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S Patel

S Choyee

J Uyanne

A L. Nguyen

P Lee

See next page for additional authors

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At the time of publication, author Songtao Shi was affiliated with Herman Ostrow School of Dentistry of University of Southern California. Currently, (s)he is a faculty member at the School of Dental Medicine at the University of Pennsylvania.
At the time of publication, author Anh D. Le was affiliated with Herman Ostrow School of Dentistry of University of Southern California and LAC+USC Medical Center. Currently, (s)he is a faculty member at the School of Dental Medicine at the University of Pennsylvania.

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Abstract

Non-exposed bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a newly reported complication arising from bisphosphonate therapy that presents with atypical symptoms and no apparent mucosal fenestration or exposure of necrotic bone. The clinical observation of the presence of necrotic bone underneath normal epithelial coverage was not conclusive for the diagnosis of BRONJ based on current guidelines established by the American Association of Oral and Maxillofacial Surgeons (AAOMS) and the American Society for Bone and Mineral Research (ASBMR), which specify the presence of clinically exposed necrotic bone for more than 8weeks. Hence, the purpose of this review is to critically assess the current guidelines for diagnosis and management of BRONJ and propose a modified staging system and treatment guidelines to properly address the non-exposed variant of BRONJ lesions. © 2012 John Wiley & Sons A/S.

Keywords

Author keywords: Craniofacial, Diagnostics, Medicine, Oncology MeSH: Angiogenesis Inhibitors, Anti-Bacterial Agents, Antibodies, Monoclonal, Humanized, Bisphosphonate-Associated Osteonecrosis of the Jaw, Humans, Jaw Diseases, Osteonecrosis, Practice Guidelines as Topic, Terminology as Topic EMTREE drug terms: antibiotic agent, bisphosphonic acid derivative EMTREE medical terms: adverse drug reaction, antibiotic therapy, article, disease course, human, jaw osteonecrosis, medical assessment, nonexposed bisphosphonate related jaw osteonecrosis, practice guideline, priority journal, staging

Disciplines

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Comments

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Author(s)

S Patel, S Choyee, J Uyanne, A L. Nguyen, P Lee, P P. Sedghizadeh, S K S Kumar, J Lytle, S Shi, and A D. Le

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INVITED MEDICAL REVIEW

Non-exposed bisphosphonate-related osteonecrosis of the jaw: a critical assessment of current definition, staging, and treatment guidelines

S Patel[1], S Choyee[2], J Uyanne[3], AL Nguyen[4], P Lee[4], PP Sedghizadeh[1], SKS Kumar[1], J Lytle[3], S Shi[4], AD Le[2,3,4]

[1]*Orofacial Pain and Oral Medicine Center, Herman Ostrow School of Dentistry of University of Southern California, Los Angeles, CA;* [2]*Oral and Maxillofacial Surgery, LAC+USC Medical Center, Los Angeles, CA;* [3]*Division of Endodontics, Oral and Maxillofacial Surgery, and Orthodontics, Herman Ostrow School of Dentistry of University of Southern California, Los Angeles, CA;* [4]*Center for Craniofacial Molecular Biology, Herman Ostrow School of Dentistry of University of Southern California, Los Angeles, CA, USA*

Non-exposed bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a newly reported complication arising from bisphosphonate therapy that presents with atypical symptoms and no apparent mucosal fenestration or exposure of necrotic bone. The clinical observation of the presence of necrotic bone underneath normal epithelial coverage was not conclusive for the diagnosis of BRONJ based on current guidelines established by the American Association of Oral and Maxillofacial Surgeons (AAOMS) and the American Society for Bone and Mineral Research (ASBMR), which specify the presence of clinically exposed necrotic bone for more than 8 weeks. Hence, the purpose of this review is to critically assess the current guidelines for diagnosis and management of BRONJ and propose a modified staging system and treatment guidelines to properly address the non-exposed variant of BRONJ lesions.

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Keywords: diagnostics; medicine; craniofacial; oncology

Introduction

Bisphosphonates are used across a wide range of disciplines, including endocrinology, oncology, orthopedics, and dentistry. These antiresorptive drugs have been indicated for various diseases, including osteoporosis, Paget's disease of bone, hypercalcemia of malignancies, bone metastases, and osteolytic lesions of multiple myeloma (Ruggiero and Drew, 2007; Hortobagyi *et al*, 1996; Berenson *et al*, 1996). Osteonecrosis of the jaw (ONJ) is a serious side effect of these medications that presents with high morbidity and challenging clinical management, noted within the last decade (Marx, 2003; Ruggiero *et al*, 2004). The first case of bisphosphonate-related ONJ (BRONJ) was reported in 2003, and since then, an increasing number of cases has been observed. The estimated incidence of this side effect for patients taking intravenous (IV) bisphosphonates for malignancies ranges from 0.8% to 12%, whereas for oral bisphosphonates, it ranges from 0.009% to 0.034% (Ruggiero and Mehrotra, 2009; Berenson *et al*, 2002).

As proposed by the Advisory Task Forces from both the American Association of Oral and Maxillofacial Surgeons (AAOMS) and the American Society for Bone and Mineral Research (ASBMR), a confirmed case of ONJ is defined as the persistence of exposed necrotic bone in the oral cavity for 8 weeks, despite adequate treatment, in a patient with current or previous history of bisphosphonate use, without local evidence of malignancy and no prior radiotherapy to the affected region (Ruggiero *et al*, 2006; Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws American Association of Oral and Maxillofacial Surgeons, 2007; Khosla *et al*, 2007; Ruggiero *et al*, 2009; Allen, 2011; Khosla *et al* (2007) also report that other signs and symptoms (i.e. pain, swelling, paresthesia, and suppuration) in patients exposed to bisphosphonate therapy are not sufficient to be diagnosed as BRONJ. Osteonecrotic lesions may be asymptomatic for a period of time. Common symptoms reported by patients prior to a clinically evident lesion, such as exposed necrotic bone, include pain, tooth mobility, mucosal swelling,

Correspondence: Anh D. Le, DDS, PhD, Center for Craniofacial Molecular Biology, Herman Ostrow School of Dentistry of University of Southern California, Health Sciences Campus, 2250 Alcazar Street, CSA107, Los Angeles, California 90033, USA. Tel: +323 442 2556, Fax: 323 442 2981, E-mail: anhle@usc.edu
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and erythema. Common signs seen by a clinician in this context prior to bone exposure may include parulis formation, sinus tract formation with or without active purulence, erythema, granulation tissue, tooth mobility, or pain on palpation of affected tissue; radiographs may appear normal in this context or there may be widened lamina dura around teeth or ill-defined radiographic lytic lesions of bone with or without the evidence of sequestrum. These lesions can occur spontaneously or as a result of trauma, such as a surgical procedure. A key point in the case definition of BRONJ by both task forces is the presence of necrotic bone exposed in the oral cavity (Ruggiero *et al*, 2009; Bagán *et al*, 2007; Khosla *et al*, 2007). However, bone exposure is not always observed in a subset of cases that otherwise have characteristic hallmarks of BRONJ (Junquera and Gallego, 2008; Fedele *et al*, 2010; Mawardi *et al*, 2009; Lazarovici *et al*, 2009).

Recently, a clinical variant of BRONJ with unclear development and pathophysiology has been reported. Clinical features include persistent jaw bone pain, bone enlargement, and gingival swelling in the absence of both significant dental disease and clinical evidence of necrotic bone exposure (Junquera and Gallego, 2008; Fedele *et al*, 2010; Vescovi and Nammour, 2010; Hutchinson *et al*, 2010). Here, we critically assess the current guidelines and treatment recommendations for BRONJ and propose a modified treatment protocol for these atypical BRONJ cases.

Current staging and treatment guidelines of BRONJ

A defining feature of BRONJ is the presence of exposed necrotic bone. The most recent guidelines for the diagnosis of BRONJ include the following: (i) current or previous history of bisphosphonate use, (ii) presence of exposed bone for more than 8 weeks, and (ii) no history of radiation to the head and neck region (Ruggiero and Mehrotra, 2009; Ruggiero *et al*, 2009; Fedele *et al*, 2010; Ruggiero, 2011). There are four stages by which BRONJ lesions are classified. Stage 0 shows no clinical evidence of necrotic bone, but non-specific clinical findings and symptoms may be present. The clinical features of stage 1 include the presence of exposed necrotic bone, but, no evidence of soft tissue infection; stage 2 is characterized by exposed necrotic bone that is associated with signs of infection (i.e. pain, erythema, and/or purulence); and stage 3 exhibits more extensive necrotic bone and severe infection which extends beyond the alveolar region, or osteolysis that extends to the inferior border of the mandible or the sinus floor, amenable to pathologic fracture, extra-oral fistula, oro-antral or oro-nasal communication (Ruggiero and Mehrotra, 2009; Ruggiero, 2011; Yoneda *et al*, 2010; Khan *et al*, 2008; refer to Table 1).

Aside from forming the basis for diagnosis guidelines, the staging system for BRONJ lesions helps to direct appropriate treatment for each stage (See Table 1). The AAOMS recommends that for stage 0 lesions, only symptomatic treatment will be provided (i.e. control of

Table 1 Current American Association of Oral and Maxillofacial Surgeons Guidelines on bisphosphonate-related osteonecrosis of the jaw Staging and Treatment (Ruggiero *et al*, 2009)

Staging characteristics		*Treatment recommended*
At risk	Asymptomatic No necrotic bone present History of treatment with oral or IV bisphosphonates	
Stage 0	No clinical evidence of necrotic bone Nonspecific symptoms or clinical or radiographic findings present: Symptoms Odontalgia not because of an odontogenic cause Dull, aching bone pain Sinus pain Altered neurosensory function Clinical Findings Loosening of teeth not caused by periodontal disease Periapical/periodontal fistula not associated with a necrotic pulp Radiographic Findings Alveolar bone loss/resorption not because of periodontal disease Dense, woven or persistent unremodeled bone in extraction socket Thickening of the PDL Narrowing of IA canal	Systemic management with pain medications and/or antibiotics
Stage 1	Exposed and necrotic bone present Asymptomatic with no evidence of infection	Antibacterial mouth rinse Clinical follow-up on a quarterly basis Patient education and review of indications for continued bisphosphonate therapy
Stage 2	Exposed and necrotic bone present Pain and clinical evidence of infection	Oral antibacterial mouth rinse Pain control Superficial debridement to relieve soft tissue irritation
Stage 3	Exposed and necrotic bone present Pain, infection, and one or more of: Exposed necrotic bone extending beyond the alveolar bone area Pathologic fracture Extraoral fistula Oral antral/oral nasal communication Osteolysis extending to the inferior border of the mandible or sinus floor	Antibiotic therapy and pain control Surgical debridement/resection for longer term palliation of infection and pain

local disease, pain medication, and antibiotics). For stage 1 lesions, antimicrobial oral rinses are recommended with follow-ups every 3 months. For stage 2, oral or IV antibiotics, in conjunction with superficial debridement and antimicrobial rinses, are recommended. Debridement and/or surgical resection may improve stage 3 lesions, along with oral or IV antibiotics and antimicrobial rinses. In all cases, if a mobile bony sequestrum is present, it should be removed (Ruggiero and Mehrotra, 2009; Ruggiero, 2011; Mehrotra and Ruggiero, 2006). In a recent position article by the American Academy of Oral Medicine, similar treatment recommendations were provided with a major focus on reducing sharp bony edges to avoid further trauma to the mucosal lining, treatment with antibiotics (along with microbial culture and sensitivity if needed), chlorhexidine mouth rinse and conservative sequestrectomy (Migliorati *et al*, 2005).

At present time, there appears to be no clear consensus on a standard treatment for BRONJ with a predictable clinical outcome. The stage approach to treatment is primarily based on clinical signs of exposed necrotic bone and infection, which may lead to a misrepresentation of disease severity and contribute to the poor response exhibited by a percentage of patients with atypical symptoms and absence of apparent clinical signs of bone necrosis.

Non-exposed BRONJ: Dilemma for diagnosis and treatment

Recently, several studies have reported cases of non-exposed BRONJ in patients with history of bisphosphonate use. In these patients, exposed bone was not present; however, the presence of deep periodontal pockets, purulent drainage with and without sinus tracts, advanced bone loss around involved teeth, swelling, and pain were common clinical findings. The sinus tracts usually were intraoral (Junquera and Gallego, 2008; Mawardi *et al*, 2009). Junquera and Gallego (2008) managed two patients presenting with non-exposed BRONJ with antibiotic therapy, antimicrobial rinses, sequestrectomy, and extraction of involved teeth (in one patient), which resulted in no new oral lesions after a follow-up of 8 weeks for one patient, and 18 months for the other. Mawardi *et al* (2009) reported five cases of BRONJ without clinical evidence of mucosal fenestration or exposure of necrotic bone. These patients were managed with antibiotic therapy, antimicrobial rinse, sequestrectomy, and surgical debridement. Most of these cases progressed to bone exposure later on, but eventually healed with complete mucosal coverage. The time to healing was 5–22 months after the initial visit (Mawardi *et al*, 2009).

In another study, 30 patients of 1005 presented without bone exposure, but with concerning clinical symptoms and history of bisphosphonate use (Hutchinson *et al*, 2010). These patients reported a history of alendronate therapy for osteoporosis and other existing comorbidities, including polymyalgia rheumatica treated with glucocorticoids, diabetes mellitus, and smoking. Of these 30 patients, 10 had stage 0 disease with radiographic changes of osteosclerosis in the symptomatic areas, density confluence of cortical and cancellous bone, periradicular radiolucencies, prominent IAN canal, or persisting alveolar socket (Hutchinson *et al*, 2010). None had exposed bone during a 1-year follow-up. In a larger study population, Fedele *et al* (2010) discussed characteristics of non-exposed BRONJ in 96 patients. The average duration of therapy prior to the occurrence of the lesion was 37 months. The most common clinical findings were jaw bone pain, sinus tracts, bone enlargements, and gingival enlargement. Two-thirds of the patients exhibited osteolytic changes upon radiographic examination, and about half of these patients' lesions progressed to clinical bone exposure (Fedele *et al*, 2010). Overall, these studies have shown that therapy can be long term for these patients, without a predictable success rate.

The absence of characteristic clinical signs of BRONJ, specifically exposed necrotic bone, can lead to late diagnosis, prolonged disease course, and refractory treatment. It is estimated that 30% of BRONJ cases may initially present without clinical evidence of necrotic bone exposure. These cases are usually classified as stage 0 in accordance with the current AAOMS diagnostic criteria and are quite often under-diagnosed and thus under-treated (Fusco *et al*, 2011). For instance, in a case series of 11 patients with BRONJ, three patients did not heal after long-term antibiotic therapy and minor surgical procedures (curettage and smoothening of rough bony edges). Two of these refractory patients were those that presented without bone exposure at initial diagnosis (Yarom *et al*, 2007). In another case series by Lazarovici *et al* (2009), 92 patients were diagnosed with BRONJ, of which 36 did not initially present with exposed bone. The patients were treated with long-term antibiotics and minor surgical procedures. Of these, 18% showed complete response, 52% had partial response, and 30% had no response (Lazarovici *et al*, 2009). Similarly, we have seen several non-exposed BRONJ cases classified as stage 0 by virtue of the absence of clinical bone exposure, which are refractory to current guideline-based treatment, and one representative case is shown here (Figure 1). In this case, under-diagnosis of BRONJ disease severity owing to the absence of clinically exposed bone is a potential factor contributing to the long course of antibiotic therapy and recurrent infection.

Therefore, in the non-exposed BRONJ variants, formulating an accurate diagnosis and initiating a proper treatment protocol is challenging. These necrotic lesions, in the absence of a clear mucosal breakdown, most often are undetected by clinicians during routine oral examination and cannot be diagnosed accurately according to the current guidelines; therefore, the current treatment regimen that guides clinicians to treat BRONJ based on the stage of the lesion may not be effective. Often, patients exhibiting a non-exposed variant of BRONJ may respond more favorably if managed as if the lesions were stage 2 or 3, rather than stage 0 or 1 (Ruggiero *et al*, 2009; Junquera and Gallego, 2008, Mawardi *et al*, 2009). Given this discrepancy, formulating a treatment regimen would unlikely follow any single type of treatment as

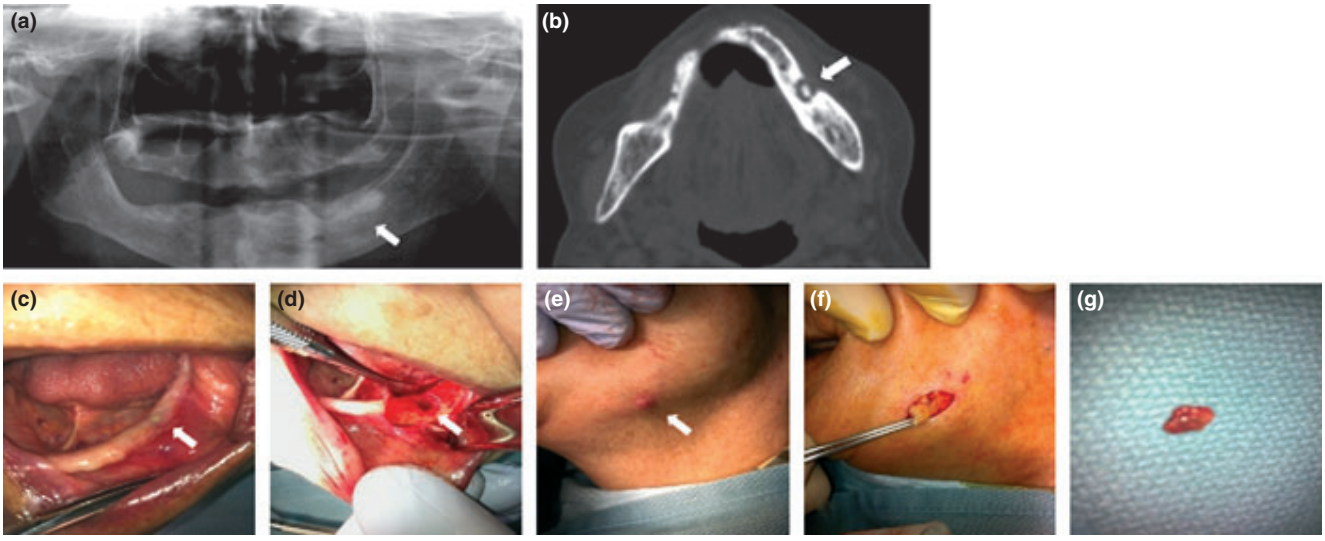

Figure 1 Non-exposed bisphosphonate-related osteonecrosis of the jaw (BRONJ) at the edentulous mandibular ridge of an 87-year-old Asian female on an oral bisphosphonate. Patient had a history of dental extraction and an 8-year history of fosamax (alendronate) treatment (dosage 5–10 mg day^{-1}) for osteoporosis. The patient reported a history of IV antibiotic treatment with partial response and relapse. Examination revealed a movable soft tissue induration (1 × 1.5 cm) at the left angle of the mandible, which subsequently drained extraorally via an orocutaneous fistula tract (**b**, **e**–**g**). Purulent drainage also appeared at a pinpoint fenestration intraorally from the mucosa (**c**). No evidence of necrotic bone exposure was observed. Panoramic radiograph revealed localized areas of increasing opacities in the mandible (see arrow, **a**). CT scan was significant for the presence of a necrotic bone island (involucrum), a lateral cortical bony defect connected to a fistula tract (see arrow, **b**). The patient underwent conservative debridement and fistulectomy. Intraoperatively, an involucrum of 3–5 mm in diameter was located in an empty bony cavity, surrounded by granulation tissue **d**). Extraoral fistulectomy showed a well-formed tract connecting to the necrotic alveolar site (**f**); Excised cutaneous fistula (**g**). At several follow-ups, the patient showed complete healing and remained with no pain and no signs of recurrent infection at 6 months

recommended by the current guidelines, and this current recommendation might have contributed to the lack of complete response in a percentage of BRONJ patients with atypical symptoms and absence of apparent signs of bone necrosis.

We propose to systematically approach the diagnosis and management of non-exposed BRONJ based on the presenting clinical symptoms, an assessment of associated risk factors (Yoneda *et al*, 2010; Sarasquete *et al*, 2009), radiographic evidence (Hutchinson *et al*, 2010; Arce *et al*, 2009), and history of refractory medical treatment; these findings in conjunction with a patient's medical and dental history will guide us to formulate a tentative diagnosis of 'Non-exposed Variant of BRONJ' and initiate management prior to the clinical onset of exposed necrotic bone (See Figure 2).

Non-exposed BRONJ: Proposal for modification of staging and management

As initially proposed by the Advisory Task Forces from both the AAOMS and the ASBMR, a confirmed case of ONJ is defined as the presence of clinical exposed necrotic bone in the oral cavity (Ruggiero *et al*, 2006; Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws American Association of Oral Maxillofacial Surgeons, 2007; Khosla *et al*, 2007). These guidelines were revised in 2009 to include patients with stage 0 disease, characterized as those with no evidence of bone necrosis but non-specific clinical findings and symptoms may be present (Ruggiero *et al*, 2009). Based on these current staging guidelines and recommended treatment protocols, cases manifested as non-exposed BRONJ would be more likely under-diagnosed and under-treated. In these patients, exposed necrotic bone was not present. However, atypical symptoms including the presence of deep periodontal pockets, purulent drainage with and without sinus tracts, advanced bone loss around involved teeth, swelling, and pain were commonly reported (Junquera and Gallego, 2008; Mawardi *et al*, 2009). These cases most often resulted in delayed diagnosis of non-exposed BRONJ, which would lead to an inadequate treatment protocol and a poorer treatment response.

Modifications to the current staging guidelines have therefore been proposed, but specific treatment recommendations to target the non-exposed variant of BRONJ have yet to be defined. Mawardi *et al* (2009) suggested inclusion of a stage 0_s, as a lesion 'suspicious' for BRONJ. This stage would include patients that do not have exposed bone, but do have sinus tracts, severe tooth mobility, or positive radiographic findings (Table 2, part I). Stage 0_s has two subcategories: Stage 0_{ss} and Stage 0_{sa}. Stage 0_{ss} would comprise patient 'suspicious' for BRONJ who is symptomatic, *vs* in stage 0_{sa} the patient is 'suspicious' for BRONJ but does not have any symptoms. Patients who are categorized as stage 0_{ss} may require antibiotic therapy, whereas those in stage 0_{sa} would be monitored periodically (Mawardi *et al*, 2009). Another suggestion to the current staging classification involves modifying stage 1 to include the presence of oral fistula or ulceration without bone exposure. Stage 2 would be divided into subcategories

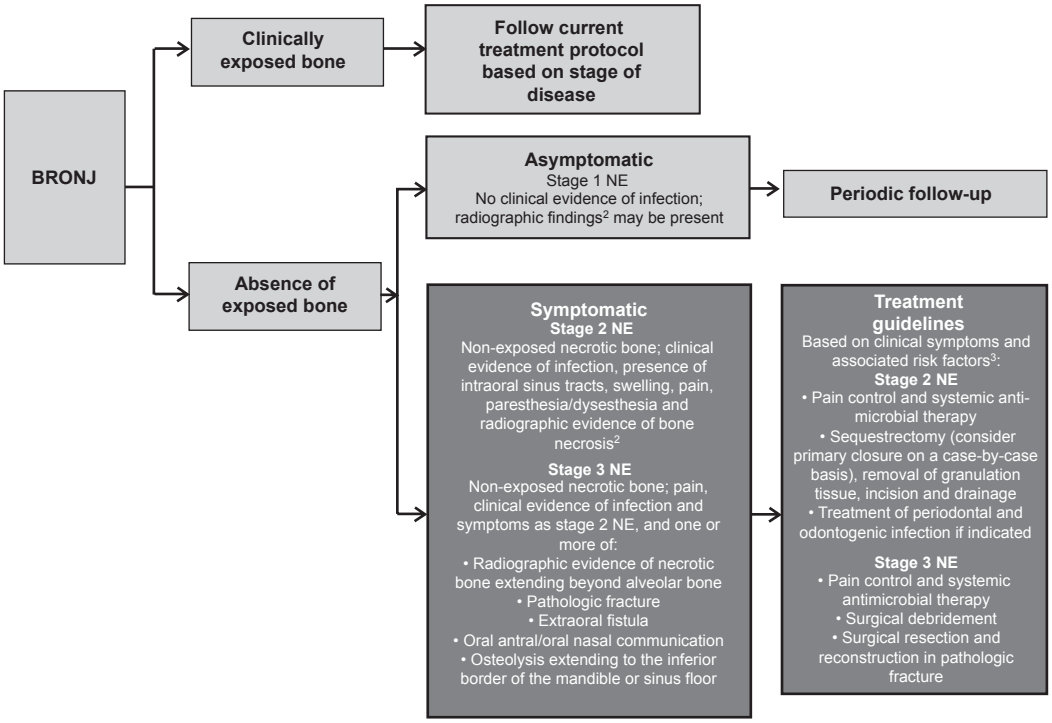

Figure 2 Modified staging and treatment guidelines for non-exposed bisphosphonate-related osteonecrosis of the jaw (BRONJ). BRONJ presenting with clinically exposed necrotic bone will follow current diagnosis, staging, and treatment guidelines as proposed by the American Association of Oral and Maxillofacial Surgeons (AAOMS)[1]. Asymptomatic patients with the history of bisphosphonate use and presence of radiographic findings of BRONJ[2] (osteosclerosis, cortical disruption, osteolysis, subperiosteal bone deposition, thickening of lamina dura, and widening of PDL space) are diagnosed as stage 0 by AAOMS or stage 1NE by our proposed staging modification. Symptomatic patients with clinical evidence of infection, such as the presence of intra-oral or oro-cutaneous fistula tracts, and radiographic findings of necrosis can be classified as stage 2NE or stage 3NE, following similar findings as stated by the AAOMS guidelines, but with the absence of necrotic bone exposure. Treatment guidelines will be based primarily on clinical symptoms and associated risk factors for BRONJ[3]. [1]Rugierro *et al*, 2009 & Yoneda *et al*, 2010; [2]Hutchinson *et al*, 2010 & Arce *et al*, 2009; [3]Yoneda *et al*, 2010 & Sarasquete *et al*, 2009

'a' and 'b.' Stage 2a would include a case of bone exposure or presence of an oral fistula without bone exposure and responds well to medical treatment. Stage 2b would include bone exposure or presence of an oral fistula without bone exposure, but in this case, the lesion would be symptomatic and not responsive to several courses of medical treatment (Bagán *et al*, 2009).

McMahon *et al* (2007) proposed categorizing BRONJ in six stages. Patients would have to be taking bisphosphonate medication(s) for at least 1 year. Stage 1 would involve no bone exposure and mild, intermittent jaw pain, with a normal dental and radiographic exam. However, a radioisotope bone scan, CT, and MRI might be abnormal (with some osteoblastic activity but no infection). Stage 2 is similar to stage 1 with the exception of constant, mild jaw pain and a dental radiographic exam significant for radiolucent and sclerotic changes. Stage 3 exhibits no exposed or necrotic bone, constant, severe jaw pain, mucosal swelling and erythema with tenderness in the alveolar bone, abnormal dental radiographs, radioisotope bone scan, CT, and MRI, and potential presence of infection. Stage 4 exhibits bone exposure (without cortical fenestration) of <2 cm in size with constant, severe jaw pain, swollen, shrinking, erythematous mucosal borders around the exposed bone. Mild edema of the peripheral tissues can be present. There is no obvious evidence of infection, but dental radiographs, radioisotope bone scan, CT, and MRI are abnormal. Stage 5 exhibits similar features of stage 4 except for the presence of >2 cm of exposed bone, without cortical fenestration, mild to moderate edema of the peripheral tissues that may or may not exhibit purulent drainage. Lastly, stage 6 is similar to stage 5 except for the presence of >4 cm of exposed or necrotic bone, with cortical fenestration and infection, strong odor, and one or more of the following findings: pathologic fracture, extraoral skin fistula, oroantral fistula, or osteolysis that extends to the inferior border of the mandible (McMahon *et al*, 2007; Table 2, part II). Furthermore, Yoneda *et al* (2010) described the staging of BRONJ similar to AAOMS (Ruggiero *et al*, 2009). However, in stage 1, the symptoms also include hyperesthesia or anesthesia of the lower lip, also known as Vincent's symptom, and presence of deep periodontal pockets (Yoneda *et al*, 2010; Table 2, part II).

Several authors have provided their opinions and commentaries on this issue as well. They have expressed the need for a modification of the current guidelines established by AAOMS to more clearly define the new variant of unexposed BRONJ (Woo *et al*, 2008; Colella *et al*, 2009; Ruggiero *et al*, 2009; Yaroma *et al*, 2010). Currently, there is no definitive guideline for diagnosis

Table 2 Proposed modifications to staging guidelines: Part I and Part II

Part: I

Mawardi et al (2009)	*Bagán et al* (2009)
Stage 0_s: 'suspicious' for BRONJ Absence of bone exposure Presence of sinus tracts, severe tooth mobility, or positive radiographic findings 2 subcategories: Stage 0_{ss}: 'suspicious' and symptomatic Stage 0_{sa}: 'suspicious' and asymptomatic	Stage 1: Exposed and necrotic bone present Asymptomatic with no evidence of infection Presence of oral fistula or ulceration without bone exposure Stage 2a: Bone exposure or presence of an oral fistula without bone exposure that responds well to medical treatment Stage 2b: Bone exposure or presence of an oral fistula without bone exposure that does not respond well to medical treatment

Part II

McMahon *et al* (2007)	Yoneda *et al* (2010)
Stage 1: No exposed/necrotic bone Intermittent, mild jaw pain Normal dental/mucosal and radiographic exam Radioisotope bone scan, CT, and MRI reveal osteoblastic activity but no evidence of infection Stage 2: (same as stage 1 except:) Constant, mild jaw pain Normal dental/mucosal exam but radiographs show radiolucent and sclerotic changes Radioisotope bone scan, CT, and MRI are abnormal No evidence of infection Stage 3: (same as stage 2 except:) Constant, severe jaw pain Mucosal edema, erythema with severe alveolar bone tenderness Dental radiographs are abnormal Infection may be present Stage 4: (same as stage 3 except:) <2 cm exposed/necrotic bone without cortical fenestration Constant, severe jaw pain requiring strong analgesics Shrinking, swollen, and erythematous mucosal edges surrounding exposed bone Mild swelling of peripheral tissues Stage 5: (same as stage 4 except) >2 cm exposed/necrotic bone with or without cortical fenestration Mild to moderate swelling of peripheral tissues with or without purulence	Same guidelines as American Association of Oral and Maxillofacial Surgeons except: Stage 0 Includes hypoesthesia or anesthesia of the lower lip Deep periodontal pockets

BRONJ, bisphosphonate-related osteonecrosis of the jaw.

and treatment of the non-exposed variant of BRONJ. Early recognition of the disease severity will allow a more definitive treatment approach and thus a better treatment outcome and faster healing.

Here, we propose to adapt the current staging terminology with the addition of the term 'non-exposed (NE)' to each stage to accurately reflect the clinical presentation of the ONJ (Figure 2). BRONJ cases are categorized based on the presence or absence of clinically exposed bone. In the absence of clinically exposed bone, BRONJ diagnosis will rely more on the patient's symptoms (pain, swelling, and paresthesia/dysesthesia), clinical evidence of infection, specifically, the presence of intraoral, oro-cutaneous or oronasal fistula tracts, associated comorbidities or radiographic findings of ONJ (Arce *et al*, 2009; Hutchinson *et al*, 2010). As such, BRONJ cases are classified as asymptomatic or symptomatic. Asymptomatic BRONJ will include stage 0 lesion as classified by the AAOMS guideline or stage 1NE by our proposed system. Stage 2 or 3 symptomatic BRONJ patients without clinically exposed necrotic bone will be classified as stage 2NE or stage 3NE. In conjunction with the modified terminology, we recommend a new treatment protocol to incorporate the atypical symptoms of non-exposed BRONJ, which would lead to early treatment intervention as these atypical lesions are more often in stage 2 or 3, and not in stage 0 as defined by the current guidelines.

A systematic approach to the treatment of BRONJ is outlined in Figure 2. Cases that present with clinically exposed bone will be treated in accordance with the current AAOMS guidelines (Ruggiero *et al*, 2009). For asymptomatic lesions (stage 1 NE), periodic follow-up is recommended. For symptomatic lesions (stage 2 NE or stage 3 NE), treatment should be based on clinical

symptoms and associated risk factors. Treatment should encompass incision and drainage with sequestrectomy of necrotic bone and wound management with local and systemic antimicrobial therapy (e.g. chlorhexidine and systemic antibiotic therapy) prior to the appearance of mucosal breakdown and bone exposure. This approach might reduce the local wound microbial load contributory to the pathology of BRONJ as previously reported (Kumar *et al*, 2010). Any periodontal or odontogenic infection contributing to these lesions should be concomitantly treated accordingly. Granulation tissue should be removed during debridement and the choice of primary closure of the wound *vs* non-closure to allow for irrigation during secondary healing should be made on a case-by-case basis considering severity of disease, patient comorbidities, and ability of patient to irrigate the wound during home care. For stage 3, NE lesions involving pathologic fracture, surgical resection and reconstruction will be required. Lastly, periodic follow-up and wound management is recommended until clinical and radiographic evidence of resolution has been achieved in such cases. This intervention is more appropriate and ethical as compared with a 'wait-and-watch' approach especially in symptomatic non-exposed BRONJ cases.

In the last few years, other non-bisphosphonate medications (denosumab and bevacizumab) have recently been implicated in some incidences of osteonecrosis of the jaw (Fizazi *et al*, 2011; Estilo *et al*, 2008). Drug-induced osteonecrosis of the jaw is an alternate term proposed by Yaromb *et al* (2010), given that sufficient evidence has now linked denosumab and bevacizumab to ONJ, besides bisphosphonates. Another term has also been proposed to account for other drugs causing ONJ: antiresorptive associated osteonecrosis of the jaw by (Kumar *et al*, 2010) and recently re-introduced by the American Dental Association Council on Scientific Affairs (Hellstein *et al*, 2011). Hence, the diagnostic term, diagnostic criteria, staging and treatment guidelines for ONJ should be revised to more accurately fit the clinical history (including the medication history, either bisphosphonate, denosumab, or bevacizumab) and the patient's signs and symptoms that guide clinicians to properly diagnose and manage this challenging bone complication.

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Author contributions

S. Patel: conception and design, manuscript writing; S. Choyee, J. Uyanne, A.L. Nguyen, P. Lee, J. Lytle: collection and assembly of data; P.P. Sedghizadeh, S.K.S. Kumar: manuscript writing and final approval; A.D. Le: conception and design, manuscript writing, final approval of the manuscript, financial support.

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