ASCO special article abstract

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

Noam Yarom, DMD[1,2]; Charles L. Shapiro, MD[3]; Douglas E. Peterson, DMD, PhD[4]; Catherine H. Van Poznak, MD[5]; Kari Bohlke, ScD[6]; Salvatore L. Ruggiero, DMD, MD[7,8,9]; Cesar A. Migliorati, DDS, MS, PhD[10]; Aliya Khan, MD[11]; Archie Morrison, DDS, MSc[12,13]; Holly Anderson[14]; Barbara A. Murphy, MD[15]; Devena Alston-Johnson, MD, MMM[16]; Rui Amaral Mendes, DMD, PhD[17]; Beth Michelle Beadle, MD, PhD[18]; Siri Beier Jensen, DDS, PhD[19]; and Deborah P. Saunders, DMD[20]

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.

J Clin Oncol 37:2270-2290. © 2019 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Appendix

Data Supplement

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

Accepted on May 2, 2019 and published at jco.org on July 22, 2019: DOI https://doi.org/10.1200/JCO.19.01186

ASCO Clinical Practice Guideline Committee Approved: April 30, 2019

MASCC Guidelines Committee Approved: April 25, 2019

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

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

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, 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

(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 reviews[32] 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 lesion[151]; 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 AAOMS[2] 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 site[60]; renal disease[3]; erythropoietin therapy[3]; hypothyroidism[95]; 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 study[77] and a case series[117] 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 maxilla[73] 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 Pathology[153]

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 *or* extract		
Apical periodontitis	Retreat	Symptomatic lesions and lesions ≥ 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 ≥ 6 mm	Probing depth ≥ 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
	Frequent rinsing as needed with basic mouth rinse
Lip care	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 system[2]
- 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 al[89] 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 al[125] 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 boney 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 al[35] 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 AAOMS[2] 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

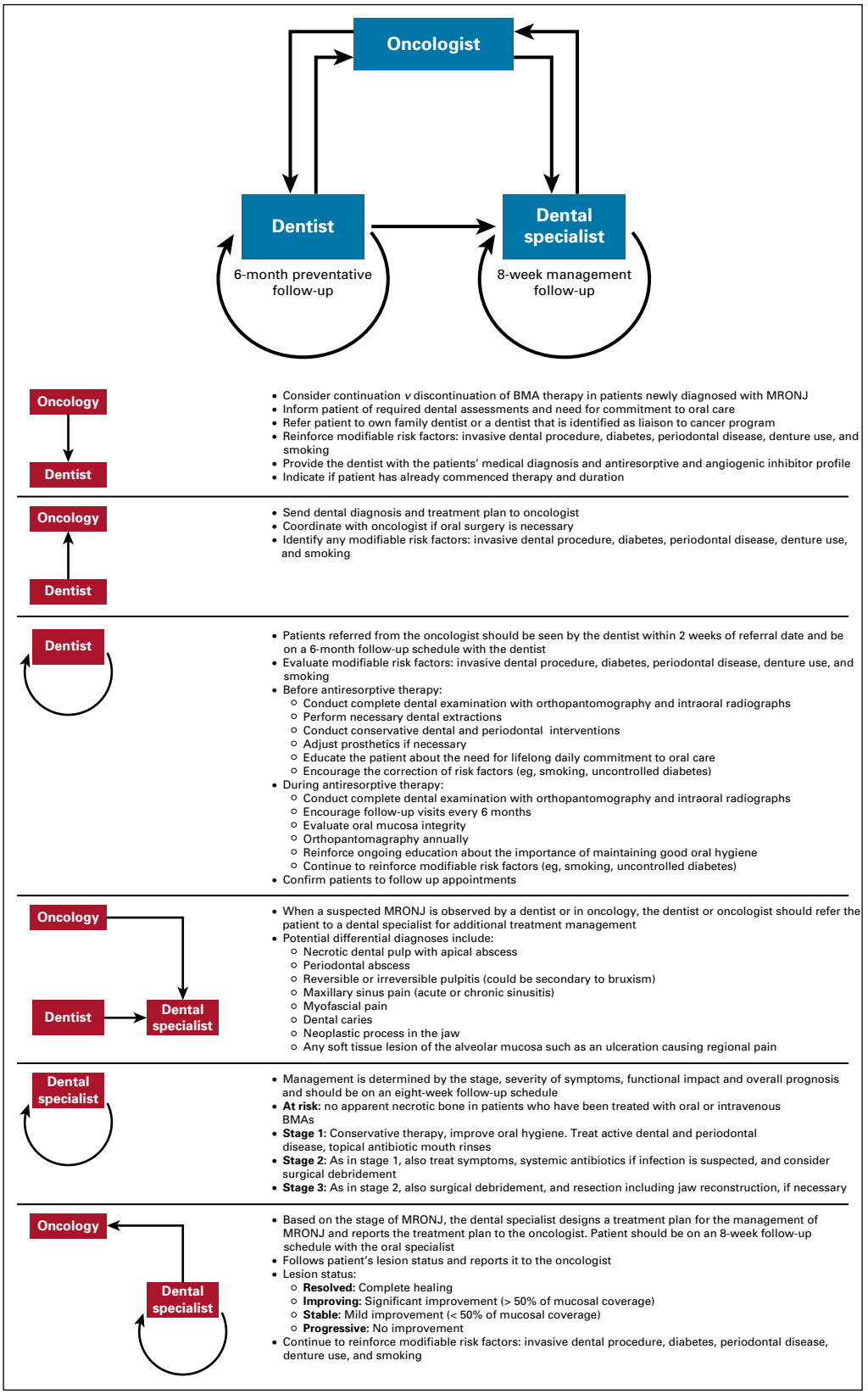

FIG 1. Medication-related osteonecrosis of the jaw (MRONJ) management flow diagram. BMA, bone-modifying agent.

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 Cancer[185] (http://ascopubs.org/doi/10.1200/JCO.2017.75.4614)
- Role of Bone-Modifying Agents in Multiple Myeloma[186] (http://ascopubs.org/doi/10.1200/JCO.2017.76.6402)
- Integration of Palliative Care into Standard Oncology Practice[187] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[174] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

AFFILIATIONS

[1]Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel
[2]Tel Aviv University, Tel Aviv, Israel
[3]Icahn School of Medicine at Mt Sinai, New York, NY
[4]UConn Health: Neag Comprehensive Cancer Center, Farmington, CT
[5]University of Michigan, Ann Arbor, MI
[6]American Society of Clinical Oncology, Alexandria, VA
[7]Hofstra North Shore-LIJ School of Medicine, Hempstead, NY
[8]Stony Brook School of Dental Medicine, Stony Brook, NY
[9]New York Center for Orthognathic and Maxillofacial Surgery, New York, NY
[10]University of Florida College of Dentistry, Gainesville, FL
[11]McMaster University, Hamilton, Ontario, Canada
[12]Dalhousie University, Halifax, Nova Scotia, Canada
[13]Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada
[14]Breast Cancer Coalition of Rochester, Rochester, NY
[15]Vanderbilt University, Nashville, TN
[16]University of North Carolina Cancer Care at Nash, Rocky Mount, NC
[17]Case Western Reserve University, Cleveland, OH
[18]Stanford University Medical Center, Stanford, CA
[19]Aarhus University, Aarhus, Denmark
[20]Northern 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.

SUPPORT

Funded by Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology and the American Society of Clinical Oncology.

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

ACKNOWLEDGMENT

The Expert Panel thanks Eben Rosenthal, MD, Alejandra Perez, MD, the ASCO Clinical Practice Guidelines Committee, and the Multinational Association of Supportive Care in Cancer Guidelines Committee for their thoughtful reviews and insightful comments on this guideline. For their contributions to the systematic review of the literature, the Expert Panel thanks Deborah P. Saunders, Tanya Rouleau, Sophie Lamoureux, Caitlyn Kusnierczyk, Jacob Belanger, Kivanc Bektas Kayhan, Ofir Morag, Bente Brokstad Herlofson, Lone Forner, Pia Lopez Jornet, Noam Yarom, Lauren Levi, Giulia Ottaviani, Ourania Nicolatou-Galitis, Ivan Alajbeg, Marisol Michelet, Yoshihiko Soga, Juan J. Toro, Andres Pinto, and Nathaniel Treister; MRONJ Section of the Oral Care Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology.

REFERENCES

1. Khan A, Morrison A, Cheung A, et al: Osteonecrosis of the jaw (ONJ): Diagnosis and management in 2015. Osteoporos Int 27:853-859, 2016
2. Ruggiero SL, Dodson TB, Fantasia J, et al: American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. J Oral Maxillofac Surg 72:1938-1956, 2014 [Erratum: J Oral Maxillofac Surg 73:1879, 2015; J Oral Maxillofac Surg 73:1440, 2015]
3. Jadu F, Lee L, Pharoah M, et al: A retrospective study assessing the incidence, risk factors and comorbidities of pamidronate-related necrosis of the jaws in multiple myeloma patients. Ann Oncol 18:2015-2019, 2007
4. Gimsing P, Carlson K, Turesson I, et al: Effect of pamidronate 30 mg versus 90 mg on physical function in patients with newly diagnosed multiple myeloma (Nordic Myeloma Study Group): A double-blind, randomised controlled trial. Lancet Oncol 11:973-982, 2010
5. Himelstein AL, Foster JC, Khatcheressian JL, et al: Effect of longer-interval vs standard dosing of zoledronic acid on skeletal events in patients with bone metastases: A randomized clinical trial. JAMA 317:48-58, 2017
6. Vahtsevanos K, Kyrgidis A, Verrou E, et al: Longitudinal cohort study of risk factors in cancer patients of bisphosphonate-related osteonecrosis of the jaw. J Clin Oncol 27:5356-5362, 2009
7. Coleman RE, Collinson M, Gregory W, et al: Benefits and risks of adjuvant treatment with zoledronic acid in stage II/III breast cancer. 10 years follow-up of the AZURE randomized clinical trial (BIG 01/04). J Bone Oncol 13:123-135, 2018
8. Hershman DL, McMahon DJ, Crew KD, et al: Zoledronic acid prevents bone loss in premenopausal women undergoing adjuvant chemotherapy for early-stage breast cancer. J Clin Oncol 26:4739-4745, 2008
9. Shapiro CL, Halabi S, Hars V, et al: Zoledronic acid preserves bone mineral density in premenopausal women who develop ovarian failure due to adjuvant chemotherapy: Final results from CALGB trial 79809. Eur J Cancer 47:683-689, 2011
10. Stopeck AT, Fizazi K, Body JJ, et al: Safety of long-term denosumab therapy: Results from the open label extension phase of two phase 3 studies in patients with metastatic breast and prostate cancer. Support Care Cancer 24:447-455, 2016 [Erratum: Support Care Cancer 24:457-458, 2016]
11. Qi WX, Tang LN, He AN, et al: Risk of osteonecrosis of the jaw in cancer patients receiving denosumab: A meta-analysis of seven randomized controlled trials. Int J Clin Oncol 19:403-410, 2014
12. Scagliotti GV, Hirsh V, Siena S, et al: Overall survival improvement in patients with lung cancer and bone metastases treated with denosumab versus zoledronic acid: Subgroup analysis from a randomized phase 3 study. J Thorac Oncol 7:1823-1829, 2012
13. Gnant M, Pfeiler G, Dubsky PC, et al: Adjuvant denosumab in breast cancer (ABCSG-18): A multicentre, randomised, double-blind, placebo-controlled trial. Lancet 386:433-443, 2015
14. Stopeck AT, Warner DJ: Response to letter to the editors: Safety of long-term denosumab therapy. Support Care Cancer 25:353-355, 2017
15. Gabbert TI, Hoffmeister B, Felsenberg D: Risk factors influencing the duration of treatment with bisphosphonates until occurrence of an osteonecrosis of the jaw in 963 cancer patients. J Cancer Res Clin Oncol 141:749-758, 2015
16. Guarneri V, Miles D, Robert N, et al: Bevacizumab and osteonecrosis of the jaw: Incidence and association with bisphosphonate therapy in three large prospective trials in advanced breast cancer. Breast Cancer Res Treat 122:181-188, 2010
17. Haidar A, Jønler M, Folkmar TB, et al: Bisphosphonate (zoledronic acid)-induced osteonecrosis of the jaw. Scand J Urol Nephrol 43:442-444, 2009
18. Kajizono M, Sada H, Sugiura Y, et al: Incidence and risk factors of osteonecrosis of the jaw in advanced cancer patients after treatment with zoledronic acid or denosumab: A retrospective cohort study. Biol Pharm Bull 38:1850-1855, 2015

19. Mavrokokki T, Cheng A, Stein B, et al: Nature and frequency of bisphosphonate-associated osteonecrosis of the jaws in Australia. J Oral Maxillofac Surg 65: 415-423, 2007
20. Merigo E, Manfredi M, Meleti M, et al: Bone necrosis of the jaws associated with bisphosphonate treatment: A report of twenty-nine cases. Acta Biomed 77: 109-117, 2006
21. Palaska PK, Cartsos V, Zavras AI: Bisphosphonates and time to osteonecrosis development. Oncologist 14:1154-1166, 2009
22. Patel CG, Yee AJ, Scullen TA, et al: Biomarkers of bone remodeling in multiple myeloma patients to tailor bisphosphonate therapy. Clin Cancer Res 20: 3955-3961, 2014
23. Pires FR, Miranda A, Cardoso ES, et al: Oral avascular bone necrosis associated with chemotherapy and biphosphonate therapy. Oral Dis 11:365-369, 2005
24. Rabelo GD, Assunção JNR Jr, Chavassieux P, et al: Bisphosphonate-related osteonecrosis of the jaws and its array of manifestations. J Maxillofac Oral Surg 14: 699-705, 2015
25. Saad F, Shore N, Van Poppel H, et al: Impact of bone-targeted therapies in chemotherapy-naïve metastatic castration-resistant prostate cancer patients treated with abiraterone acetate: Post hoc analysis of study COU-AA-302. Eur Urol 68:570-577, 2015
26. Sim IeW, Sanders KM, Borromeo GL, et al: Declining incidence of medication-related osteonecrosis of the jaw in patients with cancer. J Clin Endocrinol Metab 100:3887-3893, 2015
27. Vidal-Real C, Pérez-Sayáns M, Suárez-Peñaranda JM, et al: Osteonecrosis of the jaws in 194 patients who have undergone intravenous bisphosphonate therapy in Spain. Med Oral Patol Oral Cir Bucal 20:e267-e272, 2015
28. Walter C, Grötz KA, Kunkel M, et al: Prevalence of bisphosphonate associated osteonecrosis of the jaw within the field of osteonecrosis. Support Care Cancer 15:197-202, 2007
29. Khan AA, Morrison A, Hanley DA, et al: Diagnosis and management of osteonecrosis of the jaw: A systematic review and international consensus. J Bone Miner Res 30:3-23, 2015
30. Nicolatou-Galitis O, Kouri M, Papadopoulou E, et al: Osteonecrosis of the jaw related to non-antiresorptive medications: A systematic review. Support Care Cancer 27:383-394, 2019
31. Otto S, Pautke C, Van den Wyngaert T, et al: Medication-related osteonecrosis of the jaw: Prevention, diagnosis and management in patients with cancer and bone metastases. Cancer Treat Rev 69:177-187, 2018
32. Stroup DF, Berlin JA, Morton SC, et al: Meta-analysis of observational studies in epidemiology: A proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 283:2008-2012, 2000
33. Migliorati CA, Woo SB, Hewson I, et al: A systematic review of bisphosphonate osteonecrosis (BON) in cancer. Support Care Cancer 18:1099-1106, 2010
34. Loblaw DA, Prestrud AA, Somerfield MR, et al: American Society of Clinical Oncology Clinical Practice Guidelines: Formal systematic review-based consensus methodology. J Clin Oncol 30:3136-3140, 2012
35. Freiberger JJ, Padilla-Burgos R, McGraw T, et al: What is the role of hyperbaric oxygen in the management of bisphosphonate-related osteonecrosis of the jaw: A randomized controlled trial of hyperbaric oxygen as an adjunct to surgery and antibiotics. J Oral Maxillofac Surg 70:1573-1583, 2012
36. Hadji P, Kauka A, Ziller M, et al: Effects of zoledronic acid on bone mineral density in premenopausal women receiving neoadjuvant or adjuvant therapies for HR+ breast cancer: The ProBONE II study. Osteoporos Int 25:1369-1378, 2014
37. Lipton A, Fizazi K, Stopeck AT, et al: Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: A combined analysis of 3 pivotal, randomised, phase 3 trials. Eur J Cancer 48:3082-3092, 2012
38. Vandone AM, Donadio M, Mozzati M, et al: Impact of dental care in the prevention of bisphosphonate-associated osteonecrosis of the jaw: A single-center clinical experience. Ann Oncol 23:193-200, 2012
39. Wadhwa VK, Weston R, Parr NJ: Frequency of zoledronic acid to prevent further bone loss in osteoporotic patients undergoing androgen deprivation therapy for prostate cancer. BJU Int 105:1082-1088, 2010
40. Morgan GJ, Davies FE, Gregory WM, et al: First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): A randomised controlled trial. Lancet 376:1989-1999, 2010
41. Abu-Id MH, Warnke P. H., Gottschalk J, et al: "Bis-phossy jaws": High and low risk factors for bisphosphonate-induced osteonecrosis of the jaw. J Craniomaxillofac Surg 36:95-103, 2008
42. Aghaloo T, Hazboun R, Tetradis S: Pathophysiology of osteonecrosis of the jaws. Oral Maxillofac Surg Clin North Am 27:489-496, 2015
43. Almazrooa SA, Chen K, Nascimben L, et al: Case report: Osteonecrosis of the mandible after laryngoscopy and endotracheal tube placement. Anesth Analg 111:437-441, 2010
44. Aragon-Ching JB, Ning YM, Chen CC, et al: Higher incidence of osteonecrosis of the jaw (ONJ) in patients with metastatic castration-resistant prostate cancer treated with anti-angiogenic agents. Cancer Invest 27:221-226, 2009
45. Badros A, Weikel D, Salama A, et al: Osteonecrosis of the jaw in multiple myeloma patients: Clinical features and risk factors. J Clin Oncol 24:945-952, 2006
46. Baillargeon J, Kuo YF, Lin YL, et al: Osteonecrosis of the jaw in older osteoporosis patients treated with intravenous bisphosphonates. Ann Pharmacother 45: 1199-1206, 2011
47. Barasch A, Cunha-Cruz J, Curro F, et al: Dental risk factors for osteonecrosis of the jaws: A CONDOR case-control study. Clin Oral Investig 17:1839-1845, 2013
48. Berenson JR, Yellin O, Crowley J, et al: Prognostic factors and jaw and renal complications among multiple myeloma patients treated with zoledronic acid. Am J Hematol 86:25-30, 2011
49. Bonomi M, Nortilli R, Molino A, et al: Renal toxicity and osteonecrosis of the jaw in cancer patients treated with bisphosphonates: A long-term retrospective analysis. Med Oncol 27:224-229, 2010
50. Brufsky AM, Sereika SM, Mathew A, et al: Long-term treatment with intravenous bisphosphonates in metastatic breast cancer: A retrospective study. Breast J 19:504-511, 2013
51. Aguiar Bujanda D, Bohn Sarmiento U, Cabrera Suárez MA, et al: Assessment of renal toxicity and osteonecrosis of the jaws in patients receiving zoledronic acid for bone metastasis. Ann Oncol 18:556-560, 2007
52. Cafro AM, Barbarano L, Nosari AM, et al: Osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates: Definition and management of the risk related to zoledronic acid. Clin Lymphoma Myeloma 8:111-116, 2008 [Erratum: Clin Lymphoma Myeloma 8:260, 2008]
53. Cartsos VM, Zhu S, Zavras AI: Bisphosphonate use and the risk of adverse jaw outcomes: A medical claims study of 714,217 people. J Am Dent Assoc 139: 23-30, 2008
54. Chiandussi S, Biasotto M, Dore F, et al: Clinical and diagnostic imaging of bisphosphonate-associated osteonecrosis of the jaws. Dentomaxillofac Radiol 35: 236-243, 2006
55. Clarke BM, Boyette J, Vural E, et al: Bisphosphonates and jaw osteonecrosis: The UAMS experience. Otolaryngol Head Neck Surg 136:396-400, 2007

56. Crawford BS, McNulty RM, Kraut EH, et al: Extended use of intravenous bisphosphonate therapy for the prevention of skeletal complications in patients with cancer. Cancer Invest 27:984-988, 2009
57. Ding X, Fan Y, Ma F, et al: Prolonged administration of bisphosphonates is well-tolerated and effective for skeletal-related events in Chinese breast cancer patients with bone metastasis. Breast 21:544-549, 2012
58. Dranitsaris G, Hatzimichael E: Interpreting results from oncology clinical trials: A comparison of denosumab to zoledronic acid for the prevention of skeletal-related events in cancer patients. Support Care Cancer 20:1353-1360, 2012
59. Eckardt AM LJ, Lemound J, Lindhorst D, et al: Surgical management of bisphosphonate-related osteonecrosis of the jaw in oncologic patients: A challenging problem. Anticancer Res 31:2313-2318, 2011
60. Estilo CL, Van Poznak C. H., Wiliams T, et al: Osteonecrosis of the maxilla and mandible in patients with advanced cancer treated with bisphosphonate therapy. Oncologist 13:911-920, 2008
61. Farrugia MC, Summerlin DJ, Krowiak E, et al: Osteonecrosis of the mandible or maxilla associated with the use of new generation bisphosphonates. Laryngoscope 116:115-120, 2006
62. Graziani F, Vescovi P, Campisi G, et al: Resective surgical approach shows a high performance in the management of advanced cases of bisphosphonate-related osteonecrosis of the jaws: A retrospective survey of 347 cases. J Oral Maxillofac Surg 70:2501-2507, 2012
63. Hoff AO, Toth BB, Altundag K, et al: Osteonecrosis of the jaw in patients receiving intravenous bisphosphonate therapy. J Clin Oncol 24, 2006 (suppl; abstr 8528)
64. Hoff AO, Toth BB, Altundag K, et al: Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. J Bone Miner Res 23:826-836, 2008
65. Jung TI, Hoffmann F, Glaeske G, et al: Disease-specific risk for an osteonecrosis of the jaw under bisphosphonate therapy. J Cancer Res Clin Oncol 136: 363-370, 2010
66. Kademani D, Koka S, Lacy MQ, et al: Primary surgical therapy for osteonecrosis of the jaw secondary to bisphosphonate therapy. Mayo Clin Proc 81: 1100-1103, 2006
67. Kato GF, Lopes RN, Jaguar GC, et al: Evaluation of socket healing in patients undergoing bisphosphonate therapy: Experience of a single Institution. Med Oral Patol Oral Cir Bucal 18:e650-e656, 2013
68. Kyrgidis A, Vahtsevanos K, Koloutsos G, et al: Bisphosphonate-related osteonecrosis of the jaws: A case-control study of risk factors in breast cancer patients. J Clin Oncol 26:4634-4638, 2008
69. Lesclous P, Abi Najm S, Carrel JP, et al: Bisphosphonate-associated osteonecrosis of the jaw: A key role of inflammation? Bone 45:843-852, 2009
70. Loyson T, Van Cann T, Schöffski P, et al: Incidence of osteonecrosis of the jaw in patients with bone metastases treated sequentially with bisphosphonates and denosumab. Acta Clin Belg 73:100-109, 2018
71. Martins MAT, Martins MD, Lascala CA, et al: Association of laser phototherapy with PRP improves healing of bisphosphonate-related osteonecrosis of the jaws in cancer patients: A preliminary study. Oral Oncol 48:79-84, 2012
72. Martins AS, Correia JA, Salvado F, et al: Relevant factors for treatment outcome and time to healing in medication-related osteonecrosis of the jaws: A retrospective cohort study. J Craniomaxillofac Surg 45:1736-1742, 2017
73. Marx RE, Sawatari Y, Fortin M, et al: Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: Risk factors, recognition, prevention, and treatment. J Oral Maxillofac Surg 63:1567-1575, 2005
74. McKay RR, Lin X, Perkins JJ, et al: Prognostic significance of bone metastases and bisphosphonate therapy in patients with renal cell carcinoma. Eur Urol 66: 502-509, 2014
75. Mehrotra B, Fantasia J, Ruggiero SL: Outcomes of bisphosphonate related osteonecrosis of the jaw—Importance of staging and management: A large single institution update. J Clin Oncol 26, 2008 (suppl; abstr 20526)
76. Migliorati CA, Schubert MM, Peterson DE, et al: Bisphosphonate-associated osteonecrosis of mandibular and maxillary bone. Cancer 104:83-93, 2005
77. Montefusco V, Gay F, Spina F, et al: Antibiotic prophylaxis before dental procedures may reduce the incidence of osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates. Leuk Lymphoma 49:2156-2162, 2008
78. Morris PG, Fazio M, Farooki A, et al: Serum N-telopeptide and bone-specific alkaline phosphatase levels in patients with osteonecrosis of the jaw receiving bisphosphonates for bone metastases. J Oral Maxillofac Surg 70:2768-2775, 2012
79. Mozzati M, Gallesio G, Arata V, et al: Platelet-rich therapies in the treatment of intravenous bisphosphonate-related osteonecrosis of the jaw: A report of 32 cases. Oral Oncol 48:469-474, 2012
80. Najm MS, Solomon D. H., Woo S. B., et al: Resource utilization in cancer patients with bisphosphonate-associated osteonecrosis of the jaw. Oral Dis 20:94-99, 2014
81. Ngamphaiboon N, Frustino JL, Kossoff EB, et al: Osteonecrosis of the jaw: Dental outcomes in metastatic breast cancer patients treated with bisphosphonates with/without bevacizumab. Clin Breast Cancer 11:252-257, 2011
82. O'Ryan FS, Khoury S, Liao W, et al: Intravenous bisphosphonate-related osteonecrosis of the jaw: Bone scintigraphy as an early indicator. J Oral Maxillofac Surg 67:1363-1372, 2009
83. Parretta E, Sottosanti L, Sportiello L, et al: Bisphosphonate-related osteonecrosis of the jaw: An Italian post-marketing surveillance analysis. Expert Opin Drug Saf 13:S31-S40, 2014 (suppl 1)
84. Peters E, Lovas GL, Wysocki GP: Lingual mandibular sequestration and ulceration. Oral Surg Oral Med Oral Pathol 75:739-743, 1993
85. Pozzi S, Marcheselli R, Sacchi S, et al: Bisphosphonate-associated osteonecrosis of the jaw: A review of 35 cases and an evaluation of its frequency in multiple myeloma patients. Leuk Lymphoma 48:56-64, 2007
86. Quispe D, Shi R, Burton G: Osteonecrosis of the jaw in patients with metastatic breast cancer: Ethnic and socio-economic aspects. Breast J 17:510-513, 2011
87. Ripamonti CI, Maniezzo M, Campa T, et al: Decreased occurrence of osteonecrosis of the jaw after implementation of dental preventive measures in solid tumour patients with bone metastases treated with bisphosphonates. The experience of the National Cancer Institute of Milan. Ann Oncol 20:137-145, 2009
88. Ruggiero SL, Mehrotra B, Rosenberg TJ, et al: Osteonecrosis of the jaws associated with the use of bisphosphonates: A review of 63 cases. J Oral Maxillofac Surg 62:527-534, 2004
89. Ruggiero SL, Kohn N: Disease stage and mode of therapy are important determinants of treatment outcomes for medication-related osteonecrosis of the jaw. J Oral Maxillofac Surg 73:S94-S100, 2015 (suppl)
90. Saussez S, Javadian R, Hupin C, et al: Bisphosphonate-related osteonecrosis of the jaw and its associated risk factors: A Belgian case series. Laryngoscope 119:323-329, 2009
91. Schiodt M, Reibel J, Oturai P, et al: Comparison of nonexposed and exposed bisphosphonate-induced osteonecrosis of the jaws: A retrospective analysis from the Copenhagen cohort and a proposal for an updated classification system. Oral Surg Oral Med Oral Pathol Oral Radiol 117:204-213, 2014

92. Shimura K, Shimazaki C, Taniguchi K, et al: Hyperbaric oxygen in addition to antibiotic therapy is effective for bisphosphonate-induced osteonecrosis of the jaw in a patient with multiple myeloma. Int J Hematol 84:343-345, 2006
93. Stanton DC, Balasanian E: Outcome of surgical management of bisphosphonate-related osteonecrosis of the jaws: Review of 33 surgical cases. J Oral Maxillofac Surg 67:943-950, 2009
94. Tennis P, Rothman KJ, Bohn RL, et al: Incidence of osteonecrosis of the jaw among users of bisphosphonates with selected cancers or osteoporosis. Pharmacoepidemiol Drug Saf 21:810-817, 2012
95. Thumbigere-Math V, Tu L, Huckabay S, et al: A retrospective study evaluating frequency and risk factors of osteonecrosis of the jaw in 576 cancer patients receiving intravenous bisphosphonates. Am J Clin Oncol 35:386-392, 2012
96. Torres SR, Chen CS, Leroux BG, et al: Mandibular inferior cortical bone thickness on panoramic radiographs in patients using bisphosphonates. Oral Surg Oral Med Oral Pathol Oral Radiol 119:584-592, 2015
97. Van den Wyngaert T, Claeys T, Huizing MT, et al: Initial experience with conservative treatment in cancer patients with osteonecrosis of the jaw (ONJ) and predictors of outcome. Ann Oncol 20:331-336, 2009
98. Wessel JH, Dodson TB, Zavras AI: Zoledronate, smoking, and obesity are strong risk factors for osteonecrosis of the jaw: A case-control study. J Oral Maxillofac Surg 66:625-631, 2008
99. Wilkinson GS, Kuo YF, Freeman JL, et al: Intravenous bisphosphonate therapy and inflammatory conditions or surgery of the jaw: A population-based analysis. J Natl Cancer Inst 99:1016-1024, 2007
100. Wutzl A, Pohl S, Sulzbacher I, et al: Factors influencing surgical treatment of bisphosphonate-related osteonecrosis of the jaws. Head Neck 34:194-200, 2012
101. Yamazaki T, Yamori M, Ishizaki T, et al: Increased incidence of osteonecrosis of the jaw after tooth extraction in patients treated with bisphosphonates: A cohort study. Int J Oral Maxillofac Surg 41:1397-1403, 2012
102. Yarom N, Lazarovici TS, Whitefield S, et al: Rapid onset of osteonecrosis of the jaw in patients switching from bisphosphonates to denosumab. Oral Surg Oral Med Oral Pathol Oral Radiol 125:27-30, 2018
103. Zavras AI, Zhu S: Bisphosphonates are associated with increased risk for jaw surgery in medical claims data: Is it osteonecrosis? J Oral Maxillofac Surg 64: 917-923, 2006
104. Zervas K, Verrou E, Teleioudis Z, et al: Incidence, risk factors and management of osteonecrosis of the jaw in patients with multiple myeloma: A single-centre experience in 303 patients. Br J Haematol 134:620-623, 2006
105. Balla B, Vaszilko M, Kósa JP, et al: New approach to analyze genetic and clinical data in bisphosphonate-induced osteonecrosis of the jaw. Oral Dis 18: 580-585, 2012
106. Bamias A, Kastritis E, Bamia C, et al: Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: Incidence and risk factors. J Clin Oncol 23: 8580-8587, 2005
107. Bantis A, Zissimopoulos A, Sountoulides P, et al: Bisphosphonate-induced osteonecrosis of the jaw in patients with bone metastatic, hormone-sensitive prostate cancer. Risk factors and prevention strategies. Tumori 97:479-483, 2011
108. Bodem JP, Schaal C, Kargus S, et al: Surgical management of bisphosphonate-related osteonecrosis of the jaw stages II and III. Oral Surg Oral Med Oral Pathol Oral Radiol 121:367-372, 2016
109. Bonacina R, Mariani U, Villa F, et al: Preventive strategies and clinical implications for bisphosphonate-related osteonecrosis of the jaw: A review of 282 patients. J Can Dent Assoc 77:b147, 2011
110. Boonyapakorn T, Schirmer I, Reichart PA, et al: Bisphosphonate-induced osteonecrosis of the jaws: Prospective study of 80 patients with multiple myeloma and other malignancies. Oral Oncol 44:857-869, 2008
111. Carlson ER, Basile JD: The role of surgical resection in the management of bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 67:85-95, 2009 (suppl)
112. Crincoli V, Ballini A, Di Comite M, et al: Microbiological investigation of medication-related osteonecrosis of the jaw: Preliminary results. J Biol Regul Homeost Agents 29:977-983, 2015
113. Dimopoulos MA, Kastritis E, Anagnostopoulos A, et al: Osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates: Evidence of increased risk after treatment with zoledronic acid. Haematologica 91:968-971, 2006
114. Dimopoulos MA, Kastritis E, Bamia C, et al: Reduction of osteonecrosis of the jaw (ONJ) after implementation of preventive measures in patients with multiple myeloma treated with zoledronic acid. Ann Oncol 20:117-120, 2009
115. Elad S, Yarom N, Hamed W, et al: Osteomylelitis and necrosis of the jaw in patients treated with bisphosphonates: A comparative study focused on multiple myeloma. Clin Lab Haematol 28:393-398, 2006
116. Fedele S, Porter SR, D'Aiuto F, et al: Nonexposed variant of bisphosphonate-associated osteonecrosis of the jaw: A case series. Am J Med 123:1060-1064, 2010
117. Ferlito S, Puzzo S, Liardo C: Preventive protocol for tooth extractions in patients treated with zoledronate: A case series. J Oral Maxillofac Surg 69:e1-e4, 2011
118. Ferlito S, Puzzo S, Palermo F, et al: Treatment of bisphosphonate-related osteonecrosis of the jaws: Presentation of a protocol and an observational longitudinal study of an Italian series of cases. Br J Oral Maxillofac Surg 50:425-429, 2012
119. Ficarra G, Beninati F, Rubino I, et al: Osteonecrosis of the jaws in periodontal patients with a history of bisphosphonates treatment. J Clin Periodontol 32: 1123-1128, 2005
120. Fortuna G, Ruoppo E, Pollio A, et al: Multiple myeloma vs. breast cancer patients with bisphosphonates-related osteonecrosis of the jaws: A comparative analysis of response to treatment and predictors of outcome. J Oral Pathol Med 41:222-228, 2012
121. Gasparini G, Saponaro G, Di Nardo F, et al: Clinical experience with spiramycin in bisphosphonate-associated osteonecrosis of the jaw. Int J Immunopathol Pharmacol 23:619-626, 2010
122. Graziani F, Cei S, La Ferla F, et al: Association between osteonecrosis of the jaws and chronic high-dosage intravenous bisphosphonates therapy. J Craniofac Surg 17:876-879, 2006
123. Katz J, Gong Y, Salmasinia D, et al: Genetic polymorphisms and other risk factors associated with bisphosphonate induced osteonecrosis of the jaw. Int J Oral Maxillofac Surg 40:605-611, 2011
124. Lazarovici TS, Mesilaty-Gross S, Vered I, et al: Serologic bone markers for predicting development of osteonecrosis of the jaw in patients receiving bisphosphonates. J Oral Maxillofac Surg 68:2241-2247, 2010
125. Lesclous P, Grabar S, Abi Najm S, et al: Relevance of surgical management of patients affected by bisphosphonate-associated osteonecrosis of the jaws. A prospective clinical and radiological study. Clin Oral Investig 18:391-399, 2014
126. Lodi G, Sardella A, Salis A, et al: Tooth extraction in patients taking intravenous bisphosphonates: A preventive protocol and case series. J Oral Maxillofac Surg 68:107-110, 2010

127. Magopoulos C, Karakinaris G, Telioudis Z, et al: Osteonecrosis of the jaws due to bisphosphonate use. A review of 60 cases and treatment proposals. Am J Otolaryngol 28:158-163, 2007
128. Marx RE, Cillo JE Jr, Ulloa JJ: Oral bisphosphonate-induced osteonecrosis: Risk factors, prediction of risk using serum CTX testing, prevention, and treatment. J Oral Maxillofac Surg 65:2397-2410, 2007
129. Meattini I, Bruni A, Scotti V, et al: Oral ibandronate in metastatic bone breast cancer: The Florence University experience and a review of the literature. J Chemother 22:58-62, 2010
130. Migliorati CA, Saunders D, Conlon MS, et al: Assessing the association between bisphosphonate exposure and delayed mucosal healing after tooth extraction. J Am Dent Assoc 144:406-414, 2013
131. Mücke T, Koschinski J, Deppe H, et al: Outcome of treatment and parameters influencing recurrence in patients with bisphosphonate-related osteonecrosis of the jaws. J Cancer Res Clin Oncol 137:907-913, 2011
132. Mücke T, Jung M, Koerdt S, et al: Free flap reconstruction for patients with bisphosphonate related osteonecrosis of the jaws after mandibulectomy. J Craniomaxillofac Surg 44:142-147, 2016
133. Nicolatou-Galitis O, Papadopoulou E, Sarri T, et al: Osteonecrosis of the jaw in oncology patients treated with bisphosphonates: Pospective experience of a dental oncology referral center. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 112:195-202, 2011
134. Pelaz A, Junquera L, Gallego L, et al: Alternative treatments for oral bisphosphonate-related osteonecrosis of the jaws: A pilot study comparing fibrin rich in growth factors and teriparatide. Med Oral Patol Oral Cir Bucal 19:e320-e326, 2014
135. Raje N, Vescio R, Montgomery CW, et al: Bone marker–directed dosing of zoledronic acid for the prevention of skeletal complications in patients with multiple myeloma: Results of the Z-MARK study. Clin Cancer Res 22:1378-1384, 2016
136. Reich W, Bilkenroth U, Schubert J, et al: Surgical treatment of bisphosphonate-associated osteonecrosis: Prognostic score and long-term results. J Craniomaxillofac Surg 43:1809-1822, 2015
137. Ripamonti CI, Cislaghi E, Mariani L, et al: Efficacy and safety of medical ozone (O_3) delivered in oil suspension applications for the treatment of osteonecrosis of the jaw in patients with bone metastases treated with bisphosphonates: Preliminary results of a phase I-II study. Oral Oncol 47:185-190, 2011
138. Rodrigues P, Hering F, Imperio M: Safety of I.V. nonnitrogen bisphosphonates on the occurrence of osteonecrosis of the jaw: Long-term follow-up on prostate cancer patients. Clin Genitourin Cancer 13:199-203, 2015
139. Saad F, Brown JE, Van Poznak C, et al: Incidence, risk factors, and outcomes of osteonecrosis of the jaw: Integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. Ann Oncol 23:1341-1347, 2012
140. Schiodt M, Vadhan-Raj S, Chambers MS, et al: A multicenter case registry study on medication-related osteonecrosis of the jaw in patients with advanced cancer. Support Care Cancer 26:1905-1915, 2018
141. Schubert M, Klatte I, Linek W, et al: The Saxon bisphosphonate register: Therapy and prevention of bisphosphonate-related osteonecrosis of the jaws. Oral Oncol 48:349-354, 2012
142. Scoletta M, Arduino PG, Dalmasso P, et al: Treatment outcomes in patients with bisphosphonate-related osteonecrosis of the jaws: A prospective study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 110:46-53, 2010
143. Shintani T, Hayashido Y, Mukasa H, et al: Comparison of the prognosis of bisphosphonate-related osteonecrosis of the jaw caused by oral and intravenous bisphosphonates. Int J Oral Maxillofac Surg 44:840-844, 2015
144. Stockmann P, Vairaktaris E, Wehrhan F, et al: Osteotomy and primary wound closure in bisphosphonate-associated osteonecrosis of the jaw: A prospective clinical study with 12 months follow-up. Support Care Cancer 18:449-460, 2010
145. Tsao C, Darby I, Ebeling PR, et al: Oral health risk factors for bisphosphonate-associated jaw osteonecrosis. J Oral Maxillofac Surg 71:1360-1366, 2013
146. Walter C, Al-Nawas B, Grötz KA, et al: Prevalence and risk factors of bisphosphonate-associated osteonecrosis of the jaw in prostate cancer patients with advanced disease treated with zoledronate. Eur Urol 54:1066-1072, 2008
147. Wutzl A, Biedermann E, Wanschitz F, et al: Treatment results of bisphosphonate-related osteonecrosis of the jaws. Head Neck 30:1224-1230, 2008
148. Badros A, Terpos E, Katodritou E, et al: Natural history of osteonecrosis of the jaw in patients with multiple myeloma. J Clin Oncol 26:5904-5909, 2008
149. Choi H, Lee JH, Kim HJ, et al: Genetic association between VEGF polymorphisms and BRONJ in the Korean population. Oral Dis 21:866-871, 2015 [Erratum: Oral Dis 21:1004, 2015]
150. Nicoletti P, Cartsos VM, Palaska PK, et al: Genome-wide pharmacogenetics of bisphosphonate-induced osteonecrosis of the jaw: The role of RBMS3. Oncologist 17:279-287, 2012
151. Yarom N, Elad S, Madrid C, et al: Osteonecrosis of the jaws induced by drugs other than bisphosphonates: A call to update terminology in light of new data. Oral Oncol 46:e1, 2010
152. Bedogni A, Fusco V, Agrillo A, et al: Learning from experience. Proposal of a refined definition and staging system for bisphosphonate-related osteonecrosis of the jaw (BRONJ). Oral Dis 18:621-623, 2012
153. Hong CHL, Hu S, Haverman T, et al: A systematic review of dental disease management in cancer patients. Support Care Cancer 26:155-174, 2017
154. Haytac MC, Dogan MC, Antmen B: The results of a preventive dental program for pediatric patients with hematologic malignancies. Oral Health Prev Dent 2: 59-65, 2004
155. Melkos AB, Massenkeil G, Arnold R, et al: Dental treatment prior to stem cell transplantation and its influence on the posttransplantation outcome. Clin Oral Investig 7:113-115, 2003
156. Schuurhuis JM, Span LF, Stokman MA, et al: Effect of leaving chronic oral foci untreated on infectious complications during intensive chemotherapy. Br J Cancer 114:972-978, 2016
157. Tsuji K, Shibuya Y, Akashi M, et al: Prospective study of dental intervention for hematopoietic malignancy. J Dent Res 94:289-296, 2015
158. Gürgan CA, Özcan M, Karakuş Ö, et al: Periodontal status and post-transplantation complications following intensive periodontal treatment in patients underwent allogenic hematopoietic stem cell transplantation conditioned with myeloablative regimen. Int J Dent Hyg 11:84-90, 2013
159. Segelman AE, Doku HC: Treatment of the oral complications of leukemia. J Oral Surg 35:469-477, 1977
160. Trowbridge JE, Carl W: Oral care of the patient having head and neck irradiation. Am J Nurs 75:2146-2149, 1975
161. Maurer J: Providing optimal oral health. Nurs Clin North Am 12:671-685, 1977
162. McGuire DB, Fulton JS, Park J, et al: Systematic review of basic oral care for the management of oral mucositis in cancer patients. Support Care Cancer 21: 3165-3177, 2013
163. Jensen SB, Pedersen AM, Vissink A, et al: A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: Management strategies and economic impact. Support Care Cancer 18:1061-1079, 2010

164. National Cancer Institute: Common Terminology Criteria for Adverse Events (CTCAE) v5.0. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50
165. Khan AA, Morrison A, Kendler DL, et al: Case-based review of osteonecrosis of the jaw (ONJ) and application of the international recommendations for management from the International Task Force on ONJ. J Clin Densitom 20:8-24, 2017
166. El-Rabbany M, Sgro A, Lam DK, et al: Effectiveness of treatments for medication-related osteonecrosis of the jaw: A systematic review and meta-analysis. J Am Dent Assoc 148:584-594.e2, 2017
167. Lee SH, Chang SS, Lee M, et al: Risk of osteonecrosis in patients taking bisphosphonates for prevention of osteoporosis: A systematic review and meta-analysis. Osteoporos Int 25:1131-1139, 2014
168. Coxon FP, Thompson K, Roelofs AJ, et al: Visualizing mineral binding and uptake of bisphosphonate by osteoclasts and non-resorbing cells. Bone 42:848-860, 2008
169. Kim KM, Rhee Y, Kwon YD, et al: Medication related osteonecrosis of the jaw: 2015 position statement of the Korean Society for Bone and Mineral Research and the Korean Association of Oral and Maxillofacial Surgeons. J Bone Metab 22:151-165, 2015
170. Oizumi T, Funayama H, Yamaguchi K, et al: Inhibition of necrotic actions of nitrogen-containing bisphosphonates (NBPs) and their elimination from bone by etidronate (a non-NBP): A proposal for possible utilization of etidronate as a substitution drug for NBPs. J Oral Maxillofac Surg 68:1043-1054, 2010
171. Reid IR, Cornish J: Epidemiology and pathogenesis of osteonecrosis of the jaw. Nat Rev Rheumatol 8:90-96, 2011
172. Carlson ER, Fleisher KE, Ruggiero SL: Metastatic cancer identified in osteonecrosis specimens of the jaws in patients receiving intravenous bisphosphonate medications. J Oral Maxillofac Surg 71:2077-2086, 2013
173. Basch E: The missing voice of patients in drug-safety reporting. N Engl J Med 362:865-869, 2010
174. Gilligan T, Coyle N, Frankel RM, et al: Patient-clinician communication: American Society of Clinical Oncology consensus guideline. J Clin Oncol 35:3618-3632, 2017
175. Fischer DJ, O'Hayre M, Kusiak JW, et al: Oral health disparities: A perspective from the National Institute of Dental and Craniofacial Research. Am J Public Health 107:S36-S38, 2017 (suppl)
176. Glick M: Promoting the importance of oral health: Where are our patients' voices? J Am Dent Assoc 149:1003-1004, 2018
177. American Cancer Society: Cancer facts and figures for African Americans 2016-2018. http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-047403.pdf
178. National Cancer Institute: SEER cancer statistics review, 1975-2013. http://seer.cancer.gov/csr/1975_2013/
179. Mead H, Cartwright-Smith L, Jones K, et al. Racial and Ethnic Disparities in U.S. Health Care: A Chartbook. New York, NY, The Commonwealth Fund, 2008
180. Schnipper LE, Davidson NE, Wollins DS, et al: Updating the American Society of Clinical Oncology value framework: Revisions and reflections in response to comments received. J Clin Oncol 34:2925-2934, 2016
181. Schnipper LE, Davidson NE, Wollins DS, et al: American Society of Clinical Oncology Statement: A conceptual framework to assess the value of cancer treatment options. J Clin Oncol 33:2563-2577, 2015
182. Dusetzina SB, Winn AN, Abel GA, et al: Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia. J Clin Oncol 32:306-311, 2014
183. Streeter SB, Schwartzberg L, Husain N, et al: Patient and plan characteristics affecting abandonment of oral oncolytic prescriptions. J Oncol Pract 7:46s-51s, 2011 (suppl)
184. Meropol NJ, Schrag D, Smith TJ, et al: American Society of Clinical Oncology guidance statement: The cost of cancer care. J Clin Oncol 27:3868-3874, 2009
185. Van Poznak C, Somerfield MR, Barlow WE, et al: Role of bone-modifying agents in metastatic breast cancer: An American Society of Clinical Oncology-Cancer Care Ontario focused guideline update. J Clin Oncol 35:3978-3986, 2017
186. Anderson K, Ismaila N, Flynn PJ, et al: Role of bone-modifying agents in multiple myeloma: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 36:812-818, 2018
187. Ferrell BR, Temel JS, Temin S, et al: Integration of palliative care into standard oncology care: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 35:96-112, 2017

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Douglas E. Peterson
Stock and Other Ownership Interests: Allergan (I), Celgene (I), Gilead Sciences (I), Procter & Gamble (I), Roche (I), Bristol-Myers Squibb (I), Johnson & Johnson (I)
Consulting or Advisory Role: Amgen, PSI Pharma Support America, OptumInsight Life Sciences, Applied Glycan-Oral Health, AEC Partners

Catherine H. Van Poznak
Research Funding: Bayer (Inst)
Patents, Royalties, Other Intellectual Property: UpToDate

Salvatore L. Ruggiero
Consulting or Advisory Role: Amgen

Cesar A. Migliorati
Consulting or Advisory Role: Amgen
Travel, Accommodations, Expenses: Colgate Palmolive

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
Consulting or Advisory Role: Amgen
Research Funding: Amgen
Travel, Accommodations, Expenses: Amgen

No other potential conflicts of interest were reported.

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.