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. 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. Thus, a wide range of clinical complications occurs during and/or after the RT course, affecting negatively patients’ quality of life and oral functions.

One of the most recognized, severe, and debilitating RT complication is osteoradionecrosis (ORN) of the jaw, first reported about 100 years ago. 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. Although it has been declining in recent years, thanks to technological advances in radiation therapy.
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,[13] 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.
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.

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 severe pathological conditions such as mandibular fracture or hemimandibulectomy.

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**Table 2: Patients’ tumor and oncologic treatment**

| Primary tumor location          | Patients (\( n=47 \), \( n(\%) \)) |
|--------------------------------|-------------------------------------|
| Oral cavity                    | 14 (30)                             |
| Pharynx                        | 15 (32)                             |
| Larynx                         | 16 (34)                             |
| Occult primary                 | 1 (2)                               |
| Parotid gland                  | 1 (2)                               |
| Squamous cell carcinoma        | 46 (98)                             |
| Carcinoma expleomorphic adenoma| 1 (2)                               |
| Histological type              |                                     |
| 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)                             |

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**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).

**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.
severe pain, orocutaneous fistulas, and even pathological fractures — 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, 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. Moreover, antibiotics are easy to administer and widely available.

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. Al-Bazie et al. 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. 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. 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, 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, 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.

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. 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. 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, 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.

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, and male middle-aged patients; however, a patient had completed the RT course before 2 years from the extractions, the most critical period. 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.

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, concomitant chemotherapy,
current alcohol and tobacco use,[7,8] and absence of accurate data on the total radiation dose delivered to each tooth extraction site,[20] 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.

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Conflicts of interest
There are no conflicts of interest.

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