disease symptoms of bone pain from metastatic tumors, to prevent the development of leptomeningeal disease and brain metastases in acute leukemia and lung cancer, control of Brain metastases, reversal of spinal cord compression, superior vena cava obstruction, shrinkage of Painful masses.

Radiation therapy or Radiotherapy is the use of electromagnetic radiation like x-rays or gamma rays or particulate radiation like neutrons, protons, electrons to destroy or damage cancer cells.

The initially developed Co-60 teletherapy units that produce gamma rays failed to treat deep seated cancers. Hence to increase the depth of penetration of the charged Particle Accelerators are used.

An accelerator is a device that accelerate charged particles using electromagnetic fields. There are two types of Particle accelerators-Electrostatic accelerators –those that require electric fields that do not change with time E.g. Linear accelerator invented by Rolf Wideroe (1927), Van De Graaff Accelerator by Robert Van De Graaff (1929), Cockcroft-Walton accelerator by John cockroft and Ernest Walton (1932) and oscillating field accelerators- those that require electric fields that change with time e.g., Cyclotron by Ernest Lawrence (1928), Betatron by Donald Kerst (1940), Microtron by Vladimir Veksler (1945), Synchrotron by Frank Goward and D Barnes.

Linear Accelerator: A linear Accelerator is a device that increases or accelerates the velocity of charged particle like Electron, Neutron, Proton when subjected to combined electric and magnetic field thereby

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5321/wjs.v4.i2.56

World J Stomatol 2015 May 20; 4(2): 56-71
ISSN 2218-6263 (online)

REVIEW

Salivary gland disorders: A comprehensive review

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Author contributions: All authors contributed to this manuscript.
Conflict-of-interest: None.

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Received: December 5, 2014
Peer-review started: December 6, 2014
First decision: January 8, 2015
Revised: March 19, 2015
Accepted: April 10, 2015
Article in press: April 12, 2015
Published online: May 20, 2015

Abstract

Salivary glands are complex in nature. They could be either tubulo acinar, merocrine or exocrine glands secreting mainly saliva. Salivary gland is one of the main soft tissue structures in the maxillofacial area. Saliva is a clear, slightly acidic muco serous fluid that coats the teeth, mucosa and thereby helps to create and maintain a healthy environment in the oral cavity. Salivary glands may be affected by a number of diseases, local and systemic and the prevalence of salivary gland diseases depend on various etiological factors. The glands may be infected by viral, bacterial, rarely fungal or its ductal obstruction which may cause painful swelling or obstruction, affecting their functions. The salivary gland may also be affected by a various benign and malignant tumours. This review article briefly describes about the various salivary gland disorders, diagnostic techniques and their management including the recent advances and the future perspective.

Key words: Salivary gland disorders; Xerostomia; Salivary biomarker; Salivary diagnostics; Exocrine glands

Core tip: The aim of this article was to analyse detailed aspects of various salivary gland disorders, their diagnostic and therapeutic advances in the prevention and management of salivary gland diseases of the oral cavity, including the recent developments and their future perspective.

Krishnamurthy S, Vasudeva SB, Vijayasarathy S. Salivary gland disorders: A comprehensive review. *World J Stomatol* 2015; 4(2): 56-71 Available from: URL: http://www.wjgnet.com/2218-6263/full/v4/i2/56.htm DOI: http://dx.doi.org/10.5321/wjs.v4.i2.56

INTRODUCTION

A gland consists of specialized type of cells, wherein they produce products which are used elsewhere in the body. Salivary glands are complex, tubulo acinar, exocrine or merocrine glands secreting mainly saliva. Saliva is the product of the major and minor salivary gland dispersed throughout the oral cavity. It is a complex mixture of organic, inorganic components and water, carrying out several functions. There are three pairs of major salivary glands namely parotid, sub mandibular and sublingual glands in addtion to numerous minor salivary glands in the oral cavity[1].

Saliva Electrolyte Analysis and Xerostomia-related Quality of Life in Nasopharyngeal Carcinoma Patients Following Intensity-Modulated Radiation Therapy

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Laheij *et al. BMC Res Notes (2015) 8:639*
DOI 10.1186/s13104-015-1641-7

BMC Research Notes

RESEARCH ARTICLE Open Access

Proteins and peptides in parotid saliva of irradiated patients compared to that of healthy controls using SELDI-TOF-MS

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Abstract

Background: Radiotherapy to the head and neck area damages the salivary glands. As a consequence hyposalivation may occur, but also the protein composition of saliva may be affected possibly compromising oral health. The aim of our study was to compare the relative abundance of proteins and peptides in parotid saliva of irradiated patients to that of healthy controls.

Methods: Using Lashley cups and citric acid, saliva from the parotid glands was collected from nine irradiated patients and ten healthy controls. The samples were analyzed with SELDI-TOF-MS using a NP20 and IMAC-30 chip in the molecular weight range of 1–30 kDa.

Results: On the NP20 chip 61 (out of 217) and on the IMAC-30 chip 32 (out of 218) peaks differed significantly in intensity between the saliva of the irradiated patients and healthy controls. 55 % of the significant peaks showed higher intensity and 45 % showed lower intensity in the saliva of irradiated patients. The peaks may represent, amongst others, the salivary proteins lysozyme, histatins, cystatin, protein S100 and PRP's.

Conclusions: Large differences were found in the relative abundance of a wide range of proteins and peptides in the parotid saliva of irradiated patients compared to healthy controls.

Keywords: Head and neck cancer, Saliva, Proteomics, Parotid gland, SELDI-TOF-MS

Background

Radiotherapy is often needed for the management of a tumor in the head and neck area. Usually radiotherapy involves the primary treatment of a tumor, but it can also be used additionally to surgery or as part of palliative care. The radiation-induced consequences for the healthy oral tissues can be divided into early and late effects. The early effects consist of damage to the oral mucosa, salivary glands and taste. Late effects comprise damage to the salivary glands, dentition, periodontium, bone, muscles and the joints [1, 2].

Damage to the salivary glands leads to a rapid decrease in salivary flow after the start of radiotherapy [3]. Weeks after the start of radiotherapy, the flow rate gradually starts to recover and only after 5 years the mean parotid flow rate may return to baseline levels [4, 5]. However, 21 % of patients still suffered from a significantly lowered salivary flow 5 years after radiotherapy [5].

There are secondary effects related to changes in salivary flow and to changes in composition. Saliva is an important host defense mechanism helping to keep the oral cavity free of diseases like caries, gingivitis, periodontitis and infections as a result of antimicrobial, buffering and remineralizing capacities [6, 7]. There is a risk for radiation caries, a form of caries that develops very rapidly when salivary functions are disturbed and affects tooth surfaces that are normally resistant to the development of caries [8].

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Journal of Dental Sciences (2015) xx, 1–7
Available online at www.sciencedirect.com
ScienceDirect
ELSEVIER
journal homepage: www.e-jds.com
Journal of Dental Sciences

ORIGINAL ARTICLE

Radiation caries in nasopharyngeal carcinoma patients after intensity-modulated radiation therapy: A cross-sectional study

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Received 19 August 2015; Final revision received 4 September 2015
Available online ■ ■ ■

KEYWORDS
nasopharyngeal carcinoma;
radiation caries;
radiation dose;
radiation therapy;
tooth loss

Abstract *Background/purpose:* The exact dose of intensity-modulated radiation therapy (IMRT) associated with tooth damage is mostly unknown. We aim to evaluate the severity of dental caries after IMRT and the correlation with the radiation dose to the dentition in patients with nasopharyngeal carcinoma (NPC).

Materials and methods: This was a cross-sectional study of 42 patients with NPC who completed IMRT in 2011. Each premolar tooth was divided into 13 sites. Teeth were evaluated using a validated index and subsequently categorized at each divided site. The relationship between dose distribution and the caries severity score was analyzed using logistic models. The odds of developing caries damage were evaluated using odds ratios.

Results: A total of 4342 sites from 334 premolar teeth were evaluated. For sites exposed to 30 −60 Gy, the odds of developing caries damage were 12−200 times greater compared with sites

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http://dx.doi.org/10.1016/j.jds.2015.09.003

Please cite this article in press as: Liang X, et al., Radiation caries in nasopharyngeal carcinoma patients after intensity-modulated radiation therapy: A cross-sectional study, Journal of Dental Sciences (2015), http://dx.doi.org/10.1016/j.jds.2015.09.003

Buccal drug delivery technologies for patient-centred treatment of radiation-induced xerostomia (dry mouth)

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Abstract

Radiotherapy is a life-saving treatment for head and neck cancers, but almost 100% of patients develop dry mouth (xerostomia) because of radiation-induced damage to their salivary glands. Patients with xerostomia suffer symptoms that severely affect their health as well as physical, social and emotional aspects of their life. The current management of xerostomia is the application of saliva substitutes or systemic delivery of saliva-stimulating cholinergic agents, including pilocarpine, cevimeline or bethanechol tablets. It is almost impossible for substitutes to replicate all the functional and sensory facets of natural saliva. Salivary stimulants are a better treatment option than saliva substitutes as the former induce the secretion of natural saliva from undamaged glands; typically, these are the minor salivary glands. However, patients taking cholinergic agents systemically experience pharmacology-related side effects including sweating, excessive lacrimation and gastrointestinal tract distresses. Local delivery direct to the buccal mucosa has the potential to provide rapid onset of drug action, i.e. activation of minor salivary glands within the buccal mucosa, while sparing systemic drug exposure and off-target effects. This critical review of the technologies for the local delivery of saliva-stimulating agents includes oral disintegrating tablets (ODTs), oral disintegrating films, medicated chewing gums and implantable drug delivery devices. Our analysis makes a strong case for the development of ODTs for the buccal delivery of cholinergic agents: these must be patient-friendly delivery platforms with variable loading capacities that release the drug rapidly in fluid volumes typical of residual saliva in xerostomia (0.05 to 0.1 mL).

Keywords

Radiation-induced xerostomia, saliva, salivation, salivary substitutes, salivary stimulants, orally disintegrating films, orally disintegrating tablets, patient-centred, pilocarpine HCl, dry mouth, head and neck cancer.

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frontiers in Oncology
REVIEW
published: 22 May 2017
doi: 10.3389/fonc.2017.00089

Radiation-Induced Oral Mucositis

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Radiation-induced oral mucositis (RIOM) is a major dose-limiting toxicity in head and neck cancer patients. It is a normal tissue injury caused by radiation/radiotherapy (RT), which has marked adverse effects on patient quality of life and cancer therapy continuity. It is a challenge for radiation oncologists since it leads to cancer therapy interruption, poor local tumor control, and changes in dose fractionation. RIOM occurs in 100% of altered fractionation radiotherapy head and neck cancer patients. In the United Sates, its economic cost was estimated to reach 17,000.00 USD per patient with head and neck cancers. This review will discuss RIOM definition, epidemiology, impact and side effects, pathogenesis, scoring scales, diagnosis, differential diagnosis, prevention, and treatment.

Keywords: chemotherapy, oral mucositis, radiation, radiotherapy, normal tissue injury, pathobiology, mesenchymal stromal/stem cells

OPEN ACCESS

Edited by:
Issam El Naqa, University of Michigan, USA

Reviewed by:
Michael Andrew Samuels, Yale University, USA
John Staffurth, Cardiff University, UK

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Specialty section:
This article was submitted to Radiation Oncology, a section of the journal Frontiers in Oncology

Received: 10 July 2016
Accepted: 21 April 2017
Published: 22 May 2017

Citation:
Maria OM, Eliopoulos N and Muanza T (2017) Radiation-Induced Oral Mucositis. Front. Oncol. 7:89. doi: 10.3389/fonc.2017.00089

DEFINITION

Radiation-induced oral mucositis (RIOM) (**Figures 1**, **4** and **5C**) is one of the major ionizing radiation toxicities and normal tissue injuries that result from radiotherapy (1). RIOM was first termed in 1980 as a side effect of radiotherapy (RT) in cancer patients (2). RIOM is a normal tissue injury lasting between 7 and 98 days, which starts as an acute inflammation of oral mucosa, tongue, and pharynx after RT exposure (1, 3). This coincides with recruitment of various inflammatory cells and release of inflammatory cytokines, chemotactic mediators, and growth factors. RIOM can progress to an acute life-threatening stage as a result of severe physical obstruction of food and water intake with subsequent weight loss and septic complication due to lost protective epithelial and basement membrane barriers. This leads to limitations of local tumor control due to cancer treatment interruption and alterations in radiation dose fractionation (4–7). Studies suggested the stages of progression of RIOM as initial hyperemia and erythema during the preulcer phase, during which there is a release of various pro-inflammatory cytokines from epithelial, vascular, and connective tissue cells at the site of tissue injury. This is followed by the epithelial phase with various degrees of desquamation and basement membrane damage with loss of the protective barrier, which ends with the physical appearance of the ulceration. The postulcerative phase varies depending on the extent of the tissue toxicity. A secondary infection with Gram-negative bacteria or yeast may occur, with microcoagulation of the vasculature that worsens the inflammation by the local ischemia with more necrotic tissue yield. The final stage will be the healing phase and fibrosis (2, 8, 9).

RIOM EPIDEMIOLOGY (INCIDENCE, PREDICTORS, AND RISK FACTORS)

Radiation-induced oral mucositis occurs in up to 80% of head and neck cancer irradiated patients and reaches up to 100% in patients with altered fractionation head and neck cancer. RIOM of grade 3 and 4 have been recorded in 56% of head and neck cancer patients treated with radiotherapy (1, 12).

Review Article

Saliva as a Mirror of the Body Health

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Abstract

Saliva has an old history of study. It is of physiological importance. Saliva has hundreds of components which help detect systemic diseases and also provide biomarkers of health and disease status. Saliva has three major functions: digestion, protection and lubrication. Saliva also functions in maintenance of tooth integrity. Also, the carbohydrates of salivary glycoprotein carry the ABH blood group antigens, expressing in the salivary glands and secreted in the saliva. Saliva is a good indicator of the plasma levels of various substances such as hormones and drugs. The use of saliva as a diagnostic and monitoring method for periodontal diseases and many other infectious diseases, has been studied. The relatively easy and non-invasive nature of sample collecting is considered as a simple low-cost stage but the problem is the low concentrations of the markers in comparsion to the plasma.

INTRODUCTION

Saliva has an old history of study but its physiological importance has only been recognized recently [1]. Saliva has hundreds of components that may serve to detect systemic diseases or as evidence of exposure to various harmful substances, as well as providing biomarkers of health and disease status. Nowadays, the saliva research field is rapidly advancing due to the use of novel approaches including metabolomics, genomics, proteomics and bioinformatics [2].

SALIVA PHYSIOLOGY

Saliva is a complex liquid consisting of secretions from the major and minor salivary glands. As estimated there are 450-750 minor accessory salivary glands, situated on tongue, buccal mucosa and palate except the anterior part of the hard palate and gums [3-4].The average daily volume of saliva production is 500-1000 ml. Submandibular glands produce 70% of the overall volume, the parotid glands 25%, and the sublingual glands about 5% [5]. The greatest volume of saliva is produced before, during and after meals, reaching its maximum peak at around 12 a.m. and falls considerably at night, while sleeping. Several physiological and pathological conditions can modify saliva production quantitatively, e.g. smell and taste stimulation, chewing, psychological and hormonal status, drugs, age, hereditary , oral hygiene and physical exercise [3,6-9] . Each salivary gland contains different regions, the acinar region, which is also referred to as the secretary end piece, and the ductal region. All the salivary fluid is produced from the local vascular bed in the acinar region, and is transported through the duct system, where excess sodium and chloride are reabsorbed and some additional proteins are secreted, and then empties into the oral cavity. A sodium gradient that is actively generated within the secretary end piece causes fluid to flow into the lumen through the tight junctions between the acinar cells [10,11]. Saliva is sterile when it leaves the salivary glands. The basis of

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frontiers in ONCOLOGY
REVIEW ARTICLE
published: 08 July 2013
doi: 10.3389/fonc.2013.00172

Image-guided radiotherapy for locally advanced head and neck cancer

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Treatment of locally advanced head and neck cancer remains a challenge because of the head and neck complex anatomy and the tumor invasion to the adjacent organs and/or metastases to the cervical nodes. Postoperative irradiation or concurrent chemoradiation may lead to damage of radiosensitive structures such as the salivary glands, mandible, cochlea, larynx, and pharyngeal muscles. Xerostomia, osteoradionecrosis, deafness, hoarseness of the voice, dysphagia, and aspiration remain serious complications of head and neck irradiation and impair patient quality of life. Intensity-modulated and image-guided radiotherapy by virtue of steep dose gradient and daily imaging may allow for decreased radiation of the organs at risk for complication while preserving loco-regional control.

Keywords: head and neck cancer, image-guided radiotherapy, preservation of radiosensitive organs

TREATMENT OF LOCALLY ADVANCED HEAD AND NECK CANCER

Treatment of locally advanced head and neck cancer remains a challenge because of the high rate of loco-regional failures and the potential for serious complications following treatment. The tumor frequently invades adjacent organs and/or regional neck nodes. Standard of care has been either postoperative irradiation or concurrent chemoradiation (1). Regardless of the modality chosen, serious complications may occur because of the presence of radiosensitive organs such as the salivary glands, cochlea, mandible, larynx, and pharyngeal muscles in the radiation field. Xerostomia, deafness, osteoradionecrosis, dysphagia, weight loss, chronic hoarse voice, and aspiration are potential long-term complications of radiation treatment with conventional radiotherapy techniques. Intensity-modulated radiotherapy (IMRT) has been introduced to decrease the toxicity of irradiation because of the steep dose gradient allowing for sparing of radiosensitive organs. Randomized studies have demonstrated significant sparing of the parotid glands following IMRT of head and neck cancer and decreased severity of the xerostomia with improvement of patient quality of life (QOL) (2, 3). However, a significant amount of normal tissues is still irradiated because the inclusion of the tumor and areas at high risk for invasion with a large rim of normal tissue called planning target volume or PTV, to avoid marginal miss. Recently, image-guided radiotherapy (IGRT) by combining the steep dose gradient of IMRT and daily imaging may potentially improve further the toxicity of head and neck irradiation because of the possibility of safe PTV reduction given the reduced inter-fraction movement through daily imaging.

Significant reduction of spinal cord dose may be achieved with IGRT compared to IMRT by a reduced PTV margin (4). However, the flip side of IGRT is also the risk of under-dosing the tumor if the target area is not adequately outlined. Thus, pre-treatment imaging to meticulously delineate the tumor and areas at risk of invasion is a critical component for the success of IGRT.

IMAGING STUDIES CRITICAL FOR IGRT PLANNING

Positron-emission tomography (PET) scan or PET-computed tomography (PET-CT) allows accurate delineation of the tumor and cervical lymph nodes that can be incorporated into the planning CT. PET-CT is superior to CT for tumor imaging because of its ability to detect the tumor metabolic activity in addition to its anatomic location. In a study of 102 unresectable head and neck cancer, PET-CT significantly changed the staging and management of those patients compared to CT alone (5). Twelve patients had modifications of the radiotherapy planning following review

Therapeutics and Clinical Risk Management

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REVIEW

Xerostomia induced by radiotherapy: an overview of the physiopathology, clinical evidence, and management of the oral damage

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management
4 February 2015
Number of times this article has been viewed

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Background: The irradiation of head and neck cancer (HNC) often causes damage to the salivary glands. The resulting salivary gland hypofunction and xerostomia seriously reduce the patient's quality of life.
Purpose: To analyze the literature of actual management strategies for radiation-induced hypofunction and xerostomia in HNC patients.
Methods: MEDLINE/PubMed and the Cochrane Library databases were electronically evaluated for articles published from January 1, 1970, to June 30, 2013. Two reviewers independently screened and included papers according to the predefined selection criteria.
Results: Sixty-one articles met the inclusion criteria. The systematic review of the literature suggests that the most suitable methods for managing the clinical and pathophysiological consequences of HNC radiotherapy might be the pharmacological approach. For example, through the use of cholinergic agonists when residual secretory capacity is still present, and the use of salivary substitutes. In addition, a modified diet and the patient's motivation to enhance oral hygiene can lead to a significant improvement.
Conclusion: Radiation-induced xerostomia could be considered a multifactorial disease. It could depend on the type of cancer treatment and the cumulative radiation dose to the gland tissue. A preventive approach and the correct treatment of the particular radiotherapeutic patient can help to improve the condition of xerostomia.
Keywords: radiation-induced xerostomia, salivary gland hypofunction, management strategies

Introduction

Xerostomia is a term used to describe the subjective symptoms of a dry mouth deriving from a lack of saliva. A large variety of causes can lead to xerostomia, eg, radiotherapy and chemotherapy,[1–4] the chronic use of drugs,[5–7] and rheumatic and dysmetabolic diseases.[8,9]

Saliva is an important host defense component of the oral cavity. Major salivary glands contribute to most of the secretion volume and electrolyte content of saliva (the parotid, submandibular, and sublingual glands, which account for 90% of saliva production), whereas minor salivary glands contribute little secretion volume and most of the blood-group substance.[10] Saliva components interact in related functions in the following general areas:

1) bicarbonates, phosphates, and urea act to modulate pH and the buffering capacity of saliva;
2) macromolecule proteins and mucins serve to cleanse, aggregate, and/or attach oral microorganisms and contribute to the dental plaque metabolism;

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cells

MDPI

Review

Physiology, Pathology and Regeneration of Salivary Glands

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Received: 3 August 2019; Accepted: 17 August 2019; Published: 26 August 2019

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Abstract: Salivary glands are essential structures in the oral cavity. A variety of diseases, such as cancer, autoimmune diseases, infections and physical traumas, can alter the functionality of these glands, greatly impacting the quality of life of patients. To date, no definitive therapeutic approach can compensate the impairment of salivary glands, and treatment are purely symptomatic. Understanding the cellular and molecular control of salivary glands function is, therefore, highly relevant for therapeutic purposes. In this review, we provide a starting platform for future studies in basic biology and clinical research, reporting classical ideas on salivary gland physiology and recently developed technology to guide regeneration, reconstruction and substitution of the functional organs.

Keywords: salivary glands; oral epithelium; xerostomia; exocrine glands; salivary gland-resident stem cells

1. Introduction

Structures secreting fluid to facilitate feeding emerge progressively throughout evolution and can be found in very simple organisms (e.g., *Caenorabditis elegans*) and more complex species (e.g., *Drosophila melanogaster*, placental mammals). In humans, major and minor salivary glands produce and secrete digestive fluids or protein-rich fluids. The three pairs of major salivary glands (i.e., parotid, submandibular and sublingual glands) are responsible for the production and secretion of saliva in the oral cavity, whose moisturizing effect preserves oral hygiene and allows taste, speech and mastication [1].

The parotid gland (PG) is mainly composed of serous acini-secreting α-amylase-rich saliva [2]. The sublingual gland (SL) secretes mucous, a viscous solution rich in mucins [3–5]. The submandibular gland (SMG) is composed by a mixed population of acini with a mucous and serous function [1,4,6]. These three major salivary glands account for more than 90% of salivary secretion. Minor salivary glands are distributed throughout the oral cavity, specifically in the labial and lingual mucosa, as well as palate and floor of the mouth.

Saliva is an essential fluid for oral cavity maintenance and functionality. Digestive enzymes within saliva initiate the digestion process, and at the same time, saliva acts as a lubricant of solid nutrition, thus helping its passage through the esophagus. By moisturizing the tongue and other tissues of the oral cavity, saliva has an essential role in speech and taste sensitivity [7]. It also balances the pH of the mouth, thus protecting the soft oral tissues and teeth from an extended exposure to an acidic environment. Saliva contains several signalling molecules, such as EGF, FGF, NGF and TGF-α, that are essential for the regeneration of oral and oesophageal mucosa. Finally, the antibacterial and antifungal components of the saliva, such as lysozymes, Immunoglobulins and lactoferrin, inhibit the progression of bacterial infection and dental caries.

Physiological functions and the histological appearance of salivary glands are rather conserved between species and individuals, but clear distinctions exist in terms of anatomical position and

Periodontology 2000, Vol. 70, 2016, 11–25
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PERIODONTOLOGY 2000

The physiology of salivary secretion

GORDON B. PROCTOR

Saliva performs a number of important functions that are essential for the maintenance of oral health. Most of these functions depend upon the interaction of saliva with oral surfaces of varying texture and polarity – soft epithelial tissue surfaces with differing degrees of keratinization and roughness, along with the tooth surfaces that are hard and composed of tooth mineral. Saliva clears substances from the mouth, buffers pH, maintains tooth mineralization, facilitates wound healing, neutralizes some harmful dietary components, influences the oral microbiome and protects, lubricates and hydrates oral mucosal surfaces. The properties and effectiveness of saliva are largely determined by secretions from the major and minor salivary glands. Saliva is an accessible biofluid that contains components derived from the mucosal surfaces, gingival crevices and tooth surfaces of the mouth. Saliva also contains microorganisms that colonize the mouth and other exogenous substances and so can potentially provide an insight into the relationship of the host with the environment. These features make saliva a complex fluid. It is therefore important to understand how saliva is formed so that we can make informed interpretations of how changes in the composition of saliva are associated with physiology or disease.

Salivary gland anatomy and structure

Salivary glands are exocrine glands and secrete onto a mucosal surface. During embryonic development, major salivary glands form as initial proliferating epithelial buds from the oral epithelium and grow into the underlying mesenchyme. A tree-like ductal structure develops through a process of branching morphogenesis and canalization. The development process requires a controlled exchange of molecular signals between epithelial cells and mesenchymal cells (61). The ductal structure of the major adult salivary glands is well demonstrated by sialography, an imaging technique in which X-ray contrast medium is injected into the opening of the main excretory ducts of the gland on the oral epithelium: Stenson's (parotid) duct or Wharton's (submandibular) duct (Fig. 1).

At the ends of the fine branches of the major salivary gland ductal tree are glandular secretory end pieces referred to as acini (grape-like), which are collections of saliva-secreting epithelial cells. The mechanisms by which acinar cells secrete saliva are discussed later, but the histological appearance of acinar cells is determined by the types of secretory proteins synthesized by the cells and stored in large granules, which can fill the cytoplasm. The content of the storage granules is an indicator of the types of saliva produced, which can be broadly divided into mucin-containing and nonmucin -containing saliva. Mucins are the main components of mucous, a protective layer found on most mucosal surfaces in the body, and saliva containing high amounts of mucin tend to be viscoelastic, an important characteristic for retention of saliva on oral mucosal surfaces and maintenance of lubrication and hydration of the surfaces (95). Parotid gland acinar cells produce watery saliva with little or no mucin and characteristically stain strongly with the routinely used histological dyes hematoxylin and eosin (Fig. 2A). The submandibular gland contains a mixed population of acinar cells, some of which are mucin producing and stain weakly with hematoxylin and eosin. Most of the acinar cells in sublingual glands are mucin producing and consequently the saliva secreted tends to be viscoelastic. Some acinar cells in these glands contain low amounts of mucin, possibly because it is not fully formed within the storage granules of cells, and have a 'serous' appearance with hematoxylin and eosin staining. Most of the minor salivary glands in the oral submucosae are mucin producing and the acinar cells of these glands stain similarly to those of the

Anatomy and Physiology

Ligtenberg AJM, Veerman ECI (eds): Saliva: Secretion and Functions.
Monogr Oral Sci. Basel, Karger, 2014, vol 24, pp 14–29 (DOI: 10.1159/000358781)

Salivary Secretion: Mechanism and Neural Regulation

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Abstract

Maintenance of a film of saliva on oral surfaces is dependent upon nerve-mediated, reflex salivary gland secretion. Afferent signalling arises from taste, olfaction and mastication and is modified by signalling from other centres in the central nervous system before efferent signals are delivered to salivary glands in autonomic nerves. Salivary fluid secretion is largely dependent upon cholinergic signalling from parasympathetic nerves whilst the protein content of saliva is additionally dependent upon signalling by neuropeptides and, in the major (parotid, submandibular and sublingual) salivary glands, by sympathetic nerves and the release of noradrenaline. There have been significant recent advances in our understanding of the membrane transport proteins involved in intracellular calcium signalling in salivary acinar cells in response to nerve stimulation and of the ion transport proteins responsible for acinar cell secretion of saliva. Salivary glands retain an ability to regenerate following extreme atrophy, and autonomic nerves have an important role in both gland development and maintenance of long-term normal function. Continued advances in the understanding of the nerve-mediated regulation of salivary glands should help in the development of strategies for preventing chronic oral dryness resulting from drugs or atrophic disease associated with inflammation and irradiation.

Salivary glands fulfil a huge range of functions in different species, and even amongst mammals there is great variety in salivary gland morphology and the control of salivation by nerves, reflecting adaptation to diet and environment [1]. In man, the paired major salivary glands, parotid, submandibular and sublingual, along with hundreds of small, minor submucosal salivary glands provide a film of mixed saliva that coats and protects the oral mucosal and tooth surfaces. Salivary secretion is maintained at a 'default' rate in man creating a mobile but slow-moving film and replenishing/replacing proteins adsorbed to the underlying soft and hard oral surfaces. Upon this 'default' secretion of 'unstimulated' or 'resting' saliva there is superimposed a secretion of much greater volumes of saliva in response to taste, smell and chewing during periods of food intake [2]. The term 'unstimulated' saliva is a convenient way to discriminate from a saliva secreted in response to an overt taste or chewing stimulus but is in some ways a misnomer since salivary secretion of fluid is only unstimulated in the complete absence of neural activation, which does not apply in the conscious subject with an intact innervation.

Resting whole-mouth saliva is subject to a circadian rhythm in flow rate and salt content reach-

Accepted Manuscript

Xerostomia: Current streams of investigation

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PII: S2212-4403(16)00097-3
DOI: 10.1016/j.oooo.2016.03.002
Reference: OOOO 1448

To appear in: *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*

Received Date: 31 July 2015
Revised Date: 13 January 2016
Accepted Date: 4 March 2016

Please cite this article as: Quock RL, Xerostomia: Current streams of investigation, *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology* (2016), doi: 10.1016/j.oooo.2016.03.002.

Accepted Manuscript

Saliva: an all-rounder of our body

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PII: S0939-6411(19)30370-4
DOI: https://doi.org/10.1016/j.ejpb.2019.06.016
Reference: EJPB 13084

To appear in: *European Journal of Pharmaceutics and Biopharmaceutics*

Received Date: 28 March 2019
Revised Date: 5 June 2019
Accepted Date: 17 June 2019

Please cite this article as: E. Roblegg, A. Coughran, D. Sirjani, Saliva: an all-rounder of our body, *European Journal of Pharmaceutics and Biopharmaceutics* (2019), doi: https://doi.org/10.1016/j.ejpb.2019.06.016

Oral Science International

journal homepage: www.elsevier.com/locate/osi

Review

Development and regeneration of salivary gland toward for clinical application

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ARTICLE INFO

Article history:
Received 18 November 2015
Received in revised form
27 November 2015
Accepted 30 November 2015

Keywords:
Development
Regeneration
Salivary gland
Stem cells
Progenitor cells

ABSTRACT

Salivary gland hypofunction, also termed as xerostomia, is caused by radiation therapy for head and neck cancer or Sjögren's syndrome, leading to a detrimental impact on oral health and quality of life. This review describes current studies on salivary gland development and the translational approaches of basic science to treating patients with dysfunction and hypofunction of the salivary gland. Here, we review the most recent studies that have offered better insight into the mechanisms of salivary gland development and regeneration. Furthermore, we highlight proposed approaches with the aim of recovering salivary gland function using both gene- and cell-based therapy. A thorough understanding of the mechanisms involved in salivary gland development is necessary in order to design effective therapies for regeneration and repair of damaged salivary glands.

Contents

1. Introduction

Many papers have reported the potential of regenerative medicine. However, many scientific challenges need to be overcome. In particular, many clinicians in the field of dentistry hope to realize the regeneration of the tooth and bone. Since cultured epidermal skin was developed using tissue engineering [1], cultured dermis has also been developed and recently made available to clinics worldwide. The epithelial cells of the oral membrane are similar to skin keratinocytes. Bioengineered oral mucosae have also been developed as well as bioengineered skin. Various reports regarding the development and clinical implementation of bioengineered oral mucosa sheets have been published since 1990. Bioengineered oral mucosa sheets are expected to be a useful tool for clinical

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http://dx.doi.org/10.1016/S1348-8643(15)00040-3

Photomedicine and Laser Surgery
Volume 32, Number 10, 2014
© Mary Ann Liebert, Inc.
Pp. 546–552
DOI: 10.1089/pho.2014.3741

Effect of Low-Level Laser Therapy on Radiotherapy-Induced Hyposalivation and Xerostomia: A Pilot Study

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Abstract

Objective: The present pilot study aimed to assess the effect of low-level laser therapy (LLLT) on hyposalivation and xerostomia as a consequence of head and neck radiotherapy. ***Background data:*** The benefits of LLLT in salivary flow have been shown; however, there are no studies investigating its effects on patients who have already undergone radiotherapy and present hyposalivation and xerostomia as a sequela. ***Methods:*** Twenty-three patients with a history of head and neck malignancy, who were treated by fractioned teletherapy (dosimetry ranging from 45 to 70 Gy) in the cervicofacial region were selected. They all presented with xerostomia and severe hyposalivation. Patients were randomly distributed into a laser group ($n=12$) and a control group ($n=11$). A GaAlAs laser (830 nm, 100 mW, illuminated area 0.028 cm^2, 3.57 W/cm^2, 20 sec, 2.0 J, 71 J/cm^2) was used punctually in the major salivary glands, twice a week for 6 weeks, with a 12 session total. Stimulated and unstimulated salivary flow rate (SFR) were assessed, as well as the xerostomia and quality of life related to oral health (QLROH). ***Results:*** The analysis did not show any significant difference between the groups with regards to the SFR and xerostomia, and the QLROH. However, at the end of the treatment, the xerostomia and the QLROH showed significant improvement in both groups compared with assessments performed at baseline, highlighting the importance of advice given to the irradiated patients, and their follow-up. ***Conclusions:*** With the parameters used, LLLT was not able to increase SFR or decrease xerostomia. The results may be associated with the late effects of radiotherapy on glandular structure, such as fibrosis and acinar atrophy.

Introduction

The major salivary glands are commonly involved in the radiation sites, as they are close to primary tumor and lymph chains of the head and neck region. As a consequence of radiotherapy, they go through a degenerative process, resulting in hyposalivation and xerostomia.[1] Approximately 70% of the irradiated patients have developed such alterations,[2] with several complications, such as total or partial loss of taste; mouth burning and pain; susceptibility to oral ulcerations, cavities, and other infections; dysphagia and dysphonia; and psychological alterations that negatively influence their quality of life.[3]

The dose of ionizing radiation, amount of salivary tissue exposed, and patient's individual response are the main factors influencing glandular alterations.[4–6] Damage becomes irreversible after cumulative doses ranging from 26 to 39 Gy, and the salivary flow rate (SFR) can decrease by 10% from the one presented before radiation.[7,8] Despite being stable, as they do not have high mitotic rates, acinar cells respond quickly to radiation.[9,10] The mechanisms that lead to tissue destruction and salivary gland radiosensitivity have not been totally understood so far. Salivary gland alterations start with the damage to the cell membrane, with loss of response to the autonomic controls, and progression to edema, degeneration, and acinar cell apoptosis. Acute effects start 24 h after therapy starts, and stabilize within 72 h. Late effects are the consequence of fibrosis and acinar atrophy,[11,12] which occur as a result of mesenchymal alterations, including changes in the extra cellular matrix, specifically in the lamilin and in collagen IV.[11,13]

Low-level laser therapy (LLLT) is a simple low-cost tool that can be used as an adjuvant to conventional treatments, or alone and electively in some diseases.[14–18] Its effects are based on the modulation of several metabolic, biochemical, and photophysical processes that transform laser light into

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Critical Reviews in Biotechnology, 2013; 33(3): 246–259
© 2013 Informa Healthcare USA, Inc.
ISSN 0738-8551 print/ISSN 1549-7801 online
DOI: 10.3109/07388551.2012.687361

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REVIEW ARTICLE

Saliva proteome research: current status and future outlook

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Abstract

Human saliva harbours proteins of clinical relevance and about 30% of blood proteins are also present in saliva. This highlights that saliva can be used for clinical applications just as urine or blood. However, the translation of salivary biomarker discoveries into clinical settings is hampered by the dynamics and complexity of the salivary proteome. This review focuses on the current status of technological developments and achievements relating to approaches for unravelling the human salivary proteome. We discuss the dynamics of the salivary proteome, as well as the importance of sample preparation and processing techniques and their influence on downstream protein applications; post-translational modifications of salivary proteome and protein–protein interactions. In addition, we describe possible enrichment strategies for discerning post-translational modifications of salivary proteins, the potential utility of selected-reaction-monitoring techniques for biomarker discovery and validation, limitations to proteomics and the biomarker challenge and future perspectives. In summary, we provide recommendations for practical saliva sampling, processing and storage conditions to increase the quality of future studies in an emerging field of saliva clinical proteomics. We propose that the advent of technologies allowing sensitive and high throughput proteome-wide analyses, coupled to well-controlled study designs, will allow saliva to enter clinical practice as an alternative to blood-based methods due to its simplistic nature of sampling, non-invasiveness, easy of collection and multiple collections by untrained professionals and cost-effective advantages.

Keywords: Saliva, clinical proteomics, blood, challenges, diagnostics

Saliva an alternative diagnostic biological fluid

There is a growing interest in clinical and translational research for the discovery and development of biomarkers that are indicative of a disease status and progression (1,2). Biomarkers of clinical relevance are predominantly proteins, and the advent of new Mass Spectrometry (MS) technology platforms and the sequencing of the human genome have accelerated protein biomarker discovery, particularly in readily available body fluids such as blood, saliva, and urine (3–5). Human saliva mirrors the body's health and well-being and most of the biomolecules that are present in blood or urine can also be found in salivary secretions (6). However, biomolecular concentrations in saliva are usually one tenth to one thousandth of the levels found in blood (7). Sensitive detection technology platforms are therefore required to enable the detection of biomolecules in saliva. Another roadblock to the advancement of salivary diagnostics is the lack of information with regard to the baseline levels (reference ranges) of molecules in saliva within a healthy control group to discriminate the molecular composition and levels during a disease stage. In spite of these impediments, the use of saliva in a clinical setting is on the rise, partly due to an increase in knowledge of the basic biochemistry and physiology of human saliva and also as a result of ease of collection relative to blood for clinical applications (2,8–10). The purpose of this review is to provide an overview of current developments and challenges in the field of saliva proteomic research. We have focussed our review on the potential diagnostic utility

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(Received 12 January 2012; revised 12 April 2012; accepted 13 April 2012)

ORAL DISEASES

Oral Diseases (2015) 21, e1–e10 doi: 10.1111/odi.12222
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INVITED MEDICAL REVIEW

Current ideas to reduce or salvage radiation damage to salivary glands

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Radiation-induced hyposalivation is still a major problem after radiotherapy for head and neck cancer. Current and promising new thoughts to reduce or salvage radiation damage to salivary gland tissue are explored. The main cause underlying radiation-induced hyposalivation is a lack of functional saliva-producing acinar cells resulting from radiation-induced stem cell sterilization. Current methods to prevent that damage are radiation techniques to reduce radiation-injury to salivary gland tissue, surgical techniques to relocate salivary glands to a region receiving a lower cumulative radiation dose, and techniques to make salivary gland cells more resistant to radiation injury. These preventive techniques cannot be applied in all cases, also reduce tumor sensitivity, or do not result in a sufficient amelioration of the dryness-related complaints. Therefore, alternative methods on techniques to salvage salivary glands that are damaged by radiation are explored with promising results, such as stem cell therapies and gene transfer techniques to allow the radiation-injured salivary gland tissue to secrete water.

Oral Diseases (2015) **21**, e1–e10

Keywords: radiotherapy; hyposalivation; xerostomia; IMRT; gene transfer; stem cells

Introduction

In 2012, in the USA, more than 40 000 new patients were diagnosed with head and neck cancer (American Cancer Society, 2012). Worldwide, head and neck cancer accounts for more than 550 000 cases annually (Jemal *et al*, 2011). The majority of these patients were treated with radiotherapy alone or in combination with chemotherapy, cetuximab and/or surgery. The 5-year survival rate of these patients is approximately 50% for non-metastatic locally advanced disease (Piccirillo *et al*, 2007). While radiotherapy significantly improves the patient's chances of survival, at the same time the exposure to ionizing radiation usually results in unavoidable co-irradiation of the normal tissues surrounding the tumor. The salivary glands are among these normal tissues as the ionizing beams have to pass the salivary glands to reach the tumor.

Protocols have been developed to minimize early and late loss of gland function following radiotherapy, but even when applying intensity-modulated radiation therapy (IMRT), the current evidence-based standard technique, commonly applied technique to irradiate head and neck cancer, still 40% of head and neck cancer patients experience a moderate or severe sensation of oral dryness (xerostomia) (Burlage *et al*, 2001; Mahood *et al*, 2007; Jellema *et al*, 2007; Jensen *et al*, 2010; Vissink *et al*, 2010; Beetz *et al*, 2013). In addition, induced by or related to the radiation injury to the salivary glands and consequential hyposalivation, many other post-treatment complications occur, such as hampered speech, increased risk on oral infections and dental caries, difficulties with swallowing and food mastication, impaired taste, and nocturnal oral discomfort. These symptoms can lead to a dramatic loss in quality of life for the patient and remains extremely difficult to manage (Jansma *et al*, 1992; Vissink *et al*, 2003a,b).

In this paper, first the pathophysiology underlying radiation damage to salivary tissue is be briefly reviewed. Next, currently explored and promising new thoughts to reduce or salvage radiation damage to salivary gland tissue are discussed.

Radiation-induced hyposalivation

The salivary glands of rodents and primates are composed basically of two saliva-producing cells types, namely mucous and serous acinar cells, of myoepithelial cells,

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Received 19 December 2013; revised 23 December 2013; accepted 23 December 2013

frontiers in Cell and Developmental Biology

MINI REVIEW
published: 13 February 2020
doi: 10.3389/fcell.2020.00041

Molecular Mechanisms of Radiation-Induced Cancer Cell Death: A Primer

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Radiation therapy (RT) is responsible for at least 40% of cancer cures, however treatment resistance remains a clinical problem. There have been recent advances in understanding the molecular mechanisms of radiation-induced cell death. The type of cell death after radiation depends on a number of factors including cell type, radiation dose and quality, oxygen tension, TP53 status, DNA repair capacity, cell cycle phase at time of radiation exposure, and the microenvironment. Mitotic catastrophe (a pathway preceding cell death that happens in mitosis or as a consequence of aberrant mitotic progression) is the primary context of radiation-induced cell death in solid cancers, although in a small subset of cancers such as haematopoietic malignancies, radiation results in immediate interphase apoptosis, occurring within hours after exposure. There is intense therapeutic interest in using stereotactic ablative body radiotherapy (SABR), a precise, high dose form of RT given in a small number of fractions, to prime the immune system for cancer cell killing, but the optimal radiation dose and fractionation remain unclear. Additionally, promising novel radiosensitisers targeting the cell cycle and DNA repair pathways are being trialled. In the context of the increasing use of SABR and such novel agents in the clinic, we provide an updated primer on the major types of radiation-induced cell death, focussing on their molecular mechanisms, factors affecting their initiation, and their implications on immunogenicity.

OPEN ACCESS

Edited by:
Andrew Burgess,
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Reviewed by:
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Specialty section:
This article was submitted to Cell Growth and Division, a section of the journal Frontiers in Cell and Developmental Biology

Received: *14 November 2019*
Accepted: *17 January 2020*
Published: *13 February 2020*

Citation:
Sia J, Szmyd R, Hau E and Gee HE (2020) Molecular Mechanisms of Radiation-Induced Cancer Cell Death: A Primer. Front. Cell Dev. Biol. 8:41. doi: 10.3389/fcell.2020.00041

Keywords: radiotherapy, radiation therapy, stereotactic ablative radiotherapy, cell death, immunogenic cell death, abscopal effect

INTRODUCTION

Radiation therapy (RT) is a major cancer treatment modality and is responsible for at least 40% of cancer cures (Ringborg et al., 2003), yet treatment resistance remains a clinical problem. A primary reason for this is the capacity for cancer cells to evade radiation-induced cell death. Treatment paradigms have traditionally viewed cancer as a cell-autonomous problem of dysregulated proliferation while side-lining host-tumour interactions, but this dogma has undergone a remarkable revolution in the last few decades, with increasing appreciation of the tumour stroma and immune milieu in shaping tumour evolution. Trials of novel radiosensitisers targeting not only key cell death pathways but also the stromal and immune microenvironment, particularly together with stereotactic ablative body radiotherapy (SABR), have gained intense interest.

Here, we provide an updated primer on the major types of radiation-induced cell death, focussing on their molecular mechanisms, factors affecting their initiation, and their implications

ANALISIS SIFAT FISIKOKIMIA (LAJU ALIR, DERAJAT KEASAMAN, KEKENTALAN) SALIVA PASIEN RADIOTERAPI KANKER KEPALA DAN LEHER

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