Incidence of osteoradionecrosis of the jaws: A retrospective study of 620 head and neck cancer patients treated by radiotherapy

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Keywords: Head and neck cancer, Head and neck neoplasms, Osteoradionecrosis, Jaw diseases, Radiotherapy, Radiation therapy, Tooth extraction, Retrospective cohort study

Posted Date: May 21st, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-29543/v1>

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Abstract

Background

This study aims to assess systemic and local risk factors influencing the development of osteoradionecrosis of the jaws (ORN) and its incidence in head and neck cancer patients undergoing radiotherapy.

Methods

This was a retrospective cohort study of 620 adult patients following radiation for a head and neck cancer in 2011 or 2012.

Results

Of the 181 patients who did not require any extraction, the incidence of ORN was 0.5%. Of the 266 patients with 1491 dental extractions (mean 5.5 teeth per patient) performed before radiotherapy, the incidence of ORN was 3.7%. ORN was always observed in extraction sites located in the field of radiation. No dental extractions were done during radiotherapy. Of the 20 patients with 53 dental extractions (mean 2.7 teeth per patient) performed after radiotherapy, 15 teeth were located in the field of radiation. No case of ORN was reported in that group. For edentulous patients, ORN incidence was 1.7%.

Conclusion

Within the limitations of this study, the incidence of ORN can be minimized with a meticulous pre-radiotherapy dental examination, a comprehensive treatment plan and diligent post-radiotherapy follow-ups conducted by an experienced multidisciplinary team.

Introduction

Radiation therapy (RTH) is a major treatment modality used for head and neck malignancies. The irradiated patient is susceptible to encounter complications which can occur either during, shortly after, or long after the radiation. Xerostomia, loss of taste, trismus, radiation caries and periodontal attachment loss are the main late effects of such a treatment [1–3]. Osteoradionecrosis (ORN) was first described by Regaud in 1922, and is known as the most severe complication resulting from a reduced bone healing [4]. It is defined as an area of exposed bone present for more than two months in a previously irradiated field and in the absence of a recurrent tumor [5]. The exposed bone may either heal spontaneously and without any complications, either transform into a chronic issue and result in osteomyelitis or even fractures [6]. Clinically, the possible symptoms include swelling, pain, dysphagia, trismus, masticatory or speech disorders, refractory orocutaneous fistula, bone exposure, and pathological fracture, depending on the ORN severity [7]. Although the reported occurrence rate of ORN substantially varies, the incidence remains approximatively 7% [8]. Such variations can be explained by several factors. For example, pre-RTH successful treatment of any active oral disease and the quality and frequency of follow-ups after

RTH play a crucial role in preventing ORN. Therefore, the aim of this retrospective study is to provide objective data on the incidence of ORN as well as further information regarding its related risk factors.

Method

A retrospective evaluation of the medical charts of 620 head and neck cancer patients, all of which consecutively undergoing RTH at the Université de Montréal Hospital Center (CHUM), was carried out. All these patients had their first visit between January 1st, 2011 and December 31st, 2012. The medical charts were then studied until January 1st, 2016. Since then, data collection and in-depth file analysis has taken place. The type of RTH used for all patients was the intensity-modulated radiotherapy (IMRT), which reduces radiation exposure and dosage to healthy surroundings structures while being more effective on tumours compared to conventional RTH [9]. The pre-RTH oral examination was performed by an experienced team of dentists from the Division of Maxillofacial Prosthodontics of the Stomatology Department. Both extra-oral and intra-oral exams were carried out and a panoramic radiograph was systematically performed. For dentulous patients, the radiographic examination was completed with a full mouth series of intraoral radiographs. Dental hygiene habits and previous family medical history were also recorded. A complete periodontal examination was performed for all dentulous patients where cavities, oral lesions and active infections were reported. If the patient needed any extraction, he was referred to the Division of Oral and Maxillofacial Surgery clinic. In the cases in which the teeth were preserved, a fluoride therapy, consisting in daily topical applications of 1,1% sodium fluoride gel with custom trays for five-minutes periods, was prescribed.

The follow-ups consisted of at least of an examination immediately after RTH, and 1, 3, 6 and 12 months thereafter. A long-term maintenance schedule was determined for each patient according to the radiation dose and their dental hygiene condition. Any oral complication occurring before, during or after therapy was taken care of by the departmental dental team.

The sample of patients studied ($n = 620$) was divided into four groups according to the tooth extraction time in relation to RTH (Table 1). Some of these patients ($n = 15$) were categorized into both groups 2A and 2B, as they needed extractions both before and after radiotherapy. No patient underwent any extraction during radiotherapy. The data collected for all patients included gender, age, medical diagnosis, smoking status, location of the oncologic lesion, stage of the tumor, oncologic treatment, radiation doses, incidence of ORN, timing, number and type of extracted teeth. Central tendency and variability were used to describe numeric variables, distribution of frequency was calculated for categorical variables, and timing of ORN occurrence was outlined individually. The research proposal was reviewed and approved by the Ethics Committee of the Université de Montréal Hospital Center (CHUM).

Results

Most patients were male, with a majority of 451 men for a minority of 169 women (respectively 72.7 % and 27.3 %). The mean age was 65.4 years, ranging from 18 to 97 years with a median of 65 years. The

smoking status was noted at the pre-RTH oral examination, resulting in a repartition which goes as follows: 209 patients (33,7 %) were smokers, 140 patients (22,6 %) were former smokers and 271 patients (43,7 %) had never smoked before. The most frequent cancer diagnosed was the squamous cell carcinoma affecting 85.7% of patients, followed by lymphoma (7.9%), adenocarcinoma (2.6%), undifferentiated carcinoma (2.4%), sarcoma (0.8%) and melanoma (0.6%) (Table 2). Oropharynx was the main site involved (41.1%), followed by the oral cavity (15.3%) (Figure 1). As far as clinical stage, the majority of patients presented tumors at stage IV (66 %), followed by stage III (17.8 %), stage II and stage I (respectively 11.4 % and 4.8 %). The main oncologic treatment modality was a combination of RTH and surgery (48.5 %), followed by a combination of RTH and chemotherapy (23.2 %), RTH exclusively (21.1 %) and, finally, a combination of RTH, surgery and chemotherapy (7.2 %). For patients undergoing RTH alone or in combination, the mean radiation dose was 60 Gy (range of 20 Gy–70 Gy) while most patients received at least 50 Gy of radiation, as illustrated in Figure 2.

There was a total of 452 dentulous patients (72.9 %). For the 181 of them who did not require any extraction (group 1), the dental follow-up delay ranged from one day to 56 months, with an average duration of 18.3 months and a median value of 9 months (Figure 3). The first follow-up appointment started from the beginning of RTH. The mean dose these patients received was 56.4 Gy (median value: 60 Gy). In group 2A ($n = 266$), 1491 teeth were removed before RTH (ranging from 1 to 28 teeth per patient, mean value 5.5, median value 6). The follow-up from the beginning of RTH ranged from 1 day to 60 months, with a mean value of 25.3 months (median value: 23 months). The mean dose these patients received was 62.5 Gy (median value: 66 Gy). In group 2B ($n = 20$), 53 teeth were removed after RTH (ranging from 1 to 7 teeth per patient, mean value 2.7, median value 1). The dental follow-up time ranged from 10 to 60 months, with a mean value of 37.8 months (median value: 42 months). The average doses these patients received was 60 Gy (median value: 60 Gy). Among the 53 teeth extracted after RTH, 15 were in the field of radiation. In edentulous patients (group 3; $n = 168$), the duration of dental follow-ups ranged from 1 day to 51 months, with a mean value of 9.4 months (median value: 1.5 months). The mean dose the patient received is 59.5 Gy (median value: 60 Gy). The most frequently extracted teeth before RTH were molars (Table 3). The lower incisors were the most extracted teeth after RTH.

ORN was reported in 2.2% of the patients ($n = 14$) or 2.4% ($n = 11$) if we consider only dentulous patients. The smoking status was noted: 4 patients were smokers, 5 patients were former smokers and 5 patients had never smoked before. All but one patient diagnosed with ORN had received more than 60 Gy. The one patient who had only received 30 Gy prior to ORN in the posterior mandibular area had before osteochemonecrosis associated with IV bisphosphonates and was therefore considered at risk of developing such complications. The mean onset of ORN was 11,5 months after RTH ranging from 3–32 months with a median of 9 months. Most ORN lesions were found in the inferior molar region ($n = 11$). The other sites affected by ORN were the inferior premolar and molar regions ($n = 1$) and lower incisive region ($n = 1$). There were no reports of ORN in the maxilla. Interestingly, ORN was observed in a dentulous patient who underwent no extraction for an incidence rate of 0.5%. For patients having dental extractions performed before RTH (group 2A), the incidence of ORN was 3.7% ($n = 10$) and it was systematically observed at extraction sites located in the field of radiation. ORN occurred after an average

of 7.5 months following the extractions (median value: 9,5 months). No case of ORN was reported in the group of patients who underwent extractions after RTH (group 2B). For edentulous patients (group 3), ORN was observed in 3 cases (1.7%). The treatment of ORN consisted of a minor debridement of the affected bone with a round bur or a sharp instrument, until bleeding appeared. Sterile saline irrigation was done at the affected site and all patients were given a prescription of 0.12% chlorhexidine mouthwash to use twice a day until soft tissues covered the exposed bone. A first follow-up visit was planned 1 to 6 weeks after the procedure, and at 1, 3, 6 and 12 months thereafter.

Discussion

Most patients were diagnosed with an advanced stage of head and neck squamous cell carcinoma, majority within which the mean sampled age was 65 years old. Bonan et al. [10] reported a lower life expectancy of 58.8 years for the sample of patients from lower socioeconomic classes. Higher life expectancy may be explained by a higher socioeconomic status in earlier diagnosis and by the medical advances in the maxillofacial and oncology field in recent years. A study by Tsai et al. [11] demonstrated a 32% increased risk of development of ORN in smokers. Another study by Chronopoulos et al. [12] showed that patients who continued smoking or alcohol use were more likely to develop an ORN. For our present study, information concerning alcohol intake, drug consumption and pack-years of cigarette smoking was not consistently documented in the patients' charts. Therefore, we could not explore the association between smoking and ORN and this is a limitation of our study.

Follow-up is crucial for the prevention and management of the oral and dental complications such as xerostomia, loss of taste, radiation mucositis, trismus, malnutrition and ORN. According to Toljanic et al. [13], dental follow-ups compliance is poor in an irradiated population, especially within the edentulous population. Their review of 334 dental charts of edentulous patients over 12 years reported an average follow-up of 7.5 months, with 51% of the patients who were lost during that period. These patients are indeed least inclined to regularly visit the dentist, as indicated by the comparable follow-up time for our edentulous patients (mean duration = 9.4 months). The duration of the follow-up period is a crucial factor to prevent complications related to RTH as suggested by our observations (9.4 months) and as demonstrated with the low ORN incidence in our patient population. These results emphasize the importance of public oral cancer prevention programs facilitating patients access to oral healthcare services and long-term care.

The incidence of ORN has significantly decreased in recent years. Our average rate of ORN was 2.2%, which is similar as those reported by other oncologic centers. For example, Sulaiman et al. [8], Moon et al. [14] and Koga et al. [15] have respectively observed an ORN rate of 0.92% in 1 194 patients, 4% in 252 patients and 4.2% in 405 patients. Before 1968, the incidence was approximately 11.8% as opposed to the last two decades, where it is closer to 3% [16,17], confirming the potential of IMRT to reduce the risk of developing ORN compared to conventional RTH [18]. IMRT uses linear accelerators to safely deliver precise radiation to a tumor while minimizing the dose to surrounding normal tissue. This is most likely one of the reasons why the ORN incidence is low. Another possible explanation of a lower incidence of

ORN is the importance of dental care protocols that could have a synergistic preventive effect with IMRT [19]. The onset of ORN was early (median 9,5 months) after RTH. This is in line with other publications [11,20,21] which showed median ranges between 8 and 19 months.

Extractions prior to RTH seem to lead to a higher incidence of ORN (3.7% patients for 1,491 exodontias) and this observation is in accordance with other studies. Koga et al. [15] mentioned 0.5% ORN cases for 1,647 exodontias, Regezi et al. [22] found 2% for 311 exodontias, Sulaiman et al. [8] had 2.6% for 300 exodontias, Epstein et al. [23] described 5.4% for 454 exodontias and Bedwinek et al. [24] reported an incidence of 9%. Possible risk factors associated with ORN in patients having extractions are the unfinished alveolar bone healing in some individuals while RTH is initiated and their poorer oral health. However, as typically recommended, extractions should be carried out at least 2 weeks before starting RTH [25]. Due to oncologic imperatives and logistics, this recommendation was unfortunately not always observed in this study. The shortest delay ranged between 7 to 10 days after the extractions. Nevertheless, our incidence of ORN was similar to other studies.

Higher radiation doses are associated with increased risk of ORN [26]. In the present study, almost all ORN cases occurred in patients receiving more than 60 Gy. This emphasizes the 60 Gy threshold as a risk indicator of patients developing ORN after extraction as reported by others [6,20]. Although the risk of developing spontaneous ORN did increase with greater dose, most reported cases of ORN were induced by alveolar bone trauma such as that of dental extractions, as observed by other authors [27].

The mandible is at higher risk of developing ORN compared to the maxilla [28]. Indeed, all ORN cases in this study occurred in this region. The pattern of mandibular blood supply has been suggested as a primary reason for this site of predilection [29]. Moreover, the mandible is included in the radiation field more frequently than the maxilla. The fact that the primary tumor was located more frequently in the oropharynx region may contribute to the higher incidence of ORN in the mandible. As supported by other authors, the mandibular molar region is known to be at higher risk of developing ORN [30,31]. Moreover, since the lower molars were more frequently removed (Table III), the risk of developing ORN in that area is further increased.

Although less frequently, the maxilla can also be affected by ORN, especially in cases of nasopharyngeal cancer. Chang et al. [32] reported on 1,758 cases of nasopharyngeal carcinoma, 48 cases of ORN in the maxilla and 30 cases in the mandible. Nevertheless, the risk of ORN is lower in the maxilla than in the mandible, considering the fact that maxilla is more resistant to radiation. The absence of maxillary ORN in our sample of patients parallels this observation.

Edentulous patients may develop ORN and we found an incidence of 1.7%. Surprisingly, Widmark et al. [33] mentioned an ORN frequency of 13.5%. Chang et al. [32] argued that the smaller proportion of ORN in edentulous patients compared to that reported in patients having extractions before the RTH (14%) could be explained by the fact that being edentulous several years prior RTH seems to offer a protective effect, but becoming edentulous a few weeks prior RTH does not. Bone healing and bone remodelling in the

freshly edentulous patients likely increases the risk of ORN. Ensuring a proper fit of dentures is another effective way to avoid any trauma increasing ORN risks [34,35].

The worst moment for tooth extraction is considered to be during RTH [36]. However, a window between 6 weeks and 4 months after RTH may present less risk of complications for the bone following an extraction [37,38]. Past that window, the progressive fibrosis and loss of vascularity increase the risk of developing ORN. In the present study, no extraction was performed during RTH. This may be explained by the fact that meticulous attention was given to pre-RTH treatment planning in order to eliminate caries and periodontal diseases and extract teeth with a poor prognosis. Pre-RTH extractions are indicated when teeth are unrestorable or require significant restorations, present extensive caries into the pulp chamber, have periapical radiographic lesions, have moderate to severe periodontal disease (pockets under 5 to 6 mm), furcation involvement or mobility of grade 2 or more [23]. Moreover, all patients undergoing pre-RTH assessment were examined by dentists with an extensive experience in oral oncology. Post-extractions controls were also systematically performed to protect the process of socket healing.

If an extraction in the field of radiation is required, intraoperative efforts need to be made to prevent ORN. Koga et al. [15] reported ORN in 1.7% and Sulaiman et al. [8] showed an incidence of 1.8%, which is low compared to the 7.1% found by Epstein et al.¹⁴ and the 9.1% found by Horiot et al. [39]. However, Makkonen et al. [40] and Maxymiw et al. [27] reported no cases of ORN for, respectively, 88 and 126 teeth extracted after RTH. In a systematic review, Nabil et al. [41] highlighted that 7 % of the patients who underwent extractions post-RTH had developed an ORN and the ORN incidence per tooth extracted was 2%. In the present study, no case of ORN was related to post-RTH extracted tooth. This is also due to the small number of extractions done after RTH. The fact that extractions were done by experienced maxillofacial surgeons and carried out with minimal trauma [42] suggests that an atraumatic procedure is an important factor to prevent ORN. Importantly, hyperbaric oxygen therapy [43,44] was not systematically prescribed and pentoxifylline and tocopherol [45] were never used for our patients due to the lack of evidence backing their use [46]. Pentoxifylline and tocopherol should be considered only for the management of advanced ORN where surgical management is not appropriate [47,48].

Conclusion

In conclusion, this study highlights that the incidence of ORN may remain relatively low if a meticulous dental examination before RTH is performed. Additionally, the skills and knowledge of the practitioner in oral oncology, as well as the duration and the quality of the follow-ups, seem to be decisive factors in a successful ORN prevention. However, if extractions are necessary, we have not observed ORN in patients undergoing post-RTH extractions by experienced maxillo-facial surgeons. Further prospective controlled studies are warranted to determine the factors that may reduce the incidence of ORN and best practices in maxillofacial oncology.

Declarations

- *Ethics approval and consent to participate*
 - Attached to this article
- *Consent for publication*
 - Not applicable
- *Availability of data and materials*
- All data generated or analysed during this study are included in this published article.
- *Competing interests*
- The authors declare that they have no competing interests.
- *Funding*
 - Not applicable
- *Authors' contributions*
 - R.K.: This author collected and analyzed the data and has drafted the work.
 - M.S.: This author has drafted the work and substantively revised it.
 - D.R., R.D., E.D., P.N: These authors substantively revised the work.
 - All authors have read and approved the final manuscript.
- *Acknowledgements:*
 - Not applicable

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Tables

Table I. Timing of toot extractions and status of the head and neck cancer patients undergoing RTH (n=620)

<i>Group</i>	<i>Definition</i>	<i>n</i>
1	Dentate patients without any tooth extraction	181
2A*	Patients with tooth extractions performed before therapy	266
2B*	Patients with tooth extractions performed after therapy	20
3	Edentulous patients	168

* Some patients (n = 15) were categorized into both groups 2A and 2B, as they needed extractions both before and after RTH.

Table II. Head and neck cancer diagnosis for patients undergoing RTH (n=620)

<i>Diagnosis</i>	<i>n</i>	<i>%</i>
Squamous cell carcinoma	531	85.7
Lymphoma	49	7.9
Adenocarcinoma	16	2.6
Undifferentiated carcinoma	15	2.4
Sarcoma	5	0.8
Melanoma	4	0.6

Table III. Evaluation of the type of teeth removed in the 452 patients undergoing RTH

<i>Teeth</i>	<i>Before RTH (n)</i>	<i>After RTH (n)</i>	<i>Total (n)</i>
Maxilla			
Incisors	65	5	70
Canines	44	3	47
Premolars	117	1	118
Molars	428	3	431
Mandible			
Incisors	151	22	173
Canines	91	7	98
Premolars	180	9	189
Molars	415	3	417
Total	1 491	53	1 544

RTH, radiotherapy; *n*, number of teeth removed

Figures

Figure 1

Distribution of tumor sites for head and neck cancer patients undergoing RTH (n = 620)

Figure 2

Distribution of radiation doses for head and neck cancer patients undergoing RTH. (n: number of patients)

Figure 3

Average duration of dental follow-ups for head and neck cancer patients undergoing RTH. Group 1: no extraction; group 2A: extractions before RTH; group 2B: extractions after RTH; group 3: edentulous. (n: number of patients)