Acta Scientific Dental Sciences (ISSN: 2581-4893)

Volume 7 Issue 8 August 2023

Review Article

Risk Factors for Osteoradionecrosis of the Jaw in the Era of Modern Head and Neck Radiotherapy

Erkan Topkan[1], Efsun Somay[2], Busra Yilmaz[3], Berrin Pehlivan[4], Ugur Selek[5]

[1]*Department of Radiation Oncology, Faculty of Medicine, Baskent University, Adana, Turkey*

[2]*Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Baskent University, Ankara, Turkey*

[3]*Department of Oral and Maxillofacial Radiology, School of Dental Medicine, Bahcesehir University, Istanbul, Turkey*

[4]*Department of Radiation Oncology, Bahcesehir University, Istanbul, Turkey*

[5]*Department of Radiation Oncology, School of Medicine, Koc University, Istanbul, Turkey*

***Corresponding Author:** Erkan Topkan, Department of Radiation Oncology, Faculty of Medicine, Baskent University, Adana, Turkey.

DOI: 10.31080/ASDS.2023.07.1685

Received: July 11, 2023

Published: July 29, 2023

Abstract

Radiotherapy is an essential component of curative treatment for head and neck cancer, either as a neoadjuvant or adjuvant treatment to surgery or as a definitive treatment with or without chemotherapy, depending on the stage of the disease and general health. However, aggressive RT or chemoradiotherapy can result in radiation-induced severe late toxicities, including the severely debilitating osteoradionecrosis of the jaws (ORNJ), which may affect a relatively small but significant proportion of this patient population. ORNJ is characterized by necrosis of bone tissue and failure to heal for at least three months. In the majority of cases, ORNJ progresses gradually, worsening and becoming more painful, which results in infection and pathological fracture. In the absence of a proven curative treatment other than aggressive surgeries, the prevalence of ORNJ could theoretically be decreased by implementing a well-organized multidisciplinary oral care program and reducing the ORNJ-related risk factors. These risk factors include the patient, the tumor, pre-radiotherapy mandibular surgery, tooth extractions, implant placement, radiation modality, and radiation dosimetry-related factors. Therefore, the present paper provides a literature review and update on the established and frequently disputed risk factors underlying ORNJ and their radiobiological bases.

Keywords: Head and Neck Cancer; Toxicity; Osteoradionecrosis; Risk Factors

Introduction

Radiation therapy (RT) is an essential component of the oncological treatment of head and neck cancers (HNC). In cases of early-stage squamous cell carcinoma and locally advanced tumors, such as adenoid cystic or mucoepidermoid carcinomas of the salivary glands, where effective chemotherapy options are not available, it may be used as the sole treatment option. When combined with concurrent chemotherapy, RT may serve as the mainstay of treatment for locally advanced HNC (LA-HNC). Additionally, RT may be used as a primary palliative measure in cases of recurrent or metastatic disease or as a neoadjuvant or adjuvant treatment option in relation to surgery. HNCs are notable for being the sixth most common type of cancer worldwide and having a high rate of therapeutic failures that lead to a 5-year survival rate of 50-60% [1]. Except for laryngeal cancers, most HNCs manifest as LA-HNC, in which definitive concurrent chemoradiotherapy (CCRT), either alone or in combination with induction chemotherapy, represents the gold standard of care in terms of organ-sparing approach in such patients [2]. However, successful but aggressive RT or CCRT can result in radiation-induced severe late toxicities like submucosal fibrosis, dysphagia, xerostomia, tooth loss, trismus, and osteoradionecrosis of the jaws (ORNJ) in a considerable percentage of patients [3,4].

ORNJ is a severe late toxicity of RT and CCRT (Figure 1), with a prevalence rate ranging from 0.4 to 56% [5]. This wide range in prevalence can be attributed to a variety of factors, including the presence or absence of concurrent chemotherapy use, mandibular resection, pre- or post-treatment tooth extractions, implant placement, periodontitis, chronic infections, RT modality and technique, total and per fraction RT doses, use of dose constraints for the jaw, mean or Vx (volume receiving a specified dose or more) dose of the jaw, and likely many more. Newer, more sophisticated RT techniques, such as three-dimensional conformal RT (3D-CRT), intensity-modulated RT (IMRT), and intensity-modulated proton therapy (IMPT), have reduced the risk of ORNJ due to their improved tissue sparing properties, thanks to advancements in computer-aided technology. However, depending on the tumor and involved nodal

localization, as well as unavoidable mandibular exposure to higher radiation doses due to the tumor's proximity to the mandible, ORNJ may still occur in a significant proportion of HNC patients [6]. This claim was recently supported by Singh., *et al*. [7]. who reported that the incidence of ORNJ was 10.6% in a total of 122 patients with oral cavity- (OCC) and oropharyngeal cancer (OPC) treated with IMPT, a highly advanced RT technique.

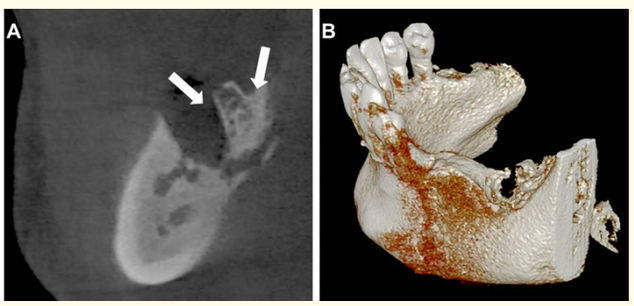

Figure 1: Cone-beam computed tomography images demonstrate extensive bone resorption and sequestration of osteoradionecrosis in the left mandibular molar region (white arrows). A) Sagittal view; B): Three-dimensionally reconstructed image showing the area of osteoradionecrosis.

Essential bodily functions like swallowing, speaking, and mastication are adversely impacted by ORNJ by causing pain, halitosis, deformity, limited mouth opening, mucosal fistulas, and pathological fractures -[8-10]. Delivery of oncologic therapy may be more difficult in affected patients due to anemia, infections, leukocytosis, hyperproteinemia, and hypercoagulation [11]. In the event that these patients live long enough, the development of trismus and numbness after ORNJ may worsen all aspects of their quality of life (QoL) measures [12]. Additional factors that can significantly lower QoL include dietary restrictions, eating in public, speech comprehension, poor communication skills, social isolation, and even major depression [13-15]. Uncontrolled and continuously advancing ORNJ may also jeopardize the lives of such patients, either through septicemia or difficulties in intubation during emergency circumstances caused by ORNJ-related trismus [16].

Although numerouslocal and systemic risk factors for the development of ORNJ have been discussed in the literature, there are still only a few well-established factors, with the remaining majority being largely controversial [17]. For example, while prescribed tumor dose is invariably proposed as one of the strongest predictors of ORNJ, dosimetric variables such as median and Vx of the mandible are frequently underrated. Contrarily, a high tumor dose may not always correspond to a high mandibular dose, especially in the era of IMRT or IMPT, where the mandibular doses can be reduced to markedly lower levels compared to conventional RT methods. Thus, the main objective of this chapter is to provide a concise overview of the established as well as frequently disputed risk factors for ORNJ and their radiobiological bases.

Risk factors linked to ORNJ

The severe late toxicity of RT and CCRT, namely ORNJ, can negatively affect a patient's QoL in many ways. Familiarity with the ORNJ risk factors may help improve the prognosis of the condition and reduce the risk of developing it through the early adoption of preventative measures and the prompt commencement of effective treatments. A higher risk of ORNJ development has been linked to several patient-, tumor-, mandibular surgery-, dental procedure-, and treatment-related risk factors [18].

Patient-related Risk Factors for ORNJ

Research to date strongly suggests that some patient-related traits are linked to an elevated risk of ORNJ, even when all other confounding factors are well-matched. One of these is having a genetic predisposition. In order to help with the creation of customized RT protocols, Brooker and colleagues recently set out to find a panel of common genetic variations that could potentially predict ORNJ [19]. DNA samples from patients who underwent prior HNC RT and at least two years of follow-ups were subjected to single nucleotide polymorphism (SNP) array analysis. A control group that had participated in an earlier clinical trial was compared to a cohort of ORNJ patients. A representative model of 18 SNPs with 92% accuracy was developed. Four SNPs; rs34798038 (A/G) (P = 0.006), rs6011731 (C/T) (P = 0.018), rs530752 (A/G) (P = 0.046), and rs2348569 (G/G) (P = 0.005) were found to be substantially linked with the lack of ORNJ in multivariate regression analysis. These findings imply the existence of a group of patients who are genetically protected from ORNJ, even though they do not provide a specific gene or gene set that may be associated with higher ORNJ risk.

Because the impact of individual radiosensitivity has been proposed as an explanation for the elevated prevalence of ORNJ in some patients, Danielsson., *et al*. undertook a study to compare a cohort of patients with stage II/III ORNJ to matched controls [20]. To examine the body's capacity to combat radiation-induced oxidative stress, blood was collected and exposed to radiation in a lab setting. Additionally, genotypes were determined for eight SNPs linked to genes that regulate oxidative stress responses. A difference in 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxo-dG) levels was found between the patient cohorts (P = 0.01). The SNP rs1695 in glutathione S-transferase p1 (GSTP1) was also found to be more frequent in the patients with ORN (P = 0.02). Multivariate analysis of the clinical and biological factors revealed concomitant brachytherapy plus the two biomarkers to be significant factors that influence the risk of ORNJ in HNC patients.

Habits, such as the most commonly reported alcohol use and cigarette smoking may also influence the risk of ORNJ. Owosho., *et*

al. reviewed the data of 1023 patients treated with IMRT for OCC and OPC at Memorial Sloan Kettering Cancer Center between 2004 and 2013 [21]. A case-control study was carried out to assess the relationship between ORNJ and risk variables. One to two ORNJ-free patients were chosen to match each ORNJ patient in terms of gender, tumor site, and size. During a median follow-up period of 52.5 months, 44 patients (4.3%) experienced ORNJ. Poor periodontal health (P = 0.03), a history of alcohol use (P = 0.002), and radiation dose (P = 0.009) were all significant risk factors in the matched case-control analysis, while alcohol use (P = 0.004) and radiation dose (P = 0.026) were meaningful risk factors on multivariate analysis. As shown by Kluth., *et al*. more than 30 years ago, cigarette smoking is another behavioral factor that enhances the risk of ORNJ [22]. The onset of ORNJ may be accelerated by smoking or chewing tobacco according to Acharya., *et al*. [23]. The authors of this retrospective study, which included 231 HNC patients, reported that of the 13 ORNJ cases (5.62%), 10 (76.9%) had a history of tobacco use, and 8 (61.5%) had a time interval of less than a year between RT and the occurrence of ORNJ. Even though the exact pathophysiologic mechanism is unexplored, this effect could be linked to the various effects of cigarette smoke on tissues, including the jaw bones [24]. Cigarette smoke can cause cell death in a concentration-dependent manner, as has already been shown: lower concentrations cause apoptosis-like cell death without the need for caspase, whereas higher concentrations disrupt apoptotic signaling and cause necrosis [25]. The fibrogenic process may differ slightly in different tissues, but the key steps are almost always the same. The steps of the fibrogenesis process have been identified as damage to the epithelial/endothelial barriers, the release of transforming growth factor-beta1 (TGF-β1), recruitment of inflammatory cells, the production of reactive oxygen species (ROS), the activation of collagen-producing cells, and the activation of myofibroblasts [26]. By activating connective tissue growth factor (CTGF), another important cytokine associated with fibrogenesis, and stimulating fibroblast functions through TGF-β1, nicotine causes fibrosis [27]. Takeuchi *et al*., for instance, recently demonstrated that nicotine increased the levels of CTGF in human gingival cells and the production of collagen in the periodontal ligament [28]. This fundamental background is supported by a recent study by Möring., *et al*. who found that smokers experience ORNJ symptoms much earlier than non-smokers do (9.3 vs. 21.4 months) [29].

Other risk factors that have been related to an elevated risk of ORNJ can be outlined as follows: Although confirmatory data is limited, Reuther., *et al*. found that men had a 3-fold higher incidence than women [30]. However, given that men are more likely than women to smoke and consume alcohol, it is difficult to suggest a genetic foundation for this data. Another risk factor that has been put forth but is difficult to verify is obesity. In this context, Goldwaser., *et al*. discovered that a high body mass index is a predictor of ORNJ after HNC irradiation [31]. Although this finding could be attributable to the unfavorable hormonal influences of obesity, more in-depth basic research is needed to prove that obesity is a substantial risk factor for ORNJ development. Most ORNJ sufferers have poor nutritional status, which is usually limited to liquid or semi-liquid diets, poor nutritional status may also be a risk factor for higher ORNJ rates in HNC patients treated with RT or CCRT. Confirming this affirmation, recently, Huang., *et al*. demonstrated that almost all ORNJ patients (95.3%) had at least one laboratory marker that was below the normal physiological range [32]. A total of 40 (37.5%) patients were classified as undernourished, with lower serum albumin (mean difference: 1.8 0.8 g/L; P = 0.02), prealbumin (mean difference: 26.8 10.8 mg/L; P = 0.02), and body mass index (3.8 0.4 kg/m^2; P = 0.0001).Other factors that are usually linked to higher prevalence of ORNJ include poor oral hygiene and dental health status [33,34]. These variables may cause dental decay, chronic infections with resistance, non-healing soft tissue wounds, and tooth decay, all of which can cause ORNJ indirectly through the need for tooth extractions or directly owing to non-healing, infected soft tissue ulcers.

Tumor-related Risk Factors for ORNJ

HNC may increase the risk of ORNJ in a variety of ways. First, the type of tumor and its location relative to the mandible may influence this risk. That, OCC, OPC, and unresectable salivary gland tumors appear to be associated with an increased ORNJ risk due to their proximity to the mandible [35,36]. However, this finding is most likely due to the higher RT doses received by a significant portion of the mandible in such tumors and not to an ORNJ-increasing specific genotype or phenotype, as no such evidence has been reported to date [37]. Higher ORNJ risk has been associated with larger tumor sizes, likely as a result of the requirement for larger planning target volumes (PTV) during high-dose RT, which may unavoidably enclose a sizeable volume of the mandible [38]. Invasion of the mandible either by the tumor or the metastatic neck nodes may increase the risk of ORNJ by mandating a mandibular resection and direct involvement of this region in the high-dose PTV [36]. Additionally, presence of metastatic intra-parotid, levels IA, IB, and IIA neck nodes may serve as an independent risk factor by mandating higher PTV doses, and unavoidable higher mandibular exposure even if they do not invade it [48]. Recurrent or second/secondary HNCs may also increase the risk of ORNJ, especially if patients are not candidates for salvage surgery and/or require definitive, intra-operative, or postoperative re-irradiation [40].

ORNJ risk factors associated with prior mandibular surgery

Mandibular resection is often required during the surgical management of OCCs adjacent to or invading the mandible. Mandibular surgery causes injury to the relatively poorly vascularized mandible, which is more drastic than tooth extraction or implant placement procedures. The presence of mandibular invasion implies the presence of a T4 stage OCC, in which adjuvant CCRT is indicated to boost the likelihood of local and systemic control by eradicating any potential residual tumor cells and microscopic distant metas-

tases. However, because the healing process is hindered or stopped completely following RT, surgically treated mandibles may become more prone to ORNJ. As a result, pre-RT mandibular surgery is usually regarded as another treatment-related risk factor for ORNJ.

In a study by Kubota., *et al*., pre-RT mandibular resection was a risk factor for the development of ORNJ in univariate analysis (P = 0.0055), even though its impact was negligible in multivariate analysis [41]. In contrast Monnier., *et al*. [36] and Sathasivam., *et al*. [42] both found that pre-RT mandibular surgery was a significant predictor of increased ORNJ rates. Tucker., *et al*. also observed that 3 (42.9%) of the seven ORNJ cases had pre-RT mandibular surgery for salivary gland tumors infiltrating the mandible [43].

When evaluating the risk of ORNJ, other factors to take into account include the extent of the surgery and the mandibular resection technique. Chen., *et al*. published a large retrospective research that included 1692 OCC patients [44]. ORNJ was diagnosed in 105 patients, resulting in a 6.2% prevalence rate. ORNJ was related with independent characteristics such as primary site, which included the mouth floor, buccal mucosa, retromolar trigone, or gum, segmental mandibulectomy, and total radiation dosage to the primary site of ≥ 75 Gy. Another notable result of this research was that patients who underwent segmental mandibulectomy had a higher ORNJ rate than those who did not and those who received marginal or hemi mandibulectomy. Although more research is needed to confirm these findings, they indicate a clear and significant association between the type of surgery and the prevalence of ORNJ, namely that the more invasive the surgery, the higher the likelihood of ORNJ.

ORNJ risk factors associated with dental procedures

Several dental procedures, which can be broadly classified as dental extraction- and implant placement-related risk factors, may be linked to increased rates of ORNJ in HNC patients undergoing RT. These patients may experience many tooth or gum problems before, during or after the RT or CCRT, posing a significant contributor to teeth losses. In addition to damaging the microvascular system in the irradiated teeth, RT also results in the loss of osteoblast and cement oblast, as will be covered in more detail later in this chapter. These changes in tooth structure, along with changes in oral flora and decreased salivary gland activity, may collectively predispose people to dental caries, root, and periodontal diseases, which may necessitate tooth extractions, a well-established risk factor for ORNJ [45-47]. Tooth extractions may be required at any point-before, during, or after the oncological treatment-with a particular risk for ORNJ. Tooth extractions are rarely practiced during the RT or CCRT course thanks to the current pretreatment oral care programs for these patients. Therefore, the primary risk factors for ORNJ in HNC patients are tooth extractions prior to and following RT, or both.

Pre-RT dental extraction-related factors

Even though pre-RT tooth extractions were linked to ORNJ in several studies, this is not a common observation. In a retrospective cohort of 1023 OCC and OPC patients, Owosho., *et al*. found that only 18% of ORNJ cases underwent tooth extractions prior to RT, indicating that pre-RT tooth extractions were not associated with an increased likelihood of ORNJ [21]. Even though this outcome might be considered evidence of the safety of pre-RT tooth extractions, the results of the available studies typically do not support it. In a large cohort study involving 23,527 patients with HNC, Wang., *et al*. discovered that the overall incidence of ORNJ was 3.93 per 100 person-years, with buccal cancer carrying the highest ORNJ risk [45]. In univariate analysis, pre-RT tooth extractions were found to be significant; however, this was lost in multivariate analysis. On the other hand, a lack of pre-RT dental extractions was found to be a reliable indicator of severe ORNJ in the study by Chopra., *et al*. and colleagues [46]. In the study by Chang., *et al*., ORNJ rates in 413 OPC were <1%, 9%, and 15% in edentulous, teeth in-field without pre-RT extractions, and teeth in-field with pre-RT extractions, respectively [47]. The incidence of ORNJ was higher in patients with poor in-field teeth and pre-RT extractions at 5 years (16% vs. 6%). The 5-year ORNJ incidence was also higher (15% vs. 2%) for individuals with in-field teeth in good condition and pre-RT extractions than for individuals without extractions. Beaumont and colleagues recently reported that the ORNJ rates of patients with pre-RT tooth extractions (5.5%) and without them (5.3%) were similar in a meta-analysis of 21 studies involving 36,294 patients [48]. In the most recently published meta-analysis of 22 studies, patients undergoing pre-RT tooth extractions were found to have a 55% increased risk of experiencing ORNJ [49]. In a meta-analysis of seven publications with 875 patients, Balermpas., *et al*. searched for evidence of ORNJ following dental extractions before or after IMRT for HNC patients (50). ORNJ was found in 28 (3.2%) of the patients. ORNJ was linked to extractions in 15 (53.6%) of the patients, with 8 and 7 cases being related to pre-IMRT and post-IMRT extractions, respectively. The risk (RR = 0.18; P = 0.031) and odds (OR = 0.16; P = 0.049) for ORNJ favored pre-IMRT extractions. All of these results point to an increased risk of ORNJ following pre-RT tooth extractions.

When teeth have suffered irreparable damage, such as caries, the loss of periodontal tissues, a dubious pulpal condition, residual roots, or partially erupted teeth that have come into contact with the oral cavity, extraction is unavoidable. Although the recovery period before the start of RT or CCRT appears to be the component of utmost importance for ORNJ development, obstacles to achieving this goal include tumor recurrence after surgery and tumor upstaging during the prolonged wait for definitive CCRT. This is because it takes at least three months for the impacted bone to fully

recover [51], which is unacceptable given the problems with tumor progression and recurrence mentioned above. As a result, the time between the tooth extraction and RT should be as short as possible without compromising any oncologic treatment or ORNJ risk, which is typically advised to be in the range of 10-14 days [52]. Additionally, wound healing must be adapted to the number of extractions to prevent ORNJ, as multiple extractions should necessitate a longer healing time [53].

Post-RT dental extraction-related factors

A considerable percentage of patients who have received radiation therapy may need to have teeth extracted due to the RT's detrimental effects on the tooth and/or its supporting soft tissues, and bad habits like continued alcohol or smoking use, or inadequate oral hygiene, For instance, Yilmaz., *et al*. recently reported that 79.4% of the study population required tooth extractions after CCRT, with 54.8% of patients needing 5 or more teeth to be removed [54]. It is frequently stated that post-RT extractions are riskier than pre-RT extractions, despite the fact that the stronger association of ORNJ with these procedure is not a consistent. According to Girardi., *et al*., there is a tendency for the risk of ORNJ to increase [odds ratio (OR): 3.04; P = 0.08], especially when tooth extraction follows RT [55]. Some authors claim that post-RT tooth extractions are significantly associated with higher rates of ORNJ than pre-RT extractions [45,56,57].

The results of Nabil and Samman's systematic review showed that the incidence rate of ORNJ following tooth extraction in patients who had received RT was 7% [58]. Pre-RT extraction did not carry any additional risk, according to the nationwide study conducted by Wang., *et al*., but post-RT extraction was connected to a gradual increase in ORNJ risk over time that peaked at 4 to 5 years [45]. Another risk factor for ORNJ is the timing of the post-RT tooth extraction. Khoo., *et al.* [59]. discovered that tooth extractions carried out more than five years after RT were linked to a lower risk of ORNJ (OR = 0.06; P < 0.001). This finding, however, contradicts research findings indicating that the greater the interval between RT and dental extraction, the greater the ORNJ risk. Wang., *et al*. found that the ORNJ rate increased steadily after the first year of RT, with a peak at 4 years [45]. Nabil and Samman reported an incidence rate of 7.5% within the first year after RT, 22.6% between 2 and 5 years, and 17% after 5 years of RT, confirming Wang's findings [58]. Marx and Johnson discovered a bimodal peak in the incidence of ORNJ [60]. with the first and second peaks manifesting in the first three months and about five years after RT, respectively. Based on these findings and the radiobiological mechanisms of tissue hypoxia, hypovascularity, apoptotic cell death, and hyper fibrosis in ORNJ, it is recommended that post-RT tooth extractions be done within the first six months after RT to lower the risk of ORN [34]. Provided the longer RT-to-tooth extraction intervals, there appears to be no safer time for tooth extractions, as ORNJ can occur even 30 years after RT [59].

Although research on the topic is ongoing, results from the available literature indicate that post-RT tooth extractions are associated with a higher risk of ORNJ than pre-RT extractions. For pre-RT tooth extractions, a healing period of at least 10 to 14 days is advised before the start of RT; however, this period should be determined on a patient-by-patient basis when there are multiple extractions. If indicated, post-RT tooth extractions should be carried out within the first six months of RT to lessen the possibility of ORNJ before the hypo vascular and hyper fibrotic tissue regeneration processes are complete.

Implant placement-related Risk for ORNJ

To improve their ability to chew, swallow, and bite; meet their daily nutritional needs; and improve their aesthetic, social, psychological, and economic quality of life, HNC patients may need dental rehabilitation either before or after receiving oncologic treatment as a result of tooth loss [61]. Because of the threat of abutment failure, traditional fixed prosthodontic replacement is not recommended in individuals with a high caries risk. A conventional removable prosthesis may not fit comfortably following oncological treatments, including the RT, due to anatomical changes in the orofacial region and jaws, such as atrophied and erythematous mucosa and/or resected jaw bones [62,63]. Thus, dental implants are widely utilized in this patient population, as they may enable more successful oral rehabilitation in terms of chewing, facial aesthetics, and speech function [64].

Endosteal implants are alloplastic materials surgically inserted into a residual bony ridge to serve as a prosthodontic foundation. They are the most preferred implant compared to their counterparts, such as transosteal and periosteal implants). Although many factors can influence the healing process, typically, the formation of a fibrin clot that restricts blood flow and provides initial support to the osteoprogenitor cells follows the placement of a dental implant. The success of the osseointegration process, which determines the direct and stable connection between bone and implant, is determined by the adequacy of clot formation [65]. However, therapeutic RT may have an impact on the success of the osseointegration process and, as a result, the implant's survival. Kudo., *et al*. demonstrated in an animal model that irradiating the implant placement site shortly after implantation prevents direct contact between the hydroxyapatite implant and the surrounding bone [66]. If delivered before complete osseointegration, post-implantation irradiation is associated with unavoidable delays or failures in bone remodeling, which may lead to the development of ORNJ.

The use of implants in patients with irradiated HNC is resisted by many clinicians who believe they are contraindicated [67]. Their primary trepidations are altered anatomy and impaired wound healing, which make implant placement challenging and increase the odds of issues like failed osseointegration, soft tissue hyperplasia, and ORNJ. Schiegnitz., *et al*. compared implant survival in

irradiated and non-irradiated bone in a meta-analysis, which revealed a significantly higher rate of implant failure in irradiated bone compared to non-irradiated bone (OR 1.97; P < .00001), with a mean overall implant survival of 87.8% [68]. Unfortunately, ORNJ incidence rates were not addressed in this meta-analysis. The systematic review reported by Koudougou., *et al*. focused on the outcomes of implants placed during ablative surgery in patients with HNC who had postoperative RT [69]. A total of 755 native mandible primary implants were analyzed in four comparative investigations. The implant survival rate with post-implant placement RT was 89.6% compared to 98.6% in individuals who did not receive RT. The success rate of implant placement was 67.4% in patients with RT delivered shortly after implant placement versus 93.1% in patients with implant surgery performed one year after RT completion. There were only 5 (0.7%) reported cases of ORNJ. Toneatti., *et al*. have conducted a meta-analysis to analyze dental implant survival, quantify the incidence rate of ORNJ, and evaluate risk variables in patients with irradiated HNC [67]. Of the 660 patients involved, RT was administered to a total of 425. In total, 2602 dental implants were placed, 1637 of which were in patients who had received RT. After respective average follow-ups of 37.7 and 39.8 months, implant survival was 97% in non-irradiated patients and 91.9% in irradiated patients. With an incidence of 3%, ORNJ occurred in 11 cases. While the authors were unable to pinpoint any factors influencing ORNJ occurrence, the main factors affecting implant survival were RT and grafting status. All of these findings imply that implant placements, whether before or after RT, are related with a slight but clinically significant increase in ORNJ rates. Hence, despite its remarkable restorative power, implant placement should be carefully discussed in a multidisciplinary setting, and the risks should be explained to the patient as the procedure is not ORNJ-free.

RT dose and technique as risk factors for ORNJ

High RT doses hinder bone turnover and increase the risk of infections, tissue atrophy, pathological fractures, and ORNJ [70]. It is well-known that some bones, like the mandible, may suffer these disastrous effects more severely due to their high susceptibility to RT effects [71]. ORNJ is recognized as a severe consequence of RT or CCRT for locally or locoregionally advanced HNC patients, which is a source of frustration for both patients and clinicians. ORNJ is identified in 2-22% of all HNC patients, despite the use of state-of-the-art RT techniques [18]. Compared to the other facial bones, the mandible shows a noticeably higher prevalence of ORNJ [48,71]. A logical explanation for this discovery is provided by the fact that the mandible's vascular supply is only one-sixth that of the maxilla [73-75]. The fact that the jaw is more frequently enclosed in the radiation portal and receives higher RT doses than the maxilla may also be a risk factor for higher ORNJ rates [76]. However, in order to comprehend the ORNJ, one must be familiar with the pathophysiologic mechanisms of radiation-induced bone injury in addition to these anatomical and clinical justifications (Figure 2).

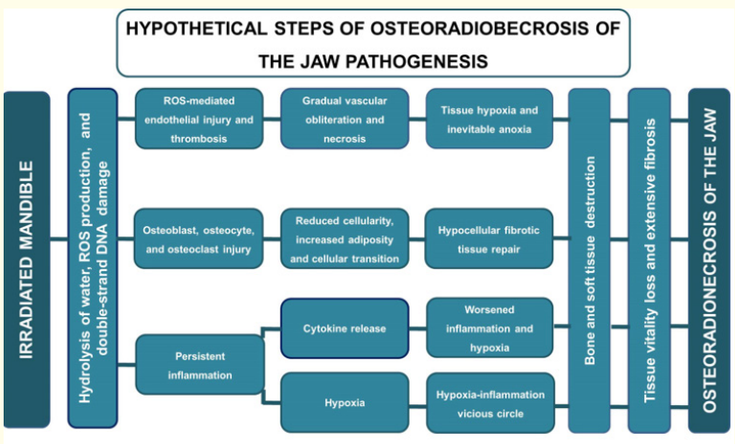

Figure 2: Hypothetical complex pathophysiologic mechanisms of the osteoradionecrosisoof the jaw (ROS: Reactive oxygen species; DNA: Deoxyribonucleic acid).

Influence of RT on bone anatomy and physiology

The bones, including the jawbone, undergo significant remodeling throughout a person's lifetime. A close balance must be struck between bone formation by osteoblasts (OBs) and bone resorption by osteoclasts (OCs) to maintain a healthy bone microenvironment and a functional skeletal system [77]. Furthermore, normal levels of various hormones and cytokines are required for properly regulated bone metabolism, while any dysregulation in this complex system can result in osteoporotic or osteopetrotic diseases depending on the dominant remodeling process, which is unrelated to the bone in question.

Due to its high calcium content and ability to absorb almost 40% more radiation than surrounding tissues, bone is a frequent site for radiation-induced injury [78]. Acute inflammation, characterized by increased vascular permeability with localized edema,

endothelial cell death, and vascular thrombosis, is brought on by the radiation-induced release of excessive amounts of cytokines and chemokines as an injury response [78,79]. In the later phases, RT also promotes fibroatrophic processes, which force tissue to be poorly vascularized and hamper appropriate healing. This unfavorable situation causes tissue to become more fragile and causes inflammation to flare up or reoccur after local injuries, such as tooth extraction or dental implant placement procedures [78,79]. RT, like osteoporotic pathologies, reduces trabecular bone volume and skeletal stem cell populations while increasing bone marrow adiposity and serum CTX/TRAP5 levels, resulting in more lagging and less efficacious fracture healing [80,81]. Also, skeletal stem cells in irradiated bones seem to favor adipogenesis over osteogenesis, leading to RT-induced bone loss, which is thought to be related to the immediate increase in osteoclast activity after RT and the subsequent latent decrease in osteoblast activity in the weeks that followed [81,82]. High-dose RT may alter the differentiation characteristics of skeletal stem cells in favor of decreased differentiation capacity but increased radiation-induced cellular senescence, as evidenced by a strong senescence-associated β-galactosidase labeling signal that overlaps with the cell death pattern [80,83].

A rapid rise in osteoclast activity can be observed shortly after bone irradiation, as demonstrated by an increase in osteocalcin and TRAP5 levels in the blood [84]. By 12 weeks after irradiation, there is a considerable drop in trabecular bone volume, most likely owing to dramatically decreased osteoblastogenesis, whereas osteoclastogenesis rebounds to nearly normal levels [84]. This observation demonstrates a decreased bone formation-to-resorption ratio, which degrades bone quality.

ORNJ is distinguished by persistent and increasing inflammation, as well as the development of hypovascular, hypocellular, and hypoxic bone and soft tissues. These changes brought on by RT increase cell death and collagen breakdown beyond the normal homeostasis of cell repair and collagen synthesis, resulting in a fibroatrophic and necrotic bone [60,78]. An innovative study compared radiation-treated samples from 40 patients treated for ORNJ who received 50.4 to 70.4 Gy to radiation-free samples from HNC patients [78]. The early effects of irradiation that persisted for up to 6 months after exposure were hyperemia and endarteritis, according to a histopathology analysis of the bone and soft tissue samples [78]. The irradiated bone samples showed greater cell loss than the soft tissue samples, and signs of increased hypocellularity appeared quickly after irradiation exposure [78,85]. Years after irradiation exposure, densely fibrous material was observed that provided evidence of thrombosis [78,85]. End-stage markers of radiation-induced injury were identified as a reduction in vascular content and an increase in tissue fibrosis, both of which increased with time after irradiation [78,85].

Hypoxia and inflammation and related cytokines appear to be key players in the genesis of ORNJ according to the basic research results, which formed a background for the Marx and colleagues' 3H (hypovascular, hypocellular, and hypoxic) and Delanian's radiation-induced fibroatrophic ORNJ theories [60,79]. Reactive oxygen species and TGF-β1 have important roles in the early inflammation, fibrosis, and remodeling that lead to terminal tissue necrosis in Delanian's fibroatrophic theory [79]. Lyons., *et al*. [86], as well as Bras., *et al*. [87], have also published similar hypotheses about how fibrosis results in vascular abnormalities in the pathophysiology of ORNJ. As shown in a minipig model, edema of endothelial cells lining vascular structures was seen just 1 day after radiation followed by the obliteration of small luminal vessels [88]. Although there was a transient increase in blood flow at two weeks after radiation, this was followed by a gradual decline. This finding shows that microvascular damage occurs much earlier than bony destruction. It also establishes the fundamental roles of vascular obliteration and related chronic hypoxia as the key players in the development of ORNJ, which may create a vicious cycle with ongoing inflammation and increased fibrosis. The existence of a radiation-induced microvascular injury in irradiated human mandibles was recently confirmed by Dekker., *et al*. [89]. The 20 edentulous, irradiated patients who received mandibular dental implants were evaluated by the authors, and the radiation-free implant patients served as the control group. At doses ≥ 50 Gy, bone biopsies revealed reduced vascular density in the irradiated group and preferential obliteration of microvascular structures. Because ORN can occur up to 6 times more frequently in the mandible than in the better-vascularized maxilla, clinical evidence also points to a vascular origin for the condition [74-76].

Despite the presence of substantial evidence indicating a strong link between ORNJ development and processes such as tissue hypoxia, increased apoptosis, chronic inflammation, and hyperfibrosis, no clinical study has been reported that evaluates related biomarkers for their potential utility in the accurate prediction of HNC patients treated with RT or CCRT. Previously, our research established that inflammation-related indicators were effective in predicting the need for tooth extractions and trismus (another hyperfinflammatory and hyperfibrotic late complication of RT) rates following RT or CCRT in nasopharyngeal and parotid gland malignancies [54,90]. If comparable results can be achieved for ORNJ in HNC patients, we believe a new window will open for elucidating the exact pathogenesis of ORNJ, and determining the best-fit preventive and therapeutic measures for this debilitating ailment.

RT technique and dose

The RT technique is one of the most effective predictors of the doses to the "organ at risk" (OAR) when administering a prescribed RT dose at any primary tumor site, including the HNC. The main objective of advanced RT is to increase the dose in the target vol-

ume while keeping the OAR doses as low as possible without sacrificing tumor coverage. OAR doses can only be reduced by using computer-aided sophisticated treatment plans and their delivery with modern treatment machines, in contrast to the primary tumor and lymphatic regions, which can receive doses that are almost comparable with any 2-dimensional (2D-RT), 3-dimensional conformal (3D-RT), IMRT, or heavy ion therapy, such as proton therapy and carbon ion therapy.

Mandibular doses must be kept as low as possible in addition to the other OARs to reduce the risk of ORNJ in HNC patients. In this regard, IMRT, image-guided RT (IGRT), or hadron therapy may reduce the excessive doses received by the mandible and, consequently, lower the risks of ORNJ.The efficiency of IMRT and IGRT in lowering the risk of ORNJ in locally advanced HNCs was evaluated by Nguyen., *et al*. [91]. This evaluation included 83 patients receiving definitive CCRT, post-operative RT or CCRT, or RT alone with IMRT or IGRT. The mandibular mean dose for the IMRT and IGRT techniques was 43.6 Gy and 43.8 Gy, respectively. Only 1 (1.2%) of the patients had ORNJ at a median follow-up of 28 months, which is less than the commonly cited incidence range of 2-22%. This finding supports the effectiveness of advanced RT techniques in lowering the risk of ORNJ. The findings of the meta-analysis by Balermpas., *et al*. provided clinical support for this dosimetric data by demonstrating that patients who underwent pre-IMRT tooth extractions experienced an ORNJ incidence of only less than 5% as a result of the IMRT technique [50]. Besides, more advanced intensity-modulated protontherapy (IMPT), with its benefit of Bragg peak dose distribution, may further lower ORNJ rates. Zhang., *et al*. compared mandibular doses and ORNJ after IMRT or IMPT in patients with OPC [92]. Mandibular doses were lower in IMPT patients (minimum 0.8 vs. 7.3 Gy; mean 25.6 vs. 41.2 Gy; P < 0.001), as were ORNJ rates: 2% IMPT and 7.7% IMRT.

Although the RT technique appears to be a reliable predictor of ORNJ, the true ORNJ risk is actually determined by the dose delivered to the mandible, and modern RT techniques lessen this risk by lowering mandibular doses: equal total doses with identical tissue dose distribution characteristics will produce similar radiobiological effects regardless of delivery technique. Numerous studies have examined various mandibular dosimetric parameters to assess the risk of ORNJ in this patient population (Table 1). Despite significant methodological variations, almost all studies consistently suggested a strong correlation between mandibular dose measurements and the risk of ORNJ, namely, the higher the dose, the more likely it is that ORNJ will occur. To assess jaw-related dose-volume histogram (DVH) parameters related to ORNJ, Kubota., *et al*. retrospectively reviewed the medical records of 616 patients with HNC treated with curative intent or postoperative RT [41]. After a median follow-up duration of 40 months (range 3-145 months) and a median time to ORNJ of 27 months (range 2-127 months), 46 (7.5%) patients experienced ORNJ.A DVH analysis showed that patients with ORNJ had significantly higher V30-V70 values than those without. Primary tumor site, pre-RT mandibular surgery, post-RT tooth extraction, and V60 > 14% were all noted as significant factors in univariate analyses, while the tumor site (P = 0.0059) and V60 > 14% (P = 0.0065) remained significant in multivariate analyses. The 3-year cumulative ORNJ incidence rates were 9.3% and 1.4% in patients with OPC or OCC and other cancers (P < 0.0001), and 2.5% and 8.6% in patients with V60 ≤ 14% and > 14% (P < 0.0001), respectively.

Reference	Treatment Modality	Overall ORNJ incidence (%)	Dosimetric factor
Nguyen., *et al*. [91]	IMRT IGRT	1.2	Dmean 43.6 Gy Dmean 43.8 Gy
Balermpas., *et al*. [58]	IMRT	5.0	-
Zhang., *et al*. [92]	IMRT IMPT	7.7 2.0	- -
Kubota., *et al*. [50]	3D-CRT IMRT	7.5	V60 > 14%
Aarup-Kristensen., *et al*. [93]	3D-CRT IMRT	4.6	Dmean continuously
The MD Anderson Head and Neck Cancer Symptom Working Group [94]	IMRT	Comparison study (with vs. without ORNJ)	V44Gy ≥ 42% V58Gy ≥ 25%
De Felice., *et al*. [95]	3D-CRT IMRT	5.5	Mean >57.6 Gy
van Dijk., *et al*. [96]	IMRT	13.7	D30% ≥ 35 Gy
Tsai., *et al*. [97]	3D-CRT IMRT	7.5%	V50 Gy V60 Gy
Caparroti., *et al*. [98]	IMRT	1-year: 3.0% 3-year: 5.0% 5-year: 7.0%	V50 Gy V60 Gy
Lang., *et al*. [99]	PORT	Comparison study (with vs. without ORNJ)	Dmean> 45 Gy Dmax> 60 Gy > 40% of PTV intersecting the mandible

Table 1: Major studies reporting the Incidence of osteoradionecrosis of the jaw and related dosimetric factors.

Abbreviations: ORNJ: Osteonecrosis of the Jaw; Gy: Gray; Dmean: Mean Dose; Vx: Volume Receiving X Gray or Higher; Dx%; Dose Received by X% of the Specified Target; IMRT: Intensity-Modulated Radiotherapy; IGRT: Image-Guided Radiotherapy; 3D-CRT: 3-Dimensional Conformal Radiotherapy; PORT: Postoperative Radiotherapy

Aarup-Kristensen and colleagues aimed to investigate the incidence of ORNJ after a total dose of 66-68 Gy RT and connected mandibular dose-volume effects in a large cohort of 1224 HNC patients [93]. With a median time to occurrence of 10.9 months (range 1.8-89.7) following RT, ORNJ was recorded in 56 (4.6%) cases, 90% of which occurred within 37.4 months. Considering DVH doses between 30 Gy and 60 Gy, significant dose-volume differences unflavored the ORNJ population compared to the non-ORNJ. Smoking (HR = 1.69), pre-RT surgery/tooth extraction (HR = 2.76; 1.48-5.14), and D mean (HR = 1.05) were all found to be significantly correlated with ORNJ in univariate analysis. In multivariate analysis, Dmean (HR = 1.04) and surgery/tooth extraction (HR = 2.09) remained significant predictors of ORNJ.

The MD Anderson Head and Neck Cancer Symptom Working Group studied the dosimetric parameters associated with ORNJ in OPC patients receiving IMRT by matching 68 ORNJ cases with 131 controls [94]. There was no statistically significant difference in the maximum doses, but the mandibular mean dose for the ORN cohort was significantly higher (48.1 vs. 43.6 Gy, $P < 0.0001$). All DVH bins in the ORN cohort from V35 to V73 were noticeably higher than controls ($P = 0.0006$). To correlate ORNJ rates, two DVH parameters=V44 ≥ 42% and V58 ≥ 25%=were found, and patients who had both of them accounted for 81% of all ORNJ cases. The mandibular Dmean of the affected bone was 57.6 Gy, and 44% had a D2% ≥ 65Gy, according to De Felice., *et al*. in a small retrospective study involving 36 patients with ORNJ (95). vanDijk and colleagues aimed to create a multivariable clinical/dose-based Normal Tissue Complication Probability (NTCP) model for predicting $ORNJ_{I-IV}$ and ORN_{IV} after RT or CCRT in patients with HNC [96]. Of 1259 included patients with HNC, 13.7% developed $ORNJ_{I-IV}$ and 5% $ORNJ_{IV}$. All dose and volume parameters of the mandible were significantly associated with the development of ORNJ in univariable models. Multivariable analyses identified D30% and pre-RT dental extraction as independent predictors for both ORN_{I-IV} and ORN_{IV}. For an ORNI-IV risk of< 5%, this model suggested that 30% of the mandible receive a dose of ≥35 Gy.

Tsai and colleagues examined the records of 402 T1-2 OPC patients who received definitive RT to ascertain the relationship between radiation doses administered to the mandible and the prevalence of ORNJ [97]. ORNJ developed in 30 individuals (7.5%), with 6 patients requiring major surgery due to grade 4 ORNJ. In the matched case-control study, the mandibular volumes of the two groups receiving 50 Gy (V50) and 60 Gy (V60) were statistically significantly different. After adjusting for matching factors and dental status (dentate or with extraction), the highest significant difference was seen at V50 ($P = 0.02$).

From prospectively collected data of 1196 OPC patients treated with IMRT, with or without chemotherapy, Caparroti., *et al*. reported the incidence of ORNJ [98]. Patients with ORNJ were compared clinically and dosimetrically to a matched control cohort without ORNJ. The mandible's actuarial ORNJ rate was 3% after one year, 5% after three years, and 7% after five years. Multivariable analysis of the matched cohort patients revealed that the mandibular V50 and V60 were related to ORNJ.

Lang., *et al*. sought to gain more understanding of the factors relating to the patient and the course of treatment that contribute to the emergence of ORNJ in OCC patients receiving postoperative RT [99]. The researchers compared 45 patients without ORNJ (the control group) to 44 individuals with ORNJ (the event group). Dental status before RT (HR 4.5; 1.8-11.5) and dosimetric parameters including Dmean> 45 Gy (HR 2.4; 1.0-5.7), Dmax> 60 Gy (HR 1.3; 1.1-2.8), and PTV proportion > 40% intersection with the lower jaw (HR 1.1; 1.0-1.1) were significantly associated with ORNJ.

Available literature suggests that mean mandibular doses >40-50 Gy and V50-60 represent the most significant dosimetric predictors of ORNJ in HNC patients. These variations between dosimetric predictors may be associated with RT techniques and dose prescription differences, including total and per-fraction doses. Regardless of the cause, their common recommendation is to keep mandibular dose metrics as low as is practical to reduce the risk of ORNJ without compromising tumor control rates.

Concluding Remarks

Both RT and CCRT, which are essential components of the most recent organ-sparing treatment modalities for HNC patients, can cause ORNJ, a severely crippling late complication. Many patient, tumor, mandibular interventions, concurrently used medications, and RT- related factors, including the prescribed dose and delivery technique may all effect the risk of ORNJ in this patient population. Numerous patient, tumor, and mandibular interventions, as well as concurrent drugs and RT-related factors, such as the prescription dose and delivery technique, may all influence the risk of ORNJ in this patient population. Among them, poor oral hygiene, cigarette smoking, alcohol consumption, pre- or post-RT tooth extractions and implant placements, aggressive mandibular surgery before RT, non-sophisticated RT technique use, and higher mandibular doses appear to be the most robust correlates of high ORNJ prevalence rates. Although highly advanced RT techniques and oral care programs appeared to lower ORNJ rates to 0-5%, we will likely encounter numerically more cases of ORNJ as the success of effective anticancer therapies makes it possible for this severely disabling complication to manifest in more patients due to noticeably longer survival rates. Because treatment and rehabilitation of ORNJ is both difficult and pricey, it is imperative to conduct further insightful large-scale studies on the pathophysiologic mechanisms and preventive measures of this challenging RT complication. Until the results of such research and preventive measures become available, we recommend the evaluation of ORNJ risk individually in multidisciplinary tumor boards involving, but not restricted to,

radiation oncologists, medical oncologists, dental oncologists, oral and maxillofacial surgeons and radiologists, head and neck surgeons, and rehabilitative disciplines.

Declarations

Availability of Data and Materials

Data cannot be shared publicly because the data is owned and saved by Baskent University Medical Faculty. Data are available from the Baskent University Institutional Data Access/Ethics Committee (contact via Baskent University Ethics Committee) for researchers who meet the criteria for access to confidential data: contact address, adanabaskent@baskent.edu.tr.

Competing Interests

All authors contributed significantly and equally; and all authors approved the final form of the manuscript.

Funding

The authors declare that they have not received any financial support.

Authors' Contributions

All authors contributed significantly and equally; and all authors approved the final form of the manuscript.

Bibliography

1. Mireștean CC., *et al*. "New horizons in modulating the radiosensitivity of head and neck cancer - 100 years after Warburg' effect discovery". *Frontiers in Oncology* 12 (2022): 908695.

2. Lacas B., *et al*. "Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 107 randomized trials and 19,805 patients, on behalf of MACH-NC Group". *Radiotherapy and Oncology* 156 (2021): 281-293.

3. Sroussi HY., *et al*. "Common oral complications of head and neck cancer radiation therapy: mucositis, infections, saliva change, fibrosis, sensory dysfunctions, dental caries, periodontal disease, and osteoradionecrosis". *Cancer Medicine* 6 (2017): 2918-2931.

4. Strojan P., *et al*. "Treatment of late sequelae after radiotherapy for head and neck cancer". *Cancer Treatment Reviews* 59 (2017): 79-92.

5. Chronopoulos A., *et al*. "Osteoradionecrosis of the jaws: definition, epidemiology, staging and clinical and radiological findings. A concise review". *International Dental Journal* 68 (2018): 22-30.

6. Frankart AJ., *et al*. "Osteoradionecrosis: Exposing theevidence not the bone". *International Journal of Radiation Oncology - Biology - Physics* 109.5 (2021): 1206-1218.

7. Singh A., *et al*. "Osteoradionecrosis of the jaw following proton radiation therapy for patients with head and neck cancer". *JAMA Otolaryngology-Head and Neck Surgery* (2022).

8. Notani K., *et al*. "Management of mandibular osteoradionecrosis corresponding to the severity of osteoradionecrosis and the method of radiotherapy". *Head Neck* 25.3 (2003): 181-186.

9. Jacobson AS., *et al*." Quality of life after manage-ment of advanced osteoradionecrosis of the mandible". *International Journal of Oral and Maxillofacial Surgery* 42.9 (2013): 1121-1128.

10. Rogers SN., *et al*. "Longitudinal evaluation of health-related quality of life after osteoradionecrosis of the mandible". *British Journal of Oral and Maxillofacial Surgery* 53.9 (2015): 854-857.

11. Jin T., *et al*. "Preoperative status and treatment of osteoradionecrosis of the jaw: a retrospective study of 252 cases". *British Journal of Oral and Maxillofacial Surgery* 58.10 (2020): e276-282.

12. Chieng CY., *et al*. "Health related quality of life and patient concerns in patients with osteoradionecrosis". *British Journal of Oral and Maxillofacial Surgery* 59.9 (2021): 1061-1066.

13. Danielsson D., *et al*. "Quality of life after microvascular mandibular reconstruction for osteoradionecrosis-A prospective study". *Head Neck* 41.7 (2019): 2225-2230.

14. de Graeff A., *et al*. "A prospective study on quality of life of laryngeal cancer patients treated with radiotherapy". *Head Neck* 21.4 (1999): 291-296.

15. List MA., *et al*. "Quality of life and performance in advanced head and neck cancer patients on concomitant chemoradiotherapy: a prospective examination". *Journal of Clinical Oncology* 17.3 (1999): 1020-1028.

16. Aoyama K., *et al*. "Jaw thrust maneuver for endotracheal intubation using a fiberoptic stylet". *Anesthesia and Analgesia* 90.6 (2000): 1457-1458.

17. Dhanda J., *et al*. "Current concepts in osteoradionecrosis after head and neck radiotherapy". *Clinical oncology (Royal College of Radiologists)* 28.7 (2016): 459-466.

18. Yilmaz B., *et al*. "Challenges in the radiological diagnosis of osteoradionecrosis of the jaw in head and neck cancer patients". In: Sergi CM, editor. *Advancements in Cancer Research. Brisbane (AU): Exon Publications*; Online first (2022): 1-22.

19. Brooker RC., *et al*. "Genetic variants associated with mandibular osteoradionecrosis following radiotherapy for head and neck malignancy". *Radiotherapy and Oncology* 165 (2021): 87-93.

20. Danielsson D., *et al*. "Influence of genetic background and oxidative stress response on risk of mandibular osteoradionecrosis after radiotherapy of head and neck cancer". *Head Neck* 38.3 (2016): 387-393.

21. Owosho AA., *et al*. "The prevalence and risk factors associated with osteoradionecrosis of the jaw in oral and oropharyngeal cancer patients treated with intensity-modulated radiation therapy (IMRT): The Memorial Sloan Kettering Cancer Center experience". *Oral Oncology* 64 (2017): 44-51.

22. Kluth EV., *et al*. "A study of factors contributing to the development of osteoradionecrosis of the jaws". *Journal of Prosthetic Dentistry* 59 (1988): 194-201.

23. Acharya S., *et al*. "Risk assessment for osteoradionecrosis of the jaws in patients with head and neck cancer". *Medicine and Pharmacy* 93.2 (2020): 195-199.

24. Topkan E., *et al*. "Comment on: Osteoradionecrosis after postoperative radiotherapy for oral cavity cancer: A retrospective cohort study". *Oral Oncology* 134 (2022): 106098.

25. Messner B., *et al*. "Apoptosis and necrosis: two different outcomes of cigarette smoke condensate-induced endothelial cell death". *Cell Death and Disease* 3.11 (2012): e424.

26. Kisseleva T and Brenner DA. "Mechanisms of fibrogenesis". *Experimental Biology and Medicine* 233.2 (2008): 109-122.

27. Frazier K., *et al*. "Stimulation of fibroblast cell growth, matrix production, and granulation tissue formation by connective tissue growth factor". *Journal of Investigative Dermatology* 107.3 (1996): 404-411.

28. Takeuchi H., *et al*. "Nicotine-induced CCN2: from smoking to periodontal fibrosis". *Journal of Dental Research* 89.1 (2010): 34-39.v

29. Möring MM., *et al*. "Osteoradionecrosis after postoperative radiotherapy for oral cavity cancer: A retrospective cohort study". *Oral Oncology* 133 (2022): 106056.

30. Reuther T., *et al*. "Osteoradionecrosis of the jaws as a side effect of radiotherapy of head and neck tumour patients--a report of a thirty year retrospective review". *International Journal of Oral and Maxillofacial Surgery* 32.3 (2003): 289-295.

31. Goldwaser BR., *et al*. "Risk factor assessment for the development of osteoradionecrosis". *Journal of Oral and Maxillofacial Surgery* 65.11 (2007): 2311-2316.

32. Huang Q., *et al*. "Nutritional status in patients of mandibular osteoradionecrosis: A single-institution experience". *Oral Diseases* 28.2 (2022): 513-520.

33. Nadella KR., *et al*. "A. Osteoradionecrosis of the jaws: Clinicotherapeutic management: A literature review and update". *Journal of Oral and Maxillofacial Surgery* 14.4 (2015): 891-901.

34. Chrcanovic BR., *et al*. "Osteoradionecrosis of the jaws--a current overview--Part 2: dental management and therapeutic options for treatment". *Oral and Maxillofacial Surgery* 14.2 (2010): 81-95.

35. Kuhnt T., *et al*. "Potential risk factors for jaw osteoradionecrosis after radiotherapy for head and neck cancer". *Radiation Oncology* 11 (2016): 101.

36. Monnier Y., *et al*. "Mandibular osteoradionecrosis in squamous cell carcinoma of the oral cavity and oropharynx: incidence and risk factors". *Otolaryngology-Head and Neck Surgery* 144.5 (2011): 726-732.

37. Yilmaz B., *et al*. "Letter to the Editor: To extract or not extract teeth prior to head and neck radiotherapy? *Supportive Care in Cancer* 31.1 (2022): 90.

38. Singh A., *et al*. "Osteoradionecrosis of the jaw: A mini review". *Front Oral Health* 3 (2022): 980786.

39. Caparrotti F., *et al*. "Osteoradionecrosis of the mandible in patients with oropharyngeal carcinoma treated with intensity-modulated radiotherapy". *Cancer* 123.19 (2017): 3691-3700.

40. Chen YC., *et al*. "Outcomes of re-irradiation for oral cavity squamous cell carcinoma". *Biomedical Journal* 45.6 (2022): 940-947.

41. Kubota H., *et al*. "Risk factors for osteoradionecrosis of the jaw in patients with head and neck squamous cell carcinoma". *Radiation Oncology* 16.1 (2021): 1.

42. Sathasivam HP., *et al*. "Predictive factors for osteoradionecrosis of the jaws: A retrospective study". *Head Neck* 40.1 (2018): 46-54.

43. Tucker JR., *et al*. "Osteoradionecrosis in patients with salivary gland malignancies". Oral Oncology 57 (2016): 1-5.

44. Chen JA., *et al*. "Osteoradionecrosis of mandible bone in patients with oral cancer--associated factors and treatment outcomes". *Head Neck* 38.5 (2016): 762-768.

45. Wang TH., *et al*. "Risk factors for and the role of dental extractions in osteoradionecrosis of the jaws: A national-based cohort study: Osteoradionecrosis of the jaws and dental extractions". *Head Neck* 39 (2017): 1313-1321.

46. Chopra S., *et al*. "Factors predictive of severity of osteoradionecrosis of the mandible". *Head Neck* 33.11 (2011): 1600-1605.v

47. Chang DT., *et al*. "Do pre-irradiation dental extractions reduce the risk of osteoradionecrosis of the mandible?". *Head Neck* 29.6 (2007): 528-536.

48. Beaumont S., *et al*. "Timing of dental extractions in patients undergoing radiotherapy and the incidence of osteoradionecrosis: a systematic review and meta-analysis". *British Journal of Oral and Maxillofacial Surgery* 59.5 (2021): 511-523.

49. Urquhart O., *et al*. "Effect of preradiation dental intervention on incidence of osteoradionecrosis in patients with head and neck cancer: A systematic review and meta-analysis". *Journal of the American Dental Association*. 153.10 (2022): 931-942. e32.

50. Balermpas P., *et al*. "Dental extraction, intensity-modulated radiotherapy of head and neck cancer, and osteoradionecrosis: A systematic review and meta-analysis". *Strahlentherapie und Onkologie* 198.3 (2022): 219-228.

51. Srinivas B., *et al*. "Wound healing and bone regeneration in postextraction sockets with and without platelet-rich fibrin". *Annals of Maxillofacial Surgery* 8.1 (2018): 28-34.

52. Hoffmann L., *et al*. "Dental management before radiotherapy of the head and neck region: 4-year single-center experience". *Clinical and Experimental Dental Research* 8.6 (2022): 1478-1486.

53. Koga DH., *et al*. "Dental extractions and radiotherapy in head and neck oncology: review of the literature". *Oral Diseases* 14.1 (2008): 40-44.

54. Yilmaz B., *et al*. "Pretreatment systemic immune-inflammation index predict needs for teeth extractions for locally advanced head and neck cancer patients undergoing concurrent chemoradiotherapy". *Therapeutics and Clinical Risk Management* 17 (2021): 1113-1121.

55. Girardi FM., *et al*. "Risk factors for jaw osteoradionecrosis: a case control study". *Brazilian Oral Research* 36 (2022): e132.

56. Jereczek-Fossa BA and Orecchia R. "Radiotherapy-induced mandibular bone complications". *Cancer Treatment Reviews* 28 (2002): 65-74.

57. Kuo TJ., *et al*. "Jaw osteoradionecrosis and dental extraction after head and neck radiotherapy: a nationwide population-based retrospective study in Taiwan". *Oral Oncology* 56 (2016): 71-77.

58. Nabil S and Samman N. "Incidence and prevention of osteoradionecrosis after dental extraction in irradiated patients: a systematic review". *International Journal of Oral and Maxillofacial Surgery* 40.3 (2011): 229-243.

59. Khoo SC., *et al*. "Predictors of osteoradionecrosis following irradiated tooth extraction". *Radiation Oncology* 16.1 (2021): 130.

60. Marx RE and Johnson RP. "Studies in the radiobiology of osteoradionecrosis and their clinical significance". *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology* 64.4 (1987): 379-390.

61. Somay E., *et al*. "Quality of life changes in patients with osteoradionecrosis and their measurement". *Journal of Advances in Medicine and Medical Research* 21 (2022): 48-61.

62. Nelson K., *et al*. "Survival analysis and clinical evaluation of implant-retained prostheses in oral cancer resection patients over a mean follow-up period of 10 years". *Journal of Prosthetic Dentistry* 98 (2007): 405-410.

63. Buddula A., *et al*. "Survival of turned and roughened dental implants in irradiated head and neck cancer patients: a retrospective analysis". *Journal of Prosthetic Dentistry* 106 (2011): 290-296.

64. De Angelis F., *et al*. "Implant survival and success rates in patients with risk factors: results from a longterm retrospective study with a 10 to 18 years follow-up". *European Review for Medical and Pharmacological Sciences* 21.3 (2017): 433-437.

65. Vanegas-Acosta JC., *et al*. "Mathematical model of the coagulation in the bone-dental implant interface". *Computers in Biology and Medicine* 40.10 (2010): 791-801.

66. Kudo M., *et al*. "A histomorphometric study of the tissue reaction around hydroxyapatite implants irradiated after placement". *Journal of Oral and Maxillofacial Surgery* 59.3 (2001): 293-300; discussion 301.

67. Toneatti DJ., *et al*. "Survival of dental implants and occurrence of osteoradionecrosis in irradiated head and neck cancer patients: a systematic review and meta-analysis". *Journal Clinical Oral Investigations* 25.10 (2021): 5579-5593.

68. Schiegnitz E., *et al*. "Dental implants in patients with head and neck cancer-A systematic review and meta-analysis of the influence of radiotherapy on implant survival". *Clinical Oral Implants Research* 33.10 (2022): 967-999.

69. Koudougou C., *et al*. "Postimplantation radiation therapy in head and neck cancer patients: Literature review". *Head Neck* 42.4 (2020): 794-802.

70. Phulpin B., *et al*. "Feasibility of treating irradiated bone with intramedullary delivered autologous mesenchymal stem cells". *Journal of Biotechnology and Biomedicine* (2011): 560257.

71. Engleman MA., *et al*. "Radiation-induced skeletal injury". *Cancer Treatment and Research* 128 (2006): 155-169.

72. Lajolo C., *et al*. "Tooth extraction before radiotherapy is a risk factor for developing osteoradionecrosis of the jaws: A systematic review". *Oral Diseases* 27.7 (2021): 1595-1605.

73. Beech N., *et al*. "Preradiotherapy dental extractions and health-related quality of life". Oral Surgery, Oral Medicine, Oral Pathology Oral Radiology 122.6 (2016): 672-679.

74. Wahl MJ. "Osteoradionecrosis prevention myths". *International Journal of Radiation Oncology - Biology - Physics* 64.3 (2006): 661-669.

75. Beumer J., *et al.* "Osteoradionecrosis: predisposing factors and outcomesof therapy". *Head Neck Surgery* 6.4 (1984): 819-827.

76. Jawad H., *et al*. "A review of dental treatment of head and neck cancer patientsbefore, during and after radiotherapy: par 2". *British Dental Journal* 218.2 (2015): 69-74.

77. Okamoto K., *et al*. "Osteoimmunology: The conceptual framework unifying the immune and skeletal systems". *Physiological Reviews* 97.4 (2017): 1295-1349.

78. Curi MM., *et al*. "Histopathologic and histomorphometric analysis of irradiation injury in bone and the surrounding soft tissues of the jaws". *Journal of Oral and Maxillofacial Surgery* 74 (2016): 190-199.

79. Delanian S and Lefaix JL. "The radiation-induced fibroatrophic process: therapeutic perspective via the antioxidant pathway". *Radiotherapy and Oncology* 73 (2004): 119-131.

80. Chandra A., *et al*. "Potential role of senescence in radiation-induced damage of the aged skeleton". *Bone* 120 (2019): 423-431.

81. Herberg S., *et al*. "Total body irradiation is permissive for mesenchymal stem cell-mediated new bone formation following local transplantation". *Tissue Engineering (Part A)* 20 (2014): 3212-3227.

82. Green DE., *et al*. "Devastation of adult stem cell pools by irradiation precedes collapse of trabecular bone quality and quantity". *Journal of Bone and Mineral Research*27 (2012): 749-759.

83. Preciado S., *et al*. "Mesenchymal stromal cell irradiation interferes with the adipogenic/osteogenic differentiation balance and improves their hematopoietic-supporting ability". *Biology of Blood and Marrow Transplantation* 24 (2018): 443-451.

84. Zou Q., *et al*. "Bone marrow stem cell dysfunction in radiation-induced abscopal bone loss". Journal of Orthopaedic Surgery and Research 11 (2016): 3.

85. Marx RE and Johnson RP. "Studies in the radiobiology of osteoradionecrosis and their clinical significance". *Oral Surgery, Oral Medicine, Oral Pathology Oral Radiology* 64 (1987): 379-390.

86. Lyons A and Ghazali N. "Osteoradionecrosis of the jaws: current understanding of its pathophysiology and treatment". *British Journal of Oral and Maxillofacial Surgery* 46.8 (2008): 653-660.

87. Bras J., *et al*. "Osteoradionecrosis of the mandible: pathogenesis". *American Journal of Otolaryngology* 11.4 (1990): 244-250.

88. Xu J., *et al*. "Early-stage pathogenic sequence of jaw osteoradionecrosis *in vivo*". *Journal of Dental Research* 91.7 (2012): 702-708.

89. Dekker H., *et al*. "The irradiated human mandible: A quantitative study on bone vascularity". *Oral Oncology* 87 (2018): 126-130.

90. Somay E., *et al*. "Initial neutrophil-to-lymphocyte ratio predicts radiation-induced trismus in parotid gland cancer". *Oral Diseases* (2022).

91. Nguyen NP., *et al*. "Effectiveness of intensity-modulated and image-guided radiotherapy to spare the mandible from excessive radiation". Oral Oncology 48.7 (2012): 653-657.

92. Zhang W., *et al*. "Intensity-modulated proton therapy and osteoradionecrosis in oropharyngeal cancer". *Radiotherapy and Oncology* 123.3 (2017): 401-405.

93. Aarup-Kristensen S., *et al*. "Osteoradionecrosis of the mandible after radiotherapy for head and neck cancer: risk factors and dose-volume correlations". *Acta Oncologica* 58.10 (2019): 1373-1377.

94. MD Anderson and Head and Neck Cancer Symptom Working Group. "Dose-volume correlates of mandibular osteoradionecrosis in oropharynx cancer patients receiving intensity-modulated radiotherapy: Results from a case-matched comparison". *Radiotherapy and Oncolo*gy 124.2 (2017): 232-239.

95. De Felice F., *et al*. "Osteoradionecrosis following treatment for head and neck cancer and the effect of radiotherapy dosimetry: the Guy's and St Thomas' Head and Neck Cancer Unit experience". *Oral Surgery, Oral Medicine, Oral Pathology Oral Radiology* 122.1 (2016): 28-34.

96. vanDijk LV., *et al*. "Normal Tissue Complication Probability (NTCP) prediction model for osteoradionecrosis of the mandible in patients with head and neck cancer after radiation therapy: large-scale observational cohort". *International Journal of Radiation Oncology - Biology - Physics* 111.2 (2021): 549-558.

97. Tsai CJ., *et al*. "Osteoradionecrosis and radiation dose to the mandible in patients with oropharyngealcancer". *International Journal of Radiation Oncology - Biology - Physics* 85.2 (2013): 415-420.

98. Caparrotti F., *et al*. "Osteoradionecrosis of the mandible in patients with oropharyngeal carcinoma treated with intensity-modulated radiotherapy". *Cancer* 123.19 (2017): 3691-3700.

99. Lang K., *et al*. "Frequency of osteoradionecrosis of the lower jaw after radiotherapy of oral cancer patients correlated with dosimetric parameters and other risk factors". *Head and Face Medicine* 18.1 (2022): 7.