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ORIGINAL ARTICLE

Dental panoramic radiographic evaluation in bisphosphonate-associated osteonecrosis of the jaws

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OBJECTIVES: To determine the extent to which clinical and radiographic features of bisphosphonate-associated osteonecrosis of the jaw (BONJ) are correlated.
DESIGN: Retrospective case review.
METHODS: The records of 39 patients diagnosed with BONJ and examined by panoramic radiography were retrospectively evaluated. The arches were divided into sextants (*n* = 234) and evaluated for the following signs: sclerosis, surface irregularity, sockets, fragmentation and lysis.
MAIN OUTCOME MEASURES: The McNemar, Kruskall–Wallis and equivalency tests were performed to analyze the association between clinical and radiographic signs and BONJ severity.
RESULTS: Sixty-two out of 234 sextants were abnormal by clinical criteria and 61 out of 234 sextants demonstrated at least one radiographic abnormality. There was agreement between clinical and radiographic detection in 41 sextants. The data showed equivalency between BONJ diagnosis and both sclerosis and surface irregularity. The correlation between number of clinical sites and any radiographic finding was significant in the maxilla ($P < 0.001$) but not in the mandible ($P = 0.178$). The total number of radiographic signs per patient increased with BONJ stage.
CONCLUSION: Focal panoramic radiographic findings of sclerosis and surface irregularity correlate with clinical sites of BONJ. This may be a useful and reliable tool to detect early changes of BONJ or to confirm a clinical diagnosis.
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Keywords: osteonecrosis of the jaws; bisphosphonates; panoramic radiography

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Introduction

Bisphosphonate-associated osteonecrosis of the jaw (BONJ) is increasingly being recognized as a potentially serious complication in cancer patients who are treated with high potency intravenous bisphosphonate therapy (Marx, 2003; Ruggiero *et al*, 2004; Woo *et al*, 2006). It is rare in those taking oral bisphosphonates for osteoporosis (Merck, 2007). While the American Association of Oral and Maxillofacial Surgeons (AAOMS) and the American Society for Bone and Mineral Research have recently introduced similar diagnostic criteria to define cases, the diagnosis is entirely dependent on the clinical detection of exposed bone in the oral cavity, indicating a period that is likely late in the stage of pathogenesis (American Association of Oral and Maxillofacial Surgeons, 2007; Khosla *et al*, 2007).

Despite being a pathologic condition of bone, there are no established diagnostic radiographic criteria for BONJ. Several studies have reported various radiographic findings from panoramic films and computed tomography (CT) that include sclerosis, cortical surface irregularities, persistent extraction sockets, bone fragmentation (sequestration) and lytic or radiolucent changes (Marx *et al*, 2005; Chiandussi *et al*, 2006; Groetz and Al-Nawas, 2006; Bianchi *et al*, 2007; Fullmer *et al*, 2007; Milillo *et al*, 2007). However, the frequency and consistency of these findings, and the relationship between clinical and radiographic signs remain unclear. The objective of this study was to determine the extent to which clinical and radiographic features of BONJ are correlated.

Methods

This is a retrospective study that evaluated digital panoramic radiographs from 39 patients diagnosed with BONJ at the Division of Oral Medicine and Dentistry, Brigham and Women's Hospital in Boston, MA, USA. All patients were clinically evaluated by two examiners (NST or SW). Diagnosis and staging was based on the AAOMS guidelines (Stages 1–3) with only the initial

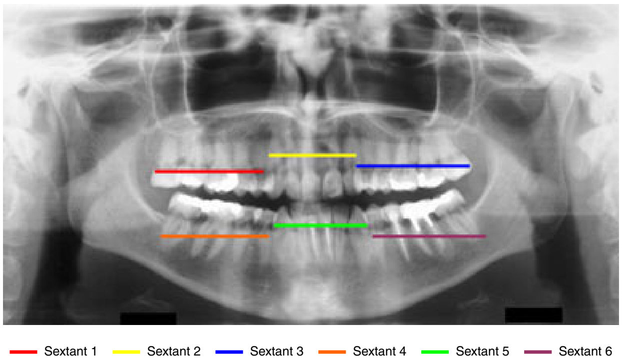

Figure 1 Schematic of radiographic sextants used for radiographic analyses

visit and radiograph included for staging and analysis (American Association of Oral and Maxillofacial Surgeons, 2007). Subjects who did not strictly fulfill the AAOMS diagnostic criteria were excluded. Eighteen control radiographs were included from patients with multiple myeloma with a history of intravenous bisphosphonate therapy but without clinically exposed bone in the oral cavity. This study was approved by the Dana Farber/Harvard Cancer Center Institutional Review Board.

For the purposes of analysis, the arches were divided into sextants: each arch was divided into three segments by lines extending through the posterior aspects of the canines (Figure 1). The images were reviewed on a Gendex (Lake Zurich, IL, USA) work station by two radiologists with 5 years (NS) and 22 years (BF) experience in oral and maxillofacial radiology. Each sextant was evaluated for the five following signs: sclerosis, surface irregularity, presence of sockets, bone fragmentation and osteolysis (Figures 2a–c). The signs were marked as being present or absent in each sextant. The radiologists were blinded to clinical details and differences were resolved by consensus.

Statistical methods

The consistency between BONJ clinical location/site and panoramic radiograph findings was evaluated by McNemar's test and equivalency test. Cases with previous dental extraction were secondarily analyzed. Pearson's correlation between the number of positive clinical sites and any positive radiographic BONJ finding was tested for both the maxilla and mandible. The total number of positive radiographic signs per patient was analyzed for each BONJ stage using the non-parametric Kruskall–Wallis test. The statistical analysis was performed using SPSS 15.0 for Windows (SPSS, Chicago, IL, USA) and SAS 9.1 for Windows (SAS, Cary, NC, USA).

Results

Demographic data on the 39 patients are reported in Table 1. Medical diagnoses for which patients were treated with intravenous bisphosphonates included multiple myeloma (64.1%), breast cancer (15.4%),

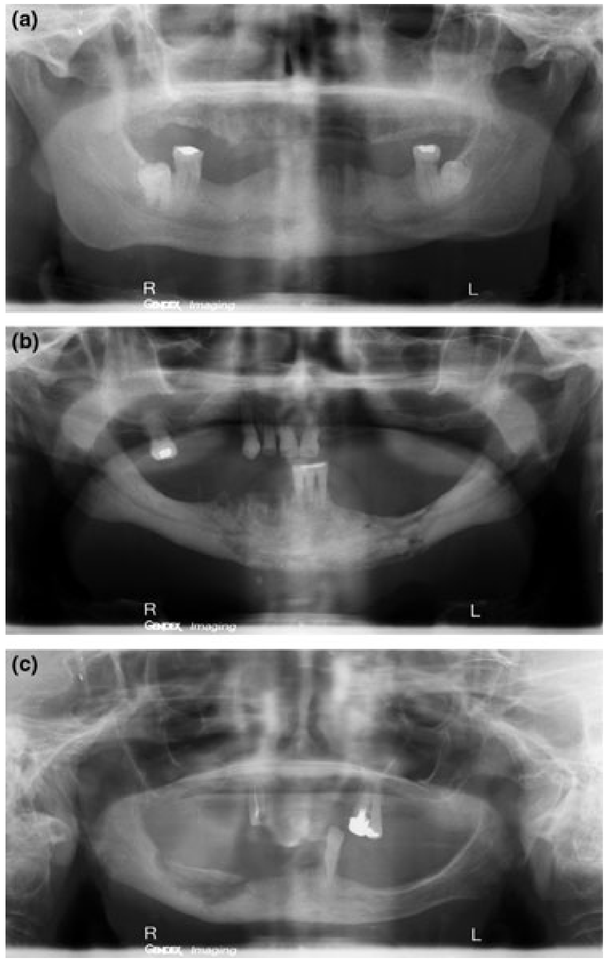

Figure 2 Representative digital panoramic radiographs demonstrating. **(a)** Persistent extraction sockets and surface irregularity; **(b)** sclerosis and lysis; and **(c)** bone fragmentation

prostate cancer (10.3%), Gaucher disease (2.6%), lung cancer (2.6%), combination of lung and prostate cancer (2.6%), and osteoporosis (2.6%). Twenty-five patients (64.1%) had had a previous tooth extraction. The majority of patients at initial visit were Stage 2 (61.5%).

There were 234 assessments (39 patients × 6 assessment sites) categorized by clinical and radiographic diagnosis. Sixty-two out of 234 sextants were abnormal by the clinical criterion of exposed bone, and 61 out of 234 sextants demonstrated at least one radiographic abnormality. Both clinical and radiographic findings detected a positive BONJ diagnosis in 41 out of 234 sextants (18%), and a negative diagnosis in 152 out of 234 sextants (65%). McNemar's test demonstrated no statistical difference between clinical finding and positive radiographic detection (for any of the five radiographic signs; Table 2), suggesting a possible significant association. All control radiographs were negative except for a single case with two focal areas of sclerosis in the region of previously extracted third molars.

Based on the McNemar's test results, the equivalency test was performed to detect the equivalency between clinical and radiographic detection (Table 3, Blackwel-

Table 1 Patient demographics. Staging according to the AAOMS guidelines. Sites refer to sextants

		n
Size	Total	39
Gender	Female	15 (38.5%)
	Male	24 (61.5%)
Age		40–83 (66 ± 3.2)
BONJ Stage	1	10 (25.6%)
	2	24 (61.5%)
	3	5 (12.8%)
Diagnosis	Multiple myeloma	25 (64.1%)
	Breast cancer	6 (15.4%)
	Prostate cancer	4 (10.3%)
	Gaucher's disease	1 (2.6%)
	Lung cancer	1 (2.6%)
	Lung and prostate cancer	1 (2.6%)
	Osteoporosis	1 (2.6%)
Clinical BONJ sign	0 of 6 sites	0
	1 of 6 sites	23 (59.0%)
	2 of 6 sites	10 (25.6%)
	3 of 6 sites	6 (15.4%)
	4 or more	0
Radiographic sign	0 of 6 sites	4 (10.3%)
	1 of 6 sites	20 (51.3%)
	2 of 6 sites	8 (20.5%)
	3 of 6 sites	4 (10.3%)
	4 of 6 sites	2 (5.1%)
	5 of 6 sites	0
	6 of 6 sites	1 (2.6%)
Extraction	No	14 (35.9%)
	Yes	25 (64.1%)

Table 2 Cross-tabulation for clinical finding and radiographic finding of BONJ signs. 'Positive' radiograph signifies *any* positive radiographic finding

		Clinical		
		Negative	*Positive*	*Total*
Radiograph	Negative	152	20	172
	Positive	21	41	62
Total		173	61	234

P-value = 1.00 (McNemar's test).

Table 3 Summary of equivalency test between clinical and radiographic detection for overall (total) data as well as those with history of dental extraction. Yes = Equivalent detection between clinical and radiographic diagnosis; No = Not equivalent detection between clinical and radiographic diagnosis

	Total Data	*Extraction Data*
Any radiographic signs	Yes	Yes
Sclerosis	Yes	Yes
Surface Irregularity	Yes	Yes
Socket	No	Yes
Fragment	No	No
Lysis	No	No

der, 1982). This test examines the equivalency among treatments (opposite to the common hypothesis test that rejects the null hypothesis of equality). The data showed equivalency between BONJ diagnosis and both sclerosis and surface irregularity but not fragmentation or lysis; extraction data further demonstrated equivalency for persistent sockets.

Table 4 Cross-tabulation between BONJ clinical stage and total number of sextants with radiographical findings. All *P* values > 0.05

	Any radiographic finding (%)	*Sclerosis (%)*	*Surface (%)*	*Socket (%)*	*Fragment (%)*	*Lysis (%)*
BONJ1	14 (2.3)	11 (1.8)	11 (1.8)	7 (1.2)	0 (0)	2 (0.3)
BONJ2	34 (23.6)	32 (22.2)	20 (13.9)	14 (9.7)	2 (1.4)	7 (4.9)
BONJ3	14 (46.7)	14 (46.7)	10 (33.3)	8 (26.7)	4 (13.3)	2 (6.7)

The correlation between the number of positive clinical sites and any positive radiographic BONJ finding was statistically significant in the maxilla (Pearson correlation = 0.624, $P < 0.001$) but not significant in the mandible (Pearson correlation = 0.22, $P = 0.178$). Although the Kruskal-–Wallis test failed to detect a significant difference ($\chi^2 = 4.5922$, $P = 0.1006$), the total number of positive radiographic signs per patient demonstrated a trend toward higher BONJ stage (Table 4).

Discussion

This represents the first study specifically evaluating the panoramic radiographic features of BONJ and their relationship with both the location and extent of clinical findings. Panoramic radiology is routinely used to image the hard tissues of the maxillofacial region and is a modality readily accessible to the majority of oral health care specialists. Compared with CT, both the radiation exposure and financial cost of maxillofacial panoramic radiology are substantially lower (Brenner and Hall, 2007). While CT has generally demonstrated greater sensitivity in detecting BONJ radiographic changes compared with panoramic films (Bianchi *et al*, 2007; Bedogni *et al*, 2008), the clinical utility of obtaining this data outside of surgical planning has not been demonstrated. Furthermore, in most dental settings, a panoramic radiograph can be obtained and interpreted within minutes at the time of clinical examination. For these reasons, unless there are specific indications, maxillofacial CT imaging is not routinely obtained at our center for evaluating patients with BONJ (or suspected BONJ).

Our data demonstrated that radiographic findings of sclerosis, surface irregularity and persistent sockets correlate significantly with clinical sites of BONJ. By dividing the maxilla and mandible into sextants, the clinical and radiographic findings were accurately and reliably correlated with respect to location. While we did not specifically evaluate the actual dimensions of clinical *vs* radiographic findings, in many cases the radiographic changes were more extensive than the clinically evident area of exposed bone (data not shown), consistent with the findings of others (Bedogni *et al*, 2008). While precise mechanisms in the development of bone pathology in BONJ remain to be elucidated, radiographic sclerosis is putatively attributed to mineralization in the absence of balanced bone resorption, because of suppressed osteoclast activity. This similarly explains the finding of persistent extraction sockets that result from marked inhibition of remodeling following removal of the tooth.

There are some potential shortfalls in interpreting panoramic radiographs. The anterior regions of panoramic images are particularly sensitive to patient positioning. Even relatively small errors in patient positioning may result in the anterior region being outside the focal trough and thus being poorly defined (Serman, 1989). It is unclear to what extent this may have impacted the quality and interpretation of the radiographs in this study. Furthermore, changes in the body of the bone may be difficult to visualize in the panoramic view as the buccal and lingual cortical plates may mask any internal changes.

Given the range of diagnoses and presenting stages, our cohort appeared to be representative of previously reported series of BONJ from academic medical centers (Woo *et al*, 2006). Nearly 75% of patients were symptomatic (Stages 2 and 3) with none having greater than three sextants involved and the majority (59%) with only a single sextant affected by BONJ. The underlying medical diagnoses were similar to previous reports, minimizing any disease- or treatment-specific confounding factors. Importantly, as with all previous reports of BONJ, there was a wide range in the duration of both bisphosphonate therapy and presence of BONJ lesions. Because of this, no conclusions can be made on how radiographic findings may or may not change during the development and progression of BONJ.

Various radiographic features of BONJ have been previously reported. In Marx *et al*'s report of 119 cases, 73.1% demonstrated positive radiographic findings that included osteolysis, osteosclerosis, and mixed lytic/sclerotic lesions (Marx *et al*, 2005). No specific methods of evaluation were described and it is unclear what imaging techniques were used, although manuscript figures appear to be panoramic radiographs. Ruggiero *et al* reported radiographic changes of mottled bone and osteolysis (from both panoramic radiographs and CT based on included figures), but specific methods and numbers were not given (Ruggiero *et al*, 2004). While our data failed to identify a correlation between lytic changes and clinical findings, sclerosis was a statistically significant finding. It is likely that equivalency was not demonstrated between clinical findings and lysis/fragmentation because of an insufficient number of cases; however, all six fragmentation cases and seven out of eight lysis cases were associated with clinical disease. Groetz and Al-Nawas suggested that 'persistent alveolar sockets' is a significant sign of BONJ following dental extraction (Groetz and Al-Nawas, 2006); our data demonstrated that this is indeed a statistically significant radiographic feature. Both persistent sockets and sclerosis can be explained by bisphosphonate-induced osteoclast inhibition, resulting in suppressed bone turnover and remodeling but continued mineralization (Clezardin *et al*, 2005; Ott, 2005).

Several studies have specifically evaluated both CT and panoramic imaging of BONJ. Bianchi *et al* reported that CT was superior to panoramic radiography in detecting changes in 32 patients with BONJ, in particular with respect to sequestrum formation and extent of changes three dimensionally; however, the relationship between these findings and actual clinical changes (i.e. staging) was not explored (Bianchi *et al*, 2007). Fullmer *et al* reported both sclerosis and surface irregularities with cone beam CT (CBCT) imaging of two cases of BONJ (Fullmer *et al*, 2007). While only recently introduced into clinical practice, CBCT is an attractive imaging modality for future research in the field of BONJ given its lower radiation exposure and high resolution compared with conventional CT (Tsiklakis *et al*, 2005; Ludlow *et al*, 2006; Scarfe *et al*, 2006). Chiandussi *et al* reported that panoramic radiography demonstrated areas of bone changes (mixed radiopaque/radiolucent lesions and persistent sockets) that corresponded with areas of clinical involvement; CT scans confirmed but did not add significant additional data (Chiandussi *et al*, 2006). The authors did note, however, that CT better demonstrated extent of changes, and cautioned that metastatic disease cannot be ruled out in the case of purely lytic lesions, as has been described by others (Bedogni *et al*, 2007). Milillo *et al* reported bone abnormalities in all 38 patients evaluated by CT; however, specific findings and how these related to prior panoramic radiographs were not described (Milillo *et al*, 2007).

While we found a trend towards higher stage with greater radiographic findings, this did not reach statistical significance. This may be because of several explanations. First, in many cases, symptoms result from secondary soft tissue infection and inflammation, which may not be directly related to the size or extent of exposed bone, and would not be reflected radiographically. In fact, nearly one-third (20/61) of clinically involved sites showed no radiographic changes at all (Table 2). Second, there were only five cases of Stage 3 BONJ, defined by the presence of extraoral fistulae, pathologic fracture or osteolysis extending to the inferior cortical bone. While radiographic evidence of pathologic fracture is easy to detect, Stage 3 disease presenting with only extraoral fistula formation may or may not demonstrate severe radiographic changes. A greater number of carefully documented cases will be required to determine if there is indeed a correlation between staging and extent of bone disease. For staging and diagnostic purposes, radiographic findings may be of utility in confirming the diagnosis of BONJ; however, it is unclear to what extent these findings may be of use in determining prognosis or guiding management. Furthermore, there are no published data demonstrating how these findings change in the context of treatment, clinical improvement, or progression.

Despite efforts to minimize risk and prevent occurrence, BONJ will likely continue to be a diagnostic and clinical challenge facing oral health care specialists, medical oncologists, and their patients. As we begin to investigate the underlying pathobiology of BONJ, and design prospective epidemiological and interventional trials, characterization of the basic clinical, biochemical, and radiographic features will be critical. Given that the incidence of BONJ in cancer patients is approximately 5% (Bamias *et al*, 2005; Durie *et al*, 2005; Zervas *et al*, 2006; Murad *et al*, 2007), careful documentation and reporting of retrospective data will continue to provide significant insight into this emerging oral disease.

Author contributions

Nathaniel Treister designed and oversaw the conduct of the study, conducted clinical examinations, and was the primary author of the manuscript. Niall Sheehy contributed to the design of the study, conducted the radiographic evaluations, and participated in the writing of the manuscript. Erica Bae provided the biostatistical analyses for the study and contributed to the writing of the manuscript. Bernard Friedland contributed to the design of the study, conducted the radiographic evaluations, and participated in the writing of the manuscript. Mark Lerman contributed to the writing of the manuscript. Sook Woo contributed to the design of the study, conducted clinical examinations, and contributed to the writing of the manuscript.

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