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Review Article

Identifying and Integrating Predictive Factors for Mandibular Osteoradionecrosis after Irradiation of Head and Neck Cancers.

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Abstract

Testing for various risk factors for mandibular osteoradionecrosis (ORN) should be performed before and after treatment in patients with head and neck cancer. The different clinical criteria for this severe radiation-induced complication are patient-dependent (intrinsic radiosensitivity, undernutrition due to weight loss, smoking, microcapillary involvement, unstable oral status, hyposalivation) and/or disease-related (oral cancer). The risk factors are also related to the disease (e.g., advanced tumor size, mandibular tumor invasion). Therapeutic risk factors are also associated with a higher risk of ORN (primary tumor surgery, chemotherapy with radiotherapy, tooth extraction after radiotherapy, stomatological follow-up and daily fluoride groove placement, non-observance of prophylaxis in case of absence, and non-observance of curative treatment). Finally, various dose studies have specified parameters targeting dose levels delivered to the mandible that increased the risk of ORN. Mean mandibular doses above 48-54 Gy and a high proportion of mandibular volumes receiving 30-60 Gy appear to discriminate against the risk of developing ORN.

Key word: *Head and neck cancers – Mandibular osteoradionecrosis – Predictive factors – Dosimetric parameters*

1.1 Introduction

Radiotherapy is used in nearly 80% of cases of patients with operated or unoperated upper aerodigestive tract cancer (1). Its side effects are the consequence of the specific radiosensitivity of the tissue and the treatment modalities of the carcinological pathology (technique used, weekly dose, total dose, spread) (2).

Mandibular osteoradionecrosis (ORN) is one of the most severe complications following radiotherapy of the head and neck cancers (3). Its management is complex and depends on the locoregional severity. To date, few studies have identified dosimetric predictors of mandibular ORN in the management of patients with oral cavity or oropharyngeal cancer. The objective of this review is to discuss risk factors for ORN and to identify dosimetric parameters to minimize the risk of this complication.

1.2 Incidence and time of occurence

The time of occurence of osteoradionecrosis varies from study to study. In the retrospective study by Reuther *et al.* between 1969 and 1999, among 830 patients treated with radiotherapy for head and neck neoplasia, 68 (8.2%) had mandibular ONR. This complication appeared between 2 months and 10 years after irradiation with a median of 13 months after the end of radiotherapy (4). Despite the use of IMRT, the incidence is estimated to be between 4.6 and 10% (5).

1.3 Definitions of ORN

The evolution of the definitions of mandibular ORN reflects the relative complexity of the diagnosis of this pathology, which takes into account clinico-radiological aspects as well as a notion of time (time of onset and duration). For some authors, it is a mandibular bone denudation of more than 1 cm for more than 3 months (6) or 6 months (7) in an irradiation field without any sign of healing. Epstein *et al.* define mandibular ORN as a chronic, resolving or active necrotic bone lesion with or without fracture in three stages (8). Wong *et al.* define it as progressive radiation-induced ischemic necrosis of bone associated with soft tissue necrosis of variable extension outside of tumor, recurrence, or metastatic disease (9). Store *et al.* introduce radiologic parameters into the definition. Mandibular ORN corresponds to the presence of radiological evidence of bone necrosis in a radiation field where tumor recurrence has been excluded (10). More recently, Mendenhall *et al.* have given a more clinical definition without a notion of time relative to the end of radiotherapy. They characterize ORN as radiation-induced bone exposure in the absence of evidence of local tumor recurrence (5).

1.4 Pathophysiology of mandibular ORN.

In 1922, Claudius Regaud described the clinical appearance of post-radiation mandibular osteitis in patients treated for head and neck cancers.

After irradiation of healthy bone tissue, a lesional phase with signs of osteoporosis resulting in thinning of the bone trabeculae and normal calcification takes place (11). This is followed by a so-called constituted lesion phase, which presents a pagetoid bone appearance with a disorganized and demineralized trabecular structure. The vascular endothelium is made up of rapidly dividing cells and is therefore more sensitive to the effects of ionizing radiation. Early dilation of the vessels, followed by chronic vasoconstriction, has been observed after therapeutic dose irradiation (12,13). Irradiation also causes a dose- and time-dependent capillary decay, affecting both the medullary and cortical compartments. There is a correlation between capillary density and the number of remaining osteocytes, and between capillary density and bone porosity. A decrease in bone

perfusion leading to de facto tissue ischemia seems to be the result of this vascular rarefaction (12,13).

In 1970, Meyer proposed that post-radiation osteocytic and osteoblastic necrosis associated with a decrease in the vascularization of bone tissue was the initial phase leading to ORN. If a triggering factor (dental avulsion, ill-fitting prosthesis, etc.) is present in this irradiated area, the risk of secondary infection of this weakened bone tissue becomes major. In these circumstances, radiation-induced osteomyelitis may develop and lead to an ORN (14).

In 1983, Marx drew an analogy between mandibular ORN and the chronic ulcer of the diabetic patient by excluding an infectious component in the mechanism of ORN (7). According to Marx's theory, four successive stages lead to mandibular ORN. These are the radiation phase, the so-called hypoxic-hypocellular-hypovascular tissue stage, the so-called breakdown of tissue integrity and finally the chronic non-healing wound phase. For Marx, the effect of irradiation on the endothelium, the periosteum, the connective tissue, the mucosa and the skin leads, on the one hand, to endothelial necrosis associated with vascular thrombi, making the tissue hypovascular and therefore hypoxic, and on the other hand, to a hyalinization phenomenon.

In 1990, Bras *et al.* confirmed the vascular phenomenon of ischemia of the mandibular ORN in 17 patients operated on for severe ORN compared with a group of individuals who had not been irradiated or irradiated without ORN (15). Pathology revealed a normal cortical and bone framework in irradiated bone without ORN, but with fibrotic periosteum and submucosa, enriched in collagenous extracellular matrix and depleted in cells. In contrast, in the ORN area, the cortical bone was necrotic, characterized by osteocytic loss and areas of resorption without stroma. Numerous thrombi were visible in the branches of the inferior alveolar artery. This hypothesis would explain the higher frequency of mandibular ORN compared to the overlying maxillary bone.

In 2002 and 2004, Delanian used the "3H" terminology (Hypocellularity, Hypovascularity, Hypoxia) and stated the three phases of radiation-induced fibrosis (RIF) leading to mandibular ORN: the so-called asymptomatic pre-fibrotic phase in which there is necrosis of osteocytes and osteoblasts, which develops from the first months after irradiation. A destruction of the endothelial barrier is associated with this, leading to a non-specific inflammatory reaction with local ischemia as well as a transformation of fibroblasts into myofibroblasts. In a second phase, the so-called constitutive phase is a phase in which myofibroblasts predominate, resulting in an increase in the synthesis of a defective extracellular matrix giving the appearance of fibrosis. Then, the so-called late fibro-trophic phase which is the consequence of a clear decrease in cellular renewal due to the major rarefaction of fibroblasts. This tissue atrophy may lead to radionecrosis (16,17).

In 2007, d'Hauthuille *et al*. integrated this association and introduced the notion of triggering factors that can accelerate the process of ORN and aggravating factors that maintain the evolution (18). In contrast to triggers,

aggravating factors stimulate the pathophysiological process of ORN.

Figure 1 summarizes the different theories and incorporates other risk factors involved in mandibular ORN.

1.5 Diagnosis of ORN

The diagnosis of ORN is clinico-radiological. It is imperative to rule out local tumor recurrence before making the diagnosis of ORN (9). In case of local recurrence, the existence of ORN foci can be observed. The presence of mandibular bone tumor recurrence in the irradiated field acts as a traumatic factor and may favor the secondary development of an ORN. In this case, the ORN is the consequence of the continued evolution of the disease (9).

1.5.1Clinical aspects

Mandibular pain is the main complaint of the patients and is the cause of weight loss secondary to the limitation of food intake. An infectious presentation of mandibular cellulitis may be observed. The notion of spontaneous mandibular cracking or chewing followed by pain is often of poor prognosis. Other complaints include homolateral otalgia, dysgeusia, foul breath, upper dysphagia associated with swallowing disorders, possible limitation of mouth opening and in some cases phonation disorder (19). In the case of infectious presentation, local inflammatory swelling, vestibular filling, purulent endobuccal discharge, skin erythema and even fistulization may be seen.

On endobuccal examination, a loss of mucosal substance opposite the mandibular bone structure, more or less associated with bone denudation, is most often diagnostic.

1.5.2 Radiological aspects

Cervicofacial CT is the gold standard imaging test for confirming and evaluating the severity of ORN. However, the dental panoramic or orthopantomogram (OPG), is used for the evaluation of suspected ORN. Early bone changes are only detected when there is at least a 30% to 50% reduction in bone mineral density to be visualized on conventional imaging (20). However, OPG is not able to accurately describe the soft tissue changes associated with ORN. OPG can be used for follow-up and monitoring of patients at risk for ORN (21).

In a group of 31 patients, Store *et al.* compared the effectiveness of CT and OPG in the diagnosis and preoperative evaluation of mandibular ORN. The study showed that CT had superiority in visualizing the radiologic features of the ORN and the anteroposterior extent of the lesion compared with OPG. They

recommended CT in a diagnostic dilemma or when surgery is being considered (22).

ORN may present as loss of bony trabeculae in cancellous bone on CT. It may be manifested by osteolytic mandibular lesions or cortical erosions. Reactive soft tissue augmentation, particularly of the masticatory muscles, may be observed, resulting in a pseudomass (22). The absence of soft tissue associated with bone changes in the irradiated field suggests tumor recurrence or sarcomatous change and not ORN.

MRI describes spinal cord alterations, cortical erosions, soft tissue changes, and complications of ORN (23–25). MRI of patients with ORN reveals altered spinal cord signal intensity in the involved portion of the mandible, typically appearing hypointense on T1-weighted images, hyperintense on T2-weighted recovery.

The ^{18}FDG PET scan, a functional imaging technique, has been advocated to detect tumor recurrence and differentiate it from ORN. The sensitivity and specificity of PET scanning have been shown to be better than CT scanning for detecting tumor recurrence in many studies (92.9-100% versus 72% and 64-96% versus 88%, respectively) (26,27). Semi-quantitative PET-scanner studies have shown that the cellular washout phase of ^{18}FDG is delayed in malignant lesions compared with benign lesions (28,29). More recently, Akashi *et al.* showed in a retrospective study the interest of using PET-scanner in the post-radiotherapy follow-up to evaluate tumor recurrence, the appearance of metastasis, but also to detect early the developmental modalities of the ORN (30).

1.5.3Anatomo-pathological confirmation

Although improved imaging techniques make it possible to suspect the appearance of an ORN, only pathological evidence can distinguish between an ORN and a tumor recurrence.

1.6 ORN classifications

Several classifications of ORN have been developed to assess the severity of bone involvement and to assist in therapeutic management. One of the first clinical-radiological classification systems for ORN was developed by Marx and Myers in 1990 (31). This classification is considered one of the most interesting for drug management and classifies ORN into 3 stages: (1): bone exposure of less than 2 mm with or without pain associated with radiological signs of diffuse demineralization; (2): bone denudation of more than 2 mm; (3): pathological fracture, orostoma, fistula, or involvement of the basilar margin of the mandible.

The recent simplified classification based like the previous one on a clinico-radiological approach by Karagozoglu *et al.* takes into account the symptoms in their model of ORN classification (32). In 2014, Karagozoglu *et al.* define ORN into 4 stages: (0) mandibular bone exposure for less than 1 month without

distinct changes on standard radiographs; (I) mandibular bone exposure for at least 1 month without distinct changes on standard radiographs, (IA) asymptomatic (no pain or presence of skin fistulas), or (IB) symptomatic (pain or presence of skin fistulas) ; (II) exposure of the mandibular bone for at least one month with distinct changes present but not involving the lower border of the mandible on standard radiographs, (IIA) asymptomatic (no pain or presence of skin fistulas), or (IIB) symptomatic (pain or presence of skin fistulas); (III) exposure of the mandibular bone for at least one month with clear changes involving the lower border of the mandible on standard radiographs, regardless of any other signs or symptoms (32).

The CTCAE version 5.0 common classification criteria for adverse events, less therapeutically used than the previous two, defines ORN in 5 grades in relation to the Lawton (Instrumental Activities of Daily Living (ADL)) and Katz (Activities of Daily Living (ADL)) scales.

1.7 Therapeutic management of ORN

The management of pain, local care, antibiotic therapy in case of superinfection and the elimination of risk factors (hygiene, mouthwash, adapted diet or even enteral feeding) are the basis of the management. In this article, only the so-called conservative approaches will be discussed.

Hyperbaric oxygen therapy (HBOT)

HBOT increases oxygen supply to hypoxic tissues and stimulates fibroblast proliferation, angiogenesis and collagen formation. HBOT may also have bactericidal or bacteriostatic effects (33). However, studies evaluating HBOT and its effect on ORN are limited by heterogeneous results. The only study evaluating the efficacy of HBOT in ORN was stopped early because no benefit over placebo was observed after one year (34). However, this study has been severely criticized because of several methodological problems, including a lack of precision on the HBOT protocol and exclusion criteria and a lack of power (35–37). Regarding the preventive role of HBOT, the English HOPON (Hyperbaric Oxygen for the Prevention of Osteoradionecrosis) randomized, controlled, multicenter, phase III trial is one of the most robust trials to evaluate the preventive role of HBOT in ON (38). 144 patients were randomized and 100 were analyzed for the primary endpoint. The incidence of ORN at 6 months was 6.4% and 5.7% for the HBOT and control groups, respectively, OR = 1.13; p = 1 (95% CI: 0.14 to 8.92). Patients in the hyperbaric arm had fewer acute symptoms but no significant differences in late pain or quality of life. The dropout rate was higher in the HBOT arm, but baseline characteristics of the groups that completed the trial were comparable between the two arms (39). The objective of the Cochrane review, published in November 2019, was to determine the level of evidence for

the use of either platelet-rich plasma placed in dental extraction sockets as a prophylactic, high-fluoride (1350 parts per million (ppm)) fluoride gel and toothpaste in the prevention of post-radiotherapy caries, or HBOT as a protective factor against the development of an ORN (40). This review analyzed 4 randomized controlled trials including 342 patients with ORN cancer who received curative or adjuvant radiotherapy. Given the inadequate sample sizes of the included studies, the levels of evidence for the interventions evaluated by the trials included in this review were considered insufficient.

PENTOCLO protocol

A better physio-pathological understanding of radiation-induced mucosal atrophy and fibrosis and bone involvement theoretically allows for better management and prevention of ORN. Delanian *et al.* have developed strategies for clinical management of this pre-necrotic phase and have selected treatments that focus on limiting aggravating factors and progression to the necrotic phase (41).The strategy also depends on a variety of other factors, including: (1) the stage of development of late normal tissue damage (i.e., prefibrosis, established fibrosis, late fibrosis, and atrophy/necrosis) and therefore the primary process of each phase (inflammatory phase, vascular phase, and stromal phase) ; (2) assessment of the severity of the fibroatrophic condition using recent subjective and objective quantitative criteria, such as the subjective, objective, medical management, analytical lesion assessment (SOMA-LENT) score to accurately determine improvement, stabilization, or deterioration; (3) the existence, availability, and safety of effective therapies; (4) sufficient duration of treatment in this chronic disease; and (5) whether the value of treatment has been established by randomized controlled trials despite the small number of symptomatic patients for their fibro-atrophic tissue damage secondary to radiation. Based on a better understanding of the complex fibro-atrophic and then necrotic process, Delanian *et al.* established the PENTOCLO (pentoxifylline, tocopherol, clodronate) protocol (42). This reference treatment is spread over several months (until complete healing) and is carried out in two distinct and successive phases: the first part of the treatment, known as "disinfiltration", lasts 4 weeks and consists of a daily treatment combining: 2g of amoxicillin-clavulanic acid, 1g of ciprofloxacin, 50mg of fluconazole, 20mg of prednisone and 20mg of omeprazole. The 2nd part of the treatment, maintained for about 6 months, until complete healing, combines in a daily intake 800mg of pentoxifylline, tocopherol 1g, 1600mg of clodronate 5 days / 7 from monday to friday, 20mg of prednisone and 20mg of omeprazole 2 days / 7, on saturday and sunday Four to six weekly mouthwashes combining 500mL of 1.4% sodium bicarbonate, 1 bottle of fungizone and 3 tablespoons of glycothymoline should be performed during the entire treatment. In the Robard *et al.* study, improvement of mucosal ulceration was observed in 16 of 21 patients at 3 months and 12

of 17 patients at 6 months of the PENTOCLO protocol. Healing was achieved in 16 patients. The median healing time was 82 days (32-266), and was shorter after surgery and radiotherapy (49 days) and longer after radio-chemotherapy (169 days). Tolerance and efficacy of treatment were assessed by endobuccal clinical examination, diet, weight, and analgesics. There was no discontinuation of treatment due to side effects (3).

1.8.1 Risk factors for mandibular ORN

The risk factors for mandibular ORN have been identified and can be grouped into four parts.

Patient-related factors

Global systemic affection must be distinguished from local risk factors.

The identification of genetic variants in patients irradiated under the same circumstances but with varying toxicities could become a must before any irradiation treatment. Some nucleotide polymorphisms (SNPs) can influence radiotoxicity on tissues. Knowing which patients are at risk of ORN from the beginning of treatment in order to have a preventive attitude and a more targeted monitoring seems to be part of a global patient management logic. For example, some patients with congenital diseases such as ataxia telangiectasia and xeroderma pigmentosum have deficits in the DNA repair mechanism making these patients very sensitive to ionizing radiation (43). After irradiation, the response to DNA damage is essential for the preservation of genome integrity. There are different DNA repair pathways depending on the damage sustained.

In 2012, in a systematic review including 5 case-control studies and 2 cohort studies, Ghazali *et al.* identified 14 SNPs of 9 genes involved in DNA damage response, post-radiation fibrosis and oxidative metabolism (44). Irradiated tissues exhibit high oxidative stress and the ability to manage this oxidative stress influences the risk of developing late side effects. Acute radiotoxicity appears to be associated with SNPs of DNA repair genes. SNPs of TGFβ1 were associated with ORN (OR at 4.2) and subcutaneous fibrosis. For Danielsson *et al.*, reduced levels of 8-oxo-dG and the SNP rs1695 of glutathione s-transferase p1 (GSTP1) are associated with elevated radiosensitivity and ORN risk (45).

In addition, the existence of alcohol and tobacco intoxication, chronic arterial hypertension, hypercholesterolemia, unbalanced diabetes or systemic diseases (vasculitis, anti-phospholipid syndrome, Raynaud's disease) are likely to lead to a defect in healing due to damage to the microvessels. Furthermore, if the body mass index increases by 1 point, the risk of developing mandibular ORN decreases by 27% (RR = 0.73) (46,47). However, Renda *et al.* demonstrated that patients who were at least overweight (BMI ≥ 25) had a higher risk of developing ORN (p = 0.002) (48). This same team developed a nomogram that could a priori predict the risk of developing ORN at 1 and 3 years according to: diabetic status, body mass index, type of

mandibular surgery, and mean mandibular dose.

The existence of a precarious oral condition associated with periodontal disease before the initiation of radiation therapy would favor the risk of ORN (49–51). Dental avulsion is the main risk factor for the development of non-spontaneous mandibular ORN.

Continued smoking, lack of regular stomatological surveillance, and trauma to the mandible, especially in connection with dental work, all contribute to the development of ORN. Radiation-induced hyposiality increases the risk of dental demineralization, caries and oral infection (46). Starting at about 10 Gy, the viscosity of saliva is disturbed, becoming thicker, less fluid, and more acidic in connection with radiation-induced alteration of the serous acini. As the radiation dose increases, the glandular acini are also damaged, resulting in a decrease in saliva production. Generally, a possible recovery to a previous salivation state can be observed at 18-24 months post-radiation (52). It is mainly during this phase that the risk of developing mandibular ORN is predominant.

1.8.2 Disease-related factors

Tumor location increases the risk of ORN when bone is involved by contiguity. For Barrelier, the incidence of ORN increases, depending on tumor location, by: 4.14% without bone contact, 14.6% with bone contact, and 19.35% with bone invasion (53).

The areas most likely to develop ORN lesions are tumors of the oral cavity followed by tumors of the oropharynx (35). Irradiation targeting tumors located in these areas will more likely include the mandible in the treatment fields in contrast to tumors of the hypopharynx and larynx.

The TNM of the carcinological disease, in particular the tumor size, seems to have an impact on the risk of developing ORN. Stage T4 appears to increase the risk of ORN due to tumor-induced bone fragility. Tumor necrosis and insufficient postoperative healing time before postoperative radiotherapy would be responsible (54).

1.8.3 Factors related to treatment

Vascular endothelial cells play a major role in bone metabolism by secreting various growth factors and chemokines that act on the target cells of bone remodeling (55). Thus, the involvement of the vascular network seems to be a key parameter in the initiation and development of the ORN process.

The existence of a primary carcinological surgery, often consisting of a mandibular osteotomy or even a mandibulotomy or an interrupted or non-interrupted mandibulectomy, results in a mandibular vascular

sacrifice, thus creating a bone trauma and consequently a predisposing ground for bone suffering. This first surgery, before adjuvant radiotherapy, constitutes, according to some authors, the most significant risk factor for ORN (49,56). Postoperative irradiation disrupts the healing process.

In locally advanced stages, radiation therapy may be combined with concomitant chemotherapy or targeted therapy. Cisplatin and cetuximab are the main agents used. Concomitant cisplatin-based radio-chemotherapy is the standard treatment for patients with histopathological factors of poor prognosis. Vascular thromboembolic events have been reported in 8.2-9.4% of patients undergoing platinum-based therapy (57). Some studies suggest that cisplatin may induce platelet activation, alter endothelial cell integrity, increase von Willebrand factor (58–60). No in vivo studies have been found demonstrating cisplatin toxicity directly to osteoblastic and osteoclastic bone cells. However, chemotherapy alone does not appear to be a risk factor for mandibular ORN (61–63). Renal damage secondary to cisplatin presents as acute renal failure with preserved diuresis, usually reversible, primarily affecting the tubulointerstitial compartment. The proximal tubules are selectively injured by cisplatin, which induces apoptosis of the tubular cells, characterized by a urinary leakage of magnesium. An American study showed that the presence of hypomagnesemia was predictive of the development of ORN in patients with oropharyngeal and oral cavity cancers receiving platinum-based induction chemotherapy followed by concomitant chemo-radiotherapy. Magnesium is an essential cofactor for approximately 300 enzymes, some of which are actively involved in bone metabolism. Hypomagnesemia induced by platinum-based therapy and to a lesser extent by cetuximab may further impair bone healing that is compromised by the vasculitis secondary to irradiation. This may explain why concomitant platinum-based chemoradiotherapy is associated with a higher risk of ORN than radiation therapy alone (64).

Cetuximab, a chimeric anti-EGFR antibody, is a therapeutic option when cisplatin cannot be used for the treatment of non-operated DSV cancers (65,66). Miroddi *et al*, in a meta-analysis including 12,870 patients from 17 randomized clinical trials, highlighted that patients receiving irradiation combined with cetuximab were approximately 1.5 times more likely to develop a thromboembolic event, reinforcing the idea of vascular toxicity of cetuximab (67).

The combination of carboplatin and 5-fluorouracil is also used concomitantly with radiotherapy for the treatment of patients with head and neck cancer (68). 5-fluorouracil also has a known vascular toxicity.

1.8.4 Factors related to irradiation technique

The risk factors for ORN related to radiation therapy are subdivided into different subparts: fractionation, spread, dose per fraction, daily dose, weekly dose, total dose, volume of treatment field delivered, mean and

maximum mandibular dose, mandibular volume irradiated, nature of radiation, and irradiation techniques. Table 1 summarizes various studies showing the incidence of ORN, mean mandibular doses, and some dosimetric parameters that favor the risk of ORN development. ORN is four times more frequent with external beam radiation therapy combined with interstitial brachytherapy than with external beam radiation therapy alone (10). Murray *et al*. showed that the risk of ORN was greater in patients treated with brachytherapy alone, then in patients who received a combination of external beam and brachytherapy, and finally in patients treated with radiotherapy alone (49).

In 2007, an American study, Chang et *al.* investigated in 413 patients treated for oropharyngeal carcinomas whether tooth extraction before radiotherapy decreased the risk of occurrence of ORN (69). Extractions before radiation were performed in 163 patients (39%). The study endpoint was ORN grade 2 or higher; grade 2 was defined as exposed cortical plaque requiring more than 3 months for healing. The median follow-up was 3.8 years (0.3 to 17.4 years). The incidence of ORN was 0.8% in edentulous patients, 15% in the dental extraction before radiation group, and 9% in the no dental extraction before radiation group. Multivariate analysis revealed that the following factors were significantly related to an increased risk of ORN: total dose ≥70 Gy ($p = 0.0054$), one fraction per day ($p = 0.0004$), performance of brachytherapy ($p = 0.0002$), and dental extractions before irradiation ($p = 0.00154$). Schuurhuis *et al.* presented a retrospective study of 185 patients treated with exclusive radiotherapy or postoperative irradiation from 2004 to 2008. The mean prescribed dose to the target was 64 Gy (50 to 70 Gy) (70). Patients with periodontal pockets larger than 6 mm had an increased risk of developing ORN (19%), especially when the pretreatment strategy was initial periodontal treatment (33%) rather than removal of these teeth (14%), emphasizing the importance of dental care in preventing the risk of postradiation mandibular complications.

In a 2009 retrospective study, Lee *et al.* investigated dosimetric parameters in 198 patients treated with exclusive radiotherapy or surgery followed by radiotherapy between 1990 and 2000 for cancer of the oral cavity (45%) or oropharynx (55%). The median total dose delivered was 60 Gy (71). All patients had a dental check-up before radiotherapy. Thirteen patients had a NRO. The probability of ORN was significantly increased in patients with mandibular surgery ($p = 0.001$) and in those with a biologically equivalent dose greater than 54 Gy in a fraction of 1.8 Gy ($p = 0.008$). In addition, the type of carcinological surgery modulates the risk of developing an ORN. Segmental and marginal mandibulectomies are at risk of developing ORN in contrast to hemi-mandibulectomy (72). Chen et al. reported the results of 142 patients with mandibular surgery with fibula free flap placement (73). Forty-eight patients were irradiated, 21 preoperatively and 27

postoperatively. Postoperative irradiation was an independent risk factor for bone complications (HR = 0.23; p = 0.009). The existence of mandibular surgery with placement of titanium-based osteosynthesis mini-plates would favor the ORN process (73).

In 2011, in a North American study, Gomez *et al.* investigated the management of 168 patients treated with IMRT between 2000 and 2007 for cancers of the oral cavity (36 patients), nasopharynx (25 patients), larynx/hypopharynx (31 patients), paranasal sinuses (35 patients) and oropharynx (41 patients). All patients had a dental evaluation before treatment, and those who were dentate received fluoride-based dental treatment. Seventy-one patients (42%) also underwent surgery and 110 patients (65%) received adjuvant chemotherapy. Pretreatment dental extractions were performed in 30 patients (18%) and 7 patients (4%) were edentulous. The median maximum mandibular dose was 67.98 Gy and the mean mandibular dose was 38.45 Gy. The median follow-up was 37.4 months (0.8 and 89.6 months). Two patients, initially with oral cavity cancer, developed ORN. Thus, the overall risk was 1.2% (2 of 168 patients) and the relative risk for patients with oral cancer was 5.5% (2 of 36 patients). The maximum mandibular doses for these 2 patients were 71.83 and 68.28 Gy, respectively, while the mean mandibular doses were 58.12 and 53.35 Gy, respectively (74).

In 2012, Nabil and Samman, referring to 22 randomized controlled trials from 1995 to 2010, recorded a total of 117 cases of ORN among 5742 patients irradiated for head and neck cancer, giving an incidence of 2%. It appeared that the addition of chemotherapy to radiation therapy did not increase the risk of developing ORN. Similarly, when subjects who received exclusive radiotherapy were compared with those receiving postoperative irradiation. No significant difference in the risk of developing ORN was observed. Also, no difference in the risk of developing ORN with the use of hyperfractionated radiotherapy without dose reduction was observed compared with conventional treatment. In contrast, when accelerated fractionation with total dose reduction was used, a reduction in the incidence of ORN compared with conventional fractionation was demonstrated (63).

In a 2013 North American retrospective study, Tsai *et al.* investigated the influence of dosimetric parameters in the risk of occurrence of ORN in 402 patients matched for age, sex, type of radiotherapy, and year of treatment treated with exclusive radiotherapy for oropharyngeal cancers classified as T1 and T2 (75). Thirty (7.5%) of the 402 patients developed an ORN with a median time to onset of 8 months. Mandibular volumes receiving 60 Gy and 50 Gy (p = 0.02) were significantly higher in patients with ORN(for 50 Gy: 40.5% vs. 30.8%; and for 60 Gy: 23.9% vs. 16.3%) after adjustment for dental factors.

In 2016, Kuo *et al.* reported a Taiwanese retrospective study that included 1759 patients with head and neck cancer treated with radiation therapy between 2000 and 2013. The objective of the study was to determine the risk of developing ORN in patients who had postradiation dental avulsion. Post-radiation dental avulsions were performed in 522 of 1759 patients. Moderate to severe ORN developed in 39 (2.2%) of the 1759 patients, with a mean time to onset of 3.02 years (0.62 to 8.89 years). ORN was observed in 27 (5.1%) of 522 patients who had post-radiotherapy dental avulsion and in 12 (0.97%) of 1237 patients who did not have avulsion. In addition, this study showed that the number of teeth extracted as well as the delay in performing post-radiotherapy dental avulsions were risk factors for ORN. ORN was observed in 9 (2.4%) of 373 postradiotherapy avulsion patients with 1 to 5 teeth removed, compared with 18 (12.1%) of 149 patients with ≥6 teeth avulsed ($p < 0.0001$). Patients with post-irradiation avulsions within 6 months had a significantly higher risk of ORN compared with those for whom the interval was greater than 6 months ($p < 0.0315$) (76).

In 2016, in a German study, Kuhnt *et al.* studied 776 patients treated with three-dimensional radiotherapy or IMRT exclusively or postoperatively between 2003 and 2013 for neoplasia: nasopharynx (43 patients), oropharynx (226 patients), oral cavity (259 patients), parotid (34 patients), and hypopharynx-larynx region (214 patients). Total post-surgical radiation doses ranged from 64 to 70 Gy, and exclusive radiation doses were around 77.6 Gy. Concomitant chemotherapy was used in 365 patients (47%). Moderate to severe ENT developed in 51 patients (6.6%) with a mean latency of 9 months (0 to 90 months). Carcinological bone surgery was required in 90 patients (11.6%). Bone surgery (HR = 5.87) and tumor site of the primary (oral cavity) (HR = 4.69) were associated with an increased risk of ORN. Gender, dental status, and chemotherapy did not appear to be correlated with the risk of ORN (61).

In 2017, in a retrospective North American 1:2 case-control study from the MD Anderson cancer center, Mohamed *et al.* determined dosimetric parameters associated with ORN in oropharyngeal cancer patients treated with IMRT between 2002 and 2013. Sixty-eight ORN cases and 131 controls were matched. The median follow-up was 41 months and the median time to ORN onset was 16 months. The mean mandibular dose was significantly higher in the ORN cohort (48.1 vs 43.6 Gy, $p < 0.0001$). The histogram-dose-volume curves from V35 to V73 (mandibular volume receiving 35 to 73 Gy, respectively) were all significantly higher in the ORN cohort compared with controls ($p < 0.0006$). Two parameters were identified in the statistical RPA (Recursive Partitioning Analysis): V43 and V58. The majority (81%) of patients with ORN had V43 ≥42% and V58 ≥25%. However, this combination was also present in 41% of patients in the non-ORN group (77).

In 2017, Sathasivam *et al.* studied a population of 285 patients with head and neck cancer, of whom 96 (68%) received primary surgery (47). Patients received either concomitant chemoradiotherapy or exclusive radiation.

Inclusion was from 1999 to 2008, median follow-up was 44.1 months (6 to 60 months), time to ORN was 10.8 months (6 to 54 months). Fifty-nine patients (20.7%) had mandibular ORN during their oncologic follow-up with a Dmoy in this group of patients at 65.8 Gy versus 62.8Gy in the control group ($p < 0.0001$). The authors emphasize that dosimetric criteria alone are not sufficient and that it is more a matter of a cluster of events to allow the development of mandibular ORN. Among the variables found to be significant in the risk of ORN occurrence are: dentoalveolar surgery, mandibular peri-resecting surgery, active smoking persisting after radiotherapy, type 2 diabetes, and total radiation dose.

In 2019, Aarup-Kristensen *et al.* reported a cohort of 1224 patients treated with IMRT (94%) with an ORN rate of 4.6% (78). Concomitant cisplatin chemotherapy was not found to be a risk factor for ORN (HR = 0.97; 95% CI: 0.53-1.75; p = 0.91). The prognostic factors were dental avulsions before radiotherapy (HR = 2.09; 95% CI: 1.1-3.98; p = 0.02), and mean dose to the mandible (HR = 1.04; 95% CI: 1.01-1.07; p = 0.02). In the same series, the ORN group was matched with a control group (1:2), (56 patients with ORN and 112 without ORN). Three quarters of the patients had received cisplatin chemotherapy. The ORN group had a mean dose of 41.7 Gy versus 37.7 Gy in the non-ORN group (p = 0.02). Mandible volumes receiving 30-60 Gy were the most significant on the risk of ORN (approximately V40 >50%, V50 >35%, V60 >20%).

In 2021, van Djik *et al.* reported a cohort of 1259 patients and suggested that less than 30% of the mandibule should receive a dose of 35 Gy or more for an ORNI-IV risk lower than 5%. By analysing the dose-volume histograms in patients who did not have osteoradionecrosis, the following criteria can also be proposed i.e V30 <60%, V40 <45%, V50 <30% and V60 <18Gy (79).

In 2021, Kubota *et al.* reported the results on 616 patients treated with curative intent or postoperative radiation therapy. The rate of ORN was 7.5%. In multivariate analyses, the 3-year cumulative ORN incidence rates were 2.5% and 8.6% in patients with V60 ≤14% and >14%, respectively ($p < 0.0001$). Total dose was not found to be a predictive factor of ORN (80).

In 2022, in a Dutch retrospective study, Mörig *et al.* observed 41 cases of mandibular ORN among 227 patients with primary surgery treated with IMRT (81). The cumulative incidence of mandibular ORN was 8.4% at 1 year, 13.2% at 2 years, 15.9% at 3 years, 18.9% at 4 years and 19.8% at 5 years. The median time to onset was 13.6 months (range 3-81 months). The mean dose to the mandible was 37.1 Gy and the V60 was 25.9%). Patients treated with mandibular surgery had higher mandibular dosimetric values than those without surgery, mean dose at 42 Gy versus 34 Gy and V60 at 35% versus 19%, respectively. Four risk factors for ORN were identified in multivariate analysis: smoking, mandibulotomy or segmental mandibular resection, cervical radiotherapy, and V60. Active smoking and higher V60 remained statistically significant with hazard ratios

of: HR 2.13 (95%CI 1.12-4.06) and 1.02, respectively. Furthermore, active smokers receiving a high mandibular irradiation dose (V60 ≥ 40%) had a 5-fold increased risk of developing mandibular ORN compared to other patients in the study (29% vs. 6%, $p < 0.01$).

1.9 Conclusion

Various clinical (large tumor size for cancers of the oral cavity or oropharynx, mandibular tumor invasion), therapeutic (primary tumor surgery, post-radiotherapy dental extraction) and dosimetric (high mean mandibular dose, volume dose effect at the mandible) criteria appear to be correlated with the risk of ORN. Most of these studies on the risk factors for the development of ORN were performed with old radiotherapy techniques and are all retrospective studies of small to medium size. The modernization of irradiation techniques over the last twenty years (conformal irradiation with intensity modulation), with the control of dose distribution in particular in the mandible, should make it possible to reduce the risk of ORN. Taking into account the data in the literature, it would be possible to propose as "simple and rounded" dosimetric objectives a mean dose to the mandible of less than 48 Gy with doses/volumes of the order of V40 < 40%, V50 < 30% and V60 < 20%.

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