**Ionizing Radiation Side Effects on Salivary Glands Post External Beam Radiation Therapy of Head and Neck Tumors**

**Abstract**

**Introduction:** External beam radiation therapy is a treatment modality for a group of malignancies clustered under one diagnostic heading as head and neck tumors [1]. Radiation therapy may be administered post-surgery. However, depending on the nature of the tumors, these tumors may be treated using the external beam without surgery. Furthermore, external beam radiation therapy may also be used in combination with chemotherapy [2]. However, it has since been established that the external beam radiation therapy technique leads to salivary gland injury resulting in long term health complications for people previously treated for head and neck tumors [1-3].

**Methods:** A literature search using Google search engine, Science Direct and Medline was conducted to find publications detailing the side effects of ionizing radiation on the salivary glands and the consequential effects on the quality of life of people previously treated for head and neck tumors using external radiation beam therapy.

**Results:** Ionizing radiation causes structural and physiological alteration of the salivary glands resulting in reduced functional capacity and reduced saliva flow rates. People previously treated for head and neck tumors suffer from dry mouth, dental caries, oral candidiasis, mouth pain and sleeping problems.

**Conclusion:** People treated for head and neck tumors with ionizing radiation suffer from dry mouth, dental caries, and malnutrition among other associated health problems.

**Keywords:** Salivary glands; External beam radiation therapy; Dry mouth; Ionizing radiation

**Introduction**

External beam radiation therapy is a treatment modality for a group of malignancies clustered under one diagnostic heading as head and neck tumors [1]. Radiation therapy may be administered post-surgery. However, depending on the nature of the tumors, these tumors may be treated using the external beam without surgery. Furthermore, external beam radiation therapy may also be used in combination with chemotherapy [2]. However, it has since been established that the external beam radiation therapy technique leads to salivary gland injury resulting in long term health complications for people previously treated for head and neck tumors [1-3].

**Literature Review**

Treatment of head and neck tumors with external radiation beam may involve use of any of the following techniques; intensity-modulated radiation therapy (IMRT), two-dimensional radiation therapy (2D-RT) and three-dimensional conformal radiation therapy (3D-CRT) [4]. The external beam radiation therapy relies on the use of ionizing radiation to destroy the DNA of the malignant cells leading to their death [1]. Treatment may last between three and seven weeks. However, this depends on tumor size and the purpose of treatment whether it is curative or palliative. The head and neck tumors maybe treated with doses...
of between 50 Gy and 70 Gy. A patient would generally receive 2 Gy a day in a week of five consecutive days excluding weekends [2].

The IMRT is the most favorable technique during radiation therapy of head and neck tumors because it has the potential to spare the parotid glands from the intense radiation beam [4] thus reducing the impact of the long-term complications among which may include; xerostomia, hoarseness and erythema [3]. However, radiation treatment despite its effectiveness on tumor destruction leads to side effects that contribute to a low quality of life for people previously treated for head and neck tumors [5].

The head and neck tumors occur in various anatomical parts of the head and neck which include; the oral cavity, the larynx, the nasopharynx, the hypopharynx, the nose, the cervical esophagus, the lips and the paranasal sinuses [1]. The most common type of head neck tumors is the squamous cell carcinoma. The highest incidences of head and neck cancers are the lip and oral cavity cancers and the thyroid cancers. The salivary glands tumors, sarcomas and lymphomas constitute another group of head and neck carcinoma [2].

The salivary glands can be categorized into major and minor [1]. The major salivary glands are the paired parotid, submandibular and the sublingual [1,4]. The minor salivary glands vary from one individual to the other and they are found on their lips, in the inner cheek area or throughout the pharynx [6,7].

Salivary glands consist of many functional units called the acini which encompasses of the myoepithelial cells, connective tissue and the collecting ducts [1,8,9]. The acinar cells can either be mucous or serous in nature [8,9]. The secretions (saliva) produced by the acini are fluid in nature. They comprise of water, enzymes, electrolytes and mucus [6]. The secretions pass through a series of intercalated ducts, past striated ducts and terminal lobular ducts until they reach the main ducts which transport them to the oral cavity [10].

The salivary glands and the ducts cells are often referred to as “reverting post mitotic cells”. Regeneration is through proliferation of secretory and duct cells. The acini are replenished by stem cells in the distal segments of the duct system [10]. The saliva secreted by the acini apparatus is controlled by the autonomic nervous system. Most of it is produced by the parotid, submandibular and sublingual glands [6,8]. The parotid salivary glands produce most of the saliva either when eating or under stimulation while the submandibular salivary glands are responsible for production of most of the saliva while at rest [4].

The minor salivary glands produce a small quantity of saliva [6,8]. However, most of the mucins are produced by the minor salivary glands and the submandibular glands. The mucins are responsible for oral lubrication while also conferring a sense of hydration thorough absorption of water molecules as well as adhering to the mucosa [4]. This study aimed at examining the side effects of ionizing radiation on salivary glands post external beam radiation therapy of head and neck tumors.

Materials and Methods
A systematic literature review using Google search engine, Sciencedirect.com and Medline was conducted for publications on salivary gland anatomy, radio sensitivity, injuries following treatment of head and neck tumors using radiation therapy. Abstracts and full texts were thoroughly examined to extract information related to salivary glands anatomy, external radiation beam treatment techniques, side effects associated with treatment and lastly the quality of life of people post treatment for head and neck tumors. Only articles written in English were considered. Additional information was obtained from the articles listed in the references of the articles obtained using the search engines. Articles that presented information of salivary glands injury following radioiodine treatment of thyroid cancers were excluded even though they had information related to salivary glands injury because of radiation injury.

An initial search yielded over 1200 articles. However, these narrowed to 34 after restricting the treatment technique to external beam radiation therapy (Figure 1).

Results
From most of the articles meeting the selection criteria (Table 1), it was established that people treated for head and neck cancers may develop oral cavity complications [1-5,11-13]. Atri et al. [14] established that irradiated serous acinar cells of the parotid and the submandibular salivary glands undergo interphase death. A closer analysis of Table 1 shows that xerostomia is the most common oral complication. As many as 73.5 to 93% of people previously treated for head and neck showed symptoms of xerostomia. Those with severe xerostomia were found to exhibit diminished abilities of chewing and swallowing food, often leading to malnutrition and weight loss. In cases where patients experienced insufficient saliva flow rates results, in formation of dental curies, wearing of dentures, mouth pain, and oral infections, tasting disorders and sleeping problems [15-19]. It was also established that patients may awake at night with the
Table 1 Overview of studies including ionizing radiation side effects on salivary glands post external beam radiation therapy of head and neck tumour.

<table>
<thead>
<tr>
<th>Author/ journal/year</th>
<th>Reference</th>
<th>Study design</th>
<th>Sample size</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Pinna et. al. (2015) Xerostomia induced by radiotherapy: an overview of the physiopathology, clinical evidence, and management of the oral damage. Ther Clin Risk Manag 11: 171-188.</td>
<td>12</td>
<td>Systematic literature Review</td>
<td>70 articles</td>
<td>Ionizing radiation damages the salivary glands tissue. Severe tissue damage at doses greater than 52Gy. Reduction of saliva output due to damage of salivary tissue is observed at onset of treatment up to 3 months after therapy. Treatment results in alteration of saliva electrolyte levels; sodium chloride, calcium and magnesium levels increase whereas potassium is minimally affected. Secreted saliva post radiation found to be vicious with reduced pH in the range 5.0 to 7.0; may turn yellow, brown or even white. Lack of saliva because of salivary glands injury may result in angular cheilitis, cracked lips, periodontal disease, aching of the mouth and halitosis. Lack of saliva may also lead to loss of appetite as the dry mouth makes eating and swallowing difficult. Patients treated for head and neck tumours may lose sense of taste.</td>
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<tr>
<td>Gómez GJA et al. (2017) Alterations found in the mouth of patients treated with head and neck radiotherapy. Medellin, Colombia. Revista Odontológica Mexicana 86-96.</td>
<td>14</td>
<td>Exploratory Study</td>
<td>52 patients</td>
<td>High frequency of oral alterations in patients subjected to external beam radiation dosage varying from 3001 to 5 000 cGy. Hyposalivation common in patients with stage IV tumours (50%).</td>
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<tr>
<td>Maes et al (2002) Preservation of parotid function with uncomplicated conformal radiotherapy. Radiother Oncol 63: 203-211.</td>
<td>17</td>
<td>Prospective cohort study</td>
<td>39 patients</td>
<td>The parotid salivary should at least receive &lt;20 Gy to spare them from severe radiation injury that leads xerostomia.</td>
</tr>
<tr>
<td>Verdonck-de Leeuw et al. (2008) Impact of Late Treatment-Related Toxicity on Quality of Life Among Patients with Head and Neck Cancer Treated with Radiotherapy. J Clin Oncol 26: 3770-3776.</td>
<td>18</td>
<td>Prospective cohort study, assessments of patients taking place at 6,12,18, and 24 months after completion of radiotherapy</td>
<td>425 disease free patients</td>
<td>Radiation induced xerostomia found to be the most advert side effect of radiation therapy of head and neck tumours arising from irradiation of salivary glands. Patients treated for head and neck tumours registered swallowing problems</td>
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<tr>
<td>Authors</td>
<td>Title</td>
<td>Methodology</td>
<td>Sample Size</td>
<td>Summary</td>
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<td>Kakoei et al. (2012)</td>
<td>Xerostomia after Radiotherapy and its Effect on Quality of Life in Head and Neck Cancer Patients. Arch Iran Med 15: 214-218.</td>
<td>Longitudinal prospective study of 63 patients assessed over six months, the subjects were selected from the only radiotherapy referral center at Shafa Hospital, Kerman, Iran</td>
<td>63 patients</td>
<td>The quantity of saliva did not change significantly during therapy. Patients suffered xerostomia after treatment due to permanent damage of salivary glands in the treatment zone.</td>
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<td>Preethi et al. (2011)</td>
<td>Assessment of parotid salivary gland function in head and neck tumours receiving radiation therapy of head and neck cancer patients receiving radiation therapy using quantitative salivary gland scintigraphy. Pak J Physiol 7:1</td>
<td>Prospective salivary gland study</td>
<td>35 patients planned for radiotherapy for head and neck tumours</td>
<td>Severe salivary glands dysfunction for patients receiving radiation doses greater than 50 Gy. The submandibular salivary glands and the sublingual salivary glands are less radiosensitive compared to the parotid salivary glands.</td>
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<tr>
<td>Atri et al. (2007)</td>
<td>Management of Radiation Induced Xerostomia in Head and Neck Cancers. J Oral Health Comm Dent 1: 33-39</td>
<td>Systematic literature review</td>
<td>32 Sample sizes</td>
<td>Dose tolerance of salivary glands varies between 32Gy and 46Gy. Curative external beam radiotherapy is usually 60Gy or more, however results in a complication called xerostomia. Xerostomia interferes with chewing and nutrition, deterioration of oral hygiene, dental curies,</td>
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<tr>
<td>Plemons et al (2015)</td>
<td>Managing xerostomia and salivary gland Hypofunction. American Dental Association.</td>
<td>Systematic literature review</td>
<td>80 articles</td>
<td>Xerostomia is the most common symptom of salivary gland injury arising from irradiation of head and neck cancer. Xerostomia refers to subjective feeling of a dry mouth, may range from mild oral discomfort to significant oral disease that can compromise patients' health, dietary intake and quality of life.</td>
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<tr>
<td>Baijal et al. (2012)</td>
<td>Radiation Induced Xerostomia. Int J Head Neck Sur 3: 82-86.</td>
<td>Systematic literature review</td>
<td>39 articles</td>
<td>Irradiation of salivary glands during radiation treatment of head and neck tumours leads to Xerostomia. Xerostomia is a late side effect of radiation therapy of head and neck cancers which manifests as dry mouth, sore throat, altered taste, dental decay, changes in the quality of voice, impaired chewing and difficulties in swallowing, nutritional issues and weight loss.</td>
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<tr>
<td>Eisbruch A (2007)</td>
<td>Reducing Xerostomia by IMRT: What may, and what may not be, be achieved. J Clin Oncol 25: 4863-4864.</td>
<td>Systematic literature review</td>
<td>17 articles</td>
<td>Salivary glands acinar cells apoptosis is associated with low doses while necrosis occurs at high doses. Xerostomia is the side effect of external beam radiation therapy of head and neck cancers. Patients have subjective feeling of dry mouth. diminished salivary output resulting in mastication and deglutition difficulties contributing to nutritional deficiencies, predisposing the patient to mucosal fissures, ulcers, changing composition of the oral flora, promoting dental caries.</td>
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Zhang et al. [27] established that adaptive radiotherapy reduces the parotid salivary gland mean radiation dose. However, a previous study by Sood et al. [28] encouraged salivary gland transfer before therapy to preserve them from radiation injury.

Several researchers have established that xerostomia owing to irradiation of salivary glands may either be acute or chronic [16,19]. However, irrespective of its degree, xerostomia has a deleterious effect on the life of patients treated for head and neck tumors. Baijal et al. [20] reported that people treated for head and neck may experience sore throat, altered taste, dental decay, changes in the quality of voice, impaired chewing and difficulties in swallowing, nutritional issues and weight loss. A further study by Deasy et al. [21] established that people treated for head and neck tumors are highly likely to have difficulties in chewing and swallowing and sleep disturbances. It has also been established that xerostomia may also manifest in individuals with dry mouth due to reduced saliva output [21,22]. Reduced saliva in the oral cavity leads to oral discomfort, dietary intake and weight loss thus compromising the patients’ health [19]. De Souza Tolentio et al. [23] reported that a compromised integrity of the oral leaves patients prone to infections by bacteria, yeasts and viruses.

Management of patients treated with external beam radiation therapy needs a multidisciplinary approach that should involve physicians and dentists. Andreas and Griffiths [29] proposed use of moistening agents and saliva substitute to alleviate the symptoms of xerostomia. De Souza Tolentio et al. [23] reported on studies that encouraged use of antimicrobial agents for prevention of fungal and bacterial infections. They further encourage discontinued use of dentures. However, where the need of dentures was inevitable, they should be cleaned in a solution of 0.5% of hypochlorite solution for 30 minutes.

Despite the knowledge that the degree of injury of the salivary glands is dose related [4,20] the mechanisms of salivary glands degradation by ionizing radiation remains not well understood. Furthermore, the side effects which are a consequence of xerostomia remain difficult to quantify. An attempt by Maes et al. [2] to quantify severity of the salivary glands hypofunction did not have much objectivity due to the listener and patient influence. However, a recent phantom study by Nyathi [30] provided an objective phantom method for quantifying salivary gland function post radiation therapy of head and neck tumors. However, it still must be tested in human studies.

**Table:**

<table>
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<th>Authors (Year)</th>
<th>Title</th>
<th>Articles</th>
<th>English Language Articles</th>
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Discussion

Radiation therapy either as full-dose curative treatment or with the palliative intent has been found to be an ideal therapy for head and neck cancers [1-5]. However, during treatment the salivary glands are always included in the radiation field hence their injury leading to dysfunction [11,20-26]. The parotid salivary glands which consist purely of the serous gland [6-9] are the most sensitive compared to the submandibular glands from a clinical perspective [26]. The radio sensitivity of the parotid salivary glands may be because they contain heavy metal granules. During therapy, the ionizing radiation causes the disruption of the metal granules by means of a metal-catalyzed induction of lipid peroxidation causing release of lytic enzymes into the cell’s cytoplasm, hence autolysis and eventual death of the affected cell. However, even though the parotid salivary glands are more radiosensitive compared to the submandibular glands, the damage response by both pairs of the salivary glands is the same [11].

The ionizing radiation causes the salivary glands to undergo structural degradation [1-5,13]. According to Eisbruch [13] the salivary glands acinar cells apoptosis occurs at low doses while necrosis occurs at high doses. Atri et al. [18] found that dose tolerance of the salivary glands varied between 32 Gy and 46 Gy. However, the curative dose of head and neck tumors may rise to 60 Gy or more. This value is well above the dose tolerance range of the salivary glands. Exceeding the dose tolerance range of the salivary glands may lead to permanent injury and dysfunction of the salivary glands and consequent xerostomia. People treated for head and neck tumors may begin to suffer from xerostomia after the start of treatment of head and neck tumors [15]. Xerostomia is a sensation of dry mouth mainly attributed to reduced saliva flow rates, it varies from one patient to the next. However, recovery of salivary function may be temporary or may be permanent [23]. A study by Hawkins et al. [4] concluded that the degree of xerostomia is dose dependent. Therefore, to preserve the function of the salivary glands of people treated for head and neck tumors, it is important that radiation techniques that minimize the intensity of the radiation field on the salivary glands be used.

Zhang et al. [27] established that adaptive radiotherapy reduces tongue adhered to the hard palate and may have to manually remove the thick saliva.
Conclusion
The use of IMRT technique during treatment of head and neck tumors minimizes salivary gland injury thus reducing the degree of xerostomia and related side effects among patients treated for head and neck tumor. Prevalence of xerostomia is dose dependent, therefore reducing the intensity of ionizing radiation beam on the salivary glands will reduce the impact of dry mouth and consequences such as dental caries and malnutrition among other associated health problems. Management of people treated for head and neck tumors needs a multidisciplinary approach involving dentists, doctors and clinicians. The dentists should be involved with dental care during and post radiation therapy while clinicians should continue to investigate the means of quantifying the degree of xerostomia. Furthermore, clinicians need to determine the methods of alleviating the symptoms of dry mouth to reduce the discomfort arising from reduced saliva production.

References
1 Nyathi M (2015) Quantitative evaluation of the parotid and the salivary glands function post radiation therapy of head and neck tumours. Sefako Makgatho Health Sciences University, South Africa.
