

## RESEARCH ARTICLE

# Oral Complications of The Oromaxillofacial Area Radiotherapy

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### Abstract

**Background:** The incidence of malignancies is on the rise in different communities, making them the second most important cause of mortality in developed countries. One of the treatment modalities for these malignancies, apart from surgery and chemotherapy, is radiotherapy which might in itself lead to some complications in the area receiving radiation. The present study was undertaken to evaluate the prevalence of oral complications in patients undergoing radiotherapy of the oromaxillofacial area in Shahid Ramazanzadeh Radiotherapy Center in Shahid Sadoughi University of Medical Sciences. **Materials and Methods:** The present descriptive/analytical study was carried out from 2014 to 2015 on 144 patients with head and neck malignancies, referring to Shahid Ramazanzadeh Radiotherapy Center, Yazd, Iran. The patients underwent intraoral examinations before radiotherapy, during the second week after radiotherapy and at the end of radiotherapy. The patients' background data and the presence of oral complications were recorded in special forms. Data were analyzed with SPSS 17, using chi-squared test. **Results:** Of 144 patients evaluated, 51 were male and 93 were female. During the final examination, all the subjects (100%) had mucositis, xerostomia and candidiasis, with 85.4% of the subjects (123 patients) suffering from gustatory disturbances. Although only 38.1% of the subjects had oral ulcers at the end of the second week, all of them (100%) exhibited such lesions in the final examination. The prevalence rate of tooth hypersensitivity at this stage was 22.9%. During the second examination, 117 subjects (83.3%) exhibited grade I trismus, 42 of which exhibited deterioration toward grade II during the final examination. **Conclusion:** The results of the present study showed a high rate of oral complications in patients undergoing head and neck radiotherapy. Mucositis, xerostomia and candidiasis were the most prevalent complications.

**Keywords:** Oral complications- cancer- radiotherapy

*Asian Pac J Cancer Prev*, **18** (3), 721-725

### Introduction

The incidence of malignancies is increasing world wide and they have become the second most important cause of death in developed countries (Duncan et al., 2005; Taheri et al., 2006; Hashemipour et al., 2008; Cheng et al., 2011; Little et al., 2013). Oral and pharyngeal cancers account for approximately 4% of these malignancies (Gellrich et al., 2003; Duncan et al., 2005; Taheri et al., 2006; Hashemipour et al., 2008; Cheng et al., 2011; Little et al., 2013). One of the treatment modalities applied to such patients, apart from surgery and chemotherapy, is radiotherapy. Some of the acute complications of radiotherapy in the head and neck region are nausea, vomiting, mucositis, xerostomia, loss of the taste sensation, trismus, tooth hypersensitivity, secondary infections (viral, bacterial and fungal), periodontal changes and desquamation of skin, which occur during the treatment (Shafer et al., 1983; Carl, 1993; Rodney and McBride, 1998; Andrews and Griffiths, 2001; Devita et al., 2001; Vissink et al., 2003).

Inflammation and mucosal rubor are usually the first visible reactions on the skin that are manifested a few days after radiotherapy (Carl, 1993; Vissink et al., 2003; Greenberg and Glick, 2015). In addition, changes in the oral mucosa are essentially the same as those occurring in skin; however, due to the low resistance of the mucosa compared to skin, the mucosa manifests a faster response to radiation. However, due to the higher turnover of mucosal cells, the induced inflammation recovers faster than dermatitis (Ghavam, 2001).

The major salivary glands, also, inadvertently receive 20-30 Gy of radiation during the radiotherapy of the oropharyngeal area. The parenchymal components of salivary glands are very sensitive to radiation, and xerostomia is the most common complication in patients undergoing head and neck radiotherapy. In addition, patients their parotid glands on both side receive radiation are more prone to xerostomia compared to those whose parotid gland receives radiation only from one side (Carl, 1993; Newman et al., 2002). Since radiation decreases the salivary flow, the self-cleaning activity of the oral cavity

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by the saliva is disturbed, leading to dental caries (Shafer et al., 1983; Robbins, 2000; Andrews and Griffiths, 2001; Newman et al., 2002; White and Pharoah, 2014; Greenberg and Glick, 2015).

Other complications of radiotherapy are injuries to the blood vessels of the periosteum, a decrease in the activity of osteoblasts and osteoclasts, and an increase in adipose tissue and fibrotic connective tissue in the bone marrow, resulting in a decrease in blood vessels and cellularity, which make the bone marrow hypoxic. A decrease in bone mineralization gives rise to an increase in bone brittleness, all of which result in osteoradionecrosis (Shafer et al., 1983; Andrews and Griffiths, 2001; Newman et al., 2002; White and Pharoah, 2014; Greenberg and Glick, 2015). Since the saliva contains a large number of antimicrobial agents, including mucins, electrolytes, proline, IgA and histidine, each with a specific defensive action, the ionizing radiation causes important changes in the host defense action by inflicting injuries on the salivary glands, giving rise to candidiasis and dental caries. An increase in the number of cariogenic microorganisms such as *S. mutans*, *Lactobacilli*, *S. sanguis*, *Neiseria*, *Fusobacterium* and *Actinomyces*, is of significance (Shafer et al., 1983; Shrout, 1991; Andrews and Griffiths, 2001; Little et al., 2013; Greenberg and Glick, 2015).

Considering the effect of oral health on the quality of life, the present study was carried out to evaluate the oral complications in patients undergoing oromaxillofacial radiotherapy, referring to Shahid Ramazanzadeh Radiotherapy Center, Shahid Sadoughi University of Medical Sciences in 2014.

## Materials and Methods

The present descriptive/analytical cross-sectional study was carried out on 144 patients with head and maxillofacial malignancies from September 23rd 2014 to September 23rd 2015, referring to Shahid Ramazanzadeh Radiotherapy Center, who underwent radiotherapy. Consecutive sampling technique was used to include patients in the study. Before any action, Research Ethics Committee approval for this research was obtained (number: 34,267). Patients willing to cooperate were included after signing an informed consent form. The inclusion criteria consisted of patients with at least a part of the orol or maxillofacial region undergoing radiotherapy, no systemic conditions affecting the oral health, being in the first session of their treatment and no history of radiotherapy or chemotherapy. The patients were clinically examined three times: before radiotherapy, during the second week of radiotherapy and at the end of radiotherapy. Oral examinations of all areas of the mouth was done with lip retraction and mirror, under standard condition in dental chair by dental student trained in this field.

*The following clinical entities were evaluated*

**Mucositis:** Erythema and rubor in the mucosa, which is sometimes associated with a burning sensation, erosion or ulceration (Greenberg and Glick, 2015). In addition, mucositis was evaluated based on WHO criteria (patient's

description) and NCI-CIC (clinical evaluation) (Shrout, 1991).

**Oral ulcers:** These lesions are usually well-demarcated and indented with epithelial defects and are covered with a fibrin coagulum with a white or yellow surface appearance (Greenberg et al., 2008).

**Xerostomia:** Xerostomia is diagnosed when, based on a questionnaire introduced by Fox et al, the patient provides a positive response to at least one of the following questions (Browning et al., 1987):

- 1) Do you need liquids to swallow dry foods?
- 2) Do you have a dry mouth when you are having food?
- 3) Do you have any problems when you swallow food?

**Taste disturbance:** Taste disturbance is defined as any change in taste sensation or feeling of an abnormal taste in the oral cavity (Hashemipour et al., 2008). This problem was evaluated by asking the following questions: 1) Do you have any unpleasant taste in your mouth? 2) Do you feel that you are unable to feel one or more than one taste? 3) Have there been any changes in your diet? 4) Have taste disturbances resulted in changes in your daily activities? 5) Are you able to feel the bitter taste of coffee, the sweet taste of ice cream, the salty taste of potato chips and the sour taste of lemons?

**Trismus:** Trismus was scored based on the following criteria: (Dijkstra et al., 2004) grade I, mouth opening between 31 and 40 mm; grade II, mouth opening between 25 and 30 mm; grade III, mouth opening less than 25 mm.

**Tooth hypersensitivity:** It was defined as a reaction higher than normal to stimuli in the oral cavity.

**candidiasis (thrush):** The condition is characterized by the presence of white plaques or papules that are removed by a piece of gauze, revealing an underlying erythematous or bleeding area (Greenberg and Glick, 2015).

The radiotherapy machine used in the present study was a NEPTUN 10 P linear accelerator (Poland), with 9 MV of energy and a daily dose of 180–200 cGy for 5 days a week. All the subjects were examined with dental mirrors, tongue depressors, gauze pieces, dental explorers, periodontal probes and transparent graduated rulers. Data were analyzed with SPSS 17, using chi-squared test.

## Results

Of 144 subjects included in this study, 51 were male and 93 were female, with a mean age of 49.33±16.03

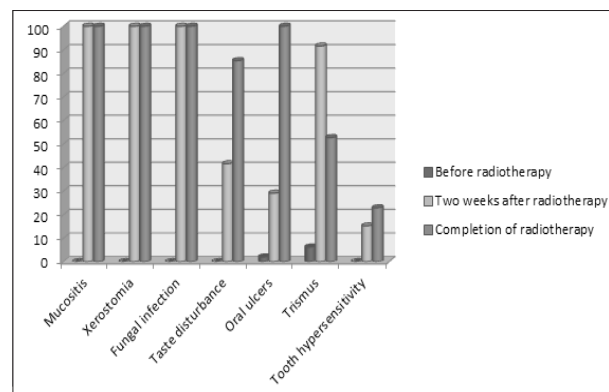


Figure 1. Frequency Distribution of Oral Complications (%)

years. Based on the results, none of the subjects exhibited mucositis, xerostomia and Candida infections during the first examination; however, at the end of the second week, all the subjects (100%) exhibited the complications mentioned above, which persisted until the end of the study (Table 1, Figure 1).

In the first examination, none of the subjects exhibited gustatory disturbances; however at the end of the second week, 60 subjects (41.6%) and during the final examination, 123 subjects (85.4%) suffered from taste disturbances.

In the first examination, 3 subjects had oral ulcers; at the end of the second week, 42 subjects (29.1%) had oral ulcers at the final examination, all the subjects had oral ulcers.

In the first examination, 3 subjects exhibited mouth opening between 31 and 40 mm (grade I), which progressed to grade II during the second examination and remained grade II until the end of the treatment. In the second examination, of the subjects healthy in relation to trismus, 117 (81.2%) exhibited grade I trismus; of these 117 subjects, 42 subjects exhibited grade II trismus. 15 subjects, also exhibited grade II trismus during the second examination, demonstrating exacerbation at the end of treatment, reaching a mouth opening less than 25 mm (grade III). These observations showed the incidence of trismus during the different stages of radiotherapy, which is significant ( $P < 0.001$ ).

Of 144 patients included in this study, 6 patients were edentulous and tooth hypersensitivity was evaluated in 138 patients. During the second examination, 21 subjects exhibited tooth hypersensitivity (15.2%). Of 117 remaining subjects, 12 subjects exhibited tooth hypersensitivity during the final stage of treatment. On the whole, 22.9% of subjects exhibited tooth hypersensitivity, which was not statistically significant.

## Discussion

Radiotherapy has a great role in controlling head and neck cancers. One of the most common complications of patients undergoing radiotherapy of the head and neck region is xerostomia. A decrease in or cessation of salivary flow begins at the end of week 1 or week 2 of radiotherapy, which is secondary to the irradiation of major salivary glands (Greenberg et al., 2008). In the majority of studies, such as those by Taheri et al., (2006) (96.7%) and Hashemi et al., (2008) (95.2%), xerostomia was the most common complaint of patients undergoing head and neck radiotherapy. In addition, a study by Duncan et al showed a significant increase in xerostomia severity during the radiotherapy period, which was reported to be one of the most common complications of head and neck radiotherapy in a systematic review by Turner et al. In addition, Chung et al., (2011) reported xerostomia as the most common complication after radiotherapy that affects the patients' quality of life. After irradiation of 20–30 Gy (over 23 Gy) to the head and neck region in radiotherapy patients, xerostomia certainly occurs in the majority of patients, which is due to the sensitivity of the parenchyma of salivary glands to radiation. In the present study, at the

Table 1. Frequency Distribution of Oral Complications Subsequent to Radiotherapy in Patients Referring to Shahdramazanzadeh Radiotherapy Center (N=144)

Variable	Mucositis	Xerostomia	Fungal infection	Taste disturbance	Oral ulcers	Trismus			Tooth hypersensitivity
						I	II	III	
Before radiotherapy					3 subjects (2%)				
Two weeks after radiotherapy	144 subjects (100%)	144 subjects (100%)	144 subjects (100%)	60 subjects (41.6%)	42 subjects (29.1%)	117 subjects (81.2%)	15 subjects (10.4%)	21 subjects (15.2%)	
Completion of radiotherapy	144 subjects (100%)	144 subjects (100%)	144 subjects (100%)	123 subjects (85.4%)	144 subjects (100%)	18 subjects (12.5%)	42 subjects (29.1%)	33 subjects (22.9%)	

end of week 2 all the patients (100%) exhibited xerostomia which persisted until the end of the study.

Direct injury by radiation to basal epithelial cells and the underlying tissue through injury to cellular DNA results in the atrophy of the epithelium and the subsequent mucositis (S. et al., 2009; Turner et al., 2013). Mucositis is one of the most common complications secondary to radiotherapy, which begins during the first two weeks of radiotherapy and even with a radiation dose of 10–20 Gy (especially a dose over 30 Gy) to the oral mucosa (Alvarino-Martin and Sarrion-Perez, 2014) and is exacerbated with the continuation of radiotherapy. The condition gradually subsides over 3–6 weeks after completion of radiotherapy (Turner et al., 2013). The pain and burning sensation due to mucositis may encourage the patient to discontinue the treatment.

Kurnatowski et al., (2014) showed that during the third week and the last day of radiotherapy the majority of patients suffered from mucositis. In a study by Durlacher., (2010) too, mucositis was the most common complication in 10–100% of the patients undergoing radiotherapy for head and neck cancers, which was attributed to or proportional to factors related to the patient, the type of the cytotoxic drugs used and the radiation dose. In addition, in a study by Taheri et al, mucositis was observed in 66.7% of the subjects during the first stage of the study, increasing to 86.7% during the second stage and to 100% in the final stage (Taheri et al., 2006). On the other hand, Hashemipour et al., (2008) reported mucositis in 83.3% of patients they evaluated. In the present study, non of subjects exhibited oral mucositis at the beginning of the study and 100% of the subjects had mucositis during the second week, which increased in severity until the end of the study.

Oral ulcers are the secondary complications of mucositis and xerostomia in patients undergoing radiotherapy of the head and neck region. In the present study, 29.1% of patients had oral ulcers during the second week, which increased to 100% at the end of the study. Taheri et al., (2006) reported oral ulcers in 30% of the patients during the second week and in the next stage, 53.3% and 90% of patients exhibited oral ulcers. Oral ulcers increase the severity of pain and burning sensation of patients, increasing interference with the normal function of the oral cavity and the risk of secondary infections.

Candidiasis is a common infection in patients undergoing radiotherapy; studies have reported an 80% rate in such patients (Taheri et al., 2006). This infection is usually manifested in the form of pseudomembranous candidiasis or the inflammation of the labial commissures.

Kurnatowski showed the presence of fungi in 66.2% of the patients before initiation of radiotherapy; however, at the third week of treatment 80% of the patients had a positive test result for fungal growth; 4–6 weeks after completion of radiotherapy only 57.1% of patients exhibited fungal infection (Kurnatowski et al., 2014).

In the present study, no apparent fungal infection was observed before treatment; however, in the second week 100% of the patients had candidiasis (thrush), which continued until the end of treatment. This finding is much more than that reported by Hashemipour (57%)

and Taheri, who showed candidiasis in only 16.7%, 20% and 33.3% of patients during different stages of treatment. The differences in the percentages reported might be attributed to differences in the clinical criteria used for the evaluation of candidiasis, the intensity of the radiation dose used in the three studies and simultaneous use of antifungal agents by the patients. Shrouf (1991) reported the presence of mild candidiasis in a number of patients, which persisted even after the end of treatment.

A disturbance in perceiving food tastes secondary to the direct effect of radiation on taste buds occurs in a number of patients, and changes in salivary flow, too, might have a role in its initiation and exacerbation (Greenberg et al., 2008). In the present study, 41.6% of the subjects reported gustatory disturbances in the second week after initiation of radiotherapy, which increased to 85.4% at the end of the study. Hashemipour et al., (2008) reported a qualitative disturbance in taste sensation in 22 patients in their study.

A limitation in mouth opening takes place with unpredictable frequency and severity after radiotherapy if masticatory muscles or TMJ are in the field of radiation, usually being manifested 3–6 months after completion of radiotherapy and persisting as a problems for life (Vissink et al., 2003; Sciubba and Goldenberg, 2006) Fibrosis and scarring of masticatory muscles, fibrosis of ligaments around the TMJ and scarring of pterygomandibular raphe on both sides, which is proportional to the source and dose of radiation, might have a role in trismus (Vissink et al., 2003; Turner et al., 2013). In the study carried out by Hashemipour et al., (2008), 30.9% of subjects exhibited grade I trismus in the first stage of the study, which turned to grade II in 45.2% of the cases and to grade III in 23.4% of cases at the end of the study. In the present study, 9 patients exhibited grade I trismus before the initiation of treatment, which was converted to grade II in the second stage and persisted until the end of the study. At the end of the second week, 81.2% of subjects exhibited grade I trismus, 42 of which (of 117 subjects) exhibited grade II trismus at the end of the study. 15 patients exhibited grade II trismus in the second stage, which was converted to grade III at the end of week 4, indicating the significance of the increase in trismus severity with an increase in the duration of irradiation and the amount of radiation received. Since placement of the pterygoid muscle in the radiation field is considered an important factor in trismus, the differences in the results of studies might be attributed to radiotherapy treatment plan (Vissink et al., 2003).

In the present study, there was no significant difference in tooth hypersensitivity between patients in different examination sessions. Such a lack of difference might be attributed to the resistance of teeth to radiation (Hashemipour et al., 2008) and absence of a significant effect of radiation on the permeability of organic components of enamel, as reported by Vissink et al., (2003).

The results of the present study showed that a large number of patients undergoing radiotherapy exhibit complications, the most common of which are mucositis, xerostomia and candidiasis. In addition, the high frequencies of oral ulcers, disturbances in taste sensation,



tooth hypersensitivity and trismus were significant in these patients.

## Acknowledgments

This study was supported by a grant of Re-search Vice Chancellor of ShahidSadoughi University of Medical Sciences (Grant No: 3,722). There is no conflict of interest in this research. Funding: This research was funded by ShahidSadoughi University of Medical Sciences, Yazd, Iran.

## References

- Alvarino-Martin C, Sarrion-Perez MG (2014). Prevention and treatment of oral mucositis in patients receiving chemotherapy. *J Clin Exp Dent*, **6**, 74-80.
- Andrews N, Griffiths C (2001). Dental complications of head and neck radiotherapy: Part 1. *Aust Dent J*, **46**, 88-94.
- Browning S, Hislop S, Scully C, Shirlaw P (1987). The association between burning mouth syndrome and psychosocial disorders. *Oral Surg Oral Med Oral Pathol*, **64**, 171-4.
- Carl W (1993). Local radiation and systemic chemotherapy: preventing and managing the oral complications. *J Am Dent Assoc*, **124**, 119-23.
- Cheng SC, Wu VW, Kwong DL, Ying MT (2011). Assessment of post-radiotherapy salivary glands. *Br J Radiol*, **84**, 393-402.
- Devita VT, Samuel JR, Rosenberg SA (2001). Oral complications. In Cancer (ed. by A. M. Berger and T. J. Kilroy), Lippincott Williams and Wilkins, Philadelphia, p 2881.
- Dijkstra PU, Kalk WW, Roodenburg JL (2004). Trismus in head and neck oncology: a systematic review. *Oral Oncol*, **40**, 879-89.
- Duncan GG, Epstein JB, Tu D, et al (2005). Quality of life, mucositis, and xerostomia from radiotherapy for head and neck cancers: a report from the NCIC CTG HN2 randomized trial of an antimicrobial lozenge to prevent mucositis. *Head Neck*, **27**, 421-8.
- Gellrich NC, Suarez-Cunquero MM, Bremerich A, Schramm A (2003). Characteristics of oral cancer in a central European population: defining the dentist's role. *J Am Dent Assoc*, **134**, 307-14.
- Ghavam M (2001). Oral lesions following radiation therapy and their preventive considerations. *J Dent Tehran Univ Med Sci*, **14**, 60-7.
- Greenberg MS, Glick M (2015). Burkett's oral medicine diagnosis and treatment Bc Decker, Hamilton, pp 201-18.
- Greenberg MS, Glick M, Ship JA (2008). Burkett's oral medicine diagnosis and treatment Mosby St. Louis, pp 48-86.
- Hashemipour M, Kakoei S, Bahador M, Arab-Solghar M (2008). The prevalence of oral complications in head and neck radiotherapy. *J Isfahan Dent Sch*, **3**, 95-104.
- Kurnatowski P, Moqbil S, Kaczmarczyk D (2014). Signs, symptoms and the prevalence of fungi detected from the oral cavity and pharynx of radiotherapy subjects with head and neck tumors, and their susceptibility to chemotherapeutics. *Ann Parasitol*, **60**, 207-13.
- Little JW, Falace DA, Miller CS, Rhodus NL (2013). Dental management of the medically compromised Patient. Mosby, St. Louis, pp 452-92.
- Newman MG, Takei HH, Carranza FA (2002). Carranza's clinical periodontology. WB Saunders, Philadelphia, pp 186-202.
- Raber-Durlacher JE, Elad S, Barasch A (2010) Oral mucositis. *Oral Oncol*, **46**, 452-456.
- Robbins MR (2000). Oral care of the patient receiving radiation therapy. In Oral Cancer, (ed. by RA Ord and RH Blanchaert). Quintessence Chicago. pp 149.
- Rodney H, McBride W (1998). Biologic basis of Radiation therapy. In Principle and practice of radiation oncology (ed. by B. L. Perez C), Lippincott-Raven, Philadelphia. p 79.
- SKP Balan A, Sankar A, Bose T (2009). Radiation induced oral mucositis. *Indian J Palliat Care*, **15**, 95-102.
- Sciubba JJ, Goldenberg D (2006). Oral complications of radiotherapy. *Lancet Oncol*, **7**, 175-83.
- Shafer WG, Hine MK, Levy BM, Tomich CE (1983). A textbook of oral pathology. WB Saunders Philadelphia, p 562.
- Shrout MK (1991). Managing patients undergoing radiation. *J Am Dent Assoc*, **122**, 69-70, 72.
- Taheri M, Najafi MH, Salehi MH (2006). Clinical evaluation of the effects of radiotherapy on oral mucosa and gingival health in radiotherapycenter of Ghaem hospital. *J Mashhad Dent Sch*, **30**, 87-98.
- Turner L, Mupparapu M, Akintoye SO (2013). Review of the complications associated with treatment of oropharyngeal cancer: a guide for the dental practitioner. *Quintessence Int*, **44**, 267-79.
- Vissink A, Jansma J, Spijkervet FK, Burlage FR, Coppes RP (2003). Oral sequelae of head and neck radiotherapy. *Crit Rev Oral Biol Med*, **14**, 199-212.
- White SC, Pharoah MJ (2014). Oral radiology principles and interpretation. Mosby, St. Louis. pp 20-4.