

Medication-Related Osteonecrosis of the Jaw: MASCC/ISOO/ASCO Clinical Practice Guideline

Noam Yarom, DMD^{1,2}; Charles L. Shapiro, MD³; Douglas E. Peterson, DMD, PhD⁴; Catherine H. Van Poznak, MD⁵; Kari Bohlke, ScD⁶; Salvatore L. Ruggiero, DMD, MD^{7,8,9}; Cesar A. Migliorati, DDS, MS, PhD¹⁰; Aliya Khan, MD¹¹; Archie Morrison, DDS, MSc^{12,13}; Holly Anderson¹⁴; Barbara A. Murphy, MD¹⁵; Devena Alston-Johnson, MD, MMM¹⁶; Rui Amaral Mendes, DMD, PhD¹⁷; Beth Michelle Beadle, MD, PhD¹⁸; Siri Beier Jensen, DDS, PhD¹⁹; and Deborah P. Saunders, DMD²⁰

PURPOSE To provide guidance regarding best practices in the prevention and management of medication-related osteonecrosis of the jaw (MRONJ) in patients with cancer.

METHODS Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) and ASCO convened a multidisciplinary Expert Panel to evaluate the evidence and formulate recommendations. Guideline development involved a systematic review of the literature and a formal consensus process. PubMed and EMBASE were searched for studies of the prevention and management of MRONJ related to bone-modifying agents (BMAs) for oncologic indications published between January 2009 and December 2017. Results from an earlier systematic review (2003 to 2008) were also included.

RESULTS The systematic review identified 132 publications, only 10 of which were randomized controlled trials. Recommendations underwent two rounds of consensus voting.

RECOMMENDATIONS Currently, MRONJ is defined by (1) current or previous treatment with a BMA or angiogenic inhibitor, (2) exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region and that has persisted for longer than 8 weeks, and (3) no history of radiation therapy to the jaws or metastatic disease to the jaws. In patients who initiate a BMA, preventive care includes comprehensive dental assessments, discussion of modifiable risk factors, and avoidance of elective dentoalveolar surgery (ie, surgery that involves the teeth or contiguous alveolar bone) during BMA treatment. It remains uncertain whether BMAs should be discontinued before dentoalveolar surgery. Staging of MRONJ should be performed by a clinician with experience in the management of MRONJ. Conservative measures comprise the initial approach to MRONJ treatment. Ongoing collaboration among the dentist, dental specialist, and oncologist is essential to optimal patient care.

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INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is defined as exposed bone or bone that can be probed through an intraoral or extra oral fistula(e) in the maxillofacial region and that does not heal within 8 weeks and that occurs in a patient who has received a bone-modifying agent (BMA) or an angiogenic inhibitor agent and has no history of head and neck radiation.^{1,2} The condition may involve the mandible or the maxilla. BMAs that have been linked with MRONJ principally include bisphosphonates and denosumab. BMAs are a key component of the management of patients with cancer with skeletal metastases. These medications provide a number of clinical benefits, including a reduced incidence of skeletal-related events (eg, pathologic fractures and spinal cord compression) and reduced need for radiation or surgery to bone. Use of BMAs is associated with MRONJ, which occurs in approximately 1% to 9% of patients with advanced

cancer (Table 1). MRONJ can be challenging to treat and can cause significant pain and reduced quality of life. Many studies have established that preventive oral care methods combined with effective oral health practices are associated with a lower rate of MRONJ.¹⁵⁻²⁸

This guideline focuses on the prevention and management of MRONJ in patients with cancer who receive BMAs for oncologic indications. The guideline does not address BMAs that are used for osteoporosis, which are administered at a lower dose and carry a lower risk for MRONJ.²⁹ Nor does the guideline address the prevention or management of MRONJ due to medications other than BMAs. MRONJ has been reported in patients who have been treated with other agents,^{30,31} and angiogenic inhibitors are included in a widely used definition of MRONJ,² but evidence regarding the prevention and management of MRONJ due to these other

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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Reprint Requests: 2318 Mill Road, Suite 800, Alexandria, VA 22314; e-mail: guidelines@asco.org

THE BOTTOM LINE

Medication-Related Osteonecrosis of the Jaw: MASCC/ISOO/ASCO Clinical Practice Guideline

Guideline Question

What are the recommended best practices for preventing and managing medication-related osteonecrosis of the jaw (MRONJ) in patients with cancer?

Target Population

Adult patients with cancer who are receiving bone-modifying agents (BMAs) for any oncologic indication.

Target Audience

Oncologists and other physicians, dentists, dental specialists, oncology nurses, clinical researchers, oncology pharmacists, advanced practitioners, and patients with cancer.

Methods

A systematic review of the medical literature was conducted and a multidisciplinary Expert Panel was convened to evaluate the evidence and develop recommendations. Given the low volume of high-quality evidence, a majority of the recommendations are based on consensus using ASCO's formal consensus process.

Recommendations

Clinical Question 1. What is the preferred terminology and definition for osteonecrosis of the jaw (maxilla and mandible) associated with pharmacologic therapies in oncology patients?

Recommendation 1.1. It is recommended that the term medication-related osteonecrosis of the jaw be used when referring to bone necrosis associated with pharmacologic therapies (Type: formal consensus; Evidence quality: insufficient; Strength of recommendation: weak).

Recommendation 1.2. Clinicians should confirm the presence of all three of the following criteria to establish a diagnosis of MRONJ: (1) current or previous treatment with a BMA or angiogenic inhibitor, (2) exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region and that has persisted for longer than 8 weeks, and (3) no history of radiation therapy to the jaws or metastatic disease to the jaws (Type: formal consensus; Evidence quality: insufficient; Strength of recommendation: weak).

Clinical Question 2. What steps should be taken to reduce the risk of MRONJ?

Recommendation 2.1: Coordination of care. For patients with cancer who are scheduled to receive a BMA in a nonurgent setting, oral care assessment (including a comprehensive dental, periodontal, and oral radiographic exam when feasible to do so) should be undertaken before initiating therapy. Based on the assessment, a dental care plan should be developed and implemented. The care plan should be coordinated between the dentist and the oncologist to ensure that medically necessary dental procedures are undertaken before the initiation of the BMA. Follow-up by the dentist should then be performed on a routine schedule, for example every 6 months once therapy with a BMA has commenced (Type: evidence based; Evidence quality: low/intermediate; Strength of recommendation: moderate).

Recommendation 2.2. Modifiable risk factors: members of the multidisciplinary team should address modifiable risk factors for MRONJ with the patient as early as possible. These risk factors include poor oral health, invasive dental procedures, ill-fitting dentures, uncontrolled diabetes mellitus, and tobacco use (Type: formal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 2.3. Elective dentoalveolar surgery: elective dentoalveolar surgical procedures (eg, non-medically necessary extractions, alveoloplasties, and implants) should not be performed during active therapy with a BMA at an oncologic dose. Exceptions may be considered when a dental specialist with expertise in the prevention and treatment of MRONJ has reviewed the benefits and risks of the proposed invasive procedure with the patient and the oncology team (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 2.4. Dentoalveolar surgery follow-up: if dentoalveolar surgery is performed, patients should be evaluated by the dental specialist on a systematic and frequently scheduled basis (eg, every 6 to 8 weeks) until full mucosal coverage of the surgical site has occurred. Communication with the oncologist regarding the status of healing is encouraged, particularly when considering future use of BMA (Table 2) (Type: formal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 2.5. Temporary discontinuation of BMAs before dentoalveolar surgery: for patients with cancer who are receiving a BMA at an oncologic dose, there is insufficient evidence to support or refute the

(continued on following page)

THE BOTTOM LINE (CONTINUED)

need for discontinuation of the BMA before dentoalveolar surgery. Administration of the BMA may be deferred at the discretion of the treating physician, in conjunction with discussion with the patient and the oral health provider (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: weak).

Clinical Question 3. How should MRONJ be staged?

Recommendation 3.1. A well-established staging system should be used to quantify the severity and extent of MRONJ and to guide management decisions. Options include the 2014 American Association of Oral and Maxillofacial Surgeons staging system, the Common Terminology Criteria for Adverse Events version 5.0, and the 2017 International Task Force on Osteonecrosis of the Jaw staging system for MRONJ. The same system should be used throughout the patient's MRONJ course of care. Diagnostic imaging may be used as an adjunct to these staging systems (Type: formal consensus; Evidence quality: insufficient; Strength of recommendation: weak).

Recommendation 3.2. Optimally, staging should be performed by a clinician who is experienced with the management of MRONJ (Type: formal consensus; Evidence quality: insufficient; Strength of recommendation: weak).

Clinical Question 4. How should MRONJ be managed?

Recommendation 4.1: Initial treatment of MRONJ. conservative measures comprise the initial approach to treatment of MRONJ. Conservative measures may include antimicrobial mouth rinses, antibiotics if clinically indicated, effective oral hygiene, and conservative surgical interventions, for example, removal of a superficial bone spicule (Type: formal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 4.2: Treatment of refractory MRONJ. aggressive surgical interventions (eg, mucosal flap elevation, block resection of necrotic bone, or soft tissue closure) may be used if MRONJ results in persistent symptoms or affects function despite initial conservative treatment. Aggressive surgical intervention is not recommended for asymptomatic bone exposure. In advance of the aggressive surgical intervention, the multidisciplinary care team and patient should thoroughly discuss the risks and benefits of the proposed intervention (Type: formal consensus; Evidence quality: insufficient; Strength of recommendation: weak).

Clinical Question 5. Should BMAs be temporarily discontinued after a diagnosis of MRONJ has been made?

Recommendation 5. For patients who are diagnosed with MRONJ while being treated with BMAs, there is insufficient evidence to support or refute the discontinuation of the BMAs. Administration of the BMA may be deferred at the discretion of the treating physician, in conjunction with discussion with the patient and the oral health provider (Type: formal consensus; Evidence quality: insufficient; Strength of recommendation: weak).

Clinical Question 6. What outcome measures should be used in clinical practice to describe the response of the MRONJ lesion to treatment?

Recommendation 6. During the course of MRONJ treatment, the dentist/dental specialist should communicate with the medical oncologist the objective and subjective status of the lesion—resolved, improving, stable, or progressive. The clinical course of MRONJ may affect local and/or systemic treatment decisions with respect to cessation or recommencement of BMAs (Type: formal consensus; Evidence quality: insufficient; Strength of recommendation: weak).

MASCC/ISOO and ASCO believe that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

Additional Resources

More information, including a Data Supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines. Patient information is available at www.cancer.net.

TABLE 1. Bone-Modifying Agents and Risk of MRONJ

| Medication | Indication | Route | Dose, mg | Schedule | Frequency of MRONJ, %* |
|-----------------|---------------------------------|-------|----------|-----------------------------|---------------------------|
| Pamidronate | Bone metastases of solid tumors | IV | 90 | Every 3-4 weeks | 3.2-5.0 ^{3,4} |
| | Multiple myeloma | | | | |
| Zoledronic acid | Bone metastases of solid tumors | IV | 4 | Every 3-4 weeks or 12 weeks | 1.0-8.0 ^{5,6} |
| | Multiple myeloma | | | | |
| | Adjuvant treatment | IV | 4 | Every 3-6 months | 0-1.8 ⁷⁻⁹ |
| Denosumab | Bone metastases of solid tumors | SC | 120 | Every 4 weeks | 0.7-6.9 ^{10-12†} |
| | Adjuvant treatment | SC | 60 | Every 6 months | 0 ¹³ |

Abbreviations: IV, intravenous; MRONJ, medication-related osteonecrosis of the jaw; SC, subcutaneous.

*Risk of MRONJ varies by duration of treatment.

†The estimate of 6.9% is from the open-label extension phase of two phase III studies.¹⁰ It is not adjusted for patient-years of exposure or patient follow up and does not include cases that occurred during the blinded treatment phase. The patient-year adjusted incidence of confirmed ONJ was 1.1% during the first year of denosumab treatment, 3.7% in the second year, and 4.6% per year thereafter.¹⁴

agents remains limited. Throughout this guideline, we emphasize the importance of collaboration among the cancer care team, dentists, and dental specialists.

- Dentists may be community based or hospital based and are the providers who typically complete the precancer therapy dental evaluation and long-term preventive management.
- Dental specialists as cited in this publication refers to dentists with expertise in the clinical management of MRONJ. These individuals may be oral medicine specialists, oral maxillofacial surgeons, hospital dentists, clinical oral pathologists, and/or periodontists.

GUIDELINE QUESTIONS

This clinical practice guideline addresses the following questions:

1. What is the preferred terminology and definition for osteonecrosis of the jaw associated with pharmacologic therapies in oncology patients?
2. What steps should be taken to reduce the risk of MRONJ in patients with cancer?
3. How should MRONJ be staged?
4. How should MRONJ be managed?
5. Should BMAs be temporarily discontinued after a diagnosis of MRONJ has been made?
6. What outcome measures should be used in clinical practice to describe the response of the MRONJ lesion to treatment?

METHODS

Guideline Development Process

Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) and ASCO convened an Expert Panel to consider the evidence and formulate the recommendations. Members of the

Expert Panel were identified from both community and academic settings and had collective expertise in dentistry, medical oncology, oral medicine, and oral and maxillofacial surgery (Appendix Table A1, online only). The Expert Panel also included a patient representative and an ASCO guidelines staff specialist with health research methodology expertise. The Expert Panel convened via teleconference and corresponded through e-mail. Based on the consideration of the evidence, authors were asked to contribute to the development of the guideline, provide critical review, and finalize guideline recommendations. Members of the Expert Panel were responsible for reviewing and approving the final version of guideline, which was then circulated for external review and submitted to *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guideline Committee before publication. The guideline was also reviewed by the MASCC Guidelines Committee. All funding for the administration of the project was provided by MASCC/ISOO and ASCO.

Systematic review of the literature followed the Meta-analysis of Observational Studies in Epidemiology criteria for systematic reviews³² and was conducted by MASCC/ISOO. PubMed and EMBASE were searched for randomized controlled trials or observational studies that were published from January 2009 through December 2017. This systematic review was an update to a previous MASCC/ISOO review that was published in 2010,³³ with an expansion of the search strategy to include denosumab. Publications from the earlier systematic review were included for review by the panel, along with nine additional studies that were identified by applying the current search strategy to the earlier time period. The search strategy is provided in the Data Supplement. Inclusion criteria were works that were published in the English language, in a peer-reviewed journal, and that assessed the oral

manifestations of BMAs in adult patients undergoing cancer therapy. Exclusion criteria were works that were systematic or narrative reviews, opinion papers, in a non-English language, abstracts, and animal model or in vitro studies. Formal quality assessment of included studies was not conducted, but informal assessment suggested that the overall quality of evidence was low. Before submitting the guideline for publication, the literature search strategy was rerun (December 14, 2017 to February 13, 2019) to identify studies that were published after completion of the systematic review. Results of this search were reviewed by the guideline steering group, which concluded that these more recent publications did not alter the recommendations. Systematic review of the evidence revealed a dearth of evidence on which to base the recommendations. Because of the limited evidence available for most of the clinical questions, recommendations were developed using the ASCO modified Delphi formal consensus method.³⁴ This process involved the drafting of recommendations by a subgroup of the Expert Panel using clinical expertise and available evidence, and a discussion of the draft recommendations with the Expert Panel. The Expert Panel was then supplemented by additional experts who were recruited to rate their agreement with the recommendations. The entire membership of experts is referred to as the Consensus Panel. Each recommendation had to have at least 75% agreement by Consensus Panel respondents to be accepted. This methodology is described in additional detail elsewhere.³⁴ After the consensus process was completed and the guideline was reviewed by the ASCO Clinical Practice Guidelines Committee, the committee requested the addition of a recommendation regarding discontinuation of BMAs before invasive dental procedures. This recommendation was developed by the Expert Panel using informal consensus.

Additional information regarding methods used to develop this guideline is available in the Methodology Manual at www.asco.org/guideline-methodology. The Expert Panel and guidelines staff will work with the co-chairs to keep abreast of the need for substantive updates to the guideline. Based on formal review of the emerging literature, MASCC/ISOO and ASCO will determine the need to update.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by ASCO to assist providers in clinical decision-making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to

other interventions, diseases, or stages of diseases. This information does not mandate any course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like “must,” “must not,” “should,” and “should not” indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an “as is” basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO’s Conflict of Interest Policy Implementation for Clinical Practice Guidelines (“Policy,” found at <http://www.asco.org/rwc>). All members of the Expert Panel completed ASCO’s disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact because of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker’s bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

Characteristics of Studies Identified in the Literature Search

A total of 132 papers met the eligibility criteria—10 randomized controlled trials,^{5,10,16,25,35-40} 75 retrospective studies,^{3,15,17-21,23,26-28,41-104} and 47 prospective studies.^{6,22,24,105-148} Due to the limitations of the available evidence, the guideline relied on formal consensus for most recommendations. The only two recommendations that were deemed evidence based by the Expert Panel were those for coordination of care to reduce the risk of MRONJ (Recommendation 2.1) and avoidance of elective dentoalveolar surgery during BMA therapy (Recommendation 2.3).

There were two rounds of voting by the Consensus Panel. During the first round, agreement with individual recommendations ranged from 65% to 92% (N = 26 respondents). Based on feedback from the Consensus Panel, the guideline steering group revised two recommendations, created one new recommendation (Recommendation 3.2), and deleted two recommendations. These revised or new recommendations underwent a second round of voting, in which agreement with the recommendations ranged from 85% to 96% (N = 26 respondents). Results for each recommendation and each round of voting are provided in the Data Supplement. Recommendation 2.5 was added after the consensus voting process was complete and is based on the informal consensus of the Expert Panel.

RECOMMENDATIONS

CLINICAL QUESTION 1. What is the preferred terminology and definition for osteonecrosis of the jaw associated with pharmacologic therapies in oncology patients?

Recommendation 1.1. It is recommended that the term medication-related osteonecrosis of the jaw be used when referring to bone necrosis associated with pharmacologic therapies (Type: formal consensus; Evidence quality: insufficient; Strength of recommendation: weak).

Recommendation 1.2. Clinicians should confirm the presence of all three of the following criteria to establish a diagnosis of MRONJ: (1) current or previous treatment with a BMA or angiogenic inhibitor, (2) exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region and that has persisted for longer than 8 weeks, and (3) no history of radiation therapy to the jaws or metastatic disease to the jaws (Type: formal consensus; Evidence quality: insufficient; Strength of recommendation: weak).

Literature review and analysis. Fifty-two publications used a definition of MRONJ^{15,18,22,24,26,27,42,50,59,62,64,67,70-72,76,80-82,89-91,94,95,97,100-102,105,108,109,111,112,117,118,120,121,123,124,128,131-133,136,138-140,142-144,146,147} that was based on the widely accepted American Association of Oral and Maxillofacial Surgeons (AAOMS) definition of MRONJ.² The remainder of the publications either used a modified definition or did not define the term at all.

Clinical interpretation. The decision to use the term MRONJ rather than bisphosphonate-related osteonecrosis of the jaw (BRONJ) is based on the observation that drugs other than bisphosphonates can also contribute to MRONJ.^{10,44} Panel agreement with this term was not unanimous (some favored the simpler term ONJ) but MRONJ met the criterion for consensus with 81% agreement. The importance of a uniform definition is that it allows for the determination of outcomes. The term MRONJ might be overly simplistic, as there are many known and unknown nonpharmacologic cofactors that contribute to the risk of

MRONJ. For example, inflammation and infection are often present at the site of MRONJ, in conjunction with a history of BMA treatment.^{19-21,27,38,45,47,55,64,67,85,95,103,110,122,124} Genetics may also contribute to the risk of MRONJ.^{149,150} Therefore, although MRONJ implies a causal relationship between medications and the oral condition, the etiology of MRONJ remains poorly understood. Present terminology does not incorporate other risk factors that may influence the development of the lesion¹⁵¹; however, with respect to bone necrosis of the jaw in the oncology setting, distinguishing necrosis that is secondary to pharmacotherapy (MRONJ) from necrosis due to malignancy or radiation (osteoradionecrosis) is important, as management differs.

In keeping with the contemporary definition of MRONJ,² the Expert Panel chose to include angiogenic inhibitors in the definition MRONJ. However, given that additional study of these agents and their relationships to MRONJ are needed,^{30,31} this guideline does not specifically address the prevention and management of MRONJ in patients with current or prior exposure to angiogenic inhibitors. Some authors have proposed adding criteria of radiographic findings to the work up and definition of MRONJ (eg, sclerosis, persistent unresorbed lamina dura associated with extraction sockets, decreased trabecular pattern, or bone lytic changes).^{91,152} Based on the literature, the Expert Panel elected not to use radiographic signs alone for the diagnosis of MRONJ. This approach is consistent with recommendations by AAOMS² and the International Task Force on ONJ.¹ Revising the definition to include radiographic signs alone may lead to an overestimate of true disease frequency by including cases that are suggestive of MRONJ but that are neither confirmed MRONJ, nor likely to progress to MRONJ.

CLINICAL QUESTION 2. What steps should be taken to reduce the risk of MRONJ?

Recommendation 2.1: Coordination of care. For patients with cancer who are scheduled to receive a BMA in a nonurgent setting, oral care assessment, including a comprehensive dental, periodontal, and oral radiographic exam when feasible to do so, should be undertaken before initiating therapy. Based on the assessment, a dental care plan should be developed and implemented. The care plan should be coordinated between the dentist and the oncologist to ensure that medically necessary dental procedures are undertaken before initiation of the BMA. Follow up by the dentist should then be performed on a routine schedule (eg, every 6 months) once therapy with a BMA has commenced (Type: evidence based; Evidence quality: low/intermediate; Strength of recommendation: moderate).

Recommendation 2.2: Modifiable risk factors. Members of the multidisciplinary team should address modifiable risk factors for MRONJ with the patient as early as possible. These risk factors include poor oral health, invasive

dental procedures, ill-fitting dentures, uncontrolled diabetes mellitus, and tobacco use (Type: formal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 2.3: Elective dentoalveolar surgery.

Elective dentoalveolar surgical procedures (eg, nonmedically necessary extractions, alveoloplasties, and implants) should not be performed during active therapy with a BMA at an oncologic dose. Exceptions may be considered when a dental specialist with expertise in the prevention and treatment of MRONJ has reviewed the benefits and risks of the proposed invasive procedure with the patient and the oncology team (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 2.4: Dentoalveolar surgery follow-up.

If dentoalveolar surgery is performed, patients should be evaluated by the dental specialist on a systematic and frequently scheduled basis (eg, every 6 to 8 weeks) until full mucosal coverage of the surgical site has occurred. Communication with the oncologist regarding the status of healing is encouraged, particularly when considering future use of BMA (Table 2) (Type: formal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 2.5: Temporary discontinuation of BMAs before dentoalveolar surgery.

For patients with cancer who are receiving a BMA at an oncologic dose, there is insufficient evidence to support or refute the need for discontinuation of the BMA before dentoalveolar surgery. Administration of the BMA may be deferred at the discretion of the treating physician, in conjunction with discussion with the patient and the oral health provider (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: weak).

Literature review and analysis. Significant risk factors and comorbid conditions that contribute to the development of MRONJ include pamidronate, zoledronic acid, denosumab,^{6,28,41,47,52,58,64,85,87,98,104,140} duration of therapy,^{6,28,41,47,52,64,98,104,140} dental extraction^{6,45,47,55,64,67,68,87,101,110,122,124,140,146} and other oral surgical procedures,^{19,21,27,38,43,67,85,95,103,110} periodontal

disease,^{16,60,64,69,87,110,128,140,145} denture use,^{6,68,140,145} tobacco use,^{24,55,86,95,98,123} angiogenesis inhibitors,^{16,44,74,109,140} and diabetes.⁹⁵ Other factors that may affect the risk of developing MRONJ include chemotherapy^{3,51,60}; corticosteroids^{3,60,110,140} cancer site⁶⁰; renal disease³; erythropoietin therapy³; hypothyroidism⁹⁵; and gender, ethnicity, race, and increasing age.^{3,15,45,64,65,85,86,105,123}

Thirteen studies evaluated the relationship between oral health and MRONJ in patients commencing BMA therapy. Evidence suggests that an emphasis on optimal oral hygiene and treatment of local infection reduces the risk of MRONJ.^{16-21,23-28,104} Based on these data, the Expert Panel recommends that oncology and dental providers comprehensively collaborate to maximize the oral health of patients with cancer receiving BMA.

A retrospective study⁷⁷ and a case series¹¹⁷ suggest that prophylactic antibiotics before oral surgery may reduce the risk of MRONJ, but because of the limitations of these studies, firm conclusions cannot be drawn.

A phase II study reported an exceptionally high incidence of MRONJ (20%) in patients with metastatic castration-resistant prostate cancer that was treated with the combination of zoledronic acid, bevacizumab, thalidomide, docetaxel, and prednisone.⁴⁴ These data illustrate the importance of investigating additive and/or synergistic risk factors that affect the risk of MRONJ.

Clinical interpretation. Estimates for the risk of developing MRONJ after tooth extraction in the oncology population exposed to intravenous bisphosphonates ranges from 1.6% to 14.8%.² Dental care measures that should be carried out before and during BMA therapy include the assessment of oral mucosa for frank bone exposures or fistula probable to bone in postextraction sockets as well as in sites associated with periodontal/periradicular infection. MRONJ lesions occur more commonly in the mandible than in the maxilla⁷³ and are also more prevalent in areas with thin mucosa overlying bone prominences, such as tori, exostoses, and the mylohyoid ridge.^{1,88}

TABLE 2. Proposed Terms to Characterize Osteonecrosis of the Jaw After Treatment

| Term | Mucosal Coverage | Symptom/Pain | Sign of Infection/Inflammation | Radiographic |
|-------------|---|--|--|--|
| Resolved | Complete healing | No pain | None | Trabecular pattern, formation lamina dura resorbed |
| Improving | Significant improvement (> 50% of mucosal coverage) | Significant improvement (> 50% reduction of pain, VAS) | Significant improvement (no signs of infection/inflammation) | Improved trabecular pattern, signs of sequestra |
| Stable | Mild improvement (< 50% of mucosal coverage) | Mild improvement (< 50% reduction of pain, VAS) | Mild improvement (mild signs of infection/inflammation) | No changes |
| Progressive | No improvement or worsening | No improvement or worsening | No improvement | Lytic changes, decreasing trabeculation, increased size of radiographic lesion |

Abbreviation: VAS, visual analog scale.

A dental and periodontal examination should be performed inclusive of radiographic examination (eg, panoramic radiograph and/or full mouth intraoral radiographs) before commencement of BMA therapy. Table 3 lists dental evaluation protocols. When dental procedures involve the manipulation of bone, initial healing as evidenced by mucosal coverage of the bone should occur before BMAs are initiated. Performing the medically necessary dental care in this context, however, may not be feasible in selected patients whose medical condition warrants prompt initiation of the BMA (eg, rapidly progressive bone disease or acute hypercalcemia for which the benefits of promptly starting BMAs outweigh the risk of MRONJ). For such patients, partial and minimal evaluation protocols are suggested (Table 3).

Approaches to reducing the risk of development of MRONJ are centered on medical and dental collaborations to implement preventive oral measures, as well as management of avoidable risk factors, such as poorly controlled diabetes,⁹⁵ smoking,^{24,55,86,95,98,123} ill-fitting dentures,^{6,68,140,145} and poor dental and periodontal health.^{16,60,64,69,87,110,128,140,145} In addition, educating the patient on the importance of a lifelong commitment to oral care is essential for optimal oral care in both dentate and edentulous patients. Education should begin at the evaluation before BMA treatments commence and continue at each 3- to 6-month follow up based on patients' present periodontal disease status and clinical needs.^{29,38}

Use of a systematic daily oral care plan is highly encouraged for patients receiving BMAs (eg, the MASCC/ISOO daily oral care plan; Table 4). The MASCC/ISOO oral care plan is based on fundamentals of mouth care that

incorporate nonpharmacologic oral decontamination by proper brushing and flossing techniques and frequent (eg, three times per day) rinsing with a bland oral rinse composed of 0.5% sodium bicarbonate and 0.9% saline, with intensified use when the mouth is dry or in the presence of oral mucositis. Saline solution mouthwashes are safe and economical and have been used in cancer populations as basic wound care.^{159,160} Sodium bicarbonate has also been used as a cleansing agent because of its ability to dissolve mucus and loosen debris.¹⁶¹ The combination of salt and sodium bicarbonate raises oral pH and prevents overgrowth of acidogenic bacteria. Special instructions for patients with oral prosthetics are addressed in the oral care plan and include moisturization of the oral cavity with the use of non-petroleum-based lubricants, such as plant- or animal-based fats. Use of both fluoridated and remineralizing toothpaste is recommended to maintain dental health in the presence of altered oral flora from the impact of cancer treatment-induced salivary hypofunction.^{162,163}

Although it is generally accepted that elective surgical dental and periodontal procedures are contraindicated during BMA therapy that is administered at oncologic doses, exceptions will occur. Examples of these exceptions emerge when oral function is impaired or oral disease cannot be controlled without extraction, tori removal, and/or implant placement. Not all oral surgical procedures in these scenarios result in the development of MRONJ. Reducing risk is key, yet oral function and quality of life also play roles in deciding whether a surgical procedure should be performed in a patient receiving a BMA. With respect to BMA

TABLE 3. Descriptions of Complete, Partial, and Minimal Dental Evaluation Protocols Based on the Type of Dental and/or Periodontal Pathology¹⁵³

| Dental Pathology | Complete ^{154,155} | Partial ^{156,157} | Minimal, Incomplete, or No Clearance ¹⁵⁴⁻¹⁵⁸ |
|---|--|---|---|
| Caries | Restore all teeth | Mild/moderate caries were restored if time permitted | Intervention only if symptomatic |
| Severe caries/pulp involvement/dental abscess | Root canal treatment <i>or</i> extract | | |
| Apical periodontitis | Retreat | Symptomatic lesions and lesions \geq 5 mm were treated | |
| | Apicoectomy | Asymptomatic lesions and lesions < 5 mm were observed | |
| | Extract | | |
| Advanced periodontal disease | Extract teeth with: | Extract teeth with: | |
| | Probing depth \geq 6 mm | Probing depth \geq 8 mm | |
| | Furcation I, II, III; Mobility III | Mobility III | |
| | Severe inflammation | Severe inflammation | |
| Partially erupted third molars | Extract | Asymptomatic teeth were observed | |
| | | Partially erupted third molars with purulence of pericoronitis were extracted | |

NOTE. The proper protocol should be selected by the oncologist and dentist according to the patient's medical status.

TABLE 4. Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology Daily Oral Care Plan for Patients

| Intervention | Basic Oral Care Plan |
|--|--|
| Flossing | Floss at least once daily |
| | Waxed floss may be easier to use and minimize trauma to the gingivae |
| | If flossing causes bleeding of the gums that does not stop after 2 minutes, consult your oncology team |
| Brushing | Use a small, ultra-soft-headed, rounded-end, bristle toothbrush (an ultrasonic toothbrush may be acceptable) |
| | Use prescription strength fluoride toothpaste; spit out the foam but do not rinse mouth |
| | Use remineralizing pastes and chewing gum containing calcium and phosphate |
| | Brush within 30 minutes after eating and before bed; ensure the gingival portion of the tooth and periodontal sulcus are included |
| | Rinse toothbrush in hot water to soften the brush before using |
| | Brush tongue gently from back to front |
| | Rinse brush after use in hot water and allow to air dry |
| | Change toothbrush when bristles are not standing up straight |
| For patients with dentures | Remove dentures, plates, and prostheses before brushing |
| | Brush and rinse dentures after meals and at bedtime |
| | Remove from mouth for long periods (at least 8 hours per 24 hours) and soak in rinsing solution |
| Rinsing | Rinsing the oral cavity vigorously helps maintain moisture in the mouth, removes the remaining debris, and reduces the accumulation of plaque and infection |
| | Patients should rinse, swish, and spit with a bland rinse (1 teaspoon salt, 1 teaspoon baking soda in 4 cups of water) several times a day |
| | Club soda should be avoided because of the presence of carbonic acids |
| | Commercial mouthwashes with alcohol base or astringent properties are not recommended for patients with oral complications |
| | Debriding should only be done if absolutely necessary, if tissue is loose causing gagging or choking |
| Moisturizing the oral cavity | Moisturize the mouth with water or artificial saliva products or other water-soluble lubricants for use inside the mouth |
| | Avoid glycerin or lemon-glycerin swabs as they dry the mouth and do not moisturize |
| | Apply lubricant after each cleaning, at bedtime, and as needed |
| | Water-based lubricant must be applied more frequently |
| Lip care | Frequent rinsing as needed with basic mouth rinse |
| | To keep lips lubricated and moisturized, use only animal or plant-based oils such as bees wax, cocoa butter, and lanolin. Avoid petroleum-based products as these will cause drying and cracking |
| You should be having follow-ups a minimum of every 6 months with your dentist | |
| If you notice any signs or symptoms, please advise either your dentist or oncologist | |

discontinuation before dentoalveolar procedures, there is limited evidence of benefit, and in some instances BMA discontinuation may increase the risk of fracture, hypercalcemia, and other skeletal-related events, depending on the duration of discontinuation. For those reasons, the panel leaves this decision to the treating clinicians. Dental specialists may be consulted about the risk of MRONJ, and oncologists may be consulted regarding the potential for morbidity related to BMA discontinuation.

CLINICAL QUESTION 3. How should MRONJ be staged?

Recommendation 3.1. A well-established staging system should be used to quantify the severity and extent of

MRONJ and to guide management decisions. Options include the 2014 AAOMS staging system, the Common Terminology Criteria for Adverse Events (CTCAE) 5.0, and the 2017 International Task Force on ONJ staging system for MRONJ. The same system should be used throughout the patient's MRONJ course of care. Diagnostic imaging may be used as an adjunct to these staging systems (Type: formal consensus; Evidence quality: insufficient; Strength of recommendation: weak).

Recommendation 3.2. Optimally, staging should be performed by a clinician who is experienced with the management of MRONJ (Type: formal consensus; Evidence quality: insufficient; Strength of recommendation: weak).

Literature review and analysis. Thirty-eight articles reported the use of a widely accepted scale.^{5,6,10,16,24,35,42,44,62,71,72,80-82,87,89-91,97,100,105,108,109,111,120,124,125,130-133,136,137,140,142-144,147} Of these articles, 32 used the AAOMS system,^{6,24,35,42,62,71,72,80-82,89-91,97,100,105,108,109,111,120,124,125,130-133,136,140,142-144,147} and four used the CTCAE system.^{5,10,16,44} Fifteen articles used a study-specific scale of either modified scales or scales created by the authors.^{19,21,23,27,36,53,57,64,65,85,94,99,110,122,138} No study validated the specific staging systems or conducted comparisons between different staging systems; therefore, no evidence-based recommendation could be established regarding the preferred staging system.

Clinical interpretation. The following two staging systems represent the most frequently used scales as reported in the literature:

- AAOMS system²
- ONJ severity scale (CTCAE)¹⁶⁴

In 2009, AAOMS added a stage 0, which refers to any symptoms of bone pain, fistulous track formation, abscess formation, and altered sensory function. It also includes abnormal radiographic findings that, in the absence of a fistula to bone or frank bone exposure, extend beyond the confines of the alveolar bone as a definitive precursor to MRONJ in patients receiving BMA therapy. The risk of a patient with stage 0 disease experiencing progression to a higher disease stage remains unclear, although case studies suggest that it may occur in up to 50% of patients.^{82,91,116}

Khan et al^{29,165} of the International Task Force on ONJ express concern that the use of stage 0 terminology may lead to overdiagnosis of MRONJ, because initial presenting symptoms may ultimately lead to an alternative diagnosis. For example, the demographics of dentate patients on BMAs overlap those of patients with chronic periodontal and periapical disease. Overdiagnosing patients with MRONJ could lead to detrimental effects in skeletal health if modification or discontinuation of the BMA were implemented. The MASCC/ISOO/ASCO Expert Panel shares these concerns and suggests considering stage 0 as an indicator of increased risk for MRONJ. Identifying this increased risk status could prompt a referral to a dental specialist for close follow up with assessment of early-stage MRONJ, should it develop, to optimize oral health.

CLINICAL QUESTION 4. How should MRONJ be managed?

Recommendation 4.1: Initial treatment of MRONJ. Conservative measures comprise the initial approach to the treatment of MRONJ. Conservative measures may include antimicrobial mouth rinses, antibiotics if clinically indicated, effective oral hygiene, and conservative surgical interventions, for example, removal of a superficial bone spicule (Type: formal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 4.2: Treatment of refractory MRONJ. Aggressive surgical interventions (eg, mucosal flap elevation, block resection of necrotic bone, or soft tissue closure) may

be used if MRONJ results in persistent symptoms or affects function despite initial conservative treatment. Aggressive surgical intervention is not recommended for asymptomatic bone exposure. In advance of aggressive surgical intervention, the multidisciplinary care team and the patient should thoroughly discuss the risks and benefits of the proposed intervention (Type: formal consensus; Evidence quality: insufficient; Strength of recommendation: weak).

Literature review and analysis. Twenty studies of MRONJ treatment were identified.^{35,77,79,87,89,108,115,117,118,121,125,131-134,136,141-143} Nonsurgical approaches include antimicrobial rinses, antibiotic therapy, and oral hygiene. Conservative surgical therapy includes noninvasive removal of superficial sequestered bone (sequestration) with or without the adjunctive use of antimicrobial therapy.

Data are not conclusive regarding the value of surgical intervention. Two prospective studies reported no significant difference in healing rates between surgical and nonsurgical treatments,^{115,142} and two prospective studies reported that less aggressive surgical therapy may produce better outcomes than more aggressive surgical therapy.^{136,141}

Two systematic reviews that compared surgical approaches reported similar findings.^{166,167} However, in a large retrospective study of 337 patients, Ruggiero et al⁸⁹ reported that patients who underwent surgery were 28 times more likely to have a positive outcome than patients who received nonoperative therapy (adjusted odds ratio, 28.74; 95% CI, 14.63 to 56.45). There was no significant difference, however, in outcomes between conservative or aggressive surgical interventions. A smaller retrospective series by Lesclous et al¹²⁵ also reported better outcomes with surgical therapy compared with nonsurgical therapy, with no significant difference between aggressive and conservative surgical therapies.

Antimicrobial treatment can contribute to MRONJ healing as well, including the promotion of focal sequestration of bone. The strategy of using antibiotic therapy was reviewed in six studies, all with varying study results.^{77,87,117,118,121,133} The role of antibiotics in promoting bony sequestration in conjunction with conservative surgery to avoid surgical resection was studied in a longitudinal, prospective, observational study of patients with osteoporosis (n = 18) or cancer (n = 72). Sequestration developed within 15 months in all 91 patients. Mean time to the formation of a sequestrum was 8 months (range, 5 to 11 months).¹¹⁸

Freiberger et al³⁵ in a randomized controlled trial of 46 patients assessed the benefit of hyperbaric oxygen (HBO) as an adjunct to conventional therapy of surgery and antibiotics and found significantly higher rates of improvement in the HBO group compared with the active control group that was treated with conventional therapy of surgery and antibiotics alone (unadjusted odds ratio, 3.45; 95% CI, 1.02 to 11.66; *P* = .03). Despite this improvement in progressive healing time, this study reported no significant

differences in complete gingival healing or changes to quality of life. Additional studies are thus warranted to assess the possible benefits of laser phototherapy, platelet-rich plasma, and HBO.³⁵

Clinical interpretation. Evidence remains limited for alternative therapies, such as hyperbaric oxygen, low-level laser treatment, and plasma-rich growth factors.^{35,79,134}

The Expert Panel recommends the treatment strategies listed in [Table 5](#). The treatment strategy from Ruggiero et al by the AAOMS² endorses symptomatic treatment when necessary for all stages of MRONJ. The Expert Panel does not endorse routine antibiotic therapy unless it is clinically indicated. In patients who are at increased risk of MRONJ (eg, AAOMS stage 0) a referral to a dental specialist is warranted to confirm or rule out suspected MRONJ and the need for close follow up. Communication among the dental specialist, community dentist, and medical oncologist is therefore strongly encouraged. Addressing modifiable risk factors with the patient and lifelong commitment to oral care should be encouraged at every follow-up visit.

With respect to stage 1 MRONJ, prompt referral by the oncologist to a dental specialist and communication with the medical oncologist, community dentist, or primary care physician is strongly encouraged. Continued oral care for periodontal maintenance by the community dentist is encouraged. Treatment strategies for this category include continued patient education about modifiable risk factors, promotion of meticulous oral hygiene, and implementation of antimicrobial mouth rinses. Minor surgical procedures (sequestration or removal of dead bone) to reduce soft tissue trauma are recommended. The Expert Panel recommends follow-up every 8 weeks by a dental specialist with communication on the outcome status of the lesion (resolved, improving, stable, or progressive) to the oncologist ([Table 2](#)). The oncologist can discuss the indication for continuing or discontinuing the therapy based on sound clinical outcomes.

In the case of stage 2 MRONJ, treatment strategies include the use of antibacterial oral rinses and systemic antibiotic therapy. Although infection is not the main cause of MRONJ, bacterial accumulation in the necrotic area is commonly observed and is usually controlled by antimicrobials. Formation of a bacterial membrane has been reported to interfere with the efficacy of systemic antibiotics.¹⁶⁸⁻¹⁷¹ Pain control should be addressed with analgesics, and removal of bone fragments that irritate the soft tissue should be considered in a conservative yet definitive surgical approach as per Recommendation 4.2. Patient education about meticulous oral care, compliance to antibiotic therapy, and modifiable risk factors should be discussed and communicated with the medical oncologist, dental specialist, and primary care physician.

In patients who are diagnosed with stage 3 MRONJ, treatment strategies revolve around pain control, antibacterial oral rinses, and infection control through antibiotic therapy as

needed. In some instances, surgical debridement or resection is necessary to enhance the likelihood of MRONJ resolution. A superficial, well-defined sequestrum, should it develop, should be considered for removal if atraumatic to contiguous tissue. Because cancer metastasis may be included in the differential diagnosis for the bone lesion, the removed bone fragment may be evaluated to rule out malignancy and confirm bone necrosis at the discretion of the surgeon and oncologist.¹⁷²

Treatment objectives for patients with an established diagnosis of MRONJ are to eliminate pain, control infection of the soft and hard tissues, and minimize the progression or occurrence of bone necrosis. Patients with established MRONJ should avoid elective dentoalveolar surgical procedures, as these surgical sites may result in additional areas of exposed necrotic bone. There have been several reports of successful treatment outcomes for all stages of MRONJ after operative therapy (sequestrectomy and/or resection)^{59,62,93,111,131,144,166} and nonoperative therapy.^{90,97,118,142,147,166} With the exception of the more advanced cases of stage 3 disease or in those cases with a well-defined sequestrum, a more prudent approach is to consider operative therapies when nonoperative strategies have failed.^{118,142,166}

Regardless of stage of the MRONJ lesion, areas of superficial necrotic bone that are an ongoing source of soft tissue irritation and loose bony sequestra should be removed or recontoured to optimize soft tissue healing.⁶⁶ Extraction of symptomatic teeth within exposed, necrotic bone should be considered, as it seems unlikely that the extraction will exacerbate the established necrotic process. Although a small percentage of patients who receive antiresorptive therapy develop osteonecrosis of the jaw spontaneously, most affected patients experience this complication after dentoalveolar surgery.^{45,63,101,139}

CLINICAL QUESTION 5. Should BMAs be temporarily discontinued in patients with suspected or established MRONJ?

Recommendation 5. For patients who are diagnosed with MRONJ while being treated with BMAs, there is insufficient evidence to support or refute the discontinuation of BMAs. Administration of the BMA may be deferred at the discretion of the treating physician, in conjunction with discussion with the patient and the oral health provider (Type: formal consensus; Evidence quality: insufficient; Strength of recommendation: weak).

Literature review and analysis. Literature review identified six studies that evaluated the resolution of MRONJ after cessation of BMA therapy.^{72,97,100,108,133,139} Four studies demonstrated no effect of discontinuing BMA on MRONJ outcomes,^{97,108,133,139} whereas in the other two studies there was a positive effect of BMA discontinuation on healing of MRONJ.^{72,100} All six of these studies have methodologic limitations, such as a lack of information regarding the primary reason for BMA discontinuation.

TABLE 5. Treatment Strategies by Stage of MRONJ

| Staging of MRONJ* | Treatment Strategy† |
|---|---|
| At risk: No apparent necrotic bone in patients who have been treated with oral or intravenous bone-modifying agents | No treatment indicated Patient education and reduction of modifiable risk factors |
| Increased risk: No clinical evidence of necrotic bone but nonspecific clinical findings, radiographic changes, and symptoms | Symptomatic management, including the use of pain medication and close scrutiny and follow up Refer to dental specialist and follow up every 8 weeks with communication of lesion status to the oncologist Patient education and reduction of modifiable risk factors |
| Stage 1: Exposed and necrotic bone or fistulas that probe to bone in patients who are asymptomatic and have no evidence of infection | Antibacterial mouth rinse Clinical follow up on an every-8-week basis by dental specialist with communication of lesion status to oncologist Patient education and reduction of modifiable risk factors |
| Stage 2: Exposed and necrotic bone or fistulas that probe to bone associated with infection as evidenced by pain and erythema in the region of exposed bone with or without purulent drainage | Symptomatic treatment with oral antibiotics and topical antibacterial rinse Pain control Debridement to relieve soft tissue irritation and infection control Clinical follow up on an every-8-week basis by dental specialist with communication of lesion status to oncologist Patient education and reduction of modifiable risk factors |
| Stage 3: Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone (ie, inferior border and ramus in mandible maxillary sinus, and zygoma in maxilla) resulting in pathologic fracture, extraoral fistula, oral antral or oral nasal communication, or osteolysis extending to the inferior border of the mandible or sinus floor | Symptomatic treatment with oral antibiotics and topical antibacterial rinse Pain control Surgical debridement or resection for long-term palliation of infection and pain Clinical follow up on an every-8-week basis by dental specialist with communication of lesion status to oncologist Patient education and reduction of modifiable risk factors |

NOTE. Adapted from Ruggiero et al.²

Abbreviation: MRONJ, medication-related osteonecrosis of the jaw.

*Exposed or probable bone in the maxillofacial region without resolution for longer than 8 weeks in patients who were treated with an antiresorptive or an angiogenic inhibitor and who have not received radiation therapy to the jaws.

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

Clinical interpretation. Studies report varied rates of metabolism and half-life of medications that induce MRONJ. Discontinuing the bisphosphonate at MRONJ diagnosis is not likely to affect MRONJ outcomes because of the long half-life. Denosumab has a shorter plasma half-life and there is low-level evidence that temporary discontinuation may enhance MRONJ resolution.² This potential benefit of temporary discontinuation must be weighed against the risk of skeletal-related events.

CLINICAL QUESTION 6. What outcome measures should be used in clinical practice to describe the response of the MRONJ lesion to treatment?

Recommendation 6. During the course of MRONJ treatment, the dentist/dental specialist should communicate

with the medical oncologist the objective and subjective status of the lesion—resolved, improving, stable, or progressive. The clinical course of MRONJ may affect local and/or systemic treatment decisions with respect to the cessation or recommencement of BMAs (Type: formal consensus; Evidence quality: insufficient; Strength of recommendation: weak).

Literature review and analysis. Studies have used varying terminology to describe ONJ outcomes.^{89,140} Terms proposed in the recommendation are based on the consensus of the Expert Panel.

Clinical interpretation. The Expert Panel highlighted the need for outcomes measures to be consistently reported using terminology that allows for subjective and objective findings in the status of MRONJ. Documentation in the literature of

MRONJ definition, staging, and treatment has been acceptable to date; however, documentation of its outcome is limited in the literature, which makes it difficult to measure treatment outcomes and to communicate interprofessionally. Based on clinical mucosal assessment, symptomology, and radiographic and clinical signs, the Expert Panel proposes that lesion status be described by the dental specialist as “Resolved,” “Improving,” “Stable,” and “Progressive” (Table 2).

Historically, full mucosal healing was used as the prototypic indicator to reflect the stability of the MRONJ lesion; however, it is now recognized that the decision to alter therapy based on the absence of full mucosal healing of an MRONJ lesion may not benefit the patient. In some cases, lesion stability rather than full healing may be an acceptable outcome. Our proposed outcome categories are intended to complement the AAOMS staging criteria. For example, in AAOMS stage 1, the outcome of exposed bone can be reported to the oncologist as “resolved,” “stable,” “improving,” or “progressive” based on the mucosal coverage improvement, symptomology, and inflammatory status. If an AAOMS stage 1 lesion presents on follow up with purulence and pain, this would increase the staging to AAOMS stage 2 and an outcome of progressive as its outcome measure. On follow up after antimicrobial therapy, the lesion may present with no inflammation or infection or pain but still an exposed necrotic area of bone, which would then restage the lesion as AAOMS stage 1 with an improving status.

Our hope is that the use of this outcome terminology will enhance the communication of lesion status and treatment outcomes to the medical oncologist so that the dental specialist, patient, and oncologist can make sound clinical treatment decisions based on the clinical status of the lesion. A resolved outcome indicates full mucosal healing in the absence of pain or infection with signs of radiographic changes consistent with this. Continued follow up in patients with resolved lesion status is still crucial as the risk of recurrent or secondary MRONJ is significant.¹⁴⁰ Resolved lesions can be referred back to the general dentist for routine oral care.

GUIDELINE IMPLEMENTATION

To assist clinicians in implementing recommended care, Figure 1 provides a flow diagram that addresses the timeframe of referral and follow up and factors that need to be addressed by each clinician to ensure evidence-based, timely management and prevention of MRONJ. Figure 1 demonstrates a navigable pathway of care that also includes recommended outcomes of care and the flow of interprofessional communication.

This guideline was developed for implementation across health settings. Barriers to implementation include the need to increase awareness of guideline recommendations among front-line practitioners and survivors of cancer and caregivers, as well as to provide adequate services in the

face of limited resources. The guideline Bottom Line Box was designed to facilitate the implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network, posted on the ASCO and MASCC Web sites, and submitted for publication in *Journal of Clinical Oncology*.

PATIENT AND CLINICIAN COMMUNICATION

Health care providers frequently underestimate the incidence and severity of patient symptoms and adverse effects.¹⁷³ To ensure optimal symptom management, clinicians should assess symptoms throughout therapy. In addition, discussion with patients about the importance of modifiable risk factors for MRONJ and a lifelong commitment to oral care is fundamental to MRONJ prevention. Figure 1 illustrates how this can be conducted at each encounter with the oncologist, dentist, or dental specialist.

If patients need assistance identifying a dentist or dental specialist in the United States, options include contacting a nearby dental school (www.adea.org/dentalschools/) or professional organizations, such as the American Academy of Oral Medicine (www.aaom.com/) or the American Association of Oral and Maxillofacial Surgeons (www.aaoms.org/).

For general recommendations and strategies by which to optimize patient–clinician communication, see Patient–Clinician Communication: American Society of Clinical Oncology Consensus Guideline.¹⁷⁴

HEALTH DISPARITIES

There are multiple, complex factors associated with oral health disparities.¹⁷⁵ For example, there are a number of social determinants that contribute to which patients have access to oral health care in general and medically necessary oral care in the context of cancer treatment in particular. These determinants include the patient’s socioeconomic status and degree of health literacy, as well as access to oral health care information and interprofessional oncology protocols that incorporate the management of oral complications of cancer treatment. Despite the importance of addressing the burden of oral disease at the population level and that of the individual patient,¹⁷⁶ important gaps remain in the oral management of the oncology patient.

Racial and ethnic disparities in health care contribute significantly to limited access to medical and dental care in the United States. Patients with cancer who are members of racial/ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving poor-quality care than other Americans.¹⁷⁷⁻¹⁷⁹ Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care

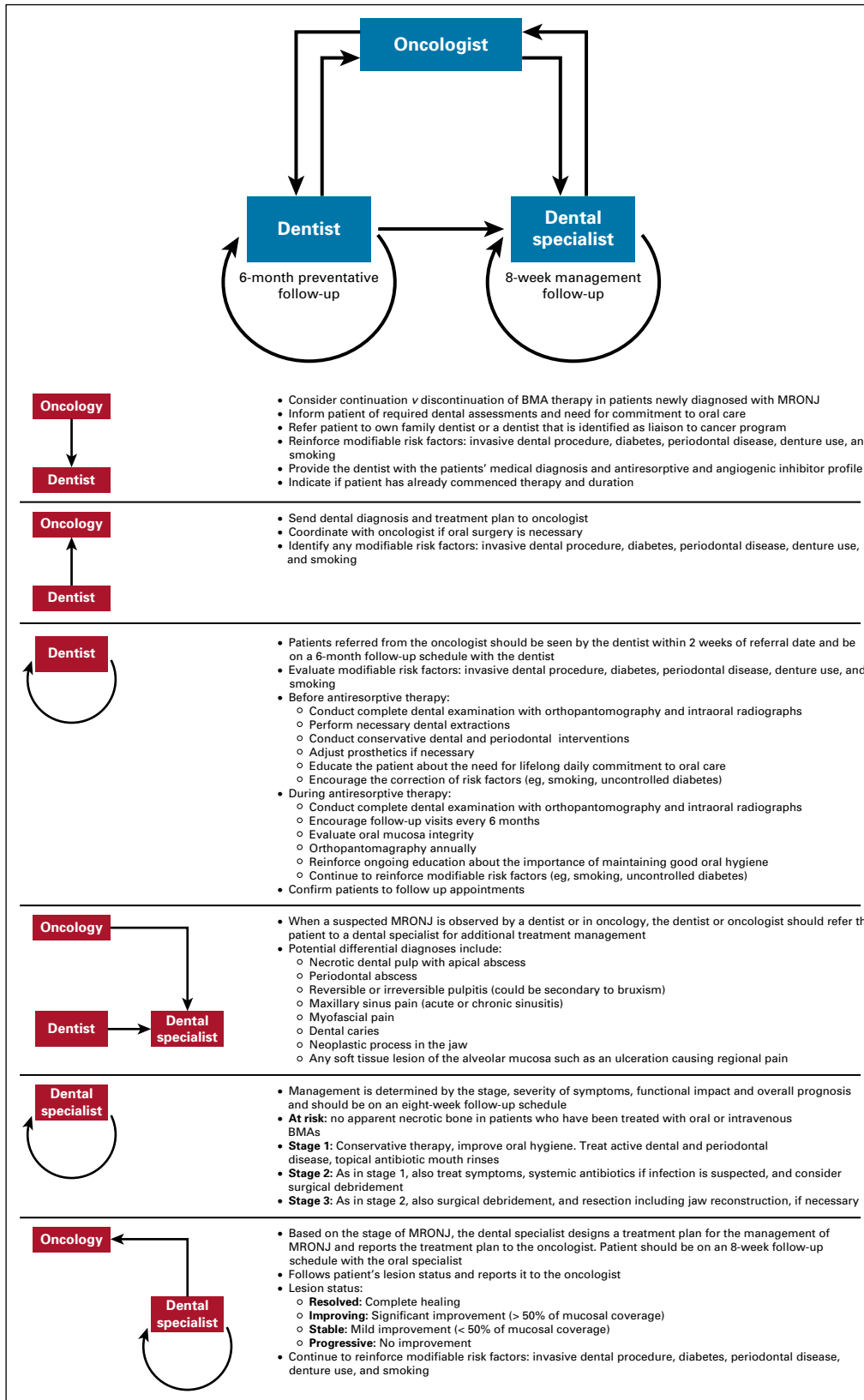


FIG 1. Medication-related osteonecrosis of the jaw (MRONJ) management flow diagram. BMA, bone-modifying agent.

providers should strive to deliver the highest level of cancer care to these vulnerable populations.

COST IMPLICATIONS

Individuals with cancer in the United States are increasingly required to pay a larger proportion of their treatment costs through deductibles and coinsurance.^{180,181} Higher patient out-of-pocket costs have been demonstrated to be a barrier to initiating and adhering to recommended cancer treatments.^{182,183}

Costs of medically necessary dental care as described in this guideline can be problematic for patients who are uninsured or underinsured, including those without dental insurance. In the United States, this problem can be acute for some patients, given the separate medical insurance and dental insurance paradigm that exists for many individuals. In such cases of no dental insurance, communication of the medical importance of complying with current oncology guidelines—provided from the oncology team directly to the patient's medical insurance carrier—may result in medical insurance payment for the dental care.

Discussion of cost can be an important part of shared decision making.¹⁸⁴ Clinicians should discuss with patients the use of less expensive alternatives when practical and feasible for the treatment of the patient's disease and there are two or more treatment options that have comparable benefits and harms.¹⁸⁴

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services that are available to address this complex and heterogeneous landscape.¹⁸⁴

EXTERNAL REVIEW

A draft of the recommendations was made available for a 2-week open comment period. Seven responses were

received. Respondents came from the fields of hematology, medical oncology, radiation oncology, oral oncology, dentistry, periodontology, and patient advocacy. Responses were reviewed and discussed by the steering group before finalizing the guideline.

FUTURE RESEARCH

Optimal treatment of patients with MRONJ remains to be established. New research, including randomized controlled trials, is warranted. The Expert Panel encourages the creation of predictive tools for the development of MRONJ, such as bone turnover markers and genetic markers. For the prescribing physician, the ability to identify patients who are at increased risk for MRONJ might allow for adjustment of BMA dose. For the dentist, such tools would allow for risk stratification before dental surgical procedures. There should also be future consideration of a staging system that incorporates both clinical and radiographic diagnostic criteria.

Agents other than BMAs have been associated with MRONJ.³⁰ The number of cases due to these other agents remains small, but as additional cases are reported it will be important to establish the incidence, prognosis, and optimal management of these cases.

RELATED ASCO GUIDELINES

Role of Bone-Modifying Agents in Metastatic Breast Cancer¹⁸⁵ (<http://ascopubs.org/doi/10.1200/JCO.2017.75.4614>)

Role of Bone-Modifying Agents in Multiple Myeloma¹⁸⁶ (<http://ascopubs.org/doi/10.1200/JCO.2017.76.6402>)

Integration of Palliative Care into Standard Oncology Practice¹⁸⁷ (<http://ascopubs.org/doi/10.1200/JCO.2016.70.1474>)

Patient-Clinician Communication¹⁷⁴ (<http://ascopubs.org/doi/10.1200/JCO.2017.75.2311>)

AFFILIATIONS

¹Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel

²Tel Aviv University, Tel Aviv, Israel

³Icahn School of Medicine at Mt Sinai, New York, NY

⁴UConn Health: Neag Comprehensive Cancer Center, Farmington, CT

⁵University of Michigan, Ann Arbor, MI

⁶American Society of Clinical Oncology, Alexandria, VA

⁷Hofstra North Shore-LIJ School of Medicine, Hempstead, NY

⁸Stony Brook School of Dental Medicine, Stony Brook, NY

⁹New York Center for Orthognathic and Maxillofacial Surgery, New York, NY

¹⁰University of Florida College of Dentistry, Gainesville, FL

¹¹McMaster University, Hamilton, Ontario, Canada

¹²Dalhousie University, Halifax, Nova Scotia, Canada

¹³Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada

¹⁴Breast Cancer Coalition of Rochester, Rochester, NY

¹⁵Vanderbilt University, Nashville, TN

¹⁶University of North Carolina Cancer Care at Nash, Rocky Mount, NC

¹⁷Case Western Reserve University, Cleveland, OH

¹⁸Stanford University Medical Center, Stanford, CA

¹⁹Aarhus University, Aarhus, Denmark

²⁰Northern Ontario School of Medicine, Sudbury, Ontario, Canada.

CORRESPONDING AUTHOR

American Society of Clinical Oncology, 2318 Mill Rd, Suite 800, Alexandria, VA 22314; e-mail: guidelines@asco.org.

EQUAL CONTRIBUTION

N.Y. and C.L.S. were Expert Panel co-chairs.

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EDITOR'S NOTE

This joint American Society of Clinical Oncology (ASCO) and Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) Clinical Practice Guideline provides recommendations for prevention and treatment of medication-related osteonecrosis of the jaw, including a comprehensive review and analysis of the relevant literature for each recommendation. Additional information, including a data supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/supportive-care-guidelines.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI <https://doi.org/10.1200/JCO.19.01186>.

AUTHOR CONTRIBUTIONS

Conception and design: Noam Yarom, Charles L. Shapiro, Douglas E. Peterson, Catherine H. Van Poznak, Salvatore L. Ruggiero, Cesar A.

Migliorati, Aliya Khan, Archie Morrison, Rui Amaral Mendes, Beth Michelle Beadle, Siri Beier Jensen, Deborah P. Saunders

Collection and assembly of data: Noam Yarom, Douglas E. Peterson, Catherine H. Van Poznak, Kari Bohlke, Rui Amaral Mendes, Beth Michelle Beadle, Siri Beier Jensen, Deborah P. Saunders

Data analysis and interpretation: Noam Yarom, Charles L. Shapiro, Douglas E. Peterson, Catherine H. Van Poznak, Kari Bohlke, Salvatore L. Ruggiero, Cesar A. Migliorati, Holly Anderson, Barbara A. Murphy, Devena Alston-Johnson, Rui Amaral Mendes, Beth Michelle Beadle, Siri Beier Jensen, Deborah P. Saunders

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Medication-Related Osteonecrosis of the Jaw: MASCC/ISOO/ASCO Clinical Practice Guideline

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Douglas E. Peterson

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Salvatore L. Ruggiero

Consulting or Advisory Role: Amgen

Cesar A. Migliorati

Consulting or Advisory Role: Amgen

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Aliya Khan

Research Funding: Amgen, Merck, Alexion Pharmaceuticals

Barbara A. Murphy

Honoraria: Merck, Bristol-Myers Squibb

Devena Alston-Johnson

Consulting or Advisory Role: Blueprint Medicines, IQvia

Rui Amaral Mendes

Expert Testimony: Amgen

Travel, Accommodations, Expenses: Amgen

Deborah P. Saunders

Honoraria: Amgen, Pfizer

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APPENDIX

TABLE A1. Medication-Related Osteonecrosis of the Jaw: MASCC/ISOO/ASCO Clinical Practice Guideline Expert Panel Membership

| Author | Affiliation/Institution | Role and/or Area of Expertise |
|--|--|--|
| Charles L. Shapiro, MD, co-chair | Icahn School of Medicine at Mt Sinai, New York, NY | Medical oncology |
| Noam Yarom, DMD, co-chair | Oral Medicine Unit, Sheba Medical Center, Tel Hashomer, and School of Dental Medicine, Tel Aviv University, Tel Aviv, Israel | Oral medicine |
| Douglas E. Peterson, DMD, PhD, FDS RCSEd, steering group | School of Dental Medicine and Neag Comprehensive Cancer Center, UConn Health, Farmington, CT | Oral medicine |
| Deborah P. Saunders, BSc, DMD, steering group | North East Cancer Center, Health Sciences North, Northern Ontario School of Medicine, Sudbury, Ontario, Canada | Hospital dentistry |
| Devena Alston-Johnson, MD, PGIN representative | University of North Carolina Cancer Care at Nash, Rocky Mount, NC | Hematology/oncology |
| Holly Anderson | Breast Cancer Coalition of Rochester, Rochester, NY | Patient advocate |
| Beth Michelle Beadle, MD, PhD | Stanford University Medical Center, Stanford, CA | Radiation oncology |
| Siri Beier Jensen, DDS, PhD | Aarhus University, Aarhus, Denmark | Oral medicine |
| Aliya Khan, MD | McMaster University, Hamilton, Ontario, Canada | Endocrinology and metabolism, geriatric medicine |
| Rui Amaral Mendes, DMD, PhD | Case Western Reserve University, Cleveland, OH | Oral medicine |
| Cesar A. Migliorati, DDS, MS, PhD | University of Florida College of Dentistry, Gainesville, FL | Oral medicine |
| Archie Morrison, DDS, MSc | Dalhousie University and the Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada | Oral and maxillofacial surgery |
| Barbara A. Murphy, MD | Vanderbilt University, Nashville, TN | Head and neck oncology |
| Salvatore L. Ruggiero, DMD, MD | Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY; Stony Brook School of Dental Medicine, Stony Brook, NY; New York Center for Orthognathic and Maxillofacial Surgery, New York, NY | Oral and maxillofacial surgery |
| Catherine H. Van Poznak, MD | University of Michigan, Ann Arbor, MI | Medical oncology |
| Kari Bohlke, ScD | American Society of Clinical Oncology, Alexandria, VA | Practice guidelines staff, health research methods |

Abbreviation: PGIN, Practice Guideline Implementation Network.