

## Periodontal Disease a Possible Risk Factor for Osteoradionecrosis in Patients Undergoing Radiation Therapy – A Systematic Review

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### Abstract

**Background:** Poor oral hygiene is one of the factor leading to periodontal disease. The effect of radiation therapy on periodontal health is dose dependent and is associated with poor periodontal health before radiotherapy initiation. Osteoradionecrosis, a serious dental complication is often seen in individuals undergoing radiation therapy; especially in individuals with poor oral hygiene.

**Aim:** To analyze the association of osteoradionecrosis with periodontal disease in oral cancer patients receiving radiation therapy.

**Materials and methods:** An electronic database search was performed at PubMed, Google Scholar, EBSCO Host, EMBASE and Science Direct from August 2021 to January 2022.

**Results:** Ninety-seven articles were identified on searching the electronic databases. Only two randomized controlled clinical trials and two case reports qualified for the qualitative synthesis. The included studies were assessed for the risk of bias.

**Conclusion:** Periodontal disease is a possible risk factor for osteoradionecrosis individuals with oral cancer undergoing radiation therapy. However there remains a need for conducting studies to further evaluate the association between osteoradionecrosis and periodontal disease.

**Keywords:** Oral cancer, Osteoradionecrosis, Periodontal disease, Radiation therapy

**Key messages:** Oral cancer patients undergoing radiation therapy may have difficulty in maintaining oral hygiene, thereby resulting in progression of periodontal disease. Proper oral hygiene maintenance protocol needs to be followed for patients with oral cancer undergoing radiation therapy.

### Introduction:

Periodontal disease (Periodontitis) is an inflammatory condition of gums and the teeth supporting tissues.<sup>1</sup> It is characterized by the destruction of connective tissue and dental bone support subsequent to infection by microorganisms.<sup>2</sup> Periodontitis has been considered as a risk factor for Osteoradionecrosis (ORN).<sup>1</sup>

Radiotherapy (RT) is one of the mainstays of treatment for any type of carcinomas. For oral cavity cancer, RT is often used in the postoperative setting after surgical resection. ORN is still one of the most serious dental complications in cancer patients who receive RT, and often occurs in patients with poor oral hygiene.

ORN is defined as exposed irradiated bone tissue that fails to heal over a period of 3 months without a residual or recurrent tumor.<sup>3</sup> Marx, described ORN as “a complex metabolic and homeostatic deficiency of tissue that is created by radiation-induced cellular injury; microorganisms play only a contaminating role in ORN, and trauma may or may not be an initiating factor.”<sup>4</sup>

The effect of radiation therapy on periodontal health is dose dependent. The local effect on periodontal tissue when high dose fraction of radiation is used, involves alterations in the cellularity, vascularity and reduced healing/remodeling potential of the periodontium.<sup>5</sup>

### Rationale:

Radiation therapy is one of the most routinely performed treatment in cancer patients. This may lead to the radiation induced disease known as osteoradionecrosis. The patients suffering from oral cancer also have difficulty in maintaining oral hygiene, thereby leading to periodontal disease. However, to our knowledge, there is limited literature available that assesses the role of periodontal disease as possible risk factor for development of osteoradionecrosis in patients with oral cancer undergoing radiation therapy. The purpose of this study was to evaluate whether ORN is associated with periodontal disease in individuals with oral cancer undergoing Radiation Therapy.

**Focused question:** Is periodontal disease a possible risk factor for osteoradionecrosis in patients undergoing radiation therapy?

**Another research question:** Does treatment of periodontal disease in osteoradionecrosis patients undergoing radiation therapy reduce further complications?

**Primary objective:** To evaluate the association of periodontal disease as a possible risk factor for osteoradionecrosis in patients undergoing radiation therapy.

**Secondary objective:** To analyze the role of periodontal disease on osteoradionecrosis in patients undergoing radiation therapy.

#### Materials and methods:

**Protocol and Registration:** The protocol was registered at: <https://crd.york.ac.uk>

**Prospero Registration number:** [CRD42022302572](https://doi.org/10.1111/crd.12302)

**Study design:** The present systematic review of case-control studies, cohort studies, randomized controlled trials, experimental studies and case reports was conducted to assess and analyze the existing evidence on role of periodontal disease on osteoradionecrosis in patients undergoing radiation therapy.

#### Inclusion criteria:

1. Case-control studies, cohort studies, randomized controlled trials, experimental studies and case reports.
2. Articles published in peer-reviewed journals in English.
3. Oral cancer patients undergoing radiation therapy.

#### Exclusion criteria:

1. Narrative and Literature Review articles
2. Animal model studies and in vitro studies
3. Head and neck cancer patients
4. Unpublished research.

#### Information sources & search strategy:

An electronic database search for case-control studies, cohort studies, randomized controlled trials, experimental studies and case reports published in English language in peer-reviewed Journals was conducted from the following

electronic databases: PubMed, Google Scholar, EBSCO Host, EMBASE and Science Direct.

#### The following terms were used for search:

Periodontal disease “OR” Periodontitis “OR” Gingivitis “AND” Osteoradionecrosis “OR” Oral cancer “OR” Radiation therapy Periodontitis “AND” Osteoradionecrosis Periodontal disease “AND” Radiation therapy “AND” osteoradionecrosis Oral cancer “AND” Periodontitis “AND” Osteoradionecrosis

#### Study selection:

Three reviewers participated in the study selection process and no duplicate data was extracted. Inter-observer reliability was achieved by calibration sessions until an almost perfect agreement was obtained. Hence there was no disagreement between the reviewers.

Study selection was carried out in two phases:

- i. Assessment of titles and abstracts
- ii. Assessment of full text.

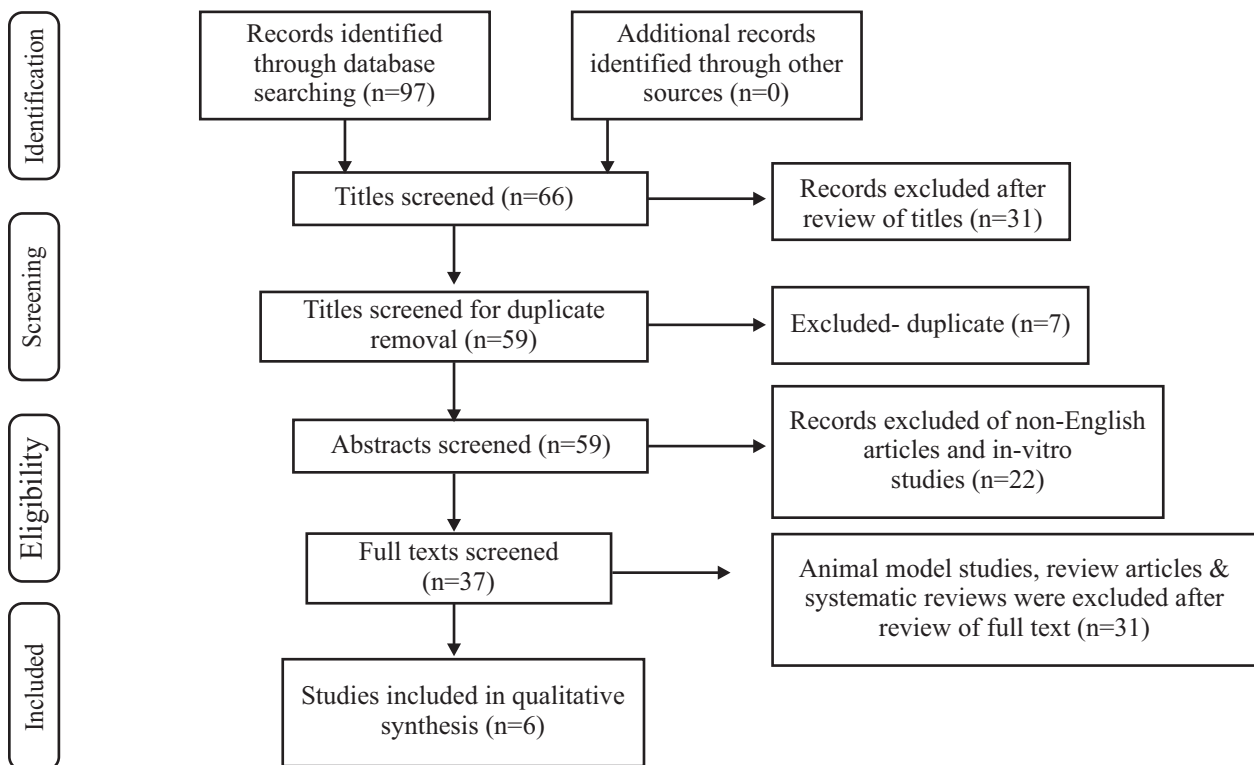
#### Data extraction process:

Data extraction sheet was prepared based on variables associated, and the articles were analyzed. Using data extraction sheet, the following data were collected: authors, year of publication, country, aim, type of study, sample size, comparison group and control group, methodology and conclusion.

**Data items:** Variables for which data was sought included Periodontal disease, Osteoradionecrosis.

1. **Periodontal disease (PD)** – Periodontal disease is defined as “an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or groups of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with increased probing depth formation, recession, or both.”
2. **Osteoradionecrosis (ORN)** – Osteoradionecrosis is an inflammatory condition of bone that occurs after the bone has been exposed to therapeutic doses of radiation usually given for a malignancy.

Figure 1: Flow chart of literature search results and study selection

**Results:**

A total of 97 articles were found after electronic search. Thirty one articles were excluded after review of titles. After excluding duplicates, abstracts of 59 articles were screened. Subsequently, 22 articles were excluded as they were in different language other than English and were in vitro studies. Thirty one articles were excluded as they did not fulfill the eligibility criteria. Six articles were included for qualitative

synthesis. Figure 1 shows the flow chart of literature search results and study selection.

**Studies included for the analysis**

Six studies were included for the qualitative synthesis. Out of the 6 studies, 2 were randomized clinical trials and 4 were retrospective cohort studies. Table 1 shows characteristics of the studies included in the systematic review.

Table 1: Characteristics of included studies:

Author and year of publication	Country	Aim	Type of cancer	Type of study	Sample size, comparison group & control group	Methodology	Conclusion
Satheeshkumar PS, Chamba MS, Balan A, Sreelatha KT, Bhatathiri VN, Bose T. (2010) <sup>6</sup>	India	1) To determine the effectiveness of triclosan in the management of radiation induced oral mucositis. 2) To compare the effectiveness of triclosan mouth rinse with conventional sodium bicarbonate mouth rinse	Oral cancer	Randomized Clinical trial	Twenty-four patients Test group: Triclosan 0.03% W/V mouthwash Control group: Sodium bicarbonate 2 mg mouth wash	Twenty-four patients who underwent radiation therapy for oral cancer and subsequently developed oral mucositis were included in the study. They were randomly allocated into two groups on noticing grade I mucositis (erythema). The	Triclosan mouthwash was found to be effective in reducing the severity of radiation-induced oral mucositis and helped in early reversal of symptoms during post treatment period.

Table 1: Characteristics of included studies:

study group was advised to use triclosan mouthwash containing triclosan 0.03% W/V and sodium bicarbonate 2 mg mouth wash for the control group. A weekly follow-up evaluation of body weight, food intake, pain and grading of mucositis were made during the radiation treatment period and post radiation treatment period.

**Studies excluded from the analysis:** 6 studies were excluded as they were review articles. An overview of the excluded studies is presented in Table 2.

Table 2: Characteristics of excluded studies

Author (year)	Reason for exclusion
Madrid C, Abarca M, Bouferrache K (2010) <sup>3</sup>	Narrative review
Haroun K, Coblens OM (2019) <sup>10</sup>	Narrative review
Abed H, Burke M, Scambler S, Scott SE (2020) <sup>11</sup>	Systematic review

Author and year of publication	Country	Aim	Type of cancer	Type of study	Sample size, comparison group & control group	Methodology	Conclusion
Kojima Y, Otsuru M, Hasegawa T, Ueda N, Kirita T, Yamada S, et al (2021) <sup>14</sup>	Japan	To evaluate the risk factors for ORN including tooth extraction before RT.	Oral cancer	Retrospective cohort study	Three hundred and sixty-six patients	Three hundred and sixty-six patients were investigated retrospectively with head and neck cancer who underwent RT exceeding a dose of 50 Gy at six hospitals between 2008 and 2018. All patients underwent panoramic radiographic examination, necessary tooth extractions as much as possible, oral hygiene	During RT for oral or oropharyngeal cancer, apical lesions, alveolar bone loss of more than 50%, and post-RT tooth extraction significantly increase the risk of ORN development, and extraction of the infected tooth or the tooth with a poor prognosis significantly reduces the risk.

To be Cont..

Table 2: Characteristics of excluded studies

						instructions, removal of dental calculus, and professional mechanical teeth cleaning by a dentist and dental hygienist before RT. Endpoints were the onset and timing of ORN, and background factors.	
Khoo SC, Nabil S, Fauzi AA, Yunus SSM, Ngeow WC and Ramli R et al (2021) <sup>15</sup>	Malaysia	To determine the predictors of osteoradionecrosis (ORN) which were associated with a dental extraction post radiotherapy.	Head and neck cancer	Retro-spective cohort study	Seventy-three patients	A retrospective analysis of medical records and dental panoramic tomogram (DPT) of patients with a history of head and neck radiotherapy who underwent dental extraction between August 2005 to October 2019 was conducted. It was conducted in two university hospitals in Malaysia: Oral and Maxillofacial Surgery Clinic, University Kebangsaan Malaysia Medical Centre (UKMMC) and Faculty of Dentistry, University of Malaya (FDUM).	The prevalence of ORN following a dental extraction was 21.9%. Dental extraction of more than five years after RT, surgical removal procedure and the upper cortical line of mandibular canal being invisible were the predictors of ORN post extraction.
Foote RL, Loprinzi CL, Frank AR, O'Fallon JR, Gulavita S, Tewfik HH, et al (1994) <sup>9</sup>	United States	To determine whether a chlorhexidine mouthwash could alleviate radiation-induced oral mucositis.	Oral cancer	Randomized trial	25 patients Test group: Chlorhexidine mouthwash Control group: Placebo mouthwash	Patients scheduled to receive radiation therapy to include greater than one third of the oral mucosa were selected for study. Following stratification, they were randomized in a double-blind manner to receive a chlorhexidine mouthwash or a placebo	Chlorhexidine mouthwash might provide benefit for patients receiving radiation therapy to the oral mucosa, they provided strong evidence concluding that a chlorhexidine mouthwash is detrimental in this clinical situation.

Table 2: Characteristics of excluded studies

						mouthwash. Both groups were then similarly evaluated for mucositis and mouthwash toxicity.	
Ito K, Takumi K, Meibom SK, Qureshi MM, Fujima N, Andreu-Arasa VC (2020) <sup>1</sup>	USA	To evaluate whether 18F-FDG PET/CT can predict ORN associated with periodontal disease in patients with oropharyngeal or oral cavity squamous cell carcinoma (OP/OC SCC) undergoing RT.	Oral cancer	Retro-spective cohort study	One hundred and five	One hundred and five OP/OC SCC patients treated with RT who underwent pretreatment F-FDG PET/CT between October 2007 and June 2016 were retrospectively reviewed. A post-treatment diagnosis of ORN was made clinically based on presence of exposed irradiated mandibular bone that failed to heal after a period of three months without persistent or recurrent tumor. The maximum standardized uptake value (SUVmax) of periodontal regions identified on PET/CT was measured for all patients. Image-based staging of periodontitis was also performed using American Academy of Periodontology staging system on CT	Pretreatment F-FDG PET/CT identification of periodontitis may be helpful to predict the future development of ORN in patients with OP/OC SCC undergoing RT.
Chang C, Liu S, Muo C, Liao Y, Chiu K, Tsai C, et al (2022) <sup>17</sup>	Taiwan	To investigate how different timelines of various dental therapies were related to osteoradionecrosis development under consideration of	Oral cancer	Retro-spective cohort study	Seven thousand one hundred and seven	A total of 7,107 oral cancer patients were enrolled, including 88 osteoradionecrosis patients treated with low radiotherapy dosages (<60 Gy)	Patients that were treated with high irradiation dosages (≥60 Gy) had a higher tendency to develop osteoradionecrosis if they received dental surgery during



To be Cont..

Table 2: Characteristics of excluded studies

radiotherapy dosage in patients with oral cancer.	or high radiotherapy dosages ( $\geq 60$ Gy), from the Longitudinal Health Insurance Database for Catastrophic Illness Patients of Taiwan. Cox proportional hazard regression was used to compare the osteoradionecrosis risk of various dental treatment time lines under different irradiation dosages.	radiotherapy. Those who were treated with low radiation dosages ( $< 60$ Gy) and received periodontal therapy during radiotherapy might have an increased risk in developing osteoradionecrosis.
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**Assessment of risk of bias in included studies**

This assessment was conducted using the recommended approach for assessing the risk of bias in studies included in Cochrane Reviews (Higgins 2011) using the RevMan 5.0 tool for randomized controlled trials and Robin tool for non-randomized controlled trials (retrospective studies). We used the two-part tool to address the six specific domains (namely random sequence generation, allocation concealment,

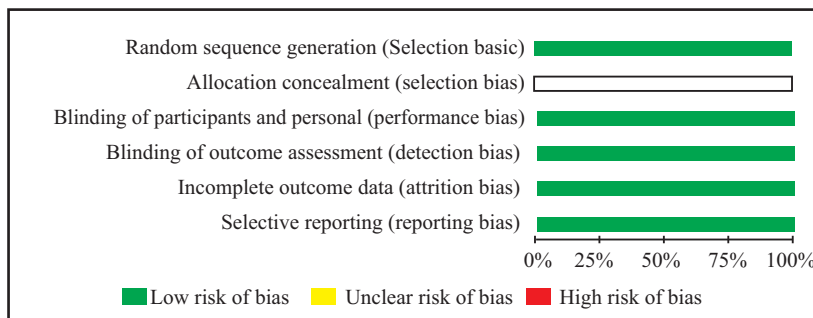
blinding, incomplete outcome data, selective reporting and other bias). Each domain includes one or more specific entries in a risk of bias table. Within each entry, the first part of the tool involves describing what was reported to have happened in the study. The second part of the tool involves assigning a judgment relating to the risk of bias for that entry: either low risk, unclear risk or high risk. The risk of bias of the included studies is presented in Table 3 & 4 and Graphs 1, 2.

Table 3: Risk of bias assessment for RCT studies

Sr No.	Authors (Year)	Type of study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome	Incomplete outcome data	Selective reporting
1	Satheeshkumar PS et al (2010)	RCT	Low	Unclear	Low	Low	Low	Low
2	Foote RL et al (1994)	RCT	Low	Unclear	Low	Low	Low	Low

Table 4 : Risk of bias assessment for Non-RCT studies

Sr No	Author (Year)	TYPE OF STUDY	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
1	Kojima Y et al	Retrospective cohort study	Yes	No	Unclear	Yes	No	Yes	Unclear
2	Khoo SC et al (2021)	Retrospective cohort study	No	No	No	Yes	Yes	Yes	Yes
3	Ito K et al (2020)	Retrospective cohort study	No	No	No	No	No	No	No
4	Chang C et al (2022)	Retrospective cohort study	No	No	No	No	No	No	No



Graph 1: Risk of Bias Assessment - Part 1

	Satheeshkumar PS et al (2010)	Footte RL et al (1994)
Random sequence generation (selection bias)	+	+
Allocation concealment (selection bias)		
Blinding of participants and personnel (performance bias)	+	+
Blinding of outcome assessment (detection bias)	+	+
Incomplete outcome data (attrition bias)	+	+
Selective reporting (reporting bias)	+	+

Graph 2: Risk of Bias Assessment - Part 2

**Discussion**

Osteoradionecrosis is bone death due to radiation. In a review by Singh A et al (2022)<sup>13</sup>, it was stated that one of the alarming complication of radiation therapy of the head and neck region was osteoradionecrosis with clinical signs such as exposed bone area, formation of a fistula, mobility of tooth/teeth and/or spontaneous exfoliation of tooth/teeth. Hypoxia, hypovascularity and hypocellularity resulted due to radiation induced endarteritis for which hyperbaric oxygen therapy was used for osteoradionecrosis patients as well. Such conditions are favorable for the growth of anaerobic microorganisms and thereby forming subgingival periodontal pocket formation hence suggesting periodontitis having role in osteoradionecrosis.

Xerostomia or dry mouth is a routinely observed side effect of cancer treatment, which is found most frequently among patients undergoing targeted radiotherapy especially in oral cancer patients. Dry mouth is also common among patients taking certain chemotherapy regimens (anti-sialagogue) known to decrease salivary secretion and thereby result in dry

mouth. Even the available evidence is limited, with patients on certain drugs known to include salivary gland hypofunction.<sup>16</sup> Association of all these factors lead to poor oral hygiene and thereby result in periodontal disease. Therefore, periodontal disease is considered as a possible risk factor for development of osteoradionecrosis in patients undergoing radiation therapy.

The present systematic review outlines the observations of the studies that evaluated whether osteoradionecrosis is associated with periodontal disease in individuals having oral cancer and receiving radiation therapy. There were few studies available, which evaluated the role of periodontal disease on radiation induced osteoradionecrosis. In-vitro studies, animal studies, review articles were excluded as they provide low level of evidence.

Six studies were considered for qualitative synthesis, in which 2 studies were randomized clinical trials and 4 were retrospective cohort studies.

Satheeshkumar PS et al (2010)<sup>6</sup> assessed subjects who developed mucositis after they underwent radiation therapy for oral cancer. Twenty-four subjects were randomly divided into two groups, one receiving triclosan mouthwash and other



sodium bicarbonate mouthwash. They concluded that the severity of radiation-induced oral mucositis reduced after using Triclosan mouthwash.

Foote RL et al (1994)<sup>9</sup> included subjects who were scheduled to undergo radiation therapy. The subjects were randomized into two groups by double-blinding to receive either placebo mouthwash or chlorhexidine mouthwash. They concluded that in individuals undergoing radiation therapy chlorhexidine mouthwash might provide benefit in reducing oral mucositis.

Kojima Y et al (2022)<sup>14</sup> conducted a study to evaluate risk factor of tooth extraction before radiation therapy. They found out that oral problems such as caries, poor oral hygiene and periodontal disease were known to induce osteoradionecrosis, hence treatment of all these factors before radiation therapy is mandatory. One of the most common oral cancers is squamous cell carcinoma. Radiation therapy has been routinely used for treatment of oral cancer. Hence, an association of periodontal disease as a possible risk factor for osteoradionecrosis in patients undergoing radiation therapy can be suggested.

In a study by Khoo et al (2021)<sup>15</sup>, individuals who underwent extraction after radiation therapy, who were at risk for development of osteoradionecrosis (ORN) were included. They stated that dental extraction of more than five years after RT, surgical removal procedure and the invisible upper cortical line of mandibular canal being were the risk factors of ORN post extraction. Hence, extraction of teeth due to severe periodontal destruction may contribute to development of osteoradionecrosis.

Ito K (2020)<sup>1</sup> studied one hundred and five oral cancer patients treated with RT who underwent pretreatment F-FDG PET/ CT. They performed image-based staging of periodontitis using American Academy of Periodontology staging system on CT. They concluded that pretreatment F-FDG PET/CT identification of periodontitis may be helpful to predict the future development of ORN in patients with oral cancer undergoing RT.

Chang C (2022)<sup>17</sup> studied 7107 patients treated with low radiotherapy dosages (<60 Gy) or high radiotherapy dosages ( $\geq 60$  Gy) to compare the osteoradionecrosis risk of various dental treatment timelines under different irradiation dosages. They concluded that those who were treated with low radiation dosages (<60 Gy) and received periodontal therapy during radiotherapy might have an increased risk in developing osteoradionecrosis

The risk of bias was low for both the randomized clinical trials except for unclear allocation concealment. Based on the studies assessed, it was observed that poor oral hygiene leading to periodontal disease could be a possible risk factor

for osteoradionecrosis. Hence, maintenance of oral hygiene and periodontal health is essential to minimize the risk of osteoradionecrosis in individuals undergoing radiation therapy for oral cancer. Also, they reported that chlorhexidine mouthwash was found to be effective in the periodontal management of patients suffering from osteoradionecrosis.

A scope for conducting randomized clinical studies in future may be helpful in establishing the association between periodontal disease and osteoradionecrosis. Further, the awareness of good oral hygiene maintenance among individuals, especially those undergoing radiation therapy for oral cancer has to be stressed upon to minimize the risk of osteoradionecrosis and its subsequent complications.

### Conclusions

Periodontal disease develops very commonly in patients suffering from oral cancer because of difficulty in maintaining proper oral hygiene due to inadequate mouth opening. Radiation therapy is carried out in such patients as a treatment modality after chemotherapy is performed. This leads to development of osteoradionecrosis in few patients. Hence, it can be concluded that periodontal disease is a possible risk factor for osteoradionecrosis in patients undergoing radiation therapy.

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