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Letter to the Editor (Oral Diseases, or 0000 or Eur Jr Cranio Maxillofacial Surgery)

European Workshop on Medication Related Osteonecrosis of the Jaws:
"The Challenge of Classifying Medication Related Osteonecrosis of the Jaws (MRONJ)".

September 28, 2017 in Copenhagen, Denmark

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Purpose:

The purpose of this paper is to report the conclusions of a workshop on classification of MRONJ held in Copenhagen September 28, 2017 among the above authors. The participants are all active researchers on various aspects of diagnosis and classification of MRONJ, including management and treatment for a number of years, and together, the group have published more than 100 scientific papers on MRONJ. The outcome purpose was to identify and possibly address key research questions to be solved in order to develop comprehensive criteria for classification of MRONJ.

Introduction:

Medication Related OsteoNecrosis of the Jaws (MRONJ) is a serious complication to antiresorptive (AR) treatment in patients with metastases of the skeleton due to various cancers as well in osteoporosis. MRONJ may also result from targeted monotherapy for a number of cancers (Abdel, Nielsen & Schiodt 2018, Monotarget treatment paper).

The global use of antiresorptive medicine for treating osteoporosis (estimated xxxx (world population???), cancer metastases of the skeleton (notably breast, prostate, multiple myeloma (world population?????), and the more recent adjunctive use of AR for cancer patients without metastases (estimate world population???), as well as the recently recognized additional group of patients on mono-targeted chemotherapy, incl. tyrosine kinase inhibitors involving a new group of cancer diagnoses (lung, kidney, gastro-intestinal, ovary, leukemia, glioblastoma and others) (Abdel, Nielsen & Schiodt 2018 and other refs xxxx), must be expected to continously raise, not least considering the increase of long term cancer survivors, although the size of this total population is presently unknown.

The duration of AR is the most important single systemic risk factor with the incidence raising with increasing duration of treatment (refsxxxx). (may be add figures with incidence rates)
Recently, the incidence and prevalence of MRONJ has raised in the industrialized world and is now a significant health problem (refs xxxxx). (Do we have documentation for this??)
MRONJ may lead to jaw pain, loss of teeth and jaw bone, decreased chewing function, and loss of life quality (refs xxxx).

Present classification:

Numerous consensus papers on diagnosis and classification of MRONJ have been published. This letter to the editor will only deal with the consensus papers by Ruggiero et al. representing the American Association of Oral and Maxillofacial Surgeons (AOMFS) (2006, 2009 and 2014) (1-3) as they have been instrumental in the process of establishing understanding and acceptance of a universally accepted definition and classification of MRONJ.

The 2006 paper (4) defined criteria for MRONJ as the presence of exposed jaw bone in a patient receiving antiresorptive treatment (bisphosphonate), who had not received radiation therapy for head and neck cancer. They classifed MRONJ into 4 stages (table 1).

Describing classification problems:

It was early recognized that a particular patient group, the so called ”non-exposed MRONJ”, seems to represent the same disease (osteonecrosis) as those with exposed bone, but was characterized by the absence of exposed bone, and therefore did not formally fullfil the inclusion criteria (5, 6)(Refs Patel et al. Fedele et al, Fedele at al. 2015, Schiodt et al. 2014, Alberto et al 2012, others xxxxx). Some of these patients did have an intraoral fistula, but without frank visible exposed bone (Schiodt et al. 2014, refs xxxx). The 2014 Ruggerio et al. paper (3) partially addressed this issue and the definition was modified from their 2009 paper to include patients with exposed bone and/or patients with fistulas through which the bone could be probed (3).

This modification was a **clear improvement** of the definition. However, non-exposed MRONJ in patients **without fistulas will not be diagnosed following the Ruggerio et al. 2014 – criteria** (Schiodt et al. 2014). Furthermore, in 2015, a multicenter study by Fedele et al. documented that **up to one quarter of patients with osteonecrosis of the jaws remain undiagnosed** (7). A number

of these patients have no fistula. In their paper the authors documented a number of clinical symptoms (except exposed bone), which characterized the patients (may be a table from the Fedele paper here ?).

Since the introduction of Denosumab in 2010 a significant number of MRONJ cases have been documented (refs xxx), and the Ruggerio et al. 2014 paper therefore suggested the term: ”Medication Related Osteonecrosis of the Jaws (MRONJ)”, which seem to be widely accepted, and also fit with the cases related to tyrosine kinase inhibitors related osteonecrosis as well. Basically, any medication leading to osteonecrosis may therefore fit the definition, and the diagnosis can still be destinguisted from osteo-radionecrosis.

Once the diagnosis is acknowledged, MRONJ can often be treated with a high degree of success (Schiodt et al. 2016, Otto et al. 2017, 18, Alberto et al. other refsxxx). Otherwise the dead bone can progress and require removal of large parts of the jaw (ref to the silent MRONJ find refs xxx) . Therefore, an **early diagnosis is of utmost importance.** Furthermore, in this context the requirement of 8 weeks of exposed bone for acceptance of the diagnosis MRONJ may be a limitation for start of relevant and needed treatment.

The **most important local risk factor for MRONJ seems to be an Infection around a tooth** rather than tooth extraction itself which are often done after diagnosing the bad tooth (Otto et al. refs xxxx). The majority (50-70%) of MRONJ onset are preceeded by tooth extraction and often identified when an extraction socket will not heal (8). In patients on high dose AR (cancer patients) the risk is bigger than in patients on low dose AR (osteoporosis). It is documented that controlled tooth extraction with primary closure can be done without developing MRONJ (Heufeld et al., Otto

et al, Schiodt et al). Thus, **if all tooth extractions needed in patients already on high dose AR are done this way, theoretically up to two thirds of MRONJ cases may be prevented.**

Presence of necrotic bone in relation to extracted teeth.

A number of papers have described that facial bone adjacent to teeth to be extracted are actually necrotic, in patients on high dose AR treatment. These findings relate to patients with clinical suspicion of MRONJ related to a periodontally affected teeth as well as patients with no suspicion of MRONJ and therefore showing **surprising histologic findings of dead bone** (Schiodt et al. 2018, Oruania and Migliorati, Alberto ??, other).

Once diagnosis of MRONJ is made, the patient can be treated with a great deal of success, and by proper tooth extraction methods including timing we can potentially prevent the majority.

(May be a small section on **prevention** including dental examination and repairing and extracting bad teeth before start of AR treatment to be inserted here).

What is left?

Left is early diagnosis, including the proper non-exposed MRONJ cases without fistula.

How do we do that?

Many authors of non-exposed MRONJ have suggested criteria to include non-exposed MRONJ (Patel et al., Fedele et al., Schiodt et al.). Some of the critera include histologic verification of dead bone (Schiodt et al. 2014,), others include imaging techniques (refs Alberto et al. xxxxx). The aims of these criteria are to be comprehensive, that is to include the non-exposed MRONJ as well, but

most authors do recognise the difficulty to distinguish between non-exposed MRONJ and other causes of pathology (i.e. peridental, periapical infections, ostomyelitis etc).

Referring to existing 2014 Ruggerio Classification comprising stage 1, 2, and 3 which are straight forward, but also include stage 0, which is defined as no exposed bone in a patient on AR and who have non-specific symptoms like pain, swelling, etc to come….. and even increased lamina dura around teeth, etc . …… (refer to paper……..).

What is the association between Ruggerio's stage 0 and the non-exposed MRONJ?

In summary, Stage 0 comprise two groups of patients: One is those at risk (for MRONJ). That is f.ex. those on AR treatment where radiology shows increased lamina dura around teeth. This phenomenon is not MRONJ. The other group include those with symptoms of pain, swelling, non-specific radiologic changes, who have no exposed bone.

The present authors find it likely that the second group (stage 0 with symptoms) in fact may have non-exposed MRONJ. However, the proof lies on a biopsy proven dead bone.

Summarizing the papers on non-exposed MRONJ and suggestions for criteria we can note that **none of the proposed criteria are tested and validated on a representative group of patients at risk for MRONJ.**

Conclusions:

The working group agreed on the following key **statements**:

- The current classification criteria by Ruggerio et al. (June 2014) does not identify all patients suffering from MRONJ
- Stage 0 is not a valuable classification
- Stage 0 includes two subgroups:
    - 1: is patients on antiresorptive treatment at risk for MRONJ, but not having MRONJ

      (example: patient on AR with increased lamina dura around teeth)

      2: patients with non-exposed MRONJ (with no fistula)
- Stage 0 should be abandoned as a classification criteria
- Imaging should have a place in classification of MRONJ
- The criteria of 8 weeks clinical exposure of bone may be a limitation for start of treatment
- The expanding group of medications (mono-targeted therapy, Tyrosine kinase inhibitors) and expanding group of cancer diagnoses is a new and growing challenge.

The working group agreed on the following key **questions**:

- How do we distinguish between periodontal disease and MRONJ?
- How do we identify early MRONJ?
- How do we distinguish between periapical periodontitis with fistula from MRONJ?
- How do we secure the diagnosis when we cannot wait 8 weeks to treat?
- How do we develop comprehensive classification criteria?

- Is it possible to establish strict classification criteria for non-exposed MRONJ?
- Which imaging techniques should be applied in a “routine diagnostic work-out” on a specialized MRONJ Clinic?
- How should imaging be included in classification criteria?
- Can we develop an international plan for developing and validation of comprehensive criteria?

The working group will meet again to continue the work on classification of MRONJ.

Table:
Mismatch between diagnostic criteria (Ruggerieo et al. 2014) and clinical manifestations.

Exposed MRONJ
Frank Bone exposure included in definition

Non-exposed MRONJ

- Sinus tract (not due to infection) included in definition
- Bone pain not included in definition
- Bone Swelling not included
- Gingival Swelling not included
- Tooth mobility not included
- Mandibular fracture not included
- Sinus Pain not included

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