

LAURA MARIA DOS SANTOS REIS ROCHA DE CASTRO

Terapias adjuvantes no manejo da osteorradionecrose: uma série de casos

*Adjuvant therapies in the management of osteoradionecrosis: a case
series*

Dissertação apresentada à Faculdade de
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Resumo

A osteorradionecrose é uma complicação crônica e grave resultante do tratamento radioterápico em pacientes com neoplasias malignas de cabeça e pescoço. Clinicamente, a osteorradionecrose pode variar desde exposições ósseas mínimas até situações severas com fraturas patológicas. Diversas terapias são utilizadas no manejo da osteorradionecrose, incluindo antibióticos, debridamento, ressecção cirúrgica, ozonioterapia e fatores de crescimento celular. Este estudo relata três casos de osteorradionecrose tratados com ozonioterapia, isolada ou em combinação com fibrina rica em plaquetas e cirurgia ressectiva. Os resultados destacam os benefícios dessas abordagens como estratégias terapêuticas, auxiliando na regeneração tecidual e cicatrização de feridas. A ozonioterapia demonstra propriedades antimicrobianas e regenerativas, enquanto a fibrina rica em plaquetas está associada à promoção de angiogênese e reparo tecidual, contribuindo significativamente para a melhoria dos desfechos clínicos. A integração dessas terapias pode ser considerada para a condução de casos mais complexos, com o objetivo de otimizar os resultados clínicos e promover uma recuperação mais eficaz.

Palavras-chave: Osteorradionecrose; Ozônio; Fibrina rica em plaquetas; Neoplasias de Cabeça e Pescoço.

Abstract

Osteoradionecrosis is a chronic and serious complication of radiation therapy in patients with malignant head and neck tumors. Clinically, osteoradionecrosis can range from minimal bone exposure to severe situations with pathologic fractures. Various therapies have been used to treat ORN, including antibiotics, debridement, surgical resection, ozone therapy, and cellular growth factors. This study reports on three cases of osteoradionecrosis treated with ozone therapy, either alone or in combination with platelet-rich fibrin and surgical resection. The results highlight the benefits of these approaches as therapeutic strategies to promote tissue regeneration and wound healing. Ozone therapy has antimicrobial and regenerative properties, while platelet-rich fibrin has been associated with the promotion of angiogenesis and tissue repair, contributing significantly to improved clinical outcomes. The integration of these therapies may be considered for the management of more complex cases with the goal of optimizing clinical outcomes and promoting more effective healing.

Keywords: Osteoradionecrosis; Ozone; Platelet-Rich Fibrin; Head and Neck Neoplasms.

1. Introdução e Referencial Teórico

O câncer de cabeça e pescoço representa um desafio devido às suas elevadas taxas de mortalidade e morbidade, sendo o sétimo tipo de câncer mais comum no mundo (Karaca *et al.*, 2024). A radioterapia é um dos principais métodos de tratamento, especialmente em casos de doença localmente avançada ou com metástases linfonodais (Lang *et al.*, 2022). Embora eficaz no controle tumoral, a radioterapia pode resultar em complicações graves, dentre as quais a osteorradionecrose (ORN) se destaca como uma das mais preocupantes (O'Dell & Sinha, 2011; Lang *et al.*, 2022).

A ORN é uma condição caracterizada pela necrose óssea induzida por radiação ionizante, persistente por um período mínimo de três meses, sem sinais de cicatrização ou recorrência tumoral (Kubota *et al.*, 2021). A ORN ocorre predominantemente na mandíbula devido à sua vascularização (Haroun & Coblens, 2019). Quando acomete a maxila, a progressão tende a ser mais lenta e os defeitos são menos severos (Girardi *et al.*, 2022). O diagnóstico de ORN baseia-se em achados clínicos, incluindo dor, disfagia, trismo, fraturas, sequestro de osso desvitalizado e fístulas (O'Dell & Sinha, 2011; Girardi *et al.*, 2022), sendo indispensável o exame histológico para a exclusão de recidiva tumoral (Kün-Darbois & Fauvel, 2020).

A fisiopatologia da ORN envolve uma complexa interação de fatores etiológicos, destacando-se a deficiência na cicatrização óssea e a oclusão dos vasos sanguíneos, que resulta na redução na vascularização, oxigenação e aporte celular ao osso (Schwartz & Kagan, 2002; Bianco *et al.*, 2019). Fatores de risco como a localização e extensão do tumor primário, extrações dentárias realizadas após a radioterapia e a dose de radiação recebida estão associadas ao desenvolvimento da ORN (Kubota *et al.*, 2021). A infecção bacteriana contribui significativamente para a progressão da condição, exacerbada pela alteração do pH salivar induzida pela radioterapia, que favorece o crescimento de microrganismos patogênicos (Schwartz & Kagan, 2002; Lagarrigue *et al.*, 2022).

A prevenção da ORN é crucial, dada a dificuldade de sua condução (Kubota *et al.*, 2021). Medidas como antibioticoterapia perioperatória e cuidados locais têm se demonstrado eficazes quando a extração dentária é inevitável (Sultan *et al.*, 2017). Contudo, mesmo com tais medidas, as taxas de incidência de ORN permanecem elevadas, variando entre 5 a 10% nos primeiros dois anos após a radioterapia (Lagarrigue *et al.*, 2022).

O tratamento para a osteorradionecrose é baseado na gravidade da lesão (Schwartz & Kagan, 2002). Para casos classificados como de baixo grau, são indicadas abordagens conservadoras, que incluem terapias locais e debridamento (O'Dell & Sinha, 2011). Em

contrapartida, os casos mais complexos, que não apresentam resposta adequada à terapia conservadora e que envolvem disfunção oral significativa (Haroun & Coblens, 2019), requerem intervenções mais invasivas, como cirurgias ressectivas acompanhadas de reconstrução com retalho livre (Kün-Darbois & Fauvel, 2020).

A ozonioterapia surge como uma opção adjuvante no tratamento da ORN, destacando-se por suas propriedades antimicrobianas, anti-inflamatórias e de promoção da cicatrização tecidual (Batinjan *et al.*, 2014; Borges *et al.*, 2017; Bianco *et al.*, 2019). O ozônio, ao ser aplicado, gera uma série de efeitos biológicos benéficos, incluindo a estimulação da angiogênese e a melhora da circulação sanguínea local, favorecendo a oxigenação tecidual (Bianco *et al.*, 2019). Além disso, o ozônio modula a resposta imunológica, aumentando a produção de citocinas anti-inflamatórias, com efeitos positivos no controle de infecções e inflamações crônicas presentes na osteorradionecrose (Elvis & Ekta, 2011; Batinjan *et al.*, 2014). Outro aspecto importante é a indução da migração de fibroblastos e da proliferação de queratinócitos, fatores chave no processo de cicatrização de feridas e regeneração tecidual (Borges *et al.*, 2017).

Uma estratégia terapêutica promissora para o manejo da ORN é a utilização da fibrina rica em plaquetas (PRF) (Yalcin-Ülker *et al.*, 2023). A integração do tratamento cirúrgico com membranas autólogas de PRF objetiva enriquecer o sítio cirúrgico com fatores de crescimento, favorecendo a cicatrização tecidual (Alrmali *et al.*, 2023). Este método aproveita as propriedades regenerativas das plaquetas, além de promover a proliferação de osteoblastos e a liberação de citocinas e outros fatores de crescimento (Jamalpour *et al.*, 2022). Esses elementos são grandes estimuladores da regeneração local dos tecidos, potencializando a resposta biológica e otimizando os resultados clínicos no tratamento da ORN (Cano-Durán *et al.*, 2017).

Isto posto, este estudo visa relatar uma série de três casos, destacando o papel da ozonioterapia e da utilização de fibrina rica em plaquetas como estratégias terapêuticas complementares no manejo da osteorradionecrose.

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Adjuvant therapies in the management of osteoradionecrosis: A case series

Authors: Laura Maria dos Santos Reis Rocha de Castro, Lívia Bonjardim Lima, Luiz Fernando Barbosa de Paulo, Priscilla Barbosa Ferreira Soares

Abstract

Purpose: This study reports three cases of osteoradionecrosis (ORN) in patients following head and neck radiation therapy and highlights the results of treatment with ozone therapy alone or in combination with platelet-rich fibrin (PRF) and resective surgery.

Materials and Methods: This case series highlights the efficacy of adjuvant therapies in the treatment of ORN. Patients were selected based on diagnosis and treatment of ORN at the Specialized Care Program for Dental Diseases at the Dental Hospital of the Federal University of Uberlândia, with no tumor recurrence. All patients had previously received radiotherapy for head and neck cancer.

Results: The three ORN cases, at different stages of the disease, showed significant clinical improvement with adjuvant therapies. Symptoms and inflammatory signs were reduced and complete epithelialization of the affected area was achieved, demonstrating the efficacy of the therapeutic approaches.

Conclusion: Ozone therapy and PRF are promising strategies for promoting tissue regeneration and healing in ORN-associated wounds.

Key-words: Osteoradionecrosis; Ozone Therapy; Platelet-Rich Fibrin; Radiotherapy.

Introduction

Osteoradionecrosis (ORN) is a serious and debilitating chronic complication resulting from radiotherapy treatment in patients with malignant neoplasms of the head and neck¹, characterized by persistent bone exposure in the irradiated area for at least 3-6 months without a tendency to heal²⁻³. Exposure may occur spontaneously or be triggered by surgical or traumatic procedures in the previously irradiated area, presenting a complex challenge due to the variety of clinical manifestations^{1,4}.

Clinically, ORN ranges from minimal bone exposure, usually asymptomatic and amenable to conservative management, to more severe situations characterized by extensive areas of necrotic bone tissue associated with pathologic fractures⁵. Clinical examination shows signs such as fistula formation, mucosal ulceration with bone exposure, pathologic fractures, and secondary infections, making early diagnosis imperative to exclude neoplastic recurrence and surgical intervention in the most severe cases⁶⁻⁷.

The increasing incidence of ORN reflects the increase in the number of patients undergoing advanced radiotherapy treatments, thus necessitating the development of effective strategies for its prevention and treatment⁶. In this context, various therapeutic approaches have been proposed, such as the use of antibiotics⁵, bone sequestration removal^{1,5}, hyperbaric oxygen therapy², surgical resection^{3,8}, ozone therapy⁹, and platelet-rich fibrin¹⁰.

Ozone therapy demonstrates regenerative potential and plays a role in promoting wound healing, facilitating early closure of acute and chronic wounds⁹. Its antimicrobial efficacy is due to its ability to modulate biological oxidative stress, affecting a wide range of microorganisms^{9,11-12}. Topical application shows beneficial immunological effects and potential for adequate oxygenation, which can be applied via ozonated water, ozone gas, and ozonated oil¹³. When applied to tissues, the resulting oxygen improves local metabolism, activates the immune system, and stimulates cell proliferation, thereby promoting the healing process^{12,14}.

Another treatment used to enhance repair processes is platelet-rich fibrin (PRF), which is emerging as a promising alternative to enhance the benefits in the treatment of ORN¹⁰. Derived from the patient's own blood, PRF is fully biocompatible and contains intrinsic growth factors that promote angiogenesis¹⁵. Its essential role is to optimize tissue repair by stimulating cell proliferation, differentiation, and activity¹⁶. In addition to increasing the number of osteoblasts at the site of application, PRF influences the production of collagen-related proteins, which significantly affects wound closure and contributes to bone regeneration¹⁰.

The purpose of this article is to report three cases of patients who developed ORN following head and neck radiation therapy, with emphasis on the treatment outcomes using adjuvant therapy such as ozone therapy, either alone or in combination with PRF application and surgical resection.

Case report

The evaluation of these cases was conducted in accordance with the protocols approved by the Research Ethics Committee (CAAE: 64415522.0.0000.5152), ensuring that all practices complied with established ethical and regulatory requirements.

Case 1

A 57-year-old male patient, feoderma, was referred to the Dental Service of the Special Care Program for Stomatological Diseases of the Dental Hospital of the Federal University of Uberlândia (PROCEDE-UFU) after completion of head and neck radiotherapy for a previous diagnosis of metastatic cervical cancer with an occult primary site. The patient's medical history included radiotherapy of 70 Gy in 35 fractions. During follow-up was see an area of erythroleukoplakia on the hard palate, which was subjected to incisional biopsy and revealed squamous cell carcinoma. The palatal lesion was removed and the patient developed oroantral communication. At follow-up, palatal bone exposure was observed (Figure 1) with the presence of a fistula connecting the palatal region of the alveolar ridge to the vestibular region without evidence of infection, corresponding to stage 2 of ORN¹⁷.

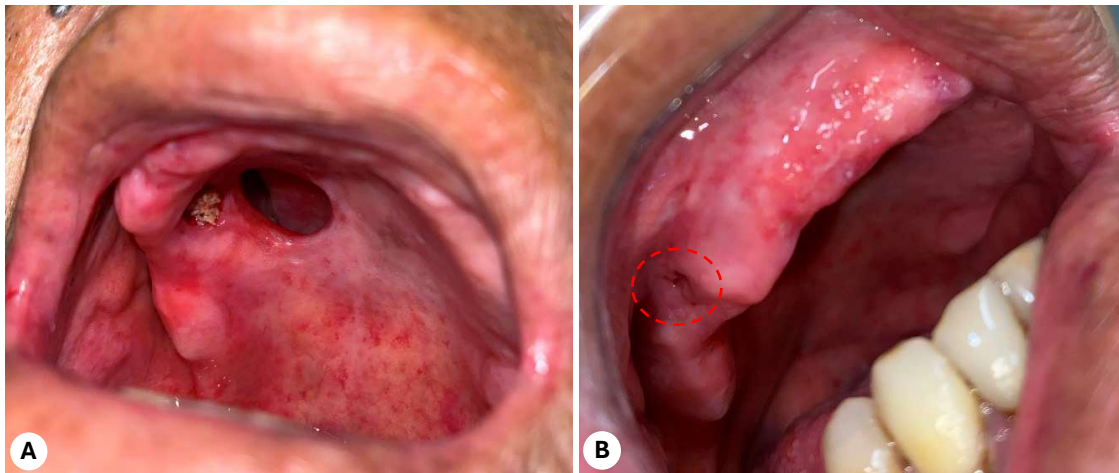


Figure 1. Intraoral aspect of the hard palate region. (A) Bone exposure and buccal-nasal communication; (B) Vestibular fistula resulting from communication with the palate.

The ozone therapy protocol was performed weekly and was determined based on the patient's clinical condition and the absence of inflammatory signs. It includes irrigation with ozonated water, ozonated oil and ozone gas. The solution was prepared using deionized water subjected to an ozonation protocol with an ozone concentration of 60 µg/mL for 5 minutes. The water was cooled to 5,5°C before the procedure, and ozonation was performed using an ozone generator (Medplus V, Philozon™, Santa Catarina, Brazil). In addition, a 3-milliliter (mL) infiltration of ozone gas at a concentration of 15 µg/mL was administered. This treatment was combined with the application of ozonized sunflower oil (Philozon™, Brazil), characterized by a peroxide index exceeding 2500 meq/1000g. The ozonized sunflower oil was given to the patient with the instruction to apply it once a day until the doctor advises to stop the therapy. The recommended dosage is 2-3 drops applied directly to the area affected by osteoradionecrosis, and the product should be stored in a refrigerated place. Two months later, the patient presented a bone sequestrum in the palatal region that was easily detached, facilitating atraumatic removal. After 1 year of bi-weekly ozone therapy, the surgical wound showed complete epithelialization of the area of communication between the palatal ridge and the vestibular surface of the maxillary ridge (Figure 2), with the patient reporting no pain or signs of inflammation.

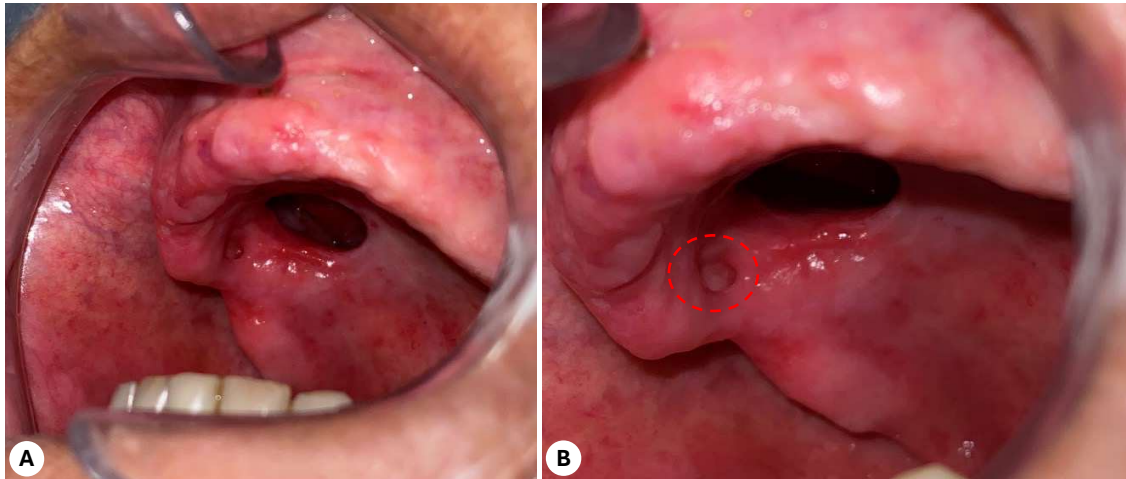


Figure 2. Complete epithelialization of the communication between the palate and the vestibular surface of the maxillary ridge. (A) Overview. (B) Palatal fistula magnified view.

Case 2

A 67-year-old male patient, leukoderma, diagnosed with squamous cell carcinoma (SCC) of the soft palate, was referred to the PROCEDURE-UFU for the treatment of severe pain associated with an area of exposed bone that had not closed following a tooth extraction. The patient received 72 Gy for 2 months as part of the SCC treatment. Eight months after completion of radiotherapy, he underwent extraction of tooth 38 at an outside service. Due to the lack of healing and associated pain, evaluation by a specialized team was recommended. The initial clinical examination revealed nonhealing of the socket of tooth 38 with bone exposure (Figure 3A). The panoramic radiograph (Figure 3B) showed radiolucency in the alveolar crest of tooth 38, consistent with ORN. The patient's condition was consistent with stage 2 ORN¹⁷.

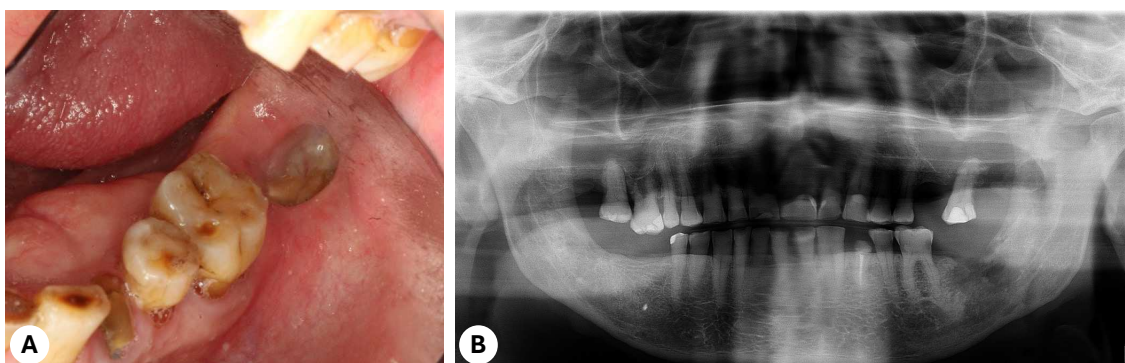


Figure 3. (A) Poorly sealed socket after tooth extraction showing lack of mucosal coverage and exposed bone; (B) Panoramic radiograph showing radiolucency in the region of tooth 38, suggestive of ORN.

The proposed treatment was ozone therapy, initially consisting of irrigation with 60 milliliters of ozonated water, ozonized as previously described, perilesional infiltration with 3 mL of ozone gas at 15 $\mu\text{g/mL}$ (Figure 4A), and the use of ozonized sunflower oil. This protocol was administered weekly for 1 year (Figure 4B). The recommendation was to continue using ozonized sunflower oil at home, maintaining the same dosage as in the previous case.

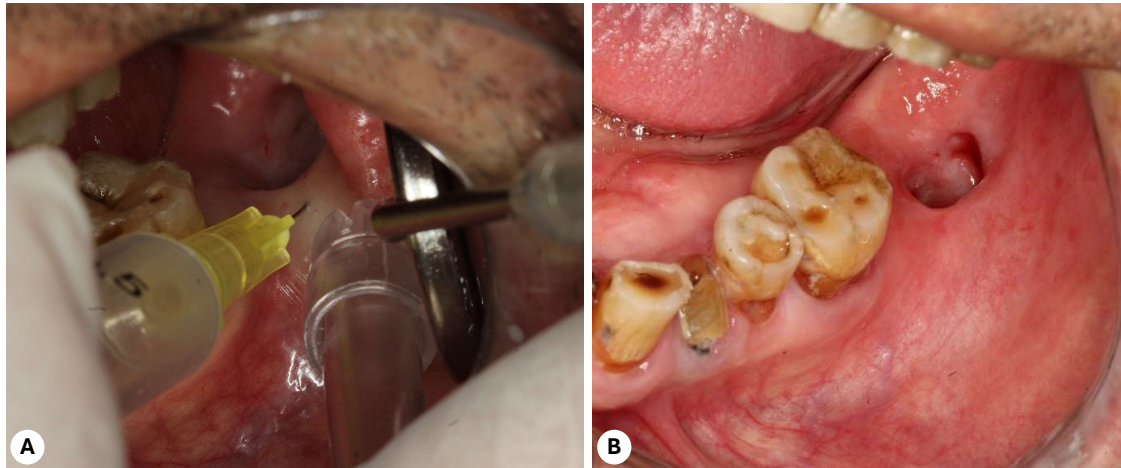


Figure 4. (A) Performing ozone therapy of perilesional infiltration with ozone gas; (B) Alveolus demonstrating epithelialization within after ozone therapy for a period of 1 year.

After 1 year of ozone therapy in the region of tooth 38, the wound was completely epithelialized and the patient started to come for evaluation once a month. However, after three months, the patient presented a slight bone exposure without pain complaints. Clinical examination revealed an 8-millimeter bone sequestrum in the alveolus. This was removed atraumatically, and 60 mL of ozonated water was used for irrigation, along with injection of 3 mL of ozone gas at 15 $\mu\text{g/mL}$ and ozonized sunflower oil applied to the wound. Daily use of ozonized sunflower oil was maintained at home, with applications once a day. Fifteen days after the procedure, despite the absence of inflammatory signs and pain symptoms, the panoramic radiograph (Figure 5) showed an increase in the area of ORN in the supero-inferior and anteroposterior dimensions.

Surgical debridement was performed under local anesthesia (Figures 6 A-D) and a PRF membrane was placed to protect the area. Amoxicillin 500 milligrams was prescribed every 8 hours for 3 days preoperatively and continued postoperatively for 7 days, with weekly follow-up visits for ongoing ozone therapy. One month after sequestrum removal and membrane placement combined with ozone therapy, complete wound closure and complete epithelialization were observed (Figure 7A). Follow-up visits were conducted every other month for 2 years, during which time ozone therapy sessions were administered at each visit.

These sessions included 60 mL of ozonized water, 3 mL of ozone gas at 15 µg/mL, and ozonized sunflower oil, according to the previously mentioned protocol. The patient remained asymptomatic with no evidence of infection or bone exposure (Figure 7B). Radiographic examination showed stability of bone tissue (Figure 8) with evidence of repair, including involution of radiolucent areas. Histopathologic analysis of the debrided tissue revealed the presence of necrotic bone with evidence of remodeling, inflammation, and bacterial contamination (Figure 9).



Figure 5. Panoramic radiograph demonstrating an increase in the radiolucent area of ORN.

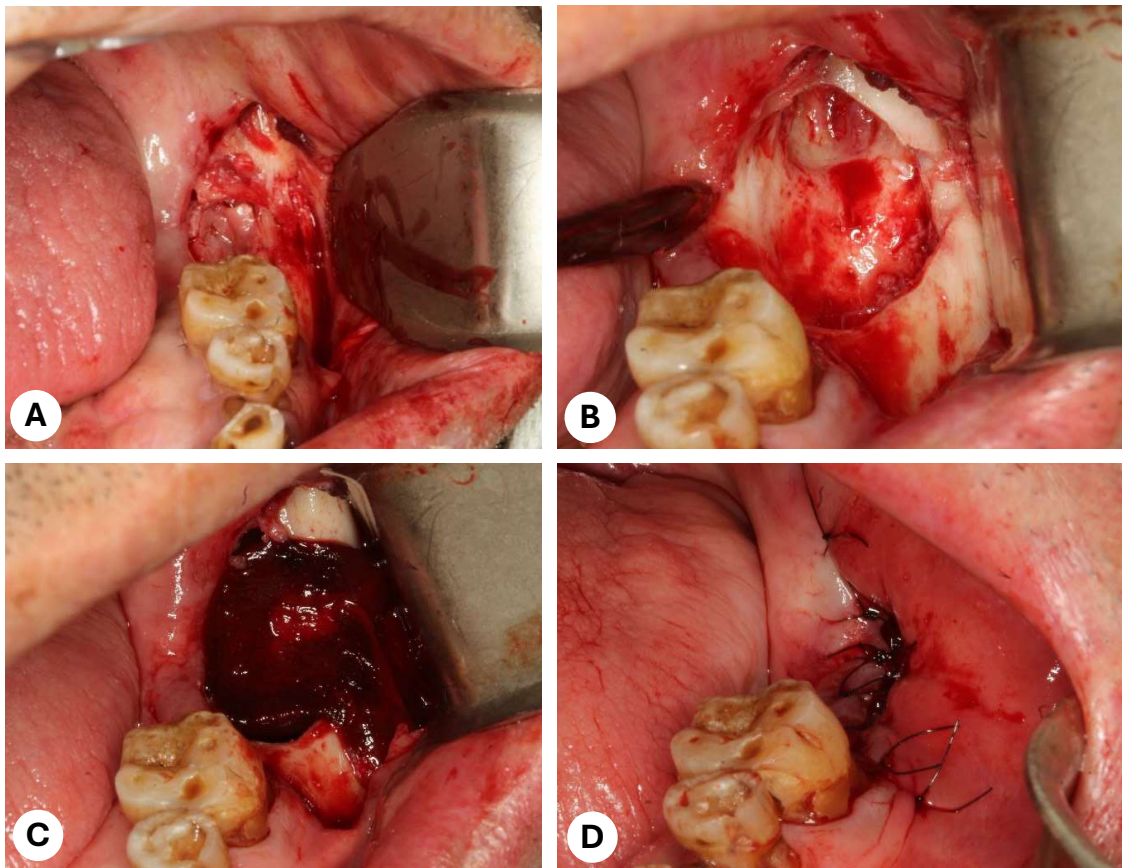


Figure 6. (A) Presence of bone sequestrum and the need for surgical removal under local anesthesia; (B) Debridement of the area of bone necrosis; (C) PRF membrane placed to protect de area; (D) Suture.

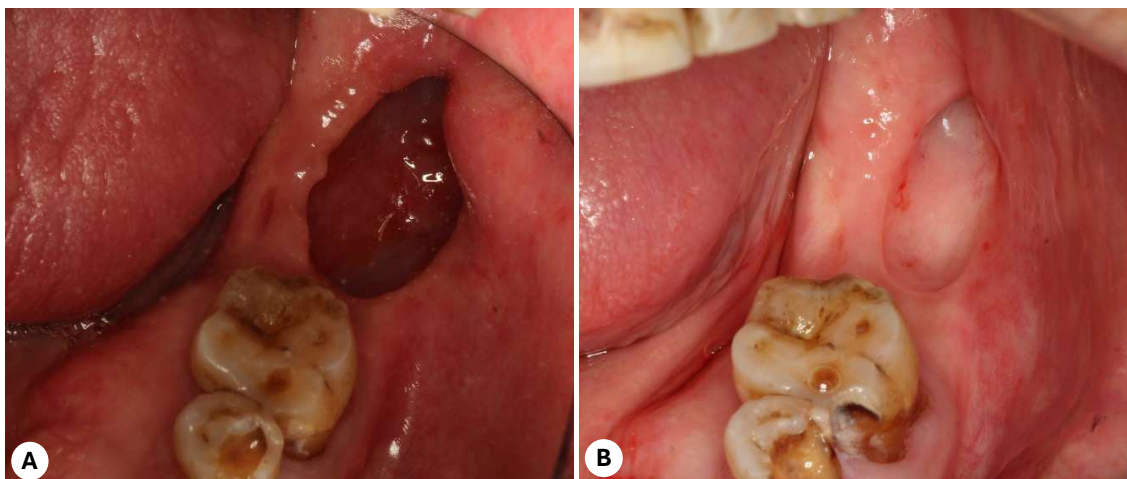


Figure 7. Postoperative outcomes of debridement associated with the use of PRF membrane associated with ozone therapy. (A) One month postoperative; (B) 12 months postoperative.



Figure 8. Panoramic radiograph at 2 years of follow-up.

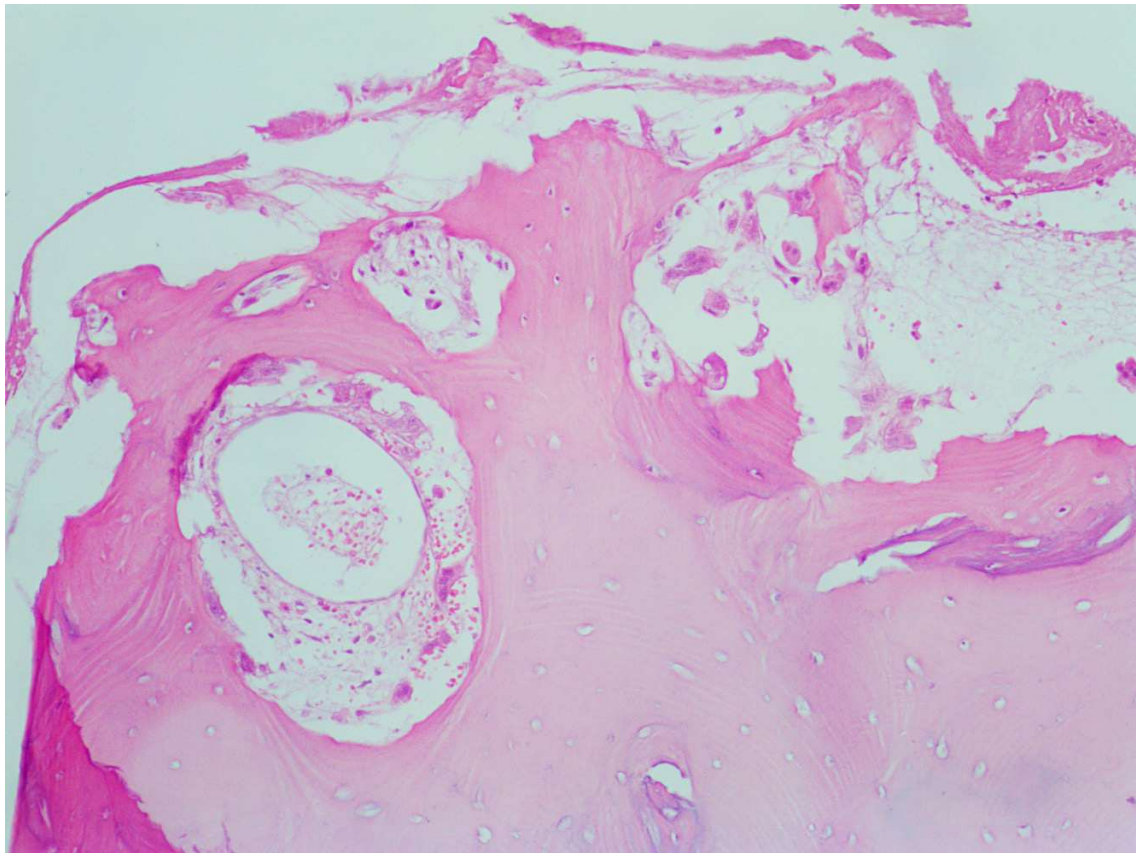


Figure 9. Margin of partially viable osseous tissue with scalloped borders, numerous osteoclasts, and granulation tissue.

Case 3

A 48-year-old male patient, melanoderma, referred to the PROCEDE-UFU by the Cancer Hospital for osteoradionecrosis in the mandible after radiotherapy and chemotherapy for squamous cell carcinoma at the base of the tongue. The patient's medical history included radiotherapy of 70 Gy in 35 fractions. After radiotherapy, there was spontaneous exposure of necrotic bone in the oral cavity and through submandibular area. Clinical examination revealed extensive tissue necrosis in the mandibular region, with exposure extending to the right mandibular base and body, presenting an eroded appearance with darkening, associated with severe pain, foul odor, and purulent discharge (Figure 10), corresponding to stage 3 of ORN¹⁷.

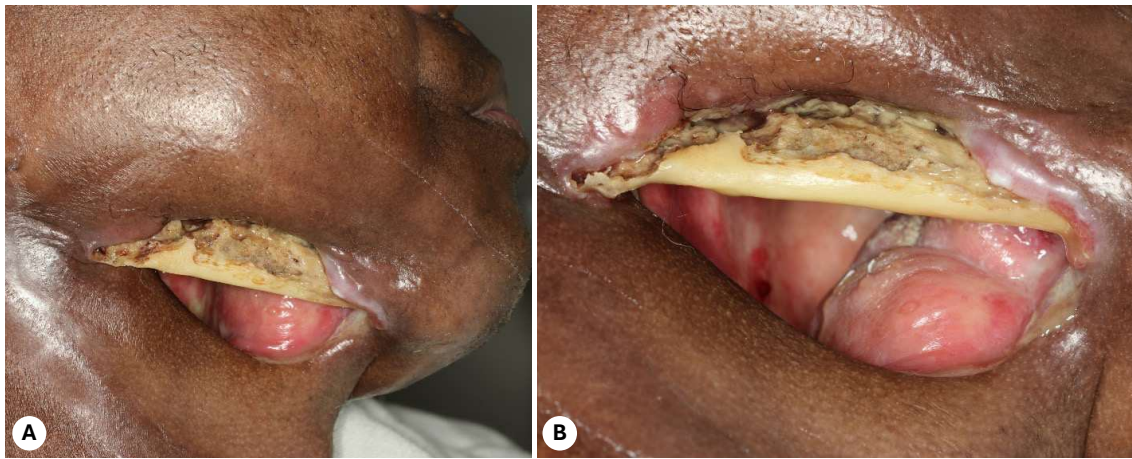


Figure 10. (A) Extraoral bone exposure of ORN involving the mandibular right body. (B) Image magnification revealing intraoral structures.

The panoramic radiograph (Figure 11) showed extensive bone rarefaction involving the mandibular parasymphysis, body, angle, and right ramus. Initial treatment included ozone therapy as an adjunct to treat the established infection while definitive surgical planning was underway.



Figure 11. Panoramic radiograph at initial visit showing extensive bone rarefaction in the mandible.

Regarding the ozone therapy protocol used intra- and extraorally during the sessions, wound irrigation with 100 mL (depending on the extent of the affected area) of ozonized water, prepared as in case 1, application of 5 mL of gas at 60 $\mu\text{g/mL}$, and topical application of ozonized sunflower oil were used. Considering the infectious context, the gas concentration was determined based on the need to ensure the antimicrobial efficacy of ozone. The patient was instructed to return for weekly ozone therapy sessions at each visit, in addition to daily application of ozonized sunflower oil. After three weeks, despite gradual improvement in pain, reduction in purulent discharge and foul odor, the patient developed a pathological fracture of the mandible, requiring urgent surgical intervention for mandibular resection under general anesthesia. A hemimandibulectomy (Figure 12) was performed through a submandibular and retromandibular approach. A tracheostomy was performed to maintain the airway. On the second postoperative day, dehiscence of the extraoral surgical wound occurred (Figure 13).

The excised specimen was sent for histopathologic examination and revealed non-vital bone tissue associated with intense fibrosis, necrotic debris, and granulation tissue, consistent with findings seen in radiation-induced osteonecrotic lesions (Figure 14).

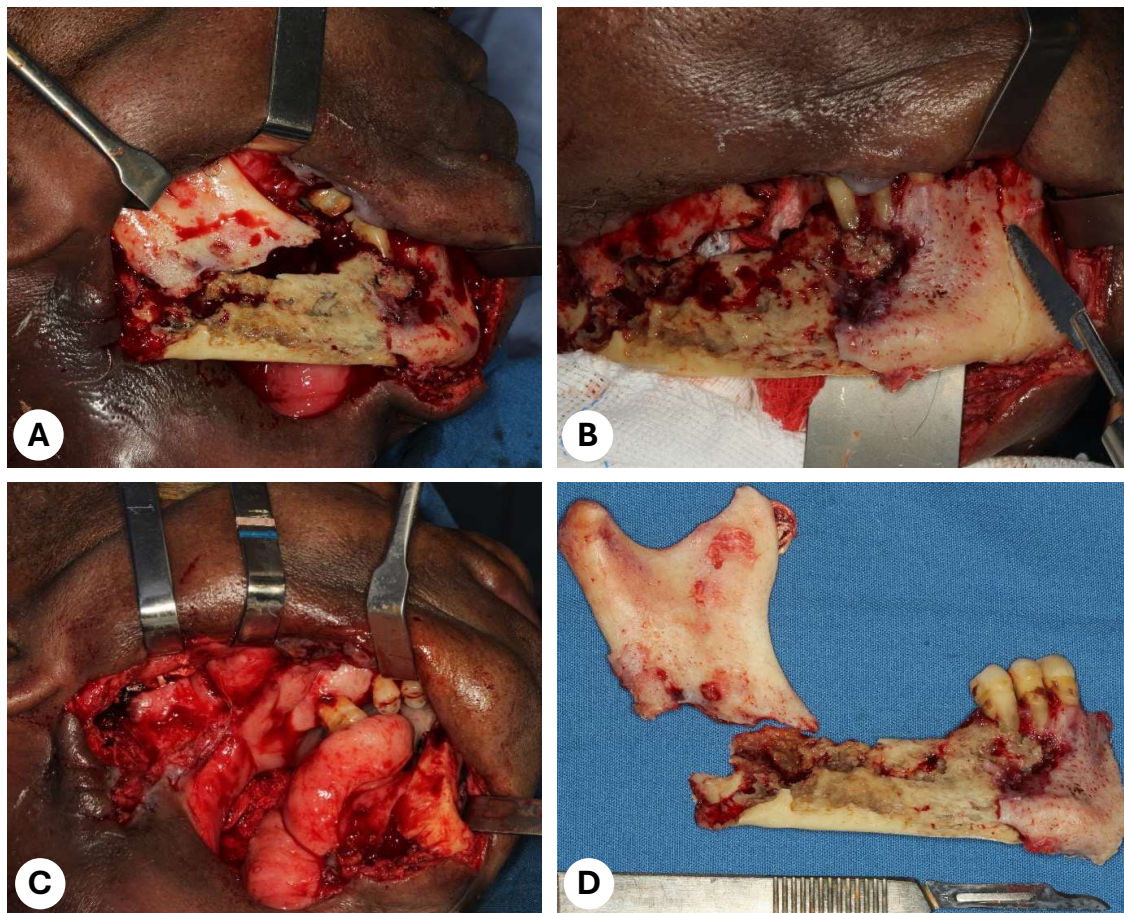


Figure 12. Surgical procedure of hemimandibulectomy for the treatment of ORN. (A) Presence of pathological fracture; (B) Anterior region of the osteotomy; (C) Maxillomandibular region after removal of necrotic bone; (D) Removed affected bone.



Figure 13. Extraoral aspect of the surgical wound showing dehiscence. (A) Second postoperative day; (B) 2 months postoperative.

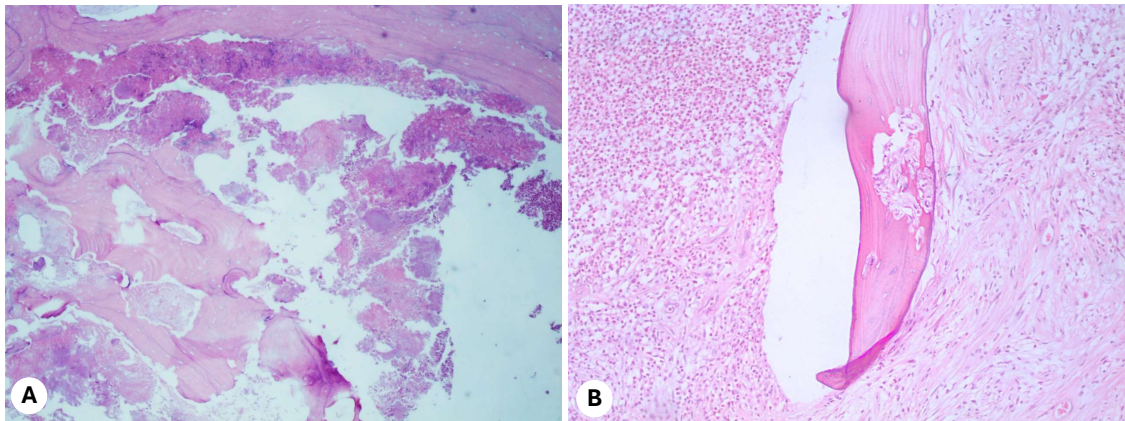


Figure 14. Pathological aspects of osteoradionecrosis. (A) Bone necrosis with empty osteocyte lacunae and sequestration, accompanied by bacterial colonization and leukocyte infiltrate; (B) Bone with irregular resorption lacunae, marrow fibrosis and acute inflammatory infiltrate. Hematoxylin-eosin stain.

During the postoperative period, ozone therapy was maintained to improve tissue quality. However, at this point, infiltration with ozone gas at 15 µg/mL was performed due to the absence of infection. After 8 months, the area was closed with a pectoralis major myocutaneous flap (Figure 15), which progressed with good healing, without wound dehiscence or signs of infection (Figure 16A). At 1 year postoperative (Figure 16B), the surgical wound maintained a good scar appearance.



Figure 15. Pectoral muscle myocutaneous surgery. (A) Rotation of the pectoral muscle myocutaneous flap. (B) Final suture.



Figure 16. Approach for the new repositioning of the pectoral muscle myocutaneous flap. (A) Immediate postoperative period; (B) One year postoperative.

Discussion

The head and neck region is one of the most common sites for malignant neoplasms worldwide, and its treatment involves multidisciplinary approaches including surgery, chemotherapy, and radiation therapy^{4,18}. Radiotherapy, an important therapeutic tool, stands out as an adjuvant in the treatment of these tumors and has demonstrated significant efficacy^{6,19}. However, its application is not without challenges, with osteoradionecrosis (ORN) being one of the most debilitating and clinically relevant complications associated with this procedure^{5,10}.

Due to its aggressive nature, ORN has a significant impact on the patient's quality of life. This condition is defined by the presence of exposed and devitalized bone tissue that undergoes changes such as hypoxia, hypovascularization, and reduced cellular density following radiation therapy^{3,18}. This process of change is characterized by the absence of tissue repair for at least 3 to 6 months from the time of diagnosis, culminating in tissue necrosis as the ability for bone reconstruction is compromised^{1,3}.

The understanding of the pathogenesis of ORN remains partially unclear in the literature, as its manifestation occurs both spontaneously and in association with trauma in areas previously irradiated⁷. ORN is a dysfunction in the healing process, separate from an infectious nature⁴. Exposure to ionizing radiation triggers changes in bone vascularization, resulting in a

significant decrease in repair capacity⁸, compromising the tissue response to injury and culminating in necrosis⁴. Several factors have been identified as potential aggravators of the risk of developing ORN, including the patient's systemic status⁶, the dose of radiation administered⁸, the location and stage of the tumor¹, and the practice of tooth extraction⁶.

The treatment of ORN is determined by the severity and complexity of the clinical situation, making an individualized approach essential, ranging from more conservative therapies to surgical interventions involving resection and reconstruction^{7,19}. Understanding the classification of ORN is critical to guide the selection of the most appropriate treatment and provides valuable information about the specific stage of the disease^{2,18}.

Osteoradionecrosis can be classified into stages based on clinical and radiographic features¹⁹. Stage 0 involves only mucosal involvement with no radiographic changes. Stage 1 shows radiographic evidence of bone necrosis with intact mucosa. Stage 2 involves bone exposure and radiographic evidence of necrosis without evidence of infection. Stage 3 is characterized by exposed bone, infection with drainage, oro-cutaneous fistula, mandibular fracture, and radiographic bone changes^{1,17,19}. Another classification system divides osteoradionecrosis (ORN) into three stages⁸. Stage I involves localized damage to the alveolar bone. Stage II shows necrosis extending above the inferior alveolar canal but not affecting critical structures. Stage III, the most severe, includes necrosis beyond the inferior alveolar canal with complications such as pathological fractures and oro-cutaneous fistulas^{8,19}.

In the early stages, a conservative approach is used with various combined or isolated therapies, including debridement of non-vital bone, systemic antibiotic therapy, hyperbaric oxygen therapy, laser therapy, ozone therapy, and the platelet-rich fibrin^{5,10-11}. However, advanced cases characterized by skin fistulas, extensive mandibular bone involvement, and pathologic fractures require a more invasive approach. This involves not only complete resection of the affected mandible and surrounding necrotic soft tissue, but also reconstruction of soft and hard tissue defects³⁻⁴.

In the cases discussed, measures were taken to ensure oral adequacy and prevent local trauma. In situations where preservation was not feasible, surgery was chosen along with pre- and post-operative antibiotic therapy and a protocol of ozone therapy, either alone or in combination with the application of platelet-rich fibrin. Despite the time required for complete wound closure due to the limited repair capacity of previously irradiated tissues⁴, the benefits of these therapies were observed in improving clinical outcomes, culminating in complete epithelialization of the affected area.

Ozone therapy in dentistry aims to induce controlled oxidative stress using low concentrations of ozone while maintaining high therapeutic efficacy^{11,13}. This approach ensures that the ozone does not exceed the body's intrinsic antioxidant capacity. Typically, the therapeutic mixture consists of up to 5% ozone and 95% oxygen, carefully formulated to balance efficacy and safety^{9,20}. While ozone therapy is widely used systemically in various medical specialties and has demonstrated significant regenerative potential²¹ its application in dentistry remains primarily topical⁹.

The ozone therapy protocol adopted is based on maximizing the therapeutic properties by targeting the body's response⁹. For topical applications, ozone concentrations between 10-40 µg/mL are used, which have been proven effective in promoting analgesic and anti-inflammatory effects, as well as accelerating the healing process²²⁻²³. Concentrations of 60-100 µg/mL are used to achieve an antibiotic effect²¹. The duration of treatment varies according to the individual needs of each patient and extends to complete healing and resolution of infection²³.

The different modalities of ozone therapy application in dentistry, including water, gas and oil, are characterized by their practicality and versatility, allowing easy adaptation to different clinical scenarios and professional preferences^{9,20}. From a therapeutic point of view, ozone therapy is characterized by its anti-inflammatory and antiseptic properties, as well as its ability to modulate oxidative stress, resulting in improved oxygenation and stimulation of local circulation¹². Through the oxidative process, the therapy facilitates tissue repair, promotes healing and activates the immune response, playing a crucial role in the treatment of infectious changes or those resulting from hypovascularization¹⁴. These properties support the indication of this adjuvant in the three reported cases of ORN, which showed improvements in clinical appearance, either through a reduction in symptoms or inflammatory signs following its use.

Ripamonti *et al* (2011) highlighted the benefits of ozone in the treatment of bone necrosis, emphasizing the occurrence of spontaneous exfoliation of the sequestrum¹¹. Complete healing of lesions and epithelialization of intraoral soft tissues during ozone therapy can occur with the use of ozonated oil¹⁴. In the three cases presented, significant improvement in tissue conditions, easy removal of necrotic bone tissue, and complete wound closure were observed. Considering the antiseptic properties of ozone, case 3 had an infection associated with ORN and showed improvement in signs and symptoms after ozone application.

In addition, PRF is a blood derivative composed of leukocytes and platelets, which is responsible for its distinct biological properties⁴. Due to its angiogenesis-stimulating potential and the presence of growth factors, this resource plays a role in cellular proliferation,

differentiation and activity, contributing significantly to tissue regeneration and consequently optimizing clinical outcomes¹⁵⁻¹⁶. The advanced platelet-rich fibrin (A-PRF) variant used in case 2 is characterized by its release of growth factors and ease of handling. Its use in the post-extraction socket is strategically aimed at accelerating the healing process⁴.

The perspective of this study is to assist professionals in the management of ORN by providing insight into the use of therapeutic adjuncts to promote treatment and, consequently, restore quality of life for affected patients. However, it is important to understand the inherent limitations of treatment in oncology patients. The tissue fragility and potentially low immunity of these patients may predispose them to wound dehiscence, requiring additional interventions. An individualized approach and close monitoring are critical to optimizing clinical outcomes and minimizing complications.

The management of patients with head and neck cancer undergoing radiotherapy requires a careful approach aimed at optimizing treatment efficacy while minimizing adverse complications. In this context, the implementation of ozone therapy and the use of PRF have emerged as promising strategies, demonstrating positive effects on tissue regeneration and wound healing associated with osteoradionecrosis. These interventions not only improve the prognosis but also the quality of life for patients and are valuable components in the multidisciplinary approach to complex clinical conditions.

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Conflict of interest

The authors declare to have no conflict of interest.

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