

Conference Report

# ONJ (MRONJ) Update 2021—Osteonecrosis of Jaw Related to Bisphosphonates and Other Drugs—Prevention, Diagnosis, Pharmacovigilance, Treatment: A 2021 Web Event

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**Abstract:** On the 8th and 9th of May 2021, an online conference was organized to connect Italian physicians, dentists and oral care specialists, students, nurses, psychologists, dental hygiene experts, and other professionals to discuss controversial issues about Medication-Related Osteonecrosis of Jaw (MRONJ). The first section evaluated differences between Italian recommendations, released on 2020 by Italian Societies of Oral Pathology and Medicine (SIPMO) and Maxillofacial Surgery (SICMF), and other international practice guidelines or documents. A first round table gathered expert opinions about MRONJ definitions and staging systems. Another round table was dedicated to opinion of drug prescribers (oncologists, hematologists, rheumatologists, and other physicians treating osteoporosis). Educational sessions illustrated the main differences between previous (2013) and more recent (2020) Italian recommendations. A large space was dedicated to the presentation of scientific contributions from centers in Italy, divided in specific sessions (epidemiology; case series; special case reports; prevention experiences; MRONJ treatment). Conclusions: in an innovative web conference, talks and scientific reports underlined importance of adequate imaging study of bone in definition and staging of MRONJ cases, the role of surgery in treatment of the disease, and the value of oral hygiene in the prevention.

**Keywords:** osteonecrosis; jaw; jaws; osteonecrosis of jaw; bisphosphonate; denosumab; ONJ; BRONJ; MRONJ; staging

## 1. Introduction

Osteonecrosis of the Jaw (ONJ), or Medication-Related Osteonecrosis of the Jaw (MRONJ), is 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 [1].

ONJ has been commonly named as Medication-Related Osteonecrosis of Jaw (MRONJ) since 2014 [2].

MRONJ is an uncommon (not rare) disease, recognized since 2003 [3] and is associated with treatment with some drugs (increasing in number and classes). MRONJ is more frequently observed in bone metastatic cancer and myeloma patients receiving antiresorptive

treatments (bisphosphonates and denosumab) with/without biological agents, but it is also diagnosed in patients receiving bisphosphonates and denosumab for osteoporosis and other nonmalignant bone disorders. Awareness of MRONJ has increased since 2003 but knowledge about risk assessment, predictive factors, management, and treatment strategies is still insufficient.

Since 2003, alerts about Bisphosphonate-Related Osteonecrosis of Jaw (BRONJ), the first known form of MRONJ, started among clinicians and researchers in Italy; in following years a relevant part of first scientific contributes to BRONJ knowledge was published by Italian professionals that were involved in ONJ study and research [4,5].

Particularly, alerts about ONJ were largely diffused among some oncologists, hematologists, and oral care specialists in Piedmont and Aosta Valley (globally 4.4 million population) in North-Western Italy after observation of apparently unexplainable first cases of jaw alterations in cancer and myeloma patients. The “Rete Oncologica di Piemonte e Valle d’Aosta” is a cancer network that includes professionals (physicians, nurses, technicians, supporting staff, data managers, etc.) of all the healthcare units that manage and treat patients with cancer and hematologic disorders in these two regions. In November 2005, the network organized a regional meeting among several figures involved in ONJ diagnosis, management, and treatment, and a systematic collection of BRONJ patient data began [6].

In January 2007 in Alessandria (Piedmont), a national meeting collected first-hand experiences about BRONJ diagnosis, management, prevention, and therapy from centers around Italy. Other dedicated meetings and conferences were held in Alessandria in 2008, 2009, 2010, 2011, 2014, and 2018, thanks to the regional cancer network of Piedmont (Rete Oncologica) in collaboration with members of Italian scientific societies of oral medicine and pathology (SIPMO, Società Italiana di Patologia e Medicina Orale) and maxillofacial surgery (SICMF, Società Italiana di Chirurgia Maxillo-Facciale).

Slides of presentations and reports of communications (mostly in Italian) were published and are available on the website of the Piedmont cancer network [7,8]. Abstracts of communications of invited speakers and of proffered contributions relating to 2014 and 2018 meeting editions were published in English in scientific journals [9,10].

In 2019 and 2020, new important practice guidelines and documents about MRONJ diagnosis, treatment, and management were published. A clinical practice guideline about MRONJ was jointly published by MASCC, ISOO, and ASCO [11]. A European group of experts analyzed current challenges [12]. An Italian commission of experts revised previous recommendations (published in 2013 and limited to BRONJ) [13] and in 2020 released new recommendations online [14] in Italian, which were at the base of a later publication in English [15]. The 2020 recommendations were designed by an expert specialist team for SIPMO and SICMF and was endorsed by a series of Italian scientific societies and organizations (operating in fields of medical oncology, radiology, osteoncology, supportive care in cancer, oral care, bone health, etc.) [14].

Consequently in 2020, a new edition of the “ONJ UPDATE” conference was planned to be held in Alessandria to discuss the recent documents and ongoing issues about MRONJ. Unfortunately, due to the COVID-19 pandemic the conference was delayed to 2021 and was planned as a web event.

## 2. Materials and Methods

The event Scientific Committee (G.C., P.C., A.B., V.F.) planned the program (see *Supplement S1*) and invited the speakers of talks and round tables for discussion of controversial issues and of educational sessions. Foreign speakers were invited to speak in English, and Italian speakers were invited to speak in Italian with slides preferably in English (to permit diffusion of congress reports abroad).

Furthermore a “call for abstract” was launched via email to Italian professionals and published on several websites, to look for researchers interested in proffering and presenting scientific communications inherent to MRONJ, divided in five subgroups:

1. MRONJ case series (at least 10 cases) and epidemiological studies;
2. Case reports/recent issues;
3. MRONJ prevention and follow-up experiences;
4. MRONJ treatment experience reports (at least 10 cases);
5. Miscellanea.

After a first analysis of proffered titles (maximum of 20 words) and short abstracts (at least 150 words) received by the Scientific Committee, the authors of the accepted proposals were invited to publish their work (as a short paper or full paper) in English on Qeios [16], a free scientific platform for a new integrated system of research production and quality check [17]. Instructions for authors included: English language; original works (or update of previous papers) not yet presented to Italian or international congresses in this form; contribution to knowledge about recent MRONJ issues; and no limits of words, figures, tables. All the papers were included in a special section of Qeios, through a tag “ONJ UPDATE 2021” [18]. The contributes published on Qeios within a communicated deadline (10th April 2021) could have been selected for oral presentations; other contributions would have right to publication only.

Five groups of MRONJ experts (oral care specialists, maxillofacial surgeons, oncologists, etc.) were named by the Scientific Committee as reviewers of the papers, asking votes for the works published on Qeios (except for contributions of their own center). On the basis of the median votes given by reviewers, the Scientific Committee selected the papers for oral presentation (8 minutes and discussion by a reviewer) or for short oral presentations (3 minutes), as pre-recorded talks with slides. All the oral presentations were pre-recorded in order to be fully available on a YouTube channel, as whole registration [19] or separate talks or group of talks [20] (See *Supplement S1* for details).

CME (Continuous Medical Education) accreditation for all healthcare professionals was given by the Italian Health Minister, both for the web event and for the recorded form (as a post-hoc course), after answering an evaluation questionnaire.

Links to scientific contributions and oral presentations were planned to be inserted in the educational website [www.onjupdate.it](http://www.onjupdate.it) (accessed on 9 April 2022).

### 3. Results

The meeting was held on the 8 and 9 May 2021, as a web event.

A warm welcome was given to the online audience (400 pre-registered participants; more than 220 online at the start of the event) by the pro tempore Director of the Rete Oncologica Piemonte e Valle d’Aosta (Franca Fagioli, Turin) and the President of SIPMO (Michele Mignogna, Naples).

The program was shortly introduced by members of the Scientific Committee: Giuseppina Campisi, Palermo; Alberto Bedogni, Padua; Paola Carcieri, Turin; and Vittorio Fusco, Alessandria.

#### 3.1. First Session

The first part of the morning of 8 May [19] was dedicated to debated issues (MRONJ definition, diagnosis, treatment). Michele Mignogna (Naples, Italy) and Umberto Romeo (Rome, Italy) were chairmen of the session.

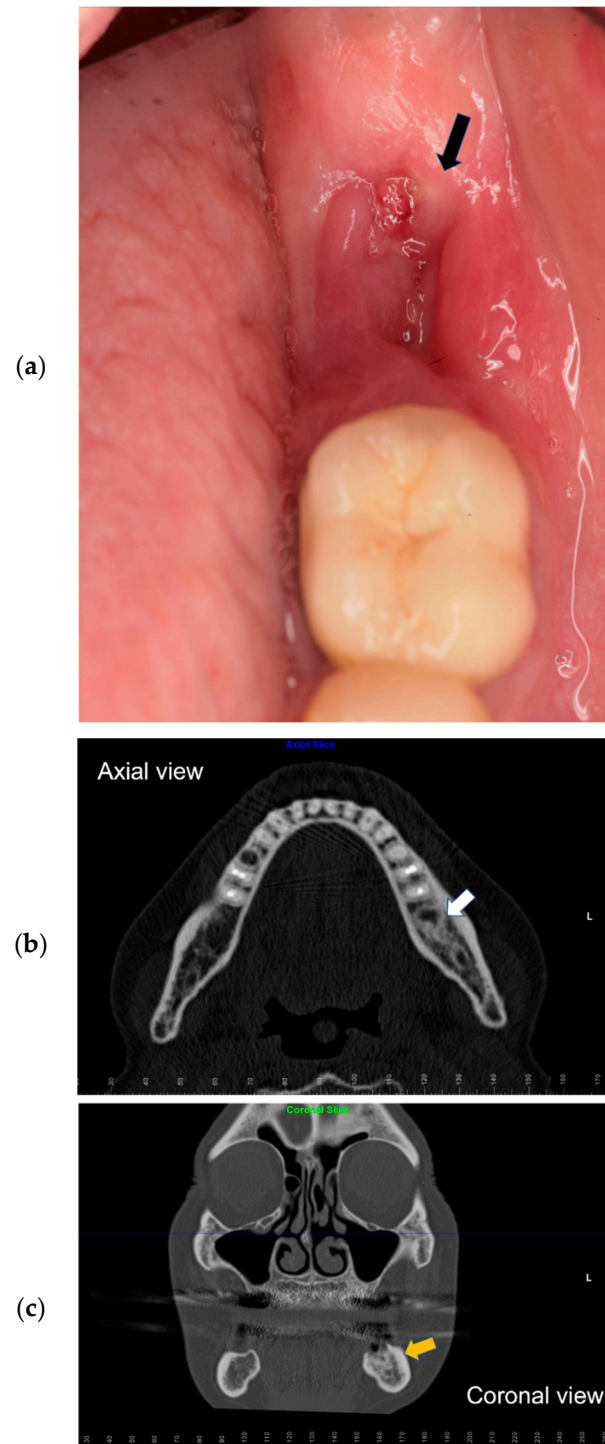
Noam Yarom (oral care specialist at Tel Aviv, Israel) sent a pre-recorded presentation (in English language) that illustrated the 2019 MASCC/ISOO/ASCO Guidelines [11].

Sven Otto (maxillofacial surgeon at Munich, Germany) talked (in English language) about the 2019 European document [12] and honored the memory of Morten Schiodt (Copenhagen, Denmark).

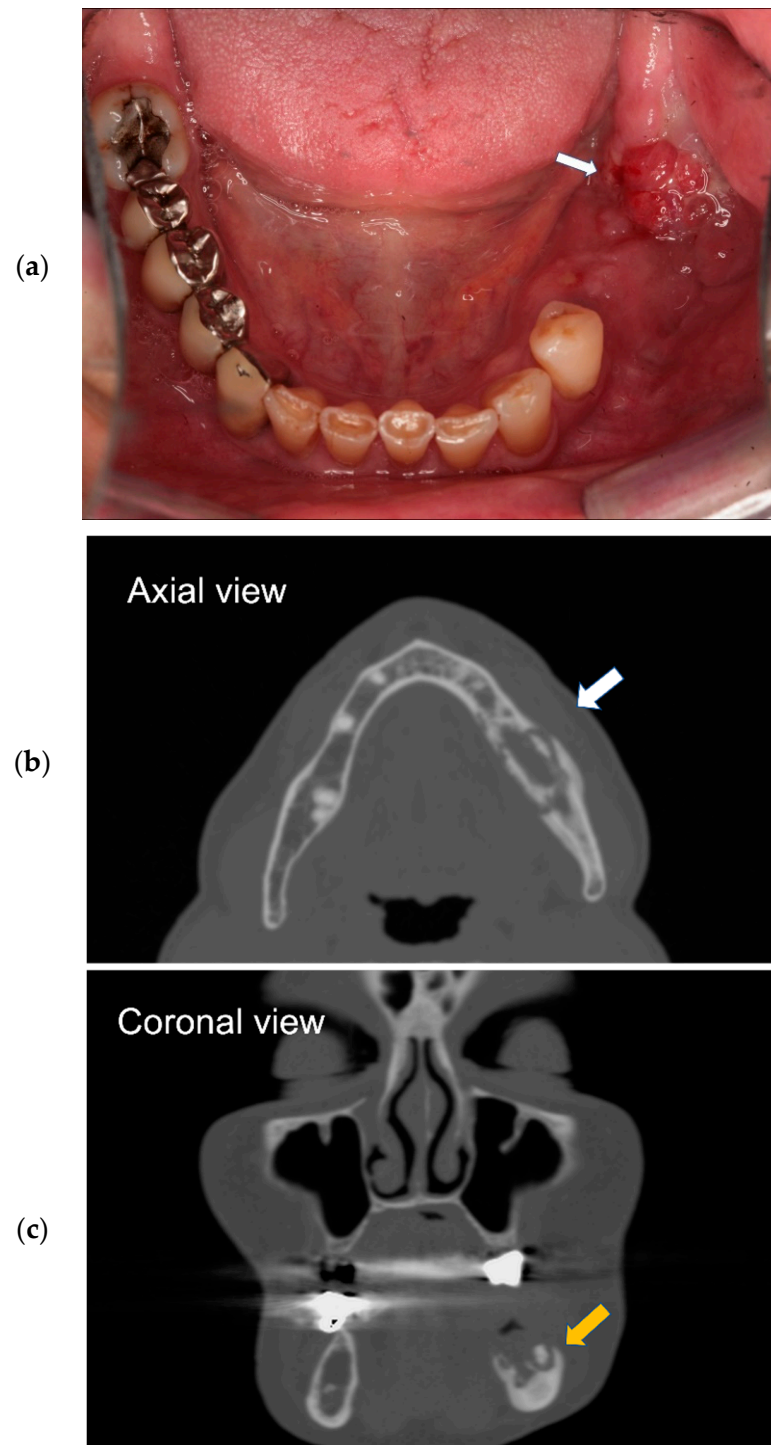
Alberto Bedogni (maxillofacial surgeon at Padua, Italy) reported about work in progress of a European group of specialists, planning a MRONJ data systematic review and an eventual MRONJ consensus statement.

Giuseppina Campisi (oral care specialist at Palermo, Italy) illustrated sums of the 2020 Italian recommendations, approved by a series of Italian scientific societies and

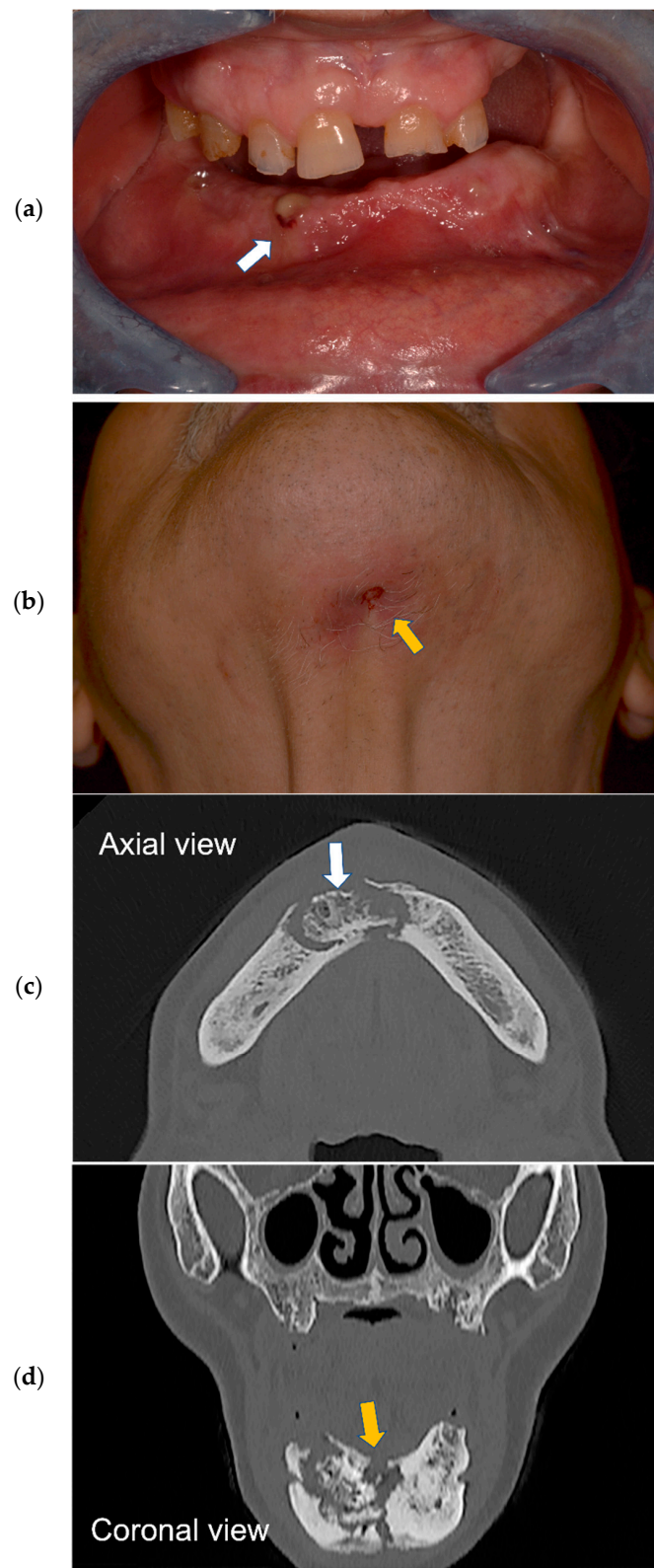
organizations [14,15], focusing on MRONJ definition, MRONJ clinical and radiological pathway to diagnosis (including imaging by Computed Tomography, CT), and SICMF-SIPMO staging system (Figures 1–3).



**Figure 1.** Stage 1 according to SICMF-SIPMO staging system: Focal MRONJ. (a) non-exposed MRONJ following simple tooth extraction; alveolar socket filled up with inflammatory tissue without frank bone exposure (black arrow). (b,c) CT scan axial view showing increased bone density (trabecular thickening and focal osteosclerosis) surrounding the post-extraction socket (white arrow); in the coronal view the increased bone density signal is limited to the alveolar bone region, above the inferior alveolar nerve canal (yellow arrow).



**Figure 2.** Stage 2 according to SICMF-SIPMO staging system: Diffuse MRONJ. (a) Non-exposed MRONJ following simple tooth extraction; the alveolar socket is filled up with inflammatory tissue (white arrow); the bone can be probed through the fistula. (b,c) CT scan axial view showing increased bone density (diffuse bone condensation and osteosclerosis) of the left mandibular body with sequester formation and periosteal reaction (white arrow); in the coronal view, the increased bone density signal is extended to the basal bone, with the loss of cortical and trabecular bone differentiation (yellow arrow).



**Figure 3.** Stage 3 according to SICMF-SIPMO staging system: complicated MRONJ. (a,b) Probing bone fistula and suppuration without frank bone exposure of the mandible in the oral cavity (white arrow); extraoral cutaneous fistula of the submental region (yellow arrow). (c,d) CT scan axial view showing increased bone density (diffuse bone condensation and osteosclerosis) of the entire mandibular arch with massive sequester formation (white arrow); in the coronal view, pathologic fracture of the mandibular symphysis is clearly visible (yellow arrow).

Umberto Romeo (oral care specialist at Rome, Italy) and Vittorio Fusco (oncologist at Alessandria, Italy) collected questions from the web audience.

In the first round table, some Italian oral care and maxillofacial surgery experts debated about different MRONJ definitions and staging systems, both in scientific reports and in clinical practice. Giuseppina Campisi (Palermo, Italy) and Alberto Bedogni (Padua, Italy) were the chairmen of the round table. Participants included: Luigi Califano (maxillofacial surgeon, Naples, Italy), Gianfranco Favia (oral care specialist, Bari, Italy), Amerigo Giudice (oral care specialist, Catanzaro, Italy), Claudio Marchetti (maxillofacial surgeon, Bologna, Italy), Marco Nisi (oral care specialist, Pisa, Italy), Giacomo Oteri (oral care specialist, Messina, Italy), and Andrea Santarelli (oral care specialist, Ancona, Italy). (See *Supplement S1*).

In another round table, Lorenzo Lo Muzio (oral care specialist, Foggia, Italy) and Vittorio Fusco (oncologist, Alessandria, Italy) introduced some oncologists, hematologists, and bone health specialists to report the point of view of drug prescribers about MRONJ debated issues. Participants included: Francesco Bertoldo (bone health specialist, Verona, Italy), Paolo Bossi (oncologist and supportive care specialist, Brescia, Italy), Monica Nancy Fornier (oncologist, New York, USA), Roberto Freilone (hematologist, Turin, Italy), Marco Ladetto (hematologist, Novara and Alessandria, Italy), Gaetano Lanzetta (oncologist and bone disease specialist, Rome, Italy), Emanuela Palmerini (oncologist and Giant Cell Tumor of Bone expert, Bologna, Italy), Maurizio Rossini (rheumatologist, Verona, Italy), Daniele Santini (oncologist and bone health specialist, Rome, Italy) (see *Supplement*).

### 3.2. Second Session

An educational session was dedicated to the main differences between the 2020 Italian ONJ recommendations [14,15] and the previous 2013 BRONJ Recommendations [13].

Olga Di Fedè (oral care specialist, Palermo, Italy) shortly described parts of Recommendations [14,15] about definition of MRONJ [1] based on clinical and radiological features; the diagnosis work-up (with relevance of both clinical signs and symptoms, and radiological facilities and results); the imaging pathway including Computed Tomography (CT) scan; the staging system proposed by SICMF and SIPMO (based on bone involvement at CT scan evaluation).

Rodolfo Mauçeri (oral care specialist, Palermo, Italy) described the recommended measures of MRONJ prevention (before start of treatment with bisphosphonates or denosumab), follow-up (during the antiresorptive therapy), and management of intercurrent oral health disease [14,15].

Paolo Vescovi (oral care specialist, Parma, Italy) revised the treatment options of MRONJ cases, with particular attention to surgery and other treatments (laser, ozone, platelet-derived materials, etc.), beside “conservative” therapy (antibiotics and supportive care).

### 3.3. Lecture

Oscar Bertetto, founder and former director of the Rete Oncologica network (oncologist, Turin, Italy) presented a lecture about the importance of supportive care in oncology and hematology [19].

### 3.4. Scientific Contributions

A total of 62 communications were published on Qeios, as pre-prints [18].

The reviewer committee (all Italian experts, known as authors of papers inherent MRONJ) included: Paolo Arduino (oral care specialist, Turin), Pierantonio Bellini (oralsurgeon, Modena), Matteo Biasotto (oral care specialist, Trieste), Giuseppe Colella (maxillofacial surgeon, Naples), Antonella Fasciolo (maxillofacial surgeon, Alessandria), Vittorio Fusco (oncologist, Alessandria), Michele Giuliani (oral care specialist, Foggia), Alessandra Majorana (oral care specialist, Brescia), Maddalena Manfredi (oral care specialist, Parma), Mario Migliario (oral care specialist, Novara), Vera Panzarella (oral care specialist, Palermo), and Monica Pentenero (oral care specialist, Turin).

Out of 62 papers, 8 were selected for oral presentations [19,20], relevant to: incidence of MRONJ in a large oncology center in Padua (with 1211 patients receiving antiresorptive agents); survival of metastatic cancer and myeloma patients after the diagnosis of MRONJ (609 MRONJ cases of the Rete Oncologica regional database); need of a multidisciplinary approach to MRONJ (case report by Trieste oral care specialists); histological findings of osteonecrosis detected prior to tooth extractions in a patient receiving antiresorptive treatment and consideration of tooth extractions as a trigger event (by Palermo and Messina oral care colleagues); the importance of oral hygiene and correct lifestyles to prevent MRONJ (by Brindisi oral hygiene specialists); curative rates of MRONJ following application of the SICMF-SIPMO surgical treatment algorithm, at Padua maxillofacial center; a “drug holiday” evaluation in MRONJ cases related to denosumab followed at Parma oral care unit (see *Supplement S1* for details).

Further 43 contributions were selected for short oral presentations [19,20], from Italian hospitals, universities, oral care private centers (in Acquaviva delle Fonti, Alessandria, Ancona, Bologna, Brescia, Brindisi, Cagliari, Catania, Catanzaro, L’Aquila, Messina, Milan, Modena, Naples, Novara, Padua, Palermo, Parma, Rome, Treviso, Trieste, Turin, Varese, Vercelli, Verona) and collaborative groups (e.g., the Rete Oncologica MRONJ study group) (see *Supplement S1*).

Eleven short papers, received after the deadline for reviewers’ selection (10 April 2021), are published and available on Qeios [18] (see *Supplement S1*).

### 3.5. Oral Hygiene Specialist—Special Session

On the 9 May, a special session was dedicated to oral hygiene issues in patients receiving antiresorptive drugs. The talks and slides are available together with those of the previous day [19,20]. (See also *Supplement S1*). Chairmen and speakers were all from Italian centers.

Tiziana Francone (Turin), Luigi Morello (Alessandria), Emilia D’Agostino (Genoa) were the chairmen of the session.

Martina Gangale, Michela Rossini, and Lorenzo Azzi (Varese-Como) described psychological and communication aspects of management of patients receiving antiresorptive treatment and at risk of MRONJ.

Valentina Zoi, Costanza Frattini, and Matteo Biasotto (Trieste) reported about the oral hygiene management of cancer and myeloma patients receiving antiresorptive drugs.

Elisabetta Polizzi, Alessandra Lissoni, and Silvio Abati (Milan) described effects of laser bio-stimulating and role of oral hygiene specialist in the treatment of MRONJ.

Paola Zunino, Paola Gavoglio, and Paolo Pera (Genoa) talked about dental implants and MRONJ.

Paola Carcieri, Francesco Erovigni, Paolo Arduino, and Alessandro Dell’Acqua (Turin) reported about non-surgical therapy of periodontal disease in patients receiving antiresorptive agents.

Antonella Abbinante (Bari), Giuseppina Campisi (Palermo), and Domenico Tomassi (Rome) proposed a consensus statement for oral hygiene specialists dealing with patients receiving antiresorptive drugs.

## 4. Discussion

Definition, diagnosis, imaging, prevention, and treatment of MRON presents several controversial aspects [11,12,21,22].

In Italy, MRONJ cases are commonly observed in oncology/hematology units and in oral care centers [4,5]. In a recent paper [23], it was calculated that every year up to 930 new MRON cases might be expected on a national basis throughout Italy.

All the meetings organized at Alessandria between 2007 and 2018 included numerous physicians of many specialties, oral care specialists, dentists, and other health professionals in attendance to discuss the “new” disease that was identified after 2003 and its discussion points.



After the COVID-19 pandemic inhibited usual forms of meetings in 2020 and 2021, new forms of scientific meetings were experimented. At the same time, the need for quick diffusion of COVID-19 research accelerated the use of pre-print publications (papers and scientific communications published without a formal peer review evaluation) and of scientific platforms (as an alternative to traditional scientific journals).

The 2021 edition of ONJ UPDATE meeting was consequently organized as a web event, on 8th and 9th May 2021. The use of pre-recorded communications (with slides and talk of the invited speakers) avoided possible connection problems and moreover permitted a free post-date access (on a YouTube channel). The invited participants of two round tables were free to choose between two alternatives: to send to the Scientific Secretary a pre-recorded comment or to participate live.

Similar to the 2014 and 2018 editions, a “call for abstracts” was published on websites and e-mailed to lists of scholars involved in MRONJ research as well as to university centers. In two previous meetings, abstracts accepted by the Scientific Secretary (as inherent to the meeting) were anonymously evaluated by some MRONJ experts, to be selected for oral communication or poster exhibition; all the abstracts were published on supplement issues of scientific journals [9,10]. For the 2021 ONJ UPDATE meeting the active participants were invited to send a presumptive title and a short abstract; proffered contributions that were considered suitable by the Scientific Secretary could be directly published in an innovative manner, as “pre-print” papers (short papers or full papers, without limitations of words, tables, figures, or number of references) on the Qeios platform. In this manner the authors had not precluded the possibility of definitive succeeding publication, on Qeios or on a traditional scientific journal. Advantages of this new procedure were transparency and gratuitousness of contributing publications, and possibility of public comments by all the meeting participants and even other scholars not participating in the event (as a sort of post-publication peer review). The main disadvantage was the loss of blind evaluation of proffered contributions by expert reviewers for oral presentation selection.

Overall, the experience was positive, and organizers received fair feedback from speakers, round table discussants, and participants. Most of the invited speakers and scientific reports contributed to discuss controversial issues.

Importance of adequate imaging of bone (i.e., Computed Tomography), in both early diagnosis and staging of MRONJ cases was underlined in many talks and a large part of inherent proffered contributions; the limits of previous definition and staging system based on clinical features only [2,11] and the possible advantages of clinical *and* radiological ones [13,14] were shown and discussed.

Equally, the advantages of surgery in treatment of early stages of MRONJ, in comparison with so-called conservative therapy (antibiotics and observation) were underlined.

Furthermore, the value of oral hygiene expertise was focused for MRONJ prevention in patients with bone metastatic cancer and myeloma.

## 5. Conclusions

The COVID-19 pandemic inhibited a regular 2020 ONJ (MRONJ) UPDATE meeting in Alessandria, an awaited appointment for Italian physicians, dentists and scholars interested in disease prevention and management. However, the pandemic’s difficulties pushed towards unexplored forms of organization which created new possibilities of sharing knowledge and expertise. We hope that the 2021 ONJ (MRONJ) UPDATE web event might have been useful and fruitful for both patients and caregivers.

**Supplementary Materials:** The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/oral2020014/s1>. *Supplement S1* (English translation of the web event program and list of communications).

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### Abbreviations

The following abbreviations are used in this manuscript:

ONJ	Osteonecrosis of the Jaw; Osteonecrosis of Jaw; Osteonecrosis of the Jaws
MRONJ	Medication-Related Osteonecrosis of the Jaw
BRONJ	Bisphosphonate-Related Osteonecrosis of the Jaw
SIPMO	Società Italiana di Patologia e Medicina Orale
SICMF	Società Italiana di Chirurgia Maxillo-facciale
MASCC	Multinational Association for Supportive Care in Cancer
ASCO	American Society of Clinical Oncology
ISOO	International Society of Oral Oncology
CT	Computed Tomography

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