

Antibiotic therapy for the prevention of osteoradionecrosis following tooth extraction in head-and-neck cancer patients postradiotherapy: An 11-year retrospective study

ABSTRACT

Introduction: One of the most important complications of radiotherapy (RT) for head-and-neck cancer (HNC) is osteoradionecrosis (ORN) of the jaws, which mostly arises from tooth extractions. The ORN treatment still represents a great challenge; therefore, the prevention is of paramount importance. Thus, the present study aimed to evaluate retrospectively a perioperative systemic antibiotic therapy protocol for the prevention of ORN following tooth extraction in head-and-neck patients post-3D conformal RT.

Materials and Methods: A retrospective medical record review was performed considering HNC patients submitted to RT in the period between 2008 and 2019. They necessarily received oral antibiotic therapy with Clindamycin 300 mg every 8 h for 10 days, with the first dose 3 days before the tooth extraction.

Results: Forty-nine patients met the study criteria, with a total of 107 teeth extracted. Regarding the 47 patients who did not develop ORN, 103 tooth extractions were identified (96.3%). Only two patients developed ORN at two adjacent teeth sites (3.7%).

Conclusion: The proposed perioperative systemic antibiotic therapy protocol seems to be efficient to prevent ORN following tooth extraction in postirradiated HNC patients.

Keywords: Head-and-neck cancer, osteoradionecrosis, radiotherapy, tooth extraction

INTRODUCTION

The treatment for head-and-neck cancer (HNC) is based on radiotherapy (RT), chemotherapy, and surgery. According to the disease stage and location, such therapeutic modalities may be combined or not.^[1,2] RT aims to control or eliminate tumors while preserving normal tissues; however, nonneoplastic cells included in or close to the irradiation fields suffer radiation-induced damages as well.^[3] Thus, a wide range of clinical complications occurs during and/or after the RT course, affecting negatively patients' quality of life and oral functions.^[4]

One of the most recognized, severe, and debilitating RT complication is osteoradionecrosis (ORN) of the jaw,^[5] first reported about 100 years ago.^[6] The most accepted ORN definition is characterized by exposed devitalized irradiated bone that fails to heal over a period of 3 months without

local tumor recurrence.^[7] Although it has been declining in recent years, thanks to technological advances in radiation

LUIZ FELIPE PALMA¹, MARCELO MARCUCCI², CÍNTIA MARIA REMONDES², LEANDRO CHAMBRONE^{1,3,4}

¹Graduate Dentistry Program, Ibirapuera University, ²Stomatology and Oral and Maxillofacial Surgery Center, Hospital Heliópolis, São Paulo, São Paulo, Brazil, ³Evidence-Based Hub - CiiEM, Egas Moniz - Cooperativa de Ensino Superior, Caparica, Almada, Portugal, ⁴Unit of Basic Oral Investigation (UIBO), Faculty of Dentistry, Universidade El Bosque, Bogota, Colombia


Address for correspondence: Dr. Luiz Felipe Palma, Av. Interlagos, 1329 - Chácara Flora, São Paulo 04661-100, SP, Brazil.
E-mail: luizfelipep@hotmail.com

Received: 05 June 2021, **Revised:** 15 July 2021, **Accepted:** 26 August 2021, **Published:** 13 December 2021

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Palma LF, Marcucci M, Remondes CM, Chambrone L. Antibiotic therapy for the prevention of osteoradionecrosis following tooth extraction in head-and-neck cancer patients postradiotherapy: An 11-year retrospective study. *Natl J Maxillofac Surg* 2021;12:333-8.

Access this article online	
Website: www.njms.in	Quick Response Code 
DOI: 10.4103/njms.njms_413_21	

oncology,^[8,9] ORN incidence still ranges from 2% to 22% in the literature.^[6]

ORN is prevalent after total radiation doses higher than 60 Gy, when delivered alongside chemotherapy,^[6] and at the first 3 years post-RT (70% incidence rate).^[7] In addition, the mandible is more affected than the maxillae probably as a result of decreased and poor vascularity, higher bone density,^[10] thinner mucosa, and intense bone remodeling in response to mechanical occlusal forces.^[7]

Tooth extraction is considered to be the main initiating factor for ORN, but it may also occur spontaneously due to residual foci of periodontal or periapical disease and trauma resulting from poorly adapted prostheses.^[11,12] Despite the continuous debate in the literature, most authors have generally recommended performing tooth extractions between 10 and 14 days before RT.^[13] Some patients, however, will require tooth extractions during or after the RT course.^[14] In these cases, prophylactic measures are used,^[15] but a lot of information about this subject is based more on folklore than evidence.^[13]

The aim of the present study is to evaluate retrospectively a perioperative systemic antibiotic therapy protocol for the prevention of ORN following tooth extraction in postirradiated HNC patients.

MATERIALS AND METHODS

Study design and ethical issues

A retrospective analysis was carried out with medical records from the Stomatology and Oral and Maxillofacial Surgery Center at Heliópolis Hospital (São Paulo, SP, Brazil). The present study was performed in accordance with the declaration of Helsinki and received approval from the local research ethics committee (CAAE 82947318.4.0000.5449). The patients read and signed the informed consent form.

Selection of patients and data collection

All the available medical records from 2008 to 2019 were evaluated to identify patients who had undergone 3D conformal RT for HNC (cervicofacial and supraclavicular fossa fields) and submitted to tooth extraction later.

Perioperative systemic antibiotic therapy protocol

All the patients took a 300 mg dose of clindamycin, three times daily, for a total of 10 days. The first dose was taken 3 days before surgery.

Statistical analysis

The data from patients, tumors, and oncologic treatments were gathered, as well as details about the tooth extractions,

ORN development, and the proposed therapeutic approaches. Descriptive statistical analysis was used to summarize and present the data. The Chi-square test with continuity correction was applied to check the association between the variables and ORN development, considering a $P < 0.05$ as statistically significant.

RESULTS

Overall: Patients and tooth extractions

Forty-nine patients met the study criteria, with a total of 107 teeth extracted.

Outcome: Normal healing

Forty-seven patients underwent tooth extraction and did not develop ORN. The patients' average age was 61.7 years (± 9.7), ranging from 44 to 82, and with a median of 59. Additional data on the patients are shown in Table 1 and information on the tumors and oncologic treatments in Table 2.

One hundred and three tooth extractions were identified (96.3%), located predominantly in maxillae and molar tooth sites [Table 3]. In relation to the period after RT completion, most procedures were performed between 1 and 2 years later [Table 4].

Outcome: Osteoradionecrosis

Two middle-aged male patients developed ORN following extractions of two adjacent teeth (3.7%). Similarly, both had a history of previous alcohol abuse, underwent oncologic surgery, and did not receive chemotherapy.

Case 1

A 53-year-old Afro-descendant patient received a total radiation dose of 66 Gy for a parotid gland myoepithelial carcinoma.

Table 1: Patients' additional demographic data

	Patients (n=47), n (%)
Sex	
Female	6 (13)
Male	41 (87)
Skin color/ethnicity	
Brown	9 (19)
White	30 (64)
Black	7 (15)
Yellow	1 (2)
Alcohol use	
No	10 (21)
Previous	28 (60)
Current	9 (19)
Tobacco use	
No	5 (11)
Previous	26 (55)
Current	16 (34)

He was submitted to tooth extractions of the second and third left mandibular molars in a period between 2 and 3 years from RT completion. The initial treatment proposed was conservative in essence, based on antibiotic therapy, simple and localized debridement of nonviable tissues, periodic irrigations, and low-level laser therapy. The patient has been under clinical observation for approximately 5 years, with intermittent periods of stabilization or even a slight improvement. Figure 1 presents the patient's radiographic evolution over the years, from the presurgical appointment for tooth extractions to the present day.

Case 2

A 56-year-old Caucasian patient, ex-smoker, received a total radiation dose of 70 Gy for an oral squamous cell carcinoma.

Table 2: Patients' tumor and oncologic treatment

	Patients (n=47), n (%)
Primary tumor location	
Oral cavity	14 (30)
Pharynx	15 (32)
Larynx	16 (34)
Occult primary	1 (2)
Parotid gland	1 (2)
Histological type	
Squamous cell carcinoma	46 (98)
Carcinoma expleomorphic adenoma	1 (2)
Total radiation dose (Gy)	
50	1 (2)
60-61	11 (23)
63-67	14 (30)
70	21 (45)
Chemotherapy	
No	24 (51)
Cisplatin	13 (28)
Paclitaxel	9 (19)
Cisplatin and paclitaxel	1 (2)
Oncologic surgery	
No	23 (49)
Yes	24 (51)

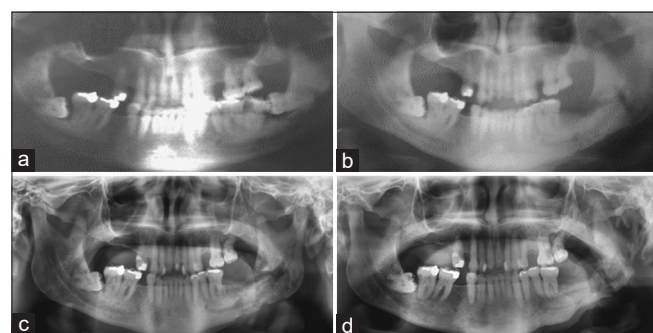


Figure 1: Osteoradionecrosis Case 1- Radiographic evolution over 5 years approximately. (a) Analog radiograph for tooth extraction planning. (b) Analog radiograph, 6 months after extraction. (c) Digital radiograph, 12 months after extraction. (d) Digital radiograph, 5 years after extraction (present-day)

He was submitted to tooth extractions of the left mandibular canine and first premolar in a period of up to a year from RT completion. The initial treatment proposed was conservative in essence, based on antibiotic therapy, simple and localized debridement of nonviable tissues, periodic irrigations, and low-level laser therapy; however, the condition progressed unsatisfactorily, leading to a pathological mandibular fracture. He thus underwent hemimandibulectomy and has been asymptomatic and under clinical observation for approximately 3 years. Figure 2 presents the patient's radiographic evolution over the years, from the presurgical appointment for tooth extractions to the pathological mandibular fracture.

Osteoradionecrosis × variables

Regarding ORN development, no statistically significant difference was obtained for gender ($P = 0.59$), skin color/ethnicity ($P = 0.587$), alcohol ($P = 0.517$) or tobacco use ($P = 0.210$), total radiation dose ($P = 0.991$), chemotherapy ($P = 0.605$), oncologic surgery ($P = 0.174$), tooth extracted ($P = 0.177$), and period after RT completion ($P = 0.427$). Primary tumor location ($P = 0.015$), histological type ($P = 0.000006$), and mandibular involvement ($P = 0.027$) were statistically significant.

DISCUSSION

This study investigated retrospectively whether the proposed antibiotic therapy protocol is effective for the prevention of ORN following tooth extraction, according to its strictly clinical definition.^[10] There is a large discrepancy in the literature concerning ORN incidences (range 0.4%–56%);^[10] however, the presented rate (3.7%) was lower than the most reported ones (5%–15%).^[7] The current study can thus be considered of clinical relevance, given the ORN treatment difficulties and associated symptoms, which vary from localized mild algesia, dysesthesia, and halitosis to

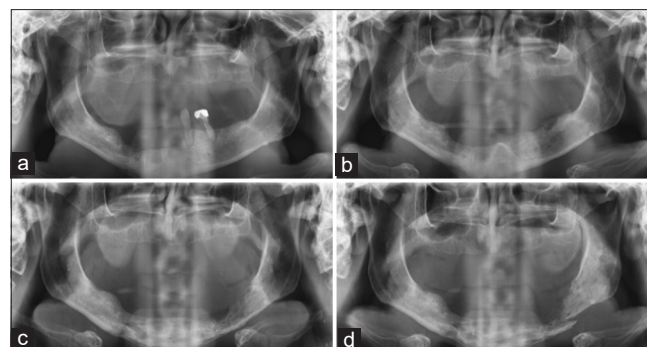


Figure 2: Osteoradionecrosis Case 2 - Radiographic evolution over 3 years approximately. (a) Digital radiograph for tooth extraction planning. (b) Digital radiograph, 6 months after extraction. (c) Digital radiograph, 12 months after extraction. (d) Digital radiograph, a year after extraction. Note the pathological fracture

Table 3: Teeth extracted at sites without osteoradionecrosis development

	Tooth extraction (n=103), n (%)
Maxilla	
Incisives	16 (16)
Canines	4 (4)
Premolars	13 (13)
Molars	25 (24)
Mandible	
Incisives	17 (17)
Canines	5 (5)
Premolars	9 (9)
Molars	14 (14)

Table 4: Period between radiotherapy completion and tooth extraction in cases without osteoradionecrosis development

Period (years)	Tooth extraction (n=103), n (%)
Up to a year	20 (19)
1-2	24 (23)
2-3	10 (10)
3-4	8 (8)
4-5	9 (9)
5-6	2 (2)
6-7	3 (3)
7-8	11 (11)
8-9	4 (4)
9-10	5 (5)
Over 10	7 (7)

severe pain, orocutaneous fistulas, and even pathological fractures^[16] - as seen in the second case.

Taking into account the theory of ORN pathophysiology that suggests a subsequent infection after local trauma in the bone previously exposed to ionizing radiation,^[6] perioperative systemic antibiotic administration seems to be essential. Despite little evidence to support the prevention of alveolitis and infections in nonirradiated individuals and the possible adverse effects, any small clinical benefit would justify the prophylactic antibiotic therapy, considering ORN morbidity and severity.^[14] Moreover, antibiotics are easy to administer and widely available.^[11]

Studies with different antibiotic therapy approaches to prevent ORN after tooth extraction have reported variable success rates, but the lack of protocols and clinical standards regarding the drug of choice, dosages, duration, and administration period hampers the clinical decision-making.^[17] Al-Bazie *et al.*^[12] combined chlorhexidine mouthwashes with amoxicillin (500 mg, three times daily), starting it 10 days before tooth extraction and continuing for 7 days and reported a 100% success rate. Maxymiw *et al.*^[18] proposed a protocol based on 2 g of penicillin V

an hour before surgery and 600 mg four times daily for 7 days, and no case of ORN was seen. On the other hand, Lye *et al.*^[19] observed a 1.9% ORN rate when 2 g of penicillin V (or 600 mg of clindamycin for penicillin-allergic patients) was administered an hour before surgery and prolonged for 7 days in combination with metronidazole (or clindamycin only) and chlorhexidine mouthwashes.

Despite the conflicting results and a slight preference for a drug from the penicillin family, since these are effective against most oral bacteria,^[14] clindamycin was adopted in the current study. It is active against most strains of *Staphylococcus aureus*, several other Gram-positive cocci and gram-negative anaerobic pathogens,^[20] besides being a good option for β -lactam-allergic patients and available for free in the Brazilian Public Health System-SUS. Furthermore, clindamycin provides good penetration into bone tissue and has been historically successful in the treatment of osteomyelitis.^[20]

The clindamycin prescribed dosage (300 mg every 8 h) followed the usual recommendations (150–300 mg, three times daily) for the treatment of odontogenic infections in adults.^[21] Concerning the proposed period of antibiotic therapy, some patients were submitted to tooth extraction as the only possible treatment for acute dentoalveolar infection, justifying then the beginning of antibiotic administration 72 h before the procedure and the subsequent maintenance for further 7 days, as suggested by some authors.^[12,18,19] It is important to point out that the administration of clindamycin for periods >10 days is thought to be highly associated with the development of *Clostridium difficile* infection in hospitalized patients,^[21] the rationale behind the total period of antibiotic therapy herein used. Furthermore, a very recent study conducted by this same group showed that the protocol was strongly effective in ORN prevention, both using or not a platelet concentrate concomitantly.^[22]

In relation to both ORN cases herein presented, some risk factors in common may be identified such as mandibular involvement, total radiation dose >60 Gy,^[7] and male^[5] middle-aged patients;^[23] however, a patient had completed the RT course before 2 years from the extractions, the most critical period.^[7] Curiously, both of them did not receive chemotherapy and were no longer tobacco and alcohol users, conditions related to a higher risk for ORN development.^[7]

Although the present results are encouraging, they should be interpreted with caution. Some factors that would increase the risk of ORN such as the period between RT completion and tooth extraction,^[13] concomitant chemotherapy,^[24]

current alcohol and tobacco use,^[7,8] and absence of accurate data on the total radiation dose delivered to each tooth extraction site^[25] may be considered as study bias. In this way, only medical records from patients who underwent 3D-conformal RT with cervicofacial and supraclavicular fossa fields were enrolled, a fact that makes the sample less prone to large radiation variations in the maxillae and mandible and provides strong evidence that tooth extraction sites received substantial radiation doses. Because intensity-modulated RT, another radiation delivery technique used for HNC treatment, deposits radiation more precisely to the tumor and spares substantially surrounding normal tissues,^[6,8] all the patients submitted to it were excluded from the analysis.

Another limiting factor of this study was the lack of standardization of surgical techniques and procedures as tooth extractions were performed routinely by different surgeons and under adverse clinical situations and conditions. Some preventive factors for ORN applied during tooth extraction have already been suggested and it seems to be reasonable to incorporate them into the daily surgical routine (e.g. atraumatic surgical technique, alveolectomy with careful bone trimming, primary closure without tension, removal of few teeth per session,^[26] minimal periosteal stripping, epinephrine-free local anesthesia, and perioperative chlorhexidine mouthwashes).^[12] As it was a retrospective study carried out in a big Health Public Center, a lot of information about the surgical procedures and these preventive measures was missing from the medical records.

CONCLUSION

Within the study limitations, the proposed perioperative systemic antibiotic therapy protocol seems to be efficient to prevent ORN following tooth extraction in postirradiated HNC patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Palma LF, Gonnelli FA, Marcucci M, Dias RS, Giordani AJ, Segreto RA, *et al.* Impact of low-level laser therapy on hyposalivation, salivary pH, and quality of life in head and neck cancer patients post-radiotherapy. *Lasers Med Sci* 2017;32:827-32.
- Palma LF, Gonnelli FA, Marcucci M, Giordani AJ, Dias RS, Segreto RA, *et al.* A novel method to evaluate salivary flow rates of head and neck cancer patients after radiotherapy: A pilot study. *Braz J Otorhinolaryngol* 2018;84:227-31.
- Gonnelli FA, Palma LF, Giordani AJ, Deboni AL, Dias RS, Segreto RA, *et al.* Low-level laser therapy for the prevention of low salivary flow rate after radiotherapy and chemotherapy in patients with head and neck cancer. *Radiol Bras* 2016;49:86-91.
- Gonnelli FA, Palma LF, Giordani AJ, Deboni AL, Dias RS, Segreto RA, *et al.* Low-level laser for mitigation of low salivary flow rate in head and neck cancer patients undergoing radiochemotherapy: A prospective longitudinal study. *Photomed Laser Surg* 2016;34:326-30.
- Grisar K, Schol M, Schoenaers J, Dormaar T, Coropciuc R, Vander Poorten V, *et al.* Osteoradionecrosis and medication-related osteonecrosis of the jaw: Similarities and differences. *Int J Oral Maxillofac Surg* 2016;45:1592-9.
- Dhanda J, Pasquier D, Newman L, Shaw R. Current concepts in osteoradionecrosis after head and neck radiotherapy. *Clin Oncol* 2016;28:459-66.
- Costa DA, Costa TP, Netto EC, Joaquim N, Ventura I, Pratas AC, *et al.* New perspectives on the conservative management of osteoradionecrosis of the mandible: A literature review. *Head Neck* 2016;38:1708-16.
- Moon DH, Moon SH, Wang K, Weissler MC, Hackman TG, Zanation AM, *et al.* Incidence of, and risk factors for, mandibular osteoradionecrosis in patients with oral cavity and oropharynx cancers. *Oral Oncol* 2017;72:98-103.
- Raggio BS, Winters RD. Role of steroids in preventing osteoradionecrosis of the head and neck: A systematic review. *Ann Otol Rhinol Laryngol* 2019;128:441-6.
- Chronopoulos A, Zarra T, Ehrenfeld M, Otto S. Osteoradionecrosis of the jaws: Definition, epidemiology, staging and clinical and radiological findings. A concise review. *Int Dent J* 2018;68:22-30.
- Nabil S, Samman N. Incidence and prevention of osteoradionecrosis after dental extraction in irradiated patients: A systematic review. *Int J Oral Maxillofac Surg* 2011;40:229-43.
- Al-Bazie S, Bahatheq M, Al-Ghazi M, Al-Rajhi N, Ramalingam S. Antibiotic protocol for the prevention of osteoradionecrosis following dental extractions in irradiated head and neck cancer patients: A 10 years prospective study. *J Cancer Res Ther* 2016;12:565-70.
- Wahl MJ. Osteoradionecrosis prevention myths. *Int J Radiat Oncol Biol Phys* 2006;64:661-9.
- McLeod NM, Bater MC, Brennan PA. Management of patients at risk of osteoradionecrosis: Results of survey of dentists and oral and maxillofacial surgery units in the United Kingdom, and suggestions for best practice. *Br J Oral Maxillofac Surg* 2010;48:301-4.
- Carl W, Ikner C. Dental extractions after radiation therapy in the head and neck area and hard tissue replacement (HTR) therapy: A preliminary study. *J Prosthet Dent* 1998;79:317-22.
- Nadella KR, Kodali RM, Guttikonda LK, Jonnalagadda A. Osteoradionecrosis of the Jaws: Clinico-therapeutic management: A literature review and update. *J Maxillofac Oral Surg* 2015;14:891-901.
- Kanatas AN, Rogers SN, Martin MV. A survey of antibiotic prescribing by maxillofacial consultants for dental extractions following radiotherapy to the oral cavity. *Br Dent J* 2002;192:157-60.
- Maxymiw WG, Wood RE, Liu FF. Postradiation dental extractions without hyperbaric oxygen. *Oral Surg Oral Med Oral Pathol* 1991;72:270-4.
- Lye KW, Wee J, Gao F, Neo PS, Soong YL, Poon CY. The effect of prior radiation therapy for treatment of nasopharyngeal cancer on wound healing following extractions: Incidence of complications and risk factors. *Int J Oral Maxillofac Surg* 2007;36:315-20.
- Naal FD, Salzmann GM, von Knoch F, Tuebel J, Diehl P, Gradinger R, *et al.* The effects of clindamycin on human osteoblasts *in vitro*. *Arch Orthop Trauma Surg* 2008;128:317-23.
- Donaldson M, Goodchild JH. Is clindamycin dangerous? *Gen Dent* 2017;65:12-5.
- Palma LF, Marcucci M, Remondes CM, Chambrone L. Leukocyte- and

- platelet-rich fibrin does not provide any additional benefit for tooth extraction in head and neck cancer patients post-radiotherapy: A randomized clinical trial. *Med Oral Patol Oral Cir Bucal* 2020;25:e799-804.
23. Kuo TJ, Leung CM, Chang HS, Wu CN, Chen WL, Chen GJ, *et al.* Jaw osteoradionecrosis and dental extraction after head and neck radiotherapy: A nationwide population-based retrospective study in Taiwan. *Oral Oncol* 2016;56:71-7.
 24. Huang YF, Liu SP, Muo CH, Tsai CH, Chang CT. The association between dental therapy timelines and osteoradionecrosis: A nationwide population-based cohort study. *Clin Oral Investig* 2020;24:455-63.
 25. Epstein JB, Rea G, Wong FL, Spinelli J, Stevenson-More P. Osteonecrosis: Study of the relationship of dental extractions in patients receiving radiotherapy. *Head Neck Surg* 1987;10:48-54.
 26. Koga DH, Salvajoli JV, Kowalski LP, Nishimoto IN, Alves FA. Dental extractions related to head and neck radiotherapy: Ten-year experience of a single institution. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol* 2008;105:3-8.