

JESSICA FERREIRA RODRIGUES

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desproteinizado no reparo ósseo em pacientes com câncer de cabeça e
pescoço: um estudo clínico controlado e randomizado**

*Stimulatory potential of the combination of PRF and deproteinized bovine
bone in the bone repair in patients with head and neck cancer: a
randomized controlled clinical trial*

Dissertação apresentada à Faculdade de
Odontologia da Universidade de Uberlândia, para
obtenção do Título de Mestre em Odontologia na
Área de Clínica Odontológica Integrada.

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Iniciando os trabalhos o(a) presidente da mesa, Dr(a). Priscilla Barbosa Ferreira Soares, apresentou a Comissão Examinadora e o candidato(a), agradeceu a presença do público, e concedeu ao Discente a palavra para a exposição do seu trabalho. A duração da apresentação do Discente e o tempo de arguição e resposta foram conforme as normas do Programa.

A seguir o senhor(a) presidente concedeu a palavra, pela ordem sucessivamente, aos(às) examinadores(as), que passaram a arguir o(a) candidato(a). Ultimada a arguição, que se desenvolveu dentro dos termos regimentais, a Banca, em sessão secreta, atribuiu o resultado final, considerando o(a) candidato(a):

Aprovada.

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Resumo

O câncer de cabeça e pescoço afeta consideravelmente a qualidade de vida dos pacientes. Entre as opções de tratamento, a radioterapia apresenta grande eficácia, mas também prejudica os tecidos saudáveis circundantes. Este estudo teve como objetivo avaliar os benefícios da aplicação de fibrina rica em plaquetas (PRF) combinada com osso bovino desproteinizado (Sticky Bone) na formação óssea após extração dentária em pacientes submetidos à radioterapia. Quinze pacientes foram selecionados e randomizados em relação aos alvéolos para receber um coágulo de sangue (controle) ou Sticky Bone (experimental). No final do estudo, seis pacientes concluíram todas as etapas de avaliação e foram acompanhados durante 60 dias após o tratamento oncológico. Foram realizados acompanhamentos clínicos para avaliar o leito cirúrgico, e o processo de reparo ósseo foi analisado por meio de avaliações radiográficas qualitativas conduzidas por três examinadores cegos. Os dados foram examinados utilizando os testes de Mann-Whitney, regressão binária multinível e regressão de efeitos mistos para explorar a associação entre as intervenções e os resultados ($\alpha = 0,05$). Independentemente do período de avaliação, o uso do PRF não influenciou significativamente os resultados. No entanto, observou-se uma melhora notável nos escores da avaliação realizada 7 dias após a cirurgia em comparação com as avaliações subsequentes. O Sticky Bone apresenta potencial para aprimorar o tratamento da osteorradionecrose; entretanto, não foram observados impactos significativos na regeneração tecidual e óssea dentro de 60 dias após a radioterapia.

Palavras-chave: Radioterapia; sticky bone; reparo ósseo.

Abstract

Head and neck cancer significantly impacts the quality of life of patients. Among treatment options, radiotherapy is highly effective but also damages surrounding healthy tissues. This study aimed to assess the benefits of applying platelet-rich fibrin (PRF) combined with deproteinized bovine bone (Sticky Bone) for bone formation after tooth extraction in radiotherapy patients. Fifteen patients were selected and randomized regarding the sockets to receive either a blood clot (control) or Sticky Bone (experimental). Six patients completed all follow-ups and were evaluated during 60 days post-oncological treatment. Clinical follow-ups were conducted to assess the surgical site, and bone repair was analyzed using qualitative radiographic assessments by three blinded examiners. Data were analyzed using the Mann-Whitney test, multilevel binary regression, and mixed-effects regression to explore the association between interventions and outcomes ($\alpha = 0.05$). Regardless of the evaluation period, PRF use did not significantly influence outcomes. However, there was a notable improvement in evaluation scores at 7 days post-surgery compared to subsequent assessments. Sticky Bone shows potential to enhance osteoradionecrosis treatment; however, no significant impact on tissue and bone regeneration was observed within 60 days of radiotherapy.

Keywords: Radiotherapy; sticky bone; bone repair.

1. Introdução e Referencial Teórico

A radioterapia (RT) é amplamente empregada no tratamento de diversos tipos de câncer de cabeça e pescoço (CCP). Seu principal objetivo é controlar o crescimento tumoral ou eliminar o tumor, reduzindo a possibilidade de recorrência e melhorando a qualidade de vida dos pacientes (Prisinoto *et al.*, 2023). Grande parte dos pacientes com CCP precisam de radioterapia, seja como tratamento principal, como complemento à cirurgia, em combinação com quimioterapia ou como tratamento paliativo (Spijkervet *et al.*, 2019).

O tratamento ionizante proporcionado pela RT não é seletivo e também atinge células saudáveis, de forma a danificar a capacidade de reparo tecidual (Beech *et al.*, 2014) resultando em sequelas orais, como mucosite, candidíase orofaríngea, dor nas mucosas e disfunção do paladar, trismo, disfunção temporomandibular, cáries dentárias, inflamação gengival e osteorradionecrose (ORN) (Sroussi *et al.*, 2017; Sohn *et al.*, 2018).

Após o tratamento oncológico, o tecido sofre várias alterações, tornando-se hipóxico, hipovascular e hipocelular (Schuurhuis *et al.*, 2018), de forma a prejudicar o processo de reparo ósseo e com isso favorecendo a ocorrência da ORN (Limirio *et al.*, 2019), que é caracterizada pela necrose do tecido ósseo submetido à radiação, sem sinais de recidiva tumoral, persistindo por um período de pelo menos três meses (Goh *et al.*, 2023), sua causa está associada a procedimentos odontológicos mais invasivos, como as extrações dentárias (Beech *et al.*, 2014; Goh *et al.*, 2023).

Dessa forma, a avaliação odontológica pré-radioterapia e a eliminação dos focos de infecção são extremamente importantes (Sroussi *et al.*, 2017; Balermipas *et al.*, 2022). Durante essa fase, o cirurgião-dentista planeja o tratamento necessário para adequação do meio bucal antes do início da radioterapia, incluindo a extração de dentes inviabilizados de serem reabilitados, restaurações, endodontia e terapia periodontal, tanto não cirúrgica quanto cirúrgica. Essas medidas são essenciais para prevenir complicações dentárias subsequentes (El-Rabbany *et al.*, 2019; Balermipas *et al.*, 2022; Hoffmann *et al.*, 2022).

O tratamento de pacientes com neoplasias orais deve ir além da cura da malignidade, abrangendo também a manutenção completa do sistema estomatognático. As reabilitações protéticas melhoram significativamente a qualidade de vida dos

pacientes, restaurando a fonética, a oclusão estável e a autoestima (Pompa *et al.*, 2015; Chrcanovic *et al.*, 2016). O sucesso desses procedimentos é influenciado por fatores como a dose de irradiação, a localização da neoplasia, os hábitos do paciente, a saúde periodontal, a necessidade de enxertos ósseos e o intervalo entre o final da radioterapia e a colocação do implante (Di Carlo *et al.*, 2019). Portanto, em planos de tratamento que envolvem a instalação de implantes dentários após a radioterapia, a preservação do osso alveolar é essencial, pois a osseointegração e a durabilidade dos implantes dependem da quantidade e qualidade do osso alveolar no momento da instalação (Stumbras *et al.*, 2019; Idiri *et al.*, 2023).

Entre os recursos disponíveis para a preservação do alvéolo, a fibrina rica em plaquetas (PRF), que é um concentrado autólogo de fatores de crescimento, contendo alta concentração de plaquetas, leucócitos e proteínas bioativas. Desde que foi introduzido por Joseph Choukroun (Malcangi *et al.*, 2023), tem sido amplamente utilizado para auxiliar na regeneração tecidual, promovendo a cicatrização e melhorando os resultados cirúrgicos. O mecanismo de ação do PRF na aceleração da regeneração tecidual ocorre devido à estimulação da angiogênese e presença de fatores de crescimento que impulsionam a proliferação, diferenciação e atividade celular nos tecidos (Pereira *et al.*, 2022; Idiri *et al.*, 2023).

A variação no protocolo de centrifugação pode resultar em diferentes tipos de concentrados de PRF, afetando a quantidade de células, fatores de crescimento e características físicas do material (Idiri *et al.*, 2023). As evidências do papel das células brancas na regeneração óssea e no crescimento dos vasos sanguíneos levaram Joseph Choukroun a introduzir O S-PRF, um tipo de PRF avançado, que se destaca por sua capacidade de reter leucócitos, plaquetas e fatores de crescimento, sendo eficaz na regeneração óssea (Malcangi *et al.*, 2023).

Evidências demonstram que o PRF tem grande potencial para acelerar a cicatrização pós-extração, tanto isoladamente quanto em combinação com substitutos ósseos, conhecido como Sticky Bone (Pereira *et al.*, 2022; Idiri *et al.*, 2023). O osso bovino desproteinizado, amplamente utilizado em procedimentos reconstrutivos para aumentar o volume ósseo, é composto por hidroxiapatita bovina. Este biomaterial apresenta boa biocompatibilidade e propriedades osteocondutivas, além de possuir

reabsorção extremamente lenta ou até mesmo ausência de reabsorção ao longo de vários anos (Comuzzi *et al.*, 2022) e atua como arcabouço para a neoformação óssea, facilitando a atuação de células osteogênicas e vasos sanguíneos (Idiri *et al.*, 2023).

Seus benefícios são potencializados quando utilizados com concentrados sanguíneos ricos em fatores de crescimento, devido à capacidade do PRF de aglutinar o enxerto ósseo, promovendo sua estabilização no defeito e acelerando a cicatrização dos tecidos, uma característica distintiva do Sticky Bone (Stumbras *et al.*, 2019). Este material é conhecido por sua eficácia na estabilização do defeito ósseo e na prevenção da perda do enxerto, demonstrando resultados promissores na cicatrização tecidual e no reparo de defeitos alveolares. Além disso, sua forte interconexão de fibrina facilita o manuseio, mantendo-o firmemente no alvéolo (Tony *et al.*, 2022; Malcangi *et al.*, 2023).

Apesar das evidências promissoras sobre o potencial do PRF e dos substitutos ósseos na manutenção do alvéolo após extração, há uma lacuna na literatura sobre sua aplicabilidade em pacientes com câncer de cabeça e pescoço submetidos a radioterapia. Isso destaca a necessidade de desenvolver protocolos específicos para preservar o tecido ósseo irradiado após extrações dentárias, garantindo o cuidado integral do sistema estomatognático e a manutenção óssea para possibilitar a reabilitação futura e melhorar a qualidade de vida a longo prazo. Portanto, este estudo teve como objetivo avaliar a eficácia do S-PRF com substituto ósseo bovino na estimulação do reparo ósseo após extração dentária em pacientes submetidos a radioterapia de cabeça e pescoço.

2. Capítulo. Artigo: Stimulatory potential of the combination of PRF and deproteinized bovine bone in the bone repair in patients with head and neck cancer: a randomized controlled clinical trial

Artigo será enviado para Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology

Authors: Jessica Ferreira Rodrigues, Dhiancarlo Rocha Macedo, Roberta de Oliveira Alves, Luiz Fernando Barbosa de Paulo, Gabriella Lopes de Rezende Barbosa, Priscilla Barbosa Ferreira Soares.

Abstract

Head and neck cancer significantly impact the patients' quality of life of patients. While radiotherapy is effective, it also compromises the surrounding healthy tissues. This study aimed to evaluate the benefit of applying platelet-rich fibrin (PRF) combined with deproteinized bovine bone (sticky bone) on bone formation after tooth extraction in patients undergoing radiotherapy. Fifteen patients were selected and randomized regarding the sockets to receive either a blood clot (control) or sticky bone (experimental). Six patients completed all follow-ups and were evaluated during 60 days post-oncological treatment. Bone repair was assessed through qualitative radiographic analyses performed by three examiners. Data were analyzed by Mann-Whitney, multilevel binary regression and mixed-effects regression to explore the association between interventions and outcomes ($\alpha = 0.05$). Regardless of the assessment time, the use of PRF did not influence the outcomes. However, a notable improvement in scores was observed from the evaluation conducted 7 days after the surgery to those carried out subsequently. The Sticky Bone has the potential to improve osteoradionecrosis treatment, however no significant impacts on tissue and bone repair was observed within 60 days post-radiotherapy.

Keywords: Head and neck cancer; radiotherapy; sticky bone; bone repair.

Introduction

Head and neck cancer is one of the most significant and prevalent malignant neoplasms, with an annual incidence of over half a million diagnosed cases (Moore *et al.*, 2020; Alfouzan *et al.*, 2021). Therapeutic approaches to treat these cancers predominantly include surgery, chemotherapy, radiotherapy, or a combination of these protocols (Alfouzan *et al.*, 2021). However, high doses of radiotherapy compromise the normality and functionality of healthy cells, and tissue damage is dose-dependent, affecting cell survival rates (Alterio *et al.*, 2019; Alfouzan *et al.*, 2021).

Ionizing radiation compromises bone formation and affects cortical bone microarchitecture in a time- dependent manner. Result in changes in cellularity and vascularization and a reduction in healing and remodeling potential (Irie *et al.*, 2018; Kawashita *et al.*, 2020; Borges *et al.*, 2021) increasing the risk of infection and necrosis (Urquhart *et al.*, 2022). The damage to the repair of irradiated bone tissue is evident, especially in the repair of alveolar bone, highlighting the adverse impacts on the regeneration process (Mendes *et al.*, 2019; Borges *et al.*, 2023).

The radiation result in various alteration in the oral cavity, which can manifest as temporary or long-term complications (Irie *et al.*, 2018; Abed, 2023). Acute effects include oral mucositis, dysgeusia, xerostomia, and trismus (Alfouzan *et al.*, 2021). Chronic effects encompass dental caries (Abed, 2023), progressive loss of periodontal attachment (Irie *et al.*, 2018), soft tissue necrosis (Lalla *et al.*, 2023) and osteoradionecrosis (Irie *et al.*, 2018; Kawashita *et al.*, 2020; Alfouzan *et al.*, 2021; Abed, 2023). Osteoradionecrosis is characterized by non-healing exposure of the bone with persistent necrosis for at least three months in patients undergoing radiotherapy (Kawashita *et al.*, 2020; Abed, 2023). This condition can lead to symptoms such as pain, infection, fistula, paresthesia, and jaw fracture, usually triggered by tooth extraction or odontogenic and periodontal infections (Kawashita *et al.*, 2020; Lalla *et al.*, 2023; Abed, 2023).

To minimize oral complications during head and neck radiotherapy, it is crucial to refer patients for pre-treatment dental evaluation as soon as diagnosis and planning are completed (Irie *et al.*, 2018; Bhandari *et al.*, 2022; Abed, 2023). Patients requiring oral procedures prior to radiotherapy have a higher risk of osteoradionecrosis, emphasizing the importance of oral health for cancer treatment prognosis and timely management

(Urquhart *et al.*, 2022). During these pre-treatment assessments, it is essential to extract non-viable teeth for rehabilitation and eliminate possible infectious foci (Moore *et al.*, 2020; Alfouzan *et al.*, 2021). Since the risk of developing osteoradionecrosis increases after post-radiotherapy surgical interventions, dental management before radiotherapy treatment is crucial to reduce the need for post-procedure tooth extractions (Irie *et al.*, 2018; Lalla *et al.*, 2023; Abed, 2023).

The oral rehabilitation undergoing radiation therapy requires careful planning, considering the frequent loss of attachment (Irie *et al.*, 2018). Among the rehabilitation options for managing tooth loss during radiotherapy, the placement of dental implants in conjunction with fixed or removable prostheses stands out as an excellent alternative. Implant-supported restorations have the potential to restore masticatory function, improve patients' self-esteem and ability to speak, and significantly enhance quality of life and personal satisfaction. (Pitorro *et al.*, 2022). Although implant placement in irradiated patients is no longer contraindicated (Shokouhi & Cerajewska, 2021), criterious planning is crucial, particularly considering the radiation doses received (Li *et al.*, 2021; Lee *et al.*, 2022).

After tooth extractions, the reduction in the horizontal of the alveolar ridge dimension can compromise the success of implant therapy, especially in regions with insufficient alveolar bone volume (Pan *et al.*, 2019). To tackle this issue, various surgical techniques and biomaterials have been developed to preserve or regenerate tissue, creating a favorable environment for the placement of adequately sized implants in optimal positions (Kollati *et al.*, 2019). Recognition of the significant changes in the alveolar ridge post-extraction has spurred the development of techniques and materials aimed at promoting bone regeneration and preventing bone resorption (Yewale *et al.*, 2021). Consequently, a range of well-established bone substitutes are now available (Zhao *et al.*, 2021). Additionally, blood concentrates, such as platelet-rich fibrin (PRF), are utilized either alone (Pan *et al.*, 2019) or in combination with other biomaterials for bone repair (Clark *et al.*, 2018; Amaral *et al.*, 2020).

A combination of deproteinized bovine bone and Platelet-rich fibrin (Sticky Bone), has been recognized for its efficacy to preserve the surgical socket (Rupawala *et al.*, 2020). This biomaterial is utilized in bone reconstructions due to its osteoconductive properties, which promote bone formation by stimulating cells and blood vessels

(Hallman *et al.*, 2001). Variations in centrifugation protocols can yield different types of PRF concentrates, affecting their cellular content, growth factors, and physical characteristics (Miron & Choukroun, 2018). Among the PRF protocols introduced by Joseph Choukroun in 2001, S-PRF stands out, known for its capacity to retain leukocytes, platelets, and growth factors, and its effectiveness in bone regeneration (Kobayashi *et al.*, 2016; Liu *et al.*, 2023). This PRF is also notable for the stability in bone defects and prevention capacity of graft loss, demonstrating promising outcomes in gingival healing and ossification of alveolar defects, leveraging its robust fibrin integration that secures it within the alveolus (Thanasrisuebwong *et al.*, 2019; Rupawala *et al.*, 2020).

Despite the promising evidence regarding the potential of PRF and bone substitutes for maintaining alveolus after extraction, on the best of the author's knowledge there is a gap in the literature regarding their applicability in the alveolus of patients with head and neck cancer undergoing radiotherapy treatment. These highlights and stimulates the need to design specific protocols for preserving irradiated bone tissue after extraction. Involving protocols that not only aim to treat the cancer patients but also that recognize the importance of comprehensive care for the stomatognathic system, including bone maintenance, to enable future rehabilitation and improve their long-term quality of life.

Therefore, this study aimed to evaluate the efficacy of S-PRF with bovine bone substitute in stimulating bone repair after tooth extraction in patients undergoing head and neck radiotherapy. The null hypothesis was that the use of S-PRF has no benefit on the clinical and radiographic parameters compared to the use of blood clot for patients ongoing radiotherapy of head and neck cancer treatment.

Material and Methods Ethical Considerations

This study was a randomized double blinded controlled clinical trial that included patients diagnosed with head and neck cancer who required radiotherapy treatment and extraction prior to oncological treatment, from May to December 2023. The study was approved by the Research Ethics Committee of the Federal University of Uberlândia under protocol (# 64499722.8.0000.5152). Registered in the Brazilian Registry of Clinical Trials (REBEC # U1111-1288-2914). All individuals who participated in this study signed an informed consent form and the research followed the ethical precepts determined by the Declaration of Helsinki.

Inclusion and Exclusion Criteria

This study included adult patients over 18 years old of both sexes, with indications for extractions prior to radiotherapy treatment for a variety of reasons, such as adaptation of the oral environment, unfeasible teeth for rehabilitation, severe periodontal disease and other dental emergencies. Only individuals who authorized the proposed treatment and provided informed consent to participate in the research project were included. Patients that did not agree or did not sign the Informed Consent Form, patients with advanced tumors that started the urgency radiotherapy, did not have time to perform the extractions and those who were severely debilitated due to health issues were excluded of the study. The pre- and post-radiotherapy dental treatment was conducted at the Dental Hospital of the Federal University of Uberlândia, Brazil. This institution, part of the public health system, provides free comprehensive care to patients diagnosed with head and neck cancer, both from the city and other regions.

Surgical Procedure

Initially, a detailed analysis of the patients' clinical and radiographic condition was carried out to determine the need of the procedures. When indicated, laboratory tests were ordered to assess the patients' systemic condition and, or medical advice was obtained to ensure the safety of the procedure.

After patient selection and dental extractions, each alveolus was randomized using random.org online platform. The patients were allocated in two groups: (a) experimental group, alveoli were filled with a combination of PRF (Platelet Rich Fibrin) and exogenous graft (Cerabone®, Straumann®, 0.5-1.0 mm, 1 × 0.5 cc), along with the application of autologous PRF membrane (Figure 1); and (b) control group, alveoli were maintained exclusively with blood clot. All procedures were conducted in a minimally traumatic manner, with delicate sutures to ensure absence of tissue tension in the area and minimize tissue manipulation. The suture was removed after 14 days. All surgeries were performed by an experienced professional trained in the clinical management to this dental service.

The post-operative medication protocol for all patients was as follows: systemic antibiotic therapy for 7 days after surgery, using amoxicillin 500 mg or clindamycin 300 mg every 8 hours. For pain control, analgesics were indicated, such as dipyrone sodium

500 mg or paracetamol 500 mg, for 3 days every 6 hours, all for oral consumption. An antiseptic mouthwash based on 0.12% chlorhexidine digluconate was prescribed to rinse the mouth for 7 days to minimize possible infections and help with hygiene during the post-operative period. All the post-surgical guidelines and care were given to the patients in detail, with the aim of ensuring an adequate and complication-free recovery

PRF Protocol

To obtain PRF, venous blood was collected from the patient in two 10 ml tubes (A-PRF and S-PRF | Process for PRF® by Choukroun, Nice, France) (Figure 2A). The distinction between the tubes lies in the type of coating: one tube, identified by a green cap, is intended for S-PRF (used in Sticky Bone guided bone regeneration), while the other, identified by a red cap, is for A-PRF (used to produce a membrane) (Figure 2B). The tubes were carefully placed in the centrifuge to maintain balance in terms of time and speed. They were then subjected to a uniform centrifugation process for 14 minutes at 1300 rpm, using Duo Quattro equipment (by Choukroun). This procedure resulted in two different materials: S-PRF and A-PRF (Figure 2C).

At the end of the centrifugation process, was obtained a tube containing S-PRF, fluid blood concentrate rich in cells and growth factors. This S-PRF was divided into a lower red cell fraction and an upper phase. The upper phase was aspirated with a 10 ml syringe (Injex®, Brazil) and an 18G x 1/2 hypodermic needle (Injex®, Brazil) (Figure 2D) and then incorporated into Cerabone® (Straumann®, 0.5-1.0 mm, 1 × 0.5 cc) (Figure 2E). This combination, forming Sticky Bone, was carefully inserted into the socket after extraction to promote bone regeneration (Figure 2F).

In contrast, A-PRF consists of a membrane (Figure 2G) obtained from the second tube, which underwent the same centrifugation process. This membrane was inserted under the surgical bed immediately after extraction to accommodate the biomaterial and protect the surgical area during the healing process. Both products, S-PRF and A-PRF, represent distinct but complementary approaches to promoting tissue and bone regeneration after tooth extraction.

Clinical Analysis

After extractions, patients were clinically evaluated on days 7 and 14 to assess edema,

pain, bleeding, suppuration, bone exposure, and soft tissue healing using scoring systems. Additionally, a VAS scale was used to assess pain, ranging from 0 to 10, where 0 represents no pain and 10 represents the worst possible pain.

Once normal postoperative conditions were confirmed, patients were allowed to initiate the radiotherapy treatment 14 days after the tooth extraction. Patients were regularly monitored, including clinical evaluations and complementary imaging exams, performed immediately after the completion of oncological treatment and again 60 days after radiotherapy. These evaluations were conducted by a trained and blinded examiner, qualified in the clinical management of cancer patients.

Radiographic Analysis

The panoramic radiographs used in the study were captured using the OP200 D equipment (Orthopantomograph®, Instrumentarium Dental®). The sockets included in the study were qualitatively assessed by three blinded examiners, who conducted comparative analyses of bone repair 60 days after radiotherapy, using reference radiographs taken immediately after tooth extraction (Figure 3). Each socket was graded on a 4-point scale with regard to the stage of healing and alveolar repair, as follows: 0 - clear alveolar boundaries, delineated by a continuous radiopaque contour of the lamina dura; 1 - bone neoformation with radiopaque areas close to the lamina dura, extending towards the central area of the alveolus; 2 - bone neoformation with radiopaque areas in the central region of the alveolus; 3 - post-extraction alveoli completely filled with neoformed bone tissue and remodeled alveolar ridge crest.

Statistical Analysis

The potential relationship between interventions and outcomes was investigated through binary multilevel regression analysis (generalized mixed models), with adjustments made for the covariate 'tooth' and the clustering effect of 'patient'. For outcomes assessed using scores, data were analyzed using mixed-effects regression analysis, with p-values adjusted for the covariate 'tooth' and the clustering effect of 'patient'.

Radiographic analyses were carried out by three examiners, who qualitatively assessed the areas of interest. The statistical analysis compared two groups: an experimental group, where PRF was used, and a control group, where the clot was kept

in the socket without the use of PRF. Descriptive statistics and the Mann-Whitney test were used. Jamovi (Version 2.3) and R Core Team (Version 4.1) were used for the statistical analysis. The all statistical tests were applied at a significant level of $\alpha = 0.05$.

Results

A total of 37 patients were referred to the dental care clinic for cancer patients, with an indication for extractions before radiotherapy treatment. Subsequently, 22 patients were excluded from the study: 4 refused to take part in the study; 7 were extremely weak and/or had complications during dental treatment; 7 needed urgent radiotherapy treatment, with no time to complete the dental plan; 2 had teeth in the tumor area and 2 did not have enough blood samples for PRF processing. In total, 15 participants were included in the study, of whom at least completed the pre-radiotherapy clinical assessments. However, only 6 patients completed all the clinical assessments and underwent the radiographic examinations along all periods. (Figure 4).

The sociodemographic data of all the randomized patients are shown in Table I. The majority of participants were male (73.3%), with predominantly brown(40%) or white (33.3%) skin color. Regarding marital status, 40% were married, while 33.3% were single. In terms of education, 60% had incomplete primary education, and the majority (80%) reported a monthly family income of less than two minimum wages. A significant proportion were current smokers (40%) or ex-smokers (53.3%), and likewise, the majority reported being ex-drinkers (53.3%). Common health problems included hypertension (33.3%) and hypothyroidism (20%). Among the reported medications, painkillers and antihypertensives were the most prevalent (26.7% for both). On average, the participants were 62.3 (± 9.7) years old. The details of the dental treatment of the head and neck cancer patients who completed all the follow-ups are shown in Table II, while the specifics of the oncological treatment are described in Table III.

Only data from participants who underwent a wound closure follow-up analysis lasting a minimum of 7 days were considered. In an intention-to-treat approach, missing data for subsequent follow-up appointments were imputed from previous assessments. It was observed that the use of PRF did not improved the wound closure after tooth extraction, regardless of the assessment time (Table IV). Furthermore, there was no effect of PRF on the risk of postoperative pain in assessments conducted 7 or 14 days after tooth

extractions (Table V), and no cases of pain were reported in assessments following radiotherapy. Edema, bone exposure, and osteoradionecrosis were not observed in the study.

Regardless of the assessment time, the use of PRF did not influence the outcomes. However, a notable improvement in scores was observed from the evaluation conducted 7 days after the surgery to those carried out subsequently. The results of bleeding evaluations (Figure 5A), reports few cases, except at 7 days postoperatively, where PRF did not affect the assigned score. Some sockets exhibited erythema and gingival mobility, both in the PRF and control groups (Figure 5B). The distribution of suppuration scores (Figure 5C) revealed no significant differences between groups, but a notable reduction was observed after 7 days post-surgery. Scores for tissue color and consistency (Figure 5D) had no significant difference for PRF use, suggesting a stronger association with postoperative hygiene care. Data on bone exposure, edema, and osteoradionecrosis were not analyzed due to the lack of observed events in the study. Radiographic evaluation showed no significant differences in bone repair measures between the groups (Table VI).

Discussion

The null hypothesis of this study was accepted, the use of Sticky Bone had no benefit on clinical and radiographic parameter compared to the blood clot in patients with head and neck cancer after 60-day period post-radiotherapy. This study stands out for its applicability and methodology in interventions for cancer patients, being a pioneer in evaluating the effectiveness of this material after radiotherapy.

After tooth extraction, significant changes occur in the alveolar crest, with bone remodeling taking place three to six months' post-surgery (Kollati *et al.*, 2019). Maintaining the alveoli after extraction is crucial, as the alveolar bone, primarily composed of bone bundles, undergoes resorption once it loses its function following tooth removal. Reductions in alveolar bone volume can occur for up to twelve months post-extraction, with two-thirds of this loss happening within the initial three months of healing. Recent studies on grafting in extraction sites indicate less dimensional loss of the alveolar ridge compared to non-grafted sites, underscoring the efficacy of these procedures in bone preservation (Pohl *et al.*, 2020).

Despite the evidence on the benefits of alternative treatments for bone

maintenance after tooth extraction, this study found that the application of Sticky Bone in the alveolus before radiotherapy had no significant influence tissue healing after short post-radiotherapy time. The absence of osteoradionecrosis raises questions about the possibility of its prevention being due to the use of Sticky Bone, further emphasizing the need for prolonged follow-up to obtain conclusive results. This study reveals a significant gap in the literature regarding its application in patients with head and neck cancer, especially after oncological treatment. These raises questions about the influence of the conditions on tissue repair, as well as the possibility of masking the reparative potential of Sticky Bone, suggesting that its effectiveness may also be dependent on radiation dose, similarly like bone tissue (Li *et al.*, 2021; Lee *et al.*, 2022). Most studies have been carried out on healthy patients, which makes it challenging to make such comparisons, especially given the scarcity of evidence regarding the use of methods that seek to enable the maintenance of bone tissue for future rehabilitation. (Pohl *et al.*, 2020; Ustaoglu *et al.*, 2020; Yewale *et al.*, 2020; Ponte *et al.*, 2021).

In addition, data on the characteristics of patients with head and neck cancer reflect the complexity inherent in conducting clinical studies involving oncologic patients. Factors such as the duration of radiotherapy treatment, the doses of administered, the specifics of the cancer type, and the individual physiological considerations of each patient influence the tissue repair process (Chan *et al.*, 2016; Munhoz *et al.*, 2021). Despite efforts to standardize the methodology, it is speculated that these aspects may affect the final result.

One bias to consider in this study was the potential compromise of radiographic images and their influence on the results, posing a limitation in comparisons between groups due to a reduction in intraosseous vascularization caused by exposure to ionizing radiation. This phenomenon results in changes in the number of bone cells, progressive fibrosis, and local necrosis, which are radiologically reflected in low bone mineral density, trabecular fractures, and loss and destruction of cortical structures (Palma *et al.*, 2020). Analysis of panoramic images of patients with head and neck cancer also revealed a decrease in the average pixel intensity and fractal dimension values of the mandibular bone as side effects of ionizing irradiation (Oliveira *et al.*, 2021).

In a study similar to Oliveira's (2021), which focused on assessing bone repair in irradiated patients through analysis of radiographic images, no statistically significant

discrepancies were identified in bone formation 60 days after tooth extraction. However, a statistically significant difference was observed between the initial radiographs and those taken one year post-tooth extraction, emphasizing once again the importance of prolonged clinical and radiographic follow-up. This approach appears to be a valuable alternative for this study.

However, this study presents promising and viable possibilities. Despite its limitations, the proposed clinical methodology was successfully implemented, effectively answering the question: “Can this study be carried out?”. Although the sample size was smaller than expected, there is potential for success in the suggested protocol for the use of Sticky Bone in pre-radiotherapy alveoli, indicating possible efficacy in preventing osteoradionecrosis and suggesting personalized adaptations based on individual clinical findings, considering the benefits of PRF combined with other adjuvant therapies in the treatment of osteoradionecrosis (Chen *et al.*, 2019; Vorakulpipat *et al.*, 2023). There is a shortage of available studies on the specific use of PRF as an adjuvant in treating such lesions, underscoring the need to establish a gold standard for the treatment of these conditions (Harris *et al.*, 2022).

The aim of this study goes beyond the simple generalization of results, emphasizing the importance of a thorough description of the methodology to allow for applicability and replicability in subsequent studies. This need is particularly evident given the gap in the literature regarding interventions in cancer patients pre-radiotherapy, focusing on preventing long-term bone damage and reducing the risk of osteoradionecrosis.

Conclusion

Sticky Bone did not show reparative potential within 60 days post-radiotherapy. These findings provide a solid foundation for future, more comprehensive studies that incorporate longer follow-up periods.

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Conflict of Interest

The authors declare to have no conflict of interest.

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Table I. Characteristics of participants enrolled in the study.

Variable	Levels	n (%)
Gender	Male	11 (73.3)
	Female	4 (26.7)
Skin color	White	5 (33.3)
	Brown	6 (40.0)
	Black	2 (13.3)
	Yellow	2 (13.3)
Marital status	Single	5 (33.3)
	Married	6 (40.0)
	Separated	1 (6.7)
	Widowed	2 (13.3)
	Non-informed	1 (6.7)
Education	Illiterate	1 (6.7)
	Incomplete Elementary	9 (60.0)
	Incomplete High School	1 (6.7)
	Complete High School	3 (20.0)
	Complete Higher Education	1 (6.7)
Monthly Family Income	Up to two minimum wages	12 (80.0)
	From two to four minimum wages	2 (13.3)
	From four to ten minimum wages	1 (6.7)
Smoker	Yes	6 (40.0)
	No	1 (6.7)
	Ex-smoker	8 (53.3)
Alcohol consumption	Chronic yes	2 (13.3)
	Yes, socially	1 (6.7)
	No	4 (26.7)
	Ex-drinker	8 ((53.3)
Systemic Health Issues*	No reported health issue	7 (46.7)
	Hypertension	5 (33.3)
	Hypothyroidism	3 (20.0)
	Diabetes	2 (13.3)
	Hepatic disorder	2 (13.3)
	Respiratory disorder	2 (13.3)
	Gastrointestinal disorder	1 (6.7)
Medications in use*	Does not report use	5 (33.3)
	Analgesics	4 (26.7)
	Antihypertensive	4 (26.7)
	Antihypertensive	2 (13.3)
	Hypercholesterolemia, anticoagulant, anxiolytic, antidepressant, or	1 (6.7)
	hypoglycemic	

* The total can exceed 100% as a single patient may have multiple systemic health issues or betaking more than one medication.

Table II. Specifications of the dental treatment prior to radiotherapy for patients included in the study who completed all follow-up (n=6)

Patient	Extracted Teeth	Release for Radiotherapy
1	41, 31, 32, 33, 35, 42, 43, 44	28/06/ 23
2	47, 38, 48	09/08/23
3	11, 12, 13, 14, 15, 16, 18, 24	09/08/23
4	31, 32, 33, 37, 41, 42, 43, 44, 45	25/08/23
5	31, 32, 33, 34, 41, 42, 43	11/10/23
6	48, 44, 45, 35	07/12/23

* Patients were cleared to begin radiotherapy 14 days after the reported date of release.

Table III. Characteristics of patients with head and neck cancer included in the study who completed all the follow-up (n=6)

Patient	Gender	Age (Yars)	Type of Cancer	Tumor Location	Stagin	Total Radiation	Treatment	Start of Radiotherapy	Completion of Radiotherapy
1	M	58	SCC	Larynx	T3N1	7000cGy	RT+CT+SUR	02/08/23	25/09/23
2	M	32	CBC	Skin with invasion parotid	T4N1Mx	7572cGy	RT+SUR	05/10/23	05/12/23
3	M	68	SCC	Skin	T4N0M1	7000cGy	RT+SUR	24/09/23	06/12/23
4	M	74	SCC	Floor of mouth	T2N0Nx	6600cGy	RT+SUR	06/12/23	25/01/24
5	F	63	SCC	Larynx	T3PN1	6000cGy	RT+SUR	21/09/23	21/12/23
6	M	68	SCC	Floor of Mouth	T2N1M0	6000cGy	RT+SUR	10/01/24	23/02/24

M: Male; F: Female; CCB: Basal cell carcinoma; SCC: Squamous cell carcinoma; SUR: Surgery; CT: Chemotherapy; RT: Radiotherapy

Table IV: Results for association between using PRF and the occurrence of wound closure after tooth extraction according to the assessment time.

Assessment time	Absolute risk Yes/ No (%)		Relative risk (95% CI)	p-value*
	Experimental	Control		
7 days	14/20 (41.2)	20/30 (40.0)	1.03 (0.61 – 1.74)	0.402
14 days	28/6 (82.4)	37/13 (74.0)	1.11 (0.89 – 1.40)	0.148
After RT	29/5 (85.3)	39/11 (78.0)	1.09 (0.89 – 1.34)	0.061
60 days	29/5 (85.3)	39/11 (78.0)	1.09 (0.89 – 1.34)	0.061

* Logistic multilevel regression analysis adjusted for the covariable “tooth” and cluster variable “patient”. CI: confidence interval; RT: radiotherapy.

Table V. Results for association between using PRF and the occurrence of pain after tooth extraction according to the assessment time.

Assessment time	Absolute risk Yes/ No (%)		Relative risk (95% CI)	p-value*
	Experimental	Control		
7 days	15/19 (44.1)	24/26 (48.0)	0.92 (0.57 – 1.48)	0.969
14 days	4/30 (11.8)	1/49 (2.0)	5.88 (0.69 – 50.38)	0.060

* Logistic multilevel regression analysis adjusted for the covariable “tooth” and cluster variable “patient”. CI: confidence interval; RT: radiotherapy.

Table VI: Descriptive statistics between the PRF group and the control group in radiographic analyses

	Group	Repair
N	Experimental	51
	Control	66
Median	Experimental	2
	Control	3.00
Standard Deviation	Experimental	0.89
	Control	0.70
Minimum	Experimental	0
	Control	1
Maximum	Experimental	3
	Control	3
25th percentile	Experimental	2.00
	Control	2.00
50th percentile	Experimental	2.00
	Control	3.00
75th percentile	Experimental	3.00
	Control	3.00

* Radiographic assessment of repair - t-test for independent samples - $p > 0.05$
Experimental = PRF; Control = Clot

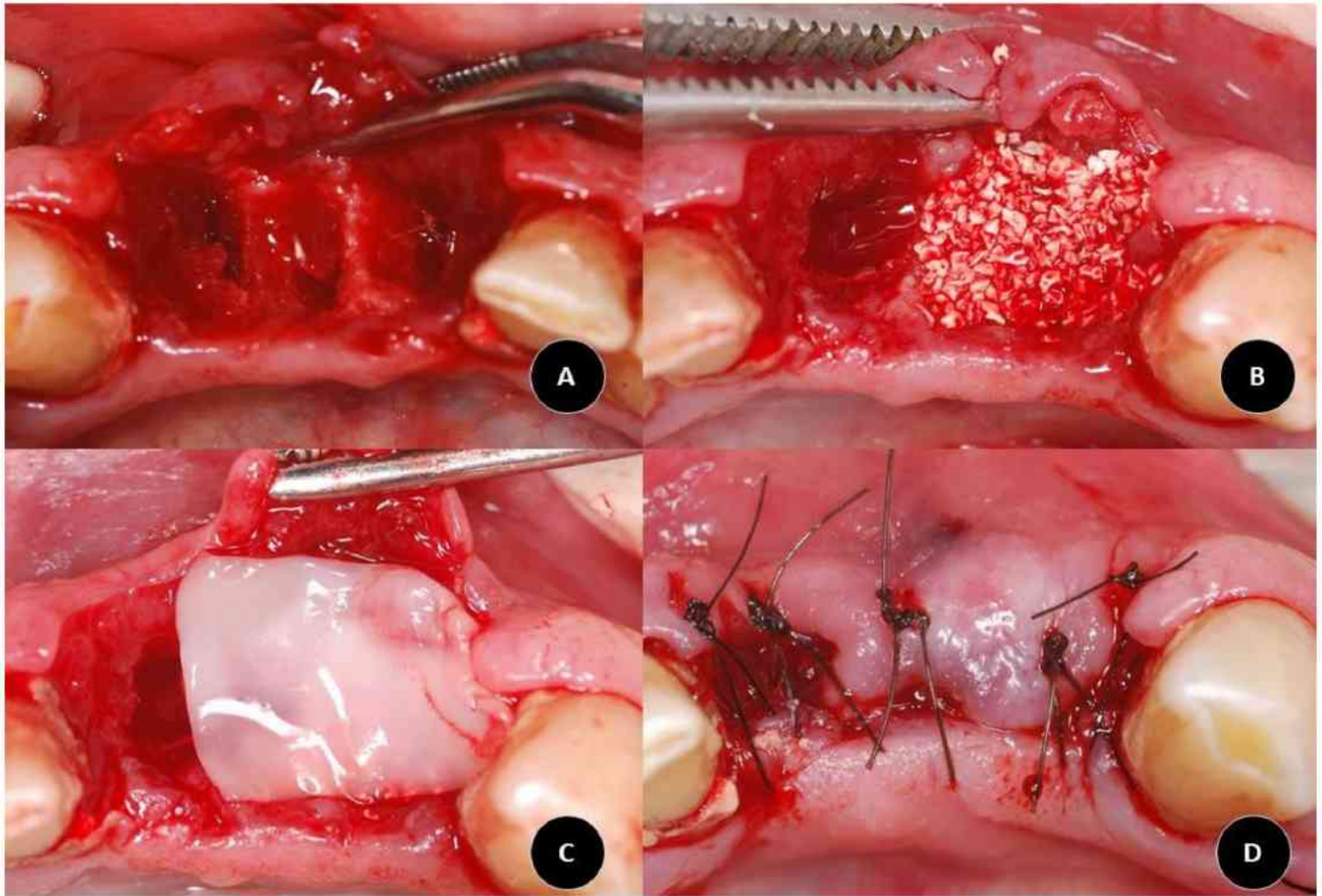


Figure 1: Surgical procedure. **A.** Alveolus after exodontia; **B.** Inclusion of Sticky Bone in the alveolus; **C.** Insertion of A-PRF membrane; **D.** Final appearance after suturing.

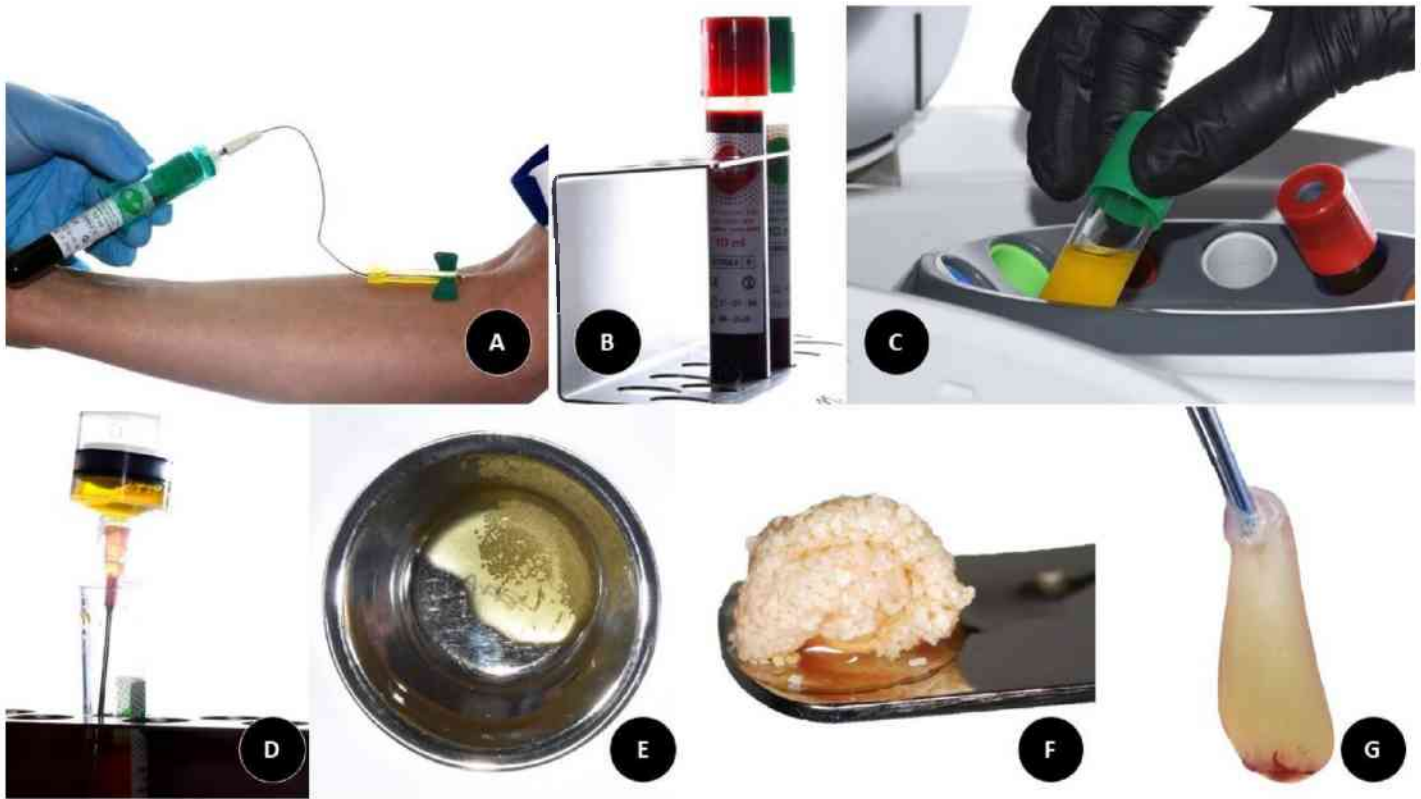


Figure 2: PRF protocol. **A.** Collection of venous blood from the patient; **B.** Obtained material: 2 tubes of 13 ml blood; **C.** Centrifuge (Duo Quattro (by Choukroun) | PRF Process®, Nice, France); **D.** S-PRF aspiration; **E.** PRF agglutination with Cerabone®; **F.** Sticky Bone after setting; **G.** PRF membrane obtained at the end of the centrifugation process.



Figure 3: Radiographic examinations. **A.** Immediate post-extraction radiograph(baseline); **b.** Radiograph 60 days post-radiotherapy.

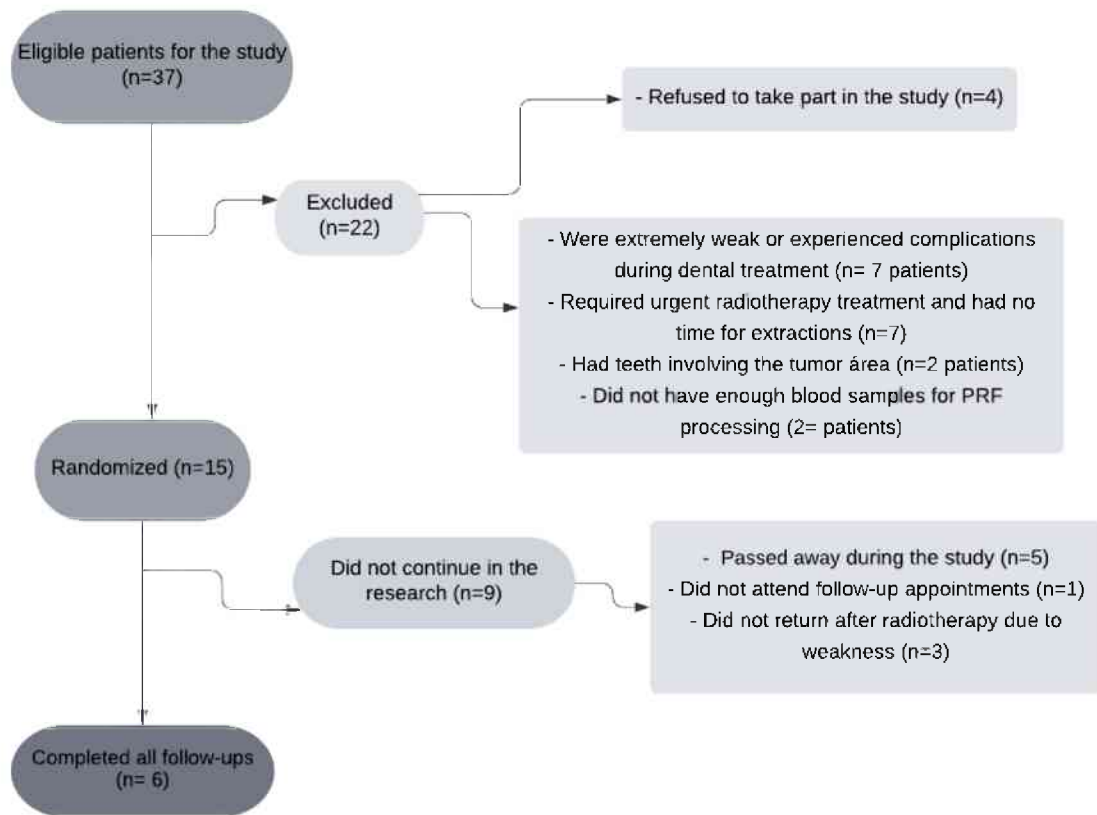


Figure 4. Flowchart diagram illustrating the procedures and the exclusions observed in this study.



* Distribution of scores by intervention and assessment times

Figure 5: Clinical tissue analysis measurements. **A.** The results of bleeding evaluations; **B.** The distribution of scores related to tissue color; **C.** The distribution of scores attributed to suppuration; **D.** The scores assigned to tissue color and consistency.

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