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ORIGINAL ARTICLE

Mandibular osteoradionecrosis (ORN) as a side effect of head and neck cancer treatment: Factors that induce it

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Abstract

Introduction: *Osteoradionecrosis of the mandible is a relatively common complication in patients with head and neck cancer undergoing radiotherapy or concomitant chemoradiotherapy, characterized by exposure of the mandibular bone either in the mouth or in the facial skin, with no improvement with conservative treatment for six months. The risk factors are radiotherapy in head and neck region, lack of dental prophylaxis before treatment and dental extraction.* **Material and methods:** *Retrospective observational study analyzing incidence and etiologic factors of osteoradionecrosis in 250 patients undergoing radiotherapy or combined treatment of cervicofacial area between 2002 and 2010.* **Results:** *25 patients were included; the horizontal branch was the most affected area, followed by the anterior arch. Associated factors were: stage (T4a and T4b), tumor location (oral cavity), dental extraction pre or post-radiotherapy, and radiotherapy time (pre-or postoperative); 72% had association with tooth extraction. Only five patients had control with conservative measures, and 20 required some type of mandibulectomy, only three of them were candidates for reconstruction with fibular free flap; none received treatment in a hyperbaric chamber.* **Conclusions:** *The data suggest that osteoradionecrosis has a multifactorial origin, and prevention is the best alternative and includes pretreatment dental prophylaxis to avoid tooth extractions and close monitoring and surveillance in order to identify early osteoradionecrosis. Most patients require mandible resection as definitive treatment.* (Gac Med Mex. 2016;152:652-5)

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Introduction

Osteoradionecrosis (ORN) is one most the serious complications of cervicofacial cancer treatment. It is a serious lesion caused in a delayed form by radiation treatment o by the association of chemotherapy and radiotherapy, characterized by practically irreversible bone necrosis. There may be exposure of the mandible, either in the mouth, the neck or facial skin, or in both sides, as well as communication between the oral cavity and the exterior[1,2]. Evolution is characterized by stabilization of the lesion for a long time, or else by progression and even more serious complications, such as deep neck abscesses formation and sepsis. It causes an important deterioration of the quality of life and it is life threatening.

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In general, ORN is characterized by the radiation-trauma-bone exposure sequence[3], and it is more common with ≥ 55 Gy doses[4].

Typically recommended treatment has been aggressive and it is usually mutilating for the patient[5], and includes antibiotic therapy, hyperbaric oxygen and mandibulectomy. However, the goal in the treatment of this complication should be its prevention, and to that end, the most important factor is peri-therapeutic dental care and dental prophylaxis[6,7].

The prevalence of ORN ranges from less than 1% to up to 56%, and different factors have been associated with its occurrence[4]. There are systemic factors, such as nutritional status, diabetes mellitus and nutritional deficit; local factors, such as tumor stage, its proximity to the mandible and poor oral hygiene, and surgical factors such as mandibular partial resection during neoplastic resection, mandibular devascularization during neck dissection and facial artery ligation during rescue surgery. However, probably the most important factors are dental extraction after radiotherapy and constant bone trauma in previously radiated patients, especially when they received more than 55 Gy. The mandible is the most affected bone of the central facial skeleton due to endothelial damage to the arteries intraosseusly and diffusely irrigating it; its irrigation is relatively limited and easily damaged. In contrast, the maxilla has more profuse irrigation and, therefore, ORN is less common[4,5].

About one third of ORNs occurs spontaneously and has no triggering factor.

The purpose of this work is to know the evolution of a group of patients with ORN associated with treatment with radiation or chemotherapy in association with radiation for squamous cell carcinoma originating in head and neck mucosae.

Material and methods

This was a retrospective, observational study assessing the evolution of a group of patients that, having been treated with radiotherapy or chemotherapy in association with radiotherapy for squamous cell carcinoma of the head and neck area, developed ORN.

Two-hundred and fifty patients who underwent radical radiotherapy to the cervicofacial area for neoplasms originating in the upper aerodigestive tract were identified; from that group, those who developed any degree of ORN during their follow-up were selected.

Mean radiotherapy received dose, ORN degree, mean time for its occurrence, received treatment and patient evolution with a 3-year mean follow-up was assessed.

Table 1. Clinical characteristics of 25 patients with ORN. The condition was more common in patients who had received more than 65 Gy

Characteristics	Patients n (%)
Horizontal branch	15 (60%)
Symphysis	7 (28)
Angle and ascending branch	3 (12%)
Dose < 65 Gy	20 (80)
T2	4 (16)
T3	5 (20)
T4A	9 (36)
T4B	7 (28)
Tumor originating in oral cavity	19 (76)
Tumor originating in oropharynx	6 (24)
Unicortical lesion	3 (12)
Bicortical lesion	16 (64)
Cortico-medullary lesion	6 (24)
Preoperative radiotherapy	2 (8)
Postoperative radiotherapy	15 (60)
Radio-chemotherapy	7 (28)
Epstein 2	10 (40)
Epstein 3	15 (60)

Results

A total of 250 patients who received radiotherapy to the cervicofacial area, associated or not with chemotherapy, could be evaluated within an 8-year period, from 2002 to 2010. Out of them, 25 (10%) had some degree of ORN. All patients had head and neck squamous cell carcinoma as their oncologic diagnosis, and none of them received pre-treatment routine dental prophylaxis. There were 15 females and 10 males, with a mean age of 57 years.

Average time between radiotherapy and ORN diagnosis was 2 years, with a range of 4 months to 4 years.

Patient characteristics are shown in table 1. The vast majority of them had ORN of the horizontal mandibular branch (60%) and bicortically (64%), grades 2 and

Table 2. ORN most common triggering factor is dental extraction after radiotherapy

Triggering factor	Patients n (%)
Dental extraction	18 (72)
Surgical treatment (curettage)	3 (12)
No triggering factor	4 (16)

3 of Epstein's classification[8]. Eight (32%) had orocutaneous fistula at some point of evolution. Sixty percent of patients had the radiotherapy administered postoperatively, and in 28%, the treatment was associated with chemotherapy.

The factors that were associated with the occurrence of ORN were dental extraction (72%), followed by bone curettage (12%). In 16% of patients, the diagnosis could not be associated with any triggering factor (Table 2).

First treatment in all patients was with conservative attempt, and they received anti-inflammatory drugs, oral topical treatment and antibiotic therapy, in addition to surgical curettage and drainage when it was required. No one received hyperbaric chamber therapy.

Finally, only 5 patients were able to preserve mandibular continuity, all of them with limited ORN (unicortical).

In 20 patients, conservative treatment was not successful and had to undergo some type of mandibular resection: 16 underwent hemimandibulectomy and 4 segmental madibulectomy and reconstruction with fibular free flap. Of them, two were successful and one had necrosis of the flap (this patient could not be reconstructed anymore for a second occasion).

In one female patient, initial ORN was unilateral and underwent hemimandibulectomy, but 8 months later she had ORN progression to the remaining mandible and required the completion of total mandibulectomy, with soft tissue reconstruction with pectoralis major pediculated flap.

Four of the 20 patients that underwent surgery required pectoralis major flap for oral mucosa or facial skin occlusion.

There was no perioperative mortality and no patient had neck abscess or sepsis secondary to ORN.

Discussion

ORN is a serious, fortunately infrequent complication that occurs in patients who have received more than 55-Gy radiation to the head and neck area. Up to 30%

Figure 1. *ORN of the horizontal branch and anterior arch in a patient with history of mouth floor squamous cell carcinoma, cT4b (which corresponds to Epstein 3 classification).*

of ORNs occur spontaneously[4], although there are triggering factors such as dental extraction (most important), poor oral hygiene and local trauma.

It can occur months or years after the completion of radiation therapy; in this series, mean presentation time was 2 years. However, a patient undergoing radiation therapy on this area has a life-long risk for the development of ORN.

The most important in ORN treatment is primary prevention[6] (dental prophylaxis prior to radiation therapy, adequate dental hygiene, dental care after treatment and avoidance of dental extractions), since subsequent therapeutics is complex, difficult and sometimes disappointing. Antibiotic treatment, both systemic and local, as well as debridement, surgical lavage and sequestrectomy, are only useful at initial stages; at advanced stages, most patients require mandibular bone resection. In the present series, only 5 patients could preserve mandibular continuity with adequate functioning.

Any type of curettage or partial mandibular bone resection should be avoided when not strictly necessary, since it can be an ORN-triggering factor.

Close follow-up and surveillance are important in patients with a history of radiation to the head and neck area to identify early signs and symptoms of ORN, in order to decrease the likelihood of mutilating surgery.

Recently, the Saint Louis Hospital group, in Paris, reported quite encouraging results, with objective responses in all patients treated with the PENTOCLO protocol[9], which includes pentoxifylline, tocopherol and clodronate. All patients showed a clear improvement with long-term treatment (9 months). We have started

this treatment in at least 3 patients with Epstein 2 ORN, with only stability of the process being so far obtained, although with a short follow-up.

With the advent of this therapeutics, probably prognosis for these patients will be better by combining debridement, sequestrectomy and drug association. In any case, the best alternative so far is prevention, instructing the patient on oral cavity care, close follow-up and health education in first-contact professionals (dentists), in order to avoid dental extraction in areas with previous history of radiotherapy to the extent possible[9,10].

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