UNIVERSIDADE ESTADUAL DE CAMPINAS
FACULDADE DE ODONTOLOGIA DE PIRACICABA

KARINA MORAIS FARIA

PADRÕES RADIOGRÁFICOS CRANIOFACIAIS DO MIELOMA MÚLTIPLO EM PACIENTES TRATADOS COM BISFOSFONATOS

CRANIOFACIAL RADIOGRAPHIC PATTERNS OF MULTIPLE MYELOMA IN PATIENTS TREATED WITH BISPHOSPHONATES

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Tese apresentada à Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas como parte dos requisitos exigidos para obtenção do título de Doutora em Estomatopatologia, na Área Estomatologia.

Thesis presented to the Piracicaba Dental School of the University of Campinas in partial fulfillment of the requirements for the degree of Doctor in Oral Medicine and Oral Pathology, in Oral Medicine area.

Orientador: PROF.DR. ALAN ROGER DOS SANTOS SILVA
Coorientador: PROF. DR. MARIO FERNANDO DE GOES

ESTE EXEMPLAR CORRESPONDE À VERSÃO
FINAL DA TESE DEFENDIDA PELA ALUNA
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"Se as coisas são inatingíveis... ora!
Não é motivo para não querê-las...
Que tristes os caminhos, se não fora...
A presença distante das estrelas"

Mario Quintanta

RESUMO

Esta tese de doutoramento avaliou a frequência e os padrões de manifestação radiográfica do mieloma múltiplo (MM) nos ossos craniofaciais por meio de investigações clinicopatológicas de natureza retrospectiva. Os resultados da consecução desta tese estão apresentados em 2 artigos. No primeiro capítulo (artigo 1), comparou-se uma série de 88 pacientes diagnosticados com MM que receberam bisfosfonatos administrados por via endovenosa (BFs e.v.) (grupo estudo) com a uma série de 100 pacientes diagnosticados com MM que não utilizaram BFs e.v. (grupo controle). Radiografias panorâmicas digitais foram estudadas em ambos os grupos para avaliação da presença (ou ausência) dos seguintes critérios: imagens osteolíticas solitárias, imagens osteolíticas múltiplas, osteoporose difusa, esclerose difusa, anormalidades de lâmina dura, alvéolo pós-extração não cicatrizado e sequestro ósseo. A análise dos dados revelou que múltiplas lesões osteolíticas (p=0.001), osteoporose difusa (p=0.001) e esclerose difusa (p=0.0036) foram mais frequentemente observadas em mandíbula do que em maxila em ambos os grupos estudados. A presença de lesão osteolítica solitária foi observada com menor frequência no grupo que recebeu BFs e.v. (p=0.0078, OR=0.1994, CI95%=0.057-0.696). As anormalidades de lâmina dura (p=0.0006, OR=2.447, CI95%=1.47-4.08) e alvéolo ósseo persistente (p=0.0021, OR=20.23, CI95%=1.158-353.3) também estavam associados ao tratamento com BFs e.v. Concluiu-se que o tratamento com BFs e.v. altera os padrões radiográficos de manifestação do MM em mandíbula e maxila. O segundo capítulo (artigo 2) comparou a frequência da detecção radiográfica de imagens osteolíticas do MM nos ossos craniofaciais de uma série de 155 pacientes por meio de três técnicas digitais (radiografia panorâmica, radiografia frontal e radiografia lateral de crânio).

Radiografias panorâmicas detectaram imagens osteolíticas em 137 (88,3%) casos, radiografia frontal de crânio em 141 (91%) casos e radiografia lateral de crânio em 144 (93%) casos. Apenas 18 (11,61%) casos se manifestaram exclusivamente no crânio e 6 (3,87%) exclusivamente em mandíbula e maxila; entretanto, 129 (83,23%) pacientes apresentaram imagens osteolíticas sincrônicas em crânio, mandíbula e maxila. Concluiu-se que apesar da radiografia lateral de crânio ter apresentado maior frequência de detecção de imagens osteolíticas do MM, as três técnicas radiográficas utilizadas neste estudo demonstraram altas frequências de detecção de imagens osteolíticas relacionadas ao MM nos ossos craniofaciais.

Palavras-chave: Mieloma múltiplo, radiografia panorâmica, bisfosfonatos

ABSTRACT

This thesis evaluated the frequency and radiographic patterns of multiple myeloma (MM) in craniofacial bones through clinical, pathological and radiographic investigations in a retrospective approach. The results are presented in two papers. The first chapter (manuscript 1) compared a series of 88 patients diagnosed with MM who received intravenous bisphosphonates (i.v. BPs) (study group) with a series of 100 MM patients naive to i.v. BPs (group control).Digital panoramic radiographs were analized in both groups to evaluate the presence (or absence) of the following criteria: solitary osteolytic lesions, multiple osteolytic lesions, diffuse osteoporosis, diffuse sclerosis, abnormalities of the lamina dura, non-healing alveolar sockets and bone sequestration. Data analysis revealed multiple osteolytic lesions (p=0.001), diffuse osteoporosis (p=0.001) and diffuse sclerosis (p=0.0036) were more often observed in the mandible than in the maxilla in both studied groups**.** The presence of solitary osteolytic lesions showed to be reduced in the BPs group (p=0.0078, OR=0.1994, CI95%=0.057-0.696). Abnormalities of the lamina dura (p=0.0006, OR=2.447, CI95%=1.47-4.08) and non-healing alveolar sockets (p=0.0021, OR=20.23, CI95%=1.158-353.3) were also associated with BPs treatment. I.v. BPs therapy changes the typical radiographic patterns of MM in the jawbones. The second chapter (manuscript 2) compared the frequency of radiographic detection of osteolytic MM lesions in craniofacial bones of a series of 155 patients, using three digital techniques (panoramic radiograph, frontal radiograph and lateral radiograph of the skull).Panoramic radiographs detected osteolytic images in 137 (88.3%) cases, frontal radiograph of skull in 141 (91%) cases and lateral radiograph of skull in 144 (93%) cases. Eighteen (11.61%) cases showed images affecting exclusively the skull and 6

(3.87%) cases only affected mandible and maxilla; however, 129 (83.23%) patients presented MM osteolytic images synchronously affecting skull and jawbones. It was concluded that although the lateral radiograph of skull presented increased rates of osteolytic MM lesions detection, all studied radiographic techniques were effective in detecting osteolytic images related to MM in craniofacial bones.

Key Words: Multiple myeloma, panoramic radiographic, bisphosphonates.

SUMÁRIO

1 INTRODUÇÃO

O mieloma múltiplo (MM) é uma neoplasia hematopoiética maligna de plasmócitos originada na medula óssea e associada a uma significante heterogeneidade molecular. Os plasmócitos malignos produzem e secretam imunoglobulina monoclonal conhecida como "proteína M", que, progressivamente, ocasiona anemia, insuficiência renal, destruição óssea multifocal e supressão imunológica, entre outros eventos clínicopatológicos (Fairfield *et al*., 2016; Kyle e Rajkumar, 2008).

A etiologia do MM permanece desconhecida, contudo, evidências científicas sugerem um aumento do risco de seu desenvolvimento em pacientes afetados por doenças crônicas imunologicamente mediadas, exposição a fontes de radiação ionizante, exposição ocupacional a inseticidas, exposição a benzeno e outros solventes orgânicos (Durie, 2001; Schwartz, 1997). O MM corresponde a aproximadamente 1% de todas as doenças neoplásicas e a aproximadamente 15% das neoplasias hematológicas malignas - em países ocidentais, sua incidência anual é de 5,6 casos por 100.000 pessoas. O MM possui leve predileção pelo gênero masculino com média de idade de 66 anos no momento do diagnóstico, sendo que cerca de 2% dos pacientes são diagnosticados antes dos 40 anos de idade (Palumbo e Anderson, 2011; Rajkumar e Kumar, 2016).

Os sintomas mais comumente associados ao MM - podendo ocorrer em aproximadamente 75% dos pacientes - incluem fadiga, dor óssea e anemia (Kyle *et al*., 2003). Lesões ósseas osteolíticas representam um dos sinais mais importantes da doença e podem ser detectadas em mais de 80% dos pacientes diagnosticados com MM. Outros achados clínicos comuns incluem a hipercalcemia (15%), o aumento nos valores de creatinina sérica (20%) (Rajkumar e Kumar, 2016) e a presença de plasmocitomas ósseos (7%), que constituem tumores isolados derivados dos plasmócitos (Dimopoulos *et al*., 2000).

Um dos principais desafios no diagnóstico do MM é o fato da doença apresentar uma miríade de sintomas e sinais de intensidade muito variável tanto do ponto de vista clínico, quanto laboratorial; incluindo, na maioria das vezes, associação de lesões osteolíticas, hipercalcemia, anemia e insuficiência renal (Rajkumar e Kumar, 2016). Diante desse cenário desafiador, em 2014, a organização *International Myeloma Working Group* (IMWG) se organizou a fim de contribuir para aprimorar o diagnóstico e o tratamento do MM, sobretudo, por meio da identificação e validação de biomarcadores para finalidade diagnóstica, possibilitando o desenvolvimento de estratégias de tratamento adequado (Rajkumar *et al*., 2014).

A principal sugestão desta organização para atualização dos critérios diagnósticos do MM foi à adição de 3 eventos/biomarcadores considerados específicos: (a). presença de ≥ 60% plasmócitos malignos na medula óssea; (b). taxa de proteína sérica de cadeia leve ≥100 (c). > 1 lesão óssea do MM observada em ressonância magnética com tamanho mínimo de 5 mm em seu maior diâmetro (Rajkumar *et al*., 2014; Rajkumar e Kumar, 2016).

Além da identificação dos critérios supramencionados e atualizados em 2014, aceita-se que o diagnóstico do MM requer a presença de um ou mais dos seguintes eventos:(a). hipercalcemia, valores de cálcio sérico >11 mg/dL; (b). insuficiência renal, creatinina sérica >2 mg/dL; (c). anemia, valores de hemoglobina >2g/dL e (d). presença de uma ou mais lesões osteolíticas identificadas no protocolo de investigação radiográfica para o MM (Rajkumar *et al*., 2014).

Além dos achados laboratoriais, doença óssea, hipercalcemia, insuficiência renal e anemia, a infiltração por plasmócitos malignos pode afetar vários outros tecidos do indivíduo (Durie, 2001), assim causando uma grande diversidade de complicações indesejáveis como infecções (ocasionadas pelo desequilíbrio CD4/CD8 e redução da atividade dos granulócitos), complicações neurológicas decorrentes de deposição amilóide na bainha de mielina e compressão ou deslocamento de nervos da medula espinhal (Bladé e Rosiñol, 2007). Os plasmocitomas secundários são complicações observadas em 10% dos pacientes e podem ocorrer por extensão direta para a pele, a partir de lesões ósseas subjacentes, ou por disseminação hematogênica corroborando com a infiltração plasmocitária em vários órgãos e piores prognósticos (Requena *et al*., 2003).

A destruição óssea é uma complicação que acomete mais de 80% dos pacientes diagnosticados com MM levando à osteopenia generalizada, dor, fraturas patológicas e complicações neurológicas (Hameed *et al*., 2014). Apesar do componente ósseo do MM não ser a principal causa de morbidade, ele acaba por elevar os custos no tratamento e diminuir a qualidade de vida dos pacientes afetados pela doença (Walker *et al*., 2007). As principais lesões ósseas observadas no MM compreendem um padrão predominantemente osteolítico - padrão clássico conhecido como “lesão em punch” - caracterizado por imagem radiolúcida com ausência de borda esclerótica. Estas lesões têm potencial para gerar o envolvimento de múltiplos ossos do esqueleto, porém, afetam preferencialmente a coluna vertebral, o crânio e os ossos longos (Kyle *et al*., 2004). Para o diagnóstico das lesões ósseas, o IMWG recomenda um protocolo de investigação imaginológico que corresponde às tomadas radiográficas das seguintes regiões: crânio, colunas cervical, torácica e lombar (posição frontal e lateral), tórax

(posição frontal), pélvis (posição frontal) e ossos longos em posição frontal (Rajkumar *et al*., 2014).

São poucos os estudos já publicados relacionados à caracterização das manifestações radiográficas do MM no complexo craniofacial. A título de exemplo, em 1997, Witt e colaboradores publicaram resultados de um estudo baseado em radiografias panorâmicas convencionais de 77 pacientes diagnosticados com MM e relataram que apenas 15,6% dos pacientes apresentaram manifestações do MM em mandíbula. Alguns outros pesquisadores como Bruce e Royer (1953) e Miller *et al*. (1969) relataram que 20% a 30% dos pacientes com MM mostraram manifestação óssea mandibular. Importante esclarecer que as lesões em mandíbula podem ser a manifestação inicial do MM em até 15% dos casos (Bruce e Royer, 1953; Zachriades *et al*., 1987). Neste contexto, dor, parestesia e inchaço podem ser sintomas em pacientes com MM frequentemente correlacionados à presença de lesões ósseas osteolíticas (Lambertenghi *et al*., 1988;Lee *et al*.,1996; Pisano *et al*., 1997; Senn *et al*, 1985; Vicent*et al*., 1993). Hipoestesia e déficit sensorial também foram observados em pacientes com MM e associados ao comprometimento ósseo mandibular (Raubenheimer *et al*., 1988; Tamir*et al*., 1992; Witt *et al*., 1997; Zachriades *et al*., 1987).

De acordo com Witt *et al.* (1997), existem quatro tipos predominantes de padrões radiográficos associados ao envolvimento ósseo da mandíbula por MM: a) tipo 1 ou solitário, lesão osteolítica tipo “punched-out”; b) tipo 2, múltiplas lesões osteolíticas sem esclerose marginal (variante central e periférica); c) tipo 3,osteoporose difusa com o envolvimento generalizado e d) tipo 4,esclerose difusa.

Devido à tendência de manifestação óssea generalizada, o tratamento do MM é realizado, predominantemente, por meio de medicamentos com ação inibidora da reabsorção óssea, incluindo, sobretudo, drogas pertencentes à classe dos bisfosfonatos (BFs). O uso dos BFs inibe potentemente a atividade osteoclástica, reduzindo a ocorrência de fraturas patológicas, dor e, portanto, aprimorando a qualidade de vida dos pacientes. Além do benefício notório dos BFs no tratamento de complicações ósseas do MM, sua administração causa uma série de efeitos colaterais, incluindo, no contexto odontológico, a osteonecrose por BFs (Marx, 2003; Migliorati *et al*., 2005; Ruggiero *et al*., 2014), doença considerada uma das principais toxicidades odontológicos que afetam pacientes oncológicos.

Recentemente, pesquisadores descreveram alterações nos aspectos anatômicos normais ósseos, induzidas por BFs, contudo, não relacionadas à osteonecrose. Sugeriu-se que o potencial dos BFs para gerar alterações no padrão dos ossos craniofaciais, poderia também ter impacto nos padrões radiográficos das manifestações do MM no complexo buco-maxilo-

facial; algumas vezes, mimetizando outras patologias ósseas (Arce *et al*., 2009; Rocha *et al*., 2012; Treister *et al*., 2009). Estas evidências representam um desafio adicional à já complexa identificação precoce das manifestações do MM nos ossos craniofaciais.

É oportuno esclarecer que poucos são os estudos disponíveis na literatura científica de língua inglesa que se concentraram a descrever as manifestações clinicopatológicas e radiográficas do MM nos ossos craniofaciais; campo agravado pelo fato destes estudos - já numericamente limitados - se tratarem predominantemente de pequenas séries de casos investigados por radiografias convencionais (Bruce e Royer, 1953; Epstein *et al*., 1984; Furutani *et al*., 1994; Lambertenghi-Deliliers *et al*., 1988; Miller *et al.*,1969; Ramaiah *et* al., 2015; Raubenheimer *et al*., 1988; Senn *et al*., 1985; Smith, 1957; Vieira-Leite-Segundo *et al*., 2008; Witt *et al*., 1997).

Tendo em vista os desafios diagnósticos expostos no conteúdo desta introdução acerca do MM, esta proposta de tese de doutoramento teve por objetivo avaliar (e descrever) retrospectivamente as características clínicas, patológicas e radiográficas (radiografias panorâmicas, radiografia frontal de crânio e radiografia lateral de crânio. Todas por meio de aquisições digitais) de uma coorte de 188 pacientes diagnosticados com MM e tratados nos Serviços de Hematologia e de Odontologia Oncológica do Instituto do Câncer do Estado de São Paulo (ICESP-FMUSP). Foram testadas as seguintes hipóteses: (1). O tratamento com BFs endovenosos (e.v.) tem a capacidade de alterar os padrões radiográficos das manifestações do MM em mandíbula e maxila e (2). A radiografia panorâmica de mandíbula é uma técnica útil na identificação de imagens osteolíticas do MM nos ossos craniofaciais quando comparada à radiografia frontal de crânio e à radiografia lateral de crânio.

Os resultados apresentados a seguir representam estudos colaborativos entre as equipes da Faculdade de Odontologia de Piracicaba, Universidade Estadual de Campinas, Brasil; dos Serviços de Hematologia e de Odontologia Oncológica do ICESP-FMUSP, Brasil e da *The University of Tennessee Health Science Center College of Dentistry in Memphis* (UTHSC-CD), Estados Unidos.

2 ARTIGOS

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2.1 The impact of intravenous bisphosphonate therapy in the radiographic patterns of jaw lesions in multiple myeloma

Karina Morais Faria (Morais-Faria K), Ana Carolina Prado Ribeiro (Ribeiro ACP), Thais Bianca Brandão (Brandão TB), Wagner Gomes Silva (Silva WG), Marcio Ajudarte Lopes (Lopes, MA), Juliana Pereira (Pereira J), Marcelo Corrêa Alves (Alves MC),), Luiz Alcino Gueiros (LAG) , Werner Harumiti Shintaku (WHS), Cesar Augusto Migliorati (Migliorati CA), Alan Roger Santos-Silva (Santos-Silva AR).

Artigo submetido ao periódico *Oral surgery, Oral medicine, Oral pathology, Oral radiology* (ANEXO2)

2.2 Evaluation of skull x-ray radiography for diagnosing multiple myeloma: panoramic radiographic correlation in 155 cases

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2.1 Artigo: The impact of intravenous bisphosphonate therapy in the radiographic patterns of jaw lesions in multiple myeloma

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ABSTRACT

Objectives: Radiographic presentation of multiple myeloma (MM) in jawbones frequently shows osteolytic lesions. The bisphosphonate (BPs) are drugs successfully used in the treatment of MM, but can cause several side effects and bone changes. Therefore, the purpose of this study was to evaluate whether intravenous (i.v.) BPs therapy has the ability to change the radiographic patterns of MM in the jawbones. **Study design:** A cross sectional study was performed with digital panoramic radiographs of 188 patients diagnosed with MM aiming to evaluate the presence of solitary osteolytic lesions, multiple osteolytic lesions, diffuse osteoporosis, diffuse sclerosis, abnormalities of the lamina dura, non-healing alveolar sockets, and bone sequestration. Results were compared with patients treated with i.v. bisphosphonates (BPs) and those naive to BPs. **Results:** Data analysis revealed multiple osteolytic lesions (p=0.001), diffuse osteoporosis (p=0.001) and diffuse sclerosis (p=0.0036) were more often observed in the mandible than in the maxilla in both studied groups**.** The presence of solitary osteolytic lesions showed to be reduced in the BPs group (p=0.0078, OR=0.1994, CI95%=0.057-0.696). Abnormalities of the lamina dura (p=0.0006, OR=2.447, CI95%=1.47-4.08) and non-healing alveolar sockets (p=0.0021, OR=20.23, CI95%=1.158-353.3) were associated with BPs treatment. No case of medication-related osteonecrosis in jawbones was detected in any group. **Conclusions:** I.v. BPs therapy changes the typical radiographic patterns of MM in the jawbones.

Keywords: Multiple myeloma, bisphosphonate, panoramic radiography.

INTRODUCTION

Multiple myeloma (MM) is a malignant monoclonal plasma cell disorder of the bone marrow, which produces mediators that stimulate osteoclasts and leads to the formation of generalized osteolytic bone lesions. Common locations of such lesions include the skull, the axial skeleton and pelvis; consequently, patients with MM are at increased risk for pathological bone fractures [1-4]. The diagnosis of MM is supported by the detection of paraproteins in the serum and urine as well as by the histopathological evidence of excessive amounts of monoclonal plasma cells in the bone marrow[5]. In addition, the detection of maxillofacial manifestations of MM, such as soft tissue amyloid deposits, external dental root resorption and, most importantly, several bone changes including poorly marginated jaw osteolytic lesions (reported in more than 30% of MM patients) may represent important diagnostic features [6,8].

MM patients are currently living longer because of remarkable advances in therapy, such as novel agents that include immunomodulatory drugs, proteasome inhibitors, monoclonal antibodies and antiresorptive drugs, including bisphosphonates (BPs)[7,9-11]. BPs inhibits the progression of osteoclastic activity in MM patients and has been used to reduce the occurrence of bone fractures and pain[12]. In addition to inducing osteoclast apoptosis, BPs also increase bone mineral density when associated with novel anti-myeloma agents[3,13]. According to the International Myeloma Working Group, BPs must be prescribed to all patients receiving MM therapy in which osteolytic lesion was detected at diagnosis[14]. Although beneficial in the management of MM patients, the BPs may cause a myriad of jawbone changes, which can mimic other dental or bone pathologies, representing an important challenge to the early diagnosis and management of medication-related osteonecrosis of the jaw (MRONJ)[10,15-18]. Therefore, the main goal of the current study was to review the radiographic features observed in digital panoramic radiographs of MM patients exposed or naive to intravenous (i.v.) BPs and test the hypothesis that i.v. BPs therapy has the ability to change the typical radiographic patterns of MM in the jawbones.

MATERIALS AND METHODS

The present study was a collaboration among the University of Campinas, Piracicaba Dental School, Brazil; the Dental Oncology Service of the Instituto do Câncer do Estado de São Paulo (ICESP), Brazil; and the University of Tennessee Health Science Center College of Dentistry in Memphis (UTHSC-CD), United States. This was a cross sectional retrospective

study performed with individuals treated at the Dental Oncology and Hematology Services of Instituto do Câncer do Estado de São Paulo, Brazil, from april/2010 to june/2014.

The research protocol was approved by the Ethics Committee of the University of Campinas (number118/2014) and the Institutional Review Board of The University of Tennessee Health Science Center-UTHSC (number 516827). In order to be included in the study the patients had: (1) a confirmed diagnosis of MM presenting with bone disease after complete clinical workup according to International Myeloma Working Group criteria[14]; (2) a digital panoramic radiograph obtained upon diagnosis or after (i.v.) BPs and (3) complete medical record. The exclusion criteria were the presence of non-MM neoplastic bone disease, long-term osteoporosis and previous use of BPs.

The Durie- Salmon[19,20] staging default method was used for the clinical staging of MM. Patients were divided into two groups: group 1 was composed of 88 MM patients who received i.v. BPs as part of the institutional treatment protocol for MM and group 2 (control) was composed of 100 MM patients who had never been exposed to BPs.

All radiographs were taken in a dental X-ray machine (PaX-400, Hawseong-si, Gyeonggi-do, Korea), using 68 kVp, 8 mA, and an exposure time of 14s. The radiographs were coded to protect the patients' health information. Radiographic images were independently evaluated at the UTHSC-CD by a radiologist certified by the American Board of Oral and Maxillofacial Radiology and an oral medicine practitioner certified by the American Board of Oral Medicine. Images were displayed on a 24-inch LCD flat panel display (UltraSharp 2408WFP, Dell Inc., USA) with a screen resolution of 1920x1200 pixels in a room with reduced light. The evaluators were blinded to clinical data. In order to avoid inter-examiner variability in interpretation of the panoramic images, the evaluators performed all assessments in the same viewing room with optimal lighting viewing conditions and no adjustment to the display system was allowed.

All anatomical structures in the maxillo-mandibular complex were included in radiographic panoramic evaluation. Maxilla and mandible images were evaluated separately for seven bone abnormalities as follows:

- solitary bone lesion
- multiple osteolytic lesion
- diffuse osteoporosis
- diffuse sclerosis
- abnormalities of the lamina dura: (sclerosis and/or thickening)

- non-healing alveolar sockets
- bone sequestration

Radiographic aspects were classified according to the previously published radiographic criteria for jawbone lesions of MM[15,16,17,18].

Data obtained were classified as a binary response model. Statistical analysis included Qui-square test or Fisher's exact test, and Odds Ratio was determined for the statistically significant variables. For statistical analysis, events of both maxilla and mandible were evaluated together so that 376 bones of 188 patients were included. Interexaminer agreements were assessed using Cohen's Kappa test to analyze the reliability of the examiners and the agreement was considered fair when Kappa was between 0,20-0,40, moderate if Kappa was between 0,40-0,60 and substantial when Kappa was between 0,60-0,80.[19]

The effects of the test model were performed using SAS software (Institute Inc. The SAS System, release 9.3. SAS Institute Inc., Cary: NC. 2010)

RESULTS

One hundred and eighty eight patients were included in the study and divided into 2 groups according to the use of BPs (**Table 1**).

Among all 188 patients enrolled in this study, 188 (100%) presented MM bone disease. Overall, a variety of radiographic findings for MM were observed in both mandible and maxilla (**Table 2**). Interexaminer Kappa test was 0.7916 and was considered appropriate for this study. Multiple osteolytic lesions (p=0.001), diffuse osteoporosis (p=0.001) and diffuse sclerosis (p=0.0036) were more often observed in the mandible than in the maxilla in both studied groups. The presence of the solitary bone lesions, multiple osteolytic lesions, diffuse osteoporosis (mottled bone appearance) and diffuse sclerosis was seen in both groups **(Fig. 1)** and **(Fig.2).**

Intravenous BPs therapy showed to be associated with 3 radiographic patterns. The presence of solitary osteolytic lesions showed to be reduced in the BPs group (p=0.0078, OR=0.1994, CI95%=0.057-0.696). Abnormalities of the lamina dura **(Fig. 3)** and non-healing alveolar sockets **(Fig. 4)** were associated with BPs treatment (p=0.0006, OR=2.447, CI95%=1.47-4.08 and p=0.0021, OR=20.23, CI95%=1.158-353.3, respectively).

In all cases, osteolytic lesions had the "punched-out" appearance. Any case of bone sequestration or MRONJ was detected in this study population.

DISCUSSION

This study evaluated the pattern of radiographic alterations in the maxilla and mandible of patients diagnosed with MM and exposed to BPs treatment. To the best of our knowledge, this seems to be one of the largest case series evaluating maxillary and mandibular radiographic patterns of MM. The drug use seemed to increase the odds of having alterations of the lamina dura, persisting alveolar sockets and a reduced presence of solitary osteolytic lesions. In this clinical scenario, it is important to distinguish the common drug-related alterations from MRONJ to avoid overtreatment and inadequate management.

MM is a cytogenetically heterogeneous clonal plasma cell proliferative disorder[14], counted as one of the most frequent hematological malignancies worldwide, with an incidence rate of six per 100,000 persons per year in the United States and Europe. The incidence of MM is two to three times higher in African Americans, making it the most common hematological malignancy in this ethnic group [22]. The international incidence of MM has been increasing by 0.7% each year for the last 10 years, accounting for 10% of all hematological malignancies. In addition, the number of deaths is 3.4 per 100.000 persons per year. MM is slightly more prevalent in males than in females and the mean age at diagnosis is 66 years, with only 2% of patients being diagnosed at less than 40 years of age[23,24]. In this study, most of the patients were elderly men, presenting MM in an advanced stage at the time of diagnosis. The time of radiographic follow-up was variable due to the high death rate by the advanced stage of disease.

A major complication of MM is the development of bone disease characterized by osteolytic lesions, fractures and bone pain. Bone disease in MM patients is associated with an advanced stage and can have devastating clinical effects by increasing morbidity[1,6]. Skeletal radiographic surveys have an important role in the Durie-Salmon[20,21] clinical staging criteria for MM diagnosis, where the presence of two clearly defined lytic lesions indicates high tumor burden and stage III disease[1]. Bone disease in MM commonly shows numerous punched-out areas of radiolucency on radiographs, being most commonly observed in the pelvis, spine, ribs, and skull[25,26]. The detection of osteolytic lesions has a pivotal role in decision-making treatment protocols, since the International Myeloma Working Group recommends the use BPs therapy in patients with active MM and at least one osteolytic lesion[3,14]. The present study was based on the premise that the radiographic identification of jawbone lesions frequently leads to the diagnosis of MM and also founded on the ability of

i.v. BPs to cause bone changes that could alter typical osteolytic lesions, leading to a delay in the diagnosis and treatment of MM.

Second generation BPs (pamidronate and zoledronate) play a fundamental role in minimizing bone complications in MM[3]. Pamidronate and zoledronate present higher bioavailability and lower elimination during resorption and bone remodeling, compared with oral BPs [27]. In a recent study, Jarnibring *et al*.[28] concluded that zoledronate is a more potent inducer of jawbones changes than pamidronate in MM patients. In the current study, patients received both of the above-mentioned drugs and some of the patients had taken both pamidronate and zoledronate in combination. However, we couldn't study the effects of pamidronate and zoledronate separately because only a few patients received isolated zoledronate. The numbers of cycles of BPs therapy were decided based on International Myeloma Working Group recommendation for the treatment of MM-related bone disease. This study included patients that received at least 3 i.v BPs cycles. According to literature the risk of MRONJ begins to significantly increase after a medication period of up to 90 days[29]. In our study, some of the patients died with advanced MM and did not complete all recommended BPs cycles.

Although a wide spectrum of radiographic findings, including sclerotic areas, disorganized medullar trabeculation, dense osteosclerosis in alveolar margins, abnormalities of the lamina dura, bone sequestrations, areas of mottled bone similar to diffuse osteoporosis and MRONJ have been recently reported in cancer patients, including MM patients that have been exposed to i.v. BPs therapy[8,15,16,17,27,30,31] this seems to be the first study to evaluate whether i.v. BPs therapy changes MM manifestations in jawbones.

Imaging exams are essential to the primary diagnostic study of destructive bone changes in MM, since previous studies suggest that up to 75% of MM patients will have positive radiographic findings[1]. According to the literature, panoramic radiographs, computed tomography (CT), and cone-beam computed tomography are considered useful tools for maxillofacial diagnostic workup in MM patients[32,33,34,35,36]. Most authors consider panoramic radiographs the preferred method in this scenario because it is a low-cost routine exam, and it is readily accessible to dental healthcare professionals. Moreover, panoramic radiograph allows the visualization of the entire maxilla, mandible, temporomandibular joints, and associated bone structures[16,17,34]. This is the first study to use digital mandible panoramic radiographs to access jawbone manifestations of MM.

The involvement of maxillofacial bones in MM is usually less common when compared with other skeletal bones because of the lower hematopoietic marrow content[37] and

apparently, the maxilla is rarely affected when compared with the mandible. In the 80's, Lambertenghi-Deliliers *et al.*[35] reviewed 193 cases of MM using non-digital radiographs of the skull, and found no involvement of the maxilla. We originally observed the presence of well-defined osteolytic lesions (multiple punched-out lesions) in the maxilla without any peripheral osteosclerotic bone reaction, a characteristic feature of MM lesions.

We must consider that, according to the Durie-Salmon[20,21] criteria, our study enrolled a large number of patients with advanced disease. Thus, confirming literature reports, the presence of multiple mandibular lesions in MM patients may represent an unfavorable prognosis[33, 38]. The patients performing bone disease treatment that received i.v. BPs, were associated with a lower prevalence of solitary osteolytic lesions, confirming that i.v. BPs may control MM skeletal-related events. Thus, when considering the potential effects of BPs on bone metabolism and presence of osteolytic lesions, it is important to consider which drug was administered at what dose and frequency, and over what period of time. Our study presented a variable number of BPs cycles and it was not possible to determine the exact number of cycles necessary to reduce the presence of solitary osteolytic lesions.

Diffuse osteoporosis with generalized involvement is a type of bone manifestation in patients with MM[18]. However, when Witt and colleagues[18] performed a radiographic evaluation in 77 patients with MM, none of the patients presented diffuse osteoporosis. In our study, a large number of patients presented with diffuse osteoporosis, mostly affecting the mandible. Osteoporosis may also occur in patients presenting smoldering, asymptomatic, or indolent myeloma[39]. As stated before, we enrolled a large number of elderly patients with advanced disease and this may account for the presence of this manifestation. In some cases, the mandibular involvement affected the entire bone. Oral BPs have a well-established role in the treatment of osteoporosis reducing osteoporotic fracture risk [5, 37, 39] but none of the patients enrolled in our study were taking oral BPs at the time of diagnosis of MM.

A review of the literature revealed that primary osteosclerosis in myeloma is a rare entity with an estimated incidence of only 3%[40]. Beyond osteolytic lesions Gosh *et al.*[41] reported that osteosclerosis in MM patients also constitutes a component of the disease, sclerotic lesions may be mixed and, as in other types of myelomatous deposits, the axial skeleton is primarily involved, although osteosclerosis in skull lesions occur. We observed changes in trabecular pattern with diffuse sclerosis in both groups

In the BPs group, a significantly increased thickness of the lamina dura associated with thickening of the alveolar crest with osteosclerosis of the alveolar margin was noted. Such sclerotic changes in the jaws of patients treated with BPs have been previously observed

in patients with MRONJ[42]. This finding was statistically significant when compared with patients in the control group. Osteosclerosis is a specific radiographic finding that has to be identified and considered within other oral and medical information, since it has been described as an indicator of the risk for MRONJ development in patients exposed to i.v. BPs therapy [43].

Tooth extractions have been labeled as the main risk factor for MRONJ[30,31,44]. Thus, the prevention of MRONJ is an important clinical consideration in patients with MM receiving BPs therapy[31,45]. Groetz and Al-Nawas[46] reviewed radiographic features in a series of osteonecrosis of the jaw cases and concluded that non-healing alveolar sockets might be an early radiographic sign of preclinical MRONJ. In addition, Migliorati and colleagues[44] recently proposed that post-extraction healing was delayed in patients taking BPs. In our study, non-healing alveolar sockets were associated with BPs treatment but no cases of MRONJ were observed.

This study presented some issues that should be considered. Although it could demonstrate the impact of BPs treatment on the jawbones lesions of MM, the lack of baseline panoramic radiograph limits the comprehension of these findings. Also, the patients were not clinically evaluated so clinical diagnosis of early MRONJ was limited. Radiographic data pre-BPs therapy for the BPs group was not available for most of the patients, making it impossible to determine when the jawbones lesions had started.

In conclusion, digital panoramic radiography was able to detect several MM manifestations in the jawbones. The current study accepted the tested hypothesis that i.v. BPs therapy is associated with differences in the radiographic patterns of MM in the jawbones.

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Tables

Table 1. Patient characteristics.

Characteristic	Control Group	BPs Group
Gender		
Men	52(52%)	53(60.2%)
Woman	48(48%)	35(39.8%)
Age	64.9 years(31 to 90)	63.54 years (33 to 86)
Stage*		
IA	0(0%)	0(0%)
IIA	10(10%)	6(6.8%)
IIIA	70(70%)	63(71.6%)
IB	0(0%)	0(0%)
IIB	0(0%)	0(0%)
IIIB	20(20%)	19(21.6%)
Bisphosphonate		
Pamidronate 90mg**	0(0%)	64(72.7%)
Zoledronate 4mg***	0(0%)	7(8%)
Pamidronate 90mg**+ Zoledronate 4mg***	0(0%)	17(19.3%)
Medical conditions		
Hypertension	45(45%)	36(41%)
Diabetes mellitus	18(18%)	10(11.3%)
Heart disease	12(12%)	15(17%)
Depression	2(2%)	3(3.4%)
Renal insufficiency	2(2%)	8(9%)
Hyperparathyroidism	5(5%)	2(2.3%)
Hypothyroidism	2(2%)	2(2.3%)
Hepatitis	2(2%)	0(0%)
No medical complication	9(9%)	12(13.7%)

* According to the Durie-Salmon staging method

** I.V. pamidronate 90mg every 28 days (mean of 9 cycles ranging from 3 to 25)

*** I.V. zoledronate 4mg every 28 days (mean of 5 cycles ranging from 3 to 11)

Table 2. Radiographic features of 188 MM patients.

Radiographic Features	**BPs Group (Mandible)**	**Control Group (Mandible)**	**BPs Group (Maxilla)**	**Control Group (Maxilla)**
Solitary type bone lesion	0 (0%)	2 (2%)	3 (3.4%)	14 (14%)
Multiple osteolytic lesions	76 (86.36%)	86 (86%)	17 (19.3%)	11 (11%)
Diffuse osteoporosis	69 (78.4%)	73(73%)	35 (39.7%)	37 (37%)
Diffuse sclerosis	57 (64.7%)	55 (55%)	38 (43.1%)	51 (51%)
Abnormalities of lamina dura	39 (44.3%) NE=15	25 (25%) NE=23	23 (26.1%) NE=33	13 (13%) NE=40
Non-healing alveolar sockets*	8 (9%)	0 (0%)	0 (0%)	0 (0%)
Bone sequestration	0 (0%)	0 (0%)	0 (0%)	0 (0%)

NE= Not evaluable, edentulous, (*) after 4 weeks tooth extraction

FIGURES

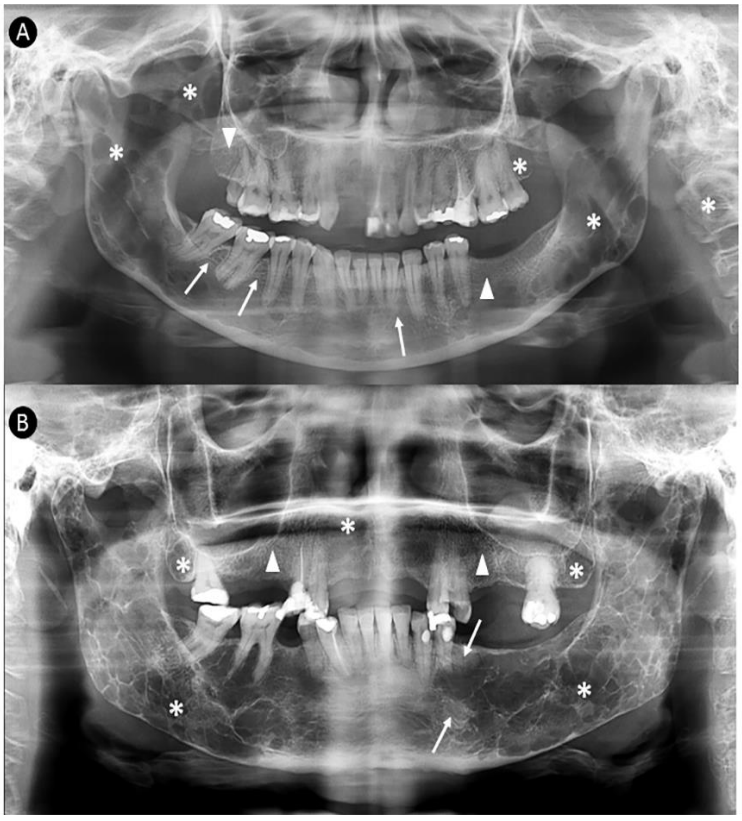

Figure 1. Digital panoramic radiographic images of MM patients.**A.** Radiologic evaluation of a BPs group patient, generalized presence of osteolytic lesions (*) with multiple punched-out appearance in maxillo-mandibular complex also presenting zygomatic arch and cervical spine involvement. Mandible reveals sclerosis of the lamina dura (arrow), maxilla and mandible reveal diffuse osteoporosis with mottled bone appearance (arrowhead). **B.** Radiologic evaluation of a control group patient, maxilla and mandible demonstrate multiple osteolytic lesions (*) with punched-out appearance, mandible reveals diffuse sclerosis (arrow), maxilla reveal diffuse osteoporosis (arrowhead) with mottled bone appearance.

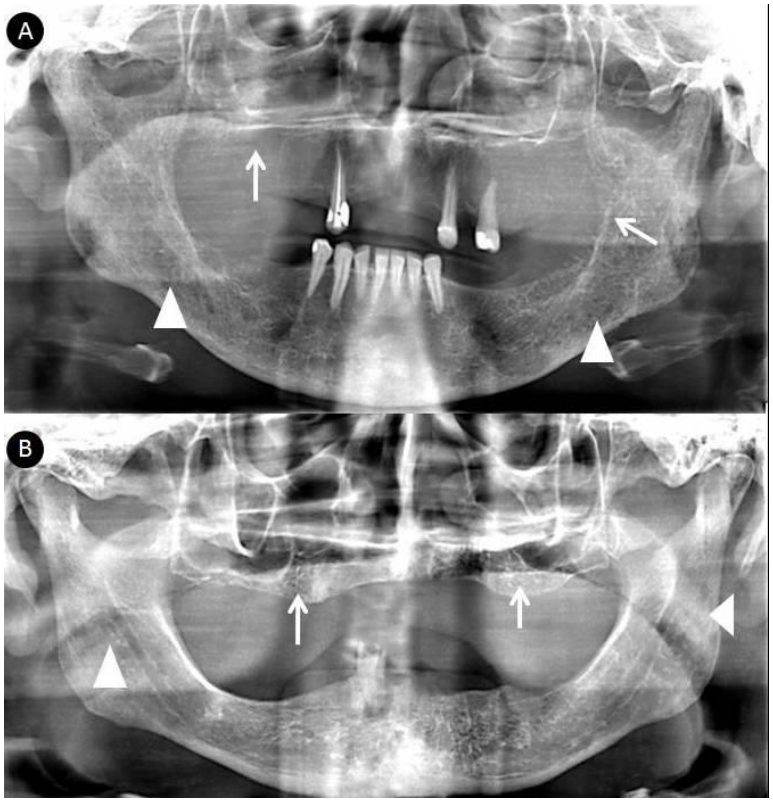

Figure 2. Digital panoramic radiographic images of MM patients. **A.** Radiologic evaluation of a BPs group patient, presence of diffuse osteoporosis (arrow) mandible reveals osteolytic lesions (arrowhead). **B.** Radiologic evaluation of a control group patient, maxilla reveal diffuse osteoporosis (arrow) and mandible demonstrates multiple osteolytic lesions (arrowhead).

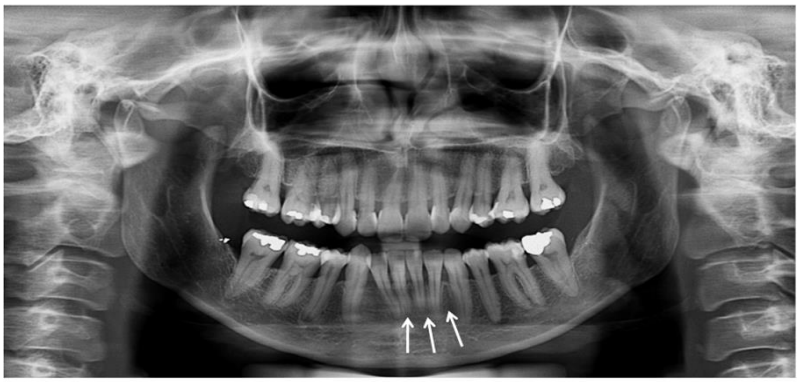

Figure 3. Abnormalities of the lamina dura in MM patients. Radiologic evaluation of BPs group. Mandible presenting thickening of the alveolar crest and sclerosis of the alveolar margin in anterior teeth area (arrow).

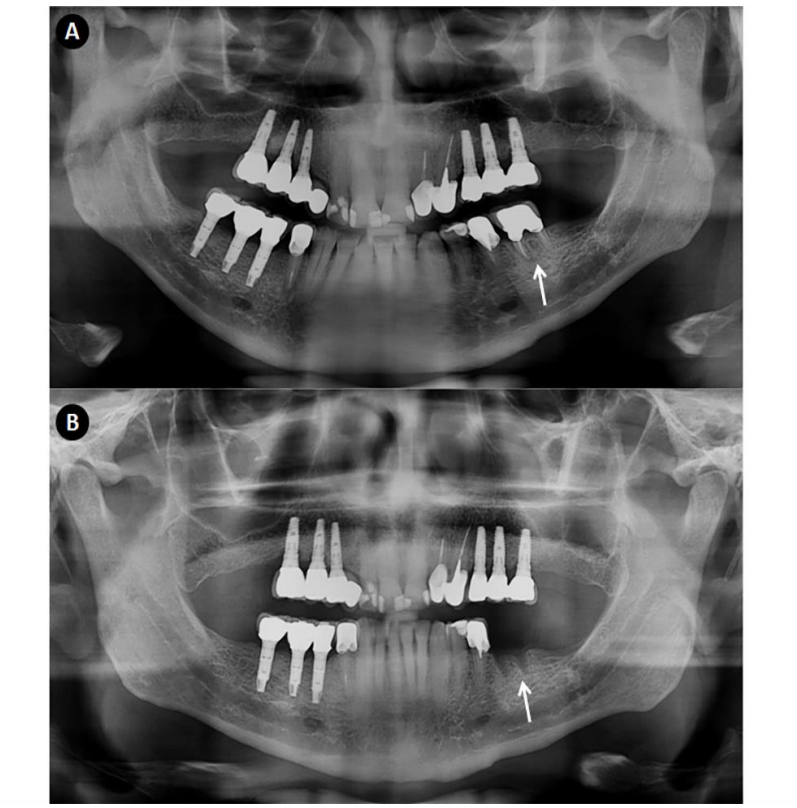

Figure 4. Radiographic findings in non-healing alveolar sockets associated with i.v. BPs therapy. **A.** Panoramic radiographic from i.v .BPs patient before tooth extraction (arrow).**B.** Follow-up panoramic radiographic of the same patient showing non-healing alveolar socket (arrow) 12 months after extraction.

2.2 Artigo: Evaluation of skull x-ray radiography for diagnosing multiple myeloma: panoramic radiographic correlation in 155 cases

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ABSTRACT

Objectives: The purpose of this study was to investigate the presence of punched-out lesions in craniofacial bones (skull and maxillofacial complex) using three different radiographic protocols in a large court of patients. **Methods:** One hundred fifty-five MM patients were evaluated using skull (frontal and lateral) radiographs as well as panoramic radiographs, which were performed in all patients at the time of MM diagnosis. The diagnostic potential for detecting punched-out lesions was compared among used radiographic techniques. **Results:** MM punched-out lesions were identified in 137 (88.3%) panoramic radiographs, 141 (91%) frontal and 144 (93%) lateral skull radiographs. Punched out-lesions were synchronously present in skull and jawbones in 129 (83.23 %) cases. The lesions were detected exclusively in skull in 18 (11.61%) cases and exclusively in jawbones in 6 (3.87%) cases. Punched out-lesion mainly affected the skull and the jawbones in a synchronous way ($p<0.001$) than separately. **Conclusion:** The diagnosis of osteolytic lesions in maxillofacial complex and skull is an important tool to establish the stage of the disease and planning the treatment. All investigated radiographic techniques (panoramic, anterior and lateral skull approaches) demonstrated high detection rates for MM punched-out lesions in craniofacial bones.

Keywords: Multiple myeloma, osteolytic lesions, panoramic radiography.

INTRODUCTION

Multiple myeloma (MM) is a malignant neoplasm of plasma cells, which results in the production of abnormal antibodies (M proteins). A high level of M protein in the blood is the hallmark characteristic of the disease. Thus, large quantities of M proteins may cause clinical manifestations, such as bone damage[1]. One of the major challenges in MM diagnosis is that, unlike other malignancies, the disease definition is clinicopathological; it needs overt clinical manifestations, such as bone lesions, hypercalcemia and renal failure, before the diagnosis can be performed[2,3]. According to the new diagnostic criteria for MM, one or more osteolytic lesions have to be visualized on skeletal radiograph for the diagnosis of MM[4].

The International Myeloma Working Group (IMWG) recommends performing conventional radiographs, whereas X-rays images are of crucial importance for diagnosis, as well as for differentiation of MM from other monoclonal plasma cell diseases[4,5]. According to the Durie-Salmon-Staging[5] system, the presence and number of osseous lesions identified on X-rays contribute directly to the staging of the disease and thereby to the prognosis[6].

The common characteristic of the bone lesions visualized is a multiple sharply defined small lytic lesion with the so-called "punched-out" appearance[7]. These multiple well-defined punched-out radiolucencies, without a definitive cortical margin are common radiographic features and often present as the first signal of MM. Nearly 80% of all newly diagnosed cases of MM reveal these bone changes in conventional radiography[6,8].

The following sites are most commonly affected in MM patients: vertebrae (65%), ribs (45%), skull (40%), shoulders (40%), pelvis (30%), long bones (25%) and jawbones (20% to 30%)[6,7,9]. The IMWG recommends for each newly diagnosed patient with MM a complete conventional radiograph status, including skull, cervical, thoracic and lumbar spine (frontal and lateral views), chest (frontal view), pelvis (anterior-posterior view) and long proximal bones (anterior-posterior view) [7], additional views of any symptomatic area should also be acquired[9]. In some cases, considering early stage disease, the role of the X-rays is limited and some MM deposits may be not visualized. Estimations suggest that approximately 50% of bone destruction due to MM occurs before there is any detectable radiographic alteration[10,11].

MM can occur in craniofacial bones as a primary manifestation, Bruce and Royer (1953) [12] and Miller et al. (1969) [13] reported that 20% to 30% of cases showed radiographic involvement of the jawbones. Symptoms associated with jawbones involvement in MM are uncommon. The most frequent clinical manifestations of this disease in the jawbones are paresthesia, pain, swelling and tooth mobility[14-17]. In some cases, jawbones involvement

presenting punched-out lesions may occur with a similar presentation to other cysts and odontogenic lesions[18]. The osteolytic lesions are more common in the mandible than maxilla, especially in posterior teeth region, ramus, and condyle, probably due to the increased hematopoietic activity in these areas[19]. In this context, the identification of the MM pattern manifestations in craniofacial bones is necessary to avoid delays in diagnosis. The early detection of bone lesions with risk of fractures can take the important decision for treatment (prophylactic surgery or radiotherapy)[6,7,20]. Furthermore, the bone disease is important for the evaluation of the response to systemic treatment[21,22].

As the major clinical manifestation of MM is bone-related disease, the conventional radiographs are still universally used for the evaluation of such patients. X-rays have wide availability and low costs. They are considered the gold standard to identify osteolytic lesions and monitoring MM patients[6,7].

The initial manifestation of MM can occur in jawbones, therefore, a better understanding of the radiographic aspects of MM on the craniofacial bones can contribute to improving the prognosis of the disease. In spite of that, there are only a few previous published studies that have investigated the radiographic aspects of MM affecting the craniofacial bones using panoramic radiography. Based on the above, the aim of this study was to investigate and compare the frequency of osteolytic lesions detected in digital panoramic radiographs and skull x-rays (frontal and lateral) in a large cohort of MM patients.

MATERIAL AND METHODS

Patients and study design

The present study was a collaboration among the University of Campinas, Piracicaba Dental School, Brazil; the Dental Oncology Service of the Instituto do Câncer do Estado de Sao Paulo (ICESP), Brazil and the University of Tennessee Health Science Center, College of Dentistry in Memphis (UTHSC-CD), United States. This study was approved by the Ethics Committee of the University of Campinas (protocol 118/2014) and the Institutional Review Board of The University of Tennessee Health Science Center-UTHSC (number 516827). This was a cross sectional retrospective study performed with individuals treated at the Hematology Service of Instituto do Câncer do Estado de São Paulo from April/2010 to June/2014.

One hundred fifty-five patients diagnosed with MM were included in this retrospective study. Criteria for patients' inclusion were: (1) a confirmed diagnosis of MM presenting with bone disease after complete clinical workup according to International Myeloma Working Group criteria[4]; (2) a digital panoramic radiograph obtained upon diagnosis; (3) skull radiographs (anterior and lateral approaches); (4) complete medical records. The exclusion criteria were the presence of non-MM neoplastic bone disease or absence of head and neck radiographs (panoramic, anterior and lateral skull). The Durie-Salmon[5] staging default method was used for the clinical staging of MM.

To assess the involvement of craniofacial bones, a descriptive approach was performed in 155 frontal and 155 lateral radiographs of the skull. In addition, digital panoramic radiographs (n=155) were analyzed for each patient involved in this study. The electronic records were consulted to access for information about the occurrence of skeletal complications.

Radiographic evaluation

All panoramic radiographs were taken in a dental X-ray machine (PaX- 400, Hawseong-si, Gyeonggi-do, Korea), using 68 kVp, 8 mA with an exposure time of 14s. All skull radiographs were taken in X-ray machine (OPTILIX 150/30/50 HC-100;Siemens, focal spot 0.6/1.0 mm), using 65 kVp, 10 mA and exposure time of 125ms. The radiographs were coded to protect health information. Radiographic images were independently evaluated at the UTHSC-CD by a radiologist certified by the American Board of Oral and Maxillofacial Radiology and an oral medicine practitioner certified by the American Board of Oral Medicine, images were displayed on a 24 inch LCD flat panel display (UltraSharp 2408WFP, Dell Inc., USA) with a screen resolution of 1920 x 1200 pixels in a room with reduced light.

Digital panoramic, lateral and frontal radiographs were evaluated separately. For identification of the presence of the osteolytic lesions, X-rays were classified as score considering present (1) or absent (0). All anatomical structures in the maxillo-mandibular complex were included in the radiographic evaluation. The observers were blinded to clinical data. In order to avoid inter-examiner variability in interpretation of the images, the observers performed all assessments under dim light conditions, without brightness and contrast adjustment. Interexaminer agreements were assessed using Cohen's Kappa test to analyze the reliability of the examiners and the agreement was considered fair if Kappa was between

0,20-0,40, moderate if Kappa was between 0,40-0,60 and substantial if Kappa was between 0,60-0,80.[23]

Data analysis

To verify the presence of punched-out lesions affecting skull and the jawbones the chi-square test of likelihood ratio was applied to test the capacity of diagnostic for both radiographic techniques (digital panoramic and skull X-rays). The significance level of 5% was adopted and the analyses were performed through the system SAS (Institute Inc. The SAS System, release 9.3. SAS Institute Inc., Cary: NC.2010)

RESULTS

Clinicopathological data of studied patients are described in **Table 1.** Bone complications status is described in **Table 2.** Sixty-eight (43.8%) patients received intravenous bisphosphonate therapy for bone disease control. In terms of comorbidities, 63 (41%) patients reported hypertension, 26 (17%) heart conditions, 18 (12%) diabetes mellitus, 17 (11%) renal insufficiency, 4 (3%) hyperparathyroidism and 3 (2%) hypothyroidism.

Radiographic alterations

A total of 137 (88.3%) patients presented punched-out lesions on the jawbones detected on panoramic radiographs, 141 (91%) patients presented punched-out lesions in frontal skull radiographs and 144 (93%) patients presented punched-out lesions in lateral skull radiographs. All punched-out osteolytic lesions in the skull were observed in frontal, parietal and occipital bone **(Fig 1A, 1B and 1C).** Punched out-lesions were present both in the skull and jawbones X-rays in 129 (83.23 %) of the cases, detected exclusively in the skull in 17 (11.61%) cases and exclusively in jawbones in 6 (3.87%) cases. The chi-square test revealed that punched out-lesions mainly affected the skull and the jawbones in a synchronous way ($p<0.001$) than separately. When skull bones were independently evaluated, it was possible to observe that punched-out lesions affected the parietal bones in 139 (89.6%) patients, the frontal bone in 113 (72.9%) patients and occipital bone in 72 (46.4%). When jawbones were independently evaluated, it was possible to observe that punched-out lesions affected the mandible in 137 (88.3%) patients and maxilla in 20 (13%) patients.

DISCUSSION

MM is a devastating malignancy of antibody-producing plasma cells that extensively affects the bone marrow. There is a slight male predominance. The median age at onset is 66 years, and only 2% of patients are younger than 40 years of age at diagnosis[24,25,26]. The clinicopathological profile of the patients evaluated in the present study is in accordance with previous reports for clinical aspects of myeloma. A court of patients observed in this study presents MM advanced stage, bone disease and the presence of diffuse skeletal complications (osteolytic lesions, fractures and plasmacytoma) in the spine, thoracic cage and appendicular skeleton.

Bone fractures are an important health care concern among MM patients with advanced disease. Therefore, fractures can interfere with functional independence and shorten survival. Approximately 45% of patients with MM experience a fracture in the first year after diagnosis[27,28]. In accordance to the literature[28] our study presented a high number of patients with fractures, which were identified by MM diagnosis and demonstrated that appendicular skeleton was more affected.

MM bone disease can involve craniofacial structures; approximately 30% of patients with MM develop osteolytic lesions in the jawbones and frequently occurs in the advanced stage of the disease[17]. Osteolytic lesions in the jawbones can present as well-circumscribed unilocular radiolucent lesions or poorly defined osteolytic areas with irregular border[26]. We observed the presence of well-defined osteolytic lesions in the maxillofacial complex without any peripheral sclerotic bone reaction, a characteristic feature of the MM lesions.

Jawbones osteolytic lesions are not usually an isolated radiographic finding in MM patients, they are often observed synchronously to lesions on the skull and other bones[29]. There are only a few available studies that have previously described the radiographic manifestations of MM in craniofacial bones, most of which represent small case series or isolated case reports[18,30,31,32]. Futurani et al. (1994)[11] published the only study that analyzed both jawbones and skull involvement in a series of 38 MM patients using non-digital radiographs; they found 5 (13%) patients with mandible osteolytic lesions, no lesions in the maxilla and 5 (13%) patients with skull osteolytic lesions. The current study was the first to use digital panoramic and skull radiographs to investigate MM patients. Possibly, this methodological approach explains why this seems to be the first study to report the presence of well-defined MM osteolytic lesions in the maxilla as well as the highest rates of

craniofacial bones involvement by MM osteolytic lesions (mandible: 88.3%, maxilla: 13%; parietal bones: 89.6%; frontal bone: 72.9% and occipital bone: 46.4%).

A variety of lesions in the jawbones can display radiographic characteristics similar to those of MM. Differential diagnosis includes locally aggressive tumors, vascular malformations, and aneurysmatic bone cyst[12,18]. In our study, no cases of cysts or vascular malformations similar to radiographic MM manifestations were observed.

The incorrect diagnosis can have devastating effects for the patient[26]. Thus, the use of digital panoramic radiography is an important diagnostic tool for MM manifestations in the jawbones[33-36]. Panoramic radiographic is a routine exam and it is readily accessible to dental health care professionals that present low costs if compared with medical computed tomography (medical CT)[33,36,37]. The traditional standard imaging technique for evaluation of bone disease in MM is the skeletal survey and there is no evidence in the literature that digital panoramic radiographic is included on bone protocol radiographic evaluation for MM [5-7]. The IMWG recommendation to identify bone lesions earlier include multiple other imaging techniques (MRI, medical CT, a whole-body low-dose computed tomography, WBLDCT, and FDG PET-CT)[37], however, these sensitive techniques depends on availability and access. The present study specifically described osteolytic lesions observed in digital panoramic radiographs and skull x-rays (frontal and lateral) in MM patients. Furthermore, we compared the synchronous presence of osteolytic lesions affecting the skull and the jawbones in MM patients detected by both x-rays techniques.

Bone disease in MM is usually multifocal and can potentially affect every skeletal segment including skull and jawbones[38,39,40]. Hence, for a correct evaluation of the extent of disease in craniofacial structures panoramic radiograph should be routinely performed – in addition to frontal and lateral views of the skull imaging technique -and required[5-7], since MM manifestations may occur exclusively (mainly at early stages) on the jawbones[17,39].

In a review Delorme and Baur-Melnyk[39] stated that MM manifestations in the skull occur early, resulting in multiple sharply delineated osteolytic lesions. Ippolito et al.[41] diagnosed forty-two osteolytic lesions in skull in a total of 138 MM patients by a WBLDCT. We demonstrated a large number of patients with osteolytic lesions identified in the skull upon MM diagnosis and demonstrated that bone MM manifestations in skull had the traditional “punched-out” appearance. Punched out-lesions affected the skull and the jawbones in a synchronous way, this finding was statistically significant when compared exclusively in skull cases and exclusively in jawbones. However, to date, there is no evidence that the panoramic radiographic evaluation is included in IMWG protocols for a complete

radiographic investigation status in MM patients[2,40,42]. Our study suggests that the skull X-rays are not specific to detected MM manifestations in the jawbones, and the digital panoramic radiograph investigation may help to detect punched-out lesions on the jawbones, exclude a variety of lesions that can mimic MM leading to delay in diagnosis and treatment.

The present study suggests that panoramic mandible radiograph may aid to the radiographic protocols to identify MM bone lesions affecting the jawbones, since radiographic techniques for jawbones and skull (frontal and lateral) were potentially equally able to detect punched-out lesions in each corresponding topography. The benefit for using digital panoramic radiography is the specific identification of punched-out lesions on the jawbones by a simple tool, with low cost and low exposure to radiation. Furthermore, in view of the wide availability of digital panoramic radiograph, the present study illustrates the contribution that oral assessment can provide for the early diagnosis, prompt treatment, and prognosis of MM patients.

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Tables

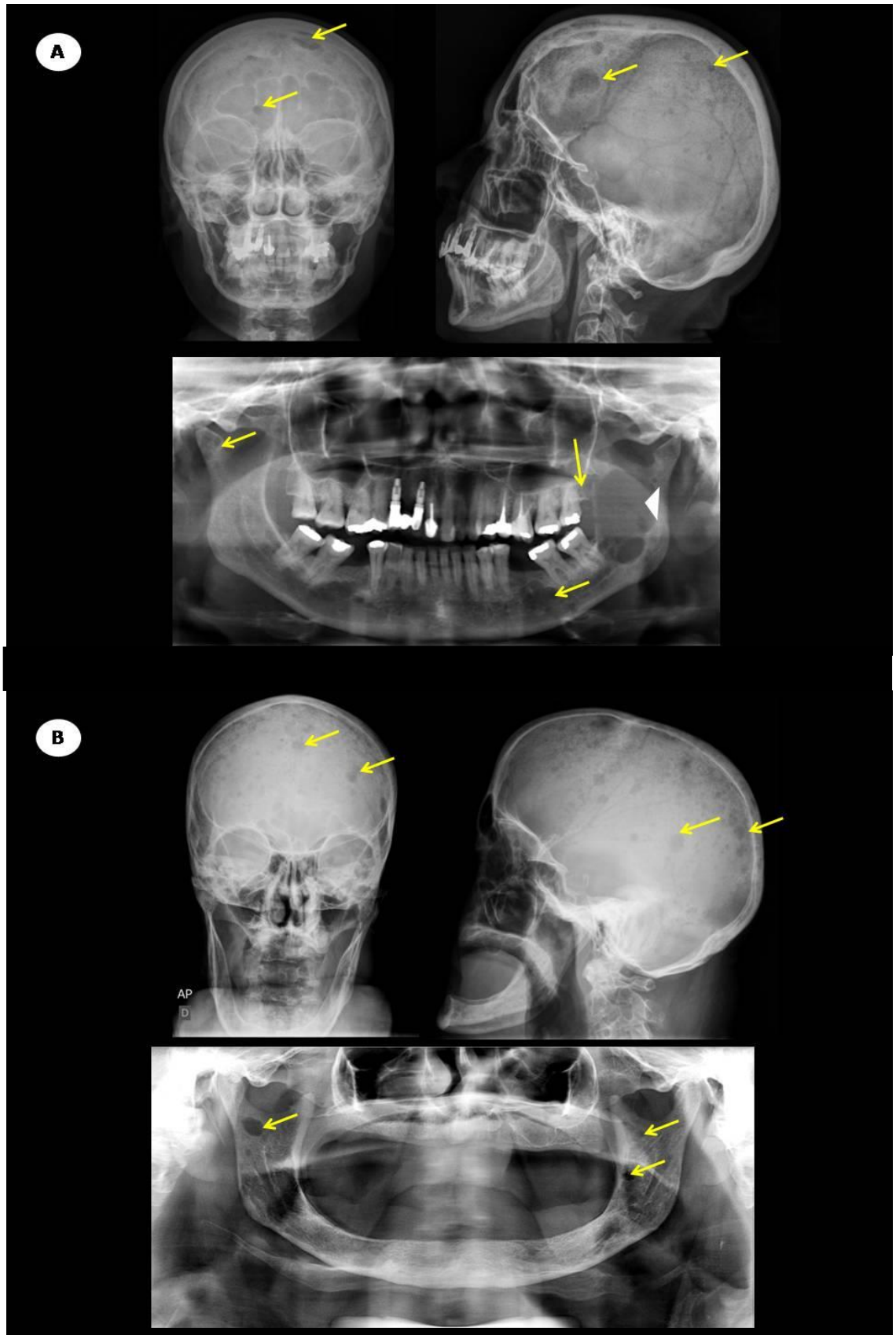
Table 1. Clinicopathological features of studied multiple myeloma patients.

Feature	Patients (n)
Mean age (years)	64.2 (31 to 90)
Men	103 (66.4%)
Woman	52 (33.6%)
Stage (Durie & Salmon)	
IA	0 (0%)
IB	0 (0%)
IIA	14 (9%)
IIB	0 (0%)
IIIA	117 (75.5%)
IIIB	24 (15.5%)
Imunoglobulin G	140 (90.3%)
Imunoglobulin A	15 (9.7%)

Table 2. Bone complication status.

Location	Osteolytic Lesion (n)	Pathological Fracture (n)
Spine	76 (49%)	16 (10.3%)
Thoraxic cage	34 (30%)	0 (0%)
Appendicular skeleton	122 (78.8%)	72 (46.4%)
Skull	144 (93%)	0 (0%)
Jawbones	137 (88.3%)	0 (0%)

Figures



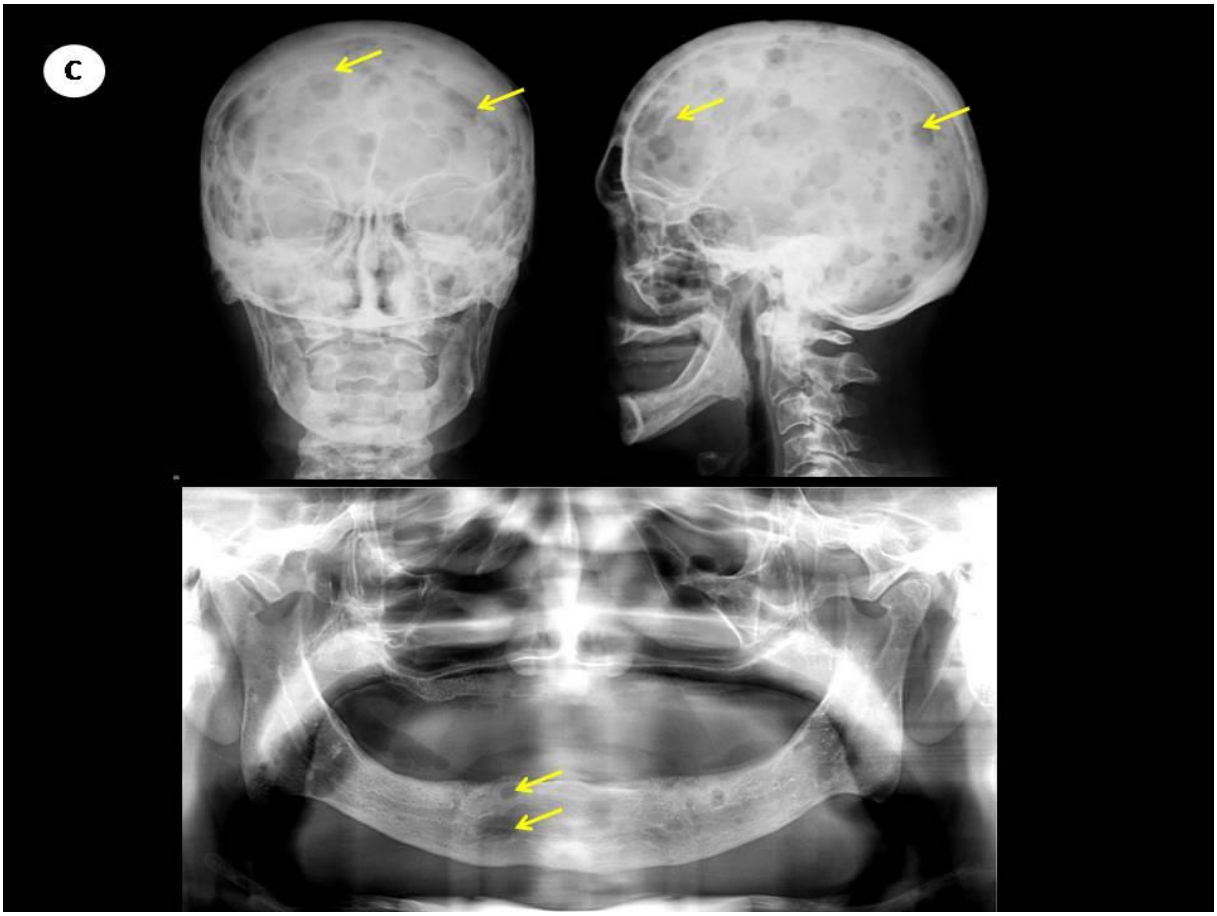


Figure 1. Radiographic patterns of MM in craniofacial bones. **A.** Panoramic radiographic evaluation showing punched-out lesions (arrows) affecting maxilla and mandible and a large osteolytic image (arrowhead) affecting the left ramus of the mandible. Frontal and lateral skull radiographs of the same patient presenting multiple punched-out lesions (arrow). **B.** Panoramic radiographic evaluation showing punched-out lesions (arrows) affecting maxilla and mandible. Frontal and lateral skull radiographs of the same patient presenting multiple punched-out lesions (arrow). **C.** Panoramic radiographic evaluation showing punched-out lesions (arrows) affecting maxilla and mandible. Frontal and lateral skull radiographs of the same patient presenting multiple punched-out lesions (arrow).

3 DISCUSSÃO

Apesar do MM representar apenas 1% de todos os tipos de câncer, ele corresponde à segunda patologia mais comum entre as neoplasias hematológicas malignas em pacientes adultos. Atualmente ainda não estão completamente elucidados os mecanismos fisiopatológicos que levam ao desenvolvimento desta doença, notoriamente reconhecida por sua alta agressividade e consequente reduzida sobrevida dos pacientes afetados (Hameed *et al*., 2014). Entretanto, acredita-se que uma combinação de fatores genéticos e ambientais levaria à maior suscetibilidade para o desenvolvimento do MM (Kyle e Rajkumar, 2008).

A principal característica do MM é o acúmulo progressivo de plasmócitos malignos que pode levar ao comprometimento da medula óssea normal, o que costuma ser refletido pela presença de anemia, hipercalcemia, liberação de proteína monoclonal, insuficiência renal e importante dano multifocal aos ossos (Croucher e Apperley, 1998; Fairfield *et al*., 2016). A doença óssea no MM é caracterizada pela presença de lesões osteolíticas, tal fato é considerado um dos sinais mais expressivos da doença. Essas lesões podem ser detectadas por meio de um protocolo de avaliação radiográfica pré-estabelecido pelo IMWG que compreende avaliação dos ossos do crânio, colunas cervical, torácica e lombar, tórax, pélvis e ossos longos (Rajkumar *et al*., 2014), num contexto de investigação radiográfica que vem ao encontro do tema desta tese de doutoramento.

Uma das principais estratégias terapêuticas para o controle da doença óssea no MM é o uso de medicamentos que inibem a reabsorção óssea, sobretudo, aqueles pertencentes à classe dos BFs (Reyes *et al*., 2016). Nas últimas décadas os BFs têm sido amplamente utilizados em pacientes tratados por MM, tendo em vista seu potencial para controle de disseminação da doença, reduzindo significativamente a morbidade e o risco de fraturas patológicas (Angtuaco *et al*., 2004; Raje *et al.*, 2014). Contudo, a despeito da eficácia dos BFs no controle do MM, uma série de efeitos colaterais foi recentemente associada ao uso desta classe de medicamentos, destacando-se no contexto odontológico a osteonecrose relacionada aos BFs (Hutchinson *et al*., 2010; Merigo *et al.*, 2015;Migliorati *et al*., 2005; Migliorati *et al*., 2011) .Neste sentido, o presente estudo foi baseado na avaliação clinicopatológica e radiográfica de uma série de pacientes diagnosticados com MM, cuja parcela significativa realizou tratamento com BFs e.v. Uma vez publicados, os trabalhos oriundos desta pesquisa terão potencial para ser a maior casuística de pacientes diagnosticados com MM avaliada por meio de radiografias digitais – panorâmicas e de crânio – direcionada para a melhor

compreensão da frequência (e dos padrões qualitativos) do envolvimento dos ossos craniofaciais por lesões osteolíticas do MM.

Em relação ao perfil clínicopatológico da amostra estudada, foi observado que todos os pacientes possuíam características similares ao padrão demográfico classicamente atribuído aos pacientes diagnosticados com MM, incluindo predileção para o gênero masculino, média de idade superior aos 60 anos e diagnóstico tardio da doença (Conte *et al*., 2008; Spasov e Goranova, 1998). Existe uma tendência de literatura que atribui às reduzidas taxas de sobrevida apresentadas pela maioria dos pacientes diagnosticados com MM ao sub-reconhecimento das manifestações clínicas e radiográficas da doença, além da escassez de políticas públicas de diagnóstico precoce e limitações no campo do desenvolvimento terapêutico (Greipp *et al*., 2005).

Os resultados do presente estudo demonstraram que o tratamento com BFs e.v alterou os padrões radiográficos de manifestações craniofaciais do MM e este parece ser o estudo pioneiro a investigar o impacto do tratamento e.v. com BFs nas manifestações radiográficas do MM em mandíbula e maxila. Logo, identificou-se espessamento significativo da lâmina dura e atraso no padrão radiográfico de reparo alveolar nos pacientes com MM que foram tratados por meio de BFs e.v. Estes eventos relacionados à lâmina dura e ao reparo alveolar estão amparados por estudos previamente publicados por Migliorati *et al*., (2011) e Rocha *et al*., (2012) e, também, por orientações publicadas em 2007 pela *American Association of Oral and Maxillofacial Surgeons* (AAOMS). Segundo a AAOMS, pacientes que receberam BFs e.v. podem apresentar alterações radiográficas inespecíficas como, por exemplo, anormalidade de lâmina dura incluindo espessamento difuso do espaço do ligamento periodontal e esclerose da lâmina dura associada a dentes hígidos. Estas mesmas diretrizes da AAOMS (2007) sugerem que os achados radiográficos mencionados acima podem estar associados ao risco aumento para o desenvolvimento de osteonecrose relacionada aos BFs. Interessantemente, nenhum paciente estudado nesta oportunidade desenvolveu osteonecrose.

No contexto do diagnóstico das manifestações radiográficas do MM, em relação ao padrão de comprometimento ósseo, é importante esclarecer que todos os pacientes incluídos neste estudo apresentaram doença óssea com presença de lesões osteolíticas em variadas topografias, compreendendo o esqueleto axial e o apendicular. Torna-se ainda oportuno enfatizar que este estudo identificou alta frequência de lesões osteolíticas em mandíbula e maxila, quando comparadas a estudos prévios (Bruce e Royer; 1953; Dimopoulos *et al*., 2000; Epstein *et al*., 1984; Futurani *et al*., 1994; Lambertenghi *et al*., 1988; Lee *et al*.,1996; Miller *et al*., 1969;Pisano *et al*., 1997; Ramaiah *et al*., 2015; Senn *et al*, 1985; Smith, 1957; Tamir

et al., 1992; Vieira-Leite-Segundo *et al* ; Vicent *et al*., 1993; Witt *et al*. 1997; Zachriades *et al*., 1987) já publicados e, interessantemente, que estas lesões estavam presentes -na maioria absoluta dos casos -com manifestações simultâneas de lesões osteolíticas nos ossos do crânio. A título de informação, apresentam-se a seguir as frequências com que se identificaram lesões osteolíticas nos ossos craniofaciais deste estudo: mandíbula, 88.3%;maxila, 13%; osso parietal, 89.6%; osso frontal, 72.9% e occipital: 46.4%. Atualmente, o protocolo de investigação radiográfico (craniofacial) sugerido pelo IMWG propõe apenas radiografias de crânio (anterior e lateral), sendo que tais métodos não são considerados específicos para identificação de lesões osteolíticas em mandíbula e maxila. Tendo em vista a expressividade dos resultados do presente estudo, sugere-se que o protocolo supramencionado seja complementado por meio da indicação da radiografia panorâmica digital.

4 CONCLUSÃO

1) A terapia endovenosa com BFs altera o padrão radiográfico das manifestações craniofaciais do MM de modo específico, apresentando um espessamento significativo da lâmina dura associada a dentes hígidos e atraso no padrão radiográfico de reparo alveolar.
2) A radiografia panorâmica de mandíbula tem potencial para ser utilizada como método rotineiro de investigação radiográfica de lesões osteolíticas do MM.
3) Este parece ser um estudo pioneiro ao lançar mão de técnicas de radiografia digital para investigar manifestações craniofaciais do MM, ao identificar lesões osteolíticas do MM em maxila e ao descrever as maiores frequências de envolvimento de ossos craniofaciais por MM.

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* De acordo com as normas da UNICAMP/FOP, baseadas na padronização do International Committee of Medical JournalEditors - Vancouver Group. Abreviatura dos periódicos em conformidade com o PubMed.

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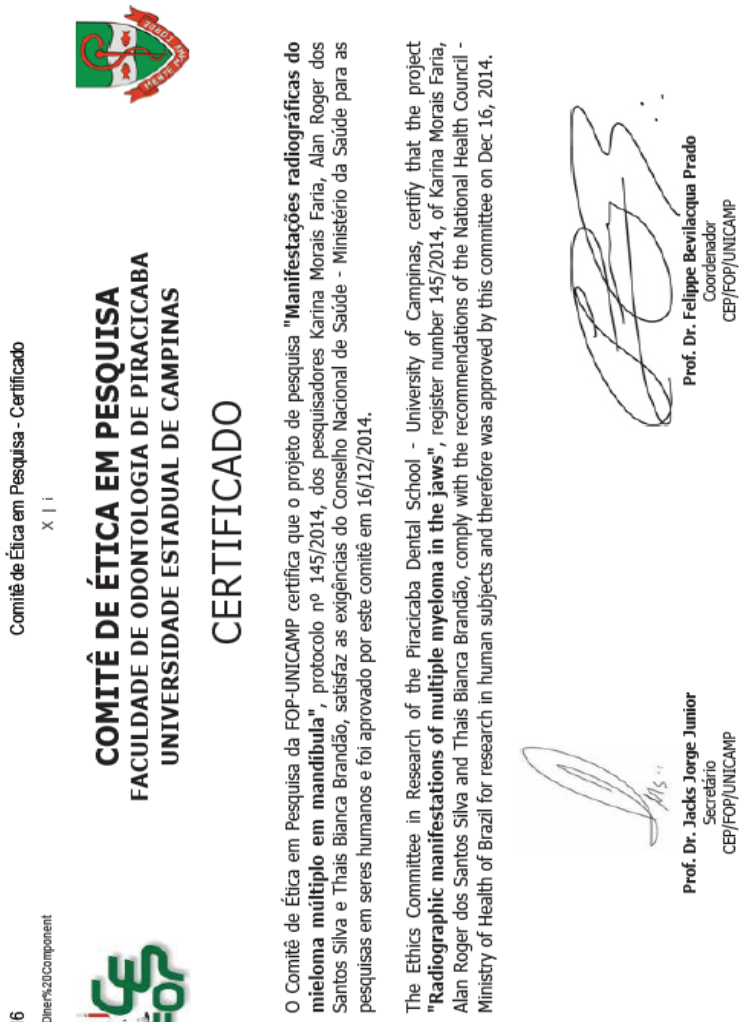
ANEXOS

ANEXO 1 – Certificado de aprovação do Comitê de Ética em Pesquisa da Faculdade de Odontologia de Piracicaba.



16/04/2016 Comitê de Ética em Pesquisa - Certificado

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COMITÊ DE ÉTICA EM PESQUISA
FACULDADE DE ODONTOLOGIA DE PIRACICABA
UNIVERSIDADE ESTADUAL DE CAMPINAS

CERTIFICADO

O Comitê de Ética em Pesquisa da FOP-UNICAMP certifica que o projeto de pesquisa **"Manifestações radiográficas do mieloma múltiplo em mandíbula"**, protocolo nº 145/2014, dos pesquisadores Karina Morais Faria, Alan Roger dos Santos Silva e Thais Bianca Brandão, satisfaz as exigências do Conselho Nacional de Saúde - Ministério da Saúde para as pesquisas em seres humanos e foi aprovado por este comitê em 16/12/2014.

The Ethics Committee in Research of the Piracicaba Dental School - University of Campinas, certify that the project **"Radiographic manifestations of multiple myeloma in the jaws"**, register number 145/2014, of Karina Morais Faria, Alan Roger dos Santos Silva and Thais Bianca Brandão, comply with the recommendations of the National Health Council - Ministry of Health of Brazil for research in human subjects and therefore was approved by this committee on Dec 16, 2014.

Prof. Dr. Jacks Jorge Junior
Secretário
CEP/FOP/UNICAMP

Prof. Dr. Felippe Bevilacqua Prado
Coordenador
CEP/FOP/UNICAMP

Nota: O título do protocolo aparece como fornecido pelos pesquisadores, sem qualquer edição.
Notice: The title of the project appears as provided by the authors, without editing.

ANEXO 2 – Approval UTHSC Institutional Review Board (IRB).

THE UNIVERSITY OF TENNESSEE
Health Science Center

Institutional Review Board
910 Madison Avenue, Suite 600
Memphis, TN 38163
Tel: (901) 448-4824

June 09, 2015

KARINA MORAIS, DDS, PhD
UTHSC - COD - Biological and Diagnostic Sci

Re: 15-03902-XM
Study Title: RADIOGRAPHIC MANIFESTATIONS OF MULTIPLE MYELOMA IN PATIENTS UNDERGOING INTRAVENOUS BISPHOSPHONATES THERAPY Research plan submitted to IRB

Dear Dr. MORAIS:

The Administrative Section of the UTHSC Institutional Review Board (IRB) has received your written acceptance of and/or response dated 06/08/2015 08:22:58 AM CDT to the provisos outlined in our correspondence of 05/29/2015 concerning the application for the above referenced project. The IRB determined that your application is eligible for **exempt** review under 45 CFR 46.101(b)(4) in that it involves the study of existing data, records, or specimens if the information will be recorded in a way that subjects cannot be identified. In accord with 45 CFR 46.116(d), informed consent is waived. Your application has been determined to comply with proper consideration for the rights and welfare of human subjects and the regulatory requirements for the protection of human subjects. Therefore, this letter constitutes full approval of your application (version 1.2) for the above referenced study.

In addition, the request for waiver of HIPAA authorization for the conduct of the study itself is approved. The waiver applies to the medical records of patients at Instituto do Cancer do Estado de Sao Paulo (ICESP) from the University of Sao Paulo Medical School diagnosed with multiple myeloma between 1-1-09 and 12-31-13.

In the event that volunteers are to be recruited using solicitation materials, such as brochures, posters, web-based advertisements, etc., these materials must receive prior approval of the IRB.

Any alterations (revisions) in the protocol must be promptly submitted to and approved by the UTHSC Institutional Review Board prior to implementation of these revisions. In addition, you are responsible for reporting any unanticipated serious adverse events or other problems involving risks to subjects or others in the manner required by the local IRB policy.

Sincerely,

Signature applied by Cameron A Barclay on 06/09/2015 02:44:20 PM CDT

Signature applied by Terrence F Ackerman on 06/09/2015 02:48:19 PM CDT

Cameron Barclay, MSA, CIM, CIP
Director
UTHSC IRB

Terrence F. Ackerman, Ph.D.
Chairman
UTHSC IRB

ANEXO 3 - Protocolo de submissão do artigo 2.1(The impact of intravenous bisphosphonate therapy in the radiographic patterns of jaw lesions in multiple myeloma)no periódico *Oral surgery, Oral medicine, Oral pathology, Oral radiology.*

From: "OOOO (Triple O) journal" <tripleojournal@gmail.com>
Date: 9 de março de 2016 18:28:03 BRT
To: alanroger@fop.unicamp.br, alanroger@hotmail.com
Subject: A manuscript number has been assigned: TRIPLEO-D-16-00304

Ms. Ref. No.: TRIPLEO-D-16-00304
Title: THE IMPACT OF INTRAVENOUS BISPHOSPHONATE THERAPY ON THE RADIOGRAPHIC PATTERNS OF JAW LESIONS IN MULTIPLE MYELOMA.
Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology

Dear Dr. Santos-Silva,

Your submission entitled "THE IMPACT OF INTRAVENOUS BISPHOSPHONATE THERAPY ON THE RADIOGRAPHIC PATTERNS OF JAW LESIONS IN MULTIPLE MYELOMA." has been been assigned the following manuscript number: TRIPLEO-D-16-00304.

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Thank you for submitting your work to this journal.

Sincerely,

Mark W. Lingen, DDS, PhD, FRCPath
Editor-in-Chief
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