

Osteoradionecrosis Of The Jaws: Risk Factors After Head And Neck Radiation.

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Abstract: Radiotherapy (RT) is an efficient therapy for head and neck tumors. Aside from its advantages, it is not free of complications, one of them being osteoradionecrosis (ORN) of the jaws. The definition of ORN is based on its clinical presentation: the irradiated bone becomes devitalized and is exposed through the skin and mucosa which covers it, for at least three months without healing, and without recurrence of the tumor. There are several theories about its etiology; nevertheless its predisposing factors are not clear yet. The objective of this study is to review the different risk factors of ORN after RT treatment for head and neck tumors.

Keywords: head and neck tumors, osteoradionecrosis, predisposing factors, radiotherapy, risk factors.

I. Introduction

Head and neck cancer represent approximately the 7% of all cancers, being the fourth cause of death in humans. More than 50% of these patients are given radiotherapy (RT) as treatment, which one of its most common complication is osteoradionecrosis (ORN) of the jaws [1, 2]. Its incidence is not well established, being of 4,7% to 37,5% depending on the literature reviewed. Thanks to preventive measures, advances in the RT techniques and the introduction of dental care protocols for head and neck cancer patients, its prevalence has declined in the last past years. Numerous factors have been associated with the risk of ORN, to the date, the most common are radiotherapy dose, dental extractions and surgery [3, 4, 5].

The objective of the present study is to determine the risk factors that increase the possibilities of developing ORN after the irradiation of head and neck tumors.

II. Material And Methods

A comprehensive search of the scientific literature was conducted without date restriction until May 18th 2017, in the following databases: Pubmed/Medline, Scopus, Web of Science and The Cochrane Library by two independent researchers (JS, VP). The search strategy used was: ("osteoradionecrosis") AND ("head and neck tumors") AND ("predisposing factors" OR "risk factors") according to each database. We performed an additional handsearch to find potential eligible studies.

Inclusion criteria: the articles included had to be (a) written in Spanish or English, (b) indexed in Pubmed, (c) carried out only in humans, (d) patients with head and neck cancer who were treated with RT and/or chemotherapy (CHT) and suffered osteoradionecrosis in maxilla or jaws.

III. Results

At the initial search, we found 105 articles, of which 75 remained after removing duplicates. We excluded those written in another language apart from English or Spanish, having a total of 85 articles. We rejected those carried out on animals, restricting the search to 76 articles. After reading the title and abstract of the identified articles, we excluded 45 because they did not focus on our search criteria. We ended up with 31 articles.

IV. Discussion

4.1 Factors related to treatment

4.1.1 Dose

One of the most important predisposing factors is high dose of RT. According to most authors, ORN usually appears with radiation dose, up to 60 Grays (Gy) [7-11]. Apparition of ORN with lower dose is unusual [6, 7]. Some authors observed that with radiation dose over 70 Gy, injuries are more extended and severe [3, 12]. A summary of the different studies which associate radiation dose with ORN of the jaws is exposed on Table 1.

4.1.2 Hyperfractionated RT

Information about hyperfractionated RT is not clear. Apart from total dose, there are other factors as dose per fraction and the interval between fractions that may have influence in the onset of ORN [4]. ORN incidence seems to be lower when we use this modality with interval periods of 6 hours compared to conventional RT [13]. When the interval period in the hyperfractionated RT is lower than 4-5 hours, the risk of ORN increases [14]. The lower the dose per fraction is, the lower the percentage of ORN [6].

4.1.3 Irradiation field

Glanzmann and Gratz observed that, when more than half of the horizontal ramus or body of the mandible was included in the irradiation field, the risk of ORN increased significantly [6]. According to some authors, this is also related with RT dose and type of RT: when using conventional RT, higher dose of RT are absorbed in the horizontal ramus (especially in the retromolar regions) followed by sinfisis and ascendant ramus [9, 15].

4.1.4 Association between RT and CHT

CHT is usually employed to achieve a better local management of the tumor [3]. Information about the risk of combining these two modalities is not clear yet. *Van den Broek et al.* studied CHT toxicity in 125 patients and ORN appeared in 9 of them [16]. However, other authors did not find higher risk when both treatments were combined [2, 4-6, 12]. *Chopra et al.* did not find significant differences in the severity of ORN in patients that had received CHT [2].

4.1.5 RT techniques: Brachytherapy

Patients that receive brachytherapy seem to have a higher risk of developing ORN. It is postulated that an increase radiation dose is absorbed because of the proximity of the implant source to the bone. It could also be related to the tumor site, since this technique is frequently used in tongue cancer [4]. Nevertheless, other authors, as *Notani et al.* suggested that external RT has more detrimental effects than brachytherapy, since the biological activity of the bone gets affected [17].

4.2 Factors related to the tumor

4.2.1 Tumor location

The risk of developing ORN is higher when the patient suffers from cancer of the oral cavity. 85%-78% of head and neck cancer that develop ORN are oral tumors, especially those located on tongue, floor of the mouth, retromolar region and alveolar crest [2, 7]. In *Van den Broek et al.* study, 27% of the patients with oral cancer developed ORN in comparison to 7% who had a tumor in a different location [16]. Although ORN of maxilla is not common, it may appear when the tumor is in the nasal area [25, 26].

Tumors of oral cavity and oropharyngeal region have a higher risk of ORN due to direct implication of the jaws in the irradiation field plus the fact that these patients usually need aggressive surgery in order to remove the tumor [4, 22, 26]. The closer the tumor to the bone, the higher the risk of ORN is [4, 10].

4.2.2 Tumor size and tumor stage

Bigger tumors usually need higher dose of RT, and this is associated to a higher risk of ORN [3, 5, 7]. The risk of suffering ORN also seems to be higher in patients with advanced tumors, since they will need higher dose or more time of receiving RT [2, 12, 27]. Nevertheless, *Curi and Dib* did not find influence of the T stage of the tumor and the onset of ORN. Some authors reported that there is a higher incidence of ORN when the tumor is N0, since the survival rate in these patients is higher and therefore, the probability of suffering ORN throughout their life is higher too [6,7].

4.3 Factors related to patients

4.3.1 Trauma

Traumas are one of the principal ORN risk factors. In 90% of the cases, ORN occurs due to trauma (as use of removable prosthesis) or surgery, the other 10% occurs spontaneously [28]. There is a statistical relationship between dental extractions and ORN, although the exact incidence is unknown yet [3, 12]. However, the risk of developing ORN after the extraction of teeth outside the irradiation field seems to be almost inexistent [11]. Table 2 summarizes the prevalence of ORN in patients with dental extractions.

Any surgery in the irradiated field increases the risk of developing ORN [3, 7, 9]

4.3.2 Dental status and oral health

Unrepairable teeth (with aggressive caries, periodontal disease or root damage) can cause bone infection that could favor ORN onset [29]. Most authors prefer the prophylactic extractions of those teeth with

bad conditions. Therefore, frequent dental checkups are important in these patients [30, 31]. Patients should be advised to take frequent dental and oral revisions, and instructions about how to have proper levels of oral health. Patients with bad oral hygiene seem to have higher risk of ORN. Maintaining good oral health is important during, and after the RT, especially the year-two years after RT treatment [3,4].

4.3.3 Other factors

Other related factors described, although less frequently reported, are tobacco and alcohol intake (these are risk factors during and after RT). Most authors agree that tobacco may increase the mandibular hypovascularity after RT. Patient's age, gender (it is three times more frequent in men than in women) and nutritional status has also been studied. Further investigations should be carried out to clarify if they are or not related to the presence of ORN [3, 10, 29, 31, 32, 33].

Table 1. Relationship between RT dose and ORN

Study (author and year)	Dose	ORN
Glanzmann et al 1995	<66 Gy	0% ORN
Curi and Dib 1997	>60 Gy	71% ORN
Thorn et al 2000	64 Gy-68 Gy	93% ORN
Reuther et al 2003	>60 Gy	Lesions > 2cm
Cheng et al 2005	≥70 Gy	ORN more severe
Goldwaser et al 2007	>66 Gy	73% ORN
Oh et al 2009	>70 Gy	16% ORN
Chopra et al 2010	>60 Gy	More cases of ORN severe
Nabil and Samman 2012	<60 Gy	0% ORN

Table 2. Dental extractions and ORN

Study	Dental extractions ORN
Reuther et al 2003	50% of ORN were due to dental extractions
	Pre-RT 24% ORN
Cheng et al 2005	Extractions are a risk for developing ORN
	There were no differences between pre or post-RT
Oh et al 2009	Pre-RT 23% ORN
	Post-RT 16% ORN
Nabil and Samman 2011	Post- RT on jaws 3% ORN
	Post- RT in maxilla 1% ORN
	Extractions outside the irradiation field 0% ORN
	Extractions in the irradiation field 3% ORN
Chopra et al 2011	Post-RT 60% ORN

V. Conclusion

ORN seems to have a multifactorial onset; therefore, preventive measures are of vital importance.

The most common risk factors for developing ORN are high radiation dose of RT (>60 Gy) and trauma, especially dental extractions. Further investigation should be carried out in order to clarify other possible related factors, in order to prevent ORN and improve the quality of life of patients who had received RT for head and neck tumors.

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