Abstract

This paper is an adaptation, with permission, of the recent systematic review published in the Journal of Bone and Mineral Research by the International Task Force on Osteonecrosis of the Jaw. This work provides a systematic review of the literature from January 2003 to April 2014 pertaining to the incidence, pathophysiology, diagnosis, and treatment of osteonecrosis of the jaw (ONJ), and offers recommendations for its management based on multidisciplinary international consensus. The goal in this review is to highlight the pertinent information that applies to the dental profession. Nine key questions were posed and answered by the task force in the context of this article. These range from definition and staging, incidence and prevalence, how common it is in the osteoporosis and oncologic populations, risk factors to the role of imaging, use of biomarkers to management and newer therapies. Some areas are dealt with in detail such as imaging for this disorder since dentistry may be the first line health care discipline to be in a position to image, assess and diagnose ONJ. As well, dentistry needs to be familiar with available management options for these patients since surgical possibilities exist which fall under the umbrella of care of the oral and maxillofacial surgeon. Conservative management is discussed as it continues to be a mainstay of ongoing care for many of these unfortunate patients. Insight into newer experimental therapies is highlighted so that dentists will be aware should they read about these methods becoming more mainstream.

Introduction

The intent of this paper is to provide a current update on osteonecrosis of the jaw (ONJ). The paper will address etiology, risk factors, diagnosis, prognosis as well as management. This paper summarizes key points from the systematic review and international consensus of ONJ developed by the International ONJ Task Force – a Canadian led initiative supported by 14 national and international societies dedicated to advancing the care of oral bone health including medicine, surgery, dentistry, oral pathology and imaging. The goal of the task force was to develop a state of the art document summarizing current knowledge pertaining to ONJ and translating this material into useful bedside information for health care providers as well as patients. The task force is of the opinion that members of the dental profession will also be significantly impacted by this content.

ONJ has been renamed BRONJ (bisphosphonate related), ARONJ (antiresorptive related) and more recently MRONJ (medication related); these terms are synonymous with ONJ, which is the preferred nomenclature recommended by the International Task Force. The entity ‘Osteonecrosis of the Jaw’ was introduced in an editorial by Marx in 2003 and subsequently in a peer-reviewed manuscript by Ruggiero et al. in 2004. Non healing exposed areas of jawbone were associated with the use of intravenous bisphosphonate therapy. Bisphosphonates are analogs of inorganic pyrophosphate and are potent inhibitors of osteoclasts. They are effective in decreasing bone remodeling and lowering rates of bone loss. These agents have been used to decrease the rate of fracture in osteoporosis. They are also effective in the treatment of other metabolic bone disease including Paget’s disease. In high doses bisphosphonates are effective in lowering the risk of skeletal related events in individuals with metastatic cancers and multiple myeloma.
Another antiresorptive agent associated with ONJ is denosumab. This molecule is a monoclonal antibody to receptor activator of nuclear factor K-B ligand (RANKL). RANKL binds to its receptor RANK on preosteoclasts as well as osteoclasts and is essential for the formation, function and survival of osteoclasts. Denosumab is effective in the treatment of osteoporosis and lowers the risk of fracture. It can also be used in high doses in individuals with metastatic cancer and has been shown to reduce the risk of skeletal related events.

ONJ has been a concern particularly in those individuals on high dose parenteral antiresorptive agents and this has been a major concern for general dentists, dental specialists (mostly OMF surgeons and pathologists) and hospital based general dentists treating medical oncology patients. As well, medical oncologists who are prescribing these drugs for their patients have become acutely aware of this condition and are concerned regarding the optimal dose and duration of therapy. Patients who receive bisphosphonate or denosumab therapy for metastatic cancer and multiple myeloma receive monthly treatment with the medication administered intravenously (for bisphosphonates) or subcutaneously (for denosumab) as an outpatient at their cancer treatment center or medical day unit. Patients with osteoporosis or other bone disease such as Paget’s disease require antiresorptive therapy at much lower doses. They receive denosumab 60 mg every 6 months or zoledronic acid 5 mg every 1–5 years.

A position paper with guidelines was produced in 2008 by a task force comprised of Canadian Physicians, Dentists, OMF Pathologists and OMF Surgeons. The new international guidelines update this document as well as other national and international recommendations and are based on a multidisciplinary, multinational consensus paper referenced above.

Methods Undertaken

An extensive literature search was undertaken by the International Task Force addressing the following 9 questions:

1. How is ONJ defined and staged?
2. How common is ONJ?
3. Who develops ONJ? What are the risk factors and co-morbidity?
4. Why does ONJ develop?
5. What is the role of imaging in diagnosis and management?
6. Are biomarkers useful in identifying ONJ?
7. Can ONJ be prevented and what is the role of drug interruption?
8. How should ONJ be managed?
9. Where is the research and future directions?

A search strategy was developed by combining medical subject headings and/or text words from 4 categories: interventions (BPs and denosumab); population (oncology and osteoporosis); areas of interest for the review (classification, diagnosis, incidence, risk factors, treatment); and outcome (osteonecrosis of the jaw). All searches were limited to human studies published in the English language and excluded reviews, editorials, and letters. The electronic search was conducted in Medline (January 1, 2003 to April 10, 2014) and EMBASE (January 1, 2003 to April 10, 2014) using OVID. The results from both databases were combined and duplicates excluded. The Cochrane Database of systematic reviews was also searched for applicable references. A manual search of the bibliography of identified published articles was also
performed. In order to obtain additional unpublished data, personal communication with relevant experts was conducted and pharmaceutical companies were invited to submit relevant information. A total of 46 papers were included from manual searches and expert communication. The total number of references reviewed was 933 and from these, 599 papers were reviewed in full.

The published literature was critically appraised and graded based on quality of evidence. All assessments were made in duplicate with disagreements discussed between reviewers until consensus was achieved. If no consensus was possible, a third reviewer would have provided the final decision. However, adjudication by a third reviewer was not necessary in any instance.

**Nomenclature, Definition, Risk Factors and Etiology of ONJ**

The International Task Force recommends simplifying this group of entities and naming them Osteonecrosis of the Jaw (ONJ for short). The reason for this is that the condition is presently known to be associated with 2 classes of drugs – bisphosphonates and denosumab. There may also be an association with antiangiogenic agents which requires further investigation. In the recent paper from the American Association of Oral and Maxillofacial Surgeons (AAOMS) the antiangiogenic agents have also been included as potential causative agents however the International Task Force believes that the data linking antiangiogenic agents and ONJ requires further substantiation. In time there may be other agents linked to ONJ as other antiresorptive agents are being developed for the treatment of osteoporosis and skeletal metastases. Following this classification, BRONJ would now be used specifically for those cases directly related to bisphosphonate use. The proposed definition of ONJ remains and is: non healing exposed bone of the jaw persisting for 8 weeks in the absence of any previous tumoricidal radiotherapy to the area.

In addition to drugs causing ONJ, it is recognized in the published literature that ONJ can develop spontaneously and has been described as lingual mandibular sequestration and ulceration (LMSU).

A confounding factor in efforts to determine ONJ incidence in those taking oral bisphosphonates is that ONJ cases have been documented in patients with no history of bisphosphonate exposure. A case series published in 1993 described 11 patients who presented with exposed necrotic bone involving lingual mandible. In 3 of 8 patients (38%) in this study, in which information regarding the duration of exposed bone was available, the exposed bone had been present for greater than 8 weeks. This raises an obvious question regarding the “prima facie” assumption of bisphosphonate causality in all ONJ cases, where bisphosphonates had been used. Since this initial study, there have been other reports of this phenomenon, more recently termed oral ulceration with bone sequestration (OUBS). The incidence and the percentage of these cases, which present past the 8 week period, is not known. A similar concern can be extended to other factors. For example, oral exostoses (an ONJ risk factor) have also been identified as an independent risk factor for sequestration, again with an unknown incidence. In this regard, a further interesting study of 154 alveolar bone specimens removed for implant purposes suggested that 35% had non-viable bone and another 15.6% had evidence of osteomyelitis. The results of this study need to be confirmed and should be further evaluated. However, it is clear that the incidence of ONJ in the absence of antiresorptive therapy in not known. It is recommended that a causal role not be attributed to bisphosphonate use in healthy patients taking oral bisphosphonates. Future research is required to determine if OUBS is an initiating event in oral ONJ cases or alternately, whether bisphosphonate use may delay the resolution of OUBS and be regarded as a distinct clinical pathologic entity.
Three stages of ONJ have been proposed and this classification is currently in use. Stage 1 is exposed bone with no infection and otherwise asymptomatic. Stage 2 is exposed bone with evidence of infection with or without purulent discharge. Stage 3 is exposed bone with infection and extension radiographically to the inferior border of the mandible or sinus floor in the maxilla or presence of an extra oral fistula or pathologic fracture. Another controversial area was whether to include a Stage 0 category, to represent cases with no bone exposure but with non-specific symptoms or radiographic findings not explained by an odontogenic cause in patients on antiresorptive medications. The International Task Force did not recommend the use of Stage 0 ONJ as it may potentially overdiagnose ONJ in a large number of individuals who may never actually develop ONJ.

A number of risk factors have been identified for ONJ. These include antiresorptive drugs, minor oral surgery such as dental extractions and periodontal surgery. It is still unknown how significant the risk is with minor oral surgery. Other factors which may increase the risk of ONJ include concomitant use of steroids, anti-angiogenic agents (used in various cancer therapies) as well as diabetes and perhaps smoking. While the AAOMS group included anti-angiogenics in their causative medication list, the evidence that this class of drugs alone increases the ONJ risk is based on case reports and requires substantiation.

The relative risk for patients taking oral bisphosphonates for osteoporosis and the development of ONJ is unknown at this time and is estimated to be very low in the order of 1:10,000–100,000 patient years on drug therapy. It is clear that the benefit with respect to fracture risk reduction is far greater than the extremely low risk of ONJ in osteoporosis patients and in oncology patients the benefit of antiresorptive therapy in lowering the risk of skeletal related events outweighed the risk of ONJ by a factor of 17.

The patients most at risk of developing ONJ are those patients on monthly IV bisphosphonates or high dose sub cutaneously administered denosumab 120 mg monthly. The reported prevalence in the oncology patient population is between 1 and 16% of patients on high dose therapy.

The details of the exact pathophysiology of ONJ are not yet clearly understood. The sequence of events leading to the development of ONJ is unclear; in particular, it is unknown whether necrosis precedes or follows infection. Suppression of bone turnover as well as the potential antiangiogenic effects of BPs may contribute to the development of ONJ.

**Histopathologic Findings**

The clinically exposed bone is necrotic and histologically exhibits irregular resorption with associated acute and chronic inflammation. The non-vital bone can show interspersed foci of vital bone. Microbial colonization of the bone surfaces, including in particular *Actinomyces* colonies, occurs primarily in superficial areas. Epithelial strands derived from overlying mucosa can extend into medullary spaces and line non-vital bone trabeculae. The zones peripheral to the exposed non-vital bone show thickened irregular trabeculae with deposition of woven bone. The trabeculae can show “reversal lines” similar to Paget’s disease.

Attempts to histologically characterize osteoclasts in this condition have not shown consistent results. There have alternately been observations indicating that osteoclasts are increased in non-vital bone but diminished in the peripheral vital bone, increased in peripheral vital bone, increased in vital and non-vital bone or diminished in exposed non-vital bone but present, albeit detached from bone surfaces, in the unexposed peripheral vascularized bone.
It is worth noting that these findings are based primarily on biopsy material derived from cancer patients receiving IV bisphosphonates. Although these features do appear characteristic for ONJ cases (at least in cancer patients), it is not certain whether they can be reliably translated to ONJ occurring in osteoporosis patients receiving oral bisphosphonates or whether they are sufficient to distinguish reliably between osteonecrosis or osteitis or osteomyelitis occurring for other reasons.

**Markers for ONJ and Predicting Susceptibility**

It has been proposed that serum C-terminal telopeptide of Type 1 collagen (CTX), a break down product of type 1 collagen during bone resorption, can be followed in the patient’s serum as a risk indicator for development of ONJ. Serum CTX is however expected to be suppressed with bisphosphonate therapy and is not a useful indicator of the risk of ONJ in those on BP or dmab therapy. Antiresorptive therapy reduces the biomarkers by approximately 50% and serum values reflect total body rates of bone remodeling. Biomarker levels are not useful in predicting the risk of ONJ or in the management of the ONJ lesions.

**Role of Imaging**

ONJ is a clinical diagnosis based on history and physical exam. Radiographic features of ONJ remain relatively non-specific. Plain film radiography is usually unremarkable in the early stages of the disease as decalcification is limited. The presence of localized or diffuse osteosclerosis or a thickening of the lamina dura on plain film imaging may predict future sites of exposed necrotic bone. Poor ossification at a previous extraction site may also be an early radiographic feature of ONJ. Findings on computed tomography (CT) are non-specific and may include areas of focal sclerosis, thickened lamina dura, early sequestrum formation and reactive periosteal bone. CT imaging is of value in delineating the extent of disease and is helpful in planning surgical intervention. Features noted on bone scanning include increased tracer uptake at sites which subsequently develop necrosis. The utility of nuclear bone scanning in patients at risk of ONJ requires further study.

Imaging modalities used as adjunctive assessment in the evaluation of the ONJ patient may include plain radiographs, CT, magnetic resonance imaging (MRI) and functional imaging with bone scintigraphy and positron emission tomography (PET). Each one of these approaches has advantages and limitations. **Figures 1 and 2** provide clinical and radiographic images of patients with Stage 1 and 2 ONJ, respectively. Plain radiographs are often sufficient to support the diagnosis of ONJ. Advanced imaging may become necessary if the diagnostic information obtained via plain films is incomplete or to assess the extent of the changes in cases of surgical intervention.

**Radiographs – Intraoral and Panoramic Radiographs**

Intraoral (periapical and bitewing) radiographs are easy to acquire, inexpensive, and deliver a low radiation dose. Images are of high resolution and are useful in assessing early features of ONJ including thickening of the lamina dura, increased trabecular density of the alveolar bone and widening of the periodontal ligament space. In addition they provide useful information regarding the presence of carious lesions, periodontal or periapical disease, which are all important risk factors for ONJ.

Panoramic radiographs are also of value and provide assessment of both arches, as well as adjacent anatomic structures including the maxillary sinus, nasal cavity, mental foramen, and
mandibular canal. The typical radiographic findings of ONJ on intraoral and panoramic radiographs are increased trabecular density, incomplete healing of extraction sockets, sequestrum formation, thickening of the mandibular canal or sinus floor cortication, and periosteal bone formation.\textsuperscript{31,34,39-41}

Limitations of the intraoral and panoramic projections include their two-dimensional representation of three-dimensional structures. Intraoral radiographs cover only a small part of the patient’s jaws and thus provide limited visualization of the bone at risk of ONJ. Panoramic images are limited by the presence of ghost shadows, unpredictable horizontal and vertical magnification and distortion of structures outside the focal trough. Also, projection geometry generated by the negative vertical angulation of the x-ray beam, and propensity to patient positioning errors do not allow consistently accurate depiction of anatomic structures. As a result, panoramic radiographs do not provide the highly detailed images that are generated by intraoral radiographs.\textsuperscript{38}

Intraoral and panoramic projections are useful screening tools for assessing the presence of dental disease and the severity and extent of osteonecrotic changes, as well as for follow-up of patients with ONJ. However, if the diagnostic information is ambiguous or more detailed investigation of the dental and osseous health is required, more advanced imaging is necessary as described below.

**Computed Tomography (CT) and Cone Beam Computed Tomography (CBCT)**

CT has clear advantages over 2D imaging in characterizing the features of ONJ. The cortical and trabecular architecture of the maxilla and mandible can be evaluated as well as the presence of periosteal bone reaction, presence of sequestrum and integrity of adjacent vital structures, allowing for earlier detection of ONJ lesions.\textsuperscript{32,40}

Common CT findings in ONJ patients include diffuse osteosclerosis, areas of osteolysis, cortical erosion, increased periosteal bone formation and sequestration. Potential fistula track formation, as well as incomplete extraction socket healing may be seen.\textsuperscript{39-43} Typically, these radiographic changes extend beyond the clinically exposed bone areas. In early stages of ONJ, increased trabecular density may not be detected on panoramic radiographs but may be seen on CT.\textsuperscript{44} CT radiographic findings may underestimate the extent of bony changes as assessed during surgery.\textsuperscript{32} CT may demonstrate radiographic evidence of altered bone architecture at the symptomatic site and aid in disease diagnosis.\textsuperscript{29,45} Radiographic features of osteosclerosis can be seen in the absence of clinically exposed bone\textsuperscript{46} and in individuals with symptoms of bone pain careful evaluation is advised as these radiographic features may be a reflection of an early prodromal phase of ONJ.

CBCT offers similar advantages to CT in evaluating the osseous structures of the face, while delivering significantly less radiation. CBCT allows improved detection of periodontal and periapical disease in comparison to dental radiographs particularly if a small field of view (FOV) is utilized.\textsuperscript{47,48} There are no conclusive definitive studies regarding the use of CBCT use and the diagnosis of ONJ. Data are limited to preliminary investigations.

A major disadvantage of CBCT is the low contrast resolution and poor soft tissue detail. However, the ability of CBCT to image bony structures is similar to that of CT.\textsuperscript{48} Due to the high resolution volumetric imaging, CBCT shows improved diagnostic ability for periodontal and periapical disease in comparison to conventional radiographs.\textsuperscript{47} CBCT imaging findings of the
osteonecrotic areas with CBCT are similar to those with CT, and include increased bone density, osteolysis, cortical erosions, sequestration and periosteal bone reaction.\textsuperscript{31,49,50}

**Magnetic Resonance Imaging (MRI)**

MRI offers similar advantages to CT in evaluating the osseous ONJ changes, while it appears to be superior in assessing bone marrow change at the early stage of ONJ, as well as the soft tissue changes surrounding the osteonecrotic area.

One of the most consistent and earliest MRI findings is a decrease of bone marrow signal intensity on T1-weighted images that can be present prior to clinical features of ONJ.\textsuperscript{32,41,44,51,52,54,55} T2-weighted and short T1 inversion recovery (STIR) sequences may show increased signal intensity due to high water content,\textsuperscript{44} while irregular gadolinium enhancement of bone marrow and soft tissues around osteolytic areas is observed.\textsuperscript{41,50,55} In advanced disease the bone marrow signal intensity on T2-weighted and STIR images can be variable: the exposed bone shows decreased signal intensity, and the unexposed diseased bone shows increased signal intensity.\textsuperscript{41,52} Sequestra display a low-signal-intensity center with a high-signal-intensity rim on the T2-weighted image.\textsuperscript{37,53} Soft tissue thickening and edema and lymph node enlargement can also be observed.\textsuperscript{51,54} Similar to CT, MRI shows increased ability to detect osseous ONJ changes compared to panoramic radiographs; however, it may also fail to demonstrate the full extent of bony changes seen on surgical exploration.\textsuperscript{32}

**Nuclear Imaging with Scintigraphy and Positron Emission Tomography (PET)**

Bone scintigraphy utilizing Tc99m methylene diphosphonate (MDP) or hydroxymethylene diphosphonate (HDP) has a high sensitivity for detecting early disease. Bone scintigraphy shows increased radionuclide uptake with increased perfusion and increased blood pool. Single-photon emission computed tomography (SPECT) and fusion SPECT/CT provide more precise localization of osteonecrotic areas with surrounding areas of increased radionuclide uptake.\textsuperscript{56,57} In 67.5% of patients with ONJ increased Tc99m-MDP or HDP was observed in areas that later developed clinical osteonecrosis and thus bone scans may be useful in early identification of ONJ.\textsuperscript{35,58} However, it is not uncommon for conditions other than ONJ to produce increased uptake in the jaw, including tumor or periodontal disease.\textsuperscript{59,60}

PET alone or in combination with CT has also been used for the assessment of ONJ patients, utilizing both F-18 fluoride (NaF) and F-18 fluorodeoxyglucose (FDG) tracers.\textsuperscript{58,61,62} Interestingly, FDG-PET uptake appears to increase with ONJ severity, although a clear relationship has not been established, possibly due to the small number of patients in the study.\textsuperscript{58}

In summary, imaging is of value in diagnosing ONJ. This is particularly the case in those individuals on anti-resorptive therapy with ONJ-like symptoms, but without obvious bone exposure. As periapical and periodontal disease is an important risk factor for ONJ, identifying early dental disease with imaging and proceeding with dental preventive measures may decrease the risk of ONJ and minimize the need for dental extractions.\textsuperscript{63,64} In addition, imaging enables exclusion of other conditions which may contribute to necrosis such as metastatic disease.\textsuperscript{65,66} There are no pathognomonic features of ONJ on imaging which definitively differentiate ONJ from other conditions.\textsuperscript{67} However, imaging can assist in identifying the extent of bone and soft tissue disease as well as providing information on dental, periodontal and periapical health. A summary of imaging findings with ONJ is presented in Table 1.
**Recommendations for Imaging**

a) Individuals on low dose anti-resorptive treatment without signs or symptoms of ONJ do not require any additional imaging beyond routine dental evaluation.\(^{68-70}\)

b) Patients on high-dose anti-resorptive treatment without ONJ are at significant risk of developing ONJ and early identification of dental disease is important.\(^{63,64}\) Following a complete examination of the oral cavity, high risk patients should ideally receive bitewing and periapical intraoral radiographs of all existing teeth and panoramic radiographs. When available, CBCT 3D imaging utilizing high-resolution protocols could also be performed, given the superior ability of CBCT (compared to conventional radiographs) in diagnosing periapical and periodontal disease. Following a baseline evaluation of oral health, additional conventional and CBCT radiographs are performed only if necessary in the presence of oral complaints or signs or symptoms of ONJ.\(^{71}\)

c) In patients in whom ONJ is a clinical consideration on low or high dose anti-resorptive therapy presenting with oral symptoms CBCT or CT imaging may aid in evaluating early changes in the cortical and trabecular architecture of the maxilla and mandible. Imaging also allows assessment of possible sequestrum or fistula track formation and to evaluate the status of any involved teeth. If both CBCT and CT are available, small FOV, high resolution CBCT is preferred as it delivers less radiation and provides similar diagnostic information as CT.

CBCT may be performed in conjunction with bitewing, periapical and panoramic radiographs. If clinically indicated, MRI may provide additional information of the presence and extent of osteonecrosis.

d) Patients with clinical ONJ under conservative management (Stage 1 and 2). The nature and extent of osseous changes around the area of clinical bone exposure can be evaluated with CT or CBCT imaging. Dental disease in all existing teeth should also be determined with bitewing, periapical and panoramic radiographs.

e) In patients with clinical ONJ where surgical intervention is considered (Stage 2 and 3), CBCT or CT may be complemented with MRI, bone scan or PET for a more thorough evaluation of involved bone and soft tissues.

**ONJ and Dental Management**

Aside from recognizing signs of this disease, it is important for dental patients at risk of developing ONJ to maintain meticulous oral hygiene and regular dental visits. Any surgical therapy should be minimized and especially if non surgery is an option – endodontics versus extraction for example. In general, dental care should be optimized in individuals at risk for developing ONJ. It is important to maintain optimal dental health of both hard and soft tissues with regular professional maintenance and very good home care. Any minor oral surgery including extractions and periodontal surgery should include antibiotic prophylaxis, both systemic and topical, careful surgical technique, minimizing sharp bony edges and providing primary closure over bony wounds wherever possible. There is no need for interruption of oral bisphosphonate therapy such as that taken for osteoporosis therapy, either before or after the minor surgical procedure. For those on high dose IV bisphosphonate or denosumab therapy or with multiple risk factors for ONJ it is recommended that the antiresorptive therapy be withheld following the oral surgery until the surgical site has healed with mature soft tissue closure over the wound. This may typically require 4–6 weeks. For these individuals at a high risk of ONJ it is
critical to achieve primary closure and utilize perioperative antibiotics up to a week following and chlorhexidine mouth rinses immediately before and for the weeks following until soft tissue coverage is achieved.

Other routine restorative, hygiene, orthodontic and endodontic dentistry can be conducted as usual.

Managing ONJ

Most of these patients will not require surgical intervention. A patient with ONJ that is failing conservative therapy or whose ONJ is progressing should be referred to and managed by an oral and maxillofacial surgeon. Not all OMF surgeons may be familiar with management of these patients and it will be necessary to refer to an experienced OMF surgeon for appropriate care. This may require traveling to a larger urban center. He or she may refer the patient back to their primary dental caregiver for ongoing care in the presence of persistent ONJ or in its absence following surgical treatment. There are however a number of experienced hospital based dentists who are able to evaluate and manage these patients non surgically in consultation with their medical oncologists. These clinicians, although few in number nationally, are most familiar with this disease and may be best to perform non surgical therapy and follow these patients conservatively.

For Stages 1 and 2, conservative therapy may be all that is required. Meticulous oral hygiene, preventive care, topical antibiotic rinses such as chlorhexidine and periodic systemic antibiotics should be used as needed. These patients require close follow-up with periodic radiographic assessment of their disease. While many patients are symptomatic from their ONJ lesions a significant number are asymptomatic and require close monitoring while maintaining excellent oral hygiene and ensuring that the affected area is clean with monitoring for progression of disease.

Spontaneous resolution of ONJ is possible. Early treatment recommendations discouraged surgical intervention, with conservative therapy continuing indefinitely or until there was progression of disease. Others have had reasonable success with surgical management.\textsuperscript{72,73} There is still no comfortable proven treatment algorithm for the various stages of this disease. The International Task Force believes that surgical intervention is required for Stage 3 disease and for those Stage 2 patients that are showing progression or require continual antibiotic or narcotic analgesic therapy in order to control their symptoms.

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**Figure 1:** Clinical and radiographic images of a patient with Stage 1 osteonecrosis of the jaw.  
A) Clinical photograph showing failure of healing and small area of bone exposure after extraction of the second right mandibular molar (yellow arrow).  
B) Part of panoramic radiograph showing lack of extraction socket healing (yellow arrow), and thickened lamina dura (green arrow).  
C) and D) Axial multislice CT images indicate lack of bone healing in the extraction socket (yellow arrow) and diffuse osteosclerosis of the alveolar bone in the posterior right mandible (black arrows).  
E) T1 weighted image shows reduced bone marrow signal intensity (white arrow) in the alveolar bone of the right mandible extending almost to the mid-line.  
F) Fat saturated T2 weighted image indicates increased signal intensity (white arrowhead) over the affected area of the alveolar ridge.
Figure 2: Clinical and radiographic images of a patient with Stage 2 osteonecrosis of the jaw. 
A) Clinical photograph shows extensive bone exposure and inflamed surrounding soft tissues in 
the posterior right mandible. B) Panoramic radiograph shows altered trabecular architecture with 
increased trabecular density (arrows) and a probable sequestrum formation (arrowhead) C) 
Sagittal, D) Axial, and E) Coronal sections of the area of interest. Near complete opacification of 
the mandible (arrows), with extensive periosteal bone formation (double arrows) and 
sequestration (arrowheads) are observed.
**Table 1** Imaging findings that may be present with osteonecrosis of the jaw.

**Radiographic Findings**
- Diffuse sclerotic changes with increased trabecular density
- Irregular areas of osteolysis
- Cortical bone destruction
- Periosteal bone formation
- Sequestrum formation
- Thickening of lamina dura
- Thickening of cortical outlines
- Incomplete healing of extraction sockets
- Fistula formation
- Widening of periodontal ligament space

**Magnetic Resonance Imaging Findings**
- Intensity changes of the cortical and subcortical bone structures
- Absence of signal with high rim in areas of sequestrum
- Contrast enhancement in lytic areas
- Soft tissue involvement
- Cervical lymphadenopathy

**Scintigraphy Findings**
- Increased extravasation of radionuclide in blood pool phase
- Abnormal localized uptake
- Photopenic areas adjacent to region of increased uptake
- SPECT/CT can improve the diagnostic accuracy of bone scans and provide anatomic correlation that might be important for treatment planning
- Tc99m-sestamibi SPECT can be used for differentiation between metastasis and ONJ

**FDG-PET and NaF-PET Findings**
- Abnormal focal uptake that tends to be more intense and extensive with NaF