Research Article

Italian Position Paper (SIPMO-SICMF) on Medication-Related Osteonecrosis of the Jaw (MRONJ)

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Despite being one of the most recently studied oral diseases, MRONJ remains a condition with uncertain and controversial issues. The aim of this updated version of the position paper on MRONJ developed by the Italian Societies of Oral Pathology and Medicine (SIPMO) and of Maxillofacial Surgery (SICMF) is to set forth an original interpretation of the current disputes on MRONJ.

The Expert panel was appointed by the SIPMO and SICMF Board of Trustees in 2010 and comprised a multidisciplinary group of clinicians and researchers with recognized expertise in the field, who tracked the available literature and released two consecutive sets of Italian recommendations on MRONJ in 2013 and 2020. The advance of scientific knowledge and the perceived need for refinements to the previous position papers were recognized by the board panel who approved the submission of this updated version.

This position paper highlights the current research status and provides a different perspective on several debated aspects of MRONJ including risk estimates, disease definition, diagnostic pathway, individual risk assessment, and the fundamental role of imaging in the diagnosis, classification, and management of MRONJ.

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The SIPMO-SICMF expert panel believes essential for the information provided to be disseminated to healthcare providers and patients at increased MRONJ risk. The SIPMO-SICMF Expert Panel recognizes that the statements and recommendations here provided warrant further confirmation and updates and highlight the need for a global and interdisciplinary scientific approach to MRONJ to overcome region-specific challenges.

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Introduction

Osteonecrosis of the Jaw (ONJ) was initially reported only in association with bisphosphonate (BP) treatment.[1] Clinical reports rapidly piled up from the initial description of ONJ in metastatic bone cancer and multiple myeloma patients receiving BPs to include osteoporosis patients treated with oral BPs and more recently patients receiving denosumab (DMB) and several biological agents.[2] Starting from 2014, ONJ related to different medications has been grouped under the term Medication-Related ONJ (MRONJ).[3] The initial frustration of clinicians who were involved in the diagnosis and treatment of a largely unknown disease is now being compensated by the growing body of knowledge that gives space to a profound change in the interpretation of the disease and the way we act to diagnose, prevent, and treat it.[4][5][6][7][8][9][10]

Here, the Authors present the latest update of the Position Paper on MRONJ of the Italian Society of Oral Pathology & Medicine (SIPMO) and the Italian Society of Maxillo-Facial Surgery (SICMF), which was initially released in Italy in 2013 and further edited in 2020.[11][12]

The purpose of this position paper is to point out several MRONJ debated issues and provide updates on the following aspects: epidemiology, disease definition, diagnostic pathway (including the role of

imaging), staging, risk assessment, preventive strategies, and treatment algorithms.

This Position Paper offers concise information for healthcare professionals who prescribe medications that increase the individual risk of MRONJ, and for oral health specialists (e.g., dentists, maxillofacial surgeons, and dental hygienists).

The SIPMO-SICMF Expert Panel highlights the importance of communicating the individual risk of MRONJ to patients and caregivers, to warrant patients' adherence to medical treatment and oral health programs in the long term; it also encourages healthcare professionals to constant literature updating to be guided in clinical decision-making, since new medications with a potential threat to patients come to market; and finally promotes the large-scale dissemination of the present document among the healthcare professionals involved.

Methodology

The SIPMO-SICMF Expert Panel was established in 2010 under the auspices of the SIPMO and the SICMF to appraise the available literature and draft the Italian Recommendations on the diagnosis, prevention, and treatment of ONJ associated with BPs, which were initially published in 2013.[11] The board panel comprised of a multidisciplinary group of clinicians and researchers with a special interest on ONJ. The Italian Recommendations were further revised and published in 2020 to include all the relevant information on the new drugs associated with ONJ and the new categories of patients at increased risk.[12] This updated version represents the standard of care for both oral health care providers and drug prescribers in Italy, and was endorsed by the following Scientific Societies: Italian Association of Medical Oncology (AIOM), Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases (SIOMMMS), Italian Society of Medical and Interventional Radiology (SIRM), Italian Board of Medical Oncology Hospital Directors (CIPOMO), Board of University Professors of Oral Disciplines (CDUO), Italian Society of Osteoncology (ISO). The Recommendations were also endorsed by the National Dental Council Register of Italy and the Interuniversity National Consortium for Bio-Oncology. This 2022 update was purposely written for publication in the English literature and approved by all panellists.

For more details on the research methodology, refer to Supplements (Appendix 1).

Definition

The up-to-date SIPMO-SICMF Expert Panel definition of Medication-Related Osteonecrosis of the Jaw (MRONJ) refers to "*an adverse drug reaction described as the progressive destruction and death of bone that affects the mandible and maxilla of patients exposed to the treatment with medications known to increase the risk of disease, in the absence of a previous radiation treatment*".[13][14]

The initial attempt to define osteonecrosis of the jaws following exposure to BPs (BRONJ) was prompted by the American Association of Oral and Maxillofacial Surgery (AAOMS) in 2007 and 2009. The case definition of BRONJ was based on the presence of "*exposed, necrotic bone in the maxillofacial region without resolution in 8 to 12 weeks in persons treated with a bisphosphonate who have not received radiation therapy to the jaws*".[15][16]

AAOMS case definition of BRONJ was visibly incomplete and raised some criticisms as it was mainly based on the clinical evidence of exposed necrotic bone, leaving patients with signs of osteonecrosis other than bone exposure undiagnosed (i.e., non-exposed ONJ variant).[4][5][6][7][8][9][10]

AAOMS case definition was finally updated in 2014 to include "*probing bone fistula*" in the clinical presentation of the disease. The acronym also changed to MRONJ to embrace new antiresorptive medications and antiangiogenic drugs that have been linked to the development of ONJ. The AAOMS definition has not been changed since then.[3][17]

The SIPMO-SICMF Expert Panel initially recognized the limitations of the 2007 and 2009 AAOMS BRONJ definition and since 2012 proposed a comprehensive definition of BRONJ that was further updated in 2018 to include ONJ-related medications other than BPs.[9][13]

Patients may be considered to have MRONJ if all the following characteristics are present: [9][14]

- Current or previous treatment with bone-modifying agents (BMAs) and/or antiangiogenic agents (AAs)
- Clinical and radiological findings of progressive bone destruction
- No history of radiation therapy to the jaws or the presence of primary oral malignancy or metastatic disease to the jaws.

Differential diagnosis should also disclose the presence of primary oral malignancy or metastatic disease.[18][19] Osteoradionecrosis should be suspected in patients with a history of radiation therapy

to the jaws.[20]

The SIPMO-SICMF Expert Panel is concerned that the AAOMS case definition of MRONJ, which is mainly based on non-specific clinical aspects of the disease, may prove unreliable and suggests that MRONJ diagnosis should be reached through a differential diagnosis against bone conditions with similar clinical and radiological features.

This position has been recently confirmed by the European Task Force on MRONJ, as patients may present with medical and oral conditions not to be confused with MRONJ.[21]

Epidemiology

Risk estimates of MRONJ are largely incomplete, biased, and difficult to compare. Measures like incidence, prevalence, occurrence, and frequency are often misinterpreted and generated data of limited value due to the inconsistency of available studies, short-term observation, and the lack of cumulative long-term incidence.

Use of the 2007 AAOMS definition of MRONJ and to a minor extent that of 2014 to adjudicate confirmed MRONJ cases in large clinical trials on BMAs from the last 15 years could have contributed to underestimating the risk of developing osteonecrosis and keep the epidemiologic estimates low.[10][22][23][24][25]

MRONJ risk profiles have gradually changed in the last two decades since the introduction of new medications to the market and the approval of supplementary indications for drugs already in use. Consequently, new categories of patients are being recognized at increased MRONJ risk.

At present, the SIPMO-SICMF Expert Panel recognizes four main categories of patients at increased MRONJ risk that are listed below:

a. *Cancer patients with Bone Metastases or Multiple Myeloma (BM/MM)*, commonly receiving monthly high doses of BMAs (HD-BMAs) in combination with other drugs (e.g., chemotherapy, endocrine hormonal therapy, immunotherapy, antiangiogenics and other biological agents). These patients present with several comorbid conditions, and show heterogeneous but relatively limited expected survival, though improved in recent years;[26][27]
b. *Patients suffering from osteoporosis (OP) and other non-malignant diseases* receiving low doses of BMAs (LD-BMAs). These patients are often elderly and with several comorbid conditions, but are

likely to have longer expected survival than BM/MM patients;[28]

c. *Cancer patients without bone metastases* receiving LD-BMAs to reduce the risk of non-metastatic bone fractures due to Cancer Treatment-Induced Bone Loss (CTIBL), and/or to improve prognosis ("adjuvant" treatment of prostate and breast cancer patients);[29][30]

d. *Patients with Giant Cell Tumour of Bone (GCTB)*; there are few but interesting data about GCTB patients treated for years with a monthly injection of DMB (HD-DMB), who display an increased risk of MRONJ occurrence.[31]

The SIPMO-SICMF Expert Panel agrees that BM/MM patients taking HD-BMAs are exposed to the highest risk of MRONJ, with data estimates ranging between 1% and >20%. Recent systematic and narrative reviews show a higher risk of MRONJ after zoledronic acid in comparison with other BPs (e.g., pamidronate, ibandronate) and a higher risk for DMB in comparison with zoledronic acid. MRONJ risk is thought to increase with time. In the case of BM/MM patients, Kaplan-Meier actuarial risk estimation curves show that MRONJ risk increases with the years of treatment.[27][32][33][34][35][36][37][38] Whether the length of BMA treatment (i.e., duration and frequency of drug exposure) prevails over the observation time (i.e., patient survival) it is not fully understood. In any case, long treatment duration and prolonged survival rates raised the actuarial risk up to 30% at 8-year observation in some metastatic cancer patient subgroups. [36]

On the contrary, the risk of MRONJ in OP patients receiving LD-BMAs is generally below 1%, with the exception of some subgroups at higher risk (e.g., patients with autoimmune or rheumatologic diseases). Real-life observation of the majority of MRONJ cases in OP patients after some years of LD-BMA treatment reflects the long-term results of the FREEDOM Extension study (<1%).[39]

The possible role of romosozumab in inducing MRONJ in OP patients is uncertain.

MRONJ occurrence ranges between 0% and 5% in breast and prostate cancer patients treated with BMAs in the "CTIBL prevention" and "adjuvant" settings, but data are scarce and somewhat questionable.[40][41][42][43]

MRONJ frequency varies among GCBT patients receiving DMB, ranging between 1% and 13%.[44][45] Additional studies are needed to confirm the risk estimates of MRONJ among CTIBL and GCBT patients.

Most relevant MRONJ quantitative estimates of patients at risk of MRONJ are detailed in Supplement (Appendix 2, Table 1).

The SIPMO-SICMF Expert Panel recognizes the existence of new populations of patients at risk of developing MRONJ, since the range of indications for the use of BMAs and AAs continues to expand.

After 2009, the use of AAs (e.g., tyrosine-kinase inhibitors; mammalian target of rapamycin inhibitors; anti-vascular endothelial growth factors), alone or in combination with BMAs, has been linked to MRONJ occurrence in different patient populations. However, risk estimates of MRONJ due to AAs could not be drawn from isolated case reports and case series so far.[46][47]

MRONJ diagnosis

As previously mentioned, MRONJ has no unique definition, and controversies exist concerning the diagnostic process to be adopted (e.g., exposed vs non-exposed variant, the role of imaging).

Ideally, both the definition and the diagnostic process of a given disease are intimately linked. Thus, a rigorous disease definition (i.e., case definition) can only lead to a definitive diagnosis when it is composed of signs and symptoms that are disease-specific (e.g., pattern recognition model). This is not the case with MRONJ, which is known to present with several non-specific clinical signs and symptoms, though some are more frequent than others (i.e., bone exposure and probing bone fistulas).

When a case definition is unlikely to be exhaustive, which is the case of AAOMS MRONJ definition, a less restrictive definition should be adopted and a logical diagnostic workflow designed including clinical and instrumental examinations to identify all potential features of the disease and thus reducing the risk of misdiagnosis (*e.g.*, hypothetical-deductive or analytical model).[48][49]

As a matter of fact, the SIPMO-SICMF Expert Panel developed a diagnostic work-up of MRONJ that is based on the clinical and imaging features of the disease.[9] The SIPMO- SICMF workflow is detailed in the next section.

Clinical features of MRONJ

MRONJ is a multifaceted disease of the bone that can present with different clinical signs and symptoms (Table 1).

Clinical signs and symptoms	
• Abscess • Bone exposure • Cutaneous fistula • Fluid discharge from the nose • Halitosis • Intraoral fistula • Jaw pain of bone origin • Mandible fracture (fragment mobility) • Mandibular deformation	• Mucosal inflammation • Non-healing post-extraction socket • Numbness of the lips* • Purulent discharge • Soft-tissue swelling • Spontaneous loss of bone fragments • Sudden dental/implant mobility • Toothache • Trismus

Table 1. Clinical signs and symptoms suspected for MRONJ (modified from Campisi *et al.*[12])

** Caused by irritation of the inferior alveolar nerve and/or infraorbital nerve.*

Despite the exposure of necrotic bone being the most common clinical feature of MRONJ, there are several other clinical signs and symptoms associated with MRONJ, including but not limited to probing bone fistula through the mucosa.[3][12]

Among symptoms, the most frequently reported is pain, though it is absent at MRONJ onset in many patients.[17][21][50][51] Numbness of the lips (i.e., Vincent's symptom) is also frequently reported by patients, but it is usually associated with advanced MRONJ.[52][53][54]

A peculiarity of MRONJ is that clinical signs and symptoms are not disease-specific, as they can be found in many other conditions, which makes the adoption of a purely clinical MRONJ case definition impractical in routine clinical care.[55]

Patients at risk for MRONJ can present with other common clinical conditions, including but not limited to plaque-related gingivitis/periodontitis, dental and periapical disease, benign fibro-osseous lesion of the jawbones, alveolar osteitis, chronic sclerosing osteomyelitis, and infectious osteomyelitis.[21] Overall, these conditions need to be excluded to make a MRONJ diagnosis. Likewise,

a differential diagnosis should also disclose primary oral malignancy and metastatic disease to the jaw. [18][56][57]

Since MRONJ is a disease that mostly affects the jawbone architecture, imaging has long been considered a necessary part of the diagnostic process by the SIPMO-SICMF Expert Panel.[9]

Imaging features of MRONJ

Similarly to clinical MRONJ features, radiological signs are not specific and cannot be used alone to diagnose MRONJ.[58] Several imaging features have been commonly associated with MRONJ, including but not limited to focal or diffuse bone marrow sclerosis, osteolytic changes, periodontal space widening, thickening of the inferior alveolar nerve canal, and sequester formation (Table 2).

Radiological signs of MRONJ	Plain radiographs	CT-based radiological investigations
Cortical erosion	X	✓
Diffuse bone marrow sclerosis*	✓	✓
Focal bone marrow sclerosis*	X	✓
Opacified maxillary sinus	✓	✓
Osteolytic changes	X	✓
Osteolysis extending to the maxillary sinus	X	✓
Osteosclerosis of adjacent bones (zygoma and hard palate)	X	✓
Pathologic fracture	✓	✓
Periodontal space widening	✓	✓
Periosteal reaction	✓	✓
Persistent post-extraction socket	✓	✓
Sequester formation	✓	✓
Sinus tract**	X	✓
Thickening of the alveolar ridge	✓	✓
Thickening of the lamina dura	✓	✓
Thickening of the inferior alveolar nerve canal	✓	✓
Trabecular thickening	X	✓

Table 2. Radiological signs suspected for MRONJ (modified from Campisi *et al.*[12])

* *Sclerosis: trabecular bone disorganization and poor corticomedullary differentiation.*

** *Oroantral, oronasal or orocutaneous communication due to bone destruction.*

Legend

✓: detectable. X: undetectable or detectable only in advanced MRONJ cases

Less clear is how to distinguish between early and late MRONJ signs. In fact, the ability to detect early bone changes in MRONJ is largely influenced by the imaging modality used.[59]

No consensus has yet been reached regarding the imaging technique of choice to diagnose and screen MRONJ. Nevertheless, plain radiographs and CT have been adopted in many centres for their ability to image the underlying bone condition and display the radiological features of MRONJ in almost every patient.[60][61][62][63] Their wide availability, routine use among dental practitioners for the differential diagnosis of common dental conditions, ease of interpretation, limited contraindication and cost further support the use of plain radiograph and CT.[64]

Dental x-rays and panoramic radiographs are the radiographic standard of care in routine dental practice and can help the dental practitioner to evaluate and definitively diagnose many oral diseases and conditions, with minimal radiation exposure.[64][65][66] Panoramic radiograph offers a fundamental understanding of the lesions and reveals bone changes suggestive of MRONJ[67][68], but it is much less accurate than 3D imaging, especially in early disease onset.[69][70]

Magnetic Resonance Imaging (MRI) and other investigations, including bone scintigraphy or Single Photon Emission Computed Tomography (SPET-CT), can be useful adjuncts in selected cases and specific settings.[61][71][72][73]

The SIPMO-SICMF Expert Panel considers dental x-rays and panoramic radiographs useful first-line screening tools to differentiate among dental conditions that could mimic MRONJ in patients receiving BMAs and/or AAs. Nevertheless, the inclusion of second-line CT-based imaging modalities, such as Cone-Beam (CBCT) and multidetector (MDCT) computed tomography, is essential to disclose early signs of MRONJ, anticipate diagnosis and correctly define stage and treatment options.

Bone biopsy

Despite the histology of bone can easily disclose necrotic bone from viable bone also in MRONJ patients, a bone biopsy is generally considered an unnecessary procedure that could exacerbate symptoms and disease progression.[14]

Location of the proper site for bone biopsy can be challenging in non-exposed MRONJ variants and it would require mucosal incisions to expose the underlying bone, amplifying the risk of bone exposure.

The use of bone biopsy in the diagnostic work-up of MRONJ is only indicated to disclose the suspect of malignancy.[18][19][57][74][75][76]

The SIPMO-SICMF Expert Panel favours a non-invasive diagnostic approach, in which bone biopsy should be provided only in the presence of suspected primary oral malignancy or metastatic bone disease in patients receiving medications at increased MRONJ risk.

MRONJ case adjudication pathway

Overall, the SIPMO-SICMF Expert Panel recommends the combined use of clinical and radiologic signs to diagnose MRONJ, which likely increases the chance of a correct diagnosis by excluding common oral conditions that could be confused with MRONJ.

In this view, a **"suspected MRONJ case"** is defined by the presence of at least one clinical sign/symptom in a patient receiving BMAs and/or AAs. Instead, a **"confirmed MRONJ case"** is defined by the concomitant presence of at least one clinical sign/symptom suggestive of MRONJ and the radiologic impairment of the jaw at Computed Tomography (CT) in a patient receiving BMAs and/or AAs.

Diagnostic workup

The SIPMO-SICMF Expert Panel endorses the adoption of a 3-Step diagnostic work-up of MRONJ as it follows (Figure 1):

Step 1*. Identification of a MRONJ suspected case*. Clinical suspicion should be raised whenever a patient receiving medications at increased MRONJ risk presents with signs and symptoms in the oral cavity like those described in MRONJ. Analysis of the patient's medical and dental history informs on the existence of systemic and local risk factors that could be linked to the disease.

Step 2*. Differential diagnosis of a MRONJ suspected case*. Oral examination can disclose several oral conditions, but supplemental radiological investigations are required to make the correct diagnosis. 2D imaging modalities (dental x-ray and panoramic radiograph) are useful tools to exclude the entire spectrum of oral conditions presenting clinical and radiological signs and/or symptoms overlapping with the initial phases of MRONJ.

Step 3*. MRONJ case confirmation*. Every suspected MRONJ case that goes beyond the second step is likely to be a MRONJ case. Second-line CT-based imaging (MDCT/CBCT) is needed to confirm the diagnosis

and accurately stage MRONJ.

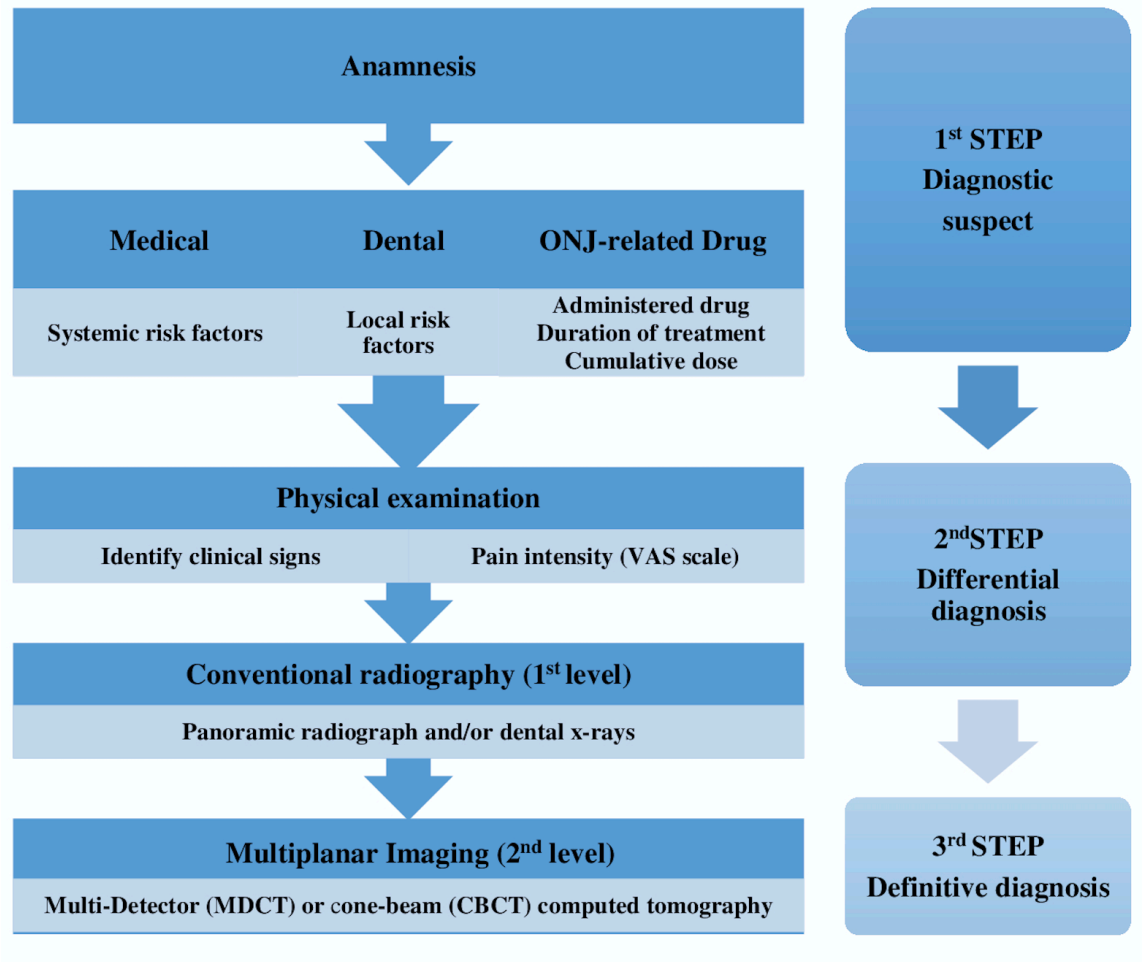

Figure 1. Diagnostic Work-up of MRONJ (modified from Campisi *et al.*[12])

Staging

Ideally, a sound staging system measures disease severity and identifies clusters of patients who require similar treatment and have similar expected outcomes. Objective measures of disease severity and extension should be used to assess disease progression.[77]

On purpose, the SIPMO-SICMF Expert Panel developed a 3-stage clinical-radiological classification system of MRONJ centred on the presence of bone marrow sclerosis at CT (Table 3) in adjunct to the patient's clinical findings.[9]

MRONJ clinical-radiological staging system	
Stage 1	**FOCAL MRONJ**: *presence of at least 1 clinical sign/symptom and increased bone density limited to the alveolar process at CT, w/ or w/o additional radiological signs.* **Clinical signs and symptoms:** abscess, bone exposure, halitosis, intraoral fistula, jaw pain of bone origin, mucosal inflammation, non-healing post-extraction socket, soft-tissue swelling, spontaneous loss of bone fragments, sudden dental/implant mobility, purulent discharge, toothache, and trismus. **CT signs:** trabecular thickening and/or focal bone marrow sclerosis, w/ or w/o cortical erosion, osteolytic changes, thickening of the alveolar ridge, thickening of the lamina dura, persistent post-extraction socket, periodontal space widening, thickening of the inferior alveolar nerve canal, sequester formation. Stage 1a: asymptomatic Stage 1b: symptomatic (presence of pain and/or purulent discharge)
Stage 2	**DIFFUSE MRONJ:** *presence of at least 1 clinical sign/symptom and increased bone density extending to the basal bone at CT, w/ or w/o additional radiological signs.* **Clinical signs and symptoms:** same as Stage 1, plus mandibular deformation, and numbness of the lips. **CT signs:** diffuse bone marrow sclerosis, w/ or w/o cortical erosion, osteolytic changes, thickening of the alveolar ridge, thickening of the lamina dura, persistent post-extraction socket, periodontal space widening, thickening of the inferior alveolar nerve canal, sequester formation, periosteal reaction, and opacified maxillary sinus. Stage 2a: asymptomatic Stage 2b: symptomatic (presence of pain and/or purulent discharge)
Stage 3	**COMPLICATED MRONJ:** *presence of at least 1 clinical sign/symptom and increased bone density extended to the basal bone at CT, plus one or more of the following:* **Clinical signs and symptoms:** cutaneous fistula, mandible fracture, fluid discharge from the nose. **CT signs:** osteosclerosis of adjacent bones (zygoma and hard palate), pathologic fracture, osteolysis extending to the maxillary sinus, sinus tract (oroantral, oronasal fistula, orocutaneous). Stage 3a: asymptomatic Stage 3b: symptomatic (presence of pain and/or purulent discharge)

Table 3. Clinical and radiological MRONJ staging system (modified from Campisi *et al.*[12])

Bone marrow sclerosis is the most frequent radiological sign of MRONJ, and it is also detected in the early phases of the disease.[58] The SIPMO-SICMF staging system recognizes the presence of a focal disease stage (Stage 1), when bone marrow sclerosis is limited to the alveolar jawbone (Figure 2); a diffuse disease stage (Stage 2), when bone marrow sclerosis encompasses the basal bone (Figure 3); and a complicated stage (Stage 3), which comprises of diffuse bone marrow sclerosis along with clinical and radiological signs of advanced disease (Figure 4).

The presence of pain and purulent discharge does not translate into a worsened disease stage as they can manifest repeatedly through the course of the disease. For this reason, the SIPMO-SICMF staging system includes (a) asymptomatic and (b) symptomatic forms within the same disease stage. This prevents the so-called "ping-pong phenomenon", which describes the cyclic transition (stage downgrading/upgrading) of MRONJ patients from one stage to another as a result of the antibiotics given to treat recurrent infection with associated pain.[9]

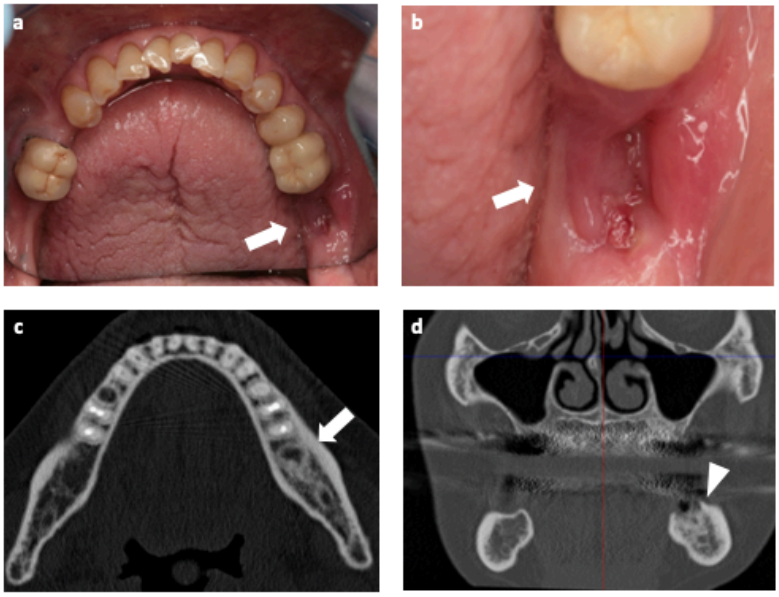

Figure 2. Stage 1, Focal MRONJ. Panel a: clinical view showing non healing post-extraction socket in the left posterior mandible (white arrow). Panel b: close-up view of the same lesion displays probing bone mucosal fistula (white arrow), gingival swelling and inflammation. Panel c and d: axial and coronal CT reconstructions show bone marrow sclerosis that is limited to the alveolar jawbone (white arrow and white arrow-head, respectively).

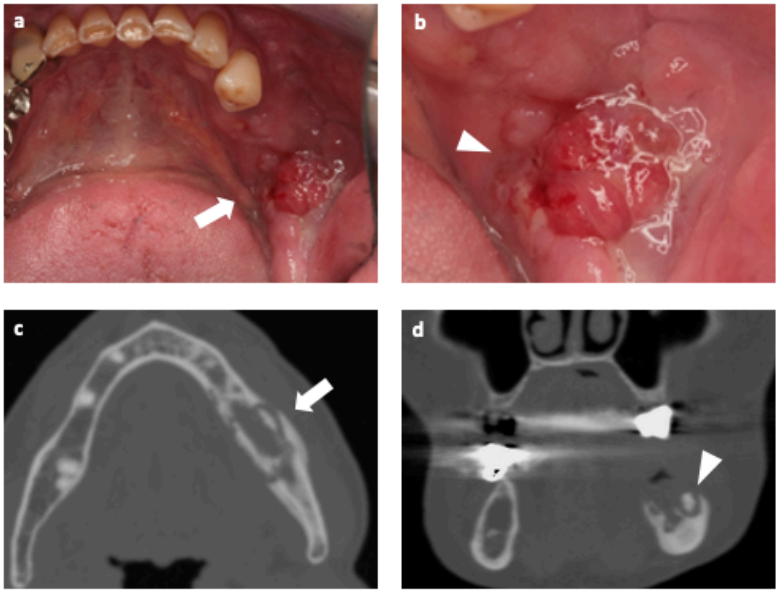

Figure 3. Stage 2 (Diffuse MRONJ): Panel a: clinical view showing hyperaemic and swollen gingiva of the alveolar socket filled with granulation tissue (white arrow). Panel b: close-up view of the lesion (white arrow-head). Panel c and d: axial and coronal CT reconstructions show bone marrow sclerosis that reaches the basal bone; bone sequestration and periosteal reaction (white arrow and white arrow-head, respectively).

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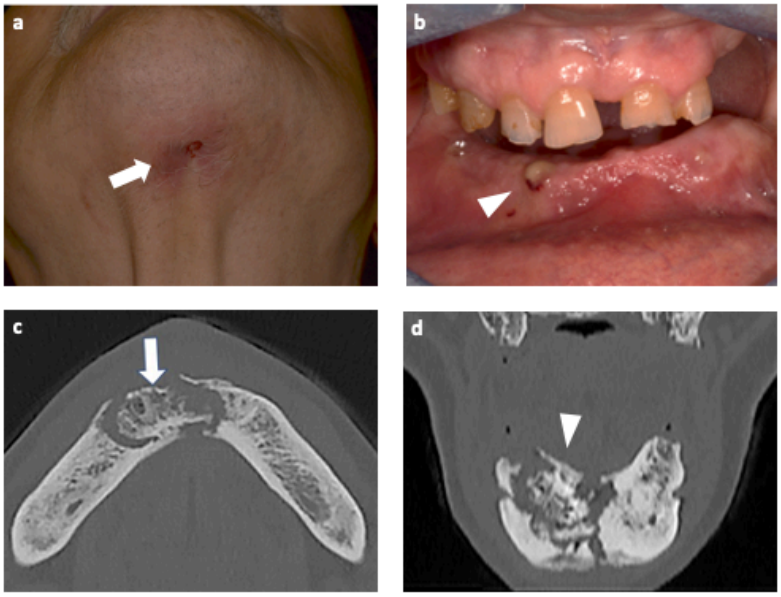

Figure 4. Stage 3, Complicated MRONJ. Panel a: clinical view showing a submental cutaneous fistula (white arrow). Panel b: intra-oral view showing single mucosal sinus track with purulent discharge at the level of the inferior gingiva (white arrow). Panel c and d: CT axial and coronal reconstructions display diffuse bone sclerosis encompassing the basal bone, sequester formation and pathologic mandibular fracture (white arrow and white arrow-head, respectively).

Historically, AAOMS introduced in 2007 a classification system of BRONJ based exclusively on the clinical presentation of the disease (presence of exposed necrotic bone, pain, infection, and clinical signs suggestive of complicated disease) to assign patients to different stages of disease severity (Stages 1-3) and treat it accordingly. While in current widespread use, the AAOMS staging system raised several criticisms since its initial publication, as many cases of MRONJ without exposed bone were being excluded from the diagnosis and treatment.[16]

Despite two consecutive updates in 2009 (introduction of "Stage 0") and 2014 (inclusion of patients with probing bone fistula in the running definition and classification system), AAOMS staging of MRONJ remained basically centred on the clinical presentation of the disease.[3][15]

The SIPMO-SICMF Expert Panel early recognized that the most significant weaknesses of the AAOMS staging system were the omission of radiological criteria to diagnose and classify the disease, and the

underestimation of the real extent of bone involvement with the use of clinical signs and symptoms only.[9]

Despite many authors had recommended the urgent need to include imaging criteria in the diagnosis and staging of MRONJ [8][10][21][60][78], AAOMS Expert Panel maintained the current classification system with no apparent modifications also in the latest 2022 update, where they formally reject the idea of including radiological features, as these latter "*may overestimate the true disease frequency by including false positives in the numerator*".[17]

The SIPMO-SICMF staging system has two major strengths when compared with the AAOMS classification: 1- it enables clustering of patients with similar disease extent in the same stage and proper delivery of stage-related therapies with increasing intensity;[79] 2- it considers clinical signs of recurrent bone infection and associated pain independent variables that cannot trigger any stage transition, as they do not correlate with the extent of bone involvement.[69]

The SIPMO-SICMF staging system of MRONJ has remained unchanged since its introduction in 2012 and it has been increasingly used in Italy for the last 10 years.[79][80][81][82][83][84][85][86][87][88][89]

The SIPMO-SICMF Expert Panel encourages the adoption of the proposed staging system on a large scale to assess MRONJ extent and to deliver stage-related treatments.

Risk factors of MRONJ

MRONJ is a multifactorial disease for which aetiology is not fully understood. While knowledge of risk factors associated with MRONJ continues to expand, the evolution of cancer therapies is likely to generate new patient populations at increased MRONJ risk. Several medical and dental comorbidities have been associated with an increased risk of BRONJ, while studies on more recent medications are still limited.[46][90][91][92]

MRONJ risk factors can be divided into three main groups: medication-related, systemic, and local (Table 4).[3][21][93]

Drug-related	*Molecule type*	• Bisphosphonates (BPs) • Denosumab (DMB) • Antiangiogenic drugs (AA)	
	Dosage and schedule		
	Duration of treatment		
	Cumulative dose		
	Concomitant therapies	• Chemotherapy and anticancer hormone therapy • Corticosteroids • Immunotherapy • Medications inducing osteoporosis • Thalidomide	
Systemic	*Underlying disease*	• Malignant disease • Osteoporosis	
	Comorbidities	• Chronic kidney disease • Diabetes mellitus • Hypocalcemia/Hyperparathyroidism and Osteomalacia/Vitamin D deficiency • Lifestyle habits (e.g., smoking) • Rheumatoid arthritis • *Others*	
Local	*Dental, periodontal, periapical, and peri-implant infection*		
	Dental implant surgery		

	Dentoalveolar surgery		
	Ill-fitting dentures (removable prostheses)		
	Anatomical variations	• Palatal and mandibular tori • Pronounced mylohyoid ridge	
	Tooth extraction		

Table 4. Risk factors of MRONJ reported in the literature

Medication-related risk factors

There are two main classes of medications linked to MRONJ onset:

- bone modifying agents (BMAs): bisphosphonates (BPs) and denosumab (DMB);
- antiangiogenic agents (AAs): anti-VEGF (e.g., bevacizumab), TKIs (e.g., sunitinib) and mTORs (e.g., everolimus).

Other molecules have been sporadically associated with MRONJ onset but they still await confirmation from clinical studies.[90]

The following aspects are relevant to assess the medication-related risk: *molecule type and dosing schedule, duration of treatment, and cumulative dose*.

BMA therapy reduces osteoclastic activity, with a consequent decrease in bone resorption and inhibition of bone turnover. BMAs proved effective in preventing skeletal-related events in metastatic cancer patients and the risk of fragility fractures due to osteoporosis.[94][95]

Bisphosphonates (BPs), and nitrogen-containing BPs (NBPs) in particular, have a high affinity for bone and persist at the skeletal level for a long period of time.[96]

On the opposite, DMB does not accumulate in the bone and suppresses bone turnover through the inhibition of the receptor activator of the nuclear factor-kB ligand complex.[96][97] DMB has a mean

half-life of approximately 30 days and its effect on bone resorption gradually declines within six months after the last dose. [98][99][100][101][102]

AAs act against pro-angiogenetic factors, with a modification of the mechanisms regulating bone repair and a reduction in bone remodelling.[103] MRONJ onset is a rare occurrence in patients treated with AAs while the risk of MRONJ likely increases when these drugs are coupled with BMAs.[26] Also, AAs possess a short half-life (e.g., 20 days for bevacizumab, 40-60 hours for sunitinib) as compared with BMAs, and they seem to be characterised by a lower accumulative effect in the bone. [47][104]

The *dosage and schedule* of BMAs are major risk factors, with the oncological dosing of intravenous BPs (e.g., zoledronate 4mg/month) and subcutaneous DMB (120mg/month) being responsible for the highest risk of MRONJ as compared with low-dose oral/parenteral BPs and subcutaneous DMB (60mg/6month) given to OP and non-metastatic cancer patients.[89][105][106][107]

The *duration of treatment* is also a relevant aspect to be considered. Most clinical studies on BM/MM patients receiving IV BPs report a median time to MRONJ onset of 1.5-2 years, despite the great variability of the published data, and some cases of MRONJ occurred after many years of continuous treatment.[36] In contrast, most cases of MRONJ in OP on BPs oral therapy usually occur after 2-3 years of treatment, with an average of 4.6 years.[96]

While several studies report a similar time-to-onset of MRONJ for BM/MM patients receiving high-dose BPs and DMB, recent findings suggest that DMB-associated ONJ occurs earlier than BRONJ in cancer patients.[32][35] In addition, the switch from BPs (i.e., zoledronic acid) to DMB significantly increases the risk of MRONJ onset in BM/MM patients (see Supplement – Appendix 2).[32][35]

In BM/MM patients treated with monthly doses of BPs, the *cumulative dose* reflects the dosage and dosing intervals, the duration of treatment, and the affinity of any given molecule for the target tissue. As the cumulative dose of BPs increases (above all with monthly administrations of zoledronic acid), the cumulative incidence of MRONJ occurrence rises.[36][108]

At present, long-term estimates of MRONJ are scanty in BM/MM patients receiving monthly DMB injections.[36][109] Similarly, little data exist on the effect of cumulative dose of BMAs on the risk of MRONJ onset in OP patients.[110]

Concomitant medical treatments, chemotherapy, anticancer hormone therapy and corticosteroids in particular, are reported as potential additional risk factors for MRONJ.[111]

Since the introduction of yearly iv infusion of Zoledronic acid and six-monthly subcutaneous injection of DMB to prevent fragility fractures in OP patients, it has become clearer that the route of administration of BMAs plays a minor role in promoting MRONJ onset as compared with the other medication-related risk factors described. In fact, the frequency of MRONJ among OP patients remains much lower than for patients receiving high-dose BMAs.[25][112]

Overall, the SIPMO-SICMF expert panel suggests downsizing the route of administration of BMAs as a risk factor of MRONJ.

Other known drug-related risk factors are described in Table 4.

Systemic risk factors

Several malignant and systemic diseases have been closely associated with an increased MRONJ risk. BM/MM patients have the greatest susceptibility to MRONJ. Multiple Myeloma, and metastatic breast and prostate cancer are responsible for the large majority of MRONJ cases reported, followed by metastatic renal cell cancer. Many other cancer types were reported to be at increased risk of MRONJ development, who merit close attention in future clinical studies.[90][113] Also GCTB has been recently associated with an increased risk of MRONJ.[31][44][45]

Osteoporosis is the most commonly reported non-malignant systemic disease associated with MRONJ onset; other conditions are rheumatoid arthritis, Sjogren syndrome, and other autoimmune diseases. [89][105][106][107][114]

Systemic conditions for which BMAs and AAs are indicated can be a risk factor *per se*, although frequently associated comorbidities (e.g., diabetes mellitus, hypertension, etc) could contribute to the individual risk. This is particularly true for the elderly population and for cancer patients.[90][113]

Hypocalcaemia and hyperparathyroidism, osteomalacia and vitamin D deficiency have been linked to MRONJ onset in the past years[115][116][117][118], but recent data oppose this hypothesis.[119]

Other systemic risk factors have been reported to increase the risk of MRONJ, most of which still await validation (see Table 4).

The SIPMO-SICMF expert panel recommends clinicians record all medication-related and systemic risk factors of patients at increased MRONJ risk at first consultation, and keep their records updated for the entire period of surveillance.

Local risk factors

All pathological conditions, which directly or indirectly compromise optimal oral health, increase the risk of MRONJ in a patient receiving BMAs and/or AAs (Table 4).

Tooth extraction has been traditionally considered the major local risk factor of MRONJ. The link between dental extraction and MRONJ development was referred to as the surgical trauma caused to the alveolar bone with a reduced bone turnover.[21][90][113][120][121][122][123][124][125]

Worthy of note, dental, periapical and periodontal infections are the first cause of dental extraction and all these local risk factors are likely to act synergically in MRONJ onset.[126][127][128]

Several experimental and clinical studies have shown the presence of early clinical, radiological, and histologic signs suggestive of MRONJ in the alveolar socket of compromised teeth before or at the time the extraction takes place, suggesting that dental, periapical and periodontal infection may play an even more relevant role than the surgically induced bone trauma.[21][129][130][131][132][133][134][135][136][137][138]

Chronic dental, periapical, and periodontal infections are generally associated with inflammatory responses that can alter osteoclast numbers and function through several pathways (e.g., direct stimulation of bone resorption, and stimulation of the release of inflammatory mediators). Overall, sites with increased bone turnover, such as extraction sites or areas of periodontal and periapical inflammation, are exposed to higher BMA intake which could explain the susceptibility of such areas to MRONJ onset.[131][132][133][136][139][140] Moreover, the presence of inflammatory cells in the alveolar bone seems to affect the physiological process of wound healing after the extraction of teeth with periapical o periodontal disease, in the presence of BMAs.[141][142][143]

Similarly, it has been suggested that infection around dental implants may represent a notable risk factor for MRONJ development.[144][145][146][147][148]

Although cases of implant surgery-triggered MRONJ have been reported soon after placement of dental fixtures in patients receiving HD-BMA therapy, the development of infectious-inflammatory processes around dental implants (e.g., peri-implantitis) is more likely to trigger MRONJ in patients who had been implanted well before the start of BMAs.[146] The absence of a barrier effect at the bone-implant interface and the development of occlusal microcracks under masticatory load conditions may partly explain the occurrence of delayed MRONJ around dental implants.[145] That said, also OP

patients receiving low-dose BPs are potentially exposed to the risk of delayed MRONJ onset around dental implants after some years of therapy, but incidence/frequency is seemingly very low.[14,5][14,7] [14,9]

Pressure sores from ill-fitting prostheses represent another established local risk factor for MRONJ. Inadequate dentures that compress oral mucosa against bony prominences cause mucosal injury with subsequent bone exposure.[150][151]

Several cases of "spontaneous MRONJ" have been frequently described in the past to distinguish them from surgically-triggered MRONJ.[152][153] With the growing body of knowledge that most of those cases were triggered by dental and periodontal infections, reports of spontaneous MRONJ cases have become marginal. At present, a "spontaneous case" defines a patient receiving medications at increased MRONJ risk, who presents with signs and symptoms of MRONJ in the absence of local risk factors. Genetic factors may play a role in these patients.[154]

Other known local risk factors are described in Table 4.

In conclusion, the SIPMO-SICMF Expert Panel reaffirms that dental, periapical, periodontal, and peri-implant infections are the main local risk factors for MRONJ, and it is concerned that many MRONJ patients in the past could have been misclassified as post-extraction cases, generating the idea that tooth extraction should be avoided in patients receiving BMA therapy.

Other groups of experts have come to the same conclusion and support the idea that tooth extraction has a clear preventative role of MRONJ, when properly and timely executed.[21][155]

Individual risk assessment

Beyond the different levels of risk recognised for the outlined categories of patients receiving BMAs and/or AAs (see Epidemiology section), individual risk assessment depends on the risk factors to which a single patient is exposed (Table 4).

Despite the lack of any reliable formula that can infer the individual risk of MRONJ occurrence at present, *the SIPMO-SICMF Expert Panel believes that is possible to grade the individual risk of MRONJ from time to time.* Though MRONJ cannot develop without exposure of patients to medications associated with an increased MRONJ risk, medication-related risk factors are decisive to figuring out the individual risk assessment, in combination with systemic risk factors to which a single patient is

exposed. Although local risk factors do not directly link to any risk category, they can trigger MRONJ development at any time if left untreated.

For the sake of better understanding, the SIPMO-SICMF Expert Panel agreed to showcase individual MRONJ risk separately for patients receiving HD-BMA and LD-BMA therapy.

Patients at increased risk of MRONJ receiving High-Dose BMAs

The SIPMO-SICMF Expert Panel considers that patients can be subgrouped based on the relative risk of MRONJ (R) (Figure 5) as follows:

- HD-BMAs R_0: antiresorptive therapy has been planned but not yet commenced. R_0 patients display a virtually null MRONJ risk.
- HD-BMAs R_+: ongoing antiresorptive therapy, in the absence of additional systemic risk factors. R_+ patients display an increased risk of MRONJ occurrence. MRONJ risk upraises in the presence of unresolved oral triggers.
- HD-BMAs R_{++}: ongoing antiresorptive therapy, in the presence of additional systemic risk factors. MRONJ risk further upraises in the presence of unresolved oral triggers. These patients, including those also receiving antiangiogenic agents, display the highest MRONJ risk and should be carefully monitored. Based on the available literature, such risk is maintained a long time after drug discontinuation in the case of patients receiving BPs.

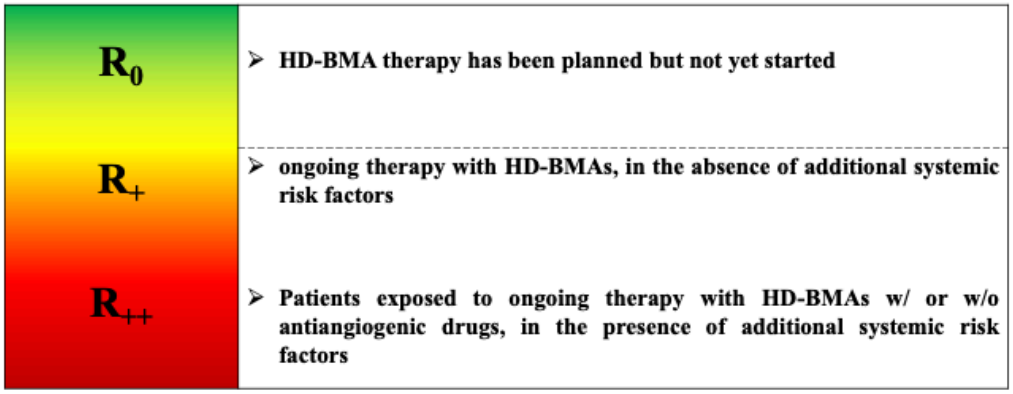

Figure 5. MRONJ risk gradient in patients receiving High-Dose (HD) BMAs (modified from Campisi *et al.* [12])

N.B. Local triggers are not used to define the risk gradient for each patient's category. Instead, they can precipitate MRONJ development when left unresolved. Patients at increased risk of skeletal-related events (SREs) who are shifted from HD-BPs to HD-DMB treatment represent a separate group where the cumulative dosage of the BP leads to the individual risk of MRONJ occurrence.

Within the limitation of the available evidence, the SIPMO-SICMF Expert Panel favours the inclusion of patients with Giant Cell Tumour of Bone (GCTB) on DMB therapy in the same at-risk category of patients receiving HD-BMAs, in light of the designated dosage and monthly schedule of BMA and the comparable frequency of MRONJ onset observed in these patients so far.

Patients at increased risk of MRONJ receiving Low-Dose BMAs

Patients receiving low-dose BMA therapy can be stratified into two subgroups, based on the relative risk of MRONJ (R) (Figure 6):

- LD-BMAs R_0: patients who are about to start BMAs, and patients who have been on BMA therapy for less than 3 years (current or previous users), in the absence of additional systemic risk factors. R_0 patients display a MRONJ risk comparable to the general population.

- LD-BMAs R_X: patients who received BMAs for more than 3 years, and patients who received BMAs therapy for less than 3 years in the presence of additional systemic risk factors. R_x patients display an increased MRONJ risk that rises in the presence of unresolved oral triggers. This risk remains very low as compared with patients who are receiving HD-BMAs, although it cannot be quantified.

Worthy of note, non-metastatic breast and prostate cancer patients on adjuvant endocrine hormonal therapy, who are being actively treated with low doses of BMAs for managing CTIBL or preventing cancer recurrence (adjuvant setting), should be included in the LD-BMA group risk stratification, in light of the small dosage and the prolonged dosing intervals.[29]

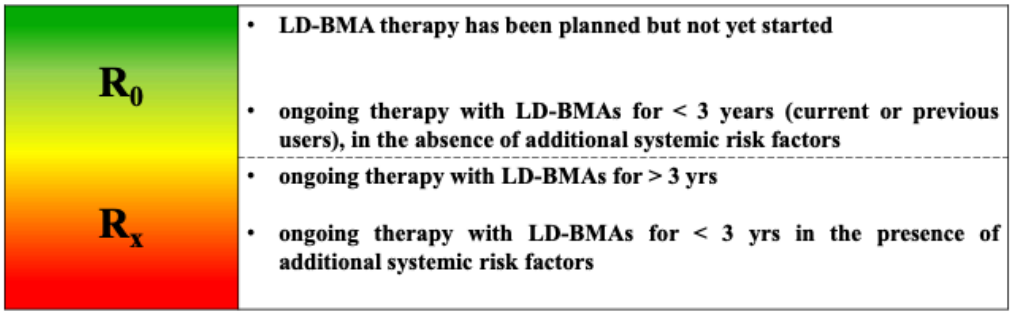

Figure 6. MRONJ risk gradient in patients receiving Low-Dose (LD) BMAs (modified from Campisi *et al.* [12])

N.B. Local triggers are not used to define the risk gradient for each patient's category. Instead, they can precipitate MRONJ development when left unresolved. Patients at increased risk of fragility fractures who are shifted from LD-BPs to LD-DMB treatment represent a separate group where the cumulative dosage of the BP leads to the individual risk of MRONJ occurrence.

MRONJ Prevention

To date, prevention of MRONJ remains the most effective strategy by which to protect the oral health of patients before the initiation, during and after treatment with medications associated with an increased risk of MRONJ.[156][157][158][159]

The aim of primary prevention of MRONJ is to identify and remove all oral conditions that are known to trigger MRONJ and restore sound oral health. Primary prevention starts prior to and continues throughout the duration of therapy with ONJ-related medications; in the case of patients who receive BP therapy, oral surveillance and appropriate dental care should be prolonged after drug cessation, due to its known long-standing inhibition of jawbone remodelling.[14][21] Unfortunately, the duration of oral surveillance after BP withdrawal is still unknown.

Additional targets of primary prevention are:

- patient counselling, through which patients are informed about their individual risk of MRONJ and the indispensable adherence to timetabled oral check-ups. Counselling should also make patients aware of the possible clinical manifestations of MRONJ, thereby facilitating their timely recognition (i.e., early diagnosis) and rapid access to treatment;
- enhanced communication between medical and oral health care providers to establish a beneficial interdisciplinary approach to at-risk patients (e.g., the timing of dental interventions, need for temporary drug withdrawal, and drug restart).

When the goals of primary prevention are not targeted, poor adherence to antiresorptive treatments is likely to be expected, being these medications perceived as potentially dangerous by patients. This is particularly true for OP patients, whose poor adherence to osteoporosis treatment is a worldwide recognized concern, with a serious impact on deaths and hospitalization (e.g., repeated fractures).[160][161]

One possible explanation for the poor OP patient's adherence to LD-BMA treatment is their fear of potential long-term side effects, including MRONJ occurrence. Awareness of medication-related risks and - most of all - knowledge of the risk reduction strategies proved effective to minimize the risk of MRONJ and might improve OP patients' adherence to antiresorptive treatment.

Prevention strategies

MRONJ risk-reduction strategies have been developed in the past years and include the following dental treatments, which should be applied routinely to maximize the oral health of at-risk patients:

- non-invasive dental procedures to maintain or restore oral health;
- invasive surgical procedures, such as dental extraction of non-restorable and compromised teeth, to eliminate potential triggering factors.

MRONJ risk-reduction strategies depend on the individual risk of patients, change over time, and vary between different patient populations.

a) Patients scheduled to start treatment with ONJ-related medications (HD-BMAs R_o and LD-BMAs R_o categories).

Pre-treatment evaluation must be performed by an oral health care provider; it should include a comprehensive clinical and radiographic dental examination, the assessment of dental, periodontal and peri-implant status, quality of restorations, and the inspection of dentures looking for areas of mucosal trauma. Timely management of potential triggers should be accomplished and initiation of antiresorptive therapy delayed until dental and periodontal health is optimized if systemic conditions permit. In the case of dental, periapical, periodontal or peri-implant infections that require invasive treatment at the bone interface, the patient should be strictly monitored and BMA treatment postponed until soft-tissue healing is achieved.[162]

In the absence of conclusive data, the SIPMO-SICMF Expert Panel agrees with other International Recommendations on the importance of pre-treatment oral evaluation and supports the idea that patients about to start HD-BMA therapy w o w/o AAs or LD-BMA therapy require a separate approach, based on their distinctive MRONJ risk.

Patients about to start HD-BMAs w o w/o AAs should always undergo thorough dental and periodontal examination and management of potential infectious foci before initiation of BMAs, due to the growing risk of MRONJ onset. Hypercalcemia of malignancy represents an exception that requires immediate start of BMA treatment. In these patients, initial oral evaluation should be performed as soon as the hypercalcaemic state has been resolved.

Alternatively, a pre-treatment oral evaluation is not mandatory for patients about to start LD-BMA therapy, because they display low to null MRONJ risk as compared with the general population in the

first few years of treatment.[14]

The SIPMO-SICMF Expert Panel recommends pre-treatment oral evaluation for patients about to start HD-BMAs. Also, it considers counselling of patients who are scheduled to receive LD-BMAs at least as important as restoring and maintaining their oral health and recommends activating prevention measures within six months from the start of BMA therapy.

b) Patients on active treatment with ONJ-related medications (HD-BMAs R_{+}, R_{++} and LD-BMAs R_{X} categories).

Although periodic oral surveillance is accomplished by oral health specialists, it is also the responsibility of the treating physicians to contribute to the patient's adherence to the scheduled recall visits, to minimize the risk of MRONJ occurrence and ensure the patient's persistence on antiresorptive medications.

Recall visits should be scheduled to maintain the oral health of patients for the entire duration of treatment with BMA, w o w/o AAs. Patients who had received BP treatment should be maintained on strict oral health surveillance for a long time after drug discontinuation. Timely management of potential triggers should be guaranteed to patients.[14][162]

The SIPMO-SICMF Expert Panel recommends maintaining oral surveillance for the entire duration of DMB treatment and much longer in case of BP therapy, with periodic recall visits on a 4-month basis for HD-BMAs R_{+}, R_{++} categories and every 6 months for LD-BMAs R_{X} category.

Dental management

Dental treatment includes *essential or emergent procedures* aimed at removing infectious triggers (e.g. pulpitis, pericoronitis, osteitis, dental or periodontal abscess, peri-implantitis, dental trauma, extensive caries or defective restorations that cause pain or tissue damage, adjustments in dentures that cause damage to oral structures) and *non-essential or elective procedures*, which include but are not limited to cosmetic procedures, orthodontic therapy, replacement of amalgam restorations for aesthetic reasons, elective periodontal care, intentional root canal treatment, prosthodontics and elective oral surgery. A major proportion of the dental treatments provided to the general population are elective in nature.

The SIPMO-SICMF Expert Panel classifies dental treatments into the following categories based on a risk/benefit ratio for patients; a traffic light colour code is used for the sake of simplicity (Table 5):

- *indicated treatments* (green light): all essential procedures required to treat emergent oral conditions and those elective non-surgical procedures that have not been associated with an increased MRONJ risk;
- *easible treatments* (yellow light): those elective procedures with uncertain MRONJ risk under specific conditions;
- *contraindicated treatments* (red light): those elective surgical procedures that are linked to a clearly unfavourable risk/benefit ratio.

	Dental treatments	HD-BMAs R+ and R++ patients	LD-BMAs R_x patients
Non-surgical Procedures	*Restorative dentistry*	Indicated	Indicated
	Endodontic treatment	Indicated	Indicated
	Orthodontic treatment	Feasible	Feasible
	Periodontal therapy	Indicated	Indicated
	Prosthetic rehabilitation	Feasible	Feasible
Surgical Procedures*	*Dentoalveolar surgery*	Indicated	Indicated
	Tooth extraction	Indicated	Indicated
	Pre-implant bone surgery	Contraindicated	Feasible
	Dental implant surgery	Contraindicated	Feasible**
	Periodontal surgery	Indicated	Indicated
	Endodontic surgery	Indicated	Indicated

Table 5. Dental management of patients who receive BMAs and are at increased MRONJ risk (modified from Campisi *et al.*[12])

** Tight soft-tissue closure must be ensured. Except for LD-DMB Rx patients who do not necessitate drug suspension before surgery, BMAs should be resumed once wound healing has been achieved (4-6 weeks).*

*** It is advisable to inform the patient about the long-term risk of implant-triggered MRONJ*

In brief, all non-surgical procedures that are essential for the resolution of infectious processes (e.g., restorative dentistry, endodontics, and periodontal therapy) are clearly indicated in all patients receiving BMA therapy w o w/o AAs, independent from their individual MRONJ risk, and they should

be delivered as soon as possible. The successful restoration/preservation of salvageable teeth is likely to reduce the need for surgical therapies and the risk of overt MRONJ.[163]

Teeth with poor prognosis or that have failed to resolve with restorative treatment should not be declined dental extraction.[21][124][129][132]

Overall, since chronic infection is the main local risk factor for MRONJ, tooth extraction has a clear preventative role of MRONJ, when properly and timely executed.[21]

While HD-BMAs R_0 and LD-BMAs R_0 patients may be safely subjected to routine dental extraction, HD-BMAs R_+/ R_{++} and LD-BMAs R_x patients should undergo dental extraction using specific surgical protocols that include mucoperiosteal flap elevation, atraumatic tooth extraction, alveolectomy and smoothing of bone edges, and tension-free soft tissue closure.[14][163][164][165] Biopsy of the alveolar bone to assess bone viability may be considered in patients at increased MRONJ risk at the time of dental extraction.[129][166] In the case of dental extraction, perioperative administration of systemic antibiotics is often prescribed to lower MRONJ risk in HD-BMAs R_+/ R_{++} and LD-BMAs R_x patients. A recent systematic review aimed at assessing the effectiveness of antibiotic therapy in preventing MRONJ in patients receiving BMA and/or AA therapies, when in need of teeth extraction. The authors found that perioperative antibiotic regimens reported in the literature are mainly empirical and lack validation. Peroral penicillin-based antibiotic therapy, either alone or accompanied by a β-lactamase inhibitor or metronidazole was found the most used perioperative protocol.[167]

The SIPMO-SICMF Expert Panel recommends the timely extraction of non-restorable teeth and the adoption of specific risk reduction strategies depending on the individual MRONJ risk profile.

Dental implant placement is generally contraindicated in patients scheduled for or already receiving HD-BMA therapy.[12][155][168]

Alternatively, implant placement is feasible in patients scheduled for or already receiving LD-BMA therapy, irrespective of the molecule type and route of administration. Yet, these patients should be informed about the low albeit non-quantifiable risk of MRONJ onset.[145][146][147]

Implant-related MRONJ has been recently classified into early (implant surgery-triggered) or late (implant presence-triggered), with the latter occurring most frequently and at sites where implants were placed prior to the initiation of BMAs.[147][169]

The SIPMO-SICMF Expert Panel recommends avoiding implant placement in patients scheduled for or already receiving HD-BMA therapy, while it considers dental implant surgery a feasible procedure in patients undergoing LD-BMA therapy. In any case, the SIPMO-SICMF Expert Panel recommends evaluating each case individually, performing a complete risk assessment and warning patients scheduled for or already receiving LD-BMA therapy on the potential threat of late MRONJ onset as well as describing all alternative strategies for the restoration of oral functions. Informed consent should be obtained on the possible long-term risks and benefits of the procedure.

Diagnostic Laboratory tests

Literature has provided insufficient data to support the use of biomarkers to predict MRONJ risk in patients on antiresorptive medication who need oral surgical procedures.[170][171][172][173] Currently, no biomarker with MRONJ specificity and sensitivity exists. Biomarkers should be interpreted in relation to the patients' clinical, radiological, and systemic conditions.[174]

The SIPMO-SICMF Expert Panel agrees that the use of biomarkers to predict MRONJ development could be misleading and does not favour their clinical use until proven otherwise.

Prophylactic drug holiday

Planned interruption of BPs before oral surgical procedures (prophylactic drug holiday) including tooth extraction has been emphasized in the past 20 years to prevent impaired wound healing in OP and BM/MM patients at risk of MRONJ.

Length of drug holiday varies in the literature from a few weeks to several months depending on the published protocols.[3][123][175]

That said, data on BP drug holidays never proved robust enough in clinical and animal studies to support its routine use as a preventive measure of MRONJ.[176][177][178][179]

The SIPMO-SICMF Expert panel agrees on the lack of evidence supporting the scientific validity of prophylactic BP discontinuation (drug holiday) prior to oral surgical procedures including tooth extraction.

Instead, the SIPMO-SICMF Expert panel considers the targeted (short-term) interruption of BPs in HD-BP R_{+}, HD-BP R_{++} and LD-BP R_{X} patients a reasonable strategy with limited side effects to prevent excess alveolar bone accumulation following oral surgical procedures and minimize toxicity

to the oral mucosa (Table 6). BPs withdrawal should start one week before surgery and last until soft-tissue healing has been achieved (4-6 weeks).[14]

Medication withdrawal in HD-BMAs R+ and R++ patients		
Molecule type	*Last dose before surgery*	*Resume treatment*
Bisphosphonates	1 week	once wound healing has been achieved (4-6 weeks after surgery)
Denosumab (Xgeva®)	3 weeks	
Bevacizumab	5-8 weeks	
Sunitinib	1 week	
Everolimus	1 week	
Medication withdrawal in LD-BMAs R_x patients		
Molecule type	*Last dose before surgery*	*Resume treatment*
Bisphosphonates	1 week	once wound healing has been achieved (4-6 weeks after surgery)
Denosumab (Prolia®)	No need for suspension*	

Table 6. Timing of perioperative withdrawalof different ONJ-related medications (modified from Campisi *et al.*[12])

** Elective surgical treatments including tooth extraction can be preferably performed without restrictions 5 months after the last dose of Prolia®, taking advantage of the reactivated bone turnover and of the recovered healing capacity of bone. This "window of opportunity" lasts about 2 months. A planned 1-month delay of the scheduled dose of DMB may be enough to foster soft-tissue healing, without added risk of fragility fractures. Instead, non-deferrable extraction of compromised teeth should be performed from the 3rd week after the last dose of Prolia® adopting specific risk reduction protocols, which include tight soft-tissue closure.*

In any case, discontinuation of BPs must be authorized by the treating physician/prescriber, who should outweigh the risks associated with discontinuation of therapy.

Differently from BPs, DMB has a short half-life. and its effect on bone resorption gradually declines within six months after the last dose.[98] The reversible mechanism of DMB on bone mineral density (BMD) supports the theoretical concern about a possible increased risk of fracture upon stopping DMB (Prolia®) in OP patients (i.e., rebound phenomenon), which usually happens 8 to 16 months from the last denosumab injection.[180][181] Indeed, while denosumab therapy increases BMD and reduces fracture risk, the disruption of bone architecture caused by osteoporosis is not reversed with treatment. In this view, withdrawal of Prolia® is largely discouraged in OP patients for the increased risk of rebound-associated vertebral fractures (RAVFs), and switching to another osteoporosis therapy is recommended.[182]

In the context of preventing skeletal-related events (SREs), DMB (Xgeva®) is initiated at diagnosis of bone metastases and continued indefinitely in many cases.[183] DMB prophylactic drug holiday has been suggested to prevent delayed bone healing and reduce the risk of MRONJ onset in HD-DMB R_{+} and HD-DMB R_{++}, but the results are controversial.[178][179]

Within the limits of the available knowledge, *the SIPMO-SICMF Expert panel considers DMB prophylactic drug holiday before oral surgical procedures hazardous and recommends a different approach to be used in patients at increased MRONJ risk, based on the dosing schedule of DMB (Xgeva® 120 mg Q4W vs. 60 mg Prolia® 60 mg twice-yearly).* In detail, indicated surgical treatments including tooth extraction (Table 5) should be performed in HD-DMB R_{+} and HD-DMB R_{++} patients at least 3 weeks after the last dose of Xgeva®, and the following injection postponed until soft-tissue healing is achieved (4-6 weeks). Specific MRONJ risk reduction protocols must be combined to further reduce the risk of MRONJ onset (see paragraph on dental management).

On the other side, oral surgical procedures including non-urgent tooth extraction (Table 5) can be performed without restrictions in LD-DMB R_{x} patients five months after the last dose of Prolia®, taking advantage of the reactivated bone turnover and of the recovered healing capacity of bone. This "window of opportunity" lasts about two months. A targeted 1-month delay of the scheduled dose of Prolia® may be enough to foster soft-tissue healing, without the added risk of RAVFs.[184]

Non-deferrable extraction of compromised teeth should be performed at least 3 weeks after the last dose of Prolia®, and specific MRONJ risk reduction protocols combined to further minimize the risk of

MRONJ onset (see paragraph on dental management).

Since the approval of AAs for the treatment of a wide range of cancer types, sporadic cases of MRONJ have been reported, especially when they are coupled with BMAs.[26] AAs possess a short half-life as compared with BMAs. These targeted medications not only exert an antiangiogenic effect on tumour cells but also on healthy tissues, thus reducing the ability of soft tissue to repair and complicate postoperative wound healing.[185]

The SIPMO-SICMF Expert panel agrees that AAs must be discontinued before any surgical operation, including oral and maxillofacial surgery, and the duration of withdrawal depends on their distinct half-life. [12][46][186] *The SIPMO-SICMF Expert Panel affirms that in any case, temporary withdrawal of AAs must be authorized by the treating physician/prescriber, who should outweigh the risks associated with discontinuation of the therapy.*

The timing of the perioperative withdrawal of different ONJ-related medications based on their distinct half-life is described in Table 6.

Treatment

The management of MRONJ is highly debated. Different treatment protocols for MRONJ have been proposed in the literature that are mainly based on case series and retrospective cohorts. To date, there is no robust evidence to support any specific treatment.[122][187] Similarly, temporary withdrawal of BMAs and AAs following MRONJ diagnosis has been suggested in the past years without conclusive validation. [123][182][188][189]

Standard non-surgical (or medical) therapy, which mainly consists of antiseptic mouth rinses, systemic antimicrobial agents, analgesics, and smoothing of exposed and sharp bony edges to prevent ulcerated lesions of the oral mucosa, has been recommended as the mainstay of MRONJ treatment for almost 20 years with the aim of eliminating pain and infection and minimising disease progress.[17]

Additional non-invasive treatments have been proposed as an adjunct to non-surgical and surgical therapy, including hyperbaric oxygen therapy, ozone therapy, low-level laser therapy, teriparatide, pentoxifylline (associated or not with tocopherol), autologous platelet-rich blood derivatives and Bone Morphogenetic Proteins, with varying degree of success in selected patient populations.[190][191][192][193][194][195][196][197]

Yet, these adjunctive treatments require definitive confirmation before being endorsed in routine clinical practice, due to extra costs and restricted availability.[122][198]

A symptomatic treatment approach as described above was based on the assumption that MRONJ is incurable and MRONJ occurs most frequently in metastatic cancer patients with comorbid conditions and limited life expectancy. Consequently, surgical therapy had been considered for a long time palliative rather than curative and offered only to patients with an advanced disease not responding to medical treatment.[3][15][16][123][199][200][201][202][203][204]

These statements have been substantially challenged in recent years when it has been cleared out that MRONJ can be cured if properly and timely managed, and that MRONJ patients can greatly benefit from surgery in terms of improved quality of life, restored oral function and access to potentially life-prolonging therapies, including BMAs.[17][205][206]

The aim of MRONJ treatment has recently shifted from palliative to curative, thanks to the reliable results of surgery.[21][79][207][208]

In fact, it is now evident that surgical treatment, in combination with medical therapy, offers more predictable results than non-surgical therapy alone in all disease stages and in the long term.[198][209][210]

The SIPMO-SICMF Expert Panel has long been considering surgery the backbone of MRONJ treatment, while being aware that medical therapy still represents a reasonable treatment option for patients unfit for surgery or who refuse it.[11][12][14][93] *Decision on surgical vs. non-surgical treatment remains patient-specific and should always undergo careful clinical judgment.*

Medication withdrawal in confirmed MRONJ cases (Therapeutic Drug Holiday)

The benefits of antiresorptive therapy far outweigh the risk of MRONJ development. Nevertheless, when MRONJ is diagnosed, BMAs are often discontinued until disease resolution is achieved in many cases.[211][212] It is controversial as to whether the withdrawal of BMAs in combination with medical and/or surgical treatments might promote or accelerate MRONJ disease resolution. Early clinical recommendations and international consensus statements theorized the withheld of BMAs, especially in the oncological setting.[123][188] More recent publications raised concern about the real benefit and potential harm of temporary BMAs discontinuation in cancer and OP patients with suspected or

established MRONJ and left the final decision at the discretion of the treating physician, after discussion with the patient and the oral health provider.[95][155][182][189]

Based on the different pharmacodynamics and kinetics of BPs as compared with DMB and AAs, *the SIPMO-SICMF Expert Panel decided to address separately the likelihood of temporary medication withdrawal in BP-associated ONJ and non-BP-associated ONJ (DMB and AAs).*

Despite the lack of robust data on the effectiveness of drug discontinuation, there is general agreement among maxillofacial surgeons and oral health care providers that long-term withdrawal of BPs does not influence the natural course of MRONJ and does not increase the chance of better treatment outcomes.[211][212][213][214]

In light of the long-lasting inhibitory effect of BPs on bone remodelling and in the absence of exhaustive data, *the SIPMO-SICMF Expert Panel considers BPs withdrawal a potentially harmful strategy for BRONJ patients and does not recommend its routine application, at least in the first years of BP treatment. Alternatively, perioperative discontinuation of BPs (short-term interruption) starting the week before surgery until complete healing is obtained, seems a reasonable strategy with limited side effects to reduce their accumulation in the surgical site, although evidence remains weak.*

Temporary withdrawal of BPs should be limited to specific cases, decided by the treating physician in agreement with the oral health provider and the pros and cons discussed with the patient.

Since its approval for the prevention of SREs in metastatic cancer patients and the prevention of fragility fractures in OP patients, DMB has been associated with the occurrence of MRONJ at least the same as the most potent BPs (i.e., monthly zoledronic acid and oral BPs in the two population subgroups). As previously mentioned, DMB does not bind to hydroxyapatite and incorporate into bone; thus, bone turnover recovers rapidly after drug discontinuation.

In light of the supposed "rebound effect" phenomenon and the increased risk of RAVFs in OP patients (see paragraph on prophylactic drug holiday), DMB withdrawal is generally contraindicated in LD-DMB patients.[215] On the contrary, the reported risk of RAVFs after DMB discontinuation in metastatic cancer patients appears low as compared with OP patients, with only a few reports in the literature.[216] It is therefore likely that DMB treatment might be temporarily interrupted in patients with a favourable prognosis who receive HD-DMB, and resumed in case of disease progression.[95][216]

Data on DMB withdrawal are scanty but it seems that discontinuation before surgery may accelerate MRONJ resolution.[211][213][214]

Within the limits of the available knowledge, *the SIPMO-SICMF Expert Panel considers a 6-month temporary DMB interruption a potentially suitable strategy to reduce the burden of surgical treatment for BP-naive metastatic cancer patients with MRONJ. On the contrary, DMB withdrawal is not recommended as an adjunctive non-surgical treatment.*

Temporary withdrawal of DMB requires accurate clinical judgment and should always be decided on a per-patient basis by the treating physician in agreement with the oral health provider and the pros and cons discussed with the patient. Close clinical and instrumental monitoring of bone turnover is required for the patient's safety and the prompt resumption of BMAs when needed.

In the case of OP and CTIBL patients with MRONJ receiving LD-DMB therapy, the SIPMO-SICMF Expert Panel hypothesizes that a planned 1-month delay of the scheduled dose of DMB may be sufficient to allow surgical operations of reduced intensity to be done 5 months after last DMB injection, while ensuring the benefit of the reactivated bone turnover on the healing capacity of bone, without the added risk of RAVFs.

As previously stated (see paragraph on Prophylactic drug holiday), AAs should be always interrupted before any surgical operation takes place, and the timing of interruption depends on the half-life of the given drug. The AAs withdrawal should last until complete soft-tissue healing has been achieved (4-6 weeks).

Surgical treatment

The SIPMO-SICMF Expert Panel recognizes the existence of several points at issue that could negatively influence the result of surgery, including: *a*- the adoption of a single surgical algorithm to treat all MRONJ patients, regardless of their underlying condition (BM/MM vs. OP), the medication received (BPs vs. DMB vs. AAs) and its dosage (high-dose vs. low-dose); *b*- the adoption of a stage-related treatment algorithm based on clinical signs and symptoms only; *c*- the lack of a common strategy to define the surgical bone margins; *d*- the ambiguity of operational definitions proposed for the different surgical interventions; *e*- the absence of standardized outcomes of surgery and the variability of follow-up.

a- There is a growing body of literature that BM/MM patients receiving high-dose BMAs, besides an increased risk of MRONJ, also display earlier disease onset, faster progression/severity, and worse

prognosis as compared with OP patients receiving low-dose BMAs.[217]

In addition, while BPs have high skeletal retention and are stored in bone for a long time, DMB does not incorporate into the bone, and its inhibitory effect on bone turnover reverses at the end of the dosing interval.[218] Likewise, the antiangiogenic activity of biological agents is time-dependent, and the blood supply to the bone and surrounding soft tissues goes back to normal a few days/weeks after drug cessation.[46][47]

Overall, these facts make it very likely that *response* to *surgery* is *not uniform* in MRONJ patients and varies with the patient clinical condition, the medication received, the dosing schedule and intervals. In other words, a given surgical procedure may be excessive for some patient categories (i.e., overtreatment) or deficient for others (i.e., undertreatment).

The SIPMO-SICMF Expert Panel, unlike other groups of experts, endorsed this hypothesis and in 2013 developed a surgical algorithm where the magnitude of surgical therapy was graded among BM/MM patients receiving high-dose BPs and OP patients receiving low-dose BPs.[11][93] Clinical results seems to confirm the need for reduced surgical treatment intensity in MRONJ patients receiving LD-BMAs.[79]

b- AAOMS task force was the first to introduce a staging system based on clinical signs and symptoms to address disease severity, cluster patients, and assign treatments accordingly.[3][15][16]

This is still the most largely recognised classification method, despite its failure to depict the real extent of osteonecrosis.[58][60][78] Therapies that rely on the use of a staging system based on clinical signs and symptoms may prove unsafe now that AAOMS has opened to the surgical treatment of MRONJ for all AAOMS disease stages.[17]

The SIPMO-SICMF clinical-radiological staging system was developed in 2012 to provide an accurate description of disease extent as the basis for the appropriate delivery of surgical treatments of increasing intensity.[9][11] The identification of increased bone density (i.e., osteosclerosis) at CT was established as a marker of disease severity to identify increasing levels of bone involvement, ranging from focal to diffuse disease. Surgery is graded so that patients with "focal disease" (Stage 1) are likely to receive less invasive surgical treatment (i.e., bone curettage and sequestrectomy) as compared with more advanced disease stages (Stage 2 and 3), who deserve more radical interventions (i.e., marginal and segmental resection of bone).[93]

The recently proposed AAOMS surgical algorithm parallels the one originally developed by the SIPMO-SICMF Expert Panel, except that they do not detail how to measure the extent of bone disease (i.e., focal vs. diffuse bone involvement).

Being concerned that delivery of surgical treatments of increasing magnitude based on clinical signs and symptoms only will pose MRONJ patients at risk of failure/relapses (undertreatment) or harmful side effects (overtreatment), the SIPMO-SICMF Expert Panel recommends the adoption of its clinical-radiological staging system to assign surgical treatment based on the radiological extent of bone involvement.

c- The amount of bone that needs to be removed surgically is paramount to prevent failures and early MRONJ relapses. Demarcation of necrotic and viable bone margins for surgery is challenging. While several authors agree on the use of preoperative imaging to better visualize the extent of bone disease, many clinicians rely on the intraoperative inspection of bone to define the margins for a "safe" resection.[17][206] Both approaches have limitations.

Among the different imaging techniques used, CT and MRI give a detailed description of the bone marrow changes and help define the boundaries of viable and necrotic bone, with respect to the uninvolved bone tissue.[73][219]

Multidetector CT (MDCT) and cone beam CT (CBCT) can also pick up the early radiological aspects of MRONJ, as compared with plain radiographs.[55][69]

Though no distinct imaging phenotype exists for MRONJ and advanced imaging modalities might overestimate the extent of disease as compared with the clinical picture, CT and CBCT could be used to accurately diagnose the extent of MRONJ lesions.[58]

Establishing healthy bone margins intraoperatively remains a major challenge. Surgeons must observe the bone colour and bleeding to distinguish the necrotic from the viable bone. Bone bleeding has been used for a long as a marker of bone health, but it proved unreliable and operator-biased.[220]

Fluorescence-guided bone surgery, with and without tetracycline fluorescence labelling, has been successfully used to increase the intraoperative accuracy of bone surgery.[220] The fluorescence technique likely improves the demarcation of viable bone, as compared with clinical inspection alone.[220][221][222] Since the way for surgical management of MRONJ has been recently cleared, the SIPMO-SICMF Expert Panel is concerned that the absence of a common strategy to define the surgical bone margins of MRONJ will negatively impact the results of future clinical research on this topic and preclude comparison of different surgical treatment strategies.

Because MRONJ is a bony disease, the SIPMO-SICMF Expert Panel recommends the adoption of CT-based imaging techniques to preoperatively assess MRONJ patients elected for surgery, for two main reasons: 1- the same imaging technique can be used to diagnose, stage and define the extent of the disease; and, 2- identification of the margins of bone surgery before the operation takes place enables the effective exchange of information between physicians and patients concerning the proposed treatment and its consequences.

d- Surgical procedures generally used to treat MRONJ patients range from superficial bone debridement to more radical interventions including the whole resection of diseased bone. The lack of standardised terminology to label MRONJ surgical procedures of different magnitude and anatomical location have made it difficult to compare treatment results in the past years. Different surgical procedures have been confused under the same term or as opposed the same surgical procedure has been termed differently.[21]

The SIPMO-SICMF Expert Panel endorses the adoption of a standardized set of surgical interventions to establish the risks and benefits of each operation and allow disease stage-related comparisons of different treatments.

e- Additional limitations of the current approach to MRONJ treatment are the lack of standardized outcomes to assess the impact of surgical procedures on patients, and the high variability of postoperative follow-up.[223]

Though the curative potential of surgery signifies a paradigm shift in MRONJ treatment compared to the past, little has been done to refine the criteria of treatment success adopted so far.

In this view, the widely used definition of painless mucosal healing seems insufficient as it only reflects the condition of the covering mucosal surface.[122]

The SIPMO-SICMF Expert Panel suggests the adoption of a more comprehensive definition of healing that encompasses the condition of the underlying bone. This can be achieved by coupling the clinical and radiological criteria of healing [14] so that treatment can be considered successful, and healing completed in the absence of both clinical and radiological signs of MRONJ [93]; in addition, any given treatment could also be considered successful in the presence of stable radiological signs of MRONJ when the clinical signs and symptoms are absent (i.e., remission).

The transition from a higher to a lower disease stage (i.e., stage improvement) following treatment of MRONJ has been considered a positive outcome in many published studies in the past years [207][224]

[225][226]. A combination of "stage improvement" and "mucosal healing" used to generate composite treatment outcomes has raised the success rate of interventions in several MRONJ cohorts but did not improve the clinical condition of treated patients, unless in early-stage diseases.[227]

The SIPMO-SICMF Expert Panel is concerned that the inclusion of "stage improvement" in the clinical outcome of MRONJ treatments does not reflect a real advantage for patients as they might experience further disease relapse.

How long surgically treated patients should be followed up before being considered cured is another debated aspect. Published clinical studies on MRONJ treatment are largely retrospective, display limited follow-up times and do not report a precise follow-up schedule for operated patients.[228][229][230][231] Based on the data available, we can only imply that MRONJ recurrences usually occur within 6 months after surgery, with a considerable number of relapses happening up to 1 year, independent from the type of treatment, the primary disease and the medication received.[206][223] Therefore, the optimistic results of surgical therapy described in previous studies with limited follow-up may have been partly overestimated.

The SIPMO-SICMF Expert Panel considers successful any MRONJ treatment (medical and/or surgical) that displays clinical-radiological signs of healing or remission at the 1-year follow-up and suggests the use of such a composite clinical outcome to assess the efficacy of surgical treatments in future clinical studies.

SIPMO-SICMF stage-related surgical algorithm.

The SIPMO-SICMF stage-related surgical algorithm has been originally developed in 2013 to specifically address increasing levels of surgical intensity based on the extent of BRONJ and the primary disease of affected patients. [93] This algorithm has been recently upgraded to include a separate treatment protocol for non-BP ONJ.[12] The SIPMO-SICMF stage-related surgical algorithm describes the combination of medical therapies and surgical techniques to be adopted in BP-ONJ (Table 7a) and non-BP ONJ (Table 8b); it also describes the non-surgical treatment of MRONJ (Table 8c).

Table 7. MRONJ Treatment

SIPMO-SICMF staging system	**Bone Metastatic Cancer patient**	**Osteoporosis patient**
Stage 1 (focal ONJ)	*Dentoalveolar surgery*: marginal resection	*Dentoalveolar surgery*: curettage and bone sequestrectomy; marginal resection for recurrent disease
Stage 2 (diffuse ONJ)	*Segmental resection* + bone reconstruction when indicated	*Dentoalveolar surgery*: marginal resection; segmental resection for recurrent disease
Stage 3 (complicated ONJ)	*Segmental resection* + bone reconstruction when indicated	*Segmental resection* + bone reconstruction when indicated

Bullet points:

- *1-month postoperative BP withdrawal starting 1 week before surgery to reduce accumulation at the surgical site that could hamper the healing process.*
- Dento-alveolar surgery can be done under loco-regional anaesthesia.
- Achieve stable mucosal coverage of the operated site irrespective of the surgical technique adopted.
- Adjunctive treatment options: use of piezoelectric or laser-assisted surgery to minimize ischemic damage to the bone.
- Perioperative topical disinfection (chlorhexidine 0.2%) for 7-10 days.
- Peroral antibiotic therapy (7-14 days long) for surgery under loco-regional anaesthesia; I.V. perioperative antibiotic therapy (7-14 days long) for hospitalised patients and surgery under general anaesthesia.
- Perioperative pain control
- Postoperative clinical follow-up at 1, 3, 6 and 12 months. CT scans at 6 and 12 months after surgery.

Table 7a. Stage-related surgical algorithm of BRONJ

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SIPMO-SICMF staging system	**Bone Metastatic Cancer patient**	**Osteoporosis patient**
Stage 1 (focal ONJ)	*Dentoalveolar surgery*: curettage and bone sequestrectomy; marginal resection for recurrent disease	*Dentoalveolar surgery*: curettage and bone sequestrectomy; marginal resection for recurrent disease
Stage 2 (diffuse ONJ)	*Dentoalveolar surgery*: curettage and bone sequestrectomy; marginal resection for recurrent disease	*Dentoalveolar surgery*: curettage and bone sequestrectomy; marginal resection for recurrent disease
stage 3 (complicated ONJ)	*Dentoalveolar surgery*: marginal resection; segmental resection for recurrent disease	*Dentoalveolar surgery*: marginal resection; segmental resection for recurrent disease

Bullet points:

- *In patients receiving Xgeva®, 6-month temporary DMB interruption is required before surgery.*
- *In patients receiving Prolia®, surgery should be performed 5 months after the last dose, with 1-month postoperative delay of the following dose, until complete healing is achieved.*
- Dento-alveolar surgery can be done with loco-regional anaesthesia.
- Achieve stable mucosal coverage of the operated site irrespective of the surgical technique adopted.
- Adjunctive treatment options: use of piezoelectric or laser-assisted surgery to minimize ischemic damage to the bone.
- Perioperative topical disinfection (chlorhexidine 0.2%) for 7-10 days.
- Peroral antibiotic therapy (7-14 days long) for surgery under loco-regional anaesthesia; I.V. perioperative antibiotic therapy (7-14 days long) for hospitalised patients and surgery under general anaesthesia.
- Perioperative pain control.
- Postoperative clinical follow-up at 1, 3, 6 and 12 months. CT scans at 6 and 12 months after surgery.

Table 7b. Stage-related surgical algorithm of DMB-ONJ

SIPMO-SICMF staging system	*Medical therapy*[#]
All disease stages	• Oral disinfectants • Systemic broad-spectrum antibiotics (7-14-day long in case of recurrent pain and suppuration; monthly schedule in refractory cases) • Pain control • Adjunctive treatment options: biostimulation with ozone or low-level laser therapy/laser photobiomodulation Aims: symptomatic (palliation); Exfoliation of the exposed, necrotic bone

Table 7c. SIPMO-SICMF Non-surgical treatment protocol of MRONJ

[#] *Suitable for systemically compromised patients for whom surgical therapy is contraindicated, or in case of patient's refusal of surgery.*

Conclusion and Future Research

This Position paper recognizes the weakness of the available evidence on MRONJ and the difficult task that both researchers and clinicians are facing to develop common strategies for the prevention and treatment of this multifaceted disease. The SIPMO-SICMF Expert Panel urges moving towards a universally accepted and less strict definition of MRONJ, an individualized MRONJ risk assessment and the recognition of the essential role of imaging in the diagnosis, classification, and management of overt MRONJ.

The SIPMO-SICMF Expert Panel recognizes that the statements and recommendations here provided warrant further confirmation and updates, and highlights the need for a global and interdisciplinary scientific approach to MRONJ to overcome region-specific challenges.

Authors Contribution Statement

† GC, RM, VF and AB equally contributed to the study conception, design, and writing of the manuscript. All authors critically revised the manuscript, read and approved the final version.

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