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Workshop of European Task Force on Medication Related Osteonecrosis of the Jaw. Current challenges

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**Workshop of European Task Force on Medication Related Osteonecrosis of the Jaw. Current challenges**

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49 Osteonecrosis, jaw, medication, bisphosphonate, cancer, osteoporosis  
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**Purpose:**

This paper reports on the conclusions of two workshops held in Copenhagen in September 2017 and November 2018 focused on medication-related osteonecrosis of the jaws (MRONJ). The workshops were organized and attended by a European task force on MRONJ, i.e. a multidisciplinary group of European clinical investigators with a special interest in the diagnosis and management of MRONJ and a track record of relevant research and publications. The aim of the workshops were to (i) highlight some of the most controversial aspects of current knowledge on MRONJ, including definition and classification, risk factors and management, and (ii) provide an expert opinion-based consensus with a view to inform clinicians and advise researchers, as a first step of reaching solutions.

**Introduction:**

MRONJ is a potentially serious complication of antiresorptive (AR) treatment in patients with skeletal metastases due to various cancers as well as osteoporosis (Campisi et al., 2014). MRONJ may also develop in antiresorptive-naive individuals exposed to a variety of anti-angiogenic agents (Mohamed, Nielsen, & Schiodt, 2018; Nicolatou-Galitis, Kouri, et al., 2019; Pimolbutr, Porter, & Fedele, 2018). MRONJ may lead to a reduced quality of life due to jaw bone infections, chronic pain, tooth loss, impaired function and disfigurement.

Since the first report by Marx 2003 (Marx, 2003) the number of cases and relevant publications have increased exponentially. Despite significant progress in our knowledge of the disease, there remain a number of controversial aspects that are of high relevance to researchers, clinicians and not least patients. The European task force on MRONJ comprises of a multidisciplinary group of European clinical investigators with a special interest in the diagnosis and management of MRONJ

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4 and a track record of relevant research and publications, who considered the current  
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6 controversies on MRONJ a reason for academic concern, a potential threat to patients, and a  
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8 limitation for better research. The Group met up in two separate workshops in order to (i)  
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10 highlight some of the most controversial aspects of current knowledge on MRONJ and (ii) provide  
11  
12 an expert opinion-based consensus on these topics with a view to help clinicians making informed  
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14 decisions on patient's care and inspire future investigators to design better clinical studies. The  
15  
16 Group agreed to focus upon three highly controversial aspects of MRONJ: 1) definition and  
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18 classification, 2) risk factors, and 3) Management/treatment of MRONJ.  
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#### 26 **Controversies on definition and classification:**

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28 The consensus papers by Ruggiero et al. representing the American Association of Oral and  
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30 Maxillofacial Surgeons (Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the  
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32 Jaws AAOMS, 2007; S. L. Ruggiero et al., 2014; Ruggiero SL, 2009), have been instrumental in the  
33  
34 process of establishing an understanding and acceptance of a widely used definition and  
35  
36 classification of MRONJ. The most recent version of the AAOMS consensus (2014) includes (i) the  
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38 MRONJ case definition as the presence of exposed jaw bone or bone that can be probed through  
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40 an intraoral or extraoral fistula(e) for at least 8 weeks in a patient receiving antiresorptive and/or  
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42 antiangiogenic therapy who had not received radiotherapy to the head and neck, and (ii) a disease  
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44 classification into 4 clinical stages (stage 0-3). The most notable change introduced in the 2014  
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46 AAOMS consensus was the modified MRONJ definition so to include patients presenting with an  
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48 intraoral or extraoral fistula(e). This important amendment was inspired by a number of reports  
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50 highlighting that a sub-group of patients can in fact present with MRONJ disease characterized by  
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52 the absence of exposed bone on visual inspection (so called non-exposed MRONJ, including the  
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4 presence of an intra-oral fistula, mandibular fracture, dentally unexplained pain and swelling,  
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6 among other manifestations), and therefore they would not fulfill the case definition of MRONJ as  
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8 suggested by the initial version of the AAOMS consensus (2007) (Ascani, Campisi, & Junquera  
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10 Gutierrez, 2014; Bedogni, Fusco, Agrillo, & Campisi, 2012; Fedele et al., 2015; Fedele et al., 2010;  
11  
12 S. Patel et al., 2012; M. Schiodt, Reibel, Oturai, & Kofod, 2014; Yarom, Fedele, Lazarovici, & Elad,  
13  
14 2010).

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18 The background was the obviously different interpretations of the term “bone exposure” by  
19  
20 different author groups and adjudicators in clinical and epidemiological studies. Some authors  
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22 regarded bone that can be probed through a fistula as exposed and diagnosed MRONJ in the  
23  
24 respective cases while other authors did not include those patients.  
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31 The 2009 update of the AAOMS consensus papers (Ruggiero SL, 2009) partially addressed this  
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33 issue as they added the new classification stage (stage 0) to include patients presenting with the  
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35 non-exposed variant of MRONJ. However, the MRONJ case definition remained paradoxically  
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37 unchanged, therefore preventing non-exposed MRONJ cases to be formally diagnosed, especially  
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39 in clinical trials and epidemiological studies. (Fedele et al., 2015).  
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46 Although the 2014 update of the AAOMS consensus represents a notable improvement, patients  
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48 presenting with non-exposed MRONJ **without** fistulas (e.g. dentally unexplained pain, mobile  
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50 teeth not due to periodontitis, numbness of the lip, mandibular fracture) continue to remain  
51  
52 excluded from MRONJ case definition (Fedele et al., 2015) (Table 1 and 2). There is therefore an  
53  
54 urgent need for expanding the case definition of MRONJ so to encompass the other  
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56 manifestations of non-exposed MRONJ and ensure that these patients can (i) be formally  
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4 diagnosed and treated, and (ii) be included in clinical and epidemiological studies. The Group  
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6 appreciated that this might be a difficult task as an accurate case definition should ensure the  
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8 exclusion of etiopathologically different disorders presenting with similar clinical manifestations,  
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10 which include plaque-related gingivitis/periodontitis, dental and periapical disease, benign fibro-  
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12 osseous lesion of the jawbones, chronic sclerosing osteomyelitis, infectious osteomyelitis, primary  
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14 jawbone malignancy, metastatic disease, and TMJ disorders (Fedele et al., 2015; S. Patel et al.,  
15  
16 2012; S. L. Ruggiero et al., 2014; M. Schiodt et al., 2014). Excluding these conditions as well as  
17  
18 describing the MRONJ lesions requires imaging. The value of imaging is described later under  
19  
20 controversies on management/treatment. Some authors have suggested that that up to one  
21  
22 quarter of MRONJ patients can present with the non-exposed variant (Fedele et al., 2015).  
23  
24 Although this proportion is expected to be somewhat reduced after the inclusion of fistula in the  
25  
26 definition (2014 AAOMS paper), efforts should be made to improve and expand case definition so  
27  
28 to capture diagnosis in these patients including those with non-exposed MRONJ without fistulas.  
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30 The Group also suggested that the requirement of 8-week observation of potential MRONJ  
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32 manifestation to fit the case definition may no longer be necessary. About one third to half of the  
33  
34 affected individuals currently develop MRONJ without a history of dental extraction or other  
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36 trauma (Otto, Pautke, Van den Wyngaert, Niepel, & Schiødt, 2018; Yazdi & Schiodt, 2015) and  
37  
38 differential diagnosis with other dental and jawbone disease can be achieved without having to  
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40 wait for 8 weeks (Bedogni et al., 2012).  
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**Table 1. Staging of MRONJ. After Ruggiero et al. 2014 (S. L. Ruggiero et al., 2014).**

<b>MRONJ† Staging</b>	
<b>At risk category</b>	No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates
<b>Stage 0</b>	No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes and symptoms
<b>Stage 1</b>	Exposed and necrotic bone, or fistulae that probes to bone, in patients who are asymptomatic and have no evidence of infection
<b>Stage 2</b>	Exposed and necrotic bone, or fistulae that probes to bone, associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage
<b>Stage 3</b>	Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone, (i.e., inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extra-oral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible of sinus floor

† Exposed or probable bone in the maxillofacial region without resolution for greater than 8 weeks in patients treated with an antiresorptive and/or an antiangiogenic agent who have not received radiation therapy to the jaws.

‡ Regardless of the disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone. The extraction of symptomatic teeth within exposed, necrotic bone should be considered since it is unlikely that the extraction will exacerbate the established necrotic process.

**Table 2:**

Mismatch between the 2014 AAOMS case definition criteria (S. L. Ruggiero et al., 2014) and clinical manifestations of MRONJ (modified from Fedele et al. (Fedele et al., 2015)).

<b>Clinical Manifestations</b>	<b>Included in the AAOMS definition</b>
<b>Exposed MRONJ</b>	
Frank bone exposure	Yes
<b>Non-exposed MRONJ</b>	
Sinus/fistula tract #	Yes
Bone pain #	No
Bone Swelling #	No
Gingival Swelling #	No
Tooth mobility #	No
Mandibular fracture #	No
Maxillary sinus Pain #	No
Lower lip numbness/dysaesthesia #	No

# Not caused by dental or other jawbone disease, which should be ruled out with clinical and radiological investigations before suspecting MRONJ diagnosis.

### Controversies on risk factors

According to the literature tooth extraction, infection, type and dosage of AR and duration of treatment are considered to be risk factors.

Approximately half to two-thirds of MRONJ cases are reported to develop following a tooth extraction (Otto et al., 2018; Yazdi & Schiodt, 2015). Dental extraction was reported as a main risk factor in 73% of the cases of ONJ (Nicolatou-Galitis et al., 2011), and historically these cases have been identified as a non-healing extraction socket (Bedogni et al., 2012). Accordingly, the vast majority of recommendations on dental treatment of patients on anti-resorptive or anti-angiogenic therapy have included advice against dental extractions as a mean to resolve dental infection (Bedogni et al., 2012; Khan et al., 2008; Khosla et al., 2007; Matsuo et al., 2014; S. L. Ruggiero et al., 2014; Yoneda et al., 2010).

However, a growing body of evidence suggests that dental infection, rather than dental extraction per se, might represent the main local risk factor for MRONJ (Otto et al., 2015; Panya et al., 2017; Saia et al., 2010). For example, a 2011 case-control study with three dental Practice-based Research Networks in US found that the likelihood of developing osteonecrosis was higher (almost double) in patients with a history of suppuration compared to those with a history of dental extractions (OR 11.9 vs 6.6) (Barasch et al., 2011). It is also increasingly reported that dental extractions in patients exposed to antiresorptive therapy usually does not translate into MRONJ development, when tooth extraction is performed using alveolectomy and primary surgical mucosal closure (Heufelder et al., 2014; Otto et al., 2015; Morten Schiodt et al., 2018). Thus, surgical intervention per se should not be over-emphasized as the main risk factor for MRONJ development. Similarly, it has been suggested that infection around the implants (peri-implantitis) represents a notable risk factor for MRONJ development (Giovannacci et al., 2016; Troeltzsch et

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4 al., 2016). This is also in line with the high success rate after surgery on the jawbone to cure  
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6 MRONJ lesions (see later).  
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9 The Group suggested that dental infection might currently be a more common and relevant risk  
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11 factor for MRONJ compared to extraction, and that a notable proportion of MRONJ cases believed  
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13 to have been triggered by dental extraction in fact represent cases of non-exposed MRONJ that  
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15 had already developed because of dental/periodontal infection before the actual extraction took  
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17 place. Recent studies have reported the presence of histologically-proven alveolar necrotic bone  
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19 associated with dental/periodontal infection at the time of the extraction of teeth (Nicolatou-  
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21 Galitis et al., 2015; Nicolatou-Galitis, Schiodt, et al., 2019; Morten Schiodt et al., 2018). Similarly,  
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23 animal studies have reported that MRONJ can develop to areas of periodontal infection in absence  
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25 of dental extraction surgery (Nowicki et al., 2019; Otto et al., 2017). Although evidence remains  
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27 not robust and further well-designed clinical trials are needed, the Group suggested that patients  
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29 on anti-resorptive therapy should not be declined dental extractions for the treatment of  
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31 recurrent dental/periodontal infections that cannot be resolved or have failed to resolve with  
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33 restorative treatment, as the persistence of the infection *per se* represents a notable risk factor for  
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35 MRONJ development. The group recommended that when needed, tooth extractions should be  
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37 performed with raising a muco-periosteal flap, alveolectomy, smoothing of bone edges,  
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39 mobilization of the flap and primary tension free closure of the alveolus with tight suturing.  
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48 The Group also highlighted the importance of appropriate stratification of the risk of MRONJ  
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50 development based on the type, dose and administration route of anti-resorptive medication.  
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52 There is robust evidence that drug-related factors associated with an increased risk of MRONJ  
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54 development include nitrogen-containing structure, cumulative high dose, use in cancer setting,  
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56 and intravenous administration (Abt, 2017; Malden & Lopes, 2012; Otto et al., 2010; S. L. Ruggiero  
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4 et al., 2014; Vahtsevanos et al., 2009). However, it should be emphasized that intravenous  
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6 administration of bisphosphonate per se should not be automatically considered an indicator of  
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8 the high risk of MRONJ development. For example, some osteoporosis patients receive yearly  
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10 intravenous bisphosphonates; however, because the cumulative dosage remains low, their risk of  
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12 developing MRONJ is also low. Furthermore, a low dose, usually quarterly or half yearly , of  
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14 prophylactic intravenous bisphosphonates has been recently introduced in the management of  
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16 breast cancer patients without metastases (adjuvant therapy), and this has been reported to be  
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18 associated with notably lower risk of MRONJ development (V. Patel et al., 2018; Rugani et al.,  
19  
20 2014). The Group suggested that, in order to optimize risk assessment and management of  
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22 patients on anti-resorptive therapy, it is important to highlight to all clinicians, and in particular in  
23  
24 the dental setting, that the risk of MRONJ development is mostly associated with high cumulative  
25  
26 dosage of nitrogen-containing bisphosphonates. (Fung et al., 2017; S. L. Ruggiero et al., 2014;  
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28 Yazdi & Schiodt, 2015).

### 41 **Controversies on management/treatment**

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43 Expert opinion-based recommendations for the management of MRONJ are included in the  
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45 AAOMS position papers (Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the  
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47 Jaws AAOMS, 2007; Salvatore L. Ruggiero et al., 2009; S. L. Ruggiero et al., 2014). The Group  
48  
49 highlighted that AAOMS treatment recommendations, which are based on a clinically-driven  
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51 staging system may fail to reflect the actual bone extension of MRONJ disease, with the risk of  
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53 assigning patients to “inappropriate” treatments (Bedogni et al., 2014).  
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4 Accordingly some authors advocated the adoption of treatments based also on the radiological  
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6 aspects of MRONJ disease (Campisi et al., 2014) in order to pick up early signs of disease or base  
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8 therapeutic decisions on accurate assessment of disease extent. However, there remains no  
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10 consensus on the efficacy of different radiological imaging modalities (e.g. CT, MRI or nuclear  
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12 imaging) in assessing, with high accuracy, the “true” MRONJ disease extent. (Bisdas et al., 2008;  
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14 Devlin et al., 2018). A number of studies have compared specific imaging modalities and found  
15  
16 inconsistent results in terms of overestimation/underestimation of the extension of MRONJ  
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18 (Guggenberger et al., 2013; Stockmann et al., 2010).  
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24 The Group advised that clinicians should be careful in adopting treatment recommendations that  
25  
26 are solely based on clinical assessment of MRONJ patients, and that further imaging studies are  
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28 needed in order to study the extension of necrotic bone disease in MRONJ patients.  
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34 The Group also highlighted the current controversy on surgical management of MRONJ patients.  
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36 The AAOMS recommendations suggest generally non-surgical treatment for stage 1 and 2, and  
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38 performing surgical debridement/resection of necrotic bone only for Stage 3 MRONJ patients  
39  
40 (Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws AAOMS, 2007;  
41  
42 Salvatore L. Ruggiero et al., 2009; S. L. Ruggiero et al., 2014).  
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47 However, there is an increasing body of evidence suggesting that surgical removal of necrotic  
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49 bone might be curative in patients with all MRONJ stages (Aljohani et al., 2019; Otto et al., 2018;  
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51 Ristow et al., 2018; Morten Schiodt, Ottesen, Dalsten, Oturai, & Kofod, 2016), where cure is  
52  
53 defined as long-term resolution of symptoms and complete mucosal closure (absence of residual  
54  
55 bone exposure). For example, Schiodt et al. reported resolution of symptoms and complete  
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57 mucosal closure in 93% of 141 MRONJ patients treated with surgical removal of necrotic bone as  
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4 compared to only 17% of 63 non-surgically treated cases (Morten Schiodt et al., 2016). Other  
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6 studies have documented high success rate of surgical treatment compared to non-surgical  
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8 treatment (Aljohani et al., 2019; Hauer et al., 2019; Yamada et al., 2018).

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12 A recent study also suggests that non-surgical therapy might lead to progression of MRONJ  
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14 disease. Ristow et al. (2019) described a longitudinal study of 92 patients with stage 1 MRONJ who  
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16 were initially treated by using a standardized conservative (non-surgical) protocol consisting of  
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18 antimicrobial mouth rinsing and gel application (with chlorhexidine). The authors reported that  
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20 only 8 patients (8.7%) showed complete mucosal healing and resolutions of symptoms whereas  
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22 the remaining 84 (91.3%) had persistent exposed jaw bone at end of the observation period (15.6  
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24 months). Among these 84 patients, 67 (80%) showed progression of their MRONJ disease (upshift  
25  
26 in AAOMS stage from 1 to 2 or 3), which eventually led to extensive bone and/or tooth loss in 28  
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28 cases (Ristow et al., 2019). The Group highlighted that, although well-designed comparative trials  
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30 are required, there is increasing evidence suggesting that surgical removal of the necrotic bone  
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32 might provide long-lasting benefits to MRONJ patients in terms of resolving symptoms, obtaining  
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34 mucosal healing, and preventing further progression of necrotic bone disease. With this growing  
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36 body of evidence, a number of clinicians have shifted their therapeutic approach from  
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38 conservative (non-surgical) to upfront surgical treatment.  
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## 51 **Recommendations**

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53 Based on the discussion points summarized above, the Group has produced a number of  
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55 consensus key statements and recommendations so to inform clinicians and advice researchers, as  
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57 a first step of reaching solutions.  
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**Key statements and recommendations relevant to definition and classifications of MRONJ:**

- Current widely adopted definition does not identify all patients affected by MRONJ
- The current description of stage 0 is controversial, does not fulfill the definition of the disease and may be misleading and difficult to interpret.
- Stage 0 of the AAOMS classification is a diagnostic challenge, as there are overlaps with dental and non-dental diseases. Stage 0 may ultimately need confirmation by imaging and/or histopathology.
- Cases of non-exposed MRONJ without fistula should be included in the definition, possibly in terms of suspected or probable MRONJ after ruling out other dental and non-dental disease. The only ultimate proof of non-exposed MRONJ might be the histopathologic confirmation of necrotic bone. Decision on biopsy should be taken on an individual basis.
- The definition criterion of 8 weeks bone exposure/probing of bone does not apply to all cases and may delay diagnosis and consequently treatment.
- The role of imaging in the definition and classification of MRONJ needs further refinement. Imaging may aid in diagnosis (especially for non-exposed cases) and help determining disease extension and planning treatment.
- Present classification/staging does not adequately capture the extension and severity of MRONJ lesions. This may potentially affect treatment and prognosis.

**Key statements and recommendations relevant to risk factors for MRONJ:**

- Tooth extraction does not automatically translate into an increased risk of developing MRONJ, as certain surgical procedures notably reduce the risk.

- The reported high risk of developing MRONJ after tooth extraction might be related to an underlying pre-existing dental/periodontal infection rather than to the surgery *per se*.
- The risk of developing MRONJ is not related to the way of administration as single factor; an accurate risk assessment should include an evaluation of the cumulative dosage and duration of anti-resorptive treatment. Typically, high dose anti-resorptive therapy given to cancer patients with metastases is associated with higher risk of MRONJ development as compared to low dose therapy given to osteoporosis patients.

#### **Key statements and recommendations relevant to management/treatment of MRONJ:**

- Because there is no accurate staging system reflecting the extension of MRONJ bone disease, it is problematic, and possibly misleading, to inform treatment recommendations on the basis of currently available staging systems.
- The term “conservative treatment” is used inconsistently in the literature and might include a number of different interventions ranging from topical antimicrobial mouthwashes to removal of superficial loose sequestra.
- The Group recommends using the terms non-surgical vs. surgical treatment.
- Recent literature suggests that non-surgical treatment may lead to disease progression.
- Surgical treatment is superior to non-surgical management in promoting long-term mucosal healing as well as absence of symptoms or radiologic signs indicative of bone necrosis.
- If the aim of treatment is reduction of symptoms (pain) and control of infection, non-surgical treatment may be a valid management option. This seems particularly appropriate in frail elderly patients and in end-of-life oncology palliative setting.



- Early surgical intervention on localized disease may prevent progression and the need for subsequent extensive surgery (consider to treat surgically and early).

## GENERAL SUMMARY

The Group has highlighted a number of controversial aspects of current knowledge and practice relevant to MRONJ, which have the potential to affect clinical management of patients as well as research. The Groups suggest that key statement and recommendations presented in this paper might represent a useful tool so to stimulate a proactive discussion and inspire new and better-designed research, as first step to reach a consensus and improve the management of patients with MRONJ.

## References:

- Abt, E. (2017). The Risk of Medication-Related Osteonecrosis of the Jaw After Dental Extraction is Higher for Patients on Intravenous as Compared With Oral Antiresorptive Drugs. *J Evid Based Dent Pract*, 17(2), 105-106. doi:10.1016/j.jebdp.2017.03.007
- Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws AAOMS. (2007). American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg*, 65(3), 369-376. doi:10.1016/j.joms.2006.11.003
- Aljohani, S., Troeltzsch, M., Hafner, S., Kaeppler, G., Mast, G., & Otto, S. (2019). Surgical treatment of medication-related osteonecrosis of the upper jaw: Case series. *Oral Dis*, 25(2), 497-507. doi:10.1111/odi.12992
- Ascani, G., Campisi, G., & Junquera Gutierrez, L. M. (2014). Current controversies in classification, management, and prevention of bisphosphonate-related osteonecrosis of the jaw. *Int J Dent*, 2014, 565743. doi:10.1155/2014/565743
- Barasch, A., Cunha-Cruz, J., Curro, F. A., Hujuel, P., Sung, A. H., Vena, D., . . . Group, C. C. (2011). Risk factors for osteonecrosis of the jaws: a case-control study from the CONDOR dental PBRN. *J Dent Res*, 90(4), 439-444. doi:10.1177/0022034510397196
- Bedogni, A., Fedele, S., Bedogni, G., Scoletta, M., Favia, G., Colella, G., . . . Campisi, G. (2014). Staging of osteonecrosis of the jaw requires computed tomography for accurate definition of the extent of bony disease. *Br J Oral Maxillofac Surg*, 52(7), 603-608. doi:10.1016/j.bjoms.2014.04.009

- 1  
2  
3  
4 Bedogni, A., Fusco, V., Agrillo, A., & Campisi, G. (2012). Learning from experience. Proposal of a refined  
5 definition and staging system for bisphosphonate-related osteonecrosis of the jaw (BRONJ). *Oral*  
6 *Dis*, *18*(6), 621-623. doi:10.1111/j.1601-0825.2012.01903.x
- 7  
8 Bisdas, S., Chambron Pinho, N., Smolarz, A., Sader, R., Vogl, T. J., & Mack, M. G. (2008). Biphosphonate-  
9 induced osteonecrosis of the jaws: CT and MRI spectrum of findings in 32 patients. *Clin Radiol*,  
10 *63*(1), 71-77. doi:10.1016/j.crad.2007.04.023
- 11 Campisi, G., Fedele, S., Fusco, V., Pizzo, G., Di Fede, O., & Bedogni, A. (2014). Epidemiology, clinical  
12 manifestations, risk reduction and treatment strategies of jaw osteonecrosis in cancer patients  
13 exposed to antiresorptive agents. *Future Oncol.*, *10*(2), 257-275.
- 14 Devlin, H., Greenwall-Cohen, J., Benton, J., Goodwin, T. L., Littlewood, A., & Horner, K. (2018). Detecting the  
15 earliest radiological signs of bisphosphonate-related osteonecrosis. *Br Dent J*, *224*(1), 26-31.  
16 doi:10.1038/sj.bdj.2017.1001
- 17  
18 Fedele, S., Bedogni, G., Scoletta, M., Favia, G., Colella, G., Agrillo, A., . . . Bedogni, A. (2015). Up to a quarter  
19 of patients with osteonecrosis of the jaw associated with antiresorptive agents remain  
20 undiagnosed. *Br J Oral Maxillofac Surg*, *53*(1), 13-17. doi:10.1016/j.bjoms.2014.09.001
- 21 Fedele, S., Porter, S. R., D'Aiuto, F., Aljohani, S., Vescovi, P., Manfredi, M., . . . Yarom, N. (2010).  
22 Nonexposed variant of bisphosphonate-associated osteonecrosis of the jaw: a case series. *Am J*  
23 *Med*, *123*(11), 1060-1064. doi:10.1016/j.amjmed.2010.04.033
- 24 Fung, P., Bedogni, G., Bedogni, A., Petrie, A., Porter, S., Campisi, G., . . . Fedele, S. (2017). Time to onset of  
25 bisphosphonate-related osteonecrosis of the jaws: a multicentre retrospective cohort study. *Oral*  
26 *Dis*, *23*(4), 477-483. doi:10.1111/odi.12632
- 27  
28 Giovannacci, I., Meleti, M., Manfredi, M., Mortellaro, C., Greco Lucchina, A., Bonanini, M., & Vescovi, P.  
29 (2016). Medication-Related Osteonecrosis of the Jaw Around Dental Implants: Implant Surgery-  
30 Triggered or Implant Presence-Triggered Osteonecrosis? *J Craniofac Surg*, *27*(3), 697-701.  
31 doi:10.1097/SCS.0000000000002564
- 32  
33 Guggenberger, R., Fischer, D. R., Metzler, P., Andreisek, G., Nanz, D., Jacobsen, C., & Schmid, D. T. (2013).  
34 Bisphosphonate-induced osteonecrosis of the jaw: comparison of disease extent on contrast-  
35 enhanced MR imaging, [18F] fluoride PET/CT, and conebeam CT imaging. *AJNR Am J Neuroradiol*,  
36 *34*(6), 1242-1247. doi:10.3174/ajnr.A3355
- 37 Hauer, L., Jambura, J., Hrusak, D., Chalupova, M., Posta, P., Rusnak, S., & Vyskocil, V. (2019). Surgical  
38 therapy for medication-related osteonecrosis of the jaw in osteoporotic patients treated with  
39 antiresorptive agents. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*.  
40 doi:10.5507/bp.2018.081
- 41 Heufelder, M. J., Hendricks, J., Remmerbach, T., Frerich, B., Hemprich, A., & Wilde, F. (2014). Principles of  
42 oral surgery for prevention of bisphosphonate-related osteonecrosis of the jaw. *Oral Surg Oral Med*  
43 *Oral Pathol Oral Radiol*, *117*(6), e429-435. doi:10.1016/j.oooo.2012.08.442
- 44  
45 Khan, A. A., Sándor, G. K., Dore, E., Morrison, A. D., Alsahli, M., Amin, F., . . . Surgeons, C. A. o. O. a. M.  
46 (2008). Canadian consensus practice guidelines for bisphosphonate associated osteonecrosis of the  
47 jaw. *J Rheumatol*, *35*(7), 1391-1397.
- 48 Khosla, S., Burr, D., Cauley, J., Dempster, D. W., Ebeling, P. R., Felsenberg, D., . . . Mineral, R. (2007).  
49 Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society  
50 for Bone and Mineral Research. *J Bone Miner Res*, *22*(10), 1479-1491. doi:10.1359/jbmr.0707onj
- 51 Malden, N., & Lopes, V. (2012). An epidemiological study of alendronate-related osteonecrosis of the jaws.  
52 A case series from the south-east of Scotland with attention given to case definition and  
53 prevalence. *J Bone Miner Metab*, *30*(2), 171-182. doi:10.1007/s00774-011-0299-z
- 54  
55 Marx, R. E. (2003). Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws:  
56 a growing epidemic. *Journal of Oral and Maxillofacial Surgery*, *61*(9), 1115-1117.  
57 doi:10.1016/s0278-2391(03)00720-1  
58  
59  
60

- 1  
2  
3  
4 Matsuo, A., Hamada, H., Kaise, H., Chikazu, D., Yamada, K., & Kohno, N. (2014). Characteristics of the early  
5 stages of intravenous bisphosphonate-related osteonecrosis of the jaw in patients with breast  
6 cancer. *Acta Odontol Scand*, *72*(8), 656-663. doi:10.3109/00016357.2014.887772
- 7  
8 Mohamed, H. A. M., Nielsen, C. E. N., & Schiodt, M. (2018). Medication related osteonecrosis of the jaws  
9 associated with targeted therapy as monotherapy and in combination with antiresorptives. A report  
10 of 7 cases from the Copenhagen Cohort. *Oral Surgery Oral Medicine Oral Pathology Oral Radiology*,  
11 *125*(2), 157-163. doi:10.1016/j.oooo.2017.10.010
- 12  
13 Nicolatou-Galitis, O., Kouri, M., Papadopoulou, E., Vardas, E., Galiti, D., Epstein, J. B., . . . Group, M. B. S.  
14 (2019). Osteonecrosis of the jaw related to non-antiresorptive medications: a systematic review.  
15 *Support Care Cancer*, *27*(2), 383-394. doi:10.1007/s00520-018-4501-x
- 16  
17 Nicolatou-Galitis, O., Papadopoulou, E., Sarri, T., Boziari, P., Karayianni, A., Kyrtsolis, M. C., . . . Migliorati, C.  
18 A. (2011). Osteonecrosis of the jaw in oncology patients treated with bisphosphonates: prospective  
19 experience of a dental oncology referral center. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*,  
20 *112*(2), 195-202. doi:10.1016/j.tripleo.2011.02.037
- 21  
22 Nicolatou-Galitis, O., Razis, E., Galiti, D., Galitis, E., Labropoulos, S., Tsimpidakis, A., . . . Migliorati, C. (2015).  
23 Periodontal disease preceding osteonecrosis of the jaw (ONJ) in cancer patients receiving  
24 antiresorptives alone or combined with targeted therapies: report of 5 cases and literature review.  
25 *Oral Surg Oral Med Oral Pathol Oral Radiol*, *120*(6), 699-706. doi:10.1016/j.oooo.2015.08.007
- 26  
27 Nicolatou-Galitis, O., Schiodt, M., Mendes, R. A., Ripamonti, C., Hope, S., Drudge-Coates, L., . . . Van den  
28 Wyngaert, T. (2019). Medication-related osteonecrosis of the jaw: definition and best practice for  
29 prevention, diagnosis, and treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol*, *127*(2), 117-135.  
30 doi:10.1016/j.oooo.2018.09.008
- 31  
32 Nowicki, B., Nehrbass, D., Arens, D., Stadelmann, V. A., Zeiter, S., Otto, S., . . . Stoddart, M. J. (2019).  
33 Medication-related osteonecrosis of the jaw in a minipig model: Parameters for developing a  
34 macroscopic, radiological, and microscopic grading scheme. *J Craniomaxillofac Surg*.  
35 doi:10.1016/j.jcms.2019.03.002
- 36  
37 Otto, S., Pautke, C., Martin Jurado, O., Nehrbass, D., Stoddart, M. J., Ehrenfeld, M., & Zeiter, S. (2017).  
38 Further development of the MRONJ minipig large animal model. *J Craniomaxillofac Surg*, *45*(9),  
39 1503-1514. doi:10.1016/j.jcms.2017.07.002
- 40  
41 Otto, S., Pautke, C., Opelz, C., Westphal, I., Drosse, I., Schwager, J., . . . Schieker, M. (2010). Osteonecrosis of  
42 the jaw: effect of bisphosphonate type, local concentration, and acidic milieu on the  
43 pathomechanism. *J Oral Maxillofac Surg*, *68*(11), 2837-2845. doi:10.1016/j.joms.2010.07.017
- 44  
45 Otto, S., Pautke, C., Van den Wyngaert, T., Niepel, D., & Schiødt, M. (2018). Medication-related  
46 osteonecrosis of the jaw: Prevention, diagnosis and management in patients with cancer and bone  
47 metastases. *Cancer Treat Rev*, *69*, 177-187. doi:10.1016/j.ctrv.2018.06.007
- 48  
49 Otto, S., Troltsch, M., Jambrovic, V., Panya, S., Probst, F., Ristow, O., . . . Pautke, C. (2015). Tooth extraction  
50 in patients receiving oral or intravenous bisphosphonate administration: A trigger for BRONJ  
51 development? *J Craniomaxillofac Surg*, *43*(6), 847-854. doi:10.1016/j.jcms.2015.03.039
- 52  
53 Panya, S., Fliefel, R., Probst, F., Troltsch, M., Ehrenfeld, M., Schubert, S., & Otto, S. (2017). Role of  
54 microbiological culture and polymerase chain reaction (PCR) of actinomyces in medication-related  
55 osteonecrosis of the jaw (MRONJ). *J Craniomaxillofac Surg*, *45*(3), 357-363.  
56 doi:10.1016/j.jcms.2017.01.006
- 57  
58 Patel, S., Choyee, S., Uyanne, J., Nguyen, A. L., Lee, P., Sedghizadeh, P. P., . . . Le, A. D. (2012). Non-exposed  
59 bisphosphonate-related osteonecrosis of the jaw: a critical assessment of current definition,  
60 staging, and treatment guidelines. *Oral Dis*, *18*(7), 625-632. doi:10.1111/j.1601-0825.2012.01911.x
- 61  
62 Patel, V., Mansi, J., Ghosh, S., Kwok, J., Burke, M., Reilly, D., . . . Chia, K. (2018). MRONJ risk of adjuvant  
63 bisphosphonates in early stage breast cancer. *Br Dent J*, *224*(2), 74-79.  
64 doi:10.1038/sj.bdj.2017.1039

- 1  
2  
3  
4 Pimolbutr, K., Porter, S., & Fedele, S. (2018). Osteonecrosis of the Jaw Associated with Antiangiogenics in  
5 Antiresorptive-Naïve Patient: A Comprehensive Review of the Literature. *Biomed Res Int*, 2018, 14.  
6 doi:10.1155/2018/8071579
- 7 Ristow, O., Rückschloß, T., Bodem, J., Berger, M., Bodem, E., Kargus, S., . . . Freudlsperger, C. (2018).  
8 Double-layer closure techniques after bone surgery of medication-related osteonecrosis of the jaw  
9 - A single center cohort study. *J Craniomaxillofac Surg*, 46(5), 815-824.  
10 doi:10.1016/j.jcms.2018.03.005
- 11 Ristow, O., Rückschloß, T., Müller, M., Berger, M., Kargus, S., Pautke, C., . . . Freudlsperger, C. (2019). Is the  
12 conservative non-surgical management of medication-related osteonecrosis of the jaw an  
13 appropriate treatment option for early stages? A long-term single-center cohort study. *J*  
14 *Craniomaxillofac Surg*, 47(3), 491-499. doi:10.1016/j.jcms.2018.12.014
- 15 Rugani, P., Luschin, G., Jakse, N., Kirnbauer, B., Lang, U., & Acham, S. (2014). Prevalence of bisphosphonate-  
16 associated osteonecrosis of the jaw after intravenous zoledronate infusions in patients with early  
17 breast cancer. *Clin Oral Investig*, 18(2), 401-407. doi:10.1007/s00784-013-1012-5
- 18 Ruggiero, S. L., Dodson, T. B., Assael, L. A., Landesberg, R., Marx, R. E., & Mehrotra, B. (2009). American  
19 Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related  
20 osteonecrosis of the jaw - 2009 update. *Aust Endod J*, 35, 119-130.
- 21 Ruggiero, S. L., Dodson, T. B., Fantasia, J., Goodday, R., Aghaloo, T., Mehrotra, B., . . . Surgeons, A. A. o. O. a.  
22 M. (2014). American Association of Oral and Maxillofacial Surgeons position paper on medication-  
23 related osteonecrosis of the jaw--2014 update. *J Oral Maxillofac Surg*, 72(10), 1938-1956.  
24 doi:10.1016/j.joms.2014.04.031
- 25 Ruggiero SL,; D. T., Assael L A. et al. . (2009). American Association of Oral and Maxillofacial Surgeons  
26 position paper on bisphosphonate-related osteonecrosis of the jaw - 2009 update. *Aust Endod J*,  
27 35, 119-130.
- 28 Saia, G., Blandamura, S., Bettini, G., Tronchet, A., Totola, A., Bedogni, G., . . . Bedogni, A. (2010). Occurrence  
29 of bisphosphonate-related osteonecrosis of the jaw after surgical tooth extraction. *J Oral*  
30 *Maxillofac Surg*, 68(4), 797-804. doi:10.1016/j.joms.2009.10.026
- 31 Schiodt, M., Nielsen, E. N., Ottesen, C., Madsen, S., Gjoedesen, C., & Reibel, J. (2018). Risk Of Osteonecrosis  
32 Of The Jaw And Histology Of Alveolar Bone After Tooth Extraction With Primary Closure In Patients  
33 On Antiresorptive Therapy [abstract]. *24th Congress of the European Association for Cranio Maxillo*  
34 *Facial Surgery Munich 2018*.
- 35 Schiodt, M., Ottesen, C., Dalsten, H., Oturai, P., & Kofod, T. (2016). Surgical treatment outcome of 141  
36 consecutive patients with medication related osteonecrosis of the jaws from the Copenhagen ONJ  
37 Cohort [abstract]. *EACMFS London 2016*.
- 38 Schiodt, M., Reibel, J., Oturai, P., & Kofod, T. (2014). Comparison of nonexposed and exposed  
39 bisphosphonate-induced osteonecrosis of the jaws: a retrospective analysis from the Copenhagen  
40 cohort and a proposal for an updated classification system. *Oral Surg Oral Med Oral Pathol Oral*  
41 *Radiol*, 117(2), 204-213. doi:10.1016/j.oooo.2013.10.010
- 42 Stockmann, P., Hinkmann, F. M., Lell, M. M., Fenner, M., Vairaktaris, E., Neukam, F. W., & Nkenke, E.  
43 (2010). Panoramic radiograph, computed tomography or magnetic resonance imaging. Which  
44 imaging technique should be preferred in bisphosphonate-associated osteonecrosis of the jaw? A  
45 prospective clinical study. *Clin Oral Investig*, 14(3), 311-317. doi:10.1007/s00784-009-0293-1
- 46 Troeltzsch, M., Cagna, D., Stähler, P., Probst, F., Kaeppler, G., Ehrenfeld, M., & Otto, S. (2016). Clinical  
47 features of peri-implant medication-related osteonecrosis of the jaw: Is there an association to  
48 peri-implantitis? *J Craniomaxillofac Surg*, 44(12), 1945-1951. doi:10.1016/j.jcms.2016.09.018
- 49 Vahtsevanos, K., Kyrgidis, A., Verrou, E., Katodritou, E., Triaridis, S., Andreadis, C. G., . . . Antoniadis, K.  
50 (2009). Longitudinal cohort study of risk factors in cancer patients of bisphosphonate-related  
51 osteonecrosis of the jaw. *J Clin Oncol*, 27(32), 5356-5362. doi:10.1200/JCO.2009.21.9584  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4 Yamada, S. I., Kurita, H., Kondo, E., Suzuki, S., Nishimaki, F., Yoshimura, N., . . . Kamata, T. (2018). Treatment  
5 outcomes and prognostic factors of medication-related osteonecrosis of the jaw: a case- and  
6 literature-based review. *Clin Oral Investig*. doi:10.1007/s00784-018-2743-0  
7  
8 Yarom, N., Fedele, S., Lazarovici, T. S., & Elad, S. (2010). Is exposure of the jawbone mandatory for  
9 establishing the diagnosis of bisphosphonate-related osteonecrosis of the jaw? *J Oral Maxillofac*  
10 *Surg*, 68(3), 705. doi:10.1016/j.joms.2009.07.086  
11  
12 Yazdi, P. M., & Schiodt, M. (2015). Dentoalveolar trauma and minor trauma as precipitating factors for  
13 medication-related osteonecrosis of the jaw (ONJ): a retrospective study of 149 consecutive  
14 patients from the Copenhagen ONJ Cohort. *Oral Surgery Oral Medicine Oral Pathology Oral*  
15 *Radiology*, 119(4), 416-422. doi:10.1016/j.oooo.2014.12.024  
16  
17 Yoneda, T., Hagino, H., Sugimoto, T., Ohta, H., Takahashi, S., Soen, S., . . . Urade, M. (2010).  
18 Bisphosphonate-related osteonecrosis of the jaw: position paper from the Allied Task Force  
19 Committee of Japanese Society for Bone and Mineral Research, Japan Osteoporosis Society,  
20 Japanese Society of Periodontology, Japanese Society for Oral and Maxillofacial Radiology, and  
21 Japanese Society of Oral and Maxillofacial Surgeons. *J Bone Miner Metab*, 28(4), 365-383.  
22 doi:10.1007/s00774-010-0162-7  
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24  
25  
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