European Review for Medical and Pharmacological Sciences 2023; 27: 11817-11831

Efficacy of guided autofluorescence laser therapy in MRONJ: a systematic review

G. DIPALMA[1], A.D. INCHINGOLO[1], F. PIRAS[1], G. PALMIERI[1], C.D. PEDE[1], A.M. CIOCIA[1], R.A. SICILIANI[1], F.D. OLIO[1], A.M. INCHINGOLO[1], A. PALERMO[2], F. INCHINGOLO[1], G. FAVIA[1], L. LIMONGELLI[1]

[1]Department of Interdisciplinary Medicine, School of Medicine, University of Bari "Aldo Moro", Bari, Italy
[2]College of Medicine and Dentistry, Birmingham B4 6BN, UK

G. Dipalma, and A.D. Inchingolo contributed equally to this work as first authors

Abstract. – OBJECTIVE: This review aims to explore the efficacy of fluorescence-guided excision in the treatment of necrotic bone and highlights the importance of fluorescence in distinguishing viable margins from necrotic ones for a more targeted and predictable management of MRONJ.

MATERIALS AND METHODS: The review was conducted according to PRISMA guidelines using PubMed, Scopus, and Web of Science databases from January 1, 2008, to May 17, 2023. The Boolean search strategy with the following keywords "osteonecrosis" AND "fluorescence" was performed. Then, the articles were subjected to screening and eligibility phases. The papers about the use of autofluorescence-guided laser therapy in patients with jaw osteonecrosis were included.

RESULTS: A total of 320 articles were initially identified through an electronic search, and ultimately, 17 papers were included in the qualitative analysis.

CONCLUSIONS: In conclusion, our findings demonstrate that the VELscope system allows for clear visualization of the bone, making guided autofluorescence a precise, safe, and reliable technique.

Key Words:
Dentistry, Laser, Low-level laser therapy, Oral surgery, MRONJ, BRONJ, ORNJ, Guided autofluorescence laser therapy.

Abbreviations

AAOMS: American Association of Oral and Maxillofacial Surgeons; AF: autofluorescence; BP: bisphos-phonates; BRONJ: Bisphosphonate Related Osteonecrosis of the Jaw; Er: YAG Erbium-doped yttrium alu-minum garnet laser; LLLT: low-level laser therapy; MRONJ: Medication-related osteonecrosis of the jaws; Nd: YAG Neodymium yttrium aluminum garnet; ORN: osteoradionecrosis; ORNJ: Osteoradionecrosis of the jaw; PICOS: population, intervention, comparison, outcome, study design; PROSPERO: International Prospective Register of Systematic Reviews; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; TKIs: Tyrosine kinase inhibitors; VEL: visually enhanced lesion scope; WHO: World Health Organization.

Introduction

The World Health Organization defines MRONJ (Medication-related osteonecrosis of the jaws) as the necrotic bone of the mandible or maxilla caused by certain drugs. The American Association of Oral and Maxillofacial Surgeons (AAOMS) in its 2022 Positional Paper defines Medication-related osteonecrosis as the "adverse drug-related reaction characterized by progressive destruction and necrosis of the mandibular and/or maxillary bone of individuals exposed to treatment with drugs for which an increased risk of disease has been established, in the absence of prior radiation treatment"[1,2]. MRONJ is localized mainly at the level of the jaws due to particular characteristics such as: more rapid bone turnover compared to the long bones; a terminal vascularization; a mucoperiosteal lining overlying the bone tissue easily subject to trauma and infection; the presence of microflora/biofilm in the oral cavity and the presence of the periodontal ligament which, in case of dental-periodontal injury, leads to the exposure of the underlying bone tissue[3-5].

Lasers have a wide application in medicine and especially in dentistry, showing numerous uses, especially in conservative dentistry, oral surgery, and in the treatment of TMDs[6-12].

The drugs most implicated in MRONJ by 97% are bisphosphonates and in particular zolendronate, alendronate and monoclonal antibodies such as Denosumab[5]. Other drugs that can give rise to osteonecrosis of the jaws but in a smaller percentage are tyrosine kinase inhibitors (TKIs), additional

Corresponding Author: Francesco Inchingolo, MD; e-mail: francesco.inchingolo@uniba.it

monoclonal antibodies, angiogenesis inhibitors, fusion proteins such as aflibercept; mTOR inhibitors such as everolimus, radiophar-maceuticals, estrogen inhibitors such as raloxifene, immunomodulators (methotrexate and corticosteroids)[12,13].

There is still no gold standard for the treatment and management of MRONJ. Saving as much bone as possible is essential to avoid a possible bone fracture, but at the same time it is important to completely remove the necrotic bone to avoid the risk of recurrence[14,15].

Many surgeons use supportive radiographic examinations, while others use bone bleeding as an index of viable bone. These methods, however, lack sensitivity and specificity. Some recent studies[16,17] have been carried out in the literature precisely to try to outline an easy and safe guide for the treatment of MRONJ. Recently, particular emphasis has been placed on fluorescence – a simple, safe and reproducible technique using the VELscope (visually enhanced lesion scope) and a fluorescent lamp (LED Dental, White Rock, BC, Canada)[18,19]. Maxillary bones show autofluorescence (AF) from collagen type 1 fibers and osteocytes. Necrotic bone, on the other hand, loses AF, probably due to changes in the calcified extracellular osteoid matrix or necrotic cells, but we have no scientific evidence of this yet. In any case, necrotic bone will appear darker than vital bone as can be seen in Figure 1[20,21]. The VELscope facilitates the recognition of vital bone. An example of machinery suitable for these functions is depicted in the Figure 2.

It excites specific collagen amino acids through light emission, which are made evident through the use of the fluorescence lamp[22-26]. Other researchers have proposed the use of tetracycline-induced fluorescence to differentiate necrotic bone from vital bone. Tetracycline, being related to calcium, is incorporated in the re-modeling areas of vital bone but not in necrotic bone. This can be viewed with light between 390 and 430 nm[26-28]. Ristow and Pautke[29] recently demonstrated that even without tetracycline marking, viable bone can be identified by AF. These natural fluorochromes are excited and show AF, highlighting vital bone[30-32]. This objective and easy-to-replicate surgical approach could be used to make standard a treatment of MRONJ that previously relied on a subjective approach of the surgeon, improving the treatment[25,33,34].

Laser technology has found diverse applications in various industries and the medical sector. Khorasani et al[35] for instance, in the field of additive manufacturing, explore the impact of absorption ratio on melt pool characteristics in the laser-based production of IN718 alloys[35]. Additionally, Gaur et al[36] investigated the influence of annealing on the physical and mechanical properties of Ti6Al4V orthopedic implants fabricated using laser-based additive manufacturing techniques. These studies exemplify the utilization of laser technology in diverse applications and highlight its potential for advancing various fields[35-40].

However, there is uncertainty regarding how to manage MRONJ. MRONJ treatment is difficult, and an effective and appropriate therapy that significantly improves the outcomes is yet to be discovered. The aim of our review is to highlight the usefulness of fluorescence in highlighting viable margins from necrotic ones for a more predictable and specific treatment of MRONJ, while also evaluating the results obtained from fluorescence-guided resection of necrotic bone.

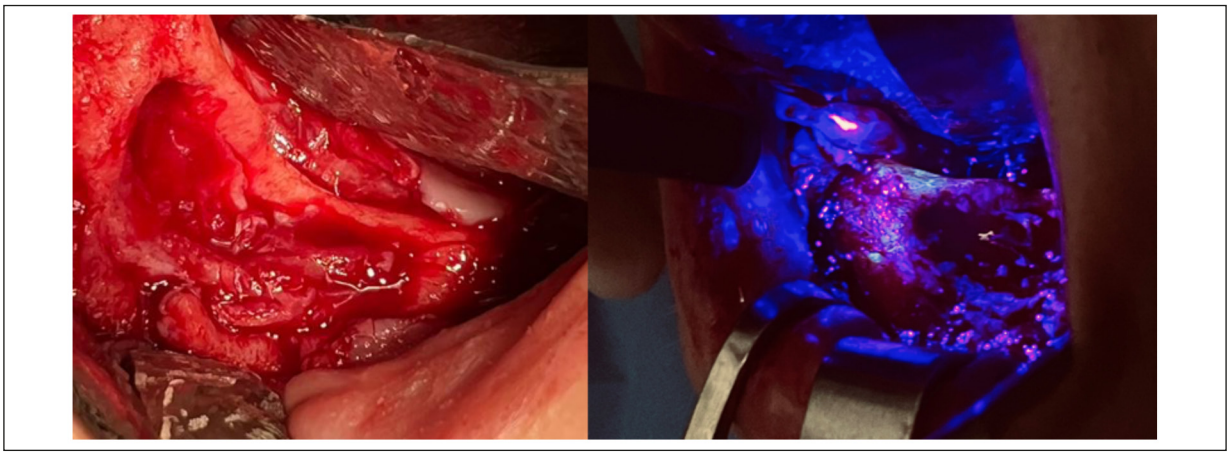

Figure 1. Bone after open flap: autofluorescence underling limits between necrotic and vital bone.

Figure 2. Lasotronix photodynamic laser used in Bari Polyclinic dental clinic for interventions during MRONJ surgeries.

Materials and Methods

Protocol and Registration

When performing this review, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and CASP (Critical Appraisal Checklist) procedures were used. This study was submitted to PROSPERO (International Prospective Register of Systematic Reviews) with the provisional number 481005.

Search Processing

We searched PubMed, Scopus, and Web of Science for English-language publications that matched our topic from 1 January 2008 to 17 May 2023. In the search technique, the Boolean keywords "osteonecrosis" AND "fluorescence" were used. These words were chosen because they best defined our investigation's purpose, which was to learn more about auto-fluorescence-guided laser in patients with jaw osteonecrosis. The search indications are shown in Table I below.

Eligibility Criteria and Study Selection

We chose studies that looked at the effects of surgical techniques, including an auto-fluorescence-guided laser. The selection method was divided into two stages: (1) title and abstract

Table I. Database search indicators.

Article screening Strategy
Database: Scopus, Web of Science and Pubmed Keywords: A "osteonecrosis"; B "fluorescence" Boolean variable: "AND" Timespan: 2008-2023 Language: English

evaluation and (2) full-text examination. Any article that met the following criteria was considered: (a) human intervention studies (clinical trials); (b) humans with osteonecrosis; (c) studies assessing surgical technique including an auto-fluorescence-guided laser; (d) treatment was compared to a group without auto-fluorescence methodology; (e) English language full text; and (f) histopathological analysis of bone. Publications that did not include original data (e.g., meta-analyses, research procedures, or conference Abstracts, *in vitro* or animal studies) were excluded. The preliminary search's titles and abstracts were retrieved and assessed for relevancy. For additional evaluation, full publications from relevant research were obtained. Two separate reviewers (F.P. and F.I.) evaluated the retrieved studies for inclusion using the criteria specified above, and disagreements were addressed by consensus.

Data Processing

Author disagreements over the article selection were discussed and settled.

Data Extraction

Data on trial design and locations, population characteristics (e.g., sex, age, presence of comorbidities), type of intervention and comparison, baseline measures, and reported outcomes were collected using a standardized form. Each study was also judged on how it handled missing data and effect measures. Two reviewers (F.P. and F.I.) worked separately on extraction accuracy; divergences were resolved by consensus. Meta-analysis was not possible due to the significant diversity in the treatments and results provided; thus, studies were synthesized qualitatively.

Data Analysis

The fixed effect model was utilized for homogeneous research, whereas the random effect model was employed for heterogeneous investigations. The standardized difference of means was used to compute the effect size in all studies.

Table II. PICOS criteria.

Criteria	Application in the present study
Population	Subjects with osteonecrosis
Intervention	Surgical technique including an Auto-fluorescence guided Er:YAG laser
Comparisons	Non Auto-fluorescence group
Outcomes	Histopathological analysis
Study design	Clinical Trials

PICOS Criteria

Table I depicts the PICOS (Population, Intervention, Comparison, Outcome, Study design) criteria components, which include population, intervention, comparison, outcomes, and research design, as well as their use in this evaluation. The search indicators are listed below in Table II.

Study Evaluation

The reviewers separately assessed the article data using a customized computerized form prepared according to the following criteria: type of study, aim of study, materials and results.

Quality Assessment

The quality of the included papers was assessed by two reviewers, RF and EI, using the reputable Cochrane risk-of-bias assessment for randomized trials (RoB 2). The following six areas of possible bias are evaluated by this tool: random sequence generation, allocation concealment, participant and staff blinding, outcome assessment blinding, inadequate outcome data, and selective reporting. A third reviewer (FI) was consulted in the event of a disagreement until an agreement was reached.

Results

A total of 320 publications were discovered from the following databases: PubMed (80), Scopus (129), and Web of Science (111), yielding 171 articles after deleting duplicates (149). The analysis of the title and abstract resulted in the elimination of 147 publications. The writers were successful in retrieving the remaining 24 papers and assessing their eligibility. Seven articles were rejected because they were off topic. The examination comprises the final 17 articles for qualitative analysis (Figure 3). The characteristics of the included studies are described in Table III.

Discussion

MRONJ is a known adverse side effect associated with certain drug therapies, including bisphosphonates (BP). The most effective approach for managing MRONJ appears to be the surgical removal of necrotic bone using Er:YAG laser technology, which has shown better outcomes compared to conventional surgical methods[41,42]. However, the identification of necrotic bone

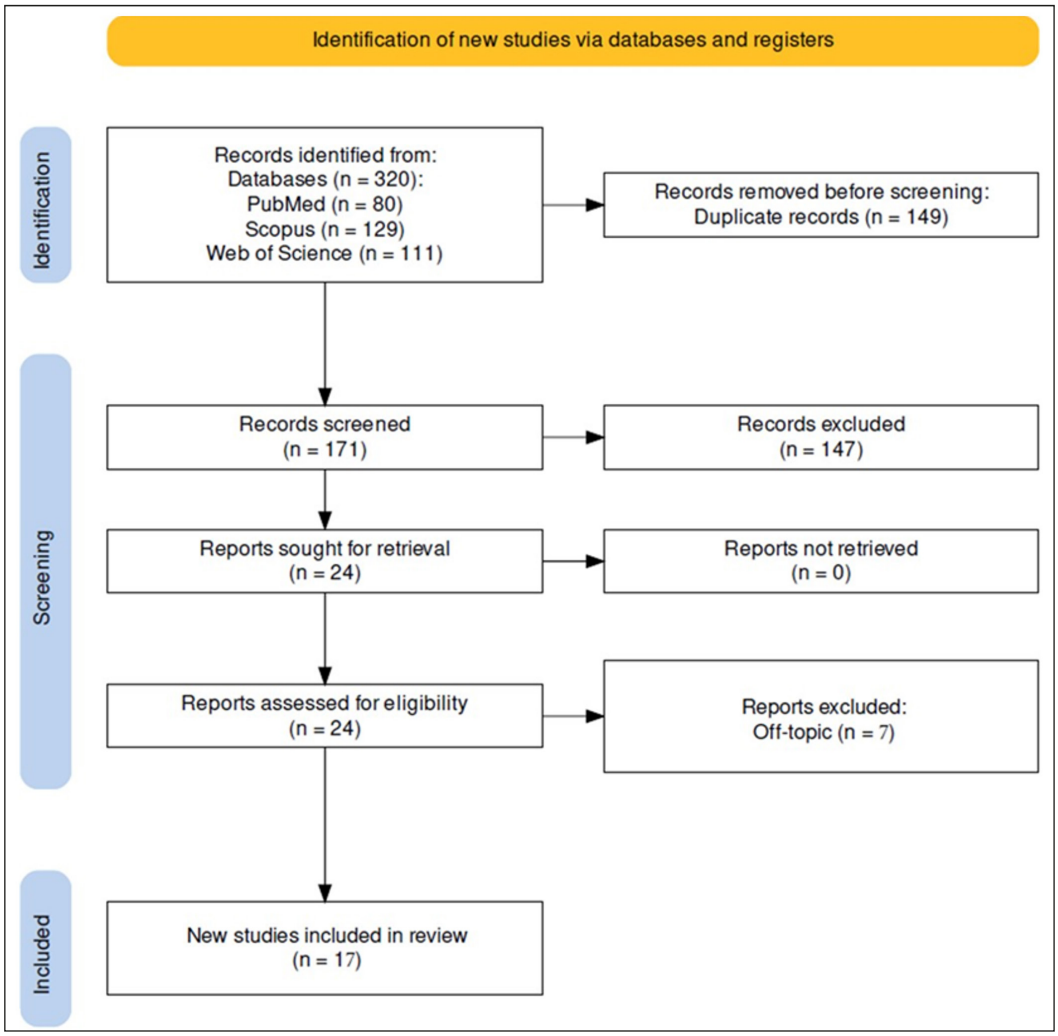

Figure 3. PRISMA flowchart diagram of the inclusion process.

edges during the excision of osteonecrosis can be challenging, as reported by AAOMS in 2007[43].

Various strategies have been proposed to address this challenge, including a groundbreaking technique called fluorescence-guided surgical method. Vescovi et al[31] introduced the use of autofluorescence (AF) of bone as a guide for visualizing necrotic bone during resection. This technique relies on the strong autofluo-rescence exhibited by viable bone, while necrotic bone appears much darker due to the loss of autofluo-rescence. The fluorescence emission is attributed to the amino acids of collagen molecules, which emit fluorescence when exposed to a fluorescence lamp[42-44]. In the same year, Giovannacci et al[24] presented a case of stage III osteonecrosis treated with a new AF-guided surgical approach using the VELscope system after bone exposure. The procedure involved Er:YAG laser osteotomy followed by Nd:YAG laser therapy (LLLT)[15,35]. The patient exhibited complete mucosal healing and remained asymptomatic after a 7-month follow-up[15].

In 2017, the same author described a case of stage II osteonecrosis where fluorescence-guided surgery was performed. The VELscope system was used to visualize necrotic bone after exposure, followed by its removal using a Lindeman bur. Er:YAG laser was then employed to vaporize the necrotic bone until strongly autofluorescent bone was detected. Post-surgery, the patient received weekly applications of LLLT (Nd:YAG)[39,45-52]. Additionally, in 2017, Giovannacci et al[53] reported on the cases of 8 patients with MRONJ treated using AF-guided surgical resection. After exposing the bone through a mucoperiosteal flap, the VELscope system was used to induce and detect bony autofluorescence.

Table III. Summary of selected articles data.

Authors	Type of the study	Aim of the study	Materials	Results
Daniel et al[67], 2021	Case report	To highlight the importance of doxycycline bone tagging in the removal of necrotic bones in MRONJ.	Cancer patient with MRONJ, age 57, treated with fluoroscopically guided bone resection	In MRONJ, doxycycline bone labeling is a useful technique for better visibility and excision of necrotic bone.
Giovannacci et al[24], 2015	Case report	To propose a new surgical technique that combines the advantages of the Er:YAG laser with the value of AF in highlighting surgical margins.	Case of osteonecrosis of the jaw stage III treated with a new surgical approach performed with AF-guided Er:YAG laser, followed by low-level laser therapy (LLLT).	By targeted ablation of non/hypofluorescent regions, this technology has enabled a highly precise and minimally invasive approach.
Giovannacci et al[53], 2017	Case report	To present a case of mandibular BRONJ successfully managed by an innovative surgical technique including an AF- guided Er:YAG laser.	Case of osteonecrosis of the jaw stage II. The FA of the mandibular bone was evaluated with the VELscope device. A Lindeman bur was used to remove necrotic bone lacking AF. Then Er:YAG vaporize the necrotic bone until strongly AF bone was identified. For three weeks after surgery, the patient underwent LLLT treatments once a week. Histopathological analysis was used to determine whether bone viability and fluorescence were correlated.	The technique presented in the study can be standardized differentially by the surgeon's experience.
Giudice et al[43], 2018	Randomised controlled trial	To define resection margins for necrotic bone, this study compared the effectiveness of the surgeon's experience with autofluorescence-guided bone surgery.	MRONJ lesions at each stage were randomly assigned: 20 lesions in the non- AF group and 19 in the AF (traditional surgery) group. Histopathological examination was performed to confirm necrosis of the bone samples taken.	Although VELscope appears to be helpful in detecting bone resection margins in patients with MRONJ, autofluorescence does not appear to be superior to typical surgical techniques in terms of mucosal healing and quality of life.
Porcaro et al[25], 2015	Case report	To provide a novel surgical technique that combines Er:YAG laser ablation guided by doxycycline fluorescence in vital bone under UV light and Nd:YAG/diode laser biostimulation.	After receiving zoledronic acid therapy, a woman had BRONJ in the left mandible. Preoperative and postoperative medications (1% chlorhexidine gel, rifamycin, and doxycycline for 10 days prior to surgery and 7 days following surgery), doxycycline fluorescence- guided Er:YAG laser ablation and Nd:YAG laser biostimulation were all given.	Following the regression of the lesion, the iefficacy of the new approach can be affirmed, which is minimally invasive and biostimulating.
Ristow et al[37], 2017	Randomised controlled trial	To compare the success rates of autofluorescence-guided bone surgery to tetracycline fluorescence-guided bone surgery in the treatment of MRONJ	The patients were thus divided into two groups: 20 (AF group) and 20 (tetracycline fluorescence group). The authors assessed mucosal integrity, presence of infection and pain in the 2 groups.	AF-guided bone surgery has success rates comparable to tetracycline fluorescence-guided bone surgery.

(Table continued)

Table III *(continued)*. Summary of selected articles data.

Authors	Type of the study	Aim of the study	Materials	Results
Giovanacci et al[55], 2019	Case series	To describe 8 patients of MRONJ treated using an AF- guided surgical resection.	After the mucoperiosteal flap exposed the bone, the VELscope system (LED Medical Diagnostics Inc, Barnaby, Canada) was utilized to induce and detect bony AF. The Lindemann drill was then used to completely resect the hypo-fluorescent bone. Then, visualization of was used to direct the laser vaporization of any remaining necrotic bone up. Finally, a histopathologic analysis was conducted.	AF guided surgical resection resulted useful in highlighting the surgical borders of necrotic bone tissue.
Ristow et al[29], 2014	Case series	To suggest the use of bone auto- fluorescence for the definition of viable and necrotic bone margins.	The VELscopesystem Vx (LED Dental, WhiteRock, British Columbia, Canada) was employed following bone exposure. All patients who received treatment had samples taken from the pale bone regions, which were histopathologically verified to be necrotic bone. Up till a brilliant fluorescence of the damaged bone was seen, the affected bone was removed.	The auto-fluorescence of bone was useful for the complete removal of the necrotic bone in BRONJ.
Pautke et al[63], 2009	Case reports	While the VELscope appears to be useful in identifying bone resection margins in MRONJ patients, autofluorescence does not shown to be superior to standard surgical procedures in terms of mucosal healing and quality of life.	2 patients affected by BRONJ, got 100 mg of doxycycline twice a day for ten days before to surgery. Bone fluorescence–guid ed resection was performed with the use of VELscope.	Doxycycline bone fluorescence enables regular and repeatable intraoperative differentiation of viable and necrotic bone. Under fluorescence guidance, the osteonecrosis (and resection) margins could be identified; however, bone hemorrhage did not correlate with bone fluorescence in either osteonecrosis entity.
Pautke et al[44], 2010	Case reports	To show the advantages of tetracycline bone fluorescence as an aid for characterizing the entities of osteonecrosis and for determining the extent of necrosis and optimizing surgical therapy.	Partial mandibulectomy was performed in two patients with extensive mandibular osteonecrosis. The limits of the resection were determined intraoperatively by bone fluorescence with VELscope system after preoperative doxycycline administration for 10 days.	
Pautke et Al[60], 2011	Prospective Pilot Study	To investigate the acceptability and repeatability of doing a fluorescence- guided bone resection on BRONJ patients.	15 patients with a history of intravenous BP therapy for metastatic bone disorders and 20 BRONJ lesions (only stages II and III). Every patient got a 10-day course of doxycycline prior to surgery. With the use of a certified fluorescent light, necrotic bone was removed using fluorescence as a guide.	At the 4-week follow-up, mucosal closure without any indication of wound healing was seen in 17 out of 20 osteonecrosis locations (85%). Three patients (15%) experienced mucosal dehiscences. Osteonecrotic bone had no or very little fluorescence intraoperatively. There was no correlation between any bone fluorescence signal and the bleeding of the bone after resection. The use of fluorescence-guided bone excision did not appreciably lengthen the duration of the procedure.

(Table continued)

Table III *(continued)*. Summary of selected articles data.

Authors	Type of the study	Aim of the study	Materials	Results
Wehrhan et al[69], 2019	Case series	To histologically examine fluorescent and non fluorescent bone areas in BRONJ patients and determine the correlation between bone vitality and fluorescence	After the mucoperiosteal flap exposed the necrotic and the VELscope system documented bone fluorescence, osteotomy was performed. Fluorescence- and non fluorescence- labeled bone areas were histologically analyzed.	Fluorescence-guided surgery is an accurate tool in intraoperatively finding and resecting the necrotic bone.
Aljohani et al[5], 2022	Retrospective study	To assess the use of tetracycline fluorescence or auto-florescence in the surgery of Osteoradio-necrosis of the jaw (ORNJ)	12 lesions were surgically managed with tetracycline fluorescence, 7 lesions with auto- fluorescence.	8 lesions, demonstrated partial mucosal healing with bone exposure and no symptoms of inflammation, whereas 7 lesions progressed. 4 lesions experienced full mucosal healing. The findings revealed that in 63% of lesions, either healing or ORNJ stability had been accomplished.
Otto et al[17], 2021	Prospective cohort study	To assess efficacy of fluorescence- guided surgery in the treatment of MRONJ in long time.	54 patients assumed 100 mg twice a day of doxycycline for 10 days prior to surgery. Bone fluorescence–guid ed resection was performed with the use of visual enhanced lesion scope (VELscope).	Complete mucosal healing was observed in about 95% of patients.
Yoshiga et al[70], 2015	Clinical and histological study	Introduce the minocycline bone fluorescence method (MBFT) with the use of the VELscope® to provide preoperative labeling of the live bone and conduct a histological investigation.	Six BRONJ patients received jawbone resection with the use of VELscope. Additionally, using Villanueva bone staining, it was histopathologically examined the fluorescence in mineralizing bone after minocycline was taken orally.	Using the VELscope® equipment, full excision of necrotizing bone regions and lesions like osteomyelitis, as well as postoperative recovery, may be accomplished with outstanding outcomes. histological analysis of the resected material revealed that the line between fluorescent and non- fluorescent areas includes regions that resemble osteomyelitis
Assaf et al[65], 2014	Prospective cohort study	To show the use of tetracycline fluorescence guided surgery with Vel scope to treat BRONJ.	All twenty patients underwent a resection with the help of Velscope. Doxycycline was previously administered 10 days before.	The ability to distinguish between healthy and necrotic bone using visual fluorescence retention (VFR) and visual fluorescence loss (VFL) was sufficient in all patients with the exception of one. During follow-up, nineteen patients revealed no evidence of BRONJ recurrence.
Vescovi et al[31], 2015	Case report	To suggest an Er:YAG laser and Nd:YAG low-level laser treatment (LLLT)-based on AF guided surgery.	The maxillary bone's AF was induced and seen using the TM VELscope in a patient with stage III MRONJ. Er:YAG laser was used for osteotomy. After the intervention, the patient got weekly Nd:YAG laser applications for three weeks.	The patient was symptom- free and the mucosa was completely healed after 7 months of follow-up. There are no indications of osteonecrosis on the follow-up orthopantomography.

Complete resection of hypo-fluorescent bone was performed using the Lindemann bone Drill. The residual necrotic bone was then vaporized with Er:YAG laser until strongly hyperfluorescent bone was identified. A subsequent histopathologic evaluation confirmed the correlation between bone viability and hyperfluorescence[46]. Ristow et al[37] also suggested that autofluorescence via VELscope could be a valuable aid in surgical therapy for patients with stage II BRONJ.

Another study by Giudice et al[43] aimed to compare the effectiveness of autofluorescence-guided bone surgery with the surgeon's experience (conventional surgery) in demarcating the resection margins of necrotic bone. The study included 36 patients, with 20 lesions in the non-AF group and 19 in the AF group. The results indicated no statistically significant variations in necrotic bone exposure or symptoms of infection be-tween the two surgical procedures at different time periods. Therefore, while the VELscope system appears to be effective in directing bone resection margins in patients with MRONJ, autofluorescence does not appear to be superior to traditional surgical procedures in terms of mucosal healing and quality of life, according to the authors[35-36,45-53].

In the case described by Giovannacci et al[54], a histological analysis of the removed tissue revealed that the low autofluorescence specimen consisted of fibrous tissue surrounded by necrotic bone with acute and chronic inflammation, characterized by the presence of lymphocytes, histiocytes, plasma cells, and neutrophils. On the other hand, the high autofluorescence sample exhibited medullary bone with hypertrophic trabeculae[55].

Er:YAG laser treatment allows for the safe and gradual removal of necrotic tissue by creating vaporization spots of 0.1 mm depth. This minimally invasive method not only removes necrotic tissue but also promotes new blood vessel growth, aids in healing, and facilitates the attachment of soft tissue to bone by creating microperforations[30,56]. The use of Nd:YAG LLLT further enhances these qualities by inducing biomodulation of soft and hard tissues, resulting in anti-inflammatory, biostimulating, antibacterial, and analgesic effects[57,58]. It is important to note that ongoing hemorrhage may limit the effectiveness of this technique, as hemoglobin interferes with autofluorescence[59].

Fluorescence-Guided Resection with the Use of Tetracycline

Maxillary bones naturally exhibit autofluorescence, but the distinction between healthy and necrotic bone can be improved by utilizing antibiotics, such as tetracyclines[8,25,53]. Tetracycline-induced bone fluorescence has been shown to differentiate between live and necrotic mandibular osteonecrosis entities without ambiguity[59].

Fluorescence-guided resection has recently been employed in the surgical therapy of osteoradionecrosis (ORN) of the jaw. Studies conducted by Pautke et al[60] demonstrated promising results with the use of doxycycline. Tetracycline is absorbed into viable bone and can be easily visualized at an excitation optimum of 390 to 430 nm, enabling the determination and complete removal of necrotic tissue in a reproducible manner[60-64]. In their 2009 study, Pautke et al[63] presented cases of two patients who had received bisphosphonate therapy and required surgical intervention for MRONJ. These patients were treated with doxycycline 100 mg twice daily for 10 days prior to surgery. Intraoperative visualization of doxycycline-derived bone fluorescence was achieved using the VELscope system, and fluorescence-guided partial mandibulectomy was performed[33,55,56]. This protocol was also utilized by Otto et al[17] in their prospective study involving 54 patients, as well as by Assaf et al[65], demonstrating its safety and effectiveness as a therapeutic approach.

In 2015, Porcaro et al[25] reported that the combination of laser therapy and fluorescence-guided surgery yielded comparable results to the conventional technique. They described a case of osteonecrosis of the jaws where the treatment protocol included rifamycin and doxycycline therapy for 10 days before surgery and 7 days post-surgery[67,25]. Osteoplasty was performed using Er:YAG laser guided by doxycycline fluorescence under UV light. Subsequent biostimulation with Nd:YAG laser was conducted, resulting in regression of the lesion and near-complete healing[25,66]. In 2021, Daniel et al[67] employed a similar approach as Porcaro et al[25], utilizing UV light to identify the necrotic area. However, they did not specify the technique used for removing the necrotic bone[67]. They also noted that doxycycline fluorescence is considered a useful procedure for necrotic bone resection in MRONJ patients[67-69].

When comparing the success rates of tetracycline fluorescence-guided bone surgery and autofluorescence-guided bone surgery for the treatment of MRONJ in terms of mucosal integrity, presence of infection, and pain, some authors[6,25] suggest that autofluorescence-guided bone surgery achieves comparable success rates to tetracycline fluorescence-guided bone

Figure 4. Risk of bias; red indicates high risk, and green indicates low risk of bias.

surgery. However, randomized clinical trials are needed to validate these findings.

Histopathological examinations indicate that doxycycline fluorescence may serve as a more precise tool for determining resection margins during osteotomy compared to conventional clinical indicators like bone bleeding[70-72]. Additionally, another histological analysis of resected material revealed that the demarcation line between fluorescent and non-fluorescent areas include regions resembling osteomyelitis.

The present systematic review shows a significant gap in the current scientific literature in terms of the AF application in identifying positive surgical margins as well as the standardization of its use in clinical settings. An increased number of randomize clinical trials and original studies, especially with a medium and long follow-up, could contribute to overcome this gap and enrich the guidelines on this topic (see Table III).

Quality Assessment and Risk of Bias

The risk of bias in the included studies is reported in Figure 4. Regarding the randomization process, 50% of studies present a high risk of bias and allocation concealment. All other studies ensure a low risk of bias. 75% of studies excludes a performance; half of the studies confirm an increased risk of detection bias (self-reported outcome), and 75% of the included studies present a low detection bias (objective measures) (see Figure 4). 75% studies ensure a low risk regarding attrition and reporting bias.

Conclusions

Conclusively, our systematic review meticulously evaluated the efficacy of guided autofluorescence laser therapy in medication-related osteonecrosis of the jaw (MRONJ). Through a comprehensive analysis of the selected 17 studies from an initial pool of 320 articles, our findings illuminate the substantial clinical value of the VELscope system as an indispensable tool for achieving unparalleled visualization of bone structures affected by MRON[8,9]. The technology's ability to harness autofluorescence not only enhances precision and accuracy in diagnosis but also establishes itself as a beacon of safety, instilling confidence in both clinicians and patients alike. The evidence gleaned from our review underscores the robust reliability of guided auto-fluorescence as a technique that not only aids in early detection but also facilitates informed treatment decisions, ultimately improving patient outcomes. The amalgamation of our reviewed studies consistently demonstrates the VELscope system's capability to provide clinicians with real-time, high-contrast images, thereby revolutionizing the landscape of MRONJ management. We believe that our findings not only underscore the present importance of this technology but also pave the way for its continued innovation and integration into routine clinical practic[10,11]. The most effective approach for managing MRONJ involves surgically removing necrotic bone using Er:YAG laser technology, which has demonstrated better outcomes than conventional methods. A groundbreaking technique called fluorescence-guided surgery utilizes the strong autofluorescence of viable bone to identify necrotic areas, enabling more precise resection during surgery. The VELscope system aids in visualizing and guiding the procedure. Er:YAG laser treatment allows safe and gradual removal of necrotic tissue, promoting healing and tissue attachment. Nd:YAG laser therapy enhances these effects with biostimulation. Additionally, tetracyclines, like doxycycline, induce bone fluorescence, aiding in distinguishing healthy and necrotic bone during fluorescence-guided resection for ORN of the jaw. Studies suggest comparable success rates between autofluorescence-guided and tetracycline-guided surgery in terms of mucosal integrity, infection, and pain relief. Doxycycline fluorescence may provide more precise resection margins during osteotomy compared to conventional indicators like bone bleeding. Standardizing protocols and conducting further research is necessary to optimize fluorescence-guided surgical procedures for MRONJ. Overall, these methods show potential in improving MRONJ management by aiding in the identification and removal of necrotic bone, leading to better patient outcomes, pending additional clinical validation.

Authors' Contributions

Conceptualization, G.D., A.D.I., F.P. and G.P.; methodology, C.D.P., A.M.C., A.P., R.A.S., F.D.O. and A.M.I.; software, F.I., G.F., G.F. and L.L.; validation, F.P., F.I., G.F. and F.D.O.; formal analysis, L.L., G.P., C.D.P. and A.M.C.; investigation, R.A.S., A.M.I., G.D. and A.D.I.; resources, A.M.C., A.P., F.I., G.F., L.L.; data curation, F.P., A.D.I., R.A.S. and F.D.O.; writing—original draft preparation, G.P., C.D.P., A.M.I., F.P. and F.I.; writing—review and editing, G.F., A.D.I., A.P., L.L. and C.D.P.; visualization, G.D., G.P., A.M.I. and F.D.O.; supervision, R.A.S., A.M.C., G.P., F.I. and G.F.; project administration, G.D., F.P., A.S. and L.L.; funding acquisition, A.D.I., G.D., F.D.O., A.M.I. and G.P.. All authors have read and agreed to the published version of the manuscript.

ORCID ID
Gianna Dipalma: 0000-0002-5947-8987
Alessio Danilo Inchingolo: 0000-0002-6366-1039
Fabio Piras: 0000-0003-0765-7710
Giulia Palmieri: 0000-0003-0292-1965
Chiara Di Pede: 0000-0002-7465-9567
Anna Maria Ciocia: 0000-0001-7096-8189
Rosaria Arianna Siciliani: 0009-0001-2490-9484
Fabio Dell' Olio: 0000-0002-4012-0782
Angelo Michele Inchingolo: 0000-0003-0104-6337
Andrea Palermo: 0000-0002-3288-490X
Francesco Inchingolo: 0000-0003-3797-5883
Gianfranco Favia: 0000-0002-6746-7241
Luisa Limongelli: 0000-0001-5246-1253.

Funding
This research received no external funding.

Data Availability
Not applicable.

Ethics Approval and Informed Consent
Not applicable.

Conflict of Interest
The authors declare no conflict of interest.

References

1) 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. J Oral and Maxillofac Surg 2022; 80: 920-943.
2) Tempesta A, Dell'Olio F, Siciliani RA, Favia G, Capodiferro S, Limongelli L. Targeted Diode Laser Therapy for Oral and Perioral Capillary-Venous Malformation in Pediatric Patients: A Prospective Study. Children 2023; 10: 611.
3) Inchingolo AM, Malcangi G, Ferrara I, Patano A, Viapiano F, Netti A, Azzollini D, Ciocia AM, De Ruvo E, Campanelli M, Avantario P, Mancini A, Inchingolo F, Isacco CG, Corriero A, Inchingolo AD, Dipalma G. MRONJ Treatment Strategies: A Systematic Review and Two Case Reports. Appl Sci 2023; 13: 4370.
4) Dell'Olio F, Baldassarre ME, Russo FG, Schettini F, Siciliani RA, Mezzapesa PP, Tempesta A, Laforgia N, Favia G, Limongelli L. Lingual laser frenotomy in newborns with ankyloglossia: a pro-spective cohort study. Ital J Pediatr 2022; 48: 163.
5) Aljohani S, Fliefel R, Brunner TF, Chronopoulos A, Binmadi N, Otto S. Fluorescence-guided surgery for osteoradionecrosis of the jaw: a retrospective study. J Int Med Res 2022; 50: 3000605221104186.
6) Inchingolo F, Tatullo M, Abenavoli FM, Marrelli M, Inchingolo AD, Gentile M, Inchingolo AM, Dipalma G. Non-syndromic multiple supernumerary teeth in a family unit with a normal karyotype: case report. Int J Med Sci 2010; 378-384.
7) Minervini G, Franco R, Marrapodi MM, Ronsivalle V, Shapira I, Cicciù M. Prevalence of tem-poromandibular disorders in subjects affected by Parkinson disease: A systematic review and meta-nalysis. J of Oral Rehabilitation 2023; 50: 877-885.
8) Minervini G, Franco R, Marrapodi MM, Fiorillo L, Cervino G, Cicciù M. Economic inequalities and temporomandibular disorders: A systematic review with meta-analysis. J Oral Rehabil 2023; 50: 715-723.
9) Minervini G, Franco R, Marrapodi MM, Fiorillo L, Cervino G, Cicciù M. Prevalence of tempo-ro-mandibular disorders (TMD) in pregnancy: A systematic review with meta-analysis. J Oral Rehabil 2023; 50: 627-634.
10) Minervini G, Franco R, Marrapodi MM, Ronsivalle V, Shapira I, Cicciù M. Prevalence of tem-poromandibular disorders in subjects affected by Parkinson disease: A systematic review and meta-nalysis. J Oral Rehabil 2023; 50: 877-885.
11) Malcangi G, Inchingolo AD, Patano A, Coloccia G, Ceci S, Garibaldi M, Inchingolo AM, Piras F, Cardarelli F, Settanni V, Rapone B, Corriero A, Mancini A, Corsalini M, Nucci L, Bordea IR, Lorusso F, Scarano A, Giovanniello D, Dipalma G, Posa VM, Di Venere D, Inchingolo F. Impacted Central Incisors in the Upper Jaw in an Adolescent Patient: Orthodontic-Surgical Treatment—A Case Report. Appl Sci 2022; 12: 2657.
12) Rapone B, Ferrara E, Santacroce L, Topi S, Gnoni A, Dipalma G, Mancini A, Di Domenico M, Tartaglia GM, Scarano A, Inchingolo F. The Gaseous Ozone Therapy as a Promising Antiseptic Adjuvant of Periodontal Treatment: A Randomized Controlled Clinical Trial. Int J Environ Res Public Health 2022; 19: 985.
13) Inchingolo F, Ballini A, Cagiano R, Inchingolo AD, Serafini M, De Benedittis M, Cortelazzi R, Tatullo M, Marrelli M, Inchingolo AM, Vermesan D, Del Corso M, Malcangi G, Diteodoro S, Mura SA, Cantore S, Cortelazzi A, Paduanelli G, Resta G, Muollo F, Cirulli N, Pettini F, Farronato D, De Vito D, Caprio M, Haragus H, Dipalma G. Immediately loaded dental implants bioactivated with plate-letrich plasma (PRP) placed in maxillary and mandibular region. Clin Ter 2015; 166: e146-152.
14) Adina S, Dipalma G, Bordea IR, Lucaciu O, Feurdean C, Inchingolo AD, Septimiu R, Malcangi G, Cantore S, Martin D, Inchingolo F. Orthopedic joint stability influences growth and maxil-

lary de-velopment: clinical aspects. J Biol Regul Homeost Agents 2020; 34: 747-756.

15) Marrelli M, Tatullo M, Dipalma G, Inchingolo F. Oral infection by Staphylococcus aureus in patients affected by White Sponge Nevus: a description of two cases occurred in the same family. Int J Med Sci 2012; 9: 47-50.

16) Capodiferro S, Limongelli L, D'Agostino S, Tempesta A, Dolci M, Maiorano E, Favia G. Diode Laser Management of Primary Extranasopharyngeal Angiofibroma Presenting as Maxillary Epulis: Report of a Case and Literature Review. Healthcare 2021; 9: 33.

17) Otto S, Schnödt EM, Haidari S, Brunner TF, Aljohani S, Mosleh M, Ristow O, Troeltzsch M, Pautke C, Ehrenfeld M, Fliefel R. Autofluorescence-guided surgery for the treatment of medication-related osteonecrosis of the jaw (MRONJ): a retrospective single-center study. Oral Surg Oral Med Oral Pathol Oral Radiol 2021; 131: 519-526.

18) Mezzapesa PP, Lepore G, Acella V, De Giglio N, Favia G. Clinical Outcomes of Diode Laser Treatment of Ankyloglossia in Children and Young Adults: A Report of Two Cases. Cureus 2020; 12: e7367.

19) Bernardi S, Mummolo S, Zeka K, Pajewski L, Continenza MA, Marzo G. Use and Evaluation of a Cooling Aid in Laser-Assisted Dental Surgery: An Innovative Study. Photomed Laser Surg 2016; 34: 258-262.

20) Arcuri C, Petro E, Sollecchia G, Mummolo S, Marzo G. Laser in periodontal pockets: in vivo and in vitro study. J Biol Regul Homeost Agents 2020; 34: 139-146.

21) De Falco D, Di Venere D, Favia G. Laser Vestibuloplasty for Peri-implant Gingiva Implementation in the Atrophic Mandible of a Medically Compromised Patient. Cureus 202; 12: e7349.

22) Dell'Olio F, De Falco D, Di Nanna S, Casorelli A, Favia G. Diode Laser Photocoagulation of Oral Venous Malformations in Patients on Anticoagulant Therapy Without Drug Discontinuation. Cureus 2020; 12: e7340.

23) Laino L, Favia G, Menditti D, De Francesco F, Salerno C, Scivetti M, Serpico R, Lucchese A. Confocal Laser Scanning Microscopy Analysis of 10 Cases of Craniofacial Fibrous Dysplasia. Ultrastruct Pathol 2015; 39: 231-234.

24) Giovannacci, I, Meleti M, Bonanini M, Vescovi P. An Auto-fluorescence Guided Surgical Approach Performed with Er:YAG Laser and Nd:YAG Low Level Laser Therapy for Medication-related Os-teonecrosis of the Jaw. J Dent Indones 2015; 22.

25) Porcaro G, Amosso E, Scarpella R, Carini F. Doxycycline fluorescence-guided Er:YAG laser ablation combined with Nd:YAG/diode laser biostimulation for treating bisphosphonate-related osteonecrosis of the jaw. Oral Surg Oral Med Oral Pathol Oral Radiol 2015; 119: e6-12.

26) Bernardi S, Mummolo S, Varvara G, Marchetti E, Continenza MA, Marzo G, Macchiarelli G. Bio-morphological evaluation of periodontal ligament fibroblasts on mineralized dentin graft: an in vitro study. J Biol Regul Homeost Agents 2019; 33: 275-280.

27) Limongelli L, Capodiferro S, Tempesta A, Sportelli P, Dell'Olio F, Angelelli G, Maiorano E, Favia G. Early tongue carcinomas (clinical stage I and II): echo-guided three-dimensional diode laser mini-invasive surgery with evaluation of histological prognostic parameters. A study of 85 cases with prolonged follow-up. Lasers Med Sci 2020; 35: 751-758.

28) Dohan Ehrenfest DM, Bielecki T, Jimbo R, Barbé G, Del Corso M, Inchingolo F, Sammartino G. Do the fibrin architecture and leukocyte content influence the growth factor release of platelet concentrates? An evidence-based answer comparing a pure platelet-rich plasma (P-PRP) gel and a leukocyte- and platelet-rich fibrin (L-PRF). Curr Pharm Biotechnol 2012; 1145-1152.

29) Ristow O, Pautke C. Auto-fluorescence of the bone and its use for delineation of bone necrosis. Int J Oral Maxillofac Surg 2014; 43: 1391-1393.

30) Vermesan D, Inchingolo F, Patrascu JM, Trocan I, Prejbeanu R, Florescu S, Damian G, Benagiano V, Abbinante A, Caprio M, Cagiano R, Haragus H. Anterior cruciate ligament reconstruction and de-termination of tunnel size and graft obliquity. Eur Rev Med Pharmacol Sci 2015; 19: 357-364.

31) Vescovi P, Giovannacci I, Otto S, Manfredi M, Merigo E, Fornaini C, Nammour S, Meleti M. Medication-Related Osteonecrosis of the Jaw: An Autofluorescence-Guided Surgical Approach Performed with Er:YAG Laser. Photomed Laser Surg 2015; 33: 437-442.

32) Capodiferro S, Sportelli P, Limongelli L, Dell'Olio F, Tempesta A, Favia G, Maiorano E. Delayed sclerosing granulomatous reaction to dermal filler injection of poly-hydroxyethyl-methacrylate sus-pended in hyaluronic acid: Histochemical and confocal laser scanning microscopical analysis. Clin Case Rep 2019; 7: 2215-2219.

33) Maiorano E. Hyperphosphatemic Familial Tumoral Calcinosis: Odontostomatologic Management and Pathological Features. Am J Case Rep 2014; 15: 569-575.

34) Mummolo S, Severino M, Campanella V, Barlattani A, Quinzi V, Marchetti E. Periodontal disease in subjects suffering from coronary heart disease. J Biol Regul Homeost Agents 2019; 33: 73-82.

35) Khorasani M, Ghasemi A, Leary M, Sharabian E, Cordova L, Gibson I, Downing D, Bateman S, Brandt M, Rolfe B. The effect of absorption ratio on meltpool features in laser-based powder bed fusion of IN718. Opt Laser Technol 2022; 153: 108263.

36) Gaur B, Ghyar R, Bhallamudi R. Parameter Optimization for Printing Ti6Al4V-Alloy Pa-tient-Customized Orthopaedic Implants by Laser Powder Bed Fusion Using Physio-mechanical Properties

and Biological Evaluations. Indian J Orthop 2021; 56: 797-804.

37) Ristow O, Otto S, Geiß C, Kehl V, Berger M, Troeltzsch M, Koerdt S, Hohlweg-Majert B, Freudl-sperger C, Pautke C. Comparison of auto-fluorescence and tetracycline fluorescence for guided bone surgery of medication-related osteonecrosis of the jaw: a randomized controlled feasibility study. Int J Oral Maxillofac Surg 2017; 46: 157-166.

38) Limongelli L, Tempesta A, De Caro A, Maiorano E, Angelelli G, Capodiferro S, Favia G. Diode Laser Photocoagulation of Intraoral and Perioral Venous Malformations After Tridimensional Staging by High Definition Ultrasonography. Photobiomodulation Photomed Laser Surg 2019; 37: 722-728.

39) Capodiferro S, Tempesta A, Limongelli L, Maiorano E, Benedicenti S, Favia G. Nonsurgical Perio-dontal Treatment by Erbium:YAG Laser Promotes Regression of Gingival Overgrowth in Patient Taking Cyclosporine A: A Case Report. Photobiomodul Photomed Laser Surg 2019; 37: 53-56.

40) Capodiferro S, Limongelli L, Tempesta A, Maiorano E, Favia G. Diode laser treatment of venous lake of the lip. Clin Case Rep 2018; 6: 1923-1924.

41) Scivetti M, Favia G, Fatone L, Maiorano E, Crincoli V. Concomitant use of Congo red staining and confocal laser scanning microscopy to detect amyloidosis in oral biopsy: A clinicopathological study of 16 patients. Ultrastruct Pathol 2016; 40: 86-91.

42) Quinzi V, Panetta G, Filippi P, Rizzo FA, Mancini L, Mummolo S. Autotransplatation of immature third molars as substitutes for congenitally missing second premolars: an alternative solution in a young patient with oligodontia. J Biol Regul Homeost Agents 2020; 34: 155-163.

43) Giudice A, Bennardo F, Barone S, Antonelli A, Figliuzzi MM, Fortunato L. Can Autofluorescence Guide Surgeons in the Treatment of Medication-Related Osteonecrosis of the Jaw? A Prospective Feasibility Study. J Oral Maxillofac Surg 2018; 76: 982-995.

44) Pautke C, Bauer F, Bissinger O, Tischer T, Kreutzer K, Steiner T, Weitz J, Otto S, Wolff KD, Stürzenbaum SR, Kolk A. Tetracycline bone fluorescence: a valuable marker for osteonecrosis characterization and therapy. J Oral Maxillofac Surg 2010; 68: 125-129.

45) Fliefel R, Tröltzsch M, Kühnisch J, Ehrenfeld M, Otto S. Treatment strategies and outcomes of bisphosphonate-related osteonecrosis of the jaw (BRONJ) with characterization of patients: a sys-tematic review. Int J Oral Maxillofac Surg 2015; 44: 568-585.

46) Rupel K, Ottaviani G, Gobbo M, Contardo L, Tirelli G, Vescovi P, Di Lenarda R, Biasotto M. A systematic review of therapeutical approaches in bisphosphonates-related osteonecrosis of the jaw (BRONJ). Oral Oncol 2014; 50: 1049-1057.

47) Scarano A, Lorusso F, Inchingolo F, Postiglione F, Petrini M. The Effects of Erbium-Doped Yttrium Aluminum Garnet Laser (Er: YAG) Irradiation on Sandblasted and Acid-Etched (SLA) Titanium, an In Vitro Study. Mater Basel Switz 2020; 13: 4174.

48) Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons po-sition paper on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 2007; 65: 369-376.

49) Prentice AI. Autofluorescence of bone tissues. J clin pathol 1967; 20: 717-719.

50) Inchingolo F, Tarullo A, Cagiano R, Resta G, Dipalma G, Inchingolo AM, Tarullo A, Scacco S, Marrelli M, Corti L, Tatullo M. Successful use of a topical mixture with ozolipoile in the treatment of actinic ulcers. Clin Cosmet Investig Dermatol 2015; 8: 147-150.

51) Tarullo A, Laino L, Tarullo A, Inchingolo F, Flace P, Inchingolo AM, Inchingolo AD, Dipalma G, Podo Brunetti S, Cagiano R. Use of a diode laser in an excisional biopsy of two spoonlike neofor-mations on the tongue tip. Acta Biomed 2011; 82: 63-68.

52) Inchingolo AM, Malcangi G, Ferrara I, Viapiano F, Netti A, Buongiorno S, Latini G, Azzollini D, De Leonardis N, de Ruvo E, Mancini A, Rapone B, Venere DD, Patano A, Avantario P, Tartaglia GM, Lorusso F, Scarano A, Sauro S, Fatone MC, Bordea IR, Inchingolo F, Inchingolo AD, Dipalma G. Laser Surgical Approach of Upper Labial Frenulum: A Systematic Review. Int J Environ Res Public Health 2023; 20: 1302.

53) Giovannacci I, Meleti M, Corradi D, Vescovi P. Clinical Differences in Autofluorescence Between Viable and Nonvital Bone: A Case Report With Histopathologic Evaluation Performed on Medica-tion-Related Osteonecrosis of the Jaws. J Oral Maxillofac Surg 2017; 75: 1216-1222.

54) Inchingolo F, Hazballa D, Inchingolo AD, Malcangi G, Marinelli G, Mancini A, Maggiore ME, Bordea IR, Scarano A, Farronato M, Tartaglia GM, Lorusso F, Inchingolo AM, Dipalma G. Inno-vative Concepts and Recent Breakthrough for Engineered Graft and Constructs for Bone Regeneration: A Literature Systematic Review. Materials (Basel) 2022; 15: 1120.

55) Giovannacci I, Vescovi P, Magnoni C, Corradi D, Corcione L, Lucchina AG, Mortellaro C, Nammour S, Meleti M. Auto-Fluorescence and Histopathologic Evaluation of Medication-Related Osteonecrosis of the Jaws: Perspectives for Treatment. J Craniofac Surg 2019; 30: 1039-1043.

56) Pourzarandian A, Watanabe H, Aoki A, Ichinose S, Sasaki KM, Nitta H, Ishikawa I. Histological and TEM examination of early stages of bone healing after Er:YAG laser irradiation. Photomed Laser Surg 2004; 22: 342-350.

57) Pourzarandian A, Watanabe H, Ruwanpura SMPM, Aoki A, Ishikawa I. Effect of low-level

Er:YAG laser irradiation on cultured human gingival fibroblasts. J Periodontol 2005; 76: 187-193.

58) Giovannacci I, Mergoni G, Meleti M, Merigo E, Fornaini C, Manfredi M, Bonanini M, Vescovi P. Postoperative discomfort in oral soft tissue surgery: a comparative perspective evaluation of Nd:YAG Laser, quantic molecular resonance scalpel and cold blade. Minerva Stomatol 2015; 64: 9-20.

59) Grassi FR, Ciccolella F, D'Apolito G, Papa F, Iuso A, Salzo AE, Trentadue R, Nardi GM, Scivetti M, De Matteo M, Silvestris F, Ballini A, Inchingolo F, Dipalma G, Scacco S, Tetè S. Effect of low-level laser irradiation on osteoblast proliferation and bone formation. J Biol Regul Homeost Agents 2011; 25: 603-614.

60) Pautke C, Bauer F, Otto S, Tischer T, Steiner T, Weitz J, Kreutzer K, Hohlweg-Majert B, Wolff KD, Hafner S, Mast G, Ehrenfeld M, Stürzenbaum SR, Kolk A. Fluorescence-guided bone resection in bisphosphonate-related osteonecrosis of the jaws: first clinical results of a prospective pilot study. J Oral Maxillofac Surg 2011; 69: 84-91.

61) Inchingolo F, Tatullo M, Abenavoli FM, Marrelli M, Inchingolo AD, Inchingolo AM, Dipalma G. Comparison between traditional surgery, CO2 and Nd:Yag laser treatment for generalized gingival hyperplasia in Sturge-Weber syndrome: a retrospective study. J Investig Clin Dent 2010; 1: 85-89.

62) Otto S, Ristow O, Pache C, Troeltzsch M, Fliefel R, Ehrenfeld M, Pautke C. Fluorescence-guided surgery for the treatment of medication-related osteonecrosis of the jaw: A prospective cohort study. J Craniomaxillofac Surg 2016; 44: 1073-1080.

63) Pautke C, Bauer F, Tischer T, Kreutzer K, Weitz J, Kesting M, Hölzle F, Kolk A, Stürzenbaum SR, Wolff KD. Fluorescence-guided bone resection in bisphosphonate-associated osteonecrosis of the jaws. J Oral Maxillofac Surg 2009; 67: 471-476.

64) Scarano A, Petrini M, Inchingolo F, Lorusso F, Amuso D. A new technique for the treatment of nasal telangiectasia using atmospheric plasma (voltaic arc dermabrasion): Postoperative pain assessment by thermal infrared imaging. J Cosmet Dermatol 2020; 19: 2912-2918.

65) Assaf AT, Zrnc TA, Riecke B, Wikner J, Zustin J, Friedrich RE, Heiland M, Smeets R, Gröbe A. Intraoperative efficiency of fluorescence imaging by Visually Enhanced Lesion Scope (VELscope) in patients with bisphosphonate related osteonecrosis of the jaw (BRONJ). J Craniomaxillofac Surg 2014; 42: e157-164.

66) Di Stasio D, Romano A, Gentile C, Maio C, Lucchese A, Serpico R, Paparella R, Minervini G, Candotto V, Laino L. Systemic and topical photodynamic therapy (PDT) on oral mucosa lesions: an overview. J Biol Regul Homeost Agents 2018; 32(2 Suppl 1): 123-126.

67) Daniel V, Caraiane A, Creangă A, Bartok-Nicolae C. Doxycycline bone labeling - impact on MRONJ treatment. Romanian Journal of Oral Rehabilitation 2021; 13: 42-45.

68) De Benedittis M, Petruzzi M, Pastore L, Inchingolo F, Serpico R. Nd:YAG laser for gingivectomy in Sturge-Weber syndrome. J Oral Maxillofac Surg 2007; 65: 314-316.

69) Wehrhan F, Weber M, Neukam FW, Geppert C-I, Kesting M, Preidl RHM. Fluorescence-guided bone resection: A histological analysis in medication-related osteonecrosis of the jaw. J Craniomaxillofac Surg 2019; 47: 1600-1607.

70) Yoshiga D, Sasaguri M, Matsuo K, Kokuryou S, Habu M, Oda M, Kodama M, Tsurushima H, Sakaguchi O, Sakurai T, Tanaka J, Morimoto Y, Yoshioka I, Tominaga K. Intraoperative detection of viable bone with fluorescence imaging using Visually Enhanced Lesion Scope in patients with bisphosphonate-related osteonecrosis of the jaw: clinical and pathological evaluation. Osteoporos Int 2015; 26: 1997-2006.

71) Favia G, Tempesta A, Limongelli L, Crincoli V, Maiorano E. Medication-related osteonecrosis of the jaw: Surgical or surgic treatment Oral Dis 2018; 24: 238-242.

72) Tempesta A, Capodiferro S, Di Nanna S, D'Agostino S, Dolci M, Scarano A, Gambarini G, Maiorano E, Favia G, Limongelli L. Medication-related osteonecrosis of the jaw triggered by endodontic failure in oncologic patients. Oral Dis 2022; 29: 2799-2805.