

Osteoradionecrosis of the Maxillofacial Region: Contemporary treatment after radiotherapy (A Literature Review)

Alexander B. Dymnikov, Mabhurasi Brian C, Manenji Caroline., Suzan Dagher, Hassan Alsayed Hachem.

Department of oral and maxillofacial surgery, Russian Friendship University, Moscow, Russian Federation

Abstract.

Osteoradionecrosis (ORN), a severe and potentially deadly bone complication arising from radiation therapy in the head and neck region, is defined by exposed, irradiated bone that fails to alleviate within three months, with no signs of remaining tumor or cancer recurrence. Research into more effective, less invasive, and safer treatments for ORN is of great importance, highlighting the need for Maxillofacial surgeons and oncologists to carefully select the most suitable treatment plan based on the disease's advancement. Considering the central role of the RANKL-RANK system in the remodelling and resorbing processes of the bone, new therapies with denosumab and bisphosphonate have been used recently with promising results.

Materials and methods. This study employed a retrospective review of articles and publications from 2018 to 2024, utilizing databases such as Google Scholar, PubMed, Springer Link, and Science Direct. A comprehensive search, utilizing the keywords such as: Jaw Osteoradionecrosis, Head and neck cancer, Radiotherapy, Denosumab, Bisphosphonates, yielded 318 articles. These articles were then meticulously screened based on their conclusions, and those deemed irrelevant to the research topic were excluded such as experiments conducted on non-human subjects, as well as treatments with unfavourable prognoses and recovery rates. Following a comprehensive analysis of the remaining publications, 47 articles were selected for inclusion in this review.

Conclusion. The management of Osteoradionecrosis (ORN) is dependent on the severity and progression stage of the condition. Early stages of ORN have demonstrated responsiveness to treatments such as PENTOCLO and ozone therapy. In contrast, stages II and III of ORN require more invasive surgical approaches. The integration of surgical methods with non-invasive therapies has been associated with enhanced patient outcomes.

Key words: Osteoradionecrosis, Head and neck cancer, Radiotherapy, Bisphosphonates, Denosumab.

Introduction

Bone alterations following radiotherapy can manifest as post-radiation osteitis or osteoradionecrosis, typically emerging approximately one year post-irradiation. The diagnosis of osteoradionecrosis is supported by the localization of bone changes to the radiation field, the absence of associated soft tissue masses, and the stability of bone lesions over time. Osteoradionecrosis (ORN) represents a significant and debilitating complication characterized by the presence of exposed irradiated bone tissue that fails to heal within a three-month period, in the absence of residual tumor or recurrence of the previously treated malignancy [1].

The phenomenon of ORN in the jaw was first identified by Regaud in 1922, who observed bone

necrosis in cancer patients receiving radiation therapy [2, 3]. Subsequently, Marx conducted an extensive investigation of the condition in the 1980s, which led to the development of a pathophysiological model and the widely recognized three-stage classification [4, 5]

ORN is associated with several risk factors which include human papillomavirus (HPV) infection [3] and the utilization of older radiation therapy methods involving substantial, unfocused radiation doses, such as 2D or 3D radiation therapy. Post Radiation therapy dental extractions have proven to be a high-risk factor for ORN [6]. This finding is supported by a systematic review conducted by Carlo Lajolo et al [7], highlighting the crucial responsibility of dentists and oral surgeons to execute all dental procedures,

including extractions and professional oral hygiene, prior to the commencement of radiation therapy. In contrast, cutting-edge techniques like Intensity Modulated Radiation Therapy (IMRT) or Intensity Modulated Proton Therapy (IMPT) minimize the risk of ORN [8].

Multiple staging methods for ORN have been developed to assist maxillofacial surgeons and oncologists in creating more effective treatment strategies. These methods consider factors such as patient response to current medication, extent of bone loss, radiological images, duration of bony exposure, ORN progression, and the presence of any other oral maxillofacial lesions. The classification of ORN severity employs various techniques, including Max's staging system, which relies on the patient's response to Hyperbaric Oxygen Therapy (HBO) [9]. Another method is Notani's classification, which categorizes ORN based on anatomical location and boundaries. This system can be seen in the following diagram:

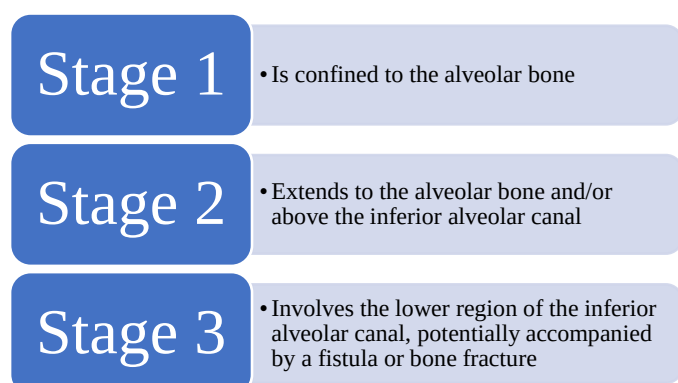


Diagram 1: Notani's classification of ORN by location [10, 11]

ORN can manifest in various clinical forms, such as pain, unsightly bone exposure, bone separation, and in certain instances, fistula development. If left untreated, ORN can advance to serious complications, potentially resulting in mandibular fractures, compromised jaw function, and ultimately sepsis, posing a grave threat to the patient's life [12].

Difference between osteoradionecrosis, medical related necrosis of the jaw and osteomyelitis

Differentiating between ORN, medication-related osteonecrosis of the jaw (MRONJ), and chronic suppurative osteomyelitis is crucial because these conditions share similarities and it can be challenging to make the correct diagnosis without

clinical, radiological, and histological information. A well-known side effect of treatment with bisphosphonates, denosumab, and other medications, including anti-angiogenic agents and cutting-edge anti-cancer medications, is MRONJ. Patients receiving these drugs for a variety of cancerous conditions as well as those with osteopenia and osteoporosis have reported experiencing it [13]. On the other hand, odontogenic microbes are the primary cause of chronic suppurative osteomyelitis, an inflammation of the bone and bone marrow [14]. Inflammation was found in 100% of the osteomyelitis cases that were included in a prior study that was discovered in the literature, but not in any MRONJ or ORN cases. Conversely, in osteomyelitis, bacteria were found inside the marrow spaces as opposed to only on the surface in MRONJ and ORN, and in 96% of cases of osteomyelitis, osteoclasts were found as opposed to none in MRONJ and ORN. These conclusions are inconsistent with those of previous studies, that's why Shuster A. et al in 2019 conducted an experiment to identify the differences between these three diagnoses by studying their histological and microbiological features. The results of this study failed to identify distinctive microscopic characteristics in any of the three entities that could be used to differentiate between them.

Therefore, it is impossible to reach a specific final diagnosis based on microscopic findings alone. The role of microscopic analysis is to serve as an aid to diagnosis that must be complemented by the patient's history and imaging [15].

The pathophysiologic mechanism of ORN is as follows: Ionizing radiation causes tissue injury by hydrolyzing intracellular water and forming free radicals, which leads to DNA misrepair and damage, triggering inflammation through proinflammatory cytokine release, vascular injury, and epithelial mesenchymal transition. Inflammation, vascular injury, tissue hypoxia, hypovascularity, and hypocellularity limit tissue remodeling and activate fibrosis, resulting in osteoradionecrosis [16, 17, 18, 19].

Therapeutic approaches beyond surgery.

1-Pentoxifylline, Tocopherol and Clodronate (PENTOCLO protocol)

Pharmacological interventions are most successful when treating diseases in their early phases or for

patients experiencing moderate symptoms [20]. Antibiotics can be beneficial for preventative measures and during surgical procedures. However, once the bone is exposed, antibiotics alone are insufficient, necessitating their combination with other agents, that typically involves 400mg of Pentoxifylline combined with 500 international units of Tocopherol (Vitamin E) twice daily, along with 1600mg of Clodronate daily for duration of five days in a regime called PENTOCLO [21]. This is followed by a two-day period of 1000mg ciprofloxacin and 20mg prednisone, concluding the week-long treatment course. [22]. This protocol is not advisable for pregnant women, individuals with drug allergies, cerebrovascular disorders, or kidney problems [11]. Pentoxifylline demonstrates effectiveness against radiation-induced tissue fibrosis, boasting antioxidant and anti-tumour necrosis alpha properties that can suppress fibroblast activation and enhance collagenase function. Similarly, Tocopherol combats radiation-induced fibrosis by targeting the suppression of procollagen gene expression. The combined use of these medications, including Clodronate which suppresses osteoclast function and consequently minimizes bone breakdown, results in enhanced therapeutic outcomes. The PENTOCLO protocol is suggested as a primary treatment for stages 0 and I, and as a supplemental therapy alongside surgery for stages II and III ORN [23].

Denosumab has garnered significant attention as a therapeutic intervention due to the pivotal role of RANK (receptor activator of nuclear factor- κ B) and its ligand RANKL in the pathophysiology of bone necrosis [24]. Denosumab is a monoclonal antibody specifically designed to target RANKL, thereby inhibiting its activation on the surface of osteoclasts, which subsequently influences the RANK receptor. By obstructing the interaction between RANKL and RANK, Denosumab effectively inhibits the differentiation, functionality, and survival of osteoclasts, leading to a reduction in bone resorption [25].

In contrast to bisphosphonates, Denosumab presents several advantages, particularly regarding its pharmacokinetics. Denosumab has a half-life of 26 days, whereas Ibandronate, for instance, has a significantly longer half-life of 10 years. Furthermore, Denosumab is associated with a lower incidence of adverse effects, including those related to renal function [26].

Angeles Vazquez et al in 2015 described a clinical case of a 4 years old male with osteoradionecrosis in the first sacral vertebra, ilium and ischium, left femur, and fibula after being treated with chemo and radiotherapy in the light of embryonal rhabdomyosarcoma of the prostate grade III. Since the patient's condition was extreme and has experienced multiple pathological fractures in rib cage, distal third of left ulna, distal shaft of left tibia, an experimental treatment with subcutaneous denosumab was proposed. The frequency with which the drug was scheduled to be administered approximately every 2 months (60mgSC every 2 or 2.5 months for 24 months; total of 10 doses). Additionally, 1000mg calcium, 800IU vitamin D3 (calcifediol), 1600mg/monosodium phosphate/daily physiotherapy sessions were added. Changes in bone-remodeling parameters were observed as soon as 1 month after the first injection. At the end of the treatment period, it was clear that denosumab administration normalized the bone remodeling parameters. The authors made a conclusion that denosumab, an antiresorptive drug, and in comparison with bisphosphonates, achieved a quick response and should be more considered as an alternative treatment because of its reversible effects after treatment stoppage if adverse effects occurred and its easy administration promotes therapeutic compliance. Nevertheless, additional research is therefore needed in this area to confirm the efficacy of denosumab and understand its mechanism of action in the treatment of osteoradionecrosis [24].

2-Ozone Therapy

Ozone therapy has demonstrated effectiveness in treating ORN and mitigating secondary infections. Oliveira, CCB, and their team [27], reported that weekly dermal injections of 30 ug/ml Ozone gas near the ORN site significantly enhance quality of life. This approach, however, yields even better results when integrated with surgical sequestrectomy and debridement procedures [28]. Ozonated oil suspensions can be utilized in the treatment of ORN, applied directly to the affected area. Research by Edoardo Bianco and his team, indicates that this method involves initial manual cleaning and debridement of the ORN region, followed by weekly applications of the ozonated oil suspension to the exposed bone for a duration of 10 minutes. This approach demonstrated a 75%

success rate, achieving complete lesion resolution within a 20-week period. The wound receives treatment with saline solution, systemic antibiotics, and a 10% hydrogen peroxide mouthwash. Two days later, the affected area is rinsed with 250 ml of double distilled water infused with ozone at a concentration of 8 µg/ml. Subsequently, a 20 ml oxygen/ozone gas blend, also at 20 µg/ml, is injected directly onto the lesion. 1ml injections of ozone gas are administered around the wound's perimeter. Finally, ozonated oil is applied directly to the wound. This entire process is replicated daily for a period of 30 days [29].

3-Ultrasound therapy

Ultrasound therapy has demonstrated its effectiveness in slowing the advancement of ORN by fostering bone regeneration and improved blood supply. This occurs through the stimulation of osteoblasts, the growth of new blood vessels (angiogenesis), and increased cell multiplication, ultimately enhancing oxygen delivery. The standard treatment protocol involves 1W/cm², 3MHz, for 15 minutes daily for a month. Due to the limited existing research on ultrasound therapy, it is suggested that clinical trials be conducted on an experimental basis [30]

4-Mesenchymal Stem Cell (MSCs) therapy

Mesenchymal Stem Cells (MSCs), potent adult cells residing in bone marrow, are crucial for blood cell formation. Medical advancements have enabled the isolation of these cells from various connective tissues, unlocking their potential for tissue repair, combating infections, and modulating inflammatory responses. MSCs release bioactive substances that stimulate anti-cell death, blood vessel growth, immune system regulation, and the prevention of fibrosis. Mesenchymal stem cell (MSC) therapy has demonstrated significant success in treating oral replantation injuries (ORN) due to its ability to stimulate tissue regeneration and accelerate healing. Furthermore, MSCs have the capacity to directly transform into osteoblasts, thereby contributing to the development of new bone tissue [31, 32].

Bone marrow-derived mesenchymal stem cell (MSC) exosomes stimulate angiogenesis by activating the Akt/mTOR pathway in response to dimethylxylglycine (DMOG). Recent research

suggests that modulating ferroptosis holds promise for tumor control and improving outcomes for osteonecrosis (ORN). These exosomes release iron, which enhances ferroptosis resistance and consequently protects against ferritin-induced osteoporosis and osteonecrosis [33, 34, 35].

Surgical treatment methods.

Surgical Sequestrectomy + Platelet rich Fibrin (PFR)

Removing dead bone, a process known as sequestrectomy, is a highly effective treatment for osteoradionecrosis. Clinical experience has demonstrated that sequestrectomy is more successful in the maxilla compared to the mandible [36]. Unlike traditional surgical burs, CO₂ laser sequestrectomy offers the advantage of instant wound disinfection, minimizing blood loss and reducing mechanical tissue trauma. This therapy has proven successful in promoting wound healing, alleviating pain, and minimizing postoperative complications. Its application extends to the early stages of osteoradionecrosis, serving as a secondary option when conservative treatments prove ineffective [37]. Prompt prosthetic obturation following maxillary sequestrectomy minimizes postoperative limitations, enabling patients to resume speaking and normal function immediately after the procedure. Furthermore, it minimizes the seepage of food and fluids into the sinus cavity, enabling patients to maintain comfort and normal function until the permanent prosthesis is created. Notably, a permanent prosthesis is only recommended once the surgical site has fully healed and achieved dimensional stability [38]. For individuals with significant aesthetic concerns, invasive procedures like mandibulectomy can be bypassed by utilizing a combination of hyperbaric oxygen therapy and sequestrectomy [39].

Fascio-cutaneous and fascio-periosteal free flaps for treatment of intermediate stage osteoradionecrosis of the jaws

Research indicates that debridement and vascularized free flap soft tissue transfer, performed at an intermediate stage of osteoradionecrosis, offer a faster recovery and present a simpler, less invasive option compared to composite reconstruction. This approach provides a viable alternative to standard ORN

treatment methods, such as medication, hyperbaric oxygen therapy, and surgical debridement without immediate reconstruction, by incorporating free flap soft tissue reconstruction. This approach proved successful in halting further bone deterioration and rapidly healing the mucosal defect [40]. Research indicates that the anterolateral thigh fascia lata rescue flap is a reliable and highly effective long-term solution for mandibular osteoradionecrosis in suitable patients [41, 42]. This 'short-stay' surgical approach leverages the flap's minimal complications, straightforward harvesting process, two-team system for ablation and reconstruction, and rapid recovery, ultimately preventing osteoradionecrosis from worsening and necessitating extensive treatment involving segmental bone resection and reconstruction [43].

Mandibular segmental resection/Mandibulectomy and osseous reconstruction

Research suggests that the mandible is more susceptible to osteoradionecrosis than the maxilla after cancer radiation therapy. This increased risk stems from the mandible's denser composition, which leads to greater radiation absorption, particularly in its posterior areas. Just like maxillary ORN, mandibular ORN can frequently involve both sides of the jaw (bilateral osteoradionecrosis), prompting the consideration of surgical interventions like marginal or segmental mandibulectomy [44].

may be deemed necessary early in the course of treatment if non-surgical approaches fail to yield positive results, as most mandibular ORN cases are believed to be progressive and untreatable without surgical intervention. Determining the optimal timing for surgical intervention is crucial and rests with the specialist. Prompt surgical intervention is preferred due to the progressive and often irreversible nature of most mORNs [45]. Simultaneous tissue flap reconstruction during necrotic jaw removal is essential for achieving positive outcomes in stages III and IV cases. For bilateral ORNJ, optimal results are obtained when a fibular musculocutaneous flap is combined with bilateral mandibular excision and subsequent fibular myocutaneous flap reconstruction. Despite facing challenges like hypoproteinemia and anemia, both pre- and post-operatively, due to restricted mouth opening and compromised nutritional status in patients undergoing partial mandibulectomy with experimental flap reconstruction, their overall quality of life remained substantially better compared to those who didn't undergo mandibulectomy.

Despite the higher success rates observed with segmental and marginal mandibulectomies, the marginal mandibulectomy group encountered a single significant complication, flap necrosis. In contrast, the segmental mandibulectomy group faced a concerning number of flap necrosis cases and deaths, directly attributable to the complexities of reconstructing the bone structure, a challenge often exacerbated by poverty and frailty [46, 47].

	Surgical Sequestromy	Fascio-cutaneous and Fascio -periosteal free flaps	Mandibular segmental resection/ mandibulectomy and osseous reconstruction
<i>Stage of ORN during which it is most effective</i>	– Early stages of osteoradionecrosis – Back up if conservative fails – In combination with hyperbaric	– Intermediate stage	– Late stages – Stage 3 and 4
<i>Prognosis</i>	– good prognosis if performed in early stages and reduces post operative complications	– Good prognosis	– Good prognosis
<i>Combination</i>	– Can be used together	– Combination with	– Combination

<i>n with other treatment methods</i>	with hyperbaric oxygen therapy	other conservative methods such as ozone therapy and hyperbaric oxygen therapy	with conservative methods and in combination with free flap
<i>Mechanism</i>	– In contrast to a surgical bur, a CO2 laser sequestrectomy disinfects the surgical wound instantly and allows for largely bloodless surgery with less mechanical trauma to the tissues	– Vascularised free flap soft tissue transfer from other part of the body for example thigh	– Removal of the necrotic part of the jaw or the whole jaw
<i>Contraindications</i>	– A definitive prosthesis is not indicated until the surgical site is healed and dimensionally stable		
<i>Complications</i>		– Vascular complications and as well as necrosis if not properly done.	– Flap necrosis – Hypoproteinemia – Anemia
<i>Important points</i>		– Short stay free flap surgery benefits from the flaps low morbidity, simplicity of harvest, two team approach to ablation and reconstruction providing speedy recovery avoiding progressing to extensive diseases	

Table 1: A comparative analysis for Surgical treatment methods of ORN

Conclusion

The management of Osteoradionecrosis (ORN) necessitates a meticulous approach that considers a variety of factors influencing patient outcomes. These factors include the patient's oral hygiene, socioeconomic status, comprehensive health history, hospital environment, individual patient preferences, and the surgeon's level of expertise. The selection and execution of the treatment plan are dependent on the severity and stage of progression of the ORN. For early-stage ORN (stage 0), conservative treatment modalities such as PENTOCLO and ozone therapy have demonstrated efficacy. The initial phase of treatment typically involves minor surgical interventions, including debridement, curettage, and the removal of fistulas. In contrast, stages II

and III of ORN require more invasive surgical procedures. When necrosis is confined to the alveolar ridge, a marginal mandibulectomy is deemed the most appropriate intervention. However, if necrosis extends beyond the alveolar ridge, a segmental mandibulectomy accompanied by enterocutaneous flaps is recommended to ensure the complete excision of all necrotic and diseased tissue. The integration of surgical techniques with non-invasive treatments, such as PENTOCLO, ozone therapy, and additional therapeutic modalities like mesenchymal stem cells (MSCs) and Platelet-Rich Fibrin, has been associated with enhanced patient outcomes.

References

1. Dissard, A., P. Dang, N., Barthelemy, I., Delbet, C., Puechmaille, M., Depeyre, A.,

- Pereira, B., Martin, F., Guillemin, F., Biau, J., Mirafzal, S., Mom, T., Gilain, L. and Saroul,

- N. (2020), Efficacy of pentoxifylline–tocopherol–clodronate in mandibular osteoradionecrosis. *The Laryngoscope*, 130: E559-E566.
<https://doi.org/10.1002/lary.28399>
2. Chronopoulos A, Zarra T, Ehrenfeld M, Otto S. Osteoradionecrosis of the jaws: definition, epidemiology, staging and clinical and radiological findings. A concise review. *Int Dent J*. 2018 Feb;68(1):22-30. English. doi: 10.1111/idj.12318. Epub 2017 Jun 25. PMID: 28649774; PMCID: PMC9378891.
3. Alfouzan AF. Radiation therapy in head and neck cancer. *Saudi medical journal*. 2021 Mar;42(3):247.
4. Mamedova E, Kolodkina A, Vasilyev EV, Petrov V, Belaya Z, Tiulpakov A. Successful use of denosumab for life-threatening hypercalcemia in a pediatric patient with primary hyperparathyroidism. *Hormone Research in Paediatrics*. 2020 Oct 19;93(4):272-8.
5. Robijns J, Nair RG, Lodewijckx J, Arany P, Barasch A, Bjordal JM, Bossi P, Chilles A, Corby PM, Epstein JB, Elad S. Photobiomodulation therapy in management of cancer therapy-induced side effects: WALT position paper 2022. *Frontiers in oncology*. 2022 Aug 30;12:927685.
6. Robijns J, Nair RG, Lodewijckx J, Arany P, Barasch A, Bjordal JM, Bossi P, Chilles A, Corby PM, Epstein JB, Elad S. Photobiomodulation therapy in management of cancer therapy-induced side effects: WALT position paper 2022. *Frontiers in oncology*. 2022 Aug 30;12:927685.
7. Da Costa Fontes KB, Picciani BL, Werneck JT, Aredes MM, Costa SF, Monteiro MC. Antimicrobial photodynamic, photobiomodulation and ozone therapies as methods for osteoradionecrosis: case report. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*. 2024 Jun 1;137(6):e263. <https://doi.org/10.1016/j.oooo.2023.12.555>
8. Chronopoulos A, Zarra T, Ehrenfeld M, Otto S. Osteoradionecrosis of the jaws: definition, epidemiology, staging and clinical and radiological findings. A concise review. *International dental journal*. 2018 Feb 1;68(1):22-30.
9. Habib, S., Sassoon, I., Thompson, I. and Patel, V. (2021), Risk factors associated with osteoradionecrosis. *Oral Surg*, 14: 227-235. <https://doi.org/10.1111/ors.12597>
10. Law, B.; Soh, H.Y.; Nabil, S.; Rajandram, R.K.; Nazimi, A.J.; Ramli, R. Autologous Platelet-Rich Fibrin (PRF) as an Adjunct in the Management of Osteoradionecrosis and Medication-Related Osteonecrosis of Jaws. Case Series in A Single Centre. *Appl. Sci*. 2021, 11, 3365. <https://doi.org/10.3390/app11083365>
11. MD, J.B.M., MD, E.Z., MD, M.A.F. et al. Overview and Emerging Trends in the Treatment of Osteoradionecrosis. *Curr. Treat. Options in Oncol*. 22, 115 (2021). <https://doi.org/10.1007/s11864-021-00915-3>
12. Watson EE, Hueniken K, Lee J, Huang SH, Maghrabi A AE, Xu W, Moreno AC, Tsai CJ, Hahn E, McPartlin AJ, Yao CM, Goldstein DP, De Almeida JR, Waldon JN, Fuller CD, Hope AJ, Ruggiero SL, Glogauer M, Hosni AA. Development and Standardization of a Classification System for Osteoradionecrosis: Implementation of a Risk-Based Model. *medRxiv [Preprint]*. Update in: *J Clin Oncol*. 2024 Jun 1;42(16):1922-1933. <https://doi.org/10.1101%2F2023.09.12.23295454>
13. Lajolo, C.; Rupe, C.; Gioco, G.; Troiano, G.; Patini, R.; Petrucci, M.; Micciche', F.; Giuliani, M. Osteoradionecrosis of the Jaws Due to Teeth Extractions during and after Radiotherapy: A Systematic Review. *Cancers* 2021, 13, 5798. <https://doi.org/10.3390/cancers13225798>
14. Ruggiero SL, Dodson TB, Aghaloo T, Carlson ER, Ward BB, Kademani D. American Association of Oral and Maxillofacial Surgeons' position paper on medication-related osteonecrosis of the jaws—2022 update. *Journal of oral and maxillofacial surgery*. 2022 May 1;80(5):920-43.
15. Johnston DT, Phero JA, Hechler BL. Necessity of antibiotics in the management of surgically treated mandibular osteomyelitis: a systematic review. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*. 2023 Jan 1;135(1):11-23.
16. Shuster A, Reiser V, Trejo L, Ianculovici C, Kleinman S, Kaplan I. Comparison of the histopathological characteristics of osteomyelitis, medication-related osteonecrosis of the jaw, and osteoradionecrosis. *International Journal of Oral and Maxillofacial Surgery*. 2019 Jan 1;48(1):17-22.

17. Topkan, E.; Kucuk, A.; Somay, E.; Yilmaz, B.; Pehlivan, B.; Selek, U. Review of Osteoradionecrosis of the Jaw: Radiotherapy Modality, Technique, and Dose as Risk Factors. *J. Clin. Med.* 2023, 12, 3025. <https://doi.org/10.3390/jcm12083025>
18. Kusumawardhany DF, Yudhasoka KL, Yusuf HY. Pathological Mandibular Fracture Secondary to Osteoradionecrosis: A Case Report. *Malaysian Journal of Medicine & Health Sciences.* 2024 Dec 4;20.
19. Wang Y, Turkstani H, Alfaifi A, Akintoye SO. Diagnostic and Therapeutic Approaches to Jaw Osteoradionecrosis. *Diagnostics.* 2024 Nov 27;14(23):2676.
20. Ogura I, Minami Y, Ono J, Kanri Y, Okada Y, Igarashi K, Haga-Tsujimura M, Nakahara K, Kobayashi E. CBCT imaging and histopathological characteristics of osteoradionecrosis and medication-related osteonecrosis of the jaw. *Imaging science in dentistry.* 2021 Jan 29;51(1):73.
21. Marjanowski, S. D., Maldonado, A., Schaller, B., & Burkhard, J.-P. M. (2021). Pentoxifyllin und Tocopherol: Die Bedeutung in der Behandlung der Osteoradionekrose – Literaturreview und Fallbericht. *SWISS DENTAL JOURNAL SSO – Science and Clinical Topics*, 131(9), 713-718. <https://doi.org/10.61872/sdj-2021-09-03>
22. Leonetti, J.P., Weishaar, J.R., Gannon, D. et al. Osteoradionecrosis of the skull base. *J Neurooncol* 150, 477–482 (2020). <https://doi.org/10.1007/s11060-020-03462-3>
23. Habib, Ahmed MD; Hanasono, Matthew M MD; DeMonte, Franco MD; Haider, Ali BS; Breshears, Jonathan D MD; Nader, Marc-Elie MD, MSc; Gidley, Paul W MD; Su, Shirley Y MBBS; Hanna, Ehab Y MD; Raza, Shaan M MD. Surgical Management of Skull Base Osteoradionecrosis in the Cancer Population – Treatment Outcomes and Predictors of Recurrence: A Case Series. *Operative Neurosurgery* 19(4):p 364-374, October 2020. | DOI: 10.1093/ons/opaa082
24. Kraus R., Laxer R.M. Characteristics, treatment options, and outcomes of chronic non-bacterial osteomyelitis in children. *Current treatment options in rheumatology.* 2020 Sep 6: 205–222. <https://doi.org/10.1007/s40674-020-00149-8>
25. Oliveira, CCB ., Dantas, JB de L., Borges, D. de PO ., Martins, GB ., Medrado , ARAP ., Reis , JVNA and Marchionni, AMT . (2021) “Ozone Therapy for the Treatment of Osteonecrosis in the Mandible Induced by Radiotherapy Associated with Bisphosphonate: Case Report”, *Brazilian Journal of Cancerology*, 67(2), p. e–02785. doi: 10.32635/2176-9745.RBC.2021v67n2.785.
26. Hallmer F, Korduner M, Møystad A, Bjørnland T. Treatment of diffuse sclerosing osteomyelitis of the jaw with denosumab shows remarkable results—A report of two cases. *Clinical Case Reports.* 2018 Dec; 6(12). e2434. <https://doi.org/10.1002/ccr3.1894>
27. Otto S, Burian E, Troeltzsch M, Kaeppler G, Ehrenfeld M. Denosumab as a potential treatment alternative for patients suffering from diffuse sclerosing osteomyelitis of the mandible—A rapid communication. *Journal of Cranio-Maxillofacial Surgery.* 2018 Apr 1; 46(4):534-537. <https://doi.org/10.1016/j.jcms.2017.10.011>
28. Mamedova E, Kolodkina A, Vasilyev EV, Petrov V, Belaya Z, Tiulpakov A. Successful use of denosumab for life-threatening hypercalcemia in a pediatric patient with primary hyperparathyroidism. *Hormone Research in Paediatrics.* 2020 Oct 19;93(4):272-8.
29. Oliveira, CCB ., Dantas, JB de L., Borges, D. de PO ., Martins, GB ., Medrado , ARAP ., Reis , JVNA and Marchionni, AMT . (2021) “Ozone Therapy for the Treatment of Osteonecrosis in the Mandible Induced by Radiotherapy Associated with Bisphosphonate: Case Report”, *Brazilian Journal of Cancerology*, 67(2), p. e–02785. doi: 10.32635/2176-9745.RBC.2021v67n2.785.
30. DANTAS JB, CARRERA M, MARCHIONNI AM, BORGES DD, REIS SR, GUIMARÃES LB, MEDRADO AP. OZONOTHERAPY IN JAW OSTEONECROSIS RELATED TO RADIOTHERAPY AND BISPHOSPHONATE: A CASE REPORT. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology.* 2020 Jan 1;129(1):e26. <https://doi.org/10.1016/j.oooo.2019.06.055>
31. Bianco E, Maddalone M, Porcaro G, Amosso E, Baldoni M. Treatment of Osteoradionecrosis of the Jaw with Ozone in the Form of Oil-based Gel: 1-year follow-up. *J Contemp Dent Pract.* 2019 Feb 1;20(2):270-276. PMID: 31058646.

32. MD, J.B.M., MD, E.Z., MD, M.A.F. et al. Overview and Emerging Trends in the Treatment of Osteoradionecrosis. *Curr. Treat. Options in Oncol.* 22, 115 (2021). <https://doi.org/10.1007/s11864-021-00915-3>
33. Gundestrup, A.K., Lynggaard, C.D., Forner, L. et al. Mesenchymal Stem Cell Therapy for Osteoradionecrosis of the Mandible: a Systematic Review of Preclinical and Human Studies. *Stem Cell Rev and Rep* 16, 1208–1221 (2020). <https://doi.org/10.1007/s12015-020-10034-5>
34. Li Y, Zhou Z, Xu S, Jiang J, Xiao J. Review of the Pathogenesis, Diagnosis, and Management of Osteoradionecrosis of the Femoral Head. *Med Sci Monit.* 2023 Jun 13;29:e940264. doi: 10.12659/MSM.940264. PMID: 37310931; PMCID: PMC10276533.
35. Zhuang XM, Zhou B. Exosome secreted by human gingival fibroblasts in radiation therapy inhibits osteogenic differentiation of bone mesenchymal stem cells by transferring miR-23a. *Biomedicine & Pharmacotherapy.* 2020 Nov 1;131:110672. <https://doi.org/10.1016/j.biopha.2020.110672>
36. Hiroyuki Hato, Ken-ichiro Sakata, Jun Sato, Akira Satoh, Toshihiko Hayashi, Yoshimasa Kitagawa, Clinical study of treatment methods and associated factors in mandibular osteoradionecrosis, *Journal of Oral Science*, 2021, Volume 63, Issue 3, Pages 289-291, Released on J-STAGE June 29, 2021, Advance online publication June 07, 2021, Online ISSN 1880-4926, Print ISSN 1343-4934, <https://doi.org/10.2334/josnurd.21-0154>
37. Li Z, Liu S, Xie S, Shan X, Zhang L, Cai Z. Advanced osteoradionecrosis of the maxilla: a 15-year, single-institution experience of surgical management. *Acta Otolaryngol.* 2020 Dec;140(12):1049-1055. doi: 10.1080/00016489.2020.1812714. Epub 2020 Sep 12. PMID: 32921212.
38. Qualliotine JR, Yousef A, Orosco RK, Fugere M, Kolb FJ, Kristallis T, Archambault K. Carbon Dioxide Laser Sequestrectomy for Osteoradionecrosis: A Case Series. *Photobiomodul Photomed Laser Surg.* 2023 Feb;41(2):73-79. doi: 10.1089/photob.2022.0090. PMID: 36780577. <https://doi.org/10.1089/photob.2022.0090>
39. Chebbi, K., 2021. Prosthetic Management of Maxillary Defect Due to an Osteoradionecrosis: A Case Report. *Saudi J Oral Dent Res*, 6(10), pp.439-444. 10.36348/sjodr.2021.v06i10.002
40. Shudo, A. Hyperbaric oxygen therapy as a conservative approach for osteoradionecrosis of the jaw in an osteoporotic patient receiving oral bisphosphonate therapy: a case report. *Bull Natl Res Cent* 46, 98 (2022). <https://doi.org/10.1186/s42269-022-00788-y>
41. Hurrell MJ, Low TH, Ch'ng S, Clark JR. Fascio-cutaneous and fascio-periosteal free flaps for treatment of intermediate stage osteoradionecrosis of the jaws. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology.* 2023 Aug 1; 136(2):128-35. <https://doi.org/10.1016/j.oooo.2022.12.002>
42. Arianpour K, Meleca JB, Liu SW, Prendes BL, Ciolek PJ, Genter DJ, Mangie C, Khanna S, Fritz MA. Evaluation of Anterolateral Thigh Fascia Lata Rescue Flap for Mandibular Osteoradionecrosis. *JAMA Otolaryngol Head Neck Surg.* 2023 Jul 1;149(7):621-627. doi: 10.1001/jamaoto.2023.1089. PMID: 37261824; PMCID: PMC10236321
43. Meleca JB, Kerr RP, Prendes BL, Fritz MA. Anterolateral Thigh Fascia Lata Rescue Flap: A New Weapon in the Battle Against Osteoradionecrosis. *Laryngoscope.* 2021 Dec;131(12):2688-2693. doi: 10.1002/lary.29709. Epub 2021 Aug 6. PMID: 34357650.
44. Haffey T, Winters R, Kerr R, Fritz M. Mandibular rescue: Application of the ALT fascia free flap to arrest osteoradionecrosis of the mandible. *Am J Otolaryngol.* 2019 Nov-Dec;40(6):102262. doi: 10.1016/j.amjoto.2019.07.006. Epub 2019 Jul 8. PMID: 31351741.
45. Vahidi N, Lee TS, Daggumati S, Shokri T, Wang W, Ducic Y. Osteoradionecrosis of the Midface and Mandible: Pathogenesis and Management. *Semin Plast Surg.* 2020 Nov;34(4):232-244. doi: 10.1055/s-0040-1721759. Epub 2020 Dec 24. PMID: 33380908; PMCID: PMC7759426.
46. Jin T, Zhou M, Li S, Wang Y, Huang Z. Preoperative status and treatment of osteoradionecrosis of the jaw: a retrospective study of 252 cases. *British Journal of Oral and Maxillofacial Surgery.* 2020 Dec 1;58(10):e276-82. <https://doi.org/10.1016/j.bjoms.2020.07.031>
47. Bettoni J, Olivetto M, Duisit J, Caula A, Testelin S, Dakpé S, Lengele B, Devauchelle B. The value of reconstructive surgery in the

management of refractory jaw
osteoradionecrosis: a single-center 10-year
experience. International journal of oral and
maxillofacial surgery. 2019 Nov
1;48(11):1398-404.