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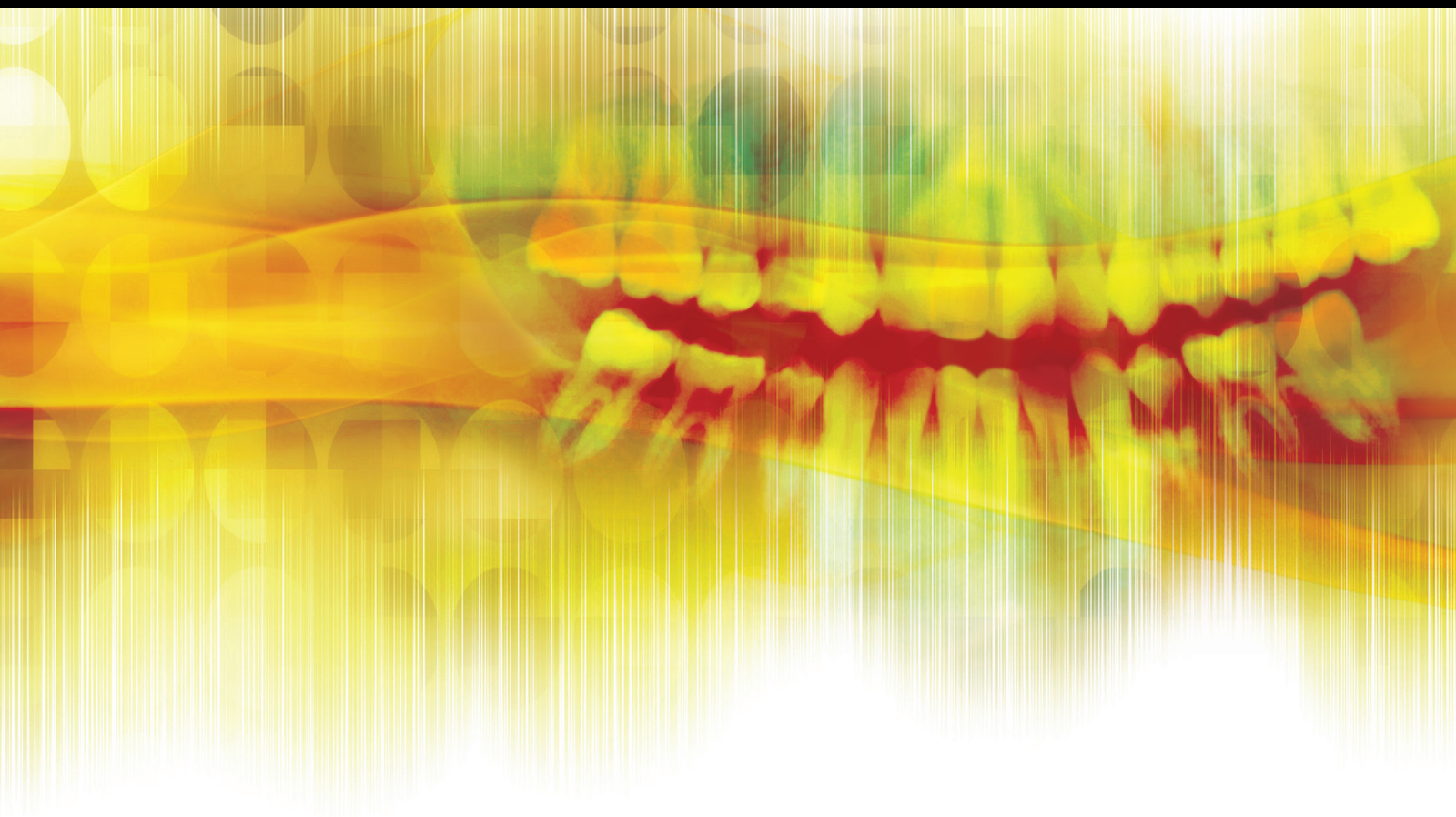
Guest Editors: Giuliano Ascani, Giuseppina Campisi, and Luis Manuel Junquera Gutierrez



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Editorial Board

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Editorial

Current Controversies in Classification, Management, and Prevention of Bisphosphonate-Related Osteonecrosis of the Jaw

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Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a serious complication associated with oral and intravenous bisphosphonate therapy that adversely affects the quality of life, producing significant morbidity.

Since the first description of bone necrosis in patients receiving bisphosphonate therapy in 2003 [1], hundreds of studies were published about this topic and various national and international medical societies have published protocols and guidelines. Nevertheless, there are still many controversies regarding the classification, management, and prevention of BRONJ.

Even the definition of BRONJ is still debated and changed with the progress of knowledge and experience. According to the original definition of the AAOMS (American Association of Oral and Maxillofacial Surgery) [2, 3] "*Patients may be considered to have BRONJ if all of the following three characteristics are present: (1) Current or previous treatment with a bisphosphonate; (2) Exposed bone in the maxillofacial region that has persisted for more than eight weeks; and (3) No history of radiation therapy to the jaws*."

Following recognition of the nonexposed BRONJ clinical variant, it became clear that the presence of exposed necrotic bone in the oral cavity is just one of the possible clinical manifestations of BRONJ and is not found in all BRONJ patients. In 2012 the SICMF (Italian Society for Maxillofacial Surgery) and the SIPMO (Italian Society of Oral Pathology and Medicine) proposed a new definition [4]: *"Bisphosphonate related osteonecrosis of the jaw (BRONJ) is an adverse drug reaction described as the progressive destruction and death of bone that affects the mandible or maxilla of patients exposed to the treatment with nitrogen-containing bisphosphonates, in the absence of a previous radiation treatment."* Recently, this definition was robustly supported by a cross-sectional study on a large population of European patients with exposed and non-exposed bisphosphonate-associated ONJ; where, according to the traditional definition, only 76% of ONJ were diagnosed, and diagnosis in the remaining 24% could not be adjudicated, as they had several abnormal features relating to the jaws but no visible necrotic bone. [5] In parallel, it was demonstrated, in a large multicentre retrospective study, that the severity of ONJ (i.e. the extent of bony disease) as main guide to its management, can be correctly identified if measured by computed tomography (CT), more accurately than by clinical inspection and radiography as proposed by several staging systems, including the widely-used American Association of Oral and Maxillofacial Surgeons (AAOMS) system [6].

Very recently the AAOMS recommends changing the nomenclature of BRONJ [7]; the AAOMS favors the term *medication-related osteonecrosis of the jaw (MRONJ)*. The change is justified to accommodate the growing number of osteonecrosis cases involving the maxilla and mandible associated with other antiresorptive (denosumab) and antiangiogenic therapies.

The interesting and scientifically significant manuscripts selected for publication in this special issue include review articles, clinical studies, and research articles, which represent an important contribution to analyze and try to solve current

controversies in classification, management, and prevention of BRONJ.

In the review article "*Bisphosphonate-related osteonecrosis of the jaw: a review of the literature*" the authors offer a perspective on how dentists should manage patients on BPs, to show the benefits of accurately diagnosing BRONJ and to present diagnostic aids and treatments strategies for the condition.

The role of infection in the etiology of bisphosphonate-related osteonecrosis of the jaw (BRONJ) is poorly understood.

In the review article *"Is bisphosphonate-related osteonecrosis of the jaw an infection? A histological and microbiological ten-year summary"* the authors present a systematic review of BRONJ histology and microbiology (including demographics, immunocompromised associations, clinical signs and symptoms, disease severity, antibiotic and surgical treatments, and recovery status) validating that infection should still be considered a prime component in the multifactorial disease.

The review article *"Bisphosphonate associated osteonecrosis of the jaw: an update on pathophysiology, risk factors, and treatment"* is a narrative review of the literature; its aims are to elaborate on the pathological mechanisms behind the condition and also to gather an update on incidence, risk factors, and treatment of bisphosphonate associated osteonecrosis of the jaw.

The review article *"Imaging findings of bisphosphonate-related osteonecrosis of the jaws: a critical review of the quantitative studies"* offers a critical review of published information on the imaging strategies used for diagnosing bisphosphonate associated osteonecrosis of the jaw in patients taking intravenous bisphosphonates, pointing at the different methodologies and results of existing literature.

The existing BRONJ staging systems are numerous, but not one is surgical oriented.

In the clinical study "*New dimensional staging of bisphosphonaterelated osteonecrosis of the jaw allowing a guided surgical treatment protocol: long-term follow-up of 266 lesions in neoplastic and osteoporotic patients from the University of Bari*" a new dimensional stage classification, guiding the surgical treatment of BRONJ patients, is proposed, and the success rate of this new management is evaluated.

The most debated topic about BRONJ is therapy and the most adequate procedure is far from being standardized. Several approaches have been evaluated for the treatment of patients who developed BRONJ and many management strategies have been proposed. Nevertheless, it seems that taking preventative measures is the most effective way to face BRONJ.

In the clinical study "*Platelet rich plasma in the treatment of bisphosphonate-related osteonecrosis of the jaw: personal experience and review of the literature*" the authors considered a group of patients affected by BRONJ with nonsurgical therapy, surgical therapy, and surgical therapy with platelet rich plasma (PRP) gel to evaluate its therapeutic effect in promoting BRONJ wounds healing.

In the clinical study *"Conservative treatment of bisphosphonaterelated osteonecrosis of the jaw in multiple myeloma patients"* the authors report a retrospective review of all their MM patients who were treated with bisphosphonates and developed BRONJ and discuss management issues.

The aim of the clinical study *"Risk assessment of BRONJ in oncologic patients treated with bisphosphonates: follow-up to 18 months"* is to monitor the BRONJ level of risk in patients with cancer, according to a preventive clinical protocol, which is firstly aimed at reducing risk factors such as the periodontal infections.

In the research article *"The "CROMa" project: a care pathway for clinical management of patients with bisphosphonate exposure"* the authors describe the activity of "CROMa" (Coordination of Research on Osteonecrosis of the Jaws) project of "Sapienza" University of Rome evaluating the risk variables of patients with past, present, or planned BP exposure, treated with periodontics, oral surgery, and operative dentistry procedures in order to treat or prevent BRONJ.

We sincerely hope that the readers can enjoy this special issue and improve their knowledge about BRONJ; we wish that the articles published will encourage further research on classification, management, and prevention of BRONJ.

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The guest editors would like to thank and acknowledge all the authors and coauthors for their excellent contributions and the reviewers for their patience and cooperation.

Giuliano Ascani
Giuseppina Campisi
Luis Manuel Junquera Gutierrez

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Research Article

The "CROMa" Project: A Care Pathway for Clinical Management of Patients with Bisphosphonate Exposure

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Aim. To describe 7 years of activity of "CROMa" (Coordination of Research on Osteonecrosis of the Jaws) project of "Sapienza" University of Rome. *Materials and Methods.* A preventive and therapeutic care pathway was created for patients with bisphosphonates (BPs) exposure. Demographic, social, behavioural, pharmacological, and clinical variables were registered in a dedicated database. *Results.* In the project, 502 patients, 403 females and 99 males, were observed. Bone pathologies were 79% osteometabolic diseases (OMD) and 21% metastatic cancer (CA). Females were 90% in OMD group and 41% in CA. BP administration was 54% oral, 31% IV, and 11% IM; 89% of BPs were amino-BP and 11% non-amino-BP. Consistently with bone pathology (OMD/CA), alendronate appears to be prevalent for OMD (40% relative), while zoledronate was indicated in 92% of CA patients. Out of 502 cases collected, 28 BRONJ were detected: 17 of them were related to IV BP treatment. Preventive oral assessment was required for 50% of CA patients and by 4% of OMD patients. *Conclusions.* The proposed care pathway protocols for BP exposed patients appeared to be useful to meet treatment and preventive needs, in both oncological and osteometabolic diseases patients. Patients' and physicians' prevention awareness can be the starting point of a multilevel prevention system.

1. Introduction

Recently, an osteonecrosis of the jaws (BRONJ) has been characterized as a main side effect of bisphosphonates (BPs) therapy [1, 2].

This adverse event, first described by Marx and Stern in 2002 [3], has been characterized as nonhealing exposed bone in the mandible or maxilla [4–7] or currently defined as an area of exposed bone in the maxillofacial region that has persisted for more than 8 weeks in a patient on previous or current treatment with a bisphosphonate and without history of radiation therapy to the jaws. Despite this definition, many cases of nonexposed variant of BRONJ have been reported [8].

Mucosal swellings, redness, and purulent exudate sometimes with fistula formation are common. Often the patient complains of pain and discomfort in the mouth, bad taste, and feeding difficulties [9–12]. BRONJ condition may easily progress to severe forms with intractable pain, inability to eat, severe maxillary sinusitis, oroantral fistula, orbital abscess, extraoral fistula, involvement of the lower margin, and fracture of the mandible, especially when it affects debilitated patients [13, 14].

BRONJ has been strongly associated with prolonged use of intravenous (IV) BP (zoledronate and pamidronate) in cancer patients, while patients affected by nonneoplastic diseases and receiving BP with lower dosage or different routes of administration (oral or intramuscular) seem to incur more rarely in this adverse event.

Osteonecrosis is often related to the removal of one or more teeth, to others invasive procedures (i.e., periodontal surgery, dental implant placement, and endodontic surgery), or to local risk factors such as periodontal disease [15], but it can also occur spontaneously, without any apparent dental disease, treatment, or trauma [11].

The cumulative incidence recorded over the years by case-series, case-control, and cohort studies is highly variable, ranging from 0.8 to 12% [2, 16–24].

For patients exposed to IV BP, the rate of spontaneous occurrence is between 0.8 and 1.15%, rising to 6.67%–9.1% when invasive dental procedures are performed. In noncancer patients, the incidence is between 0.01 and 0.04%, increasing from 0.09 to 0.34% in case of dentoalveolar surgery.

Since the first reports focused on BRONJ [1], dental surgical procedures have frequently been described as triggering factors. It is well known that BRONJ can develop with dentoalveolar surgery intervention, and tooth extraction appeared to be the main precipitating risk factor, as it is seen in up to 65% of reported cases [25].

On the other hand, the presence of odontogenic infections exposes patients to considerable risk of BRONJ occurrence. Particularly, cancer patients exposed to IV BP with a history of inflammatory dental disease showed a 7-fold increased risk of developing BRONJ [5]. In fact, many of the cases reported as "spontaneous," seemingly lacking a triggering factor, may have been the result of a not detected odontogenic focus.

From this point of view, an absolute contraindication to tooth extraction in BP patients may not be advisable. Operative dentistry, endodontics, and periodontal noninvasive treatments remain the first choice to prevent and resolve odontogenic local infections, especially in patients currently or previously treated with BP. Nevertheless "hopeless" nonrestorable teeth should be scheduled for extraction also in patients already exposed to medication, above all when their presence prevents the possibility of proper prosthetic rehabilitation or predisposes to infective conditions.

Furthermore, some inflammatory conditions, such as localized severe chronic periodontitis or extensive periapical lesions from unsuccessful endodontic therapy, not always can be treated by means of elective dental treatments such as periodontal therapy or endodontic retreatment, because they are time-consuming and with uncertain prognosis. Odontogenic infections in subjects scheduled for pharmacological therapy who urgently need to start BP administration for bone malignancies or severe metabolic bone diseases should be effectively and timely addressed, and teeth with poor prognosis or at high risk of infectious complications should be scheduled for extraction.

The aim of the study is to describe 7 years of activity of the "CROMa" (Coordination of Research on Osteonecrosis of the Jaws) project of "Sapienza" University of Rome evaluating the risk variables of patients with past, present, or planned BP exposure, treated with periodontics, oral surgery, and operative dentistry procedures in order to treat or prevent BRONJ, according also to the recent Italian Ministry of Health guidelines of April 2014 [26] and SICMF-SIPMO Italian societies recommendations [27, 28].

2. Materials and Methods

2.1. The CROMa Project. At the Department of Oral and Maxillofacial Sciences of "Sapienza" University of Rome, in January 2007, a task force of clinicians and researchers set up a Coordination of Research on Osteonecrosis of the Jaws (CROMa). The counselling consists of a multidisciplinary expert group with thorough knowledge of basic and clinical bone biology as well as expertise and daily practice in the fields of preventive dentistry, oral pathology, operative dentistry, and oral and maxillofacial surgery. The aim of CROMa is to prevent or treat established BRONJ and to give relevant pieces of information and advice both to patients and to BP prescribing providers. The task force joins several experts (dentists, oral and maxillofacial surgeons, oral pathologists, oncologists, and an expert in statistics) in order to provide a comprehensive patient-centered oral care delivery.

2.2. CROMa Patients Care Pathways. Asymptomatic patients with no signs of osteonecrosis were addressed to the most appropriate dental treatment algorithm, consistently with international protocols, as updated and summarized in Table 2, according to the recent Italian Ministry of Health guidelines [26] and SICMF-SIPMO Italian societies recommendations [27, 28].

All patients, with past, current, or planned BPs therapy, followed 3 possible care pathways.

(A) prevention, (B) surgery, and (C) oral clinics.

Specifically, in the (A) path, patients received professional oral hygiene and personal oral hygiene instructions; in the (B) path, they received surgical care: dental extractions and/or surgical treatment of BRONJ were performed; hopeless teeth, being potential or actual infection sites, were treated with extractions. In the (C) path, patients were treated with operative dentistry and/or endodontics and/or periodontal treatments, supported also by various types of laser (analgesic or biostimulating low level laser therapy, surgical lasers for soft tissues, and ablative lasers for bone treatment) in order to remove or prevent odontogenic infections and/or to relief pain [29].

Patients could follow combinations of the care pathways, according to treatment needs.

All the established BRONJ were treated combining (B) and (C) pathways, in order to give necessary surgical (traditional and/or laser guided surgery) and/or biostimulating (low level laser therapy) and/or medical treatments (antibiotics, analgesics, antibacterial rinses, integrators of the immune system, etc.). All patients exposed to BP underwent clinical procedures according to international guidelines.

2.3. Diagnostic Protocol. Oral health status was assessed and the presence of jaws pathological or anatomical conditions, acting as potential BRONJ risk factors, or the finding of suspected osteonecrosis was recorded through physical examination.

For all patients, to exclude the presence of BRONJ, in addition to anamnestic notes and clinical features, laboratory tests and radiographic data, such as orthopantomographs and full periodontal radiographic exams, were harvested and examined. No bone turnover biomarkers were used, as they were judged to be not completely reliable in predicting risk [30]. In case of suspected BRONJ, to confirm diagnosis,

Table 1: 2013 SIPMO/SIMCF clinical-radiological staging of BRONJ [28].

Stage 1	**Focal BRONJ**: in the presence of at least 1 minor clinical sign or of ***bone thickening on CT limited to mandibular or maxillary dentoalveolar process****, with or without other early radiological signs.
	Minor clinical signs and symptoms: halitosis, odontogenic abscess, mandibular asymmetry, pain of dental and/or boned origin, bone exposure, mucosal fistula, postextractive mucosal healing failure, rapid onset tooth mobility, paresthesia/dysesthesia of the lips, purulent leakage, spontaneous seizure of bone fragments, trismus, and soft tissues swelling.
	Signs on CT: ***trabecular thickening, bone marrow focal osteosclerosis***, with or without thickening of the alveolar crest, postextractive socket persistence, and periodontal space flare.
	(A) Asymptomatic.
	(B) Symptomatic (presence of pain and/or suppuration).
Stage 2	**Widespread BRONJ**: in the presence of at least 1 minor clinical sign or of ***bone thickening on CT, also extended to the mandibular or maxillary basal process***, with or without late radiological signs.
	Minor clinical signs and symptoms: as for Stage 1.
	CT signs: ***widespread osteosclerosis***, with or without oroantral and oronasal fistula, thickening of the inferior alveolar nerve canal, periosteal reaction, bone seizure, and sinusitis.
	(A) Asymptomatic.
	(B) Symptomatic (presence of pain and/or suppuration).
Stage 3	**Complicated BRONJ:** as in Stage 2, in the presence of 1 or more of the following signs.
	Minor clinical signs: extraoral fistula, leakage of fluid from the nose, and preternatural mobility of the jaw with or without occlusion preservation.
	CT signs: mucocutaneous fistula, pathologic fracture, osteolysis extended to maxillary sinus, and cheekbone and/or hard palate osteosclerosis.

*Dentoalveolar bone anatomical structure that constitutes the skeletal support for the teeth. By definition, the dentoalveolar process ends in craniocaudal direction immediately below the root of the teeth.

computed tomography (CT) scans imaging and further laboratory tests were requested, as needed. Lesions were staged in the beginning according to AAOMS Position Paper 2007 [4], modified in 2009 [5]. Later, we used SIPMO/SICMF recommendations 2011 [27] and 2013 [28] (Table 1). Every new classification we adopted through these 7 years of activity has been followed by a review of our BRONJ patient collected data (radiographies, clinical chart, pictures, etc.) to make every case up to date.

2.4. Data Collection. A unified clinical chart was developed in order to collect all necessary data in a digital online database.

Age, gender, presence of systemic diseases, use of any drugs, and the main systemic and local risk factors were registered. Patients were asked for a comprehensive history concerning the use, dose, frequency, and duration of therapy with BP.

The parameters to define a patient at higher or lower risk to develop BRONJ were identified in the limit of 3 years for oral and IM BP therapy and of 8 infusions for IV BPs [24].

Only patients with past, present, or planned BP exposure were included in the CROMa project, with or without established BRONJ.

Patients have been catalogued following a chronological sequence into a Microsoft Access database, editable and searchable online by all the main components of the CROMa project.

2.5. Data Analysis. The collected samples (January 2007–March 2014) of patients were examined according to gender (male/female), age, bone disease (osteometabolic (OMD)/oncological (CA)), type of drug (amino-BP/non-amino-BP), BP active ingredient (alendronate/zoledronate, etc.), the route of administration (oral (OS)/intramuscular (IM)/intravenous (IV), or their combination), administration time (months of therapy, then divided into 2 categories for OS/IM (< or >3 years) and 2 categories for IV (< or >8 infusions)), and the timing (current, past, or planned BP therapy).

In addition, systemic and local risk factors for BRONJ and BRONJ presence and staging were also analyzed.

Data were coded and imputed into an Excel 2013 spreadsheet (Microsoft Inc., Redmond, WA, USA) and checked to verify the accuracy. Statistical analysis was performed using Stata 13.0 (San Diego, CA, USA) for the Macintosh operating system. Initially, univariate analyses were performed on the clinical condition parameters and potential risk indicators to describe the variables and distributions. Then a descriptive statistical analysis was performed. To avoid the attenuating effect of unequal variability among groups on the value of t, a square root transformation was performed when the response variable was a count. The association between BRONJ and background factors was tested using the χ^2 test.

A stepwise logistic regression model was built using the presence of at least one BRONJ lesion as the dependent variable. Gender has been identified as a modifier effect in the statistical analysis. Therefore, two different logistic models

Table 2: Oral procedures in patients with current/past or planned BP therapy [28].

Treatment		Malignancies		Osteometabolic disorders	
		Planned BF therapy	Current/past BF therapy	Planned or <3 years of NBP therapy	>3 years of NBP therapy or <3 years with risk factors for BRONJ
Dentoalveolar surgery	Extractive procedures	*Recommended* Simple extraction[1] *To wait* until mucosal healing before starting BF therapy (4–6 weeks)	*Recommended* Surgical extraction[2] *Recommended therapy suspension* from extraction day until mucosal healing (4–6 weeks)	*Recommended* Simple extraction —	*Recommended* Surgical extraction[2] —
	Preimplant surgery	Not recommended	Not recommended	Possible	Possible[4]
Implantology		Not recommended	Not recommended	Possible[3]	Possible[3,4]
Periodontal surgery	Therapeutic	Recommended[2,5] *To wait* until mucosal healing before starting BF therapy (4–6 weeks)	Recommended[2,5] *Recommended therapy suspension* from extraction day until mucosal healing (4–6 weeks)	Recommended —	Recommended[2] —
	Elective	Not recommended	Not recommended	Possible	Possible
Endodontic surgery		Recommended[2,5]	Recommended[2,5]	Recommended	Recommended[2]
Periodontal therapy (scaling/root planning)		Recommended	Recommended (every 4 months)	Recommended	Recommended (every 4–6 months)
Conservative		Recommended	Recommended	Recommended	Recommended
Endodontics		Recommended	Recommended	Recommended	Recommended
Orthodontics		Possible	Possible (recommended low orthodontic forces)	Possible	Possible
Fixed prosthesis		Possible	Possible[6]	Possible	Possible[6]
Removable prosthesis		Possible	Possible *Avoid* injuries and pressure sores, to use soft liners eventually (control of the prosthesis every 4 months)	Possible	Possible *Avoid* injuries and pressure sores, to use soft liners eventually (control of the prosthesis every 4–6 months)

[1] If BP therapy cannot be delayed, choose surgical extraction; [2] use mucoperiosteal flap for primary closure of the surgical site; [3] informed consent for not defined long-term BRONJ risk; [4] informed consent for not defined short-term BRONJ risk; [5] only for the treatment of significant infectious-inflammatory processes, not otherwise controllable using noninvasive methods; [6] respect of the biological width (control of cervical closure-possible supragingival closure).

stratified by gender were run following robust statistics (24. Wilcox RR. Introduction to Robust Estimation and Hypothesis Testing (Third Edition) Elsevier Inc. 2013). Unless stated otherwise, the criterion for statistical significance was set at $\alpha = .05$.

3. Results

From January 2007 to March 2014, 502 patients (Table 3) were included in the CROMa project, including 403 females and 99 males aged between 8 and 90 years. Bone diseases were 79% of osteometabolic type (OMD, 398 cases, of which 310 were for osteoporosis (78% rel. | 62% tot.), 54 for osteogenesis imperfecta (13% rel. | 11% tot.), and 13 for osteopenia (3% rel. | 2,5% tot.)) and 21% of oncological type (CA, 104 cases, including 34 for bone metastases from prostate cancer (33% rel. | 7% tot.), 28 from mammary cancer (27% rel. | 5% tot.), and 14 from multiple myeloma (13% rel. | 3% tot.)).

The OMD concerned 90% of women and 10% of men, while CA patients were 41% females and 59% males. The

Table 3: Data from CROMa database.

CROMa patients	502	
	Males	99
	Females	403
	Age	8–90
	Paediatric	11%
	Adults	89%
		Number
Osteometabolic diseases (OMD)	79% (398)	
	Postmenopausal osteoporosis	310
	Osteogenesis imperfecta	54
	Osteopenia	13
	Osteoarthritis	7
	Secondary osteoporosis	6
	Glucocorticoid-induced osteoporosis	3
	Fibrous dysplasia	2
	Paget's disease	1
	Other	2
		Number
Metastatic cancer (CA)	21% (104)	
	Prostate cancer bone metastasis	34
	Mammary cancer bone metastasis	28
	Multiple myeloma	14
	Renal cancer bone metastasis	11
	Pulmonary cancer bone metastasis	9
	Other	8
BP administration	BP therapy	58 (11%)
	NBP therapy	444 (89%)
	OS	54%
	IV	31%
	IM	11%
	Association	3%
Patients with no BRONJ		474 (94,42%)
Patients with BRONJ		28 (5,58%)
BRONJ from oral BP		11
BRONJ from IV BP		17

routes of BP administration were mostly oral (54%), followed then by IV therapies (31%), IM (11%), and an association of these in 3% of cases.

The active principles administered have seen in the whole group a prevalence of amino-BP drugs (89%), including alendronate (33% tot.), zoledronic acid (21% tot.), risedronate (17% tot.), neridronate (12% tot.), and ibandronate (6% tot.), compared to non-amino-BP administration (11%) represented only by clodronate.

The distribution according to bone diseases (OMD/CA) has seen alendronate as a drug of choice for OMD (40% rel.) followed by risedronate (21% rel.), while, in the other category, zoledronic acid was indicated in 92% of patients with metastatic bone cancer.

An analysis of the BP planned therapies group highlights that, out of 155 cases of IV therapy, 78 patients (50%) were referred for oral health assessment before starting the drug administration: the trend is completely different for the oral therapies (4%, 12 cases out of 270) and IM therapies (3%, 2 cases out of 60).

Out of 502 patients (Table 4), 28 differently staged BRONJ were intercepted at first examination (3 at Stage 0, 8 at Stage 1, 12 at Stage 2, and 5 at Stage 3), 17 in the CA group (16,4%), and 11 in the OMD group (2,2%). The outcome is overlapping with the therapy regimen variable (17 from IV BP administration (11% of all IV) and 11 from oral BP drugs (4,1% of all OS)). No BRONJ in our study has been related to exposition to non-amino-BP. From the logistic regression model (Table 5), we can observe how BRONJ risk in male patients is significantly connected principally to therapy intervals, while in women the risk is influenced also by behavioral habits, oncologic type of bone disease, and therapy regimen.

Table 4: Sample distribution of CROMa patients by BRONJ presence.

	BRONJ (n %)*	Healthy (n %)*	OR (95% CI)
Osteometabolic disease	11 (2,2%)	387 (97,8%)	—
Metastatic cancer	17 (16,4%)	87 (83,6%)	0.20 (0.11–0.33)
			χ^2 for trend 28.82, $P < .01$
Therapy intervals			
No therapy	1 (1%)	92 (99%)	—
<3 years	7 (3,9%)	172 (96,1%)	0.02 (0.01–0.07)
>3 years	4 (2,7%)	146 (97,3%)	0.03 (0.01–0.07)
IV < 8 infusions	2 (11,8%)	15 (88,2%)	0.13 (0.03–0.58)
IV > 8 infusions	14 (22,2%)	49 (77,8%)	0.29 (0.16–0.52)
			χ^2 for trend 41.23, $P < .01$
Therapy regimen			
Association between methods	0 (0%)	17 (100%)	—
IV	17 (11%)	138 (89%)	0.12 (0.07–0.20)
IM	0 (0%)	60 (100%)	
OS	11 (4,1%)	259 (95,9%)	0.05 (0.02–0.07)
			χ^2 for trend 4.31, $P = .04$

*The percentage (n %) is not absolute but is relative to the specific field.

Table 5: Logistic regression model (forward stepwise procedure) for BRONJ presence, stratified for gender.

(a) Male

Variable	OR	Robust (SE)	P	95% CI
Behavioral habits	.92	.15	0.62	1.07–1.39
Therapy intervals	3.14	1.01	<.01	1.68–5.89

Number of observations= 61; log likelihood= −13.27; $\chi^2_{(2)} = 24.50$; P value < .01.

(b) Female

Variable	OR	Robust (SE)	P	95% CI
Behavioral habits	1.22	.08	<.01	1.07–1.39
Oncology bone disease	17.90	14.03	<.01	3.85–83.25
Therapy regimen	2.85	1.41	.03	1.08–7.50
Therapy intervals	2.37	.73	<.01	1.29–4.32

Number of observations= 403; log likelihood= −60.03; $\chi^2_{(4)} = 33.10$; P value < .01.

Between 28 BRONJ patients, 13 were being treated with chemotherapy, 8 were receiving prolonged therapy with glucocorticoids, 4 were smokers, and 2 had diabetes.

In addition, clinical and radiological examination underlined that 6 of them had odontogenic infections, and the same percentage had poor oral hygiene and periodontal disease.

4. Discussion

The CROMa project was created with the primary intent to be a benchmark for dental patients exposed to the BP drugs or about to take them. Meticulous collection of personal, epidemiological, and clinical data has provided a fairly complete overview of the population exposed to the drug who presented to our department. Interestingly, 86% of the patients with nonintravenous BP therapy were addressed to the Department of Dentistry for a routine dental visit or for emergency dental treatments; only 4% was asked for an oral health assessment before BP administration. Overall, these patients showed poor awareness of the clinical concerns associated with BP intake, and poor information had been provided by the prescribing physician about the possibility of BRONJ occurrence after dentoalveolar surgical procedures.

On the contrary, patients with intravenous BP therapy for bone malignancies or dysplastic bone diseases showed a greater awareness and understanding of the issue and were referred to CROMa by the specialist who treated them for the underlying disease (50% were referred before IV BP therapy).

This disparity is probably due to the statistics which define a higher risk only or above all for the IV therapies.

Nevertheless, as shown by our data, the BRONJ occurrence subsequently to oral BP administration is possible, also considering the much higher number of patients exposed to oral BP administration than to the IV one. In 2005, alendronate was the 15th most prescribed drug with approximately 18 million prescriptions and risedronate was the 37th with almost 10 million prescriptions [31]. Furthermore, our study shows how BPs are prescribed even in case of osteopenia (2,5% tot.) rather than prescribing other drugs with fewer possible side effects.

Overall, data analysis shows that the most at-risk situation is in the metastatic bone cancer group, treated with IV administration of NBP, for a long therapy interval (more than 8 infusions), with females being much more represented in the OMD group, due to postmenopausal osteoporosis.

At the state of knowledge, a specific evidence-based treatment protocol for BRONJ has not been established. At present, literature provides clinician with only a few indications of possible treatment algorithms through case reports and case series. In 2013, a new clinical-radiological staging was defined, which considers also the radiographic extension of BRONJ and the further classification of Stage 1 and Stage 2 in asymptomatic (1A) and symptomatic (1B) [28].

However, as all current treatments appear to be suboptimal and no consensus has been reached on completely effective and predictable approach once BRONJ has developed, the best chances are in prevention.

The most important goal of CROMa project is specifically prevention. Currently, preventive approach is not yet common among prescribers of oral BP. Prevention should be more strongly promoted by sharing knowledge in the involved medical community and establishing a fruitful cooperation with the specialist prescriber of the BP drug, working as a team on behalf of patient.

Moreover, in our study, all the patients with BRONJ who have been treated with surgery following our protocols and algorithms have reported a relief of the symptoms and an improvement of their quality of life. No recurrence of BRONJ has been reported during the follow-ups after 4, 8, and 12 months from surgery. Furthermore, no evidence of BRONJ has been found in any OMD or CA patient during the following planned scaling/root planning treatments.

5. Conclusions

Although BRONJ is a relatively rare side effect of BP therapy, it is still an important issue for the medical community due to the severity of the condition and the lack of a thorough understanding of the pathophysiology and predisposing risk factors. An accurate delineation of the pathogenic mechanisms at the cellular and biochemical levels, as well as clinical and laboratory markers for prediction of BRONJ susceptibility in the single subject, is still lacking. From a clinical point of view, no evidence-based recommendations exist about the dental treatments that can be performed without risk or with appropriate risk-benefit ratio. Furthermore, the protocols of treatment to manage overt disease appear to be suboptimal.

The preventive and therapeutic protocols of BRONJ currently proposed appeared to be useful.

Our patients, referred by other specialists or simply intercepted during the medical history collection in the first observation unit, have been treated in order to meet their immediate needs and then to minimize BP-related risks for oral health, following the best practice preventive and treatment protocols.

Focusing on prevention, it is important that the involved medical community share knowledge and that the physicians take a conscious attitude so as to provide patients with the highest quality of oral health care, before starting BP therapy, in order to improve the care and oral health-related quality of life of patients, in both oncological and osteometabolic diseases. Prevention awareness, aided also by the networking use of an online database, can be the starting point of a multilevel prevention system.

Authors' Contribution

All authors equally contributed to this work.

Conflict of Interests

Authors declare no conflict of interests or financial support.

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Clinical Study

Risk Assessment of BRONJ in Oncologic Patients Treated with Bisphosphonates: Follow-Up to 18 Months

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Objectives. Bisphosphonates related osteonecrosis of the jaw (BRONJ) is a pathological condition characterized by bone exposure or latent infection in patients treated with the drug. The aim of the study is to monitor the BRONJ level of risk health in patients with cancer, according to a preventive clinical protocol, which is firstly aimed at reducing risk factors such as the periodontal infections. *Materials and Methods.* 10 patients participated in the protocol and were evaluated at baseline and after 3 and 18 months of treatment with bisphosphonates, through full mouth plaque and bleeding scores (FMPS and FMBS), clinical attachment level (CAL) measurement, and the occurrence of osteonecrosis. *Results.* The mean plaque and bleeding were reduced and the CAL has not shown significant changes and in no cases was there manifestation of BRONJ. *Conclusion.* The protocol proved crucial for the maintenance of good oral health conditions by eliminating the risk of BRONJ during the observation period.

1. Introduction

Bisphosphonates are a group of drugs widely recommended and used for the treatment of moderate and severe hypercalcemia associated with cancer, for osteolytic lesions associated with metastases of breast cancer, prostate cancer, or multiple myeloma in combination with other chemotherapeutic agents. They are also used in the prevention and therapy of osteoporosis in postmenopausal women and also in the treatment of Paget's disease [1, 2].

These drugs are completely resistant to the hydrolytic cleavage, whereby this is the reason why they accumulate in the bone tissue and have a long half-life. Their rapid uptake in bone matrix allows an accumulation that goes from 30 to 70% of the administered intravenous dose or that absorbed after oral intake, while the remaining fraction is excreted unchanged into urine.

The accumulation of bisphosphonates in the bone, in particular in maxillary bones, is not reversible. Their toxic effect on osteoclasts depends on both the dose administered and the duration of therapy. The intravenous administration of high doses of aminobisphosphonates (N-BF), that is, the bisphosphonates of last generation containing nitrogen in the side chains, can cause the onset of necrosis of the jaw bone and/or of the mandibular bone [3, 4].

This pathology was identified with the acronym BRONJ (bisphosphonates related osteonecrosis of the jaw). It is a pathological condition described for the first time in 2007 [5] and in 2009 the AAOMS underlined that the presence of BRONJ is also discernible in the absence of bone exposure clinically detectable, by introducing a new stage of the disease: "stage 0" [6].

In 2012 Bedogni et al. [7] defined the BRONJ as an adverse reaction that is drug related, characterized by the destruction

and necrosis of the jaw/maxillary bone in subjects treated with aminobisphosphonates, with no previous radiation treatment. On the basis of the recommendations published by the SICMF-SIPMO 2013 [8] "stage 0" was deleted by replacing in the other stages all cases without bone exposure.

The therapy of BRONJ is currently still a dilemma. In the literature unequivocally effective treatments have not been reported, and discontinuation of therapy with N-BF does not involve the healing of necrotic disease. The surgical approach, when indicated, is very aggressive and sometimes can cause a widening of the areas of bone exposure and amplify the symptoms.

The preventive approach is certainly the best way to avoid the onset of the disease. Particularly important in the prevention of BRONJ is the cofactors evaluation, that in the absence of bisphosphonates do not lead to the onset of the disease.

The knowing of BRONJ risk factors can be very helpful in planning a protocol. As suggested in the recommendations of the SICMF-SIPMO (Italian Society of Maxillofacial Surgery and Italian Society of Pathology and Oral Medicine), we do not yet have definitive data; certainly, taking the molecule N-BF is an high risk factor as well as the way of the administration: indeed, the risk increases in proportion to the dose administered intravenously.

Besides the cancer disease, which requires the recruitment of the molecule, seems to have a correlation with the increase of the risk. Another risk factor of BRONJ is the supporting therapy with antiangiogenics or with steroids. (Even if steroids are not able to produce osteonecrosis, they are undoubtedly cytotoxic and have an effect on the synthesis of collagen and then consequently wound healing. They also increase the toxicity factor of bisphosphonates.)

The local risk factors have also a relevant role; it is just in their knowledge that many of prevention strategies is based. On the basis of the data reported in the literature [8] the dentoalveolar surgery is the most important risk factor followed by the osteointegrated implants; the dentoperiodontal or peri-implant pathology is only the third one.

Among the local risk factors, periodontal diseases have a particular relevance. It is an inflammatory process induced by bacteria, causing an alveolar bone remodeling [9]; it strikes the adult population with a frequency of 90% [10]. In the case of recruitment of N-BF there is an inhibition of the resorption process in favour of a bone necrosis.

A recent study with rats [11] showed that, after administration of a dose of zoledronic acid, corresponding to the one accumulated in humans oncology therapies, and after inducing experimentally periodontal disease with sterile ligatures, the periodontal diseases, associated with the recruitment of zoledronic acid, are a necessary and sufficient condition to develop BRONJ.

The aim of this work has been to reduce the level of risk of BRONJ in patients with cancer and in therapy with aminobisphosphonates, before the recruitment, through a protocol targeted in a particular way at control of periodontal disease and the maintenance of oral health.

2. Materials and Methods

The recruitment of patients occurred at the Surgical and Special Stomatology of the Neurological Medical Sciences Department, in the "Ospedali Riuniti" Hospital of Ancona, in the period from January 2012 to October 2012.

Since 2001 the structure adopts a protocol for the prevention of osteonecrosis (Table 1) [12, 13] in cooperation with the oncology, surgery, clinical medicine, and endocrinology division as synthetically reported:

(i) dental treatment before the therapy (phase I),

(ii) dental treatment during the therapy, without bone disease (stage II), with bone necrosis (phase III),

(iii) follow-up to 1 month–6 months.

This protocol is similar to the one proposed in the SICMF-SIPMO recommendations [8] updated to 2013 on the basis of the latest scientific evidences, in which it is possible to identify different paths depending on the type of patient and on the time in which it was intercepted. In the case of patients that have yet to start the recruitment of the drug it provides a path comparable to that described in Table 1 for phase I.

One of the main aspects, that comes out in all stages of this path, is the professional and the home oral hygiene care aimed at achieving and maintaining a state of health. The protocol has received the approval of the Marche Region Ethics Committee and is carried out in accordance with the ethical standards approved by the Declaration of Helsinki in 1964.

In 2012 43 oncology patients taken in care presented the following: 14% with lung cancer, 42% breast cancer, 23% multiple myeloma, 7% prostate cancer, and 7% bone metastases. The remaining 7% included oral carcinoma and cancer of the bladder, kidney, and colon. All patients read and signed, after careful and detailed verbal explanation, an informed consent included in the protocol of the department. In this standard format is also specified a consent to any use of the clinical data collected for scientific purposes.

All the patients were subjected to a dental visit (anamnesis; objective examination of intraoral and extraoral environment; assessment of removable prostheses; radiographic examinations) and were informed on the issues relating to the risk of the occurrence of BRONJ in relation to the level of oral health.

Carrying out a risk assessment was necessary to identify the BRONJ predisposing factors. For this purpose, each patient was subjected to questions about the diagnosis of cancer, the type and dosage of the drug administered, duration of therapy, and the presence of other drugs associated with the dental history and the oral habits (Table 2) [12].

For the present prospective study, patients were selected within 43 oncology patients, taken in care in 2012, and by considering the following inclusion criteria:

(i) people of both sexes,

(ii) patients who must begin therapy with N-BF due to cancer or metastases,

(iii) adults above the age of 30 years,

Table 1: Clinical protocol for the integrated care for oncology patient implemented from 2001 in Surgical and Special Stomatology Division—Ospedali Riuniti Hospital of Ancona [12, 13].

Protocol for the integrated care for oncology patient			
Diagnostic section	Anamnesis Clinical examination Oral radiographic Indices of oral health Periodontal status Photographic documentation		
Therapeutic section	Treatment before starting N-BF therapy step 1 (i) First visit (ii) RX exams (iii) Tooth extractions, endodontics, and restorative (iv) Professional oral hygiene and education about the oral hygiene at home (v) Prophylaxis of caries (vi) Instructions about complications and awareness of the problem	Treatment during N-BF therapy steps 2 and 3 (i) Adaptation of symptomatic and preventive therapy—follow-up oral hygiene to 15gg—1 month (ii) Follow-up tissues and clinical signs at 3-4 months	Follow-up Oral health evaluation and professional hygiene symptomatic therapy of the secondary effects—prophylaxis of caries 1–3 months—follow-up to 1–6 months

Table 2: Information to identify the risk factors for the development of BRONJ [12].

Risk factors	Description
Diagnosis of malignant neoplasia	(i) Type of cancer (ii) Presence of metastases and localization previous therapy (surgery, radiotherapy)
Drug administered	(i) Type (ii) Total dosage (iii) Recruitment (iv) Timing of therapy
Other drugs	(i) Corticosteroids (ii) Antiangiogenic
Oral history	(i) Traumas (ii) Surgical procedures (iii) Dental and gum infections (iv) Diagnosis of periodontal disease (v) Implantology (vi) Prosthesis
Oral hygiene	(i) Daily home care (ii) Annual frequency professional care (iii) Motivation and information level

(iv) complete or partial teeth,

(v) no manifestation of osteonecrosis,

(vi) no radiotherapy of cervicofacial district.

Patients with the following were excluded:

(i) total edentulous,

(ii) precarious conditions of general health (elderly patients very debilitated, patients undergoing recent surgical therapies, patients with nutritional deficiencies, patients with immune deficiency, and people who have cardiac and/or respiratory serious compromises),

(iii) lack of collaboration,

(iv) bisphosphonates therapy in act (phase II),

(v) clinical manifestation of BRONJ,

(vi) no oncological diseases.

A decisive inclusion criterion of the study was the possibility to follow the patient throughout the period of observation at the hospital. In fact in most cases, once the phase I, the patient is entrusted to the territory for monitoring and maintenance.

After the visit (T0), all the patients were subjected to the following.

(i) Assessment of the visible plaque index [14] (in this text abbreviated with the acronym FMPS, i.e., Full Mouth Plaque Score, so called by Tonetti and his collaborators in 2002) and of the dichotomous bleeding index [14] (abbreviated form now on as FMBS), both drafted, as suggested by the international scientific literature, noting the positive sites and putting them in relationship with all of the sites examined.

(ii) Assessment of the clinical attachment level (CAL); involvement of furcations; degree of dental mobility.

(iii) Professional oral hygiene care.

All patients were instructed to perform correctly the oral hygiene at home, with particular attention to use nontraumatic tools and their association with mouthwashes that are alcohol-free.

Table 3: Type of drug, administrations, and doses linked to systemic pathology.

Pathology	Drug	Dosage
Lung cancer + bone metastases	Zoledronate	4 MG × 3 administrations every 28 days
Prostate + bladder cancer + bone and lymph node metastases	Zoledronate	4 MG × 3 administrations every 28 days
Breast cancer + bone metastases	Zoledronate	4 MG × 3 administrations every 28 days
Breast cancer + bone and lymph node metastases	Zoledronate	4 MG × 3 administrations every 28 days
Lung cancer + bone metastases	Zoledronate	4 MG × 5 administrations every 28 days
Breast and colon cancer + bone metastases	Ibandronate	2,5 mg by os/day
Breast cancer + bone and lung metastases	Zoledronate	4 MG × 3 administrations every 28 days
Breast cancer + bone metastases	Ibandronate	2,5 mg by os/day
Breast cancer + bone metastases	Zoledronate	4 MG × 3 administrations every 28 days
Breast cancer + bone, pulmonary and hepatic metastases	Zoledronate	4 MG × 3 administrations every 28 days

There were also addressed the issues related to Hyposialism caused by the imminent pharmacology therapy: salivary substitutes, feeding and risk of caries, on the basis of a clinical protocol already existing [13].

Three sessions of maintenance and monitoring of oral health were made: (a) during therapy (T1); (b) at the end of the treatment with N-BF (T2) in which patients were subjected again to a session of professional oral hygiene care and to a reinforcement of education on oral hygiene care at home; (c) after 18 months from the start of therapy with N-BF (T3). The last phase included new probing and CAL, FMPS and FMBS reevaluation, and tissues and clinical signs control to exclude the occurrence of BRONJ. The data collected have been discussed and compared with the help of graphic representations. The CAL average was obtained through the use of software for the mathematical calculation.

For ethical reasons it was not possible to form a group of patients for the control.

3. Results

Out of 43 patients, 15 patients, belonging to phase 1 in 2012 and satisfying the criteria described above, were included. Due to a subsequent aggravation of the general state of health, 3 people have abandoned the study; 2 died during the observation period.

The 10 remaining patients, 7 females and 3 males, were aged between 38 and 78 years (50% over 70 years, one person less than 40 years, and 40% between 38 and 70 years) and all were to start therapy with N-BF for metastasis. The primary systemic pathology was breast cancer in 70% of the cases (7 women); two persons showed metastasis on colon and bladder.

Eight patients had to begin the periodic administration of intravenous zoledronic acid (Zometa), from 3 to 5 cycles every 28 days; 2 patients had to begin the ibandronic acid (Bondronat) by oral administration. All have completed the therapy with bisphosphonates. Six people have received the dose of 4 mg of zoledronate, pharmaceutically acceptable as a reconstituted and further diluted infusion (diluted with 100 mL of saline 0.9% w/v solution or glucose (5% w/v)), in at least 15 minutes for 3 administrations every 28 days; 1 patient received 4 doses every 28 days, and 1 person received 5 administrations of the drug with the same dosage and frequency.

Two patients have received an ibandronate daily dose of 2.5 mg per oral administration throughout the observation period (Table 3). In addition 2 patients were also subjected to chemotherapy, 2 patients were subjected to administration of corticosteroids, and 4 patients have carried out radiotherapy, at the end.

The main preexisting dental pathology proved to be the generalized chronic periodontitis and, in fact, it is present in 70% of patients. In one case apical granulomas were detected and a couple of patients also showed radicular residues.

The initial level of risk of the subjects is described in Table 4: all patients were considered at high risk of developing BRONJ. This evaluation was carried out on the basis of the high dosage of drug taken during the period of observation and on the conditions of oral health detected during the first visit.

In the first visit (T0), 4 patients out of 10 had a level of oral hygiene, expressed with the index FMPS, higher than 90%, 5 showed percentages ranging between 40 and 70%, and only one patient had a visible plaque index of 24%; the average index was 73%.

Nine people needed a tooth extraction and all were subjected to one or more sessions of professional oral hygiene before starting therapy with N-BF.

In the second control (T1), 3 months after the start of therapy, the average of the FMPS has suffered a considerable reduction coming to 50%. Only two patients have participated after 6 months in a further follow-up (T2) expressing an average percentage of 36% FMPS. The last control, performed 18 months from the beginning of therapy (T3), has been

Table 4: Risk evaluation to T0 (bold = high risk, italic = low risk, and bold italic = not definable risk).

		P. 1	P.2	P.3	P.4	P.5	P.6	P.7	P.8	P.9	P.10	
Aminobisphosphonates molecule	**Zoledronate**	X	X	X	X	X	X	X	X			Not changeable risk factors
	Ibandronate									X	X	
Other medicines/therapies	**Subsequent chemotherapy**			X		X						
	Subsequent radiotherapy				X			X	X		X	
	Concomitant corticosteroids administration	X	X									
Administration	**Intravenous**	X	X	X	X	X	X	X	X			
	Oral									X	X	
Systemic factors	**Presence of cancer**	X	X	X	X	X	X	X	X	X	X	
Local risk factors	**Periodontal pathology**	X	X	X	X	X		X			X	Modifiable risk factors
	Dental pathology	X	X		X	X	X	X	X	X	X	

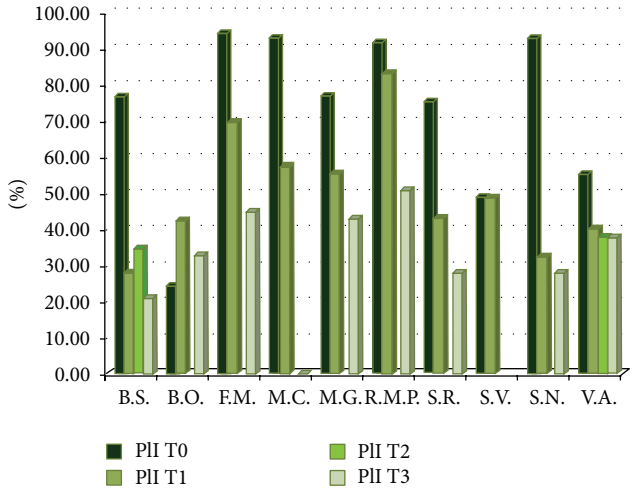

Figure 1: FMPS detected before the start of therapy (T0) and 3 months (T1), 6 months (T2), and 18 months (T3) after. The patient S.V. died before the follow-up at 18 months.

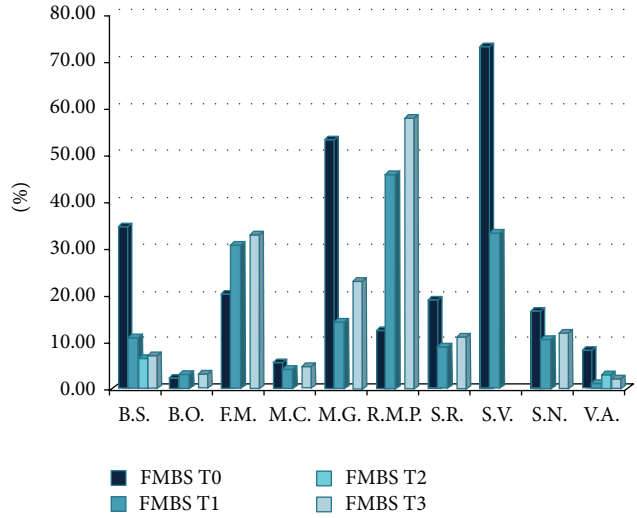

Figure 2: FMBS detected before the start of therapy (T0) and 3 months (T1), 6 months (T2), and 18 months (T3) after. The patient S.V. died before the follow-up at 18 months.

detected on 9 patients because of a supervening death. The plaque index average was 29%. Figure 1 shows the evolution of the 10 patients in the time of observation. The gingival inflammation, expressed through the FMBS, shows a sample less homogeneous with respect to the oral hygiene level.

At the first visit two patients had a FMBS greater than 50%; six out of 10 people had a percentage lower than 20% and the average is 24%. Subsequent checks showed, at 3 months, a FMBS average of 16%; at 6 months the two patients monitored had an average less than 5% and at 18 months the average of 9 people was 15%. Figure 2 shows the overall trend of FMBS in the sample examined.

The periodontal exam has highlighted the presence of a periodontal impairment with loss of clinical attachment (CAL) in all the patients: range of 2 to 4.5 mm, average of 3.15 mm. At the first follow-up the CAL average dropped to 2.9 mm and in the last control (18 months) it was 2.8 mm (Figure 3).

The last visit (follow-up at 18 months) was made through clinical examination and radiographic examination and revealed the total absence of signs of osteonecrosis in all patients.

4. Discussion

Osteonecrosis today affects about 20,000 people a year [15]. The BRONJ are complications that affect 2.8% of patients who receive N-BF for bone metastases of breast cancer [16]. The sample selected for this study, although small, is therefore representative of the most risk of osteonecrosis.

On the basis of the first reports, the literature identified BRONJ only in relation to oral surgical access to the maxillary bones (extractions) [16, 17]. Today it tends to emphasize the importance of the presence of periodontal disease, latent or not fully treated, such as infection triggers of BRONJ [18–20].

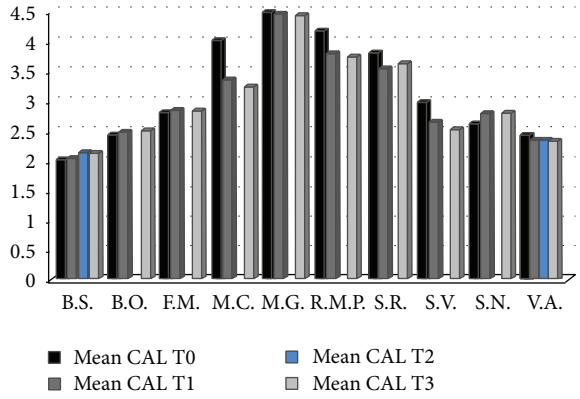

Figure 3: CAL average before and during therapy and type of drug administered.

In all cases of BRONJ treated by Marx et al. [4], the 25% of the lesions were found to be arising spontaneously, while 75% were engendered by some type of dental invasive procedure. More precisely, Marx indicates that, in 152 patients with BRONJ, more than a third, a trigging factor was due to tooth extractions. Of these, about half, was caused by periodontal disease, of which 26% was represented by untreated parodontitis, and in 25% of the cases, it seemed to be a manifestation of the osteonecrosis which the author calls "spontaneous." The latter confirmed the hypothesis that there is no doubt that the subclinical osteonecrosis also exists [21] even if there is no bone exposure. This justifies the assertion of many authors that the prevalence of BRONJ has not yet been established and its pathogenesis is not entirely clarified [18].

In the present study, the first visit revealed in all the patients the presence of oral preexisting diseases and the most popular is periodontitis [22]. The presence of this disease, manifest or latent, associated with bacterial plaque and calculus and inadequate oral hygiene; it can certainly be regarded as a serious risk factor for the onset of BRONJ [23].

The risk of developing BRONJ for these patients, in phase 1 of the protocol (T0), was judged to be very high especially in relation to the high dose of the drug taken during the period of observation and to the conditions of oral health detected during the first visit.

Optimizing oral health should therefore be the primary objective; teeth that are not treated or teeth with a poor prognosis must be extracted by delaying the start of therapy with N-BF at least 4–6 weeks to ensure complete healing of the tissues. Patients should be instructed on the importance of good hygiene at home and motivated to undergo regular checks of monitoring and maintenance.

After the first preventive intervention (T0) Figure 1 shows a general progressive reduction of the plaque index.

It is necessary to emphasize that the sample is composed of elderly people. It was possible to confirm a general improvement in the level of oral hygiene even if the educational intervention in these patients is very difficult, not only because of the age but also because often their interest is focused on pain, on the therapies that must be undergone, on emotional factor that comprises the concern for the sick, and on the outcome of care.

Most patients, during the administration of the drug, have suffered from fever, severe joint pain, general malaise, and gastrointestinal problems with consequent general debilitation. Such symptoms are immediately manifested after administration and are attenuated during the following days. In this context to speak about toothbrush and proxabrush may seem irrelevant. A correct psychological approach and respect of each patient's limits should be necessary.

At T1 the FMPS and FMBS percentages decreased, except some exceptions. In two cases the bleeding index, in the second control, resulted higher than those on the first check; it is not to exclude an effect of the drug on gingival tissue.

As regards the CAL, in the subsequent controls, differences are not significant (Figure 3) but they show the slight packaging of tissues following the periodontal therapy. It could indicate a constant maintenance of the level of periodontal health and the absence of periodontal pockets or latent osteonecrosis.

In three patients showing a greater reduction of CAL from T0 to T1, it is reasonable to assume a reduction in the depth following the professional oral hygiene. There seems to be no difference between patients who were taking N-BF intravenous and by oral administration.

The data collected show that patients observed in T0 showed a high level of risk disease; this risk was significantly reduced once included in the protocol of prevention of BRONJ. These considerations justify the result reached after 18 months, when the follow-up evaluation shows patients with good oral health and total absence of BRONJ.

5. Conclusions

BRONJ represents an unwanted complication of N-BF and its prevention begins with the close cooperation of the following specialists: oncologist, rheumatologist, maxillofacial surgeon, dentist, and dental hygienist.

In the light of the data and clinical observations reported in the present study, it is conceivable that the protocol applied and described above has been important in cancelling the incidence of the disease in the group of patients examined, that is, group considered at high risk of BRONJ.

Today the occurrence of BRONJ is calculated on the bases of retrospective studies putting it in a range from 8% to 11% [24], but these percentages are increasing. The low number of observed patients and the lack of a group of control (excluded from protocol for ethical reasons) call for further depths even if this work suggests the big importance of the preventive approach.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper and that they have not received funding for this study.

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Review Article

Bisphosphonate Associated Osteonecrosis of the Jaw: An Update on Pathophysiology, Risk Factors, and Treatment

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Osteonecrosis of the jaw in patients treated with bisphosphonates is a relatively rare but well known complication at maxillofacial units around the world. It has been speculated that the medication, especially long-term i.v. bisphosphonate treatment, could cause sterile necrosis of the jaws. The aim of this narrative review of the literature was to elaborate on the pathological mechanisms behind the condition and also to gather an update on incidence, risk factors, and treatment of bisphosphonate associated osteonecrosis of the jaw. In total, ninety-one articles were reviewed. All were published in internationally recognized journals with referee systems. We can conclude that necrotic lesions in the jaw seem to be following upon exposure of bone, for example, after tooth extractions, while other interventions like implant placement do not increase the risk of osteonecrosis. Since exposure to the bacterial environment in the oral cavity seems essential for the development of necrotic lesions, we believe that the condition is in fact chronic osteomyelitis and should be treated accordingly.

1. Introduction

The first report describing osteonecrosis of the jaw (ONJ) in patients receiving bisphosphonates came 2003 [1]. Since then this condition, sometimes called BRONJ (bisphosphonate-related osteonecrosis of the jaw), has shown increasing interest by dentists and oral-maxillofacial surgeons. It is defined as an area of exposed bone in the maxillofacial region that does not heal within 8 weeks in a patient who is currently receiving bisphosphonate medication and has not had radiation to the head-neck region. The diagnosis is usually made clinically. It is believed mainly to be associated with high dose intravenous bisphosphonate therapy, but sometimes the condition occurs also in patients with low-dose osteoporotic treatment. The current perception among dentists and oral-maxillofacial surgeons seems to be that low-dose bisphosphonate treatment for osteoporosis is linked to an increased incidence of ONJ, while on the other hand endocrinologists may suggest increased prescribing to decrease the incidence of osteoporotic fractures. This review aims to elaborate on the pathogenic mechanisms behind bisphosphate associated necrosis of the jaw and incidence, prevention, and treatment of the condition.

2. Methods

The present paper is authored as a narrative review contribution. Data synthesis and analysis: the articles were picked and sorted according to their corresponding key area of focus.

3. Results

Ninety-one studies were included, consisting of 9 reviews, 79 original papers, 2 letters and 1 thesis.

4. Discussion

4.1. Structure and Bioactivity of Bisphosphonates. Bisphosphonates (BPs) are antiresorptive drugs that act specifically on osteoclasts, thereby maintaining bone density and

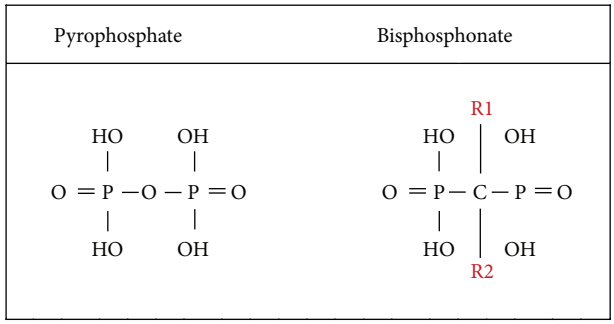


Figure 1: Chemical structure of pyrophosphate and bisphosphonate. R1 and R2 signify the side chains of bisphosphonate.

strength [2]. The drug is used for many indications including prevention and treatment of primary and secondary osteoporosis, hypercalcaemia, multiple myeloma, and osteolysis due to bone metastases and Paget's disease [3, 4]

BPs act on both osteoblast and osteoclasts. It has been shown *in vitro* that BPs promote proliferation and differentiation of human osteoblast-like cells [5] and inhibit osteoclasts. The BPs are synthetic analogs with a P–C–P bond instead of the P–O–P bond of inorganic pyrophosphates, which are used as a bone-specific radionuclide in technetium 99 m methylene diphosphonate (Tc 99 m MDP) bone scans. Unlike pyrophosphates, bisphosphonates are resistant to breakdown by enzymatic hydrolysis, which explains their accumulation in the bone matrix and their extremely long half-life [6]. The P–C–P structure (Figure 1) allows a great number of possible variations, especially by changing the two lateral chains (R1 and R2) in the carbon atom. The two phosphate groups are essential for binding to the bone mineral such as hydroxyapatite and together with the R1 side chain they act as a "bone hook." A hydroxyl (OH) group or amino group at the R1 position increases the affinity for calcium and thus for bone mineral [7, 8] Figure 1.

The structure and three-dimensional conformation of the R2 side chain determine the antiresorptive potency and the enhanced binding to hydroxyapatite [7, 9].

It is known that bisphosphonates containing a basic primary nitrogen atom in an alkyl chain such as alendronate are 10–100 times more potent at inhibiting bone resorption than earlier generation BPs like clodronate which lack this feature. Compounds that contain tertiary nitrogen such as ibandronate and olpadronate are even more potent at inhibiting bone resorption. Risedronate and zoledronate are among the most potent BPs, containing a nitrogen atom within a heterocyclic ring [10].

The gastrointestinal uptake of orally administrated BPs is low with a bioavailability of 0.3–0.7% [11, 12]. The poor absorption of BPs can probably be attributed to their very poor lipophilicity which prevents transcellular transport across epithelial barriers. Consequently BPs must be absorbed by the paracellular route, which means passage though the pores of tight junctions between the epithelial cells.

Bisphosphonates are completely ionized in blood at physiological pH (7.4). Therefore, plasma protein binding is high, expectedly as ion binding. Lin and coworkers [13] demonstrated that, in rats, alendronate binds to serum albumin and this binding seems to be dependent on serum calcium-levels and pH. Plasma protein binding in human has been found to be less with alendronate showing an unbound fraction 22% compared to 4% in rats [13].

Intravenous administration of a single dose of alendronate leads on the other hand to rapid accumulation of this drug in bone tissue, approximately 30% in 5 min and 60% in 1 hour [14]. The half-life in plasma is 1-2 hour and this rapid elimination is due to bone uptake and renal clearance. Once incorporated into the bone, bisphosphonates are liberated again only when the bone in which it was deposited is resorbed. Therefore the rate of the bone turnover influences the half-life of this drug [15].

The distribution of BPs in bone is determined by blood flow and favours deposition at sites of the skeleton undergoing active resorption [14].

Neither orally nor intravenously administrated BPs are metabolized in humans [16].

4.2. Mechanism of Action. During bone resorption, bisphosphonates impair the ability of the osteoclasts to form the ruffled border, to adhere to the bony surface and to produce the protons necessary for continued bone resorption [17–19].

Following cellular uptake, a characteristic morphological feature of bisphosphonate-treated osteoclasts is the lack of a ruffled border, leading to reduced adhesion to the bony surface. Bisphosphonates also promote osteoclast apoptosis by decreasing osteoclast progenitor development and recruitment [20]. Nevertheless, following exposure to certain bisphosphonates, inhibition of the osteoclast proton pumping H-ATPase phosphatases and lysosomal enzymes could also contribute to the loss of resorptive capacity of osteoclasts [21, 22].

Clodronates are the first generation, nonnitrogen-containing bisphosphonates which entered osteoclasts, incorporated into nonhydrolyzable analogues of adenosine triphosphate (ATP) and converted into methylene-containing (AppCp type) analogues of ATP. Accumulation of these toxic by-products interferes with mitochondrial function and ultimately leads to apoptosis of osteoclasts [23, 24].

In contrast, nitrogen-containing bisphosphonates (such as zoledronate and pamidronate) act by inhibiting farnesyl pyrophosphate (FPP) synthase and geranylgeranyl pyrophosphate (GGPP) synthase, two key enzymes in the mevalonate pathway. As a consequence, the disruption of the mevalonate pathway by nitrogen-containing bisphosphonates results in impaired protein prenylation and activation av small GTPases such as Ras, Rho, Rac, and Cdc42. The small GTPases are important signalling proteins regulating osteoclast morphology, cytoskeleton arrangement, membrane ruffling, and trafficking and cell survival [10, 25].

It has been suggested that another target of BPs could be the osteoblast, which in turn influence the osteoclasts. It has been shown experimentally that BPs inhibit the expression of receptor activator of NF-kappa B ligand (RANK-L) in rat osteoblast cells and increase the expression of osteoprotegerin

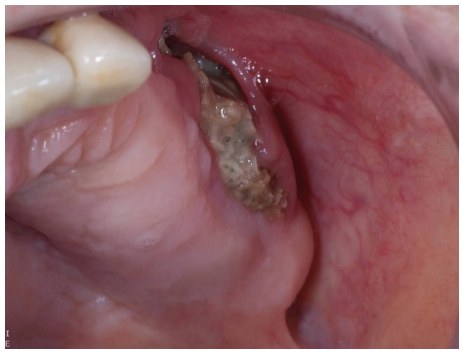


Figure 2: Exposed necrotic bone after tooth extractions in a patient treated with i.v. zoledronic acid.

(OPG) in human osteoblastic cells, suggesting that the antiresorptive effect of BPs is mediated by influence of osteoblasts on RANK-L signalling [26, 27].

4.3. Systemic and Local Delivery of Bisphosphonates. Several experimental studies showed that systemic bisphosphonates reduced alveolar bone loss [28–30]. In animal models, several investigators have shown that surface-immobilized bisphosphonates improve mechanical fixation of metal screws in terms of an increased bone-to-implant contact and pullout force [31–35]. Single systemic infusion of zoledronate has shown promising results on initial fixation of cementless orthopaedic implants [36, 37].

Local application of BPs during total joint surgery has been shown to reduce migration of metal prostheses as measured by radiostereometry [38].

In a recent series of randomized controlled trials, local treatment of periodontitis with a gel containing a very high concentration of alendronate was successful in regenerating a large part of lost bone, whereas placebo had little effect [39–41].

In the randomized study of 16 patients, a thin bisphosphonate-eluting fibrinogen coating improved the fixation of dental implants in human bone Abtahi et al. [42]. The efficacy of the topical administration of bisphosphonates in implant therapy has been investigated by Zuffetti et al. [43]. By the 5-year follow-up, no implant failure had been recorded in test group.

4.4. Osteonecrosis of the Jaw (ONJ). Historically, osteonecrosis of the jaw (ONJ) was first reported by occupational exposure to white phosphorus which was called "*phossy jaw*" [44, 45]. ONJ has also seen in osteopetrosis, a rare inherited disease with impairment of bone resorption and remodeling [46]. More recently, ONJ is defined as a complication of head and neck radiotherapy [47]. The definition of ONJ is nonhealing exposed jawbone for more than 8 weeks in patients receiving BPs and without any local radiation therapy. Clinically, the disease presents as exposed alveolar bone that becomes evident following a surgical procedure such as tooth removal or periodontal therapy [48, 49] Figure 2.

Signs and symptoms that may occur before the development of clinically detectable osteonecrosis include pain, tooth mobility, mucosal swelling, erythema, and ulceration. The incidence of ONJ in bone malignancy cases, mainly treated with high dose intravenous bisphosphonates, is about 1–12% [48, 49].

Wang and coworkers [50] found that the incidence of ONJ was at least 3.8% in patients with multiple myeloma, 2.5% in breast cancer patients, and 2.9% in prostate cancer patients. In osteoporosis, bisphosphonate associated osteonecrosis of the jaw is rare and the incidence may not be greater than the natural background incidence. Epidemiological studies have indicated an estimated incidence of less than 1 cases per 100 000 person-years of exposure to oral bisphosphonates.

4.5. Pathogenesis. The etiology of ONJ remains uncertain. Initially, when the condition was called bisphosphonate-related osteonecrosis of the jaw (BRONJ) [48] its similarities with radiation-induced osteonecrosis led to the assumption that the condition started with sterile necrosis of the jaw bone. Therefore, the term osteonecrosis was used otherwise reserved for sterile bone death usually because of impaired blood supply. At that time, it was speculated that BPs could cause osteonecrosis through effects on blood vessels in bone, possibly by inhibition of vascular endothelial growth [51].

Later, it has been suggested that the condition does not begin as a form of classical osteonecrosis but in fact osteomyelitis from the start [52, 53].

Bacterial contamination with *Actinomyces* and *Staphylococcus* may play a role in maintaining osteomyelitic wounds and because maxillofacial bone tissue containing BPs will resorb slowly, it is conceivable that contaminated bone cannot be removed fast enough to prevent the development of chronic osteomyelitis. This view is supported by the fact that similar lesions appear after treatment with anti-RANK-L antibodies that reduces osteoclast recruitment [54]. Thus, it appears that reduced resorptive activity is a key factor behind the impaired healing capacity of these lesions [55].

We suggest that the term BRONJ should be avoided and replaced by the term bisphosphonate associated osteomyelitis of the jaw, BAOJ, which better reflects the conditions aetiology.

Antibiotics can prevent the development of ONJ-like lesions in a rat model [56]. One hundred twenty animals underwent tooth extraction and received combination of dexamethasone and pamidronate during different time periods. Animals which received the same treatment except for the addition of penicillin showed four times less ONJ-like lesions than the other group. There is no clinical study on the use of antibiotics associated with ONJ. However, in the clinical situation antibiotics has its use since the condition is considered osteomyelitis of the jaw.

The antiangiogenic role of bisphosphonate is still unclear and ONJ proceeds despite the use of antibiotics in some cases. One explanation could be the fact that bacterial contamination maintains chronic osteomyelitis of the jaws. Another explanation is perhaps the reduced microcirculation of the gingiva causing the soft tissue unable to heal.

Corticosteroids and chemotherapeutics have been suggested as factors that can predispose to ONJ or increase the risk of developing ONJ; the duration of BP therapy also appears to be related to the likelihood of developing necrosis with longer treatment regimens associated with a greater risk [55]. The time to develop osteonecrosis after i.v. zoledronate treatment was in mean 1.8 years, after i.v pamidronate 2.8 years and after oral BP therapy, like alendronate, the mean time was 4.6 years [57].

Numerous studies have explored the toxic effect of BPs on a variety of epithelial cells [58–62]. There is clear documentation of bisphosphonate toxicity to gastrointestinal epithelia [63]. It has been suggested that high concentrations of bisphosphonate in the oral cavity (bone tissue) disrupt the oral mucosa [64]. Failure of healing of the soft tissue may cause secondary infection of the underlying bone. However, this theory has not yet been accepted by investigators. Recently, in a rat model of ONJ, following tooth extraction a high dose of alendronate (200 μg/kg) did not cause ONJ-like lesions [65]. When calculated as dose per body weight per day, the rat dose was 100 times higher than the human dose.

4.6. Clinical Characteristics. Blood supply to the cortical bone is derived from the periosteum and exposed bone surface is indicating necrosis in the underlying bone layers. The condition can then progress into a more severe bony lesion with nerve disturbances, mobile teeth, fistulas, and in the end fracture [66]. Pain is common and these signs and symptoms are often evident in patients with jaw bone osteomyelitis that are not on BP treatment. Radiographs may show sclerotic bone, sclerotic lamina dura around individual teeth, and widened periodontal ligaments but there are no report published indicating specific features for BP associated osteomyelitis [67].

4.7. Incidence. The incidence of BP associated osteomyelitis can be divided into 2 groups: the high dose i.v treated cancer patients and osteoporotic patients. In a systematic review, Kahn et al. found that, for the first group, the cumulative incidence varied from 1% to 12% after 36 months of treatment [66]. However, most of the reported cases have been related to intravenous use of bisphosphonates (zoledronic and pamidronic acid) to control metastatic bone disease or multiple myeloma. The incidence of ONJ in these studies ranges from 4 to 10% [1, 68, 69] and the mean time of onset varies from 1 to 3 years [55, 70, 71].

Osteoporosis is a common and costly condition that impaired quality of life [71]. It is estimated that 10 million individuals (aged >50 years) in the United States have osteoporosis, by 2010 [72]. Few studies have reported the prevalence of ONJ in persons receiving exclusive oral bisphosphonate therapy. No cases of ONJ were reported by Felsenberg et al. among clinical trials involving almost 17000 patients [73]. The authors estimated the worldwide reporting rate of ONJ to be <3/100,000 years of exposure [72]. In osteoporosis patients, by systemic review Kahn et al. estimated incidence of ONJ to be <1 case per 100,000 person-years of exposure [66]. Similar findings have been reported by German investigators, as determined by cases captured by a German Central Registry [73, 74]. By using postmarketing surveillance method Abtahi et al. identified one case of ONJ among 952 patients, who had received chronic oral bisphosphonate therapy [75]. Moreover, these findings contrast to those from an Australian study, which identified ONJ cases by nationwide maxillofacial surgeon survey [70].

The trigger for developing necrotic bone in BP treated patients seems to be dental extractions. A review of 114 cases of BP associated ONJ in Australia showed that 73% of the cases occurred after dental extractions. The frequency of ONJ in BP treated osteoporotic patients was 0.01%–0.04% and if dental extraction occurred 0.09%–0.34%. In patients on BPs for bone malignancies, the incidence was 0.33%–1.15% and after dental extractions 6.7%–9.1% [70].

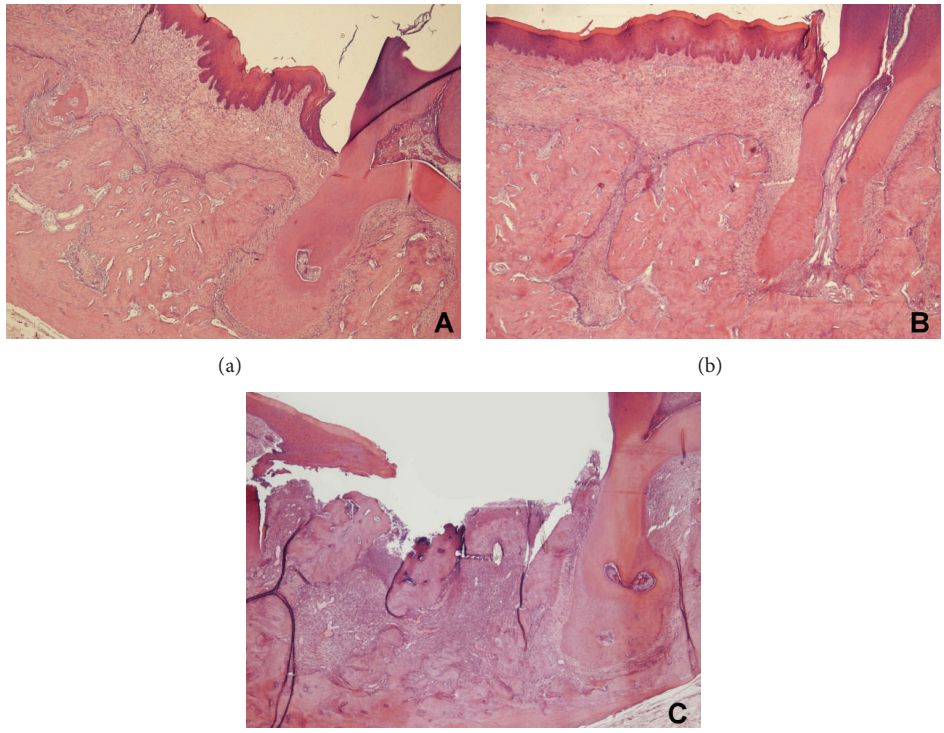
4.8. Risk Factors. There are general and local risk factors for development of ONJ.

General risk factors include malignancies, chemotherapy, glucocorticoid treatment, and high dose or long-term bisphosphonate treatment [48, 66].

Local risk factors include anatomical features where protruding cortical bone with thin mucosal coverage like tori and exostoses implies greater risk for necrosis as well as periodontal disease, any surgical intervention which breaks the mucosal lining, especially tooth extractions [48, 67]. In an experimental study by Abtahi and coworkers [75], it was shown that immediate soft tissue coverage after tooth extraction prevented ONJ completely whilst all noncovered sites developed ONJ in osteoporotic rats treated with alendronate, Figure 3.

The use of bisphosphonates is associated with the development of ONJ in some patients. Length of exposure seems to be the most important risk factor for this complication with an estimated range from 1.6 to 4.7 years, depending on BPs type [55]. Subsequent to ONJ development the minimum duration of use was reported to be 6 months [76, 77]. Barasch and coworkers showed that the risk for development of ONJ begins within 2 years of treatment, for both cancer and noncancer patients, showing that even the less potent bisphosphonates are linked to ONJ after a relatively brief treatment period [76]. Furthermore, for noncancer patients this risk seems to increase substantially after 5 years. This highlights the importance of drug holiday after 5 years of treatment. In a prospective study by Bamias et al. the incidence of ONJ was studied among patients treated with bisphosphonates for bone metastases. The incidence of ONJ increased with time to exposure from 1.5% among patients treated for 4 to 12 months to 7.7% for treatment for 37 to 48 months [77].

4.9. Bisphosphonates and Oral Implant Therapy. In a systematic review from 2009, Madrid and Sanz [78] included studies where patients had been on BP treatment for 1–4 years before implant placement. None of the patients developed osteonecrosis up to 36 months postoperatively



(a) (b)

(c)

Figure 3: Histological sections showing the region of the second molar 14 days after extraction in male Sprague-Dawley rat. (a) Control rat with no treatment, (b) BP treated with coverage, and (c) BP treated without coverage. Note necrotic tissue.

and the implant survival rate ranged from 95 to 100%. This may indicate that exposed/noncovered bone is necessary for bacterial invasion and an osteomyelitic process.

Furthermore, in a study from 2010, Koka and coworkers found high implant survival rates for both bisphosphonate users and nonusers in postmenopausal women [79].

4.10. Treatment. The optimal treatment strategy for ONJ is still to be established. Cessation of BP treatment will not be sufficient. A multidisciplinary team approach for evaluation and management of the conditions is recommended including a dentist, an oral-maxillofacial surgeon, and an oncologist. In early stages, surgical debridement and coverage has been successful [80]. Hyperbaric oxygen (HBO) is an effective adjunctive therapy in situations in which normal wound healing is impaired and the effects of HBO therapy have been discussed by several investigators [81, 82]. The authors showed that patients with ONJ, adjunctive HBO_2 therapy had remission or improvement in over 62.5% of patients. Laser therapy at low intensity has been reported for treatment of ONJ by improving reparative process, increasing osteoblastic index, and stimulating lymphatic and blood capillaries growth [83–85].

Segmental osteotomies are recommended only for severe cases [86–89], due to relatively high levels of morbidity and impaired quality of life for the patients [90].

In a study by Holzinger et al. [91], 108 patients with bisphosphonate therapy underwent surgery and 88 patients were followed for a mean period of 337 days. Surgical treatment improved the stage distribution from 19% stage I, 56% stage II, and 25% stage III to 59% intact mucosa, 19% stage I and 13% stage II and 8% stage III. The improvement in the stage of disease achieved by surgery was statistically significant. However, the choice between surgery and conservative therapy is a difficult issue and must be made on an individual basis.

Recently there have been discussions regarding the applicability of "drug holidays" to minimize long-term bisphosphonate exposure and avoid potential adverse events such as ONJ. However, given the long half-life of bisphosphonates in bone (measured in years) whether or not temporary cessation of treatment with these agents would reduce associated risks is not known. These questions require further study.

Antibiotics: Samples should be taken for culture and sensitivity testing before starting ab treatment. Traditionally, the antibiotics of choice to treat osteomyelitis will include Flucloxacillin or Clindamycin.

Prevention is a cornerstone to reduce the incidence of ONJ and before starting BP therapy, the patient should be referred for thorough dental evaluation to identify and treat any potential source of infection. Start of BP therapy should be delayed by 4–6 weeks to allow appropriate bone healing [90].

The treatment of bisphosphonate-related osteonecrosis of the jaw is generally difficult. For this reason, prevention plays a predominant role in the management of this condition.

5. Conclusion

The present narrative review, based on experimental and clinical original papers as well as previous reviews, indicates that osteonecrosis of the jaw in BP treated patients seems to be triggered by exposed bone and subsequent bacterial contamination, typically after dental extraction, and that sterile necrosis of the jaw is unlikely. We therefor suggest that the condition could be coined "*Bisphosphonate associated osteomyelitis of the jaw.*"

Conflict of Interests

Both authors declared that they have no conflict of interests.

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Review Article

Is Bisphosphonate-Related Osteonecrosis of the Jaw an Infection? A Histological and Microbiological Ten-Year Summary

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The role of infection in the etiology of bisphosphonate-related osteonecrosis of the jaw (BRONJ) is poorly understood. Large-scale epidemiological descriptions of the histology and microbiology of BRONJ are not found in the literature. Herein, we present a systematic review of BRONJ histology and microbiology (including demographics, immunocompromised associations, clinical signs and symptoms, disease severity, antibiotic and surgical treatments, and recovery status) validating that infection should still be considered a prime component in the multifactorial disease.

1. Introduction

In the early 20th century, phosphorus necrosis of the jaw or "phossy jaw" became clinically irrelevant after the manufacturing and importation of white phosphorous was banned in both Europe and the USA [1]. Then, in 2003, Marx described a previously unrecognized association between aminobisphosphonates (N-BPs) and ONJ rekindling interest in the seemingly familiar pathophysiology [2]. A thousand papers later, an association between N-BPs and ONJ is well documented. Yet, unlike white phosphorus, N-BPs are not so easily eliminated from human exposure. The benefits of N-BPs to patients suffering from severe osteoporosis, multiple myeloma, and/or metastatic tumors of the bone frequently outweigh the small but significant risk of ONJ. And, more recently, other drugs which are not bisphosphonates (e.g., denosumab) appear to share a similar presentation and pathophysiology, suggesting that the clinical relevance of ONJ is unlikely to diminish any time soon [3].

The mechanism of ONJ remains elusive at his time. Various hypotheses with convincing data suggest that inhibition of osteoclasts, diminished vascularity, direct tissue toxicity, impaired wound healing, microcracks, inflammation, and infection may all play at least some role in ONJ [4–9]. The latter is increasingly being recognized as a critical component in this multifactorial disease. However, controversy exists as to whether (1) N-BP inhibition of bone remodeling results in necrosis with subsequent infection or (2) the direct toxic effects of N-BPs on the oral mucosa allow for invasion of oral pathogens causing infection with subsequent necrosis [10].

Future advances with respect to the above debate will likely hinge on a finer appreciation for the unique setting in which BRONJ occurs. The oral cavity is perhaps the most susceptible of any anatomical location to the development of bone infection.

Repetitive mastication, tooth extraction, dental implantation, dentures, dental abscess, root canal surgery, and/or other oral trauma allow usually nonpathologic oral flora direct access to mandibular and maxillary bones [10]. In healthy individuals, a breech in the oral mucosa may be quickly overcome by proper wound healing leaving little possibility for continual infection. The patient population

exposed to N-BPs, however, is typically immunocompromised in at least one of several ways including malignancy, chemotherapy, steroids, diabetes, and smoking.

A vast majority of the literature, however, has been limited to case reports/series with relatively little to no attention applied to histological and microbiological findings. The authors suggest that this is likely due to both (1) the difficulty in culturing several of the oral pathogens and (2) a previously held notion that BRONJ was mostly an aseptic process. Various modalities have been studied (i.e., imaging) to describe bone abnormalities seen with BRONJ but thus far have not proved reliable in describing the infectious nature of the disease [11]. Recent advances using biomolecular profiling to describe BRONJ flora (colonies of organisms typically invisible to standard techniques) have narrowed this gap [12]. Metagenomic analysis, while informative, has unfortunately been limited by relatively few numbers of analytical samples making interpretation of larger microbiological patterns associated with ONJ extremely difficult.

Herein, we present a summary of the current microbiological and histological data (including relevant demographic data) of all BRONJ cases reported in the literature in an attempt to describe the role microorganisms play in the pathophysiology of ONJ.

2. Materials and Methods

A protocol that specified the inclusion criteria used in the present systematic review was developed in advance and a review exemption from the UAMS IRB was obtained.

2.1. Selection Criteria and Search Strategy. Review articles that compiled data from multiple previously published sources were excluded. Case reports, case series, and/or case-control studies relevant to ONJ (written in English) from January 2003 to December 2013 were reviewed for histological and/or microbiological data. The PubMed/MEDLINE electronic database was searched (with an English language limitation) for any published case report, case series, and/or case-control studies. Various arrangements of "osteonecrosis" in conjunction with free text (*jaw*, *jawbone*, *mandible*, *maxilla*, *bisphosphonate*, *zoledronic acid*, *zoledronate*, *pamidronate*, *alendronate*, *ibandronate*, *risedronate*, *osteomyelitis*, *infection*, *histology*, *microbiology*, *cultures*, *molecular*, *metagenomic*, and *bioprofiling*) were entered into the search engine. Resulting titles and abstracts were then scanned for potentially eligible studies. The remaining articles were read in full to determine inclusion status.

2.2. Data Extraction and Analysis. Data was entered into Microsoft Excel according to the following categories (in brevity): (1) general: article name, number of cases; (2) demographics and history: gender, age, history of dental trigger, N-BP route, and BRONJ stage; (3) clinical manifestations: bone exposure, pain, erythema, pus, and other extraoral manifestations (lymphadenopathy, swelling, sinus tract, etc.); (4) treatment: antibiotic route/duration, surgical type; (5) outcome: recovery status, time to recovery; (6) relevant comorbidities: chemotherapy, steroids, diabetes, smoking, and neoplastic disease; (7) microscopic identification of *Actinomyces* via hematoxylin-eosin (H&E), Gram, and/or periodic acid-Schiff (PAS); (8) histological descriptions: specimen number, presence of necrotic bone, bacterial colonization, inflammatory infiltrate, osteolysis, and irregular/scalloped borders; (9) culture results: growth, no growth, and name of isolated phylotype. Each numbered variable listed above was defined by reported, nonreported, sum, mean, standard deviation, median, lower quartile, upper quartile, minimum, and maximum. Summary statistics were then analyzed.

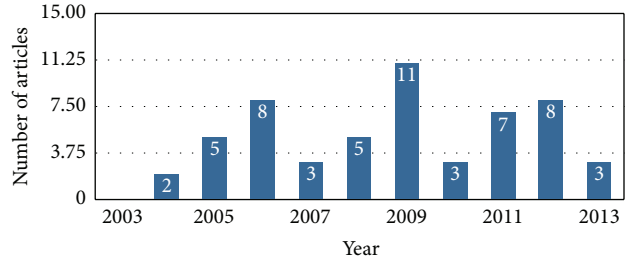

Figure 1: Published articles ($n = 55$) containing histological and microbiological data from January 2003 to December 2013.

3. Results

3.1. Search and Study Inclusion. More than 1,000 articles were initially identified by the PubMed/MEDLINE search. After exclusion of non-English articles, animal studies, and review articles, 175 papers were considered eligible and full-texts were carefully read. Articles without histological or microbiological data were excluded and this resulted in 55 articles including 814 patients. The number of eligible publications per year showed a bell-shaped distribution with a peak number of reports in 2009 (Figure 1). Age ranged from 26 to 89 years ($\overline{x} = 63.3 + 5.6$) with a male to female ratio of 1 : 1.7 (264 males, 445 females). 95 (18.0%) and 516 (81.8%) had a history of oral or parenteral N-BP exposure, respectively. Previously reported risk factors/associations included 392 (81.8%) with neoplastic disease, 488 (81.6%) with recent history of dentoalveolar procedure, 245 (63.7%) treated with chemotherapy, 133 (52.3%) with steroid exposure, 32 (30.8%) tobacco users, and 38 (27.9%) with diabetes mellitus (Figure 2(a)). Extent of disease (BRONJ Stages I–III) was recorded in 210 cases with 25.7% (I), 57.6% (II), and 16.7% (III). Clinical manifestations included pain (82.7%, $n = 321$), bone exposure in (70.9%, $n = 270$), erythema (83.6%, $n = 31$), pus (64.5%, $n = 109$), and other extraoral manifestations in 101 (57.8%) (Figure 2(b)).

3.2. Histology and Microbiology. 593 (91.4%) had at least some level of histological data (Figure 3(a)). Necrotic bone was present in 375 (85.1%) samples along with inflammatory infiltrate and bacterial colonization in 270 (81.6%) and 172

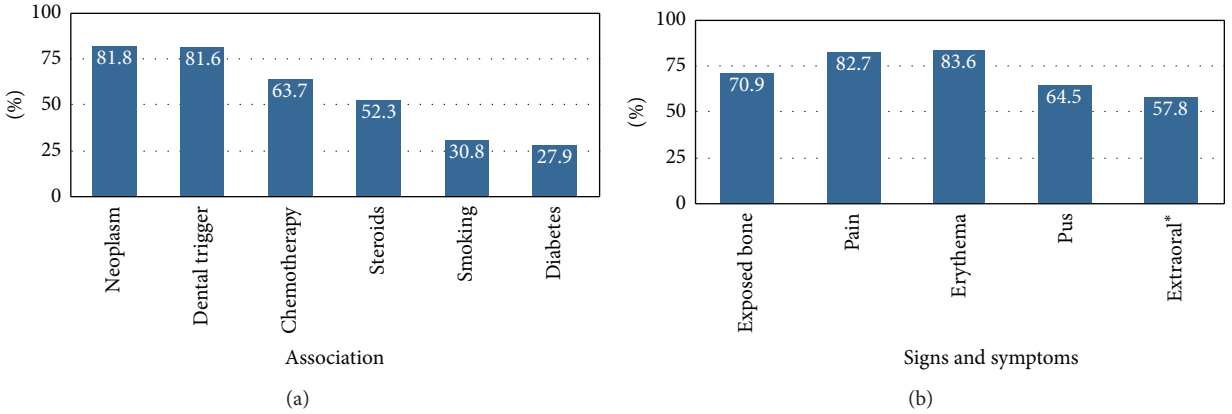

FIGURE 2: Immunosuppressed association (a) and clinical presentation (b) of the BRONJ population (n = 814).

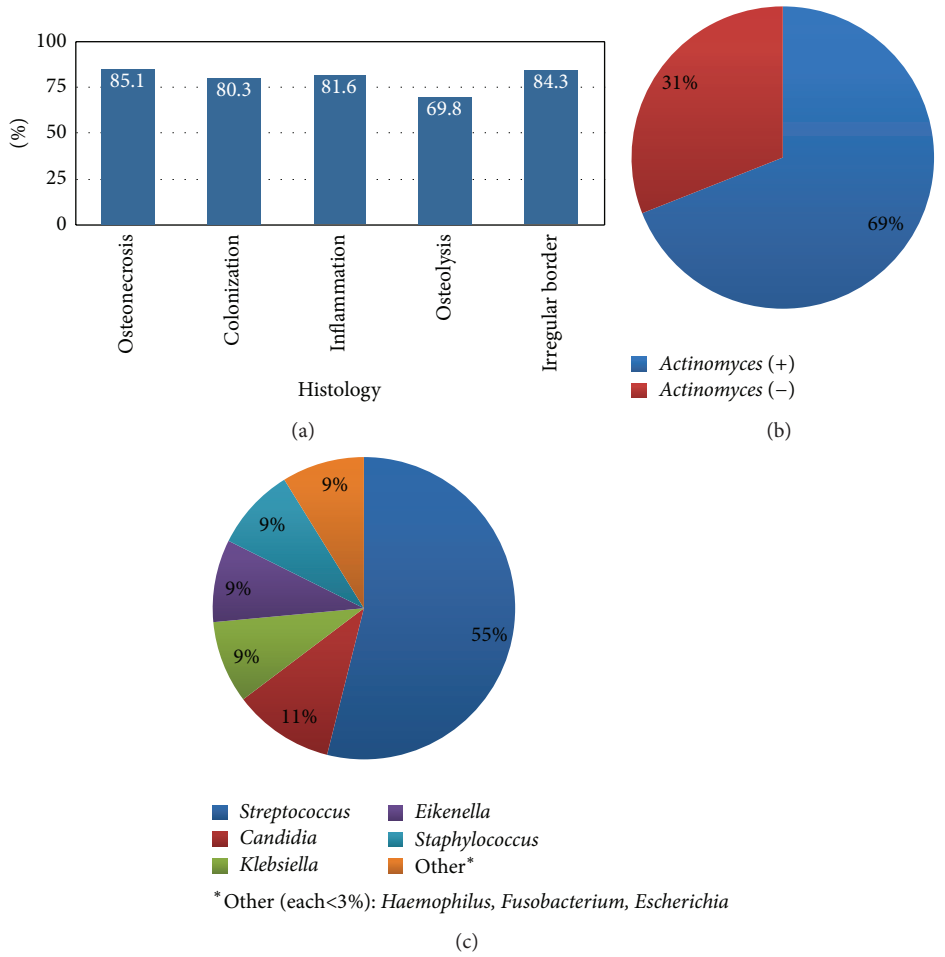

FIGURE 3: Histological results (a), microscopic identification of *Actinomyces* by H&E, Gram, and/or PAS stains (b), and culture results excluding *Actinomyces* (c).

(80.3%) cases, respectively. Nineteen (69.8%) reported osteolysis or "moth eaten" appearance and another 17 (84.3%) described irregular or "scalloped" borders.

Microscopic identification of *Actinomyces* occurred in 248 (68.8%) cases (Figure 3(b)). 166 cases obtained cultures with only 96 (57.8%) reporting growth (60.48%) or no growth (39.6%).

Excluding *Actinomyces*, *Streptococcus* was the most common organism grown from 19 (54.7%) reported lesions (Figure 3(c)). Other colonies grown (albeit much less frequently) included *Candida* (4), *Staphylococcus* (3), *Klebsiella* (3), *Eikenella* (3), *Haemophilus* (1), *Fusobacterium* (1), and *Escherichia* (1). Mixed oral flora (not otherwise specified) was reported in another 43 cases.

3.3. Treatment and Outcome. 350 (60.7%) of cases received antibiotic treatment (83.0% PO, duration $\overline{x}$ = 8.7 w, range 1.5–24 w; 16.9% IV, duration $\overline{x}$ = 2.9 w, and range 1–6 w). Several articles mentioned antibiotic administration but were unfortunately nonspecific as to the route (191 cases; duration $\overline{x}$ = 6.3 w, range 1–24 w). Unfortunately, antimicrobial rinses while being frequently reported were rarely specified to a specific patient/cohort and could not be quantified. 240 (66.8%) cases were treated with conservative surgery (i.e., superficial debridement, removal of bony sequestrum) involving local anesthetic and another 90 (22.3%) were treated with more radical measures (i.e., deep debridement, resection, etc.) under general anesthetic.

Complete recovery, partial recovery, and no recovery were reported in 108 (73.5%), 85 (47.0%), and 67 (24.7%) patients, respectively. Positive outcome NOS was reported in another 59 (53.4%) of patients. Time to described recovery in all cases showed $\overline{x}$ = 4.4 w (range 1–52 w).

4. Discussion

To our knowledge, this is the largest and most complete retrospective analysis of BRONJ at the histological/microbiological level. The aim of this paper is to (1) educate the clinician of former/current diagnostic and treatment practices, (2) summarize histological and culture results, and (3) present this information within the context of a decade of BRONJ awareness and research. This work is limited by infrequent histological and microbiological reporting from case reports/case series, which have historically made up a significant portion of BRONJ literature. Possible overreporting secondary to selection bias of the results cannot be ruled out. Finally, a significant majority of the data stems from articles where it was not possible to assign a histological sample/culture to a particular patient. Thus, direct comparisons across datasets were not performed.

4.1. A Multifactorial Disease. Favia et al. observed with scanning laser microscopy that bone exposed to N-BPs shows minimal osteoclastic activity followed by deposition of newly formed, thicker bone with a diminished vascular supply [13]. A mosaic pattern of bone remodeling appeared strikingly similar to specimens from Paget's disease (another patient population prone to developing osteomyelitis) [14]. They suggested that the N-BP induced remodeling leaves cavities of bone isolated from marrow resulting in both necrosis and subsequent infection from colonizing bacteria. The present report overwhelmingly supports the presence of infection (81.6% with inflammatory infiltrate and 80.3% with bacterial colonization) in the setting of osteonecrosis (85.1%). However, these findings do not exclude the possibility that concurrent colonization and/or infection may be present during and even facilitate N-BP remodeling of bone.

4.2. Actinomyces, Oral Flora, and Biofilms. The filamentous, anaerobe *Actinomyces* has long been associated with the necrotic bone found in BRONJ lesions, but the exact role of the bacteria is unclear [15]. Colonization has been reported in varying frequencies ranging from as few as 39.0% to as high as 100% [9, 10]. Within this range, 248 (68.8%) of samples showed microscopic evidence of *Actinomyces* colonization and/or infection. The wide range observed in the literature may be explained by (1) the stage of disease in which a tissue sample was analyzed, (2) variation in criteria for determining the presence of *Actinomyces* (i.e., H&E, PAS, Gram stains, and/or necessary presence of tissue reaction), and (3) the stage of disease in which a tissue sample was analyzed [16]. Wei et al. showed with rRNA gene based sequencing considerably less *Actinomyces* colonization than reported with traditional methods [12]. This discrepancy is likely explained by the ease in which the filamentous *Actinomyces* is observed on microscopic analysis compared to other oral flora resulting in relatively higher qualitative reporting versus gene based techniques with the capacity to detect larger numbers of microorganisms both qualitatively and quantitatively.

While interesting, the clinical utility of knowing that *Actinomyces* colonization is abundant in BRONJ lesions has thus far been limited [17]. However, a retrospective analysis by Kaplan et al. regarding antibiotic treatment and *Actinomyces* bacterial load (number of colonies/surface area of tissue) showed a direct correlation between histomorphometric parameters of *Actinomyces* colonies and clinical course [18, 19]. The implications of a histological marker that correlates with clinical disease in the BRONJ patient population are exciting and may even have utility in other areas of BRONJ research.

Ganguli et al. showed that hydroxyapatite (HA) coated with the N-BP pamidronate was 60-fold more susceptible to bacterial colonization than HA alone [20]. Kos et al. postulated that it may be the NH_3 (+) group of pamidronate acting as a steric factor to facilitate anchoring to the HA [21]. Further, they suggested that the ionic nature may even attract bacteria by direct electrostatic interaction (providing a mechanism for increased pathogenicity). Thus, in addition to bone remodeling, N-BPs may facilitate and select for growth of particular microflora. In our report, less than ten phylotypes were specified on culture (with a great majority of studies simply reporting mixed oral flora NOS) making it difficult to appreciate the biodiversity from culture alone. Culture-independent bioprofiling techniques emphasize the vast number of microorganisms and, more importantly, have shown that the BRONJ phylotype is significantly different than that seen in control groups [12].

It is unclear whether organisms present on culture or observed histologically (even if different compared to controls) are involved in the pathogenicity of the disease or are just simply present. Recent basic science, as well as clinical experience, suggests that the latter is increasingly becoming less likely. Tsurushima et al. histologically examined osteonecrotic lesions from Wistar rats (previously exposed to zoledronic acid) and observed significantly larger areas of necrotic bone in those specimens also inoculated with *Aggregatibacter actinomycetemcomitans* compared to normal saline controls [15]. This would suggest that certain phylotypes dominant in periodontal disease and BRONJ lesions, at the very least, act synergistically with N-BPs exacerbating bone remodeling and disease progression. For instance, a

high abundance of *Streptococcus* and other aciduric bacteria has been suggested as causative factors in bone necrosis (and may even enhance growth of other aciduric bacteria) [12]. *Streptococcus* was the most common phylotype growing in 54.7% of reported cultures. This finding is consistent with what is seen in culture-independent techniques [12].

Streptococcus is not alone for known pathogenicity. Mawardi et al. observed in a mouse model that *Fusobacterium* (reported in 1 cultures from our review) can directly cause BRONJ lesions and delayed epithelial wound healing (which both resolved after administration of a broad spectrum antibiotic regime) [22].

The most recent data suggests that individual phylotypes, however, may not be as important in comparison to how the microflora interacts as a whole. Sedghizadeh et al. described for the first time the presence of microbial biofilms consisting mostly of bacteria of various species (with occasional yeast) that were embedded in the extracellular matrix in BRONJ lesions [23]. Further, the biofilms were not present in control bone tissue. The biofilms consisted of Gram-positive and Gram-negative organisms, aerobes, and anaerobes/facultative anaerobes (i.e., typical oral flora). Unfortunately, conventional histopathologic techniques have not been useful in characterizing biofilms. Further characterization of the complex interactions between the microflora at this level likely represents the next stage of research in BRONJ infection pathophysiology [24].

In some cases, Sedghizadeh et al. described coaggregation (i.e., direct cell-to-cell recognition) of genetically distinct cell types [23]. Of particular interest, it should be highlighted that coaggregation was observed between *Actinomyces* species and coccal forms. We suggest that this cell-to-cell recognition with *Streptococcus* (the most reported phylotype by culture and culture-independent analysis) is significant. *Actinomyces* cell-to-cell recognition may be an alternative mechanism to explain why Kaplan et al. were able to correlate histomorphometric parameters (i.e., *Actinomyces* bacterial load with a clinical course) [19]. For instance, the 10-year retrospective analysis may have been treating an underlying predominantly *Streptococcus* infection (blunting the acidic effect known to cause and exacerbate osteonecrosis) while using *Actinomyces* as a marker for such responsiveness.

Further, it is unlikely that *Streptococcus* is unique in this respect. It is well known that actinomycosis is predominantly a polymicrobial infection, and it should not be surprising that flora sensitive to the same antibiotics would mirror trends in response to treatment. This is consistent with penicillin as the predominant antibiotic (60% of cases) used in the Kaplan study to treat infection. Future research should assess the potential of *Actinomyces* as a potentially easily identifiable and inexpensive biomarker for both the presence of biofilms (i.e., *Actinomyces* colonies at the surface of a biofilm with cell-to-cell contact, recent leave from a biofilm following pulsed shock, etc.) and BRONJ disease burden.

4.3. Immunocompromising Risk Factors. Bisphosphonate exposure to prevent bone destruction in patients with neoplastic disease remains the strongest risk factor with a 2.7- to 4.2-fold increase in the likelihood of developing BRONJ [25]. In our study, parenteral administration of bisphosphonates occurred in 81.8% ($n = 516$) versus oral administration in 18.0% ($n = 95$) while neoplastic disease accounted for 81.8% ($n = 392$) of the patient population. Malignancy frequently requires immunosuppressed states including chemotherapy (63.7%, $n = 245$) and/or steroid exposure (52.3%; $n = 133$) at some point during the clinical course. Other known immunosuppressed states associated with BRONJ included smoking (30.8%; $n = 32$) and diabetes mellitus (27.9%; $n = 38$) [26]. The cumulative effect of the above associations is illustrated at the microbiological level by the observed growth of *Candida* (typically seen in oral flora only in immunosuppressed states) in more than 10% of cultures.

4.4. BRONJ Clinical Manifestations and Acute Infection. The most common clinical manifestations of BRONJ in our analysis were pain (82.7%) and erythema (83.6%) followed by bone exposure (70.9%), pus (64.5%), and other extraoral manifestations such as lymphadenopathy, swelling, and draining abscess (57.8%). Thus, several of the most common clinical findings in patients presenting with BRONJ are also the classic signs of acute infection. Microbial infection alone is a causative factor in chronic, undiagnosed craniofacial pain and these patients are frequently misdiagnosed with trigeminal neuralgia or atypical facial pain (leaving the underlying infection untreated) [27]. The literature suggests that conservative regimens (i.e., nonsurgical treatment of infection with antimicrobials) have been effective at decreasing pain associated with BRONJ in the majority of the patient population [28].

4.5. Treatment and Outcome. Treatment recommendations for BRONJ lesions depend on clinical stage of disease and expertise of the physician. AAOMS guidelines suggest that Stage I (25.7% of our data) need only antimicrobial rinses. In Stage II (57.6% of our data), penicillin is recommended as empirical coverage unless relevant allergy or culture results dictate otherwise. Refractory cases may benefit from combined coverage, long-term coverage, or IV antibiotic therapy.

More recent reports since the 2009 guideline update suggest that combined surgical intervention (removing necrotic bone) along with antimicrobial rinses and empiric systemic antibiotic coverage (treating infected, viable bone) has been linked to complete healing in 70–87% of patients with Stages I and II of the disease [29]. A similar 73.5% (predominantly Stage II of the disease) showed complete recovery after a wide range of treatments in our report with results typically reported within a month after initiating treatment. Patients presenting in Stage III (16.7% of our data) will likely benefit from surgical debridement in combination with some form of antibiotic therapy. Deep debridement, resection, or other major surgical interventions were performed in 90 cases (22.3%).

5. Conclusions

After systematic review of the histological and microbiological data, the infectious etiology associated in BRONJ lesions

should not be ignored. The authors recommend obtaining H&E, PAS, and Gram stain (all typically positive in the presence of *Actinomyces* colonies) along with the requirement of tissue reaction (i.e., inflammatory response or fibrosis) in the immediate vicinity to differentiate colonization versus infection when BRONJ biopsy tissue is obtained and/or reported. Refractory cases nonresponsive to antibiotics may benefit from an antifungal medication. Future research should examine the role of *Actinomyces* bacterial load as a potential BRONJ biomarker for disease burden, clinical course, and presence of biofilms.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Clinical Study

Conservative Treatment of Bisphosphonate-Related Osteonecrosis of the Jaw in Multiple Myeloma Patients

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The use of intravenous bisphosphonates (pamidronate or zoledronic acid) is the cornerstone for the management of multiple myeloma-(MM-) related bone disease. However, osteonecrosis of the jaw (ONJ) is a rare, but sometimes difficult to manage, adverse effect of bisphosphonates therapy. A retrospective review of all MM patients who were treated with bisphosphonates in our department, from 2003 to 2013, and developed ONJ was performed. According to inclusion criteria, 38 patients were studied. All these patients were treated as conservatively as possible according to the American Association of Oral and Maxillofacial Surgeons criteria. Patients were managed with observation, oral antibacterial mouth rinse with chlorhexidine, oral antibiotics, pain control with analgesics, nonsurgical sequestrectomy with or without simultaneous administration of antibiotics, or major surgery with or without antibiotics. Healing of the lesions was achieved in 23 (60%) patients who were treated with conservative measures; the median time to healing was 12 months (95% CI: 4–21). The number of bisphosphonates infusions influenced the time to healing: the median time to healing for patients who received <16 infusions was 7 months and for those with >16 infusions was it 14 months ($P = 0.017$). We conclude that a primarily nonsurgical approach appears to be a successful management strategy for bisphosphonate-related ONJ.

1. Introduction

Bisphosphonate-related osteonecrosis of the jaws (BRONJ) is an avascular osteonecrosis of the jaws, associated mainly with intravenous administrated bisphosphonates but also with oral bisphosphonates. Intravenous bisphosphonates are used for the management of bone disease and bone metastases, caused by multiple myeloma and other solid tumors, for example, breast cancer, prostate cancer, and lung cancer [1, 2]. BPs main action is to inhibit osteoclast function and subsequent bone resorption, resulting in the prevention of loss of bone mass and skeletal related events, such as pathologic fractures and pain, caused by the underlying disease [3, 4]. A great number of patients with cancer benefit from the therapeutic results of BPs. Nevertheless bisphosphonate-related osteonecrosis of the jaw (BRONJ) has been described as an adverse effect of these drugs in various malignancies [5–8], with negative effect on the quality of life of the patients [9].

The diagnosis of osteonecrosis is clinical and according to suggested criteria [10] requires the presence of exposed bone in the jaw area for more than eight weeks, in a patient under current or previous treatment with a bisphosphonate, with no history of radiation therapy to the head and/or neck area.

The incidence of BRONJ ranges considerably due to various factors, such as type of bisphosphonate, type of cancer, way of administration, time of exposure, and number of infusions [11–14]. The risk of developing BRONJ in multiple myeloma patients receiving intravenous zoledronic acid or pamidronate is relatively high. Previous studies from our team as well as from other groups have identified tooth extraction or chronic trauma of the oral mucosa caused

by poorly fitting dentures, poor oral hygiene, and number and duration of zoledronic acid administration as the main triggering factors for the development of ONJ [12, 15–18]. However, spontaneous development of BRONJ is also possible and has been reported [12, 17].

Several approaches have been evaluated for the treatment of patients who developed BRONJ and many management strategies have been proposed. Nevertheless, it seems that taking preventative measures is the most effective way to face BRONJ. In our current study we report on the outcome of our series of MM patients who developed ONJ and discuss management issues.

2. Materials and Methods

A retrospective review of multiple myeloma patients who were diagnosed with BRONJ from July 2003 until September 2013 and were treated in the Department of Clinical Therapeutics (Athens, Greece) was conducted. All the patients reporting symptoms and/or signs compatible with the probability of development of osteonecrosis were prospectively evaluated. BRONJ was diagnosed by a specialized maxillofacial surgeon (IM) according to the following criteria: patients, with no history of head and/or neck radiotherapy, currently or previously treated with bisphosphonates and presence of exposed bone in the maxilla and/or the mandible for more than eight weeks. All cases with denosumab associated necrosis were excluded, as well as cases in which the whole treatment was not performed by the same group, to avoid data that was not confirmed.

From 105 patients with osteonecrosis of the jaws under treatment with antiresorptive agents for any reason (solid tumor metastasis, multiple myeloma, etc.), thirty eight patients were selected according to the aforementioned criteria, that is, multiple myeloma patients with osteonecrosis of the jaw, caused by IV bisphosphonate therapy, who were treated in our clinic from the time of diagnosis of their disease. Biopsy was performed, if exclusion of myelomatous involvement was necessary. All species removed surgically (sequestra debridement) were also histologically evaluated.

The determination of the stage of osteonecrosis was made according to the definition and staging system published by the American Association of Oral and Maxillofacial Surgeons (AAOMS) updated position paper as follows: stage 0, no clinical evidence of necrotic bone, but nonspecific clinical findings and symptoms; stage 1, exposed and necrotic bone in patients who are asymptomatic and have no evidence of infection; stage 2, exposed and necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage; and stage 3, exposed and necrotic bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus in the mandible, maxillary sinus, and zygoma in the maxilla) resulting in pathologic fracture, extra-oral fistula, oral-antral/oral-nasal communication, or osteolysis extending to the inferior border of the mandible or sinus floor.

A standardized and comprehensive history was obtained from each patient at the initial consultation. Data was abstracted, using a standardized template that collected patient information, medical history, and dental history, including recent dental extractions. Information concerning myeloma treatment, for example, number of infusions, duration of BP exposure, time for healing, and time of death, was also evaluated. All patients underwent comprehensive clinical evaluation and panoramic and/or intraoral periapical radiographs, when a com beam CT scan was performed in some cases. Management was provided according to general guidelines designed to minimize symptoms and/or achieve resolution of lesions.

The protocol we have followed since 2003 for all patients diagnosed with BRONJ was established based on the data of bibliography and the observation and personal experience of the attendant maxillofacial surgeon (IM). According to our protocol bisphosphonate therapy was interrupted in patients who developed BRONJ at the time of diagnosis according to guidelines [14]. Initial management in all cases was as conservative as possible. Regardless of stage, chlorhexidine rinses were prescribed for the majority of patients and mobile fragments of bone were managed with non-surgical sequestrectomy (simple removal of mobile bone fragments), typically without the need for local anesthesia. In patients with BRONJ and no signs of inflammation, avoidance of surgical dental treatment (extractions, implant therapy, and oral surgery procedures), amelioration of oral hygiene, and use of oral antiseptic mouth rinses (chlorhexidine 0.12% for 3 weeks per month, other antiseptic for 1 week per month) were recommended. Patients with artificial dentures were advised to remove them, in order to reduce the contact of the denture with the exposed bone and avoid further trauma of the mucosa. When inflammation was present, antimicrobial chemotherapy was given, usually metronidazole 500 mg twice a day for 2 weeks or aminopenicillins in combination with metronidazole for 15 days in more severe cases. Alternative choice for patients allergic to aminopenicillin was moxifloxacin for 10 days, as post antibiotic effect makes this treatment equal to a 15-day therapy. According to literature, the use of clindamycin in patients with BRONJ is not indicated after 2005 [12]. When bone spindles were present, only minor debridement procedures were attempted, in order to reduce trauma of the adjacent soft tissues. Observation and/or minor debridement procedures were also attempted, in case of spontaneous apoptosis of sequestra. When radiographic appearance of a sequestrum was observed, minor surgical sequestrectomy under local anesthesia and antibiotic treatment was attempted. Patients at stage 3 or patients who showed recurrence were treated with major surgical intervention, that is, peripheral ostectomy under general anaesthesia and antibiotic therapy.

Absence of exposed necrotic bone, absence of any signs of inflammation of the soft tissues, complete healing of the mucosa, and absence of subjective complains about pain and/or numbness for more than 3 months were considered as complete healing criteria.

3. Results

A total of thirty eight multiple myeloma patients were diagnosed with BRONJ, 25 males (66%) and 13 females (34%). The patients' age at time of BRONJ diagnosis ranged from 29 to 83 years, with mean age of 66 years. Twenty-six patients developed BRONJ in the mandible, 11 in the maxilla, and one patient in both mandible and maxilla. Thirty-three patients (87%) were treated with zoledronic acid (Zometa; Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA) of 4 mg infused over 15 minutes every 4 weeks, 1 patient with pamidronate (Aredia; Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA), of 90 mg infused every 4 weeks, and 4 patients (11%) were treated with both zoledronic acid and pamidronate. Mean number of BP infusions was 25.5 (6–83). The triggering factor of BRONJ development was oral surgery, such as tooth extraction in 22 cases, chronic mucosa trauma from artificial dentures in 5 cases, periodontal and/or periapical inflammation in 4 cases. Seven cases developed spontaneously, six of them at the mylohyoid ridge (Table 1).

Biopsy and histological assessment of the sequestra were performed in 29 cases, which confirmed the complication. Three patients (8%) were diagnosed with stage 0, eight patients (21%) with stage 1, seventeen cases (45%) with stage 2, and ten (26%) with stage 3 ONJ (Table 2).

Three patients were treated only with observation, mouth rinses with chlorhexidine 0.12% for 3 weeks per month, other antiseptic for 1 week per month, in order to avoid disturbance of the oral flora, and removal of the bony edges of the lesion. One showed complete healing, one remained stable, without any signs of inflammation or pain until death, and one patient developed higher stage of ONJ (stage 2) and was treated with antibiotics. Ten patients were treated with chlorhexidine 0.12% for 3 weeks per month, other antiseptic for 1 week per month, and antibiotics, whenever inflammation appeared. Eight of these patients remained stable for a mean follow-up of 24 months (3–48), one was completely healed after 8 months, with a 5 months follow-up after healing and one patient developed a higher stage of ONJ and is scheduled for surgery, whenever his health status permits. Seven patients had spontaneous apoptosis of sequestra and they all showed complete healing. Mean follow-up was 27 months (8–40) after the confirmation of healing. No recurrence was observed in any of these patients, until the last-follow up or until death. Conservative sequestrectomy was attempted after a meantime of 12 months under antibiotic therapy in 16 cases. Eleven of these cases showed complete healing; one case was not yet completely healed at the time of the last follow-up, one patient died during the follow-up after healing period, and three cases underwent a second minor surgery before achieving complete healing. Major surgical intervention was attempted in 2 patients with stage 3 BRONJ. Complete healing was observed in both cases, although one patient underwent a second surgery after a period of 5 months, in order to reverse the failure of the first surgery. The other patient underwent two surgeries in different locations each time—one in the maxilla and one in the mandible, since he had developed ONJ bilateral in the maxilla and the mandible. Mean follow-up after healing in both cases was more than 6 months (Table 3).

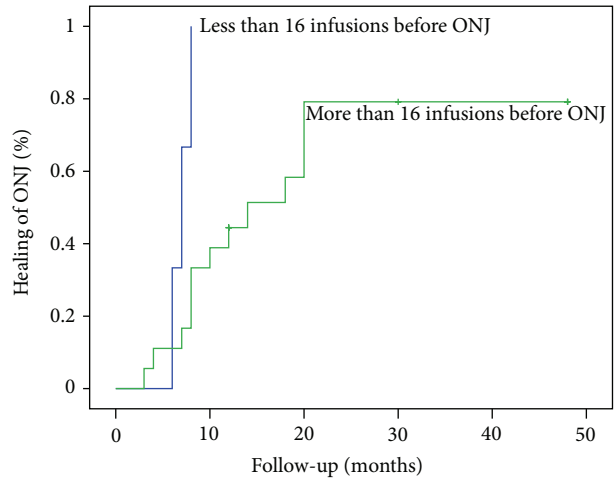

Figure 1: Median time to healing in association with the number of infusions of bisphosphonates.

In patients where healing was stated ($N = 24$, 63%), by removal of bony edges, spontaneous apoptosis of the sequestra, or sequestrectomy, the median time to healing was 12 months (95% CI 4–21). A statistically significant difference ($P = 0.017$) was found between groups with more and less than 16 infusions of bisphosphonates, when median time to healing for those with <16 infusions was 7 months and median time to healing for those with >16 infusions was 14 months ($P = 0.017$; Figure 1).

4. Discussion

The incidence of BRONJ is yet undetermined. According to many studies of patients with multiple myeloma, breast, or prostate cancer, who received intravenous amino-BP therapy, the occurrence of osteonecrosis is estimated to be approximately 4–11% [7, 13, 18]. In our study which included only multiple myeloma patients, the incidence of ONJ was almost 6%. The probability of developing BRONJ ranges due to various risk factors. The number and frequency of infusions, but mainly the cumulative dose of BP, are strongly associated with the risk of BRONJ [12, 19]. Invasive dental procedures, that is, tooth extractions, implant therapy, oral surgery, as well as mucosa trauma by poor fitting dentures have been reported as the most important triggering factors of developing this complication. However, spontaneous development of BRONJ occurs in approximately 20% of the patients who develop BRONJ [20, 21]. Indeed, in our study 57.9% of the patients who developed osteonecrosis underwent dental extraction, 13.2% had chronic mucosa trauma by artificial dentures, 10.5% of ONJ patients developed ONJ due to periodontal and/or periapical inflammation, and in 18,4% patients it occurred spontaneously, which comes in agreement with the latest reviews. The mean number of infusions was 25.5 and the mean time of BP exposure was 36.5 months. In the present study, lesions occurred more frequently in the mandible than in the maxilla (67% versus 33%). This ratio is also confirmed by several studies [22–24].

Table 1: Patients' clinical characteristics.

Patient	Gender	Age at diagnosis	BP therapy	Number of infusions	Stage of BRONJ	Triggering factor
A.G.	Male	81	ZA	12	1	Spontaneous
A.K.	Male	61	ZA and Pam	19	3	Extraction
A.E.	Female	70	ZA	25	1	Spontaneous
B.I.	Male	50	ZA	20	2	Extraction
B.A.	Male	76	ZA	11	1	Spontaneous
B.Ir.	Female	53	ZA	25	2	Extraction
B.D.	Male	65	Z.A and Pam	80	2	Extraction
B.P.	Female	43	ZA	26	3	Extraction
B.E.	Female	79	ZA	42	3	Extraction
B.S.	Male	81	ZA	32	2	Trauma from dentures
D.A.	Male	63	ZA	28	2	Extraction
D.Z.	Male	59	ZA	6	1	Extraction
D.E.	Female	72	ZA	13	0	Trauma from dentures
G.M.	Male	82	ZA	12	2	Extraction
K.K.	Male	74	ZA	17	3	Spontaneous
K.M.	Female	72	ZA	39	1	Spontaneous
K.E.	Female	68	ZA	22	3	Trauma from dentures
K.N.	Male	78	ZA	58	2	Extraction
K.P.	Male	66	ZA	17	2	Extraction
K.V.	Male	73	ZA	30	0	Periapical abscess
K.I.	Male	69	Pam	25	2	Extraction
M.T.	Female	59	ZA	31	1	Trauma from dentures
P.O.	Female	61	ZA	48	2	Extraction
P.G.	Male	81	ZA	59	1	Trauma from dentures
P.V.	Female	57	ZA	83	2	Periapical abscess
P.T.	Male	61	ZA	15	1	Spontaneous
P.M.	Female	69	ZA	21	1	Trauma from dentures
P.Ma.	Female	71	ZA	36	1	Periodontal Inflammation
P.K.	Male	59	ZA	8	3	Extraction
P.D.	Male	61	ZA and Pam	34	2	Extraction
S.E.	Male	65	Z.A	13	3	Extraction
S.D.	Male	61	Z.A	26	3	Extraction
S.K.	Male	55	Z.A	65	2	Periodontal Inflammation
S.G.	Male	80	Z.A	45	2	Spontaneous
T.P.	Male	29	ZA and Pam	38	2	Extraction
V.C.	Male	50	ZA	25	3	Extraction
X.E.	Female	67	ZA	26	0	Extraction
Z.L.	Male	72	ZA	17	3	Extraction
Total	Male: 25 female: 13	66 Years (29–83)	ZA: 33 Pam: 1 ZA + Pam: 4	25.5 (6–83)	St 0: 3 St 1: 8 St 2: 17 St 3: 10	Extraction: 22 Trauma Dentures: 5 Periodontal/periapical inflammation: 4 Spontaneous: 7

ZA: zoledronic Acid; Pam: pamidronate.

The management of BRONJ is a difficult goal to achieve and still remains controversial, since consensus standard protocol has not yet been established. According to the guidelines of the AAOMS, treatment strategies of BRONJ emphasize mainly the elimination of pain and inflammation and the reduction of the exposure of the necrotic bone and secondarily they emphasize the complete healing of the lesion. Several methods have been proposed, which can

Table 2: Management of ONJ by stage.

Stage	*N*	CHL rinses and observation plus removal of bony edges	Antibiotics plus removal of bony edges	Spontaneous apoptosis of sequestra	Minor surg. intervention-Sequstrectomy	Major surgical intervention
0	3	0	2 (67%)	0	1 (33%)	0
1	8	1 (12.5%)	1 (12.5%)	5 (62.5%)	1 (12.5%)	0
2	17	1 (5.9%)	4 (23.5%)	1 (5.9%)	11 (64.7%)	0
3	10	1 (10%)	3 (30%)	1 (10%)	3 (30%)	2 (20%)
Total	38	3 (7.9%)	10 (26.3%)	7 (18.4%)	16 (42.1%)	2 (5.3%)

Table 3: Results of ONJ treatment.

Treatment	*N*	Stable	Complete healing	Regression
CHL rinses and observation plus removal of bony edges	3	1 (33.3%)	1 (33.3%)	1 (33.3%)
Antibiotics plus removal of bony edges	10	8 (80%)	1 (10%)	1 (10%)
Spontaneous apoptosis of sequestra	7	0	7 (100%)	0
Minor surg. intervention-Sequestrectomy	16	1 (6.25%)	15 (93.75%)	0
Major surgical intervention	2	0	2 (100%)	0
Total	38	10 (26.3%)	26 (68.4%)	2 (5.3%)

be categorized as nonsurgical or conservative [25–27] and surgical approaches [28, 29].

Nonsurgical treatment includes a combination of antiseptic mouth rinses, antimicrobial chemotherapy, when inflammation occurs, and nonsurgical sequestrectomy and/or debridement. The outcomes of most studies [24–27] seem to be satisfactory. According to one of the largest—in terms of patients—retrospective study by Lerman et al., 71–80% of the cases, treated conservatively improved or remained asymptomatic and stable [25]. In our study 63% of the patients who were treated with conservative measures (removal of bony edges, spontaneous apoptosis of sequestra, or minor surgical intervention) achieved complete healing and another 23.7% remained asymptomatic and stable, while in 5.2% of the patients major surgical interpretation was performed, because of failure of the conservative treatment. Van den Wyngaert et al. suggest that there are several factors, such as stage of ONJ, patient's health condition, time of exposure to BP, type of BP therapy, use of chemotherapy before ONJ, which should be considered in order to proceed to a specific treatment of ONJ, although it seems that strictly conservative treatment at low stages of the complication can lead to healing in about half of the cases [26]. In agreement with the above results a study by Moretti et al. confirms management of pain with minimally invasive treatment in more than 60% of the cases, while all of the patients who underwent sequestrectomy—spontaneously or gently induced by the surgeon—achieved complete healing [27]. In the present study 87.5% of stage 1 patients, 59% of stage 2, and 50% of stage 3 patients were healed.

On the other hand, radical surgical treatment of ONJ, including extensive sequestrectomy and limited or extensive bone resection, has showed healing of BRONJ in several studies [29–33]. The results of the study by Wilde et al. showed that 88% of the patients, treated surgically, achieved complete healing of ONJ. Nevertheless, a statistically high failure rate in stage 3 ONJ, approximately 36%, may initiate doubts about the efficiency of the surgery, while adequate surgical planning and high degree of experience on the determination of the resection margins are clearly pointed out by the author. Stockmann et al., at a study with 80 patients, report a success rate of about 89%, which declined to 84% within 14 months postoperatively [31]. The outcomes of a review by Kühl et al. showed that, when comparing the results of conservative and surgical treatment of BRONJ, it seems that there is no difference regarding the success of treatment (e.g., 60.5% versus 60.4%), although it appeared that complete healing of BRONJ after conservative treatment is only successful in low stages of the complication [32]. We also conclude ($P = 0.017$) that the number of BP infusions is associated with the median time to healing. Patients who received less than 16 infusions achieved healing in the half time, compared with patients who received more than 16 infusions (7 versus 14 months).

Other therapeutic approaches, such as medical ozone [34] and ND:YAG laser stimulation [35, 36] have given encouraging results in the management of patients with ONJ but the experience with these methods is limited.

In the present study, major surgical intervention was decided only at high levels of ONJ or in case of failure of conservative measures. Both patients who underwent major surgery achieved complete healing. Due to bisphosphonates discontinuation, many cases (7) of spontaneous apoptosis of the sequestra have been observed. The mean time of sequestra formation was 10.2 months where the mean time for minor surgery intervention (15 patients) was 15.6 months. It could be a reasonable thought that in that period of time the bone turnover in the necrotic area starts to work. When treatment with IV bisphosphonates could be stopped, it is reasonable to treat patients conservatively until the time where sequestra formation seems to start. Therefore, in agreement with the AAOMS guidelines, we believe that the cost-benefit for patients who are already debilitated by their

malignancy leans to more conservative treatment strategies of ONJ with satisfactory results and surgical intervention should be performed only in cases of failure of the above strategies.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Imaging Findings of Bisphosphonate-Related Osteonecrosis of the Jaws: A Critical Review of the Quantitative Studies

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Objectives. This paper offers a critical review of published information on the imaging strategies used for diagnosing bisphosphonate-associated osteonecrosis of the jaw (BRONJ) in patients taking intravenous bisphosphonates, pointing at the different methodologies and results of existing literature. *Methods*. Electronic literature search was performed in order to identify as many quantitative studies that discussed the imaging findings of BRONJ up to February 2014. Initially, the search for articles was based on the following four types of imaging modalities for evaluating BRONJ: computed tomography, plain film radiographs, magnetic resonance imaging, and nuclear bone scanning. *Results*. Eleven out of the 79 initially selected articles met the inclusion criteria. Most of the selected articles were cross-sectional studies. Regarding the selected studies, 54.5% have used plain films radiographs and 54.5% were based on computed tomography findings. All of the selected studies showed a small number of patients and none of the selected studies have tested the accuracy of the imaging examination for evaluating BRONJ. *Conclusions*. This critical review showed a scarcity of quantitative studies that analyzed the typical imaging findings related to BRONJ. Further studies are necessary in order to analyze the role of different imaging techniques in the assessment of BRONJ.

1. Introduction

Bisphosphonates are the first line of treatment for metastatic bone cancer, osteoporosis, and Paget's disease. In the late 2003, cases of bisphosphonate-related osteonecrosis of the jaw (BRONJ) were first reported [1]. Since then, many studies have been performed in order to provide early diagnosis and better treatment for the patient once the BRONJ negatively affects their quality of life and increases morbidity. The cumulative incidence of BRONJ in patients taking intravenous bisphosphonates is significantly greater than in patients using oral bisphosphonates and varies from 0.8% to 12%. The estimated risk of BRONJ for oral bisphosphonate users remains uncertain but the occurrence appears to range from 1 in 10 000 to 1 in 100 000 patient-years [2–4].

The American Academy of Oral and Maxillofacial Surgeons stated that, for the clinical diagnosis of BRONJ, patients need to exhibit all of the following three characteristics: (1) current or previous treatment with a bisphosphonate; (2) exposed, necrotic bone in the maxillofacial region that has persisted for more than eight weeks; and (3) no history of radiation therapy to the jaws [2].

BRONJ is categorized according to the clinical signs and symptoms into stage I, stage II, and stage III. Clinically, the disease appears as a nonhealing exposed bone area that can be accompanied by fistulization, purulent discharge, and pain [5]. Although imaging findings neither are considered diagnostic criteria nor have radiographic features for each stage, their findings corroborate the evaluation of the course, extent, and progression of the disease. The clinical examination does not usually show the full extent and severity of BRONJ

sites beneath the mucosa [6]. Panoramic radiography, computed tomography (CT), magnetic resonance imaging (MRI), and scintigraphy are valuable imaging modalities that assist the clinical findings by revealing different aspects of bone involvement. Furthermore, these imaging examinations can help in the differential diagnosis of other diseases that resemble BRONJ in terms of clinical signs and symptoms [7–9].

Radiographic exam is additionally substantial since most patients with BRONJ are those undergoing other treatments and the imaging findings of BRONJ are not specific and can also be found in other conditions such as osteomyelitis, osteoradionecrosis, cancer metastasis, and Paget's disease [10]. The initial imaging findings in BRONJ appear to be focal medullary sclerosis with poor corticomedullary differentiation, which is clinically concomitant with the loosening of tooth. A usual sign of osteonecrosis of the jaw is the delayed socket healing after tooth extraction. In late disease, there is a sequestrum formation, fractures, and reaction, and when the maxilla is involved, there may be mucosal thickening in the adjacent sinus with fluid levels or purulent discharge [4].

Despite the lack of consensus on the radiographic evolution of BRONJ, the literature has shown through models the formation of a necrotic body or involucrum inside the trabeculae in sclerotic mandibular bone. The involucrum represents most likely dead bone, which becomes surrounded by a resorptive circumference that increases with time. Probably, this is a response by the bone cells to remove the dead bone. The involucrum follows the path of least resistance leading to an exposed sequestrum or, if the tooth is missing moves to the edentulous area, suggesting that this could be the mechanism of the formation for the clinically visible sequestrum [11].

A major challenge is the early diagnosis of BRONJ lesions, preferably when still there is no exposed bone, which allows better treatment and prevention of exposures. Therefore, studies that aimed to diagnose by imaging examinations the bone changes that precede the clinical alterations are shown to be of great value. In this regard, some authors have demonstrated the presence of regional bony sclerosis similar to cases of stages 1 to 3 BRONJ in patients characterized as stage 0 BRONJ [12].

Several imaging features of BRONJ have been previously reported [5–22], including bone sclerosis, widening of the periodontal ligament space, cortical surface irregularities, persistent extraction sockets, bone fragmentation (sequestration), and osteolytic changes. However, the frequency and consistency of these findings and the correlation between imaging and clinical findings remain unclear. The correlation between imaging findings and the temporal development of BRONJ is also unclear. Therefore, this paper offers a critical review and analysis of published information on the imaging quantitative studies for BRONJ patients, pointing at the different methodologies and results of existing literature.

2. Methodology

2.1. Search Strategy. Electronic literature search was performed in order to identify as many quantitative studies as possible that analyzed the imaging findings of BRONJ up to February 2014. Databases including Pubmed/Medline, Scielo, Cochrane's Reviews, and Scopus were searched in English.

Initially, the search for articles was based on the type of imaging examination. For this purpose, the imaging modalities for evaluating BRONJ were divided into the following four groups: (1) computed tomography (CT), including both multidetector computed tomography (MDCT) and cone beam computed tomography (CBCT); (2) plain films, including panoramic and intraoral radiographs; (3) magnetic resonance imaging (MRI); (4) nuclear bone scanning, including scintigraphy, SPECT, or PET. Figure 1 shows the flow chart of the study selection procedure.

Reports of any study design (clinical trials, cohort, case-control, and cross-sectional studies) were included investigating the imaging strategies used for diagnosing bisphosphonate-associated osteonecrosis of the jaw in patients taking intravenous bisphosphonates. All studies that performed quantitative analyses were included. The final selection was completed after eliminating the duplicated articles, case reports, case series, reviews of the literature, editorials, anecdotal letters, letters to the editors, and those articles that were not related to imaging findings for evaluating BRONJ patients.

2.2. Statistical Analysis. Statistical analysis of data from the selected studies was not attempted due to the variations in the study design, methodology, and choice of imaging modality.

3. Results

From the initial search, most of the excluded articles were not related to imaging findings of BRONJ. After eliminating the duplicated articles and those that were not related to imaging findings of BRONJ, the initial database search yielded 79 different abstracts. Nevertheless, only eleven of these initially selected studies met the inclusion criteria [6, 11, 13–21].

Regarding the excluded articles from the second search, most of the studies were case series/reports of cases (63.3%) that only described imaging features of BRONJ patients. Figures 2 and 3 show examples of the main imaging findings of BRONJ in two patients taking intravenous zoledronic acid. Furthermore, five excluded studies were performed in animals (6.3%) and 30.4% were reviews of the literature.

3.1. Characteristics of Included Papers. Information on the study patient's demographics, study design, imaging modalities, and technical parameters of the eleven included papers is outlined in Table 1. Table 2 shows the objectives, main results, and main conclusions of each selected studies.

Regarding the selected studies, 54.5% (6 studies) have used plain films radiographs and 54.5% (6 studies) were based on computed tomography findings. Only two quantitative studies were found with MRI (18.2%) and with nuclear bone scanning (18.2%).

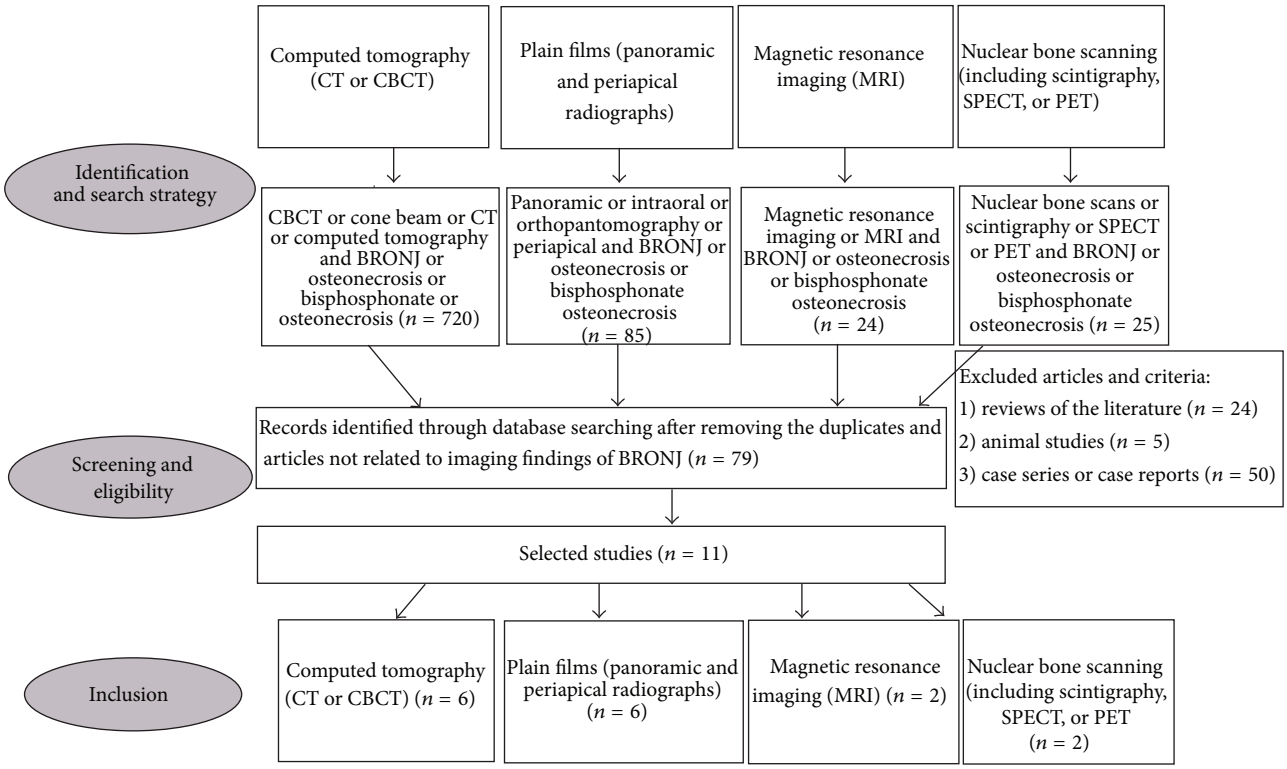


Figure 1: Flow chart of the study selection procedure.

4. Discussion

As far as we know, the present study is the first critical review aiming at discussing little evidence about imaging findings of BRONJ. Initially, we intended to perform a meta-analysis of the existing literature regarding imaging modalities for BRONJ patients. However, due to the scarcity of quantitative studies with a similar methodology, it was only possible to perform a critical review and qualitative analysis of the published studies related to this issue.

In our review, many studies (63.3%) were retrospective case series or case reports with unclear incidences and frequency estimates of imaging findings. For this reason, this kind of studies entered in the exclusion criteria of our review. An attempt has been made to collate, compare, and discuss the methodology and results of different studies that quantitatively evaluated the imaging findings of BRONJ in patients taking intravenous bisphosphonates. The reading of these selected studies showed a significant heterogeneity. In addition to the small amount of selected articles, the comparison of the findings was difficult due to the significant methodological differences between each study, conflicting results, small sample sizes, and the variability of imaging techniques. Furthermore, the absence of diagnostic test studies that report the specificity and sensitivity precluded the analysis of accuracy of each imaging modality.

Few studies have evaluated imaging findings in bisphosphonate-treated patients with stage 0 disease in the absence of bone exposure [11, 12]. The former was a prospective study conducted with clinical and dental panoramic analysis of 60 patients. Of these 60 patients, thirty were treated with zolendronate and 30 composed the control group. Patients treated with the intravenous aminobisphosphonate presented a statistically significant increase in the number of radiographic abnormalities compared with the control group. However, this selected study has not described or discussed the radiographic findings. The second aforementioned study analyzed patients receiving oral bisphosphonate therapy which is not the main risk group for developing BRONJ. As this study was only descriptive, it was excluded from our sample.

Diagnosis of BRONJ is usually made at the late stage when there is bone exposure to the oral cavity. Standard diagnosis based on clinicoradiological criteria is still lacking and there are no clinicoradiological guidelines for the health professionals to follow. In our systematic review, four of the eleven selected studies have used exclusively plain films such as panoramic and periapical radiographs [11, 14, 17, 20]. However, these studies have different objectives and methodologies and different patient populations and types of bisphosphonate therapies, which preclude a direct comparison of their results. Some authors have stated that a higher risk of developing BRONJ apparently may be predicted detecting the rise of alveolar bone mineral density that frequently occurs near the necrotic lesion [17] and by the presence of a radiographic periodontal ligament widening [14].

Dental panoramic radiograph and computed tomography can be considered as the most widely available imaging techniques for BRONJ evaluation. This can explain why most of the selected studies have used those imaging modalities [11,

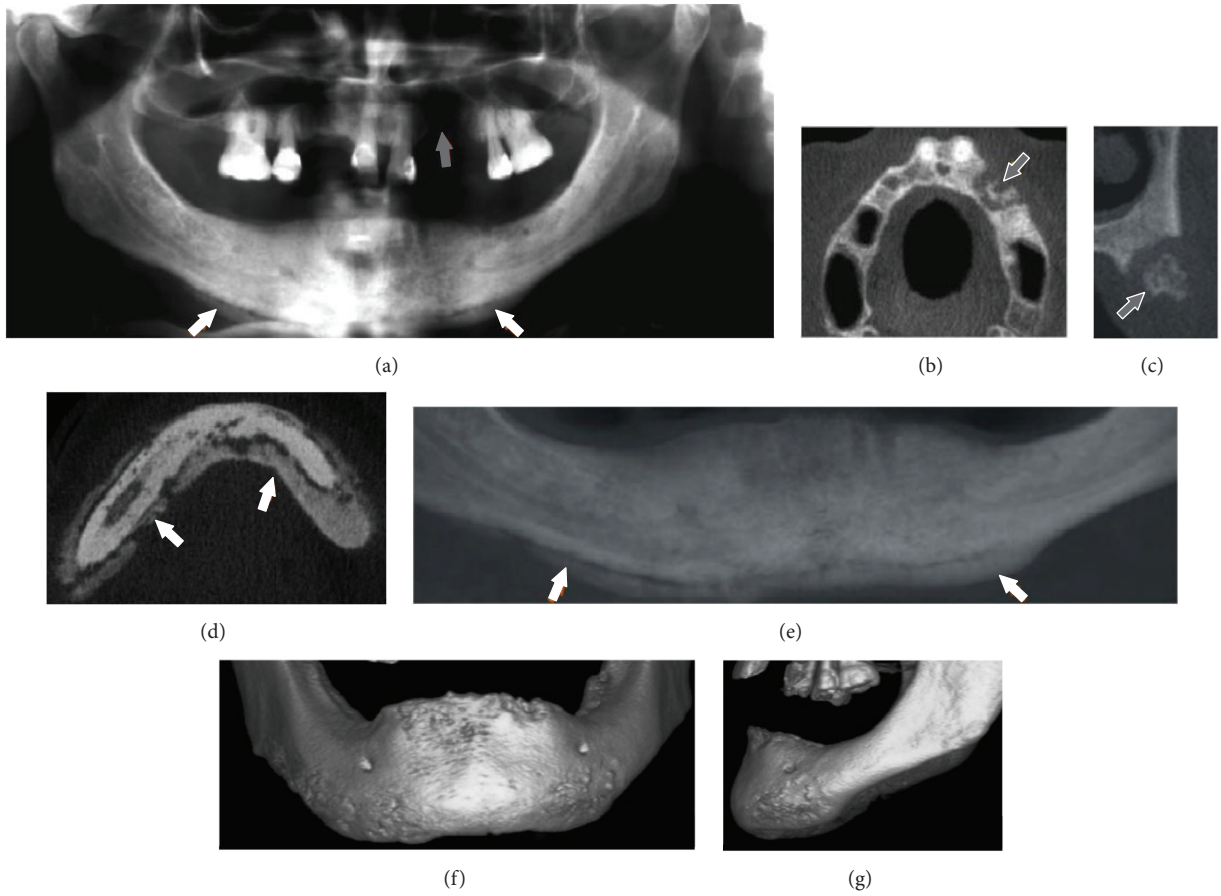
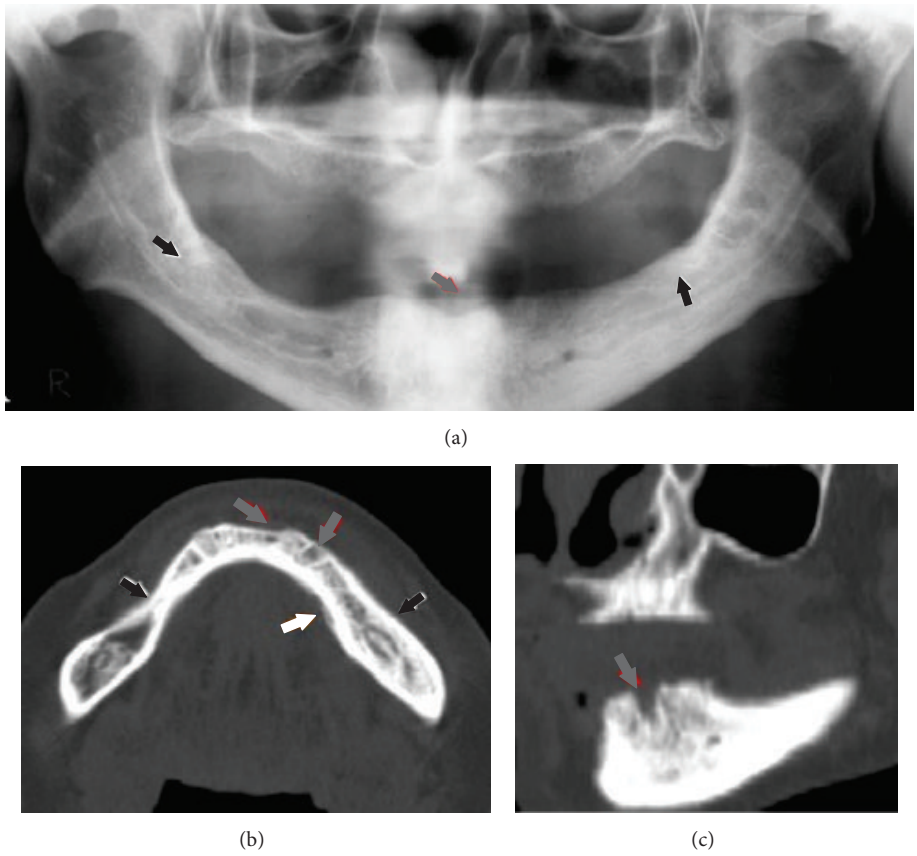


Figure 2: Imaging findings of a 57-year-old woman with metastatic breast carcinoma receiving intravenous zoledronic acid. (a) Panoramic radiograph showing maxillary involvement with radiographic evidence of osteolysis (gray arrow). (b) and (c) axial and cross-sectional CBCT views, respectively, showing the necrotic area with bone sequestrum in the left maxilla (gray arrow). (d) Axial CBCT image showing the extent of mandible bone involvement with periosteal bone reaction. The periosteal bone reaction changed the mandibular morphology, as it can be seen in the two-dimensional multiplanar reconstruction image ((e), white arrow) and in the 3D images (frontal view (f) and sagittal view (g)).

13–16, 18–20]. Furthermore, they usually detect dentoosseous changes related to this entity, including bone sclerosis, cortical surface irregularities, persistent extraction sockets, bone fragmentation (sequestration), and osteolysis.

Despite being the most used imaging modalities for BRONJ evaluation, there are some contradictory results on the selected studies. Some authors have suggested that panoramic radiographs are useful for evaluating BRONJ [11, 20]. On the other hand, other authors have stated that these radiographs are of limited value for this purpose [13, 16]. The differences may be related to the imaging modalities used in the studies. The selected studies that emphasized the role of the plain film radiographs for BRONJ evaluation have not used 3D images [11, 14, 17, 20]. On the other hand, the criticism of some authors regarding plain film radiographs was based on comparison with other 3D imaging modalities such as CT and MRI [16, 20]. Panoramic radiograph may be a useful and readily accessible imaging examination for the initial radiologic investigation in patients treated with intravenous bisphosphonates. This kind of radiography allows quick visualization of the entire affected area and seems to be able to demonstrate clear signs of osteolytic lesions mainly when radiopaque sequestra are present or when osteolysis is combined with osteosclerosis [5, 7]. In a previous cross section study with 39 patients, a correlation was found between focal panoramic radiographic findings of bone sclerosis and surface irregularity with clinical sites of BRONJ [20]. However, the disadvantages of panoramic radiograph should be recognized, such as missing definition among the margins of the necrotic areas and healthy bone, the difficulty in distinguishing osteonecrosis of a malignant lesion when an osteolytic lesion is present, and the limited image in a two-dimensional view of three-dimensional structures. Such limitations restrict the understanding of all the extent of the lesion [5, 14]. As a conventional radiograph, panoramic images often suffer from magnification, distortion, and superimposition. Moreover, a successful panoramic radiograph requires careful positioning of the patient and proper technique. Therefore, the limitations of this imaging modality for BRONJ patients should be



(a)

(b) (c)

Figure 3: Imaging findings of a 65-year-old woman with metastatic breast carcinoma receiving intravenous zoledronic acid. (a) Panoramic radiograph showing an osteolytic lesion in the anterior mandible (gray arrow) and areas of osteosclerosis in the posterior regions (black arrows). (b) Axial CBCT image reveals areas of osteolysis (gray arrows), areas of osteosclerosis (black arrows), and a periosteal bone reaction in the left mandible (white arrow). (c) Sagittal CBCT image demonstrates a nonhealing extraction socket in the anterior mandible.

emphasized, especially in elderly or noncollaborating patients [23, 24].

Computed tomography (including multidetector CT or CBCT) has been demonstrated to be superior to panoramic in detection and evaluation of BRONJ, particularly with regard to soft tissue swelling, new bone, and sequestrum [13, 16]. CBCT may also be used for detection of bone alterations by evaluating the fractal dimension of the alveolar process [18] and measuring the mandibular cortical bone that are higher in BRONJ patients [19]. CBCT may also allow the detection of subclinical, small involucra and has potential in monitoring the progression of the lesions [25]. Compared with multidetector CT, CBCT is easy to use, with short acquisition scan times and high resolution, can be performed while patients are in the upright position, and is of low cost [26].

Our systematic review has shown that the selected studies have used different imaging modalities such as periapical radiographs [14, 17], panoramic radiographs [11, 13, 14, 16, 20], multidetector computed tomography [13, 16], cone beam computed tomography [15, 18, 20], MRI [15, 16], PET/CT [15], and scintigraphy and SPECT [21]. Apparently, CT scan is extremely useful in defining the features and extent of the lesions and, in selected cases, an MRI can add value to the radiological findings by showing the soft tissue involvement. However, there have been no studies that have rigorously compared these various modalities for their utility in evaluating BRONJ, especially regarding clinically relevant end points [22].

Although imaging examination can be very useful in determining the extent of bony changes, only one selected study has compared different imaging modalities for this purpose [15]. PET/CT and MRI revealed more extensive involvement of BRONJ compared with CBCT and clinical examinations. However, only 10 patients have been evaluated in this prospective cross-sectional study. Further prospective studies are necessary to verify which imaging modality is better for evaluating the extent of BRONJ. The role of nuclear bone scanning for evaluating patients taking intravenous bisphosphonates also deserves further investigation. In a cohort study with 22 subjects, some authors have demonstrated that the relative quantification of tracer uptake provides prognostic information independent of clinical stage of BRONJ [21]. Although scintigraphy is a very sensitive investigation it may be used as a screening test to detect subclinical osteonecrosis in patients receiving bisphosphonates [7, 27], but it should be kept in mind that the rate of false positives may be high due to the lack of specificity [28].

Table 1: Study design, population characteristics, imaging methods, equipment, and set conditions of each selected study.

Authors (year)	Study design	Population characteristics	Imaging method	Equipment, contrast medium or radionucleotide, and set conditions
Bianchi et al., 2007 [13]	Cross-sectional	32 subjects (20 women; range: 48–84 years)	MDCT + PAN	PAN: Orthophos (Sirona, Bensheim, Germany; at 69–71 kV and 15 mA for 14.2 s)/MDCT: Lightspeed Pro 16 and Lightspeed QX/i (GE, Milwaukee, WI; at 120 kV and 80–120 mA, 0.6 mm slice thickness, 0.9 pitch, and 12.8 cm FOV)
Fleisher et al., 2010 [14]	Case-control	68 subjects (gender and year's range: N/E)	PER + PAN	N/S
Guggenberger et al., 2013 [15]	Cross-sectional	10 subjects (9 women; mean age 69,6; range: 53–88 years)	MRI + PET/CT + CBCT	MRI: 1.5 T scanner (Signa Excite HDxt; GE Healthcare; Milwaukee, WI). An 8-channel transmit-receive head coil was used. PET/CT: (Discovery RX or Discovery STE; GE Healthcare). CBCT: KaVo 3D eXam (KaVo, Biberach, Germany) with an amorphous silicium flat panel detector (20 × 25 cm). Exposure volume: 102 mm. Voxel size: 0.4 mm. The scan was set at a high-frequency constant potential of 120 kV (peak)
Rocha et al., 2012 [11]	Cohort	60 subjects; 30 cases and 30 controls (case: 18 women; range: 41–91 years/control: 22 women; range: 50–64 years)	PAN	Planmeca machine (Proline XC Digital model, 78 kV and 10 mA/18 s)
Stockmann et al., 2010 [16]	Cross-sectional	28 subjects (16 women; range: 57–78 years)	PAN + MRI + MDCT	PAN: Orthophos TM, Sirona, Bensheim, Germany, ×1.2 magnification; with gender specific settings (female patients, 69 kV and 15 mA; male patients, 66 kV and 8 mA)/MRI: 1.5 T (Magnetom Symphony TM, Siemens, Erlangen, Germany)/MDCT: 64-slice MDCT-Scanner (Somatom Sensation 64TM, Siemens, Forchheim, Germany). Scan settings were 120 kV, 110 mAs eff., 64 × 0.6 slice acquisition, 0.9 pitch, 1 s rotation time, 1 mm reconstructed slice thickness, 0.8 mm reconstruction increment, and sharp kernel (B70s)
Takaishi et al., 2010 [17]	Cross-sectional	48 subjects; 6 cases and 42 controls; age-matched (case: gender N/E; range: 47–75; control: gender N/E; range: 45–76 years)	PER	N/S
Torres et al., 2011 [18]	Cross-sectional	36 subjects; 9 cases and 27 controls; gender- and age-matched (case: gender N/E; range: 43–83 years; control: gender N/E; 43–84 years)	CBCT	MercuRay© CBCT System (Hitachi Medical Corporation, Tokyo, Japan)
Torres et al., 2012 [19]	Cross-sectional	58 subjects; 10 cases and 48 controls; gender- and age-matched (case: 7 women; range: 49–77 years; control: 34 women; range: 49–76 years)	CBCT	CB MercuRay equipment (Hitachi Medical Corporation, Tokyo, Japan)
Treister et al., 2009 [20]	Cross-sectional	39 subjects (15 women; range: 40–83 years)	PAN	N/S

Table 1: Continued.

Authors (year)	Study design	Population characteristics	Imaging method	Equipment, contrast medium or radionucleotide, and set conditions
Van den Wyngaert et al., 2011 [21]	Cohort	22 subjects (19 women; range 48–78 years)	SCI + SPECT	SCI: intravenous administration of medronate (methylene diphosphonate (MDP)) labeled with 740 MBq (20 mCi) Tc-99 m (Amerscan Medronate II Agent, GE Healthcare Limited, UK)/SPECT: step-and-shoot mode was used to obtain 64 projections with a zoom of 1.3, an angular range of 360° in 5.6° increments, and a duration of 30 seconds per frame. All studies were performed on a large-field-of-view dual-head whole-body camera (DST-XL or DST-Xli, General Electric/Sopha Medical Vision International, Buc, France)
Wilde et al., 2012 [6]	Cross-sectional	20 subjects (14 women; age N/E)	CBCT	Accuitomo (J. Morita MFG Corp., Kyoto, Japan) with the following parameters: 77 kV, 4 mA, scanning time 18 seconds, basis image 184, with a volume of 6×6 cm^3

MDCT: multidetector computed tomography; PAN: panoramic radiography; PER: periapical radiography; CBCT: cone beam computed tomography; SCI: planar scintigraphy; SPECT: single photon emission computed tomography; PET: positron emission tomography; N/S: not specified.

Table 2: Objectives, main results, and main conclusions of each selected study.

Authors	Objectives	Main results	Main conclusions
Bianchi et al., 2007 [13]	To verify the radiographic, demographic, and clinical features of BRONJ	MDCT was far superior to PAN in detecting all the radiologic signs. Dental panoramic radiograph may miss the correct diagnosis of sequestration. Intense reaction was often found	PAN was found to be of limited use in assessing BRONJ in patients for whom CT imaging was subsequently ordered
Fleisher et al., 2010 [14]	To verify radiographic changes that develop BRONJ after extraction and the correlation between BRONJ and reduced *serum* CTX values	All patients who had serum CTX levels <150 pg/mL healed successfully after dentoalveolar surgery or after treatment for BRONJ. 83% of patients who had BRONJ exhibited periodontal ligament (PDL) widening associated with extracted teeth, while only 11% who healed normally demonstrated PDL widening	The radiographic PDL widening may be a more sensitive indicator than CTX testing in predicting risk of BRONJ. Minimal surgical intervention may need to be revised to include alternative strategies for the elimination or management of this pathology
Guggenberger et al., 2013 [15]	To compare the extent of changes compatible with BRONJ on MRI, PET/CT, and CBCT of the jaw with clinical preoperative and intraoperative examinations	There were significant differences in BRONJ extent among modalities and examinations ($P < 0.001$).The highest median rank was seen in PET/CT and MRI imaging, followed by intraoperative examinations, CBCT, and preoperative examinations. Preoperative examinations showed significantly less extensive disease than all other modalities/examinations (all $P < 0.05$)	PET/CT and MRI imaging revealed more extensive involvement of BRONJ compared with panoramic views from CBCT and clinical examinations
Rocha et al., 2012 [11]	To compare radiographic alterations in patients taking bisphosphonate with a control group that would permit early diagnosis of BRONJ	Patients treated with zoledronate presented a statistically significant increase in the number of radiographic abnormalities compared with the control group. Female patients presented significantly more alterations than male patients, and the posterior region of the mandible was the most affected region	The use of panoramic radiographs facilitates early identification of bone alterations, which can improve early diagnosis of BRONJ
Stockmann et al., 2010 [16]	To find out the adequate imaging techniques to assess the extent of BRONJ	The detectability of BRONJ was 54% in PAN, 92% for MRI, and 96% for MDCT	MRI and MDCT have a higher detectability than PAN. The relevance of MRI and MDCT for the preoperative assessment of the extent of BRONJ is limited
Takaishi et al., 2010 [17]	To characterize alveolar bone under imminent danger for BRONJ by a radiogrammetric method on the alveolar bone mineral density	The bone mineral density surrounding the osteonecrosis lesions showed distinctly higher density in BRONJ cases compared with age-matched controls. In one subject on bisphosphonate treatment in which two extractions were simultaneously carried out, BRONJ occurred only at the location with extremely high alveolar bone density, but not at the other site with normal density	This method may be useful in detecting a rise of alveolar bone mineral density frequently occurring near the necrotic lesion in subjects with impending risk for BRONJ

Table 2: Continued.

Authors	Objectives	Main results	Main conclusions
Torres et al., 2011 [18]	To compare fractal dimensions (FD) in CBCT exams of patients with BRONJ with a control group and select the best region of interest for detecting bone alterations	The value of the FD in the area of exposed bone was the highest. The odds of being a BRONJ patient versus being a control were six times as high for individuals with a higher FD score at a region of interest in the alveolar process, although the confidence interval was quite wide owing to the small sample size	BRONJ patients had higher FD values than controls at regions close to the alveolar process. FD is a promising tool for detection of bone alterations associated with BRONJ
Torres et al., 2012 [19]	To compare cortical bone measures in CBCT exams of patients with BRONJ with a control group	The cortical bone measurements were significantly higher in cases than in controls. The bone measurements were strongly associated with BRONJ case status	Mandibular cortical bone measurement is a potentially useful tool in the detection of bone dimensional changes caused by bisphosphonates
Treister et al., 2009 [20]	To determine the extent to which clinical and radiographic features of BRONJ are correlated	There was agreement between clinical and radiographic detection. There was equivalency between BRONJ diagnosis and both sclerosis and surface irregularity. The correlation between the 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 BRONJ stage	Focal panoramic radiographic findings of sclerosis and surface irregularity correlate with clinical sites of BRONJ. This may be a useful and reliable tool to detect early changes of BRONJ or to confirm a clinical diagnosis
Van den Wyngaert et al., 2011 [21]	To identify images that predict the healing of BRONJ	SPECT acquisitions were proved superior over planar images in detecting BRONJ lesions. Quantification of tracer uptake in the BRONJ lesion relative to the unaffected side showed increasing uptake with higher stages of ONJ. The relative ratio of uptake was found to be an independent predictor of BRONJ healing BRONJ stage and relative ratio of uptake were not predictors of the occurrence of BRONJ relapses	Bone scintigraphy in patients with BRONJ is feasible. SPECT acquisitions are preferred over planar images. Relative quantification of tracer uptake provides prognostic information independent of clinical stage that may assist in identifying patients with a poor prognosis
Wilde et al., 2012 [6]	To investigate the prevalence of typical radiological findings of BRONJ in CBCT and the relationship of the imaging findings with the severity of BRONJ sites	The most common imaging findings were cancellous bone destruction and cortical bone erosion and can often be seen in all stages of the disease, including low stages. The prevalence of typical findings such as bone destruction, sequestration, and osteosclerosis seems to decrease with decreasing severity of BRONJ. The occurrence of periosteal new bone formation seems to start in high-stage BRONJ	With the exception of formation of new periosteal bone, all investigated radiological signs can be seen across all stages of BRONJ, and occurrence seems to decrease with decreasing severity of the disease. The radiological signs destruction of the cancellous bone and erosion of the cortical bone were the two most frequent and typical findings for BRONJ in CBCT scans

MDCT: multidetector computed tomography; PAN: panoramic radiography; PER: periapical radiography; CBCT: cone beam computed tomography; SCI: planar scintigraphy; SPECT: single photon emission computed tomography; PET: positron emission tomography.

This study has its own limitations. Due to the scarcity of the literature it was not possible to compare quantitatively the selected studies. Consequently, it was decided to select all the quantitative studies, despite of the significant differences in methodologies, imaging modalities, kind of studies, and populations. Although several theories about the etiology of the BRONJ have been advanced, many questions remain unanswered, especially regarding the pathophysiology [3]. The complete understanding of the pathogenesis may also contribute to the development of prevention and treatment guidelines, including the guidelines for prescription of imaging examinations.

In conclusion, this critical review showed a scarcity of quantitative studies that analyzed the typical imaging findings related to BRONJ. Further studies are necessary in order to analyze the frequency and how the typical findings appear, and also the timing of their appearance. Clinical guidelines for BRONJ need to include which imaging modality should be performed for BRONJ patients and at what time intervals. Although conventional radiographs can demonstrate evidence of BRONJ, especially when disease is advanced, there are limitations of these imaging modalities, regarding their 2D nature and also the technical characteristics. While CBCT scans provide more information regarding the extent of bone changes, the usefulness of this imaging modality in asymptomatic individuals should be better investigated. Further study would be useful to identify, based on clinical and radiographic factors, whether CBCT examinations are justified for all BRONJ patients. Nuclear medicine modalities, such as PET/CT, may also be considered as promising tools for BRONJ evaluation. Diagnostic test studies and the comparison of the various imaging modalities are still necessary.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Clinical Study

Platelet Rich Plasma in the Treatment of Bisphosphonate-Related Osteonecrosis of the Jaw: Personal Experience and Review of the Literature

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Bisphosphonates (BPs) are a class of synthetic drugs commonly used to treat bone metastasis and various bone diseases that cause osseous fragility (such as osteoporosis). Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a common complication in patients who received BPs, especially intravenously. Recently, osteonecrosis of the jaw (ONJ) caused by chemotherapeutic not belonging to BPs drug class has been reported. For this reason, it has been proposed recently to rename BRONJ in antiresorptive agents related osteonecrosis of the jaw (ARONJ), to include a wider spectrum of drugs that may cause osteonecrosis of the jaw. The most debated topic about ARONJ/BRONJ is therapy. The most adequate procedure is far from being standardized and prevention seems to play a pivotal role. In our study, we considered 72 patients with BRONJ with nonsurgical therapy, surgical therapy, and surgical therapy with platelet rich plasma (PRP) gel to evaluate its therapeutic effect in promoting ONJ wounds healing. Good results showed by PRP in improving wound healing give away to case-control randomized studies that could give definitive evidence of its effectiveness.

1. Introduction

Bisphosphonates (BPs) are a class of synthetic drugs commonly used to treat bone metastasis and various bone diseases that cause osseous fragility (such as osteoporosis). They are able to inhibit bone resorption and prevent loss of bone mass with consequent pathologic fractures, pain, and/or hypercalcemia. They can be divided into two major groups, nitrogen-containing and nonnitrogen-containing bisphosphonates, according to the presence or absence of a nitrogen atom located in the R2 group, with two different mechanisms of action on osteoclasts [1, 2].

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a pathological condition in which there is presence of exposed necrotic bone in the maxillofacial region lasting for more than 8 weeks in a patient who has received BPs and has not received radiation therapy to craniofacial region [3, 4]. There is also a "nonexposed" variant of BRONJ, where no necrotic bone is exposed, but radiographic abnormality with bone pain and swelling is present [5]. Recently, osteonecrosis of the jaw (ONJ) caused by chemotherapeutic not belonging to BPs drug class agents such as sunitinib (multikinase inhibitors) [6], bevacizumab, and everolimus (monoclonal antibody that targets vascular endothelial growth factor) [7] has been reported in patients who never have taken BPs [8]. For this reason, it has been proposed recently to rename BRONJ in antiresorptive agents related osteonecrosis of the jaw (ARONJ), to include a wider spectrum of drugs that may cause osteonecrosis of the jaw [9].

Pathogenesis of BRONJ is still unclear, but the inhibition of osteoclasts (which leads to impaired natural remodeling process, that is, a critical event for bone healing) and inhibition of angiogenesis (which slows down the healing of bone and soft tissues) are thought to play a key role. BRONJ is usually triggered by local traumas like tooth extractions, other minor dentoalveolar surgeries, and dentures [4, 10–12]. There has been reported spontaneous occurrence too [13] which is commonly caused by underlying odontogenic/periodontal infection. Anyway, it must be said that genetic/individual susceptibility is strongly involved in pathogenesis, since BRONJ does not occur in all patients [14].

Diagnosis of BRONJ is usually performed radiologically (panoramic radiographs, dental cone beam computed tomography, or spiral computed tomography). Osteolysis, osteosclerosis, thickening of lamina dura, thickening of periosteum, widening of periodontal space, subperiosteal bone formation or sequestra, fracture, and radiologic evidence of sinusitis [15] are usually seen in BRONJ lesions. Where clinically nonexposed necrotic bone can be seen, further exams such as bone scintigraphy, PET scans, or MRI may help in identifying early areas of bone involvement [16].

However, these radiological examinations have very poor specificity and similar findings may be caused in other diseases like odontogenic infections, bone involvement in multiple myeloma, or bone primary tumor/metastasis. An accurate anamnesis is thus necessary. The American Association of Oral and Maxillofacial Surgeons (AAOMS) suggested a staging system based on four stages of BRONJ/ARONJ [5, 17] as follows:

(i) stage zero is represented by the nonexposed variant, where other symptoms and signs as pain, sinus tracts, or radiologic markers are present [18];

(ii) first stage includes asymptomatic bone exposure;

(iii) second and third stage include patients with exposed bone of various extent with other concomitant symptoms and signs which are mainly a result of secondary infection of the necrotic bone. The symptoms may include increased tooth mobility, formation of sinus tracts, suppuration and traumatic ulceration of oral mucosa adjacent to exposed bone, mandibular fracture, or cervical lymphadenopathy [19].

The most debated topic about ARONJ/BRONJ is therapy. The most adequate procedure is far from being standardized and prevention seems to play a pivotal role.

Physicians who intend to treat ARONJ usually have their own protocol, which is, usually, based on drug therapy for low stage ONJs and surgical therapy (curettage or en bloc removal) for advanced stages or resistant cases [20, 21].

In our study, we treated 72 patients with BRONJ with nonsurgical therapy; in nonresponsive cases, surgical therapy or surgical therapy with platelet rich plasma (PRP) gel was performed.

2. Materials and Methods

Seventy-two patients affected by BRONJ observed at the Division of Maxillofacial & ENT Surgery, of "Istituto Nazionale Tumori, Fondazione G. Pascale-IRCCS," Naples, Italy, from May 2006 to August 2013 were included in this study. Their data/tumour history is summarised in Table 1.

Table 1: Patients data.

	Frequency
Gender (PRP)	
Male	12
Female	60
Age at diagnosis	
Minimum	37
Maximum	81
Mean	59
Primary tumor (PRP)	
Prostate	9
Breast	54
Lung	8
Multiple myeloma	1
Bisphosphonate	
Pamidronate	22
Alendronate	2
Zoledronic acid	48
Cause	
Tooth extraction	47
Prosthetic/dental trauma	25
Periodontal disease	15
ONJ status at diagnosis	
Stage 0	5
Stage I	11
Stage II	41
Stage III	15

All patients were treated with bisphosphonates (alendronate, pamidronate, or zoledronic acid) and developed osteonecrosis of the jaw. The duration of treatment with BPs varied from 4 to 62 months.

The extension and the features of the osteonecrosis were evaluated by clinical examination and radiographically with panoramic X-rays scan and CT scan. According to AAOMS suggestions, the lesions were classified as stage 0 in five cases, stage 1 in eleven, stage 2 in forty-one, and stage 3 in fifteen.

Gender, age, primary disease, and administered drug were retrospectively examined and reported in Table 1.

All patients with every grade (0, 1, 2, or 3) of lesions underwent a two-week nonsurgical treatment (per os 500 mg ciprofloxacin and chlorhexidine 0,20% mouth rinse, twice a day); thus, the status of the lesion(s) was updated. If the lesion had healed, they underwent a regular follow-up; if the lesion had improved, they continued therapy for other two weeks; if the lesion had not improved or worsened, they underwent surgical treatment (curettage or curettage + excision of necrotic bone) or surgical treatment with PRP (curettage or curettage + excision of necrotic bone, placement of autologous PRP in the residual wound, and closure of the wound), continuing the nonsurgical treatment. All the 72 patients thus underwent nonsurgical treatment; unsuccessful

nonsurgical patients were therefore moved to the surgical treatment group, for a total of 15 patients treated with surgery only and 34 patients treated with surgery and PRP.

All patients underwent regular follow-up, from 6 to 94 months.

2.1. Preparation of PRP. Autologous platelet gel was prepared at the IRCCS Pascale Foundation Transfusion Medicine OU on the same day of application; multiple samples of whole blood (total 60–100 mL) were taken from each patient and collected in 10 mL ACD vacutainers (Becton Dickinson Labware, Franklin Lakes, NJ). The amount of blood taken from each patient was based on the size, extension, and depth of the lesion to be treated. Blood was then centrifuged at 180 rpm per 10′, in order to separate concentrated erythrocytes from platelet rich plasma (PRP). Afterward, PRP was centrifuged for 10′ at 1800 rpm to separate platelet concentrate (PC) from platelet poor plasma (PPP). This process yielded 10 mL of PC, at a final concentration of $1000 \times 103/\mu$L roughly, for every 60 mL of blood.

Thrombin, used to activate platelets and accelerate the gelling process, was prepared by adding calcium gluconate to the autologous PPP, at a ratio of 0.2 mL : 1 mL, under a laminar-flow hood (Faster Bio48). After 15–40 minutes of incubation at 37°, to allow for thrombin formation, the product was centrifuged once again at 1800 g for 10–15 minutes. Then, 1 mL autologous thrombin-containing supernatant was added to the previously separated PRP, together with 0.5 mL ionized Ca in a Petri dish (Falcon, Becton Dickinson Labware), which was shaken until a gelatinous mixture was obtained (from 2 to 10 minutes).

With this technique, autologous PLT gel can be prepared in the lab in about 90 minutes; if not used in the same day, it must be aliquoted and stored at −40°C before gelling. Before administration, each sample was checked for sterility (culturing for aerobic and anaerobic bacteria and mycetes) and quality (platelet concentration in PRP).

2.2. Statistical Analysis. Different outcomes among groups were analyzed and then their statistical significance was evaluated with chi-square test (significant when $\chi^2 < 0.05$) and P value (significant when $P < 0.05$).

3. Results

Of 72 patients, 23 had complete response with nonsurgical treatment only, 15 underwent surgical treatment without PRP (8 with complete response and 7 with partial response), and 34 underwent surgical treatment with PRP (32 with complete response and 2 with partial response), as summarised in Table 2.

Success rate according to stage at diagnosis is summarized in Table 3; if stage 0 (100% of success) was not considered, no statistical difference in outcome has been found among the other staging groups.

Successful therapeutic pathway according to diagnosis stage is summarised in Table 4. For a stage 0 BRONJ, nonsurgical management was successful in every case (100%).

Table 2: Response according to treatment.

Success rates according to treatment	Frequency (%)
Nonsurgical treatment (72)	
Complete response	23 (32%)
Partial response	49 (78%)
Surgical treatment without PRP (15)	
Complete response	8 (53%)
Partial response	7 (47%)
Surgical treatment with PRP (34)	
Complete response	32 (94%)
Partial response	2 (6%)

Table 3: Treatment response according to stage at diagnosis.

Success rates according to diagnosis stage	Frequency (%)
Stage 0 (5 patients)	
Complete response	5 (100%)
Partial response	0
Stage I (11 patients)	
Complete response	9 (81%)
Partial response	2 (19%)
Stage II (41 patients)	
Complete response	31 (76%)
Partial response	10 (24%)
Stage III (15 patients)	
Complete response	11 (73%)
Partial response	4 (27%)

Table 4: Successful approaches according to stage at diagnosis.

Successful therapeutic pathway according to diagnosis stage	Frequency (%)
Stage 0 (5 patients)	
Nonsurgical	5 (100%)
Surgical without PRP	0
Surgical with PRP	0
Stage I (11 patients)	
Nonsurgical	8 (72%)
Surgical without PRP	2 (18%)
Surgical with PRP	1 (10%)
Stage II (41 patients)	
Nonsurgical	8 (20%)
Surgical without PRP	7 (17%)
Surgical with PRP	26 (63%)
Stage III (15 patients)	
Nonsurgical	2 (13%)
Surgical without PRP	6 (40%)
Surgical with PRP	7 (47%)

Nonsurgical management success rate decreases in subsequent stages (stage I: 72%; stage II: 20%; stage III: 13%).

When analyzing groups of patients who pursued the two surgical pathways (with or without PRP), PRP group was

found statistically significantly more successful ($P = 0.003$) than the surgery without PRP group.

Surgery without PRP group has shown low success percentage (53%), much lower than the PRP group (94%). Surgery with PRP group and surgery without PRP group did not show any significant difference in successful outcome among the different stages.

4. Discussion and Conclusions

Management of BRONJ is a controversial topic. Clear bone exposure is often complicated by secondary infections of the denuded bone leading to development of osteomyelitis, with abscess or fistula formation and even pathologic fractures may occur [3]. To avoid these events, which have a severe impact on the quality of life of the affected patients, different approaches have been proposed [22].

4.1. Nonsurgical Management. This approach includes antibiotics and antifungals (systemic or topical) in addition to disinfectant mouthwashes and appropriate analgesia [21, 23–27].

Some authors recommend that exposed bone should be irrigated with 0.12% chlorhexidine every 72 h for 4 weeks rather than the use of chlorhexidine mouthwash only.

It has been suggested that, before systemic antimicrobials are prescribed, wound or pus samples, or both, should be harvested for microscopy and sensitivity testing, including testing for the presence of *Actinomyces* spp. 1,5.

Among systemic antimicrobials, penicillin-based ones are commonly and widely used (phenoxymethylpenicillin, amoxicillin, co-amoxiclav, or clindamycin with or without metronidazole) [4, 25, 27, 28].

It must be highlighted that the duration of this treatment is not standardized, and suggestions range from between 7 and 15 days to very much longer treatment [27–31].

It may also be applied as a palliative approach in patients with ONJ and aggressive cancers with very poor prognosis, for whom more extensive treatment is not indicated [9].

Many authors report that nonsurgical management treats local infection and stops the progression of BRONJ even if it does not lead to the resolution of all mucosal and osseous lesions, because exposed bone in itself is not a problem [5, 28, 32].

In the short term, a conservative approach has many benefits for those who do not have advanced stage disease. Anyway relapses and progression of the disease are very common events even in patients who respond well initially [33, 34].

4.2. Surgical Management. Surgical approach founds its rationale on the evidence that exposed bone, with its sharp/irregular edges and sequestrum formation, amplifies the risk of increasing inflammation and superinfection and thus should be eliminated. Although there is a general consensus on this last topic, it is the extent of surgical intervention that causes the most debate [4, 28, 35]. Deciding the necessary quote of bone that must be removed is indeed the most difficult decision of any surgical approach proposed so far [24]. For example, French guidelines highlight that, as BPs are administered systemically, actually all margins surrounding BRONJ lesions are affected and thus should be resected [35–37]. It is a common procedure to perform resections at least until a margin of "normally bleeding" bone is obtained, as bleeding indicates a metabolic potential for healing.

Using a Wood's lamp after administration of tetracycline (250 mg four times a day for at least 3 days) or doxycycline (100 mg twice daily for 10 days) has also been suggested to help to delineate radical resection margins [38, 39].

Histologic examination of tissues should be performed only when there is a justified suspicion of underlying malignancy, because it causes further stress to soft/osseous tissues, which may exacerbate the condition [29, 30]. Types of surgical managements can be thus classified into local interventions and radical interventions.

4.3. Local Intervention. Local intervention is a surgical approach which does not involve operating on the basal bone of the mandible or maxilla, therefore removing loose or developing bony sequestra alone, but not all the necrotic zone en bloc, with minimal disturbance of overlying soft tissues and low risk of consequent bone fracture [13]. It avoids the exposure of further bone, and positive outcomes in at least 80% of cases have been reported [23–25, 29, 40–43].

Guidelines from the British Dental Association (BDA) and the American Society of Bone and Mineral Research (ASBMR) suggest a conservative surgical approach in case of small segments of necrotic bone which have not caused pathological fractures, removing sharp edges to prevent soft tissue trauma [31, 43]. Moreover, antibiotics and mouthwashes are prescribed similarly to the nonsurgical approach.

Many authors suggest the use of local flaps to expose the necrotic bone, thus aiding removal of the necrotic bone and primary closure of the wound [23, 33, 40, 42, 44–46].

Most authors recommend conservative treatment in most patients and then switching to more aggressive surgical protocol in refractory cases [20, 28, 36].

4.4. Radical Intervention. In radical management, "marginal resections" (resection of the alveolus without loss of mandibular continuity) and "segmental resections" (mandibular continuity is broken and reconstructed with bone plates) are performed. Large sections of jawbones are taken away, aiming at removing all the necrotic bone and resecting bone beyond the alveolus. AAOMS recommends using this approach in stage 3 BRONJ particularly, when lesions are very large or there is a pathological fracture [31, 43].

Authors who perform radical interventions usually report excellent results in terms of healing. Anyway, this approach exposes a major issue, which is reconstructing the defect. Options include immediate or delayed rigid plate fixation or bone graft; an obturator is recommended for maxillary defects [24, 36].

As patients thus undergo major surgical intervention(s) with this approach, medical indications for surgery must be

wisely considered, as BRONJ patients are often debilitated oncologic individuals [22, 36].

4.5. Platelet Rich Plasma. Use of PRP has been suggested by many authors to enhance postsurgical wound healing. PRP gel represents a relatively new technique, which seems, thanks to the action of multiple growth factors, to increase tissue vascularization, overtaking one of the major factors on pathogenesis of ONJs, the lack of vascularization. In addition, it is autologous and therefore it is a biocompatible and safe product. The growth factors in PRP promote angiogenesis and bone and mucosal healing. All studies report excellent results, but, as ours, they are neither case controlled nor randomized [22, 47–54].

5. Conclusions

Considering what emerges from literature reviewing and our personal experience, we consider it useful to start with any patient at any stage with a two-week nonsurgical approach. Even if it has been successful in low percentage in advanced BRONJ stages, we consider avoiding unnecessary surgical intervention to these patients a priority, avoiding both useless stress and surgical related risks; furthermore, when nonsurgical approach does not succeed, a two-week delay in performing surgery does not expose patients to major risks. Anyway, symptoms referred by patients (especially pain) must always be considered in planning treatment.

Given the necessity of properly suturing wounds when using PRP gel to enable its permanence, patients who might have had difficulties in lugging wound flaps were not included in the PRP group. Possibly for this reason, surgery without PRP group has shown low success percentage (53%), much lower than the PRP group (94%). These data and observation that surgery with PRP group and surgery without PRP group did not show any significant difference in successful outcome among the different stages highlight the importance of a satisfying closure in the complete healing of BRONJ wounds.

Good results showed by PRP in improving wound healing give a way to case-control randomized studies that could give definitive evidence of its effectiveness.

Nowadays, BRONJ management is still a controversial topic, and there is no definitive standard of care for this disease, with prevention playing a fundamental key role [12, 20, 55]. Treatment for lower stages should be conservative as possible. For advanced stages or cases refractory to nonsurgical approach, surgical resection of the necrotic bone [56] should be performed, possibly granting a proper suture of margins and, according to good reported results, inserting PRP in the residual postsurgical wound. In any case, a try of nonsurgical treatment in every patient seems mandatory.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Clinical Study

New Dimensional Staging of Bisphosphonate-Related Osteonecrosis of the Jaw Allowing a Guided Surgical Treatment Protocol: Long-Term Follow-Up of 266 Lesions in Neoplastic and Osteoporotic Patients from the University of Bari

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Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is the most serious side effect in patients receiving bisphosphonates (BPs) for neoplastic disease and osteoporosis. The aim of this study is to propose a new dimensional stage classification, guiding the surgical treatment of BRONJ patients, and to evaluate the success rate of this new management. From 2004 to 2013, 203 neoplastic and osteoporotic patients with 266 BRONJ lesions were referred to the Odontostomatology Unit of the University of Bari. All patients underwent surgery after suspension of BPs therapy and antibiotic treatment. The surgical procedure was complemented by piezosurgery and followed by the application of hyaluronate and amino acids. The new dimensional staging suggests the choice of the surgical approach, and allows the prediction of postoperative complications and soft and hard tissues healing time, guiding the surgical treatment protocol. This protocol could be a successful management strategy for BRONJ, considering the low recurrences rate and the good stabilisation of the surgical sites observed after a long-term follow-up.

1. Introduction

Bisphosphonates (BPs) are synthetic drugs analogues of inorganic pyrophosphate that can be divided into two groups, nitrogen-containing and non-nitrogen-containing BPs, with different mechanisms of action on osteoclasts [1, 2]. These compounds were originally licensed for the management of skeletal complications of malignancy, including advanced breast cancer and multiple myeloma, but now they are also the drugs of choice in the management of other bone disorders including osteoporosis, cancer-induced hypercalcaemia, Paget's disease, osteogenesis imperfecta [3–5], primary and secondary hyperparathyroidism, and other conditions that feature bone fragility [1]. The most serious side effect of BPs therapy is the bisphosphonate-related osteonecrosis of jaw (BRONJ), firstly described in 2003 by Marx [6]. BPs decrease both bone reabsorption and formation, leading to increased bone fragility and fractures caused by inability to replace old bone by young bone and to repair Microtracks [7]. According to the most widely used definition, given by the American Association of Oral and Maxillofacial Surgeons (AAOMS) and modified by Colella et al., BRONJ is the presence of exposed or otherwise necrotic bone for at least 8 weeks in patients with exposure to BPs and no history of radiotherapy to the jaw [6, 8, 9]. BRONJ can occur in patients receiving BPs therapy and appears to be associated with previous dental

traumatic injury; however, spontaneous occurrence has also been observed [6, 10–13]. Most of the incidences of BRONJ have been reported as a result of intravenous administration of high doses of aminobisphosphonates [14, 15], ranging from 0.8% to 12% [16, 17], whereas association of BRONJ and non-nitrogen BP is very rare [18], ranging from 0.01 to 0.34% [16, 17]. The risk of BRONJ development rises in the presence of long duration of BPs exposure, concomitant treatment with corticosteroids [19–21], chemotherapies [22, 23], antiangiogenic drugs [24–26], and hormone therapy or in the presence of patient comorbidities such as immunodeficiency, diabetes mellitus, obesity, hypercholesterolemia, and parodontopathies.

The existing BRONJ staging systems are numerous, and most of those systems are based on clinical findings: Ruggiero et al. in 2006 proposed a clinical staging system which recognizes three different clinical levels based on signs and symptoms [27]; then, the American Association of Oral and Maxillofacial Surgeons (AAOMS) in 2009 implemented his staging with Stage 0 [16]. Marx in 2007 [28] was the only one who divided the stages into substages according to the lesions size; and Bedogni et al. in 2012 proposed a combined clinical and radiological staging system to divide BRONJ patients into groups on the base of the radiological findings [29] (Table 1).

All of these staging systems are useful from a clinical and diagnostic point of view, but no one is surgical oriented, so no one can guide the surgeon in the management of BRONJ patients.

There are still controversies also about the adequate treatment of patients affected by BRONJ with regard to BPs discontinuation, medical therapy, surgery, or other therapies (hyperbaric oxygen therapy, ozone therapy, and laser therapy).

The rationale for BPs discontinuation is the interruption of their effects on the oral tissues, but no real good effect on BRONJ treatment connected with BPs suspension has been reported in the literature [30].

The general medical therapy consists of the combination of amoxicillin (2 g/day) and metronidazole (1.5 g/day) for at least two weeks to cover most bacteria isolated [16]. The main limitation of this therapy is the temporary clinical results, followed by a relapse of infections and symptoms after some weeks [31].

In many recent studies, surgical debridement or marginal resection, in combination with antibiotic therapy, presented better results than just medical treatment. AAOMS recommendations regarding surgery were limited just to Stage III, but several studies showed optimum results of surgical procedures also in Stage I and Stage II [32]. In last years, also other noninvasive therapies were proposed, such as hyperbaric oxygen therapy, ozone therapy, which can improve the vascular flow, and laser therapy, which can be used for biostimulation (low-level laser therapy (LLLT)) or conservative surgery, through bone vaporization by Er:YAG laser, until healthy bone is reached [30]. The aim of this study is to evaluate the outcomes of 266 BRONJ lesions in 145 neoplastic and 58 osteoporotic patients after the surgical management guided by a new dimensional stage classification.

2. Materials and Methods

From 2004 to 2013, a total of 203 patients suffering from BRONJ were referred to the Odontostomatology Unit of the University of Bari and were included in this retrospective study. The criterion for inclusion was current or previous bisphosphonate therapy due to osteoporosis or cancer disease. Patients who received radiation therapy in the oral and maxillofacial area, with an estimated overall life expectancy less than 1 year, or in presence of contraindications for general anaesthesia, were excluded from the study. A database record was designed for each included patient, with a detailed history concerning gender, age, primary disease, BPs used, administration, dose and duration of therapy, suspension of the therapy, clinical stage, size, multifocality, comorbidity, site, trigger, symptoms, signs, and recurrences.

The BRONJ lesions were staged according to their size after OPT and CT evaluation, and the surgical approach was different according to the stage (Table 2).

Our treatment protocol consisted of the following steps:

(i) radiographic evaluation;

(ii) suspension of BPs therapy if systemic conditions permit;

(iii) administration of ceftriaxone and metronidazole;

(iv) surgical debridement or marginal resection according to the stage (Figure 5);

(v) hyaluronic acid and amino acids application;

(vi) histopathological analysis;

(vii) BPs resumption not before 1 month after surgery;

(viii) clinical and radiological follow-up.

The radiographic evaluation was made through OPT examination and multislice spiral CT with 3D reconstruction (Figure 4), and all lesions were measured in centimetres to adequate the surgical treatment (Figure 1).

When it was possible, each patient suspended BPs therapy not less than 3 months before surgical procedure, and corticosteroids and chemotherapy were suspended, too, taking into account general conditions of patients and upon consultation with the treating physician and the patient. At least, 3 cycles of antibiotic therapy were administered. Every cycle consisted of a combination of ceftriaxone (1 g once a day i.m.) and metronidazole (500 mg twice a day per os) administered for 8 days with 10 days of interruption after each cycle.

The marginal bone resection included at least 1 cm of vascularized bone tissue extended in depth and in all the sides. The depth of resection was pinpointed by the bleeding evaluation of bone tissues. Noble structures and cortical bone were preserved where it was possible.

Surgery was complemented by using vibrating tips connected to a high power ultrasonic device (piezosurgery) for the osteoplasty of the residual resection margins and with the application of a medical device made of hyaluronic acid and amino acids (glycine, leucine, lysine, and proline).

The same medical device was put on the stitches from the patients (sandwich technique), after wound rinse by

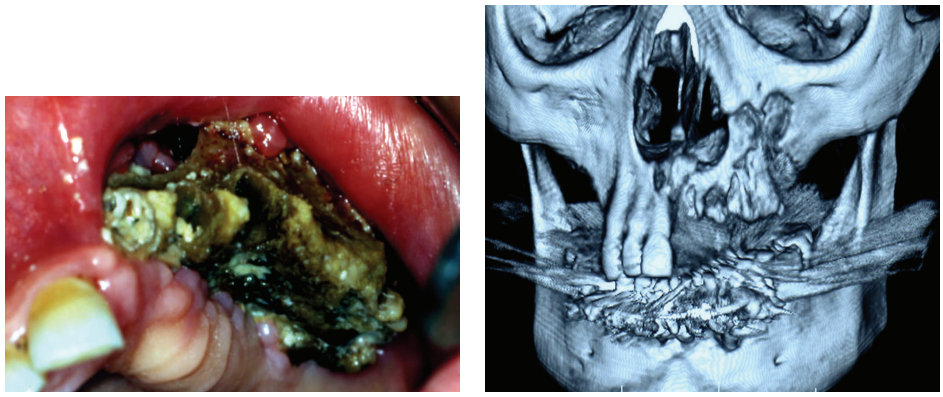
Table 1: Summary of different clinical BRONJ staging.

	Marx 2007 [28]	AAOMS 2009 [16]	SICMF and SIPMO 2012 [29]
At-risk category		No apparent exposed/necrotic bone in patients who have been treated with either oral or IV bisphosphonates	
Stage 0	Subclinical damage, microscopically represented by beginner hypocellularity osteoclast apoptosis and decrease of endosteal osteoblast	Nonspecific clinical findings and symptoms such as jaw pain or osteosclerosis but no clinical evidence of exposed bone	
Stage 1	A: painless exposed bone <1 cm B: painless exposed bone >1 cm	Exposed/necrotic bone in patients who are asymptomatic and who have no evidence of infection	Focal BRONJ Clinical signs and symptoms: bone exposure; sudden dental mobility; nonhealing postextraction socket; mucosal fistula; swelling; abscess formation; trismus; gross mandibular deformity; and/or hypoesthesia/paraesthesia of the lips CT finding: increased bone density limited to the alveolar bone region (trabecular thickening and/or focal osteosclerosis), with or without the following signs: markedly thickened and sclerotic lamina dura; persisting alveolar socket; and/or cortical disruption 1a: asymptomatic 1b: symptomatic (pain and purulent discharge)
Stage 2	A: painful and infected single exposed bone <2 cm B: painful and infected single exposed bone >2 cm	Exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage	Diffuse BRONJ Clinical signs and symptoms: the same as Stage 1 CT findings: increased bone density extended to the basal bone (diffuse osteosclerosis), with or without the following signs: prominence of the inferior alveolar nerve canal; periosteal reaction; sinusitis; sequestra formation; and/or oroantral fistula 1a: asymptomatic 1b: symptomatic (pain and purulent discharge)
Stage 3	A: multiple exposed bone areas without clinical findings of osteolysis, orocutaneous fistula, or pathological fractures B: exposed bone >3 cm or with clinical findings of osteolysis, or orocutaneous fistula, or pathological fractures	Exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border or sinus floor	Complicated BRONJ The same as Stage 2, with one or more of the following: clinical signs and symptoms: extraoral fistula; displaced mandibular stumps; nasal leakage of fluids CT findings: osteosclerosis of adjacent bones (zygoma, hard palate); pathologic mandibular fracture; and/or osteolysis extending to the sinus floor

Table 2: Dimensional staging.

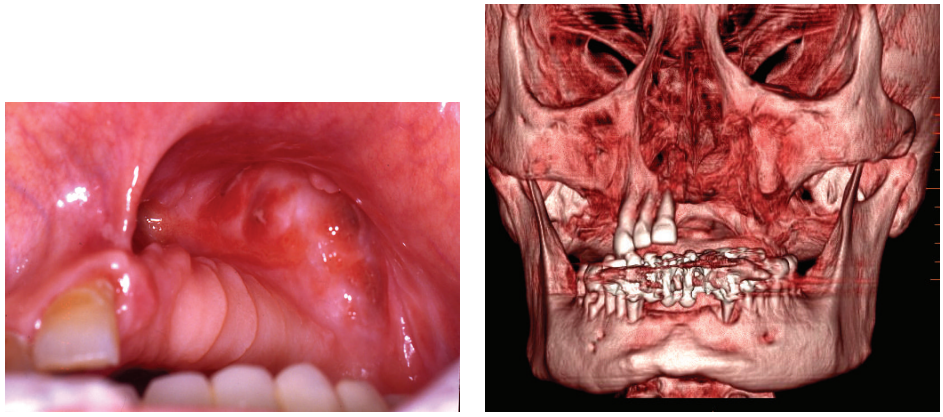
	Clinical and radiological findings	Treatment
Stage 0	No bone exposure with nonspecific radiographic findings, such as osteosclerosis and periosteal Hyperplasia, and nonspecific symptoms, such as pain	Medical therapy and clinical-radiological follow-up
Stage I	Bone exposure and/or radiographic evidences of necrotic bone*, or persisting alveolar sockets <2 cm in the major diameter, with or without pain	Medical therapy, surgical debridement, and LLLT
Stage II	Bone exposure and/or radiographic evidences of necrotic bone* between 2 and 4 cm in the major diameter, with pain responsive to NSAIDs and possible abscesses	Medical therapy and small open-access surgery with piezosurgery of bone margins
Stage III	Bone exposure and/or radiographic evidences of necrotic bone* >4 cm in the major diameter, with strong pain responsive or not to NSAIDs, abscesses, orocutaneous fistula, and/or maxillary sinus and mandibular nerve involvement	Medical therapy and wide open-access surgery with extensive maxillary or mandibular resection, the Caldwell-Luc technique, and piezosurgery of bone margins

*Radiographic evidences of necrotic bone: irregular hyper- and hypocalcified areas and/or bone sequestra.



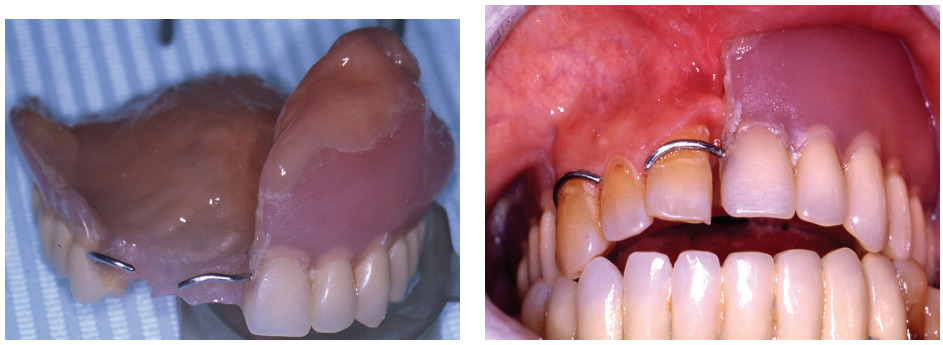
(a) (b)

Figure 1: Clinical aspect and multislice spiral CT with 3D reconstruction of Stage III BRONJ involving the maxillary sinus, in a 74-year-old female patient with multiple myeloma, who underwent zoledronic acid therapy.



(a) (b)

Figure 2: Complete bone and mucosal healing and multislice spiral CT with 3D reconstruction 13 months after surgery and intracavitary application of Aminogam gel.

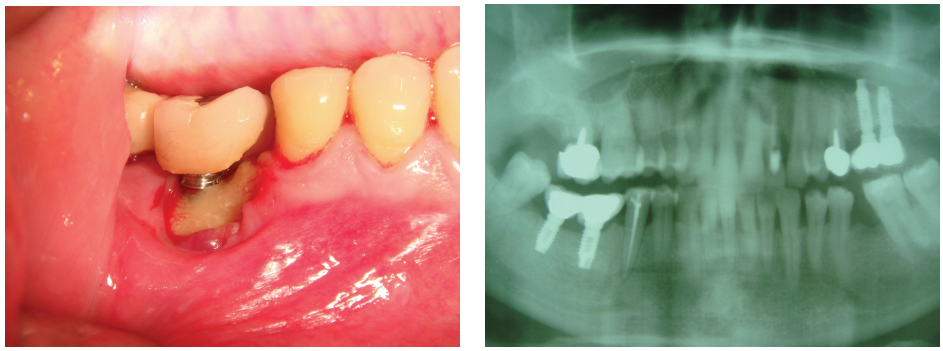


(a) (b)

Figure 3: Rehabilitation with social temporary removable prosthesis for aesthetic reasons with good stabilisation of the surgical sites.

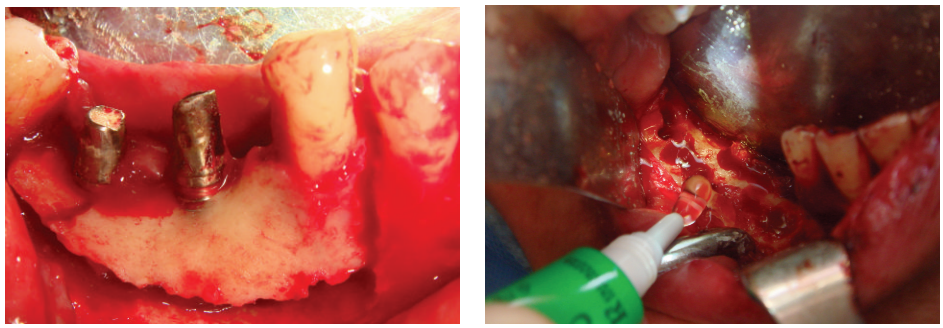
saline solution and hydrogen peroxide, at least three times a day until stitches removal. If there was sinus maxillary involvement, the Caldwell-Luc technique was used.

All the samples were fixed in 10% neutral buffered formalin and sent to the Pathological Anatomy Unit of University of Bari, paraffin embedded, thin sectioned at 3 μm, and stained with haematoxylin-eosin (Figure 6). The histological examination was carried out using Nikon Eclipse E600 microscope (Nikon Corporation, Tokyo, Japan), equipped with Argon and Helio-Neon lasers, emitting at 488 nm and 543 nm wavelengths, which allows both optical and confocal laser scanning microscope (CLSM) analysis. The Nikon EZ



(a) (b)

Figure 4: Clinical and radiological aspects of a peri-implantar Stage III BRONJ in a 55-year-old patient with breast cancer.



(a) (b)

Figure 5: Alveolar bone marginal resection and intraoperative intracavitary application of Aminogam gel.

C1 software (Nikon Corporation, ver. 2.10, Coord Automatisering) was used for bidimensional image processing. Patients could receive again BPs therapy after the complete soft tissues healing, at least 1 month after surgery. Each patient underwent an accurate clinical follow-up each week in the first month and then clinic-radiographic follow-up at 1, 3, 6, and 12 months after surgery (Figure 2).

In 20 osteoporotic patients, low-level laser therapy (LLLT) was performed for the first time during the surgical intervention directly on the residual vital bone and then three times a week for three weeks on the soft tissues. Each LLLT application was performed with Diode Laser (A2Glaser "Surgery 35") employed with a fibre of 320 μm, a wavelength of 800 ± 10 nm, and an energy output of 2 Watt. It was used in pulsed mode (on 50 ms/off 50 ms) and in a nonfocused way, at 2 mm from tissues for 1 minute, and repeated for three times.

After the 12-month follow-up, we defined "clinical success" as a treatment able to give a positive result in terms of patient quality of life that could be

(1) complete healing without symptoms or clinic-radiographic signs;

(2) transition from a higher to a lower stage of BRONJ site according to AAOMS staging (healing improvement);

(3) healing with after-effects considering bone, periodontal, or dental deficit after surgery,

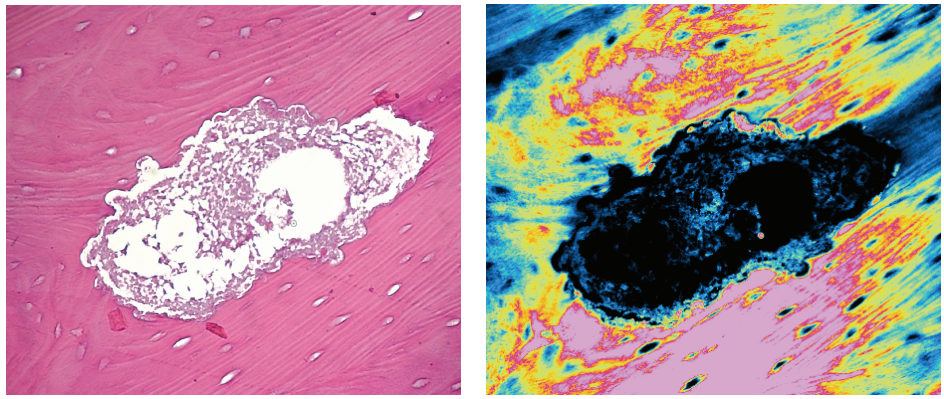
whereas we defined "recurrence" as the clinic-radiographic representation of BRONJ in the same site or in adjoining sites within 12 months from the surgery.

Data were entered into a FileMaker Pro Database and analysed using STATA MP11. The association among several variables was tested using the χ^2 test or Student's t-test, where appropriate, and a multiple logistic regression model was applied to evaluate the determinants of multifocality, stages, symptoms, and signs. Odds ratios (OR), 95% confidence intervals (CI), and the value of Z-test were calculated, and a P value ≤ 0.05 was chosen for statistical significance.

3. Results and Discussion

3.1. Sample Characteristics. Out of 203 patients, 75.37% were females; the data confirmed the high prevalence of BRONJ among women in the literature. The age range was 38 to 94 years, with a mean age of 67.8 ± 11.3 years. Among the 203 BRONJ patients, an oncologic diagnosis had been made in 71.43% of cases, whereas the 28.57% of patients received BPs for osteoporosis.

The BP most used was zoledronate, followed by alendronate, clodronate risedronate, ibandronate, and pamidronate. Off-label BPs therapy was administered in 7 osteoporotic patients. We could point out that the role of non-nitrogen-containing BPs therapy, such as clodronate, in BRONJ development should not be underestimated.



(a) (b)

Figure 6: Internal reabsorption of Haversian canals with large and irregular appearance in traditional microscopy (haematoxylin-eosin staining ×100) and the same field in confocal laser scanning microscopy with double laser inducing fluorescence (green and red).

BRONJ was due to oral administration of BPs in 22.66% of patients of this sample and to parenteral administration of BPs in the other 77.34% of patients of this sample. The mean duration of BPs therapy at presentation was 30.2 ± 28.2 months, higher in osteoporotic patients (37 ± 37.2 months) rather than in neoplastic ones (26.3 ± 17.9 months; $t = 2.8$, $P = 0.0057$) (Table 3).

The mean time of BPs therapy suspension before the surgery was 7 ± 7.6 months.

As reported in the literature, the majority of lesions were in Stage 2 AAOMS, because the BRONJ diagnosis is often linked with the appearance of symptoms, which characterize Stage 2.

According to the new dimensional staging, the majority of lesions among neoplastic patients were in Stage III, whereas among osteoporotic patients two-thirds of lesions were equally divided into Stage II and Stage III, requiring major surgery. The medium size of the lesions was 3.8±1.6 cm (range 0.6–8 cm), and the medium lesions number was 1.3 ± 0.6 per patient (range 1–4).

Comorbidity was present in 70.69% ($n = 41/58$) of osteoporotic patients and in 49.65% ($n = 72/145$) of neoplastic patients ($\chi^2 = 7.43$; $P = 0.0064$). In both neoplastic and osteoporotic patients, there was a higher predilection for mandible involvement rather than maxilla location (mandible-to-maxilla ratio 1.8 : 1), and tooth extraction was the most common triggering factor. The more common symptoms and signs detected were pain and suppuration, followed by paraesthesia, fistulas, and maxillary sinus involvement (Table 4).

The multiple logistic regression model showed a statistically significant association among the dimensional stage III and the duration of BPs exposure (OR = 1.02; $z = 2.3$; $P = 0.022$) and the recurrences (OR = 4.2; $z = 2.24$; $P = 0.025$). These results point out the determinant role of the duration of BPs exposure on the extension of the lesions and the increased odds of recurrences in major lesions. Furthermore, patients with osteoporosis showed the increase of multifocal lesions odds (OR = 1.75; $z = 11.3$; $P < 0.0001$). The result could be related to the lower importance given to this primary disease by both patients and dentists. Patients usually do not report the BPs assumptions for osteoporosis, overlooking their adverse effects, and, on the other hand, dentists do not pay attention to the medical history of the patient.

3.2. Clinical Data. The protocol we propose for the management of BRONJ showed optimum results during the follow-up period, which was not less than 12 months in all patients and more than 30 months in 80% of osteoporotic patients.

84.96% of lesions healed, whereas just 12.78% of lesions recurred. Five patients with six lesions succumbed for complications related to their neoplastic disease and chemotherapy (Table 5). Among the thirty-four lesions involving the maxillary sinus and treated by the Caldwell-Luc technique, only 14.7% recurred.

Risks and benefits of continuing BPs therapy should be planned in a multidisciplinary consultation, but, according to the Position Paper of AAOMS, BPs suspension, if systemic conditions permit it, can be indicated even in the early stage of the disease because it could stabilize BRONJ site, reduce the risk of new lesions development, reduce clinical symptoms, and improve postsurgical healing [16]. However, long cessation of BPs therapy can have severe consequences, such as hypercalcemia associated with tumours or an increase of skeletal events in patients affected by metastasis, multiple myeloma, or osteoporosis.

The three cycles of antibiotic association are mandatory remembering the two major theories, "inside-out" and "outside-in" regarding the BRONJ pathophysiology. In the "inside-out" theory, BPs inhibit the osteoclastic activity and suppress the bone turnover, together with the spread of physiologic microdamage and possibly local infection, leading the bone death within the jaw, with subsequent exposure, whereas the "outside-in" theory suggests that a break in the oral mucosa could lead to the ingress of bacteria and local infection which, coupled with poor bone remodelling, leads to bone death. BRONJ may result from a combination of

Table 3: Patients clinical data ($N = 203$).

	N	%
Patients characteristics		
Males	50	24.63%
Females	153	75.37%
Mean age	67.8 ± 11.3	
Neoplastic patients	145	71.43%
Breast cancer	58	40%
Multiple myeloma	42	28.97%
Prostate cancer	20	13.79%
Lung cancer	5	3.45%
Others	20	13.79%
Osteoporotic patients	58	28.57%
Type of BPs treatment		
Oral administration	46	22.66%
Parenteral administration	157	77.34%
Neoplastic patients		
Zoledronic acid	137	94.48%
Clodronate	4	2.76%
Risedronate	3	2.07%
Pamidronate	1	0.7%
Mean duration therapy	26.3 ± 17.9 months	
Osteoporotic patients		
Alendronate	30	51.72%
Clodronate	8	13.79%
Ibandronate	5	8.62%
Zoledronic acid	4	6.9%
Risedronate	4	6.9%
Off-label therapy	7	12.1%
Mean duration therapy	37 ± 37.2 months	

Table 4: BRONJ lesions ($N = 277$).

	N	%
Clinical stage (AAOMS)		
Lesions in neoplastic patients	195	73.3%
Stage 0	1	0.51%
Stage 1	14	7.18%
Stage 2	115	58.97%
Stage 3	65	33.33%
Lesions in osteoporotic patients	71	26.7%
Stage 0	1	1.4%
Stage 1	2	2.82%
Stage 2	53	74.65%
Stage 3	15	21.13%
Dimensional stage		
Lesions in neoplastic patients	195	73.3%
Stage 0	1	0.51%
Stage I	22	11.28%
Stage II	58	29.74%
Stage III	114	58.5%
Lesions in osteoporotic patients	71	26.7%
Stage 0	1	1.41%
Stage I	13	18.31%
Stage II	28	39.44%
Stage III	29	40.84%
Medium size	3.8 ± 1.6 cm	
History of extractions	169	63.53%
Initial symptoms per lesion ($N = 266$)		
Pain	233	87.59%
Suppuration	198	74.43%
Paraesthesia	78	29.32%
Fistulas	46	17.29%
Maxillary sinus involvement	34	12.78%

Table 5: Treatment outcomes ($N = 266$).

	N	%
Clinical success	226	84.96%
Neoplastic patients (195 lesions)	159	81.54%
Osteoporotic patients (71 lesions)	67	94.37%
Recurrences	34	12.78%
Neoplastic patients (195 lesions)	30	15.39%
Osteoporotic patients (71 lesions)	4	5.63%
Lesions in patients who succumbed		
Neoplastic patients (195 lesions)	6	3.08%

these two mechanisms, and hypovascularity also plays an important role [33, 34].

Both ceftriaxone and metronidazole could cover Gram-positive and Gram-negative bacteria, including anaerobic forms and *Actinomyces*. Particularly, ceftriaxone was preferred for its broad spectrum and relative toxicity, considering the weak defence immune system of the majority of patients with BRONJ, especially neoplastic ones.

The natural bacteria contamination of mouth suggests that a daily careful local irrigation consisting in physiological saline and hydrogen peroxide in the postoperative period is recommended.

The surgical technique, adequate to the dimensional stage and optimised to each patient, is characterized by the bone cortical preservation; thus, it improves the wound healing and implements the reossification, thanks to the scaffold function which is useful also for the gel application made of hyaluronic acid and amino acids.

As reported in the literature, the selective and micrometric cuts of piezosurgery allow the perfect integrity of the osteotomized surfaces with minimal bone loss and induce an earlier increase in BMPs and proteins, controlling the inflammatory process and stimulating the reossification. Moreover, the cavitation effect together with antibiotic therapy seems to be suitable to decrease the microbial aggregation involved in BRONJ process [35].

The intracavitary intraoperative gel filling, followed by application of the same device upon the stitches, is effective in accelerating soft and hard tissues healing, especially in minor defects. In fact, as reported in the literature, it can improve angiogenesis, fibroblast and osteoblast proliferation, collagen biosynthesis, and production of growth factors, as

Table 6: Soft tissues healing time (days).

	Stitches removal	Complete wound healing
Stage I	7–9	9–12
Stage II	12–15	14–21
Stage III	15–21	25–28
The Caldwell-Luc technique	20–23	40–45

evidenced by MTT test and alkaline phosphatase histochemical staining [36, 37]. In vivo and in vitro studies suggested that hyaluronic acid plays important roles in bone wound healing by enhancement of osteoblast differentiation through the downregulation of BMP-2 antagonists [38, 39], whereas lysine and proline are important metabolic factors regulating collagen matrix synthesis during osteogenesis [40].

This sterile gel formulation of hyaluronic acid and amino acids is a cheap, biocompatible, biodegradable, and useful medical device, able to reset postsurgical morbidity to zero. It shows immediate haemostatic and antioedema effects according to the hygroscopic properties of hyaluronic acid [40]. Furthermore, the gel viscous consistency decreases the bacteria invasion, accelerating the mucosal and bone healing time and the removal of stitches time, even in lesions involving maxillary sinus treated by the Caldwell-Luc technique (Table 6).

Histopathological examination revealed the presence of macro-osteones distant from each other in the lamellar bone, with increased separation of the Haversian canals because of the interosteonic deposition and the newly formed bone with different degrees of calcification. Abundant inflammatory infiltration with large and irregular reabsorption lacunae of the lamellar bone and abundant basophilic bacterial colonies interspersed with necrotic debris were detected.

As reported in the literature, the addition of a nonsurgical laser approach could improve the results of medical and surgical therapy, thanks to the properties of LLLT on the stimulation of reparative process, bone cells proliferation and differentiation, and lymphatic and blood vascularization [32]. The 20 patients treated with a combination of medical, surgical, and biostimulating laser therapies showed the acceleration of mucosal healing time and reossification time, suggesting that LLLT may be a valid technique to support the treatment of BRONJ. The limitation of this technique is that it needs a great cooperation of the patients who have to reach the hospital many times in the first three weeks after surgery for the phototherapy.

Patients cannot resume the BPs therapy until after the surgical area is healed, to reduce the risk of new site development.

4. Conclusions

Since the dimensional problem in the resective surgery is important, the new dimensional staging allows us to ensure better patients management considering lesions from a surgical point of view and not from a clinical aspect. The purpose of this staging is to adequate the BRONJ management to each patient choosing between general anaesthesia and conscious sedation, the number of antibiotic cycles, the way of antibiotics administration, the suitable surgical incision, the extension of surgical access, the noble structures involvement, and the adequate wound closure (simple flap, roll flap, or adipose flap), as in oncologic surgery. Furthermore, the impossibility to place bone graft in these patients makes the management worse. Thus, the different surgical approach influences the soft and hard tissues healing time and the postoperative complications (such as oedema, bleeding, wound dehiscence, infections, paraesthesia, and persistent wide bone defects), which become more predictable.

The present study showed the efficacy of the management proposed, which consisted of a combination of BPs therapy suspension, administration of ceftriaxone and metronidazole, surgical debridement or marginal resection according to the stage, hyaluronic acid and amino acids application, and resumption of BPs not before 1 month after surgery, thanks to the high success rate and the good stabilization of the surgical sites observed after a long-term follow-up (Figure 3).

Sterile gel based on hyaluronate and amino acids is a new medical device, biocompatible, extremely cheap, safe, and useful in all surgical procedures in order to obtain faster healing of both hard and soft tissues, without infective complications, thanks to the wound mechanical protection. This could be important especially in BRONJ lesions, which are often prone to difficult, slow, and complicate recovery.

Conflict of Interests

The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential, perceived, or real conflict of interests.

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Review Article

Bisphosphonate-Related Osteonecrosis of the Jaw: A Review of the Literature

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Bisphosphonates (BPs) are a class of drugs used to treat osteoporosis and malignant bone metastasis. BPs show high binding capacity to the bone matrix, especially in sites of active bone metabolism. The American Society for Bone and Mineral Research defines BRONJ as "an area of exposed bone in the maxillofacial region that has not healed within 8 weeks after identification by a healthcare provider in a patient who is receiving or has been exposed to a bisphosphonate and has not had radiation therapy to the craniofacial region." Bisphosphonate-related osteonecrosis of the jaw (BRONJ) can adversely affect quality of life, as it may produce significant morbidity. The American Association of Oral and Maxillofacial Surgeons (AAOMS) considers as vitally important that information on BRONJ be disseminated to other dental and medical specialties. The purpose of this work is to offer a perspective on how dentists should manage patients on BPs, to show the benefits of accurately diagnosing BRONJ, and to present diagnostic aids and treatments strategies for the condition.

1. Introduction

Bisphosphonates (BPs) were first synthesized in 1865 in Germany [1]. Since then, BPs have been widely used in industry, in applications such as corrosion inhibition and fertilizers. As these drugs inhibit calcium carbonate precipitation, their use as blockers of bone resorption has been strongly advocated [1]. BPs such as alendronate, risedronate, ibandronate, and clodronate are used to treat several metabolic and oncologic pathologies that promote the destruction of the skeletal system.

BPs are divided into two main categories, that is, nonnitrogenated and nitrogenated [2]. Examples of nonnitrogenated BPs are etidronate and clodronate, while zoledronic acid, pamidronate, and ibandronate are nitrogenated BPs [3].

BPs, wrongly referred to as disphosphonates in the past, are compounds characterized by two C–P bonds. If both bonds are located in the same carbon atom, the compounds are considered germinal BPs, which are analogues of pyrophosphate containing an atom of oxygen replacing an atom of carbon. While hydrolysis easily dissociates pyrophosphates, BPs are resistant to that process. Thus, they have a long half-life—one of the main reasons for BPs accumulation in the bone matrix [4]. These drugs suppress osteoclast activity, reducing bone resorption and increasing bone density. Nowadays, their main medical use is the prevention and/or treatment of osteoporosis, osteopenia, multiple myeloma, malignant tumor metastases to the bone, and Paget's disease [5].

In patients treated with oral or intravenous BPs, bisphosphonate-related osteonecrosis of the jaw (BRONJ) has been and continues to be reported as a relatively rare, but potentially severe complication. It is characterized clinically as an

Table 1: Stages of BRON-J adapted from Ruggiero et al. [17].

Stage 1	Exposed bone, asymptomatic and without evidence of inflammatory, or infectious reaction in the adjacent soft tissue
Stage 2	Exposed bone with associated pain, edema, and inflammation of the adjacent soft tissue and/or secondary infection
Stage 3	Exposed bone, with associated pain, inflammation, and infection of the adjacent soft tissue, which is hard to manage only through oral or intravenous antibiotics therapy; the presence of extraoral skin fistula secondary to osteonecrosis or a pathologic fracture is common among patients in this stage

area of exposed bone in the maxilla or the mandible that has failed to heal within a period of six to eight weeks in a patient currently or previously exposed to N-BPs who has not undergone radiation therapy in craniofacial region [6–8]. BRONJ progression is three-staged, which are identified based on clinical signs and symptoms. Recently, phase zero has been added in order to include high risk patients with no clinical evidence of necrotic bone, but with unspecific clinical signs and symptoms [9].

When administered orally, BPS absorption is low, in rates equal to or below 1% of the total dose [10]. When given intravenously, they are rapidly removed by the plasma and show a 40% renal excretion rate in the first 24 hours, without metabolization. While the half-life of BPs in the plasma is short, in bone it lasts for about 10 years [11]. Different groups of BPs may act through distinct mechanisms, but the final results are similar, that is, sharp decreases in osteoclastic activity and induction of apoptosis [12].

As BPs show great affinity for Ca^{2+} ions, mineralized bone matrix is a natural destination for these drugs. Their chemical structure provides resistance to enzymatic hydrolysis and allows BPs to bind avidly to the surface of hydroxyapatite crystals, creating a rapid and effective link between the drug and bone mineral surface [13]. Once deposited on bone surfaces, BPs promote osteoclastic apoptosis, hindering any subsequent osteoclast-mediated bone resorption [14].

Although the full mechanism of action of BPs is poorly understood, there are reports on their antiangiogenic properties as decreases in circulating levels of vascular endothelial growth factor have been observed [15]. The antiangiogenic effect of zoledronate (a 3rd generation BP) was demonstrated in rats, supporting its use in the treatment of malignant bone diseases, as well as in bone diseases with angiogenic components [15]. Oral BPs are chiefly used to treat osteoporosis and are not effective in treating malignant osteolytic lesions [16]. BPs may cause adverse reactions and most of them are related to the gastrointestinal system, such as nausea, vomiting, diarrhea, esophagitis with potential progress to esophageal ulcers; in addition, bone, muscle, and joint pain and allergic reactions are other possible adverse effects.

2. Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ)

A new complication of interest to the dental profession has been recently referred to as BRONJ. It is a serious, albeit rare adverse reaction affecting jaw bones through an unknown mechanism, with potential to cause catastrophic tissue destruction [18].

According to AAOMS, BRONJ is defined as "necrotic bone exposed in maxillofacial region lasting for more than eight weeks in BPs-treated patients who have not undergone head and neck radiation therapy" [9].

The condition seems to be restricted to maxillomandibular complex, hence the name and the acronym BRONJ; there are no works reporting on similar lesions elsewhere in the body. An explanation for such fact would be the presence of teeth [6, 7], as they render the jaws as the only bones of the body that have an unimpeded connection with the exterior [18, 19]. In addition, teeth may suffer from periodontal disease, abscesses, endodontic injuries, and other lesions, conditions that require appropriate bone metabolism and blood supply to regain homeostasis [7]. Exposure to intravenous BPs for the management of malignancy remains the sole main risk factor for the development of BRONJ, as the prevalence in such patients ranges from 0.8 to 12%. Patients on oral BPs have a considerably lower risk to develop BRONJ when compared to cancer patients receiving intravenous BPs on a monthly basis. Based on data of the manufacturers of alendronate (MERCK laboratory), the risk of BRONJ in patients on oral treatment was calculated to be 0.7/100,000 person/year of exposure [9].

3. Staging

In 2006, Ruggiero et al. [17], supported by their experience in diagnosing and managing 141 patients with BRONJ, implemented a staging system to group patients shown in Table 1.

In patients with clinically evident BRONJ, necrotic and infected bone is exposed to the oral environment, and erythema and edema of the surrounding soft tissue may be present [20]. In 25 to 40% of the cases, osteonecrosis appears in a spontaneous manner, without relation to any particular trauma or triggering condition [18, 19]. Spontaneous cases may be attributed to anatomic and physiologic traits, as they usually occur in the posterior region of the jaw where oral mucosa is thin. This is the most affected region, followed by the posterior maxilla, and mainly after dental extraction is performed [18].

In spontaneous cases, the most frequent initial symptom is an uncomfortable feeling in the mouth (paresthesia or burning sensation), with gradual changes in the mucosa, progressing to slow-healing ulcers. Pain may be intense and

it is usually caused by necrotic bone infection by oral bacterial flora. These signs and symptoms may precede clinical evidence of osteonecrosis and it is essential to recognize them in order to take all possible preventive measures, since osteonecrosis is a progressive disorder that causes extensive exposition of jaw bones that may result in bone sequestra [21].

4. Diagnosis

Diagnosis is very clear, directed by anamnesis, the history of oncologic pathology, and/or administration of BPs. Clinically evident lesions are confirmed through conventional radiographs showing radiopaque sequestrations, which are usually round with irregular peripheral radiolucencies [22].

Radiologic and nuclear medicine imaging may be valuable in recognizing and defining bone lesions in patients undergoing BPs therapy [21]. In the early phases of BRONJ, radiographic manifestations are not detected; however, as the disease progresses, osteonecrosis of the jaw may become readily identifiable in X-rays. When BRONJ is established, a poorly defined osteolytic area is seen along with cortical destruction, loss of cancellous trabeculation, and a decrease in bone density (similar to the radiological findings of osteomyelitis). Early osteonecrosis restricted to small areas of bone exposure (<1 cm) may be undetectable in panoramic radiographs; however, signs of bone destruction arising from this process may be recognized in computed tomography [23]. Computed tomography (CT) may allow a greater definition of the necrotic focuses and their relationship with neighboring anatomic structures, making it possible to quantify the status of bone sclerosis. However, CT may not be useful in staging asymptomatic patients [22].

According to Chiandussi et al. [21], scintigraphy exams may be useful in initial assessment of BRONJ patients. In some patients, there seemed to be a significant decrease or even complete absence of radioisotope intake, indicating low bone metabolism due to the absence of blood supply. However, these imaging resources are not able to show the difference between BRONJ and other causes of bone exposure in the jaw, such as osteoradionecrosis, osteomyelitis-related osteonecrosis of the jaw, or steroid-induced osteonecrosis [23]. Scintigraphy (Tc99-scan) is the most sensitive diagnostic strategy to identify edema and vascular changes and to locate bone necrosis even in the early stages of the disease. Nevertheless, this diagnostic technique has limitations: Tc99-scan is unable to distinguish BRONJ from metastatic processes [21, 24]. Biopsy of bone lesions must be carefully evaluated because the procedure itself may damage the bone tissue, causing a wound that may never heal properly [25].

Histological characteristics of osteonecrosis of the jaw include necrotic bone with bacterial colonies and granulation tissue [26] as well as decreased vascularization and number of osteoblasts [20]. Some biopsy specimens showed fungal and bacterial colonies. In malignancy patients treated with BPs, such lesions occur irrespective of existence of jaw metastases [26].

5. Risk Factors

The exact mechanism leading to BRONJ is unknown. However, risk factors to develop this condition may be divided into three: risk factors related to drug intake, local risk factors, and systemic risk factors [7]. The AAOMS, in 2009, also mentioned anatomic traits (torus palatinus and mandibular, the mylohyoid line), advanced age, being of Caucasian descent, and other genetic specificities as additional risk factors. Despite being low, the risk of developing BRONJ increases when BP use is longer than three years, and such time is reduced for patients on chronic corticosteroids [9].

6. Prevention

Before treatment with intravenous BPs, a patient should undergo thorough intraoral examination followed by comprehensive dental treatment. In addition, optimal periodontal health should be regained if not present. There seems to be no contraindications for elective oral surgery in patients on oral BPs without signs of bone exposure and less than three years of drug usage. When the therapy is shorter than three years and combined with corticosteroids, the clinician should consider a "drug holiday" of three months before elective oral surgery, extended to the following three months whenever the patient's systemic conditions allow. Such considerations should also be taken if the use of BPs is longer than three years regardless of concomitant use of steroids [9].

7. Treatment

To date, treatment option for patients with BRONJ is limited and predominantly palliative, aiming at relieving the main signs and symptoms [7]. Marx et al. [7] recommend that treatment should eliminate and control pain, as well as preventing progression of bone exposure through antibiotics therapy and mouthwash with 0.12% chlorhexidine. They also state that conservative surgical treatments are preferential, aiming at nonexposure of necrotic bone boundaries. AAOMS in 2009 recommended the removal of well-defined bone sequestrations, as well as the removal and/or relining of bone necrosis areas which are a constant source of irritation to soft tissues [9].

Montebugnoli et al. [27] also recommended the management of osteonecrosis with nonsurgical protocol. These authors conducted a study dividing patients into two groups, one treated with surgery and the other treated with antibiotics. Data analysis showed there was no statistically significant difference between outcomes for the two groups.

Curi et al. [28] reported on three clinical cases in which sequestra removal was performed and autologous platelet-rich plasma was topically applied onto the remaining defect. After six-month follow-up, complete repair of surgical site was seen, thus showing promising results.

Discontinuation of oral BPs in BRONJ patients has been associated with gradual improvement of clinical disease [29]. Discontinuation for 6–12 months may result in sequestration with spontaneous resolution after surgical debridement. Whenever systemic conditions permit, changing or stopping

oral bisphosphonate treatment must be a result of an agreement between the professionals involved and the patient [9].

8. Discussion

Intravenous BPs are usually considered stronger than those given orally. Therefore, use of intravenous BPs is one of the main risk factors to induce BRONJ, as evidenced by the higher estimates of BRONJ incidence (0–10%) in patients treated with IV drugs as compared to an oral therapy (<1%) [30, 31].

Among the BPs, those more likely to induce BRONJ are amino-BPs [25, 32, 33], possibly because they are stronger than alkyl-BPs. Pamidronate, alendronate, and zoledronate are 10, 100, and 1000 timer stronger than clodronate, respectively [31]. Bone necrosis is considered dose- and time-dependent due to the long half-life of BPs in the bone [25].

In patients who used BPs and did not experience osteonecrosis, preventive measures should be taken, since osteonecrosis may appear up to one decade after the start of bisphosphonate therapy. Patient should be advised to undergo thorough oral examination every 3 months [34].

If osteonecrosis develops, nonsurgical management may be beneficial and is based on antibiotic therapy. A "drug holiday" may be considered in severe cases if benefits overcome the risks of bone complications, although improvement has not been observed to date [33, 35]. Similarly, hyperbaric oxygen therapy is not effective and, therefore, not recommended [35].

9. Conclusions

The importance of a good anamnesis and history taking greatly helps the healthcare professional in the correct diagnosis of BRONJ lesions. Warning patients of the necessary care and the potential oral manifestations, which are often forgotten or ignored, and maintaining a professional relationship with the accompanying physician and/or oncologist are essential for the good clinical management of patients on BPs. All healthcare professionals should provide guidance for patients on BPs in the sense that good oral health should be kept by all means, since oral surgical treatment could lead to BRONJ. For those patients using BPs but who have not experienced BRONJ, preventive measures should be taken, as the condition may appear up to one decade after therapy start. Appropriate oral hygiene, along with frequent oral examination and minimally invasive dental treatment, when needed, are all clinical choices that must be adopted in order to avoid BRONJ development.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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