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CIRURGIA GUIADA POR FLUORESCÊNCIA NA OSTEONECROSE INDUZIDA POR MEDICAMENTOS

FLUORESCENCE-GUIDED SURGICAL MANAGEMENT OF MEDICATION-RELATED OSTEONECROSIS OF THE JAWS

Fernandópolis, SP
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Orientadora: Profa. Dra. Luciana Estevam Simonato

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CIRURGIA GUIADA POR FLUORESCÊNCIA NA OSTEONECROSE INDUZIDA POR MEDICAMENTOS

RESUMO

A osteonecrose da mandíbula relacionada a medicamentos (do inglês “medication-related osteonecrosis of the jaw” ou MRONJ) resulta em destruição progressiva dos ossos da mandíbula, e casos avançados exigem abordagem cirúrgica. A remoção total do osso necrótico é necessária para evitar a recorrência e infecção. No entanto, determinar os limites entre ossos necrótico e saudável é um desafio. O uso da fluorescência para detectar alterações teciduais e determinar a extensão da necrose é um método promissor para evitar desbridamento ósseo inadequado. Na literatura, existem vários estudos e casos relatados que utilizaram com sucesso a cirurgia guiada por fluorescência (do inglês “fluorescence-guided surgery” ou FGS) da MRONJ. O uso da FGS para delimitar a margem de ressecção da MRONJ é um método promissor. Não há necessidade da aplicação de fluoróforo exógeno para realizar a FGS e o dispositivo de luz mais utilizado foi o sistema VELScope®. No entanto, devido à falta de revisão crítica e comparativa dos métodos e observações sobre FGS no MRONJ tornam-se necessários novos estudos, sendo assim o objetivo deste estudo foi apresentar uma revisão crítica da literatura sobre o uso intraoperatório de fluorescência óptica para diferenciar osso saudável e necrótico na MRONJ. Os estudos que avaliaram o uso intraoperatório da fluorescência óptica para determinar as margens cirúrgicas da MRONJ foram pesquisados no banco de dados Pubmed / Medline usando os seguintes termos: “osteonecrose dos maxilares relacionada a medicamentos” e “fluorescência”. Foram selecionados 18 artigos que descrevem o uso intraoperatório de FGS no tratamento da ONJ, totalizando 218 pacientes. Ainda são necessários estudos prospectivos com amostras maiores para determinar a validade da fluorescência como método de suporte no tratamento cirúrgico da MRONJ e estabelecer protocolos clínicos.

Palavras-chave: Necrose, Osteonecrose, Fluorescência, Tetraciclina, Osteonecrose da arcada osseodentária associada a bifosfonatos, Bioengenharia.

FLUORESCENCE-GUIDED SURGICAL MANAGEMENT OF MEDICATION-RELATED OSTEONECROSIS OF THE JAWS

ABSTRACT

Medication-related osteonecrosis of the jaw (MRONJ) results in progressive destruction of the jawbones, and advanced cases demand surgical approach. The total removal of necrotic bone is required to prevent recurrence and infection. However, determining the limits between necrotic and healthy bone is a challenge. The use of fluorescence to detect tissue alterations and determinate the necrosis extension is a promising method to avoid inadequate bone debridement. In the literature, there are several studies and reported cases that successfully used the fluorescence-guided surgery (FGS) of MRONJ. The use of FGS to delimitate the resection margin of MRONJ is a promising method. There is no need for the application of exogenous fluorophore to perform FGS and the most used light device was the VELScope® system. However, due to the lack of critical and comparative review of the methods and observations about FGS in MRONJ, the objective of this study was to present a critical review of the literature regarding the intraoperative use of optic fluorescence to differentiate healthy and necrotic bone in MRONJ. Studies that evaluated the intraoperative use of optic fluorescence to determine the surgical margins of MRONJ were searched in Pubmed/Medline database using the following terms: “medication-related osteonecrosis of the jaws” and “fluorescence”. Eighteen papers describing the intraoperative use of FGS in ONJ management were selected, totalizing 218 patients. Further prospective studies with larger samples are still required to ascertain the fluorescence validity as a supporting method in MRONJ surgical treatment and to establish clinical protocols.

Keywords: Necrosis of the jaw; BRONJ; DRONJ; MRONJ; ONJ; Bisphosphonate; Osteonecrosis; Bone fluorescence; Tetracycline; Auto-fluorescence; Therapy; Bone; VELscope; Bioengineering.

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LISTA DE ABREVIATURAS, SIGLAS E SÍMBOLOS

ORN	Osteoradionecrosis
MRONJ	Medication-related osteonecrosis of the jaws
OFI	Optic fluorescence imaging
FGS	Fluorescence-guided surgery
ONJ	Osteonecrosis of the jaws
5-ALA	5-aminolevulinic acid
LLLT	Low-level laser therapy

SUMÁRIO

1. Introduction

The necrosis of the jawbones results in a dramatic decrease in the quality of life of affected patients [1]. Besides the osteoradionecrosis (ORN) of the jaws in patients who underwent radiation therapy to malignant tumors in the head and neck region, the exponential increase in cases of osteonecrosis of the jaws since the beginning of the use of antiresorptive drugs (e.g. bisphosphonates) in the treatment of osteoporosis, bone malignant neoplasms and bone metastasis of other cancers [2], made mandatory the need for innovation in treatment approaches for this condition [3,4].

Huge advances have been achieved in surgical techniques and pre-, trans- and post-operatory care for the treatment of the medication-related osteonecrosis of the jaws (MRONJ) [5-7]. However, to determine the healthy bone margin intraoperatively remains a major challenge when surgically managing this condition [8]. Surgeons must observe the bone color and bleeding to differentiate the necrotic from the healthy bone [6,9]. Nevertheless, the interpretation of these characteristics may be subjective and vary from surgeon to surgeon, which results in a high risk either for insufficient or exaggerated bone debridement [8]. The first may result in recurrence of the necrosis and infection, while the second may unnecessarily lead to severe bone defect and limited function of the jaws [9].

The study of the fluorescence interaction with biologic tissues has gained space in health sciences and helping health professionals both in the diagnosis and treatment of several diseases [10]. The use of fluorescence may be either to detect tissue alterations or to determinate the extension of the disease alteration for treatment planning [10]. In the scenario of dental/oral medicine practice, the optic fluorescence imaging (OFI), which consists of the real-time observation of the tissue fluorescence through optic filters, is now well recognized to improve the detection of oral cancer and potentially malignant disorders both in primary and specialized

care [11,12], and to identify dental biofilms and lesions to dental structure (e.g. enamel fissure and dental caries) [13].

Recently, the use of OFI to intraoperatively determinate the margins between the healthy and necrotic bone in MRONJ cases has emerged as a promising method to avoid inadequate bone debridement [8]. Several case reports and clinical studies in which surgeons successfully used the fluorescence-guided surgery (FGS) of MRONJ can be found in the literature. However, a critical and comparative review of the methods and observations described in these studies is required to give surgeons and researchers perspectives for the use of this method and insights for future research to improve the technique. Thus, in this paper, we present a critical review of the literature regarding the intraoperative use of optic fluorescence to differentiate healthy and necrotic bone in MRONJ and perspectives for future research and practical application.

2. Review of literature

A narrative review of studies that evaluated the intraoperative use of optic fluorescence to determine the surgical margins of MRONJ is presented. A search in PubMed/MedLine database was performed using the terms “medication-related osteonecrosis of the jaws” and “fluorescence”. From the 26 results, case reports, case series, technical notes, and randomized clinical studies describing the use of optic fluorescence to intraoperatively discriminate healthy and necrotic bone in MRONJ were selected and critically analyzed and discussed.

In our search, we found 18 papers published in the English literature describing the intraoperative use of FGS in osteonecrosis of the jaws (ONJ) management, totalizing 218 patients treated with this method (Table 1). Only five prospective studies were performed, of which two are randomized clinical trials. The other 12 papers are isolated case reports, case series, and two cases reported as a technical note. Despite the good intraoperative observations

and outcomes reported, there are some points to be discussed to improve the methodologies both for future research and practical application of this method.

2.1. Fluorescence-guided surgical management of MRONJ: *status a quo*;

The determination of the healthy bone margin for resection represents a major challenge in the surgical management of MRONJ [6,14]. During the resection, the white color and bleeding of the bone are the only characteristic that suggests a viable bone margin [8]. Given that, the differentiation of necrotic and healthy bone relies on the subjective impression of the surgeon, thus, there is still a high risk for leaving areas of necrotic bone, increasing the risk for infection and recurrence of the MRONJ. Methods to improve the discernment between necrotic and viable bone become evident. In the last years, the use of fluorescence methods to detect or guide the management of oral diseases/lesions as oculopharyngeal muscular dystrophy, oral squamous cell carcinoma, and dental tissue damage has demonstrated exciting results. Recently, the FGS has been described to help surgeons determine the margin of viable bone during surgical resection of ONJ [15,16].

In 2008, Fleisher et al. [15] described the surgical management of 10 cases of MRONJ with the intraoperative use of a generic ultraviolet light to contrast the necrotic and the viable bone after a 3 – 7 days of Tetracycline 250mg intake. After that, two case repot publications, describing two cases each, reproduced this technique, using the pre-operative intake of Doxycycline 100mg 2x/day as an exogenous fluorophore, and the VelScope® system as the source of light and fluorescence observation in the surgical resection of ONJ [17,18]. One of these last cases was the only case of ORN surgically managed under fluorescence guidance [18], but given that this is the single case of ORN of the jaws described in these studies, and that the ORN of the jaws follows distinct pathophysiologic and clinical courses from the MRONJ we will not include this condition in our discussion. In 2011, Pautke et al. [19]

published the results of the first prospective study, using the same technique as in the last case reports, in 15 patients receiving intravenous bisphosphonates and presenting 20 MRONJ lesions, and reported 85% of complete mucosal healing 4-weeks after surgery. From that, several case reports, technical notes, and prospective studies were performed using the FGS to manage MRONJ, and testing variations in the use of exogenous fluorophore targeting, and surgical technique (Table 1).

Biologic tissues may present an apple-green fluorescence when stimulated by a source of light in a specific wavelength either by the presence of endogenous fluorophores or by the application of an exogenous fluorophore (e.g.: 5-aminolevulinic acid (5-ALA), tetracycline) [20,21]. Most of the studies that reported the intraoperative use of fluorescence to determinate surgical margins of MRONJ prescribed an exogenous fluorophore to the patients for 3 – 10 days before the surgery (Table 1). The medication most used fluorophore was the Doxycycline 100mg 2x/day for 7 – 10 days before the surgery, which is described in 10 studies [16-19,22-27]. Only one study used the Minocycline [28], and the healthy bone labeling with Tetracycline was described by two authors [15,29]. The drugs from the Tetracycline family are recognized for being prone to accumulate in the bone tissue due to its affinity to calcium [30], therefore, given its fluorophore potential, theoretically, the pre-operatory intake of these drugs would provide a more accurate differentiation between healthy and necrotic bone under ultraviolet light stimuli. Nevertheless, in a randomized clinical trial, Ristow et al. [29] reported that there were no differences in the fluorescence characteristics between the bones with and without Tetracycline labeling. Furthermore, other five papers described cases in which the surgical resection of MRONJ was performed under fluorescence guidance without any exogenous fluorophore labeling, and Giudice et al. [8] performed a randomized clinical trial comparing two groups of MRONJ patients who were submitted to surgical resection for the necrotic bone with or without optic fluorescence guidance and none of the groups had exogenous fluorophore

intake before surgery. Moreover, a recent publication by Ristow et al. [31] reported, on a mini-pig preclinical model of experimental MRONJ, that neither macroscopic nor microscopic differences were observed between the fluorescence characteristics of tetracycline-labeled *versus* no-fluorochrome labeled groups, and confirmed that the autofluorescence of the vital bone if due to its organic components (collagen and cells). Thus, the Tetracycline bone labeling does not seem to influence the bone fluorescence despite its fluorophore potential, however, its application as prophylactic antibiotic therapy may still be recommended.

Several hand-held devices were developed to allow the examination of oral tissues under optic fluorescence and are commercially available. These devices emit light in a wavelength and allow the observation of tissue fluorescence through optical filters accoupled to it that filters the emitted light. Of the devices commercially available, the VELScope® (LEDDental, White Rock, British Columbia, Canada) system is the most known and used worldwide. Nonetheless in this review, we found that for guiding the surgical resection of ONJ under fluorescence aid, 13 of the 18 papers used the VELScope®[8,16-19,22-25,28,29,32,33]. One case report used the Ultrafire® WF-502B device [26], and the other four papers did not specify the source of light used, counting with generic or handmade systems for the emission of light and simultaneous observation of the bone fluorescence [14,15,27,34]. Since the system for the emission of light is adjusted to the adequate wavelength to stimulate the bone autofluorescence and proper optic filters are used to filter the emitted light and observe the reflected light, there is not a specific device recommended [26]. Nevertheless, there is not a comparative study of different sources of light for bone fluorescence observation.

Technically, the surgical removal of necrotic bone under optic fluorescence guidance may proceed routinely as it is in each practice. As expected, most reports (14) describe the conventional osteotomy [8,15-19,22,23,25-28,29,32], which is the most largely surgical approach for the treatment of MRONJ, with special attention to infection control [9]. Three

papers report the bone ablation with Er: YAG laser and intraoperative low-level laser therapy (LLLT) with Nd: YAG laser followed by post-operative weekly application of LLLT in a variable number of sessions [24,33,34]. Given the accumulation of antiresorptive drugs, the clinically healthy bone may not be able to undergo an adequate repair after a surgical procedure, therefore the risk of recurrence of the MRONJ induced by the osteotomy is still considerable [6,35]. Therefore, the ablation of the necrotic bone with Er: YAG laser is a promising technique given its less invasive damage to the surrounding bone, which may have an improved healing process with the subsequent LLLT with Nd: YAG laser [14,24,35]. In one case report, the authors performed a conventional osteotomy, after which they used the FGS to identify remaining necrotic bone and performed the laser ablation until the whole bone reaches a strong apple green fluorescence [34]. The optic fluorescence does not influence the surgical technique unless for guiding where there is necrotic bone to be removed, thus, under fluorescence guidance the surgical technique can be individualized for each case according to the surgeons' experience and training for performing each procedure.

The histologic confirmation of necrotic bone in dark areas and vital bone in luminescent areas under FGS is probably the most accurate analysis to confirm the observation of the surgeon. Although only 9 of the 18 papers included in this review described the histologic analysis of the bone resected under FGS (Table 1), all of these 9 papers reported that the specimens identified as dark areas were necrotic bone and the specimens identified as fluorescent areas were viable bone under histologic analysis. To date, only 2 of the 9 papers that had histologic confirmation of the necrotic bone removed under FGS were clinical studies [8,23], while the other 7 were case reports or case series [14,16,18,22,28,32,34]. In 2019 Wehrhan et al. [16] observed, in a case series, that the bone that presented fluorescent under FGS had more type-I collagen fibers under histologic analysis with Sirius red stainings than the dark bone. Furthermore, Ristow et al. [31] recently used a mini-pig preclinical model to

characterize the elements that determinate the fluorescence of the jawbones and observed that the auto-fluorescence of the bone is provided by the arrangements and structure of collagen and the cell-filled bone lacunae, what is not present in the necrotic bone.

2.2. Fluorescence-guided surgical management of MRONJ: prospects;

The value of using the FGS in the management of MRONJ relies on improving the observation of the surgeon to better discern between the necrotic and the healthy bone. Although, in general, the cases and studies reported until this moment describe this method with high success, there is no analysis focused on the surgeons' perception and capability of judge the adequate resection margin under both white and fluorescent lights. In most of the papers, there is a brief description of the observation of jawbones under FGS observation. Nevertheless, studies analyzing the surgeons' capability to interpret the bone characteristics (necrotic versus healthy) under FGS observation are required. Moreover, it is notable that few research groups have been describing this method, therefore, it is uncertain if other surgeons would experience the same confidence to discern between necrotic and healthy bone under FGS.

We suggest that two methodologies should be adequate to access the surgeons "interpretation of the jawbones" characteristics under FGS. The first one is to set a group of oral and maxillofacial surgeons with different levels of experience in surgically managing the MRONJ (e.g.: by graduation degree, years of practice or number of surgeries performed), but who had never had any experience with FGS, as the study population/sample. These surgeons must, separately, be presented to standardized high-resolution pictures taken from MRONJ of mini-pig preclinical models under white light and under ultraviolet light and asked to delimitate the area of necrotic bone, and then compare this observation to the histologic analysis of the lesions. Another method is to present to this group of surgeons intraoperative standardized high-

resolution pictures of MRONJ in humans (performed by a single surgeon) under white light and FGS and ask them to judge as adequate or inadequate the remaining bone margin. The pictures would have to be taken before the ending of the debridement in some cases, to designedly include pictures of inadequate resections. Thereafter the results of these observations should be compared to the observation of the surgeon who performed the surgery and who should be experienced in using the FGS.

Thus, using the results found in the literature, this study recommendations the surgical management guided by fluorescence of MRONJ in stages 2 and 3 (Table 2), following protocol (Figure 1).

Table 2. Medication-related osteonecrosis of the jaw (MRONJ) management.

STAGE	DESCRIPTION	MANAGEMENT
At risk	Asymptomatic patients with no apparent necrotic bone who have been treated with oral or intravenous bone-modifying agents	No treatment indicated
		Patient education and reduction of modifiable risk factors
		See dental specialist regularly
Stage 0	No clinical evidence of necrotic bone but nonspecific clinical findings, radiographic changes, and symptoms	Symptomatic management, including the use of pain medication and close scrutiny and follow up
		Refer to dental specialist and follow up every 8 weeks with communication of lesion status to the oncologist
		Patient education and reduction of modifiable risk factors
Stage 1	Exposed and necrotic bone or fistulas that probe to bone in patients who are asymptomatic and have no evidence of pain/infection	Antibacterial mouth rinse
		Clinical follow up on an every-8-week basis by dental specialist with communication of lesion status to oncologist
		Patient education and reduction of modifiable risk factors
Stage 2	Exposed and necrotic bone or fistulas that probe to bone associated with infection as evidenced by pain and erythema in the region of exposed bone with or without purulent drainage	Symptomatic treatment with oral antibiotics and topical antibacterial rinse
		Pain control
		Surgical management guided by fluorescence to relieve soft tissue irritation and infection control
		Clinical follow up on an every-8-week basis by dental specialist with communication of lesion status to oncologist
		Patient education and reduction of modifiable risk factors
Stage 3	Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one or more of the following: 1. exposed and necrotic bone extending beyond the region of alveolar bone,	Symptomatic treatment with oral antibiotics and topical antibacterial rinse
		Pain control
		Surgical management guided by fluorescenceor resection for long-term palliation of infection and pain

2. pathologic fracture, 3. extraoral fistula, 4. oral antral or oral nasal communication, 5. and/or osteolysis extending to the inferior border of the mandible or sinus floor.	Clinical follow up on an every-8-week basis by dental specialist with communication of lesion status to oncologist
	Patient education and reduction of modifiable risk factors

NOTE. Adapted from Yarom et al. [9]

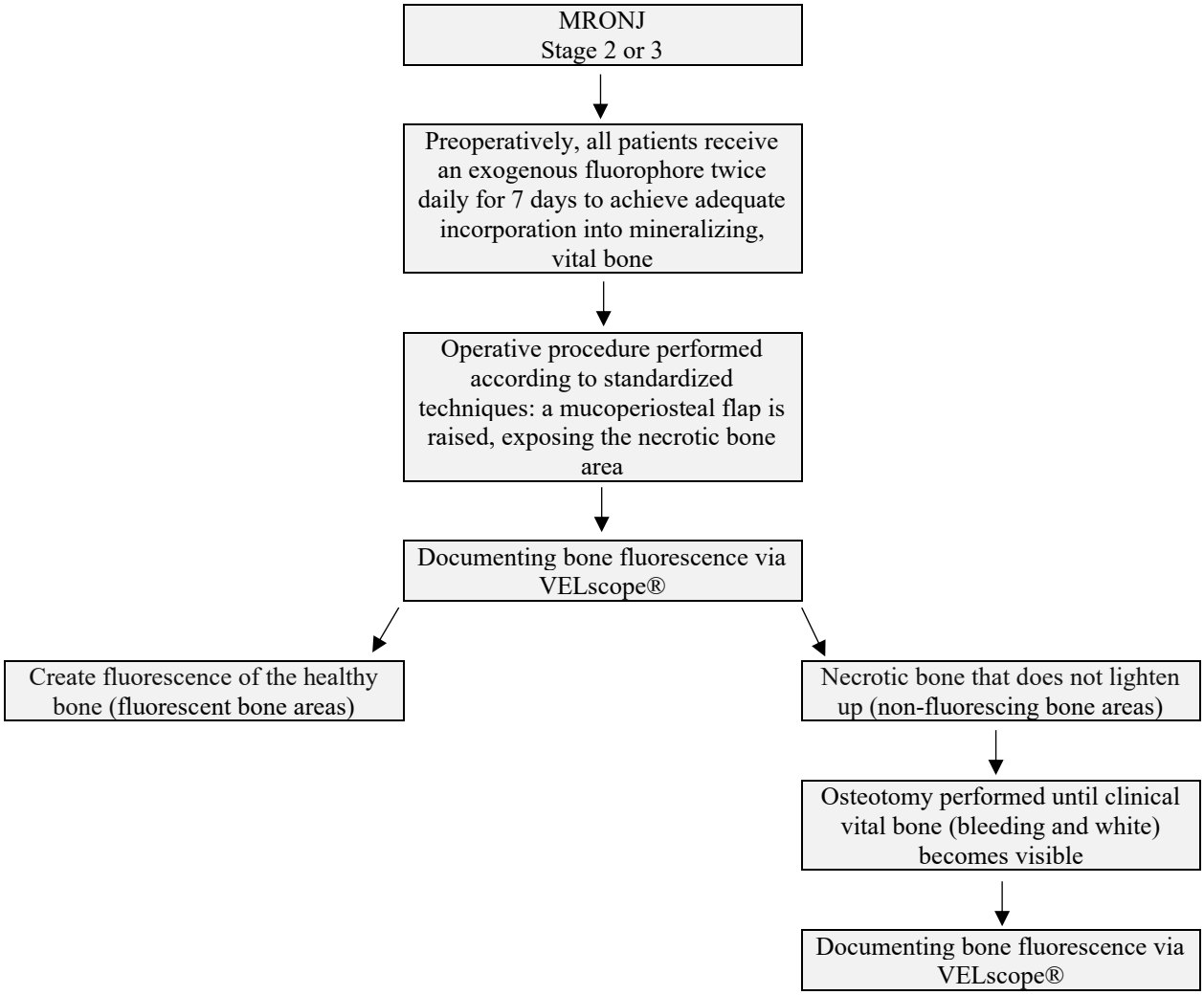

Figure 1. Protocol for fluorescence-guided surgical management of MRONJ.

3. Conclusion

The use of FGS (with no need for exogenous fluorophore) to delimitate the resection margin of MRONJ is a promising method. Nevertheless, further prospective studies with larger samples are still required. Moreover, given that this method is designed to guide the surgeons' observation of the jawbones, future studies must focus the analysis on the surgeons' judgment of the FGS.

Highlights

1. The fluorescence-guided surgical management of MRONJ improves the delimitation of the bone margin resection;
2. The bone autofluroescence is sufficient to an accurate judgement between necrotic and vital bone without the need for Tetracycline labeling;
3. The surgeons' perception of the fluorescence-guided surgery to MRONJ is still unexplored.

Conflict of interest

The authors declare that there is no potential conflict of interest regarding this work.

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Table 1. Reports of fluorescence-guided surgery to osteonecrosis of the jaws.

Author, year	Type of study	n	MRONJ/ORN stage	Base disease	Medication/RXT	Fluorescence-guided surgery technique	Intraoperative observation	Histologic confirmation	Outcome
Fleisher et al., 2008	Case series	10	NR	NR	7 oral bisphosphonates 3 intravenous bisphosphonates	Preoperatory Tetracycline 250mg 4x/day during 3 – 7 days	NR	No	All patients asymptomatic in 8-week follow-up
Pautke et al., 2009	Case report	2	NR	1 patient with bone metastasis of prostate adenocarcinoma. 1 patient with bone metastasis of mamma carcinoma.	Both patients having Zolendronate	Preoperatory Doxycycline 100mg 2x/day, 10 days before surgery. Bone resection was performed under VELScope® handpiece guide.	NR	No	NR
Pautke et al., 2010	Case report	2	NR	Patient 1 with extramedullary plasmocytoma Patient 2 with squamous cell carcinoma of the tongue	Patient 1 had pamindronate followed by zolendronate. Patient 2 received adjuvant irradiation.	Preoperatory Doxycycline 100mg 2x/day, 10 days before surgery. Bone resection was performed under VELScope® handpiece guide.	Conventional criteria, such as bone color and bleeding were not enough to determinate the resection margin.	Yes.Regions of the bone showing bleeding under naked eye examination but none or weak fluorescence under VELScope® examination were removed and histologically confirmed as necrotic bone.	NR
Pautke et al., 2011	Prospective pilot study	15 (with 20 lesions)	Satges II and III MRONJ	All patients with metastatic disease	All patients receiving intravenous bisphosphonates	Preoperatory Doxycycline 100mg 2x/day, 10 days before surgery. Bone resection was performed under VELScope® handpiece guide. Bone resected until bone showed homogeneous green fluorescence.	Necrotic bone showed no or marginal fluorescence.	No	Mucosal closure with no wound dehiscence in 85% of the lesions at 4-week follow-up.
Otto et al., 2013	Technical note	2	NR	Osteoporosis	Denosumab 60mg	Preoperatory Doxycycline 100mg 2x/day, 10 days before surgery. Bone resection was performed under VELScope® handpiece guide. Bone resected until bone showed homogeneous green fluorescence.	None to minimal fluorescence was observed in necrotic bone.	Yes	Complete healing at 6-week follow-up. One case showed bone turnover at 1-year follow-up.
Ristow and Pautke, 2014	Case series	8	Stage II MRONJ	4 patients with prostate cancer and 4 patients with breast cancer	Zolendronate	Bone resection was performed under VELScope® handpiece guide. Bone resected until bone showed homogeneous green fluorescence.	The bone fluorescence showed similar characteristics to the findings in patients who received preoperatory Doxycycline	Yes	Complete mucosal closure in 7/8 patients at 4 – 16-week follow-up.
Assaf et al., 2014	Prospective study	20	Stages I, II, III (AAOMS 2009)	7 prostate cancer, 8 breast cancer, 2 multiple myeloma, 2 osteoporosis and 1 renal cancer	Bisphosphonates	Preoperatory Doxycycline 100mg/day (1-0-0), 1 week before surgery. Bone resection was performed under VELScope® handpiece guide. Bone resected until bone showed homogeneous green fluorescence.	Fluorescence loss of the necrotic bone in 19 cases.	Yes	19 cases showed no recurrence signals at 4 – 18-week follow-up. 1 case recurred 6 weeks after surgery.
Vescovi et al., 2015	Case report	1	Stage III MRONJ	Multiple myeloma	Zolendronate	VELScope® handpiece guide. Bone ablation with Er:YAG laser until bone showed homogeneous green	Necrotic bone showed no or only pale autofluorescence.	No	Complete mucosal healing in 7-month follow-up

						fluorescence. Intraoperative LLLT with Nd:YAG laser followed by weekly LLLT for 3 weeks.			
Porcaro et al., 2015	Case report	1	Stage III MRONJ	Bone metastasis of clear cell renal cell carcinoma	Zolendronic acid	Preoperatory Doxycycline 100mg 2x/day, 10 days before surgery VELScope® handpiece guide. Bone ablation with Er:YAG laser until bone showed homogeneous green fluorescence. Intraoperative LLLT with Nd:YAG laser followed by weekly LLLT for 3 weeks.	NR	No	Regression from Stage III to stage I MRONJ
Yoshiga et al., 2015	Case series	6	MRONJ resistant to conservative treatment (lesions staging not reported)	4 patients with breast cancer and 2 patients with osteoporosis	4 patients taking zolendronate and 2 patients taking alendronate	Preoperatory Minocycline 100mg 2x/day, 10 days before surgery. Bone resection was performed under VELScope® handpiece guide. Bone resected until bone showed homogeneous green fluorescence.	The margins of MRONJ could not be seen with the naked eye. However, unhealthy bone areas were detected by using VELscope® as nonfluorescence areas.	Yes	In 6 – 12-month follow-up all cases had no bone exposure.
Otto et al., 2016	Prospective study	54	Patients with MRONJ according to the diagnosis criteria by the AAOMS 2009, 2014	45 patients with malignant diseases and 9 patients with osteoporosis	47 patients taking bisphosphonates, 3 patients taking denosumab and 4 reported sequential intake of bisphosphonate and denosumab	Preoperatory Doxycycline 100mg 2x/day, 7 days before surgery. Bone resection was performed under VELScope® handpiece guide. Bone resected until bone showed homogeneous green fluorescence.	NR	No	Successful outcome for 51 patients (of which 4 patients were submitted to a second surgery)
Giovanacci et al., 2017	Case report	1	Stage II MRONJ	Osteoporosis	Alendronate	After removal of the necrotic bone, AF was used to guide the marginal osteoplasty with Er:YAG laser in non-fluorescent areas until the detection of strongly AF bone. Intraoperative LLLT with Nd:YAG laser followed by weekly LLLT for 3 weeks.	Necrotic bone presented as non-fluorescent areas.	Yes	Complete mucosa healing and patient asymptomatic in 12-month follow-up.
Ristow et al., 2017	Ramdomized clinical trial	40	MRONJ stages I – III	34 patients with malignant disease and 6 with osteoporosis	32 received only bisphosphonate only and 8 received sequential bisphosphonates and denosumab	20 patients were submitted to VELScope guided surgical removal of necrotic bone with Tetracycline labeling, and 20 without tetracycline labeling.	There were no differences in the bone fluorescence with and without tetracycline labeling.	No	In the last follow-up 94% of patients treated without tetracycline were asymptomatic, and 89% of patients treated with tetracycline were symptomatic.
Ballardin et al., 2018	Case report	1	Stage II MRONJ	NR	Alendronate	Preoperatory Doxycycline 100mg 2x/day, 7 days before surgery. Bone resection was performed under generic violet light Ultrafire® WF-502B handpiece device guide. Bone	Healthy bone present as bright blue light and necrotic bone present no fluorescence.	No	No recurrence in 2-year follow-up

						resected until bone showed homogeneous bright blue light.			
Giudice et al., 2018	Randomized clinical trial	36	MRONJ stages 1 – 3 (12 patients of each stage)	23 patients with malignant disease and 13 patients with osteoporosis	30 patients received bisphosphonate only, 5 patients received denosumab only, and 1 received sequential bisphosphonate and denosumab	18 patients underwent conventional surgical resection of necrotic bone. 18 patients underwent surgical resection of necrotic bone under VELScope® guide with no tetracycline labeling.	Necrotic bone presented as non-fluorescent areas.	Yes	There were no significant differences in the outcome parameters between the AF and the non-AF groups.
Giovanacci et al., 2019	Clinical case series	8	MRONJ stages II and III	4 patients with malignant disease and 4 patients with osteoporosis	6 patients received bisphosphonates only, 1 patient received denosumab only, and 1 patient received sequential bisphosphonate and denosumab	After removal of the necrotic bone, AF was used to guide the marginal osteoplasty with Er:YAG laser in non-fluorescent areas until the detection of strongly AF bone. Intraoperative LLLT with Nd:YAG laser followed by weekly LLLT for 3 weeks.	NR	Yes	Complete mucosal healing in all patients (follow-up time from 4 to 26 months)
Santos et al., 2019	Case report	1	NR	Osteoporosis	Zolendronate	Bone resection was guided by ultraviolet light fluorescence through the use of 100mg doxycycline twice daily for 10 days prior to surgery.	NR	No	No recurrence in 3-year follow-up
Wehrhan et al., 2019	Clinical case series	10	Stage III MRONJ	Malignant disease	Zolendronate	Preoperatory Doxycycline 100mg 2x/day, 7 days before surgery. Bone resection was performed under VELScope® handpiece guide. Bone resected until bone showed homogeneous green fluorescence.	NR	Yes.Significant decrease of osteocytes and collagen type-I fibers in necrotic, nonfluorescing areas compared to fluorescing bone. Furthermore, the number of osteocytes was higher in fluorescing, clinically viable bone samples. The amount of immature bone was substantially increased in luminescent jawbone. RANK(L) and TRAP expression did not differ between the investigated areas, resembling a generalized decrease in osteocyte_osteoclast function all over the jaw.	NR

MRONJ: medication-related osteonecrosis of the jaws; ORN: osteoradionecrosis; RXT: radiation therapy; NR: not reported; AAOMS: American Association of Oral and Maxillofacial Surgery; LLLT: low level laser therapy; AF: autofluorescence.

ANEXO A – Normas do periódico.

PHOTODIAGNOSIS AND PHOTODYNAMIC THERAPY

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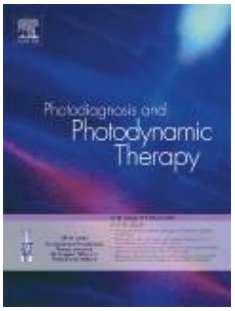

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Kind regards,
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