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Staging of osteonecrosis of the jaw requires computed tomography for accurate definition of the extent of bony disease

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Abstract

Management of osteonecrosis of the jaw associated with antiresorptive agents is challenging, and outcomes are unpredictable. The severity of disease is the main guide to management, and can help to predict prognosis. Most available staging systems for osteonecrosis, including the widely-used American Association of Oral and Maxillofacial Surgeons (AAOMS) system, classify severity on the basis of clinical and radiographic findings. However, clinical inspection and radiography are limited in their ability to identify the extent of necrotic bone disease compared with computed tomography (CT). We have organised a large multicentre retrospective study (known as MISSION) to investigate the agreement between the AAOMS staging system and the extent of osteonecrosis of the jaw (focal compared with diffuse involvement of bone) as detected on CT. We studied 799 patients with detailed clinical phenotyping who had CT images taken. Features of diffuse bone disease were identified on CT within all AAOMS stages (20%, 8%, 48%, and 24% of patients in stages 0, 1, 2, and 3, respectively). Of the patients classified as stage 0, 110/192 (57%) had diffuse disease on CT, and about 1 in 3 with CT evidence of diffuse bone disease was misclassified by the AAOMS system as having stages 0 and 1 osteonecrosis. In addition, more than a third of patients with AAOMS stage 2 (142/405, 35%) had focal bone disease on CT. We conclude that the AAOMS staging system does not correctly identify the extent of bony disease in patients with osteonecrosis of the jaw.
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Keywords: Osteonecrosis of the jaw; Bisphosphonate; Staging system; AAOMS; Computed tomography; Antiresorptive agents

Introduction

Osteonecrosis of the jaw is a potentially severe side effect of antiresorptive agents including aminobisphosphonates and denosumab, the incidence of which is reported to vary from 0 to 27.5% in patients treated with bisphosphonates intravenously, with a mean incidence of 7%.[1] It typically presents with areas of necrotic avascular jawbone exposed through the oral mucosa or facial skin.[2] Infection of necrotic bone is common and can lead to chronic pain, facial disfigurement, impaired function, and reduction of quality of life.[3] Management of osteonecrosis of the jaw is challenging and there is little evidence about the effectiveness of treatments.[1] In most cases, the outcome is unpredictable. [4] Patients with mild to moderate disease are usually offered minimally invasive treatment such as control of infection and pain, and superficial debridement of bone, whereas it has been suggested that those with advanced and refractory disease may benefit from resection. [2,5] Accurate staging is therefore crucial to making therapeutic decisions and planning.

Staging of osteonecrosis of the jaw is currently based on the classification proposed by the American Association of Oral and Maxillofacial Surgery (AAOMS), which relies on clinical and radiographic examinations.[2] Other classifications are similarly based. [6,7] However, visual inspection is likely to identify only superficial signs, which may not necessarily reflect the true extent of bony disease. [6,8,9] For instance, the non-exposed variant, which often presents with minimal superficial clinical changes (such as a sinus tract), can be associated with widespread underlying necrosis of the jaw. [10,11] Signs such as exposed bone, infection with mucosal erythema, purulent discharge, and pain, however, may not be associated with widespread bony disease.[12] Studies have also shown that routine dental radiographs (such as panoramic radiography) is inferior to other imaging techniques in detecting the extent of bony disease in osteonecrosis.[13] A new staging system has been proposed that integrates clinical manifestations and CT findings.[14] As the amount of research grows, an increasing number of authors now report the use of CT to study the extent of osteonecrosis in these patients. [15-17] There is, however, little evidence to suggest that the benefits of CT are enough to justify its routine use for staging of disease.

To test the hypothesis that the current staging system for osteonecrosis of the jaw may not correctly identify the extent of disease because of the lack of data from CT, we evaluated the agreement of AAOMS staging with CT imaging for assessment of the extent of bone disease (focal compared with diffuse).

Patients and methods

Design of the study

We performed a multicentre retrospective study known as MISSION (**M**ulticentre study on phenotype, def**I**nition and cla**SS**ification of oste**ON**ecros**I**s of the jaws associated with bisphosph**ON**ates).

Setting

Research workers from the Universities of Verona, Palermo (Italy), and University College London (UK), designed the study and sent a collaboration proposal to a network of Italian centres of Oral Medicine and Oral and Maxillofacial Surgery with a special interest in the diagnosis and management of osteonecrosis of the jaw. The main requirements for participation were availability of a large group of patients with osteonecrosis, and routine use of CT in their investigations. Ten centres replied and agreed to collaborate, so a total of 13 centres contributed to the MISSION study. The ethics

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committees of the participating centres approved the study and patients' consent to participate was obtained where specifically required. Collection of data was completed between March and December 2012. MISSION was conducted with the partnership of the Italian Society of Maxillofacial Surgery (SICMF) and of the Italian Society of Oral Medicine and Pathology (SIPMO). The study was reported according to STROBE recommendations.[18]

Criteria of eligibility

Patients referred to the participating centres between January 2004 and December 2011 were eligible for MISSION if they had: exposed osteonecrosis of the jaw defined as the presence of long-standing (more than 8 weeks) transmucosal exposure of necrotic jawbone; unexposed ostenecrosis of the jaw defined as the presence of otherwise unexplained pain in the jaw, fistula, swelling, mobile teeth, or mandibular fracture, as defined by Fedele et al., and others;[10,19] previous or current treatment with bisphosphonates; no history of radiotherapy to the jaws; no history of resection of the jaws; and availability of CT (spiral or cone-beam) of the affected jaws. Only patients with CT scans that had been done within 6 months from clinical phenotyping were included, so that we had some agreement between the clinical signs and the CT findings. Dentascan reformatted images were not considered, as they do not accurately display the ramus of the mandible and the midfacial bones. Multidisciplinary teams that included prescribers of bisphosphonates (oncologists, haematologists, and rheumatologists) and specialists in oral medicine or maxillofacial surgery, or both, decided which cases were suitable for inclusion.

Collection of data

Hospital casenotes of consecutive patients with osteonecrosis of the jaw diagnosed between January 2004 and December 2011 were reviewed retrospectively. Clinical data relevant to the study (see "*Other measurements*" below) were extracted by local clinical teams and entered into a standard electronic case report form by one clinician at each centre (GS, Padua, AB Verona; GC, Palermo; SF, London; SV, Como; AA and LO, Rome; MS, Turin; GF, Bari; GC, Naples; GO, Messina; MG Pisa; and VF, Alessandria). They were also responsible for the final allocation of patients into AAOMS stages. Radiologists with experience and a special interest in head and neck imaging assessed and reported CT scans in all centres and were blinded to the patients' AAOMS staging.

The medical statistician responsible for data analysis (GB) managed the database according to standard procedures. We used Stata 13.0 (Stata Corp., College Station, TX, US) programs to ensure reproducibility of methods.

Outcome of the study

The study aimed to evaluate the degree of agreement between the AAOMS staging system and CT imaging for the assessment of the extent of osteonecrosis (focal compared with diffuse).

Measures of outcome

AAOMS stages were defined as reported by Ruggiero et al.[2] Briefly, stage 0 included patients with clinical signs of osteonecrosis other than exposed bone. Stage 1 included those with exposed necrotic bone but no pain or suppuration. Stage 2 included those with exposure of necrotic bone together with pain or suppuration, and stage 3 included patients with exposed necrotic bone and an extraoral fistula, sequestration, or mandibular fracture. CT imaging comprised bony windowing with both axial and coronal views. The extent of involvement of the jaw was decided by the extent of sclerotic bony changes evaluated as the loss of contrast between the endosteal cortex and the subjacent medullary bone compared with healthy bone. Specific and reproducible definitions were used to differentiate between focal and diffuse bony disease by spiral or cone-beam CT. In detail, focal bony disease was defined as osteosclerotic involvement limited to alveolar bone, whereas diffuse bony disease was defined as osteosclerotic involvement of both alveolar and basal bone. [11,20] The choice of sclerotic bony changes as the main variable by which to study extension of disease was based on previous reports. [8,21,22]

Other measurements

The following data were collected from the casenotes: age, sex, indication for prescription of bisphosphonates, type of bisphosphonate, duration of treatment, cumulative dose, concurrent use of steroids, concurrent use of antiangiogenic agents (such as sunitinib and bevacizumab), presence of known risk factors for bisphosphonate-related osteonecrosis (such as extraction of teeth, dental or periodontal infection, ill-fitting prosthesis, or dental implant surgery), site of osteonecrosis, and the presence of exposed bone, pain, purulent discharge, extraoral fistula, displaced mandibular stumps, and nasal leakage of fluids.

Statistical analysis

Continuous variables are reported as 25th, 50th, and 75th centiles because of non-Gaussian distributions, and categorical variables are reported as counts or percentages. The agreement between the AAOMS staging system and CT for the detection of bone disease was evaluated by calculating the proportion of patients with diffuse disease within each stage of AAOMS. The significance of differences was assessed with the help of Stata 13.0 (Stata, College Station, TX) software. Stata programs were written to ensure the reproducibility of the analysis.

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Table 1
Continuous measurements of the ONJ patients.

	N	P_{50}	P_{25}	P_{75}
Age (years)	799*	69	62	75
Zoledronate (mg), iv.	621**	76	48	120
Pamidronate (mg), iv.	99**	2250	1200	4320
Alendronate (mg), oral	125**	13440	6160	23520
Neridronate (mg), iv.	2**	724	648	800
Risedronate (mg), oral	12**	5430	3360	11115
Ibandronate (mg), iv.	30**	3300	450	7200

* Total number of subjects
** Number of subjects who took the given bisphosphonate Abbreviations: iv.= intravenous $P_{50} = 50^{th}$ percentile; $P_{25} = 25^{th}$ percentile; $P_{75} = 75^{th}$ percentile.

Results

Details of the group studied

Overall, the data from 886 patients were collected by the study centres and sent to the scientist in charge of data analysis (GB). Eighty-seven of these 886 patients (10%) had one or more piece of missing or conflicting data among those required by the protocol and were excluded from analysis. 799 patients aged 29–94 years were available for the final analysis. All measurements made of the final study group are reported in Tables 1 and 2.

Agreement between AAOMS staging and CT imaging for the assessment of the extent of osteonecrosis

Table 3 shows the number of patients with local or diffuse disease shown on CT for each AAOMS stage. Overall 545 patients (68%) had diffuse bone disease. Stages 0,1,2 and 3 were associated with CT evidence of diffuse disease in 57%, 58%, 65% and 100% of cases, respectively. Of the 545 patients with diffuse bone disease at CT, 20% (95%CI 17–24%, $n = 110$) were in AAOMS stage 0, 8% (5%–10%, $n = 42$) in AAOMS stage 1, 48% (44–52%, $n = 263$) in AAOMS stage 2 and 24% (20–27%, $n = 130$) in AAOMS stage 3.

Discussion

We have investigated the degree of agreement between the AAOMS staging system and CT imaging for correct identification of the extent of osteonecrosis.

Accurate staging is essential to plan the correct treatment for affected patients. The most common staging system is that devised by the AAOMS, which has been used in most studies.[2] Such a system relies on clinical signs and does not include imaging of the jaws except that provided by dental radiographs. Other classification systems have a similar structure.[6,7] However, it has been increasingly reported that superficial clinical signs may not show the true extent of bony disease, and the ability of routine dental radiographs (such as panoramic radiographs) to detect the extent of bone disease is poor compared with that of other imaging techniques including CT and magnetic resonance imaging (MRI).[13,21] It is possible, therefore, that the AAOMS staging system may underestimate or overestimate the extent of bony disease, with potentially serious repercussions on therapeutic decisions.

Table 2
Categorical measurements for patients with osteonecrosis of the jaws.

Variable	No (%)
Male sex	257 (32)
Drugs:	
Zoledronate (intravenously)	621 (78)
Pamidronate (intravenously)	99 (12)
Alendronate (orally)	125 (16)
Neridronate (intravenously)	2 (<1)
Risedronate (orally)	15 (2)
Ibandronate (intravenously)	30 (4)
Other bisphosphonate	343 (43)
Steroids	224 (28)
Sunitinib	19 (2)
Bevacizumab	6 (1)
Clinical and radiological presentation:	
Site - mandibular	518 (65)
Site - maxillary	281 (35)
Exposed bone	607 (76)
Pain	623 (78)
Purulent discharge	598 (75)
Cervical fistula	95 (12)
Dislocated stump	32 (4)
Nasal leakage	48 (6)
Focal disease on computed tomography	254 (32)
Underlying disease:	
Cancer of the breast	256 32)
Renal cancer	30 (4)
Cancer of the prostate	103 (13)
Cancer of the thyroid	2 (<1)
Bronchial cancer	15 (2)
Other solid tumours	39 (5)
Myeloma	210 (26)
Osteoporosis	139 (17)
Metabolic disease	21 (3)
Oral risk factors:	
Tooth extraction	434 (54)
Prosthesis	66 (8)
Implant	23 (3)
Infection	125 (16)
Other	4 (<1)
Unidentified	149 (19)

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Table 3
Number of patients with local or diffuse bone disease on computed tomography for each American Association of Oral and Maxillofacial Surgeons' stage. Data are number (%).

Stages	Focal	Diffuse	Total
0	82 (32)	110 (20)	192 (24)
1	30 (12)	42 (8)	72 (9)
2	142 (56)	263 (48)	405 (51)
3	0	130 (24)	130 (16)
Total	254 (100)	545 (100)	799 (100)

We found poor agreement between the AAOMS staging system and CT findings in patients with osteonecrosis. Diffuse bone disease was detected by CT within all AAOMS stages. About 1 in 3 of all patients with diffuse bone disease was misclassified as having less severe disease by the AAOMS system. If we focus on stage 0, over half of those patients had diffuse disease on CT, which confirmed that the absence of clinically evident exposed bone is not a sign of low stage osteonecrosis (extension or severity of disease, or both).[14]

In addition, more than a third of patients with AAOMS stage 2 disease (35%) had focal bone disease on CT, showing that the presence of exposed bone, pain, and suppuration does not necessarily indicate a more severe stage of disease and can be associated with limited extension. Only AAOMS stage 3 showed good agreement with CT imaging, as all the patients in this group had diffuse disease.

Overall, our results have shown that AAOMS stages are unlikely to identify correctly the extent of involvement of the jaw with the exception of AAOMS stage 3 disease, which correctly identified an homogeneous group of patients with diffuse abnormalities of the jaw on CT imaging.

This study has a number of strengths, including the size of the group studied (to our knowledge the largest ever reported), the multicentre design, the accurate description of the outcome measurements, and CT imaging reported by radiologists with a special interest in head and neck imaging who were unaware of the patients' AAOMS staging. The recruitment of centres that participated in the study was based principally on their routine use of CT for the diagnosis and follow-up of osteonecrosis of the jaw. By doing this, data relevant to consecutive affected patients diagnosed between 2004 and 2011 in the participating centres could be analysed, which minimised the risk of selection bias. Although routine use of CT is not part of most available diagnostic recommendations or classification systems, [2] a number of Italian groups have focused their research on the potential advantages of CT in the measurement of the extent of bony involvement in patients with osteonecrosis. [8,21] There has been increasingly robust evidence published about the superiority of CT, as well as MRI, over panoramic radiography [11,20,22] in the investigation of osteonecrosis over the last few years, and this accounts for its routine use today in the centres that participated in the present study.

Limitations of the study include its retrospective design and limited geographical variability, with all centres but one being in Italy. The decision to use the extent of osteosclerotic changes as the main variable to define extension of osteonecrosis on CT may seem questionable. However, the presence of osteosclerosis in clinically symptomatic areas of the jaws has clearly been reported as a consistent CT feature, both in initial and advanced forms of osteonecrosis. [8,11,20–22] Most of the other well-recognised CT features of osteonecrosis (such as sequestra, osteolysis, reactive periostitis, and sinusitis) are not found consistently and are mainly associated with advanced stages of the disease.[12,23]

AAOMS stage 3 was the only stage that correctly identified a homogeneous group of patients with extensive and advanced disease. These findings may help to explain previous reports that the treatment of osteonecrosis in patients with AAOMS stage 3 disease is associated with more predictable and better outcomes than that of AAOMS stages 1 and 2.[24] We suggest that the variability of responses to treatment found in patients with AAOMS stage 1 and 2 disease could reflect the heterogeneity of the extent of disease (focal and diffuse) within these 2 groups. The consistency of outcomes reported in patients with AAOMS stage 3 may be related to the identification of a homogeneous group of patients with diffuse disease.[16,25]

Recently, the Italian Societies of Oral Medicine and Maxillofacial Surgery suggested a new staging system (the SICMF-SIPMO staging system) based on the use of CT imaging and clinical signs (Appendix 2). [14] This integrated classification is our first non-validated attempt to improve current staging systems for osteonecrosis, which we have shown here to be at high risk of underestimating or overestimating the extent of disease.

In the present study we have shown for the first time, to our knowledge, that the current AAOMS staging system is not accurate in identifying the extent of osteonecrosis, except for stage 3. The therapeutic implications of this could be important, as AAOMS staging is commonly used to guide treatment. We suggest that future staging systems should consider both clinical signs and CT features with the aim of describing the extent of bony disease accurately, together with its associated symptoms. We also suggest that the results of previous studies that have allocated treatment of osteonecrosis using the AAOMS staging system should be interpreted with caution.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bjoms.2014.04.009.

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