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CONSERVATIVE NON-SURGICAL TREATMENT OF MEDICATION-RELATED OSTEONECROSIS OF THE JAWS: A LONG-TERM PROGNOSTIC EVALUATION

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Ai nuovi inizi…

ABSTRACT

BACKGROUND: The conservative non-surgical treatment of medication-related osteonecrosis of the jaws (MRONJ) is generally advisable in patients with poor general health and/or a concomitant malignant disease as the priority is to control signs of infection and symptoms and to prevent a further bone disease progression.

AIMS: the aim of this study is to conduct an exploratory analysis on the long-term outcomes of the exclusive conservative non-surgical treatment on a big sample of MRONJ patients, all having a minimum follow-up of at least 12 months.

METHODS: A retrospective medical record review of patients diagnosed with MRONJ was carried out in three Oral Medicine /Oral Maxillofacial outpatients' departments. The conservative non-surgical treatment consisted of the use of local antiseptics with or without the use of antibiotics cycles. Regardless of stage, mobile fragments of bone were managed with non-surgical sequestrectomy. MRONJ lesions were staged according to both the American Association of Oral/Maxillofacial Surgeons staging system and the SICMF- SIPMO staging system. The primary outcome was the pain remission. Secondary outcomes were remission of signs of infection and complete clinical remission of MRONJ lesion.

RESULTS: One hundred and twenty-six patients were included in the study and observed for a mean time of 39.73 ± 27.38 months. About seventy-one percent of the sample was composed of oncologic patients. 51.1% of the MRONJ lesions had never experienced pain or relapses after the first pain remission, while in 46.8% relapses were successfully treated with medical therapy. Only in the 2.1% pain was persistent. 93% of the patients achieved either complete clinical healing of the lesions (32%), or a clinical stable disease (61%) experiencing pain and signs of infection remission. Only 7% of the patients were refractory to the non-surgical treatment and needed surgical interventions in order to achieve a better pain/infection control.

CONCLUSIONS: Although one third of the patients achieve complete clinical remission of MRONJ lesions, the non-surgical treatment had demonstrated to be effective in controlling pain and signs of infection in almost all the patients. Prospective multicenter, controlled trials are necessary to better determine the relative effectiveness of the non-surgical treatment for a more evidence-based approach to management of MRONJ.

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CONSERVATIVE NON-SURGICAL TREATMENT OF MEDICATION-RELATED OSTEONECROSIS OF THE JAWS: A LONG-TERM PROGNOSTIC EVALUATION

1. MEDICATION-RELATED OSTEONECROSIS OF THE JAWS (MRONJ)

1.1 Historical overview and definition

The exposure of necrotic bone in the oral cavity was observed for the first time in cancer patients treated with bisphosphonates by Marx and coll. in 2003 (Marx, 2003). Since then, within a few years, a growing number of bisphosphonate-related osteonecrosis of the jaws cases (BRONJ) have been reported worldwide (Filleul *et al*, 2010).

Bisphosphonates (BPs) are a group of drugs used in the treatment of several bone diseases. Particularly, they have been extensively used in the treatment of bone metastases from solid tumors of various origin - breast, prostate, kidney cancer; in the treatment of multiple myeloma or malignant hypercalcemia (Terpos *et al*, 2009; Aapro *et al*, 2009). BPs are also widely used both for the treatment of benign bone metabolic diseases such as osteoporosis and Paget's disease of bone, being effective in reducing the incidence of skeletal adverse events; both for the prevention of osteoporosis (i.e. postmenopausal osteopenia; iatrogenic drug-induced osteopenia) (Alonso-Coello *et al*, 2008). Therefore, BPs are drugs widely used with different dosages (millions of prescriptions each year, worldwide), routes of administration (mainly oral or intravenous, sometimes intramuscular) and duration (often prolonged over the years) (Abu-Id *et al*, 2008).

The etiopathogenesis of BRONJ, is multifactorial (still not fully clarified) with the participation (partial or total, even in subsequent moments) of several mechanisms and / or events, such as the anti-

resorptive activity of BPs, through osteoclastic inhibition and consequent alteration of bone turnover; the presence of infectious-inflammatory foci; the possible anti-angiogenic effect of some BP (zoledronate); the toxic effect of BPs on cells other than osteoclasts (e.g. mucosal barrier); the alteration of immunity at the level of the bone microenvironment; • amplifying effect linked to the deposit and subsequent release of BP molecules in the bone tissue; • other possible factors (not fully demonstrated), such as microtrauma repeated or deficient states (e.g. hypovitaminosis D).

However, from 2008, a number of cases of osteonecrosis of the jaws very similar to BRONJ but not associated to BIs started to be reported. Patients were on therapy with other categories of drugs such as denosumab which is a monoclonal antibody with anti-resorptive activity administered for the treatment of both osteoporosis or bone metastases from solid tumors (Stopeck *et al*, 2010; Fusco *et al*, 2011; Saad *et al*, 2012; Bagan *et al*, 2016); •or agents defined as target molecular agents (in particular with anti-angiogenetic activity), such as: bevacizumab, sunitinib, sorafenib, aflibercept, alone or in combination with BP and / or denosumab (Troeltzsch *et al*, 2012; Hamadeh *et al*, 2015; Fusco *et al*, 2016). Regulatory agencies have therefore disclosed new risk "alerts" of ONJ related to the use of drugs other than BP and, in particular, bevacizumab, sunitinib, denosumab and aflibercept. One of the peculiarities of ONJ (both BRONJ and non-BRONJ) is the localization almost exclusive to the maxillary bones (have been reported sporadic cases in the auditory canal). Possible causes of the localization in the maxillary bone and mandible are not yet fully known, but a series of reasons have been hypothesized to date, listed below: 1. physiologically higher bone turnover of the maxillary bones compared to the remaining skeleton (Marx, 2003) 34; 2. terminal vascularization of the mandible (Bagan *et al*, 2005).

The first (and most popular) definition for BRONJ was formulated in 2007 by the American Association of Oral and Maxillofacial Surgery (AAOMS): “presence of necrotic bone exposed in the oral cavity for more of eight weeks in patients on bisphosphonate therapy and never subjected head

and neck radiotherapy " (Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons, 2007). This definition identified as a diagnostic criterion, in patients exposed to BP, the exclusive recognition, purely clinical, of the most typical manifestation of disease (necrotic bone exposed in the oral cavity), persistent for more 8 weeks, with the absolute exclusion of radio-treated patients in the head-neck region.

However, several studies have later suggested that patients can present also with non-exposed ONJ, which is a clinical variant characterized by otherwise unexplained pain to the jaws, sinus tract, tooth mobility, gingival swelling, as well as bone enlargement and pathological fracture in absence of frank bone exposure(Bagan *et al*, 2005; Fedele *et al*, 2010; Mignogna *et al*, 2012; Patel *et al*, 2012). Indeed, a recent paper has demonstrated that up to 25% of patients with MRONJ induced by antiresorptive medications could remain undiagnosed because of the absence of bone exposure (Fedele *et al*, 2015) when the traditional definition/classification of ONJ by the American Association of oral and Maxillofacial Surgeons (AAOMS) is adopted.

With reference to the first definition, in 2009 it was later inserted a condition, potentially correlated to BRONJ, but in the absence of necrotic bone exposure, defined "Stage 0" 12 (‘American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws—2009 Update’, 2009). Moreover, following the ascertained etiological role of other drugs (e.g. denosumab) and the established existence of clinical pictures related to ONJ also if not clinically evident (such as exposed necrotic bone), the AAOMS changed the name of the pathology to MRONJ in 2014, replacing the previous definition in favor of the following: “presence of bone necrotic or intra / extra oral fistula in the maxillofacial area for more than 8 weeks in patients on anti-resorptive drug therapy and / or anti-angiogenics, never subjected to head and neck radiotherapy with the inclusion of cases that at least in part were in keeping with the concept of non-exposed variant (“bone that can be probed through an intraoralor extraoral fistula”) "leaving the presence of "stage 0", as previously defined (‘American Association of Oral and Maxillofacial Surgeons Position Paper on Medication-Related Osteonecrosis of the Jaw—2014 Update’, 2014).

However, a proper and thorough radiological classification of the pathology by means of specific investigations, was not covered by the definitions of the AAOMS (Colella *et al*, 2009; Yarom *et al*, 2010; Bedogni *et al*, 2012, 2014; Fedele *et al*, 2015). In light of this observation, in 2011 a Commission of experts joined with the Society of Maxillofacial Surgery (SICMF) and of the Italian Society of Pathology and Oral Medicine (SIPMO), proposed and released another disease definition and staged ONJ taking into account the radiological features rather than the pure clinical appearance (Bedogni *et al*, 2012). Below at the end of the introduction section, Tables 1 and 2 summarize the principal characteristics of the two staging systems.

1.2 Epidemiology

The real estimated incidence of MRONJ is currently unknown, as definitive prospective data are lacking in the literature. Moreover, the frequency estimates available in the different populations and subpopulations at risk present a great variability.

Indeed, due to the heterogeneity of the studies available in terms of study design, diagnostic criteria, length of therapy, and clinical manifestations, incidence and prevalence figures of MRONJ vary widely among studies. (Bagan *et al*, 2009; Malden and Lopes, 2012; Kühl *et al*, 2012). Cases of MRONJ have been reported in all categories of treated patients with anti-resorptive drugs such as bisphosphonates and denosumab, and, although with a lower incidence, in oncologic patients treated with monoclonal antibody, especially the anti-angiogenic drugs. According to the most recent evidences, MRONJ may occur in approximately 0.01-0.04% of osteoporosis patients receiving low-potency oral bisphosphonates, and in about the 7% of oncologic patients treated with high-potency intravenous bisphosphonates (Bagan *et al*, 2009; Malden and Lopes, 2012; Kühl *et al*, 2012).

Of note, the incidence and prevalence of MRONJ among cancer patients widely vary. For instance, the incidence of MRONJ ranges from 1.2% to 6.2% in patients with breast cancer, from 1.7% to 17.2% in patients with multiple myeloma, and from 2.9% to 18.6% in patients with prostate cancer (Sanna *et al*, 2005; Bamias *et al*, 2005; Kraj *et al*, 2006; Mavrokokki *et al*, 2007; Wang *et al*, 2007; Hoff *et al*, 2008; Boonyapakorn *et al*, 2008; Walter *et al*, 2008, 2009; Vescovi, Merigo, *et al*, 2012). The incidence of MRONJ associated to high dose of denosumab in oncologic patients has been reported to be approximately 1.8% after 1 year of therapy, similarly to the figures of intravenous bisphosphonates (Saad *et al*, 2012; Hinchy *et al*, 2013; Qi *et al*, 2014).

Based on the data of a large retrospective study on 2,408 cases of ONJ, multiple myeloma was the most common underlying cancer (43%), followed by metastatic breast cancer (32%), prostate cancer

(9%) and other cancers (5%) (Filleul *et al*, 2010).

While initially there were no reports of ONJ in osteoporosis patients treated with Prolia®, therefore with doses per year of denosumab much lower than those used for cancer patients, the first cases started to appear later in non-cancer patients treated with denosumab (Aghaloo *et al*, 2010; Rachner *et al*, 2013; Otto *et al*, 2013; Olate *et al*, 2014; Neuprez *et al*, 2014; Vyas *et al*, 2014; Favia *et al*, 2016).

Additionally, there are several evidences reporting an increasing risk of ONJ in patients taking number of concomitant medications including chemotherapy, corticosteroids and antiangiogenic medications (Saad *et al*, 2012; King *et al*, 2019).

Of note, after antiangiogenic agents have been introduced in cancer treatment asmonotherapy, the development of MRONJ lesions in naïve-antiresorptive agents patients started to increase (Estilo *et al*, 2008; Guarneri *et al*, 2010). Although the epidemiological data on cases of MRONJ exclusively associated to antiangiogenic agents remains unknown, according to the figures from clinical trials on breast cancer patients, the prevalence of MRONJ in patients receiving bevacizumab without exposure to bisphosphonates was first reported as 0.2% (Guarneri *et al*, 2010).

In addition, in the recent years, there has been a growing number of MRONJ cases in oncological patients treated with molecularly targeted biological drugs (so-called Target Therapy), not only with anti-angiogenic agents (i.e., bevacizumab, aflibercept), alone or in conjunction with bisphosphonates, but also with other different molecules: tyrosine kinase inhibitors (i.e., sunitinib, sorafenib, cabozantinib, regorafenib, axitinib, lenvatinib); m-TOR inhibitors (i.e., temsirolimus, everolimus). The frequency of ONJ is significantly higher among patients treated with both anti-resorptive drugs (bisphosphonates or denosumab) and with target drugs and the onset time of MRONJ lesions is shorter (Pimolbutr *et al*, 2018).

1.3 Clinical features

MRONJ may present with different clinical features, although two principal types of MRONJ have been identified: the non-exposed MRONJ and the traditional exposed MRONJ. In early stage of MRONJ, patients may present with the absence of necrotic bone exposure with or without symptoms before progressing to symptomatic necrotic bone exposure (Mawardi *et al*, 2009). Specifically, patients affected by the non-exposed MRONJ variant, may complain of unexplained pain at the affected site followed by persistent sinus tract formation, bone enlargement, gingival enlargement and severe tooth mobility (Junquera and Gallego, 2008; Mawardi *et al*, 2009; Fedele *et al*, 2010). It has been estimated that approximately one third of patients with MRONJ can develop one or more of the above mentioned signs or symptoms at the site of MRONJ without bone exposure (Fedele *et al*, 2010). Even patients with exposed MRONJ can present with a wide range of clinical signs and symptoms, such as the presence of necrosis bone exposure which may be symptomatic or asymptomatic, with smooth or irregular border of soft tissue, intraoral sinus tract with purulent discharge, cutaneous sinus tract, oronasal communication, oroantral communication,bone exposure through the skin and pathologic fracture, Vincent's sign etc. (Marx *et al*, 2005; Ruggiero *et al*, 2014).

MRONJ has been reported to develop more frequently in the mandible than the maxilla(Marx *et al*, 2005), especially in the posterior area of mandible, followed by the posterior maxilla and anterior mandible areas (Marx *et al*, 2005; Badros *et al*, 2006). Nonetheless, MRONJ lesions may occur simultaneously in both mandible and maxilla in a small number of patients (Marx *et al*, 2005; King and Umland, 2008; Saad *et al*, 2012)..

With respect to radiographic presentation, at early stage patients can present with normal radiographs (Badros *et al*, 2006) although some authors have reported minor bony changes on radiograph such as sclerosis and widening of periodontal space (Woo *et al*, 2006). In advanced cases of MRONJ, radiographic examinations show a moth-eaten ill-defined osteolysis/radiolucency area with or without sclerotic areas, compared with trabecular pattern

of surrounding bone(Marx *et al*, 2005; Woo *et al*, 2006; Hutchinson *et al*, 2010; Hamada *et al*, 2014). Computed tomography (CT) has been demonstrated to be superior in detecting disease extension and margins, as it can provide clearer views of the cortical bone destruction at the areas of MRONJ and can accurately define the extension of the disease (Bianchi *et al*, 2007; Arce *et al*, 2009). On the contrary, routine dental radiographs such as panoramic x-ray and periapical radiographs are unlikely to be able to identify the extension of involved areas of MRONJ particularly in early stage (Bedogni *et al*, 2014).

1.4 Pathogenesis

Pathogenesis of MRONJ still remains not completely explained, although different pathogenetic mechanisms have been proposed (Hinchy *et al*, 2013). Although the exact mechanisms of bone necrosis development remain unknown, the association with bisphosphonates, denosumab and antiangiogenic agents is well established, and several theories have been suggested so far, including the suppression of bone remodeling/turn-over,, the inhibition of soft and hard tissue angiogenesis, infection, and immune dysfunction(Marx *et al*, 2005; Yamashita *et al*, 2010; Ruggiero *et al*, 2014).

Suppression of bone remodeling is the most widely accepted pathogenetic hypothesis of MRONJ(Allen and Burr, 2008). As a result of bisphosphonates administration, the inhibition of osteoclast formation, the decrease in osteoclast number and the inhibition and alteration of osteoclast activity have been reported as the effects of bisphosphonates to the cells (Rodan and Fleisch, 1996).

The bone turn-over process consists of osteoclast-mediated bone resorption followed by the new bone deposition (Marx, 2014). Osteoclasts are the main target of bisphosphonates and due to highly specific affinity of hydroxyapatite, bisphosphonates are taken to mineral bone surface especially the areas of bone formation and resorption before being absorbed into osteoclasts by intracellular endocytosis pathway (Russell *et al*, 2008) inducing osteoclast

apoptosis (Russell *et al*, 2008). Moreover, bisphosphonates affect bone remodeling by inhibition of osteoclast activity and the disruption of bone remodeling also impact the bone healing process(Novince *et al*, 2009). In microscopic examination there is evidence of an altered bone- remodeling pattern in patients treated by bisphosphonates showing the decrease in osteoclast activity followed by prominent new bone formation. As a consequence, this thickening bone supplied by fewer blood vessels, may become ischemic and necrotic due to the alteration of bone remodeling resulting in inadequate blood supply (Favia *et al*, 2009). Indeed, new bone formation would not be supplied by sufficient blood vessels due to smaller and lower density of Haversian canal, thus leading to ischemic necrosisof the bone (Favia *et al*, 2009)

However, it remains unclear why the osteonecrosis process is limited to the jaw bones. It has been suggested that one of the factor may be that the blood supply in the jaws is greater than other bones in the body so that the deposition and concentration of bisphosphonates in the jaws may be higher than in other bones (Marx *et al*, 2005). Therefore, this may explain the occurrence of MRONJ in the jaw bones rather than other skeletal sites (Marx *et al*, 2005; Woo *et al*, 2006). Nonetheless there are other etiological factors to be taken into account causing MRONJ. Moreover, other factors such as comorbidities and local trauma might be involved in the initiation of MRONJ (Allen and Burr, 2009).

Another potential pathogenetic mechanism inducing MRONJ is the suppression of angiogenesis (Yamashita *et al*, 2010). Zoledronic acid, for instance, has been demonstrated to have antiangiogenic properties, (Wood *et al*, 2002; King and Umland, 2008) both in vivo and in vitro models as it can inhibit endothelial cell proliferation (Wood *et al*, 2002) and further suppress angiogenesis in the bone through a reduction in bone remodeling (Parfitt, 2000). Moreover, in the recent years, there have been a growing number of cancer patients developing MRONJ after receiving antiangiogenic agents such as bevacizumab and sunitinib as monotherapy (Hamadeh *et al*, 2015). These agents, by binding to vascular

endothelial growth factor (VEGF) or others factors in angiogenesis, inhibit vascular formation (Kerbel, 2008). These reports support the evidence that anti-angiogenesis has an important role in MRONJ development (Wynn, 2011; Hamadeh *et al*, 2015).

Also, local infection has been suggested to be a causative factor of MRONJ which may initiate the process. Indeed, MRONJ may be the consequence of local bone infection in patients who had dentoalveolar surgery or dental infection; a delayed mucosal healing, induced by bisphosphonates, may allow bacteria to get access to the underlying bone and cause bone necrosis (Hansen *et al*, 2006; Pazianas, 2011; Yamashita and McCauley, 2012). Moreover, there are histological studies reporting the presence of *Actinomyces*, and *Fusobacteria nucleatum* in MRONJ lesions(Hansen *et al*, 2007; Mawardi *et al*, 2011), even though the presence of *Actinomyces* in MRONJ lesion could represent a secondary opportunistic infection (Naik and Russo, 2009; Compston, 2011).

Furthermore, there is some evidence that the immunesuppression caused by chemotherapyand corticosteroid therapy in cancer patients, may be a contributor factor to the development of MRONJ in this category of patients. In addition, bisphosphonates can have inhibitory effects upon ϒδT cells, macrophage and monocytes, which in turn could impair local immune response, prolong wound-healing, and may play a role in the development of MRONJ (Coxon *et al*, 2008; Pazianas, 2011; Yamashita and McCauley, 2012). Bisohosphonates additionally can cause soft tissue toxicity leading to a reduced epithelial cells proliferation and function and consequently to the inhibition of mucosal healing after dental extraction or surgery (Reid *et al*, 2007)(Cornish *et al*, 2011). However MRONJ also develops in patients received with denosumab, which has not been reported to have a toxic effect on the epithelial cells (Yamashita and McCauley, 2012).

1.5 Risk Factors

A number of potential risk factors have been reported to increase the likelihood of MRONJ development (Hinchy *et al*, 2013), such as the type of medication, potency and dosage, route of administration, length of treatment, concomitant medications, underlying diseases, as well as dental infection and surgical procedures (Ruggiero *et al*, 2004; Woo *et al*, 2006; Hoff *et al*, 2008; Saad *et al*, 2012; Hinchy *et al*, 2013; Hamadeh *et al*, 2015).

Several medications have been reported as predisposing factors for MRONJ development (Hinchy *et al*, 2013) and can be categorized into three main groups: bisphosphonate agents, non-bisphosphonate antiresorptive and antiangiogenic agents (Troeltzsch *et al*, 2012; Otto *et al*, 2012; Ruggiero *et al*, 2014). The first case of MRONJ associated with bisphosphonates was reported in 2003 by Marx (Marx, 2003)and the number of reports has been increasing since (Otto *et al*, 2012; Hamadeh *et al*, 2015). Denosumab is a humanized monoclonal antibody against the receptor activator of nuclear factor-kappaB ligand (RANKL) or RANKL inhibitor (Ruggiero *et al*, 2014). By binding with RANKL, which is an important mediator in osteoclast differentiation released by osteoblast, Denosumab causes a reduction in bone resorption (Stopeck *et al*, 2010).

Also, the different potency and dosage of antiresorptive medications has been associated with a higher or lower risk of MRONJ development (King and Umland, 2008). Bisphosphonates are divided into two main groups due to their chemical structure (nitrogen and non-nitrogen containing side chain) (Rogers, 2003). Nitrogen-containing bisphosphonates (N-BPs) such as zoledronate, pamidronate, ibandronate, risedronate and alendronate have higher potency to inhibit bone resorption than non-nitrogenous bisphosphonates (Rogers, 2003; Uyanne *et al*, 2014). Zoledronic acid is the mostpotent N-BP followed by pamidronate, ibandronate and alendronate (King and Umland, 2008; Fantasia, 2009). The increased cumulative dose of bisphosphonates is potentially associated with a higher risk of MRONJ development (Woo *et al*, 2006) as cancer patients which usually receive higher dosage than patients treated for osteoporosis report a greater prevalence of MRONJ. (King and Umland, 2008;

Vescovi, Merigo, *et al*, 2012). Moreover, another study also demonstrated that patients who developed MRONJ have a history of treatment with higher median dose of bisphosphonates than those without MRONJ (Hoff *et al*, 2008). Therefore,.

Similarly, the risk of developing MRONJ is lower in osteoporosis patients taking denosumab , as it is administered subcutaneously at low dosage (60 mg every 6 months) whereas metastatic cancer patients receive subcutaneous denosumab 120 mg every 4 weeks (Stopeck *et al*, 2010; Neuprez *et al*, 2014) (Kyrgidis and Toulis, 2011).

The route of drug administration has also been associated with the risk of MRONJ development as most of the patients who develop MRONJ are given intravenous bisphosphonates for cancer treatment (King and Umland, 2008; Filleul *et al*, 2010) (Migliorati *et al*, 2011; Ruggiero *et al*, 2014) (Woo *et al*, 2006; King and Umland, 2008; Otto *et al*, 2012). Furthermore,the duration of antiresorptive therapy represents an important risk factor in the development of MRONJ (Hoff *et al*, 2008; Ruggiero *et al*, 2014) (Hoff *et al*, 2008). Indeed, the incidence of MRONJ in cancer patients who were exposed to zoledronate or denosumab increases gradually overtime, which is 0.5%or 0.8% at 1 year, 1.0% or 1.8% at 2 years and 1.3% or 1.8% at 3 years respectively (Saad *et al*, 2012). The risk of developing MRONJ increases dramatically in patients receiving intravenous bisphosphonates for longer than 1.8 years and in those taking oralbisphosphonates for more than 3 years (Ruggiero *et al*, 2009; Palaska *et al*, 2009; Malden and Lopes, 2012).

Dentoalveolar surgery is a traditional risk factor for MRONJ development (Hoff *et al*, 2008; Ruggiero *et al*, 2014). It has been suggested that cancer patients treated with intravenous bisphosphonates (Pamidronate, Zoledronate, Ibandronate) are 33 times more likely to develop MRONJ than those with no history of surgical procedures (Vahtsevanos *et al*, 2009). Another study reports that tooth extraction is associated with a 16-fold increased the risk of developing MRONJ among intravenous bisphosphonate patients (Kyrgidis *et al*, 2008). The estimates of

increased risk of MRONJ development in patients exposed to intravenous bisphosphonates after dental extraction is more than 50% in most reports (Vahtsevanos *et al*, 2009; Saad *et al*, 2012; Otto *et al*, 2012). However, the increased risk of MRONJ after surgical procedures, especially tooth extraction, in patients taking oral bisphosphonates is only0.5% (Kunchur *et al*, 2009). There have also been several reports of spontaneous MRONJ development in patients without previous extraction (Marx, 2003; Marx *et al*, 2005; Otto *et al*, 2012).

Most of the cancer patients receiving antiresorptive agents are also managed with concomitant therapies, such as corticosteroids and chemotherapy(King and Umland, 2008; Hinchy *et al*, 2013). The medications used as part of chemotherapy regimens such as methotrexate have been reported to increase the risk of MRONJ development (Malden and Lopes, 2012). Moreover, a previous study suggested that the administration of corticosteroids especially when combined with bisphosphonates could also increase the risk of developing MRONJ (Saad *et al*, 2012).

Pre-existing dental diseases such as periodontal diseases and periapical diseases couldpossibly trigger the development of MRONJ (Otto *et al*, 2012)

Minor trauma may also represent a risk factor of MRONJ (Ruggiero *et al*, 2014). The posterior lingual mandible has been reported as a common site for MRONJ possibly due to the fragility of oral mucosa and underlying periosteum, particularly the protuberant mylohyoid ridge, where minor local trauma could lead to mucosa ulceration and bone exposure(Woo *et al*, 2006). In addition, genetic factors are likely to be responsible for increased susceptibility to develop MRONJ. Previous pharmacogenetic studies reported that patients with single nucleotide polymorphisms (SNPs) in the RBMS3 and CYP2C8 gene tend to have higher risk of MRONJ development (Sarasquete *et al*, 2009; Nicoletti *et al*, 2012).

1.6 Management of MRONJ

1.6.2 Preventive treatment prior to antiresorptive/antiangiogenic therapy

Management of patients at risk of MRONJ can be divided into two phases: risk- reduction strategies and management of MRONJ (Hinchy *et al*, 2013). As early dental screening and appropriate dental care has been demonstrated to likely decrease the incidence of ONJ (Yamashita and McCauley, 2012; Bramati *et al*, 2015) before commencement of either antiresorptive or antiangiogenic agents, dental and radiographic assessment should be thoroughly performed (Ruggiero *et al*, 2014). Recommendations includes clinical and radiological examination, completion of periodontal treatment and undertaking necessary dentoalveolar surgery prior to initiation of bisphosphonate therapy (Vescovi, Merigo, *et al*, 2012). All invasive surgical dental treatment, for instance the removal of teeth with poor prognosis such as retained root and non-restorable teeth should be performed in order to reduce the risk of future complications (Yamashita and McCauley, 2012; Hinchy *et al*, 2013). Extraction sites should heal for 14-21 days prior to commencement of therapy. Dental prosthesis must be assessed to reduce the risk of trauma to oral tissues and exposure of the underlying bone (Kushner and Alpert, 2011). Sharp bone, bony protuberances, tori and exostoses should be removed where possible as these bone features may be at risk of masticatory trauma with ulceration of the mucosa (Hinchy *et al*, 2013). Routine dental examination and radiographic assessment during therapy should also beperformed to reduce the occurrence of MRONJ as reported in literatures (Bramati et al., 2015, Nicolatou-Galitis et al., 2011).

1.6.3 MRONJ treatment: Conservative non-surgical therapy

Treatment of MRONJ is challenging and there is a little evidence about the effectiveness of available treatments (Kühl *et al*, 2012). According to the AAOMS Position Paper 2014 (Ruggiero *et al*, 2014), the major goals of treatment for patients at risk of developing or who have MRONJ are:

- Prioritization and support of continued oncologic treatment in patients receiving IV antiresorptive and antiangiogenic therapy.

  - Oncology patients can benefit greatly from the therapeutic effect of antiresorptive therapy by controlling bone pain and reducing the incidence of other skeletal complications.

  - The antiangiogenic class of chemotherapy agents have demonstrated efficacy in the treatment of a variety of malignancies with proven survival benefits.

- Preservation of quality of life through:

  - Patient education and reassurance.

  - Pain control.

  - Secondary infection control

  - Prevention of lesion extension and development of new areas of necrosis.

The non-surgical approach is recommended as initial treatment (AAOMS 2014), while more invasive procedures are recommended for severe cases or in case of medical therapy failure.

Non-surgical (conservative) approaches include chlorhexidine mouthwash, local irrigations, broad-spectrum antibiotics, pain control, superficial necrotic bone debridement including removal of superficial sequestra (Woo *et al*, 2006; Rizzoli *et al*, 2008).

Surgical management of MRONJ is traditionally recommended in patients who failed to respond to conservative treatment and experienced severe pain and infection, or whennon-surgical therapy is unlikely to resolve symptoms (e.g., pathological fracture). It has been suggested that surgical manipulation of MRONJ might lead to further bone exposure, progression of necrosis and worsening of pain and infection (Marx *et al*, 2005; Ruggiero *et al*, 2009; Hinchy *et al*, 2013). (Marx et al., 2005, Ruggiero et al., 2009, Hinchy et al., 2013). Montebugnoli *et al.* reported that theoutcome of treatment in MRONJ patients undergoing surgical intervention was not statistically significant different from those treated with antibiotics (Montebugnoli *et al*, 2007).

The AAOMS recommended stage specific treatments as shown in (Table 1). It was suggested that conservative therapy is to be preferred for treating up to Stage 2 MRONJ lesions. Specifically, Stage 0 and 1, should be treated with oral antimicrobial rinses such as chlorhexidine or hydrogen peroxide. Stage 2 lesions are recommended to be managed with oral antimicrobial rinses and antibiotic therapy in order to control signs of infection and prevent potential infection worsening. Treatment recommendations for stage 3 lesions include antibiotics and adjuvant surgery such as debridement, resection, and reconstruction. Moreover, regardless of the stage, mobile bony sequestra must be removed in order to foster soft tissue healing. The decision to discontinue antiresorptive therapy should be made by the oncologist or the prescribing clinician depending on the general condition of the patients, as the priority is to guarantee the best treatment for a good prognosis of the underlying disease(Ruggiero *et al*, 2014).

Even though the scientific community has adopted the AAOMS treatment guidelines, the drawback of stage specific treatment recommendations is that they do not take into account the extent of the necrotic bone and the involvement of structures such as the maxillary sinus (Bedogni *et al*, 2014). Indeed, as per definition, AAOMS staging system does not describe nor consider the progressive extension of the necrosis as a feature of severity, rather the presence/absence of clinical signs of MRONJ such as bone exposure, pain or signs of infection. This leads to a potential poor agreement in terms of staging MRONJ lesions among different clinicians, and consequently, to the different response rates among different studies testing treatments ranging from the more conservative to the more invasive (Campisi *et al*, 2020).

Conservative management is generally advisable in patients with poor general health and/or concomitant malignant disease. Indeed, in such cases the priority is to control the signs of infection and symptoms and prevention of further bone disease progression, therefore improving quality of life (Ristow *et al*, 2019).

In the literature, data on the success rate of the conservative non-surgical therapy widely vary among the studies, possibly due to the different study-design and populations, type of non-surgical approach, follow-up and timing of the measurements. Moreover, the definitions of the treatment outcomes and outcome measures are extremely heterogeneous, making comparisons difficult. Indeed, success of conservative non-surgical therapy ranges from 14% to up to 65% success based on mucosal integrity, decrease of mucosal lesion, and cessation of stage progression (Ristow *et al*, 2019). A large retrospective study assessing conservative treatment modalities, yielded a success rate of 71-80%, the majority of patients displaying improvement or remaining asymptomatic and stable (Lerman *et al*, 2013). This finding is consistent with results from previous studies and confirms that a combination of antimicrobial rinses, antibiotic therapy, nonsurgical sequestrectomy, and local debridement are effective especially in controlling pain and infection, leading to an overall improvement of the local and systemic condition. Some data suggest that conservative management is also effective in pain resolution in 60% of the cases(Moretti *et al*, 2011)(Melea *et al*, 2014). Although the majority of the studies have demonstrated the superiority of the surgical interventions on the non-surgical treatments in terms of response rates (Vescovi, Manfredi, *et al*, 2012; Rupel *et al*, 2014; Nisi *et al*, 2018), other reports have found no difference in the success rate between conservative and surgical protocols; 60.5% and 60.4% respectively (Melea *et al*, 2014). This discrepancy may be due the different population selected. Indeed, patients with poor health status or with severe and not well defined ONJ may be not eligible for surgical therapy, and this can create an imbalance of the population treated with one or another therapy. Montebugnoli et al. (2007) concluded that antibiotic therapy alone provided long term improvement in pain relief and in prevention of progression of disease (Montebugnoli *et al*, 2007). Coropciuc et al. (2017) reported a 79.73% overall improvement following 24 months follow up (Coropciuc *et al*, 2017). Although in his study conservative therapy was defined as medical and minimally invasive therapies such as debridement and sequestrectomies. Nearly 50% of the patients underwent minimal invasive interventions.

The downfalls of conservative management are that necrotic bone does not spontaneously resolve or heal, and recurrent antibiotic therapy may worsen quality of life (Shin and Kim, 2018). According to AAOMS, conservative therapy should be carried out if there is no progression of necrosis of the bone, the patient remains pain free, and antiresorptive therapy is halted (Ruggiero *et al*, 2014). The authors advise that surgical management is undertaken by earliest for stage 2. Surgery was indicated in cases where non-surgical approaches failed or progression to stage 2 could not be reverted with antibiotic therapy after two weeks (Ristow *et al*, 2019).

MRONJ PROGNOSIS

MRONJ is a disease with poor response to treatment and typically runs a chronic course. Some patients may experience rapid disease progression with development of large areas of bone necrosis and severe pain and infection, whereas others may remain asymptomatic or mildly symptomatic for long periods, even with persistence of bone exposure (Ruggiero *et al*, 2014).

Many studies have reported about treatment outcomes of MRONJ but there remains no consistency of terminology and no consensus to define MRONJ outcomes. The meaning of complete resolution, healing, complete resolution and improvement varies widely among studies. Most studies define complete mucosal closure as complete resolution or complete remission, even though mucosal healing does not exclude the persistence of underlying necrotic bone (Van den Wyngaert *et al*, 2009; Bedogni *et al*, 2011; Nicolatou-Galitis *et al*, 2011; Saad *et al*, 2012). The reported rates of complete resolution range widely in the literature from 15 to 80 % (Nicolatou-Galitis *et al*, 2011). Some few studies have assessed pain as a part of clinical outcomes and have reported a decrease in pain scores or painful symptoms after the treatment of MRONJ after both conservative and surgical treatment in approximately 60 to 80% ofpatients (Wutzl *et al*, 2008; Nicolatou-Galitis *et al*, 2011; Fortuna *et al*, 2012).

There are various factors that could influence the prognosis of MRONJ. For example the long duration of the antiresorptive therapy, the stage of the illness itself, and the history of dental extraction have all been reported to decrease healing rates (Van den Wyngaert *et al*, 2009; Fortuna *et al*, 2012). Moreover, it has been suggested that approximately 30% of patient with MRONJ triggered by extraction are at higher risk of recurrence, delayed healing and multiple surgical procedures (O'Ryan and Lo, 2012).Migliorati *et al.* suggested that MRONJ "healing" can be achieved in 17.6%, 17.3% and 46.3% of those managed with medical therapy (systemic and topical antibacterial),superficial surgical debridement and deep surgical treatment (bone resection) respectively(Migliorati *et al*, 2011).Others report that antibiotics and topical antimicrobial are "effective" in approximately 50% of patients with MRONJ (Van den Wyngaert *et al*, 2009; Nicolatou-Galitis *et al*, 2011).

1.8 Aims of the study.

Until now, studies on the effectiveness of the non-surgical therapies have been conducted on small samples and included patients whose minimum follow-up widely varied from few months up to many years, which makes comparisons between the patients unreliable in terms of outcomes. This because the disease is chronic, and clinical behavior and outcomes are likely to be noted over a long-term follow-up rather than in the first months of observation (Montebugnoli *et al*, 2007; Van den Wyngaert *et al*, 2009; Alsehimy, 2014; Melea *et al*, 2014; Ikeda *et al*, 2015; Rugani *et al*, 2015; Bodem *et al*, 2015; Coropciuc *et al*, 2017).

Moreover, despite the fact it has been advised that the primary aim of the MRONJ treatment, according to the AAOMS recommendations, should be to control pain and signs of infection, few studies, if any, have investigated these two outcomes, either separately or combined (Montebugnoli *et al*, 2007; Van den Wyngaert *et al*, 2009; Alsehimy, 2014; Melea *et al*, 2014; Ikeda *et al*, 2015;

Rugani *et al*, 2015; Bodem *et al*, 2015; Coropciuc *et al*, 2017). Indeed, mucosal healing, defined as complete mucosal coverage of the previous exposed bone (or that can be probed through a sinus tract), often regardless of the symptomatology, has been the most popular measure outcome used among the studies, even though it has shared opinion that the only mucosal coverage is not by itself a reliable parameter of MRONJ healing: the exposed bone can be interpreted as the "tip of the iceberg" seen from the outside (Ristow *et al*, 2019; Haviv *et al*, 2021).

For the above reasons, the objective of this study was to conduct an exploratory analysis on the long-term outcomes of the exclusive conservative non-surgical treatment on a big sample of MRONJ patients, all having a minimum follow-up of at least 12 months. Specifically, the primary aim was to evaluate the presence of pain and the presence of signs of infection (the latter which has never been properly investigated until now), both separately and as unique outcome, addressing the primary goal of the MRONJ treatment according to the Position Paper. In addition, we aimed at exploring the complete clinical remission, defined as the absence of pain/infection and the presence of mucosal integrity. Finally, as per the chronic course of the disease, we aimed also at evaluating pain/infection recurrences over the long-term follow-up.

Table 1. Staging and treatment strategies based on AAOMS (Ruggiero et al., 2014).

Stages on MRONJ	Recommendations for management of MRONJ
At risk: no apparent necrotic bone in patients who have been treated with oral. or intravenous bisphosphonates	No treatment indicated Patient education
Stage 0: no clinical evidence of necroticbone but nonspecific clinical findings, radiographic changes and symptoms	Systemic management, including use of pain medication and antibiotics
Stage 1: exposed and necrotic bone or fistulas that probes to bone in patients who are asymptomatic and have no evidence of infection	Antibiotic mouth rinse Clinical follow-up on a quarterly basis Patient education and review of indications for continued bisphosphonate therapy
Stage 2: exposed and necrotic bone or fistula that probes to bone associated with infection as evidenced by pain and erythema in the region of exposed bone with or without purulent drainage	Symptomatic treatment with oral antibiotics Oral antibacterial mouth rinse Pain control Debridement to relieve soft tissue irritation and infection control
Stage 3: exposed and necrotic bone or a fistula that probe in patients with pain, infection, and ≥ 1 of the following: exposed and necrotic bone extending beyond the region of alveolar bone (inferior border and ramus in mandible, maxillary sinus and zygoma in maxilla) resulting in pathologic fracture, extraoral fistula, oral antral or oral nasal communication or osteolysis extending to inferior border of the mandible or sinus floor	Antibacterial mouth rinse Antibiotic therapy and pain control Surgical debridement or resection for longer-term palliation of infection and pain

Table 2. Clinical and radiological staging system of bisphosphonate-related osteonecrosis of the jaws (BRONJ) according to SICMF-SIPMO staging system (Bedogni *et al*, 2012).

Stage 1	**Focal BRONJ** *Clinical signs and symptoms:* bone exposure; sudden dental mobility; nonhealing post extraction socket; mucosal fistula; swelling; abscess formation; trismus; gross mandibular deformity and/or hypoesthesia/paranesthesia of the lips *CT findings:* 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/orcortical disruption 1a. Asymptomatic 1b. Symptomatic (pain and purulent discharge)
Stage 2	***Diffuse BRONJ*** *Clinical signs and symptoms:* 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; sequestrum formation; and/or oroantral fistula 2a. Asymptomatic 2b. Symptomatic (pain and purulent discharge)
Stage 3	***Complicated BRONJ*** Same as Stage 2, with one or more of the following: *clinical signs and symptoms:* extra-oral 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.

2. MATHERIALS AND METHODS

2.1. Study Design

A retrospective medical record review of patients diagnosed with MRONJ was carried out in three Oral Medicine /Oral Maxillofacial outpatients' departments: one English center, the Hospital Eastman Dental Institute, University College London (UK) and two Italian centers, the Unit of Maxillofacial Surgery, Department of Neuroscience, University of Padova and the Unit of Maxillofacial Surgery, University of Verona between January 2008 and December 2020. Ethical approvals from local ethic committees were approved as service evaluation for the clinical practice. The study was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki and the methods conformed with the STROBE (von Elm *et al*, 2008).

2.2 Patient Population

2.2.1. Eligibility Criteria

The inclusion criteria included patients with MRONJ diagnosis according to the AAOMS Position Paper, 2014 (Ruggiero *et al*, 2014):

Patients may be considered to have MRONJ if all of the following characteristics are present:

1. Current or previous treatment with antiresorptive or antiangiogenic agents.
2. Exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than eight weeks; and
3. No history of radiation therapy to the jaws or obvious metastatic disease to the jaws.

It is important to understand that patients at risk for or with established MRONJ can also present with other common clinical conditions not to be confused with MRONJ. Commonly misdiagnosed conditions may include, but are not limited to alveolar osteitis, sinusitis, gingivitis/ periodontitis, caries, periapical pathology, fibro-osseous lesion, sarcoma, chronic

sclerosing osteomyelitis, and TMJ disorders. It is also important to remember that ONJ occurs in patients not exposed to antiresorptive or antiangiogenic agents.

4. Patients treated exclusively with conservative non-surgical treatments.
5. Patients with a minimum follow-up of 12 months.
6. Patients affected by oncological or metabolic bone diseases.
7. Patients with MRONJ lesions staged from stage 0a-3.

Further in this study, "oncological patients" and "osteoporotic patients" terms will be used for referring to these two principal groups of patients.

Exclusion criteria encompassed:

1. Patients with a history of radiation therapy to the jaws or obvious metastatic disease to the jaws.
2. Patients affected by osteoradionecrosis of the jaws.
3. Patients with a follow-up < than 12 months,
4. Patients treated with surgical treatments.
5. Patients were excluded from the analyses if conservative non-surgical treatment was prescribed as preoperative therapy before the surgical intervention. While patients were included if despite the non-surgical treatment, they were non-responder and needed to be treated with surgical means in order to control signs of infection and pain.

A refractory patient was defined as a patient which did not show any clinical improvement in terms of pain and/or signs of infection, despite the non-surgical treatments and needed to be further treated by surgical interventions. This condition was also acknowledged as a failure of the medical therapy.

2.3. Conservative non-surgical treatment.

Patients were treated by conservative non-surgical treatments based on the following criteria: a) patients unwilling to receive surgical treatment, b) patients with severe systemic conditions

due to the underlined oncological disease which precluded the possibility to provide more invasive procedures; c) patients who experienced pain/signs of infection improvement over the follow-up and agreed to continue the non-surgical approaches. Management was provided according to general guidelines designed to minimize symptoms and/or achieve resolution of lesions (Ruggiero *et al*, 2014).

The conservative non-surgical treatment consisted of the use of local antiseptics with or without the use of antibiotics cycles. 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. Asymptomatic patients (stage 0sa or 1) were typically managed with observation (generally including chlorhexidine); symptomatic patients (stage 0ss, 2, or 3) were generally treated with antibiotics for management of pain/infection (Ruggiero *et al*, 2014).

The use of antibiotics, the type, the length of the cycle, was decided by each clinician based on local factors, especially the severity of the pain and signs of infection; and systemic status, especially in oncological patients under chemotherapy/immune suppressive therapies. Moreover, in patients partially responders to the prescribed regimen, swabs from the purulent discharge were also taken for the antibiogram. Therefore, as the design of the study is retrospective and the aim of the present study is to assess whether patients under non-surgical treatments are guaranteed a good control of pain and signs of infection, rather than testing a single and predefined therapeutic scheme, systemic antibiotics protocol largely differed from one patient to another. This reflects the obvious heterogeneity of the patients affected by MRONJ, due to different systemic and local factors which should be taken into account when approaching these patients and which make extremely difficult to standardize a protocol. Therefore, antibiotics schemes were rather set based on clinical presentation and systemic condition of the patient. However, some antibiotics were predominantly used: such as amoxicillin/clavulanic acid at a dosage of 3 g/day or clindamycin 600-1200 mg/day for 1-4

weeks in cases of allergy to penicillin. For the cases scarcely responsive to single-antibiotic therapy, metronidazole was added at a dosage of 500-1500 mg/day for 1-4 weeks. Antibiotics cycles were repeated as any time recurrences of pain or signs of infections occurred.

Patients were instructed to have a good oral hygiene, to clean the exposed bone and to use topical antiseptics as mouthwash in order to reduce as much as possible local bacterial contamination. The following topical antiseptics were mostly prescribed: chlorhexidine 0.12-0.20% as mouthwash two-three times a day; hydrogen peroxide 10 volumes diluted 1:1 with water to be used as mouthwash two-three times a day, water sodium bicarbonate solution, or a combination of this three. In few patients, local irrigations with metronidazole or rifampicin were also prescribed. Almost in all the cases, topical antibacterial mouthwashes were scheduled permanently in order to avoid bacterial infection. Pain was treated with painkillers as needed.

Other additional non-surgical conservative treatments were also provided as needed: i) the smoothening of sharp bone edges/spicules, performed in order to avoid soft tissue damaging and/or to relieve soft tissue irritation, to control infection and therefore to promote soft tissue healing; ii) superficial removal of mobile bony sequestra without raising muco-periostal flap; iii) tooth extraction of mobile teeth in the site of MRONJ; iv) periodontal/peri implant non-surgical treatments.

2.4 Sampling Strategy

Sampling for a retrospective study is commonly undertaken via three approaches that are convenience, quota, or systematic approach. The appropriate method adopted depends on the epidemiological nature and prevalence of the condition, population availability, and the time constraint. Medication-related osteonecrosis of the jaw is a rare condition and for that reason the sampling method indicated for this study is convenience sampling. The disadvantage of non-random convenience selection of participants is it does not reflect the population and the confidence interval and margins of error cannot be calculated.

The data was accessed and collected via electronic patient databases in all the three centers. At the Hospital Eastman Dental Institute data were accessed through a system known as Epic in the hospital premises to protect patient confidentiality under the Data Protection Act of 1998. The clinic codes for the osteonecrosis clinics that accepted referrals on suspected osteonecrosis cases were entered and a manual search of patient records were undertaken that spanned from 2008 to 2020.

Similarly, at the other two Italian centers data were accessed via electronic databases protected by security passwords. Confidential data from the patients selected were coded in order to guarantee the privacy.

2.5 Data Collection

Demographic and clinical data were collected for each included patient and recorded in a predefined Excel template whose access was protected by password. Data from the following major domains were collected:

-demographic data: age, sex, ethnicity, collected for each patient included, age, gender, systemic comorbidities (for instance diabetes, cardiovascular disease, renal insufficiency, rheumatoid arthritis, hypertension, immune-mediated or autoimmune diseases).

- data on the disease needing AR treatment: primary or secondary osteoporosis (the cause of secondary osteoporosis was also recorded); type of malignancy (Multiple Myeloma, Breast Cancer, Prostate cancer, Lung Cancer etc.) and the presence of bone metastasis for patients affected by solid tumors; the presence of corticosteroids therapy or chemotherapy at the time of the enrollment.

-data on AR history: type of AR (Zoledronate, Pamidronate, ibandronate, Alendronate, Clodronate, Risedronate, Denosumab etc.), start and suspension dates of AR; cumulative dosages. We also recorded the consumption of other potential drugs known to be related to MRONJ such as Tyrosine Kinase Inhibitors, mTOR inhibitors, anti-angiogenetic drugs etc.

-MRONJ characteristics: site of MRONJ (mandible/maxilla), the synchronous or metachronous presence of more than one MRONJ site involved, triggers of MRONJ divided in i) dental/periodontal infection, ii) tooth extraction, iii) implant placement, iv) trauma/prosthesis, v) trigger not found; stage according to the AAOMS 2014 staging system and the SICMF-SIPMO staging system (see paragraph X below).

-clinical characteristics of MRONJ:

a) *mucosal status*: the presence of exposed bone, the presence of probing bone through a sinus tract, intact mucosa.

b) *the presence of pain and oral symptomatology.*

c) *signs of infection*: intraoral soft tissue swelling, pus discharge, odontogenic abscess, extra-oral fistula, nasal leaking of fluids, facial swelling, trismus, halitosis, mandible asymmetry, preternatural mobility (mandible fracture), Vincent's sign (numb chin syndrome), loosen teeth, non-healing post-extraction sockets, and the presence of spontaneous mobile bony sequestrum.

- data on the non-surgical conservative treatment: type, length and regimen of the antibiotic cycle; type of the topical antiseptic/antibacterial agents; periodontal/peri implant treatments, mobile tooth/teeth extractions at the site of MRONJ, non-surgical bone interventions such as the smoothening of sharp bones edges/spicules in order to avoid soft tissue damaging, and/or to relieve soft tissue irritation, non-surgical removal of superficial loose bony sequestrum.

2.6 Follow-up

All the patients had been clinically and radiologically (OPT, bi and tri dimensional CT scan) followed up on a regular basis every 2-3 months for at least 12 months. Follow-up length was set depending on individual clinical characteristics and on the severity of the disease. Additionally, all the patients were instructed to refer to the clinicians in case of symptoms/infection exacerbation. Therefore, the number of follow-up visits and the time between consecutive follow-up visits varied from patient to patient. This heterogeneity with

respect to the follow-up, is justified by the retrospective nature of the present study and by the variability of the clinical behavior of the disease which is due to the difference between patients in terms of systemic and local factors.

2.7 Staging Systems

At the time of the enrollment and at each follow-up visits, MRONJ lesions were staged according to the AAOMS Position Paper of 2014. Moreover, the majority of the MRONJ lesions were also staged based on the SICMF-SIPMO staging system, which takes into account the CT scan radiological features of the osteonecrosis.

Therefore, SICMF-SIPMO staging system was adopted in association to the AAOMS' any time a CT scan was acquired. Definition of the AAOMS and SICMF-SIPMO staging system are displayed in the tables 1 and 2 in the introduction section.

2.8 Outcomes and Outcomes' measures

Outcomes' measures can be divided into patient-reported outcome measures (PROMs) and clinician-reported outcome measures (CROMs)

2.8.1 Primary outcome

PROMs

Pain Remission as a PROMs, was selected as the primary outcome of the present study. Indeed, we wanted to test the hypothesis that medical therapy should allow patients to function free from pain over their follow-up, thing which have more significance in relation to those oncologic patients not candidate for the surgical treatments "Pain" was measured as dichotomous variable, "presence or absence of pain".

2.8.2 Secondary outcomes

CROMs

With regard to CROMs, we collected many different data. Basically, we looked at two principal domains:

1) clinical signs of infection (pus discharge, intra-oral tissue swelling, odontogenic abscess, halitosis, extra-oral fistula, nasal leaking of fluids, facial swelling, mandible asymmetry, trismus, Vincent's sign etc.).
2) bone coverage status (exposed, probed by intra-oral sinus tract, non-exposed).

In our sample, the patients presented either with pain and signs of infection simultaneously, or with one of them (with pain but not infection, or with infection but no pain). As one of the principals aims of the non-surgical treatment is also to allow patients to function free of infection, the secondary outcome "Remission of signs of infection" (RI) defined as "the complete resolution of all the above clinical signs of infections" was introduced and tested as a separate CROM. Moreover, the sum of both outcomes PR and RI in a single outcome "Remission of Pain and Signs of Infection" was additionally explored, as it would reflect the degree of response to the medical treatments.

With respect to the bone coverage status, the "complete mucosal coverage of the previous exposed bone or probed by a fistula" was also evaluated as secondary outcome (MC). Indeed, the majority of the studies use the latter outcome measure to assess the clinical success of a specific treatment. However, the only presence of complete mucosal coverage is not sufficient for claiming the clinical healing of the MRONJ lesions, as despite the integrity of the mucosa the patients can still experience symptoms/infection.

For this reason, we have combined all the previous outcomes, PR + RI + MC would in a single outcome, "Complete clinical MRONJ remission" which is defined as a complete mucosal coverage of the previous exposed bone or probed by a fistula and a complete clinical remission of pain and signs of infection. This combined outcome was used to assess the clinical (not

radiological) healing of the MRONJ lesions. In all these cases, outcomes were dichotomous (present/absent).

Other secondary CROMs evaluated were for instance: recurrences (reappearance of signs of infection and/or pain); bony sequestrum formation.

Other outcomes of interest were related to the improvement, worsening or stabilization of the MRONJ stage comparing the baseline to the end of the follow-up. Therefore, "improvement" was defined as a down-staging, namely a reduction of the stage, "stabilization" as no change/stable disease, "worsening" as an upstaging, namely an increase in the stage. Improvement, worsening, or stabilization were evaluated according to both the staging systems, the AAOMS' and the SICMF-SIPMO's ones. Moreover, we were able to evaluate the MRONJ radiological status through the SICMF-SIPMO stages.

To sum up, secondary outcomes tested were:

a) Remission of signs of infection (RI)
b) Complete remission of signs of infection and pain;
c) Complete mucosal coverage;
d) Complete clinical MRONJ remission (CCR).
e) Recurrences
f) Stage improvement, stabilization, worsening.

2.9 Statistical Analyses

Descriptive statistics were reported as mean ± standard deviation, range, median and interquartile range. Comparisons between sites in osteoporotic and oncologic patients were performed through Fisher's exact test for qualitative variables and t-test for independent samples for quantitative variables.

Descriptive statistics were executed for patients and sites of MRONJ. Further descriptive statistics were performed on a subgroup of 48 patients. The presence or absence of signs of

infection, pain, mucosal coverage, and complete clinical remission was analyzed comparing the number of sites for whom specific symptomatology was registered at baseline and four endpoints (6, 12, 18, and 24 months). Statistical significance was set at 5% ($p < 0.05$).

2.9.1 Clinical Variables

About 80 variables were included in the final version of the Excel file (Microsoft Corp. Redmond, WA, USA). Statistical analysis was executed with STATA16 (Stata Corp., College Station, TX, USA). The complete list of variables included in the study was reported:

- Sex: male/female
- Age
- Ethnicity: Caucasian/Asian/Black/Chinese/Other
- Primary Disease: Tumor/Osteoporosis
- Type of solid tumor: Breast/Prostate/Lung/Kidney/Thyroid/Parathyroid
- Bone metastasis
- Multiple myeloma
- Primary or Secondary Osteoporosis
- Rheumatoid arthritis
- Diabetes
- Cardiovascular disease
- Hypertension
- Renal Insufficiency
- Other relevant diseases
- Follow-up: time between the enrollment and the last available follow-up
- Chemotherapy at enrollment: Yes/No

- Steroids at enrollment: Yes/No
- Tyrosine Kinase Inhibitor (TKI): Yes/No
- Type of TKI: Sunitinib/Imatinib/Trastuzumab
- Anti-Angiogenics (AA): Yes/No
- Type of AA
- Anti-Resorptive (AR) at enrollment: Yes/No
- AR suspension over Follow-up
- AR during Follow-up
- Duration of AR therapy: overall time of AR therapy
- Time between AR suspension and first Follow-up
- Time between enrollment and AR
- Time between enrollment and AR restart
- Time of AR restart
- Type of AR
- Systemic antibiotics at enrollment: Yes/No
- Number of antibiotics cycles during Follow-up
- Topical antiseptic/Antimicrobial: Yes/No
- Dental/Periodontal Interventions: Yes/No
- Non-Surgical Bone Interventions: Yes/No
- Number of sites involved: one site/two sites.
- Second site: already present at enrollment/involved after enrollment.
- Time between enrollment and second site involvement
- Site of MRONJ: mandible/maxilla
- Exposed Bone (at T_0 and during Follow-up): Yes/No
- Probing Bone through a sinus tract (at T_0 and during Follow-up): Yes/No

- Pain (at T_0 and during Follow-up): Yes/No
- Pus Discharge (at T_0 and during Follow-up): Yes/No
- Intraoral Soft Tissue Swelling (at T_0 and during Follow-up): Yes/No
- Odontogenic Abscess (at T_0 and during Follow-up): Yes/No
- Extra-oral Fistula (at T_0 and during Follow-up): Yes/No
- Nasal Leaking (at T_0 and during Follow-up): Yes/No
- Facial Swelling (at T_0 and during Follow-up): Yes/No
- Trismus (at T_0 and during Follow-up): Yes/No
- Halitosis (at T_0 and during Follow-up): Yes/No
- Mandible asymmetry (at T_0 and during Follow-up): Yes/No
- Vincent's sign (at T_0 and during Follow-up): Yes/No
- Loosen teeth (at T_0 and during Follow-up): Yes/No
- Preternatural mobility (at T_0 and during Follow-up): Yes/No
- Non-healing post-extraction (at T_0 and during Follow-up): Yes/No
- Spontaneous bony sequestrum (at T_0 and during Follow-up): Yes/No
- Triggers: dental or periodontal infection/tooth extraction/implant placement/trigger not found
- AAOMS stage (at T_0 and the last Follow-up)
- AAOMS stage variation during Follow-up
- Stage AAOMS at last Follow-up: down-staging, up-staging, unchanged
- SICMF (at T_0 and the last Follow-up)
- SICMF stage variation during Follow-up
- Stage SICMF at last Follow-up: down-staging, up-staging, unchanged
- Outcome:
    - Pain
    - Sign of infection

    - Sign of infection and moderate/severe pain
    - Complete Mucosal Coverage
    - Complete Clinical Remission
    - Complete Clinical Remission and moderate/severe pain
- Onset of a specific outcome (before enrollment or during the follow-up)
- 1° Remission: first remission of a specific symptom (pain, infection, no mucosal coverage, no clinical remission)
- Number of relapses (after the first remission)
- First relapse
- Time 1° relapse: time between first remission and first relapse
- 2° Remission: second remission of the specific symptom (pain, infection, no mucosal coverage, no clinical remission) after the first relapse
- Time 2° remission: time between first relapse and the second remission of the specific symptom

3. RESULTS

3.1 Patients characteristics

One hundred and twenty-six patients were included in the study and observed for a mean time of 39.73 ± 27.38 months. The sample included 89 (70.63%) female patients and 37 (29.37%) male patients, with a mean age of 67.67 years (23-68). Caucasian ethnicity represented the majority of the sample (90.48%). About seventy-one percent of the sample was composed of oncologic patients, mainly affected by solid tumors (64.4%) as breast cancer (60.34%) and prostate cancer (24.14%), most of whom with bone metastases (94.83%). Multiple myeloma was present in 35.56% of patients. Osteoporotic patients represented 28.57% of the all sample. Primary osteoporosis was reported in 26 (72.22%) patients while 10 (27.78%) had secondary osteoporosis (8 had Rheumatoid Arthritis and 2 Beta-thalassemia major). Complete patients' characteristics are reported in **Table 3**.

Table 3 – Patients' Characteristics	
Patients	126
Sex, n (%)	
Female	89 (70.63)
Male	37 (29.37)
Age, mean (SD) (range) Median (IQR)	67.67 (10.22) (23-86) - 68 (61-77)
Ethnicity, n (%)	
Caucasian	114 (90.48)
Asian	2 (1.59)
Black	3 (2.38)
Chinese	2 (1.59)
Other	5 (3.97)
Oncologic patients, n (%)	90 (71.43)
Solid tumor, n (%)	58 (64.4)
Breast	35 (60.34)
Prostate	14 (24.14)
Lung	2 (3.45)
Kidney	5 (8.62)
Thyroid	1 (1.72)
Parathyroid	1 (1.72)
Bone Metastasis, n (%)	55 (94.83)
Multiple myeloma, n (%)	32 (35.56)
Osteoporotic patients, n (%)	36 (28.57)
Primary osteoporosis	26 (72.22)
Secondary osteoporosis	10 (27.78)
Rheumatoid Arthritis, n (%)	8 (6.35)
Diabetes, n (%)	10 (7.94)
Cardiovascular Diseases, n (%)	13 (10.32)
Hypertension, n (%)	42 (33.33)
Renal Insufficiency, n (%)	4 (3.17)
Other relevant Disease, n (%)	63 (50.00)
Follow-Up, mean (SD) (range) Median (IQR)	39.73 (27.38) (1-150) - 31 (22-50)

Legend: FU = Follow-Up, AR = Anti-Resorptive, SD = Standard Deviation, IQR = Interquartile Range

Anti-resorptive treatments (AR) history widely varied from patient to patient. All the patients had been treated with AR drugs for a mean of 60.04 ± 58.42 months. The majority of them (66.6%) received one type of AR, while 33.3% were treated with two or three different types of AR over their diseases. Moreover, 12 (9.4%) of the patients also received a TKI (sunitinib, imatinib or trastuzumab) or an antiangiogenic drug (such as bevacizumab). Furthermore, also the drug-holiday patterns and duration largely differed among the patients. Forty-one (32.54%) patients were still on AR at the time of the enrollment and 32 (25.40%) of them would have suspended AR treatment during the follow-up in a mean time of 19.27 ± 18.56 months. On the contrary, 85 patients had already suspended the AR therapy at the time of the enrollment (the time between AR suspension and first follow-up was 10.31 ± 18.92 months), and only 7 (5.56%) restarted AR treatment during the follow-up after a mean time of 15.67 ± 13.44 months. The time of AR restart was 9.6 ± 7.73 months. The variety of the AR therapies and of the drug holidays patterns unfortunately prevented any possibility of regression or sensitivity analyses.

With respect to the conservative non-surgical treatments, 53 (37.32%) patients were treated with systemic antibiotics at enrollment, with similar percentages between osteoporotic and oncologic patients. During the follow-up, patients received a mean of 2.1 ± 2.49 antibiotics cycles for treating MRONJ symptomatology and/or infection. Topical antiseptic or antimicrobial was used in almost all the cases (97.89%). Dental or periodontal interventions and non-surgical bone interventions were executed for 25.35% and 40.14% of patients. Patients' pharmacological treatments are reported in **Table 4**.

Table 4 – Pharmacological Treatments	
Chemotherapy at enrollment, n (%)	70 (55.56)
Steroids at enrollment, n (%)	38 (30.16)
TKI, n (%)	6 (4.76)
Type of TKI, n (%)	
Sunitinib	3 (50.00)
Imatinib	1 (16.67)
Trastuzumab	2 (33.33)
Anti-Angiogenics, n (%)	6 (4.76)
Type of Anti-Angiogenic, n (%)	
Bevacizumab	5 (83.33)
Not Reported	1 (16.67)
Anti-Resorptive (AR) at enrollment, n (%)	41 (32.54)
AR suspension over the FU, n (%)	32 (25.40)
AR restart during FU, n (%)	7 (5.56)
Months AR therapy, mean (SD) (range) median (IQR)	60.04 (58.42) (1-301) - 39 (22.5 - 71)
Num. of patients Duration of AR therapy	124 (98.41)
Months between AR suspension and 1° FU, mean (SD) (range) median (IQR)	10.31 (18.92) (0-107) - 4 (1-7)
Num. of patients Time between AR suspension and first FU	83 (65.87)
Months between enrollment and AR suspension, mean (SD) (range) median (IQR)	19.27 (18.56) (1-66) - 14.5 (5-28)
Num. of patients for Time between enrollment and AR suspension	6 (4.76)
Months between enrollment and AR restart, mean (SD) (range) median (IQR)	15.67 (13.44) (3-40) 11.5 (7-21)
Num. of patients for Time of AR restart	5 (3.97)
Months of AR restart, mean (SD) (range) median (IQR)	9.6 (7.73) (4-23) - 7 (5-9)
Type of AR1, n (%)	
Zoledronate	63 (48.09)
Alendronate	29 (22.14)
Pamidronate	23 (17.56)
Ibandronate	4 (3.05)
Clodronate	1 (0.76)
Risendronate	3 (2.29)
Denosumab	7 (5.34)
Not Reported	1 (0.76)
Type of AR2, n (%)	
Zoledronate	22 (52.38)
Alendronate	2 (4.76)
Pamidronate	6 (14.29)
Ibandronate	3 (7.14)
Clodronate	1 (2.38)
Denosumab	8 (19.05)
Type of AR3, n (%)	
Zoledronate	4 (50.00)
Pamidronate	2 (25.00)
Risendronate	1 (12.50)
Denosumab	1 (12.50)
Systemic Antibiotics at enrollment, n (%)	53 (37.32)
N° Antibiotics Cycles during FU, mean (SD) (range) median (IQR)	2.1 (2.49) (0.12) - 1 (1-3)
Topical antiseptic/Antimicrobial, n (%)	139 (97.89)
Dental/Periodontal Interventions, n (%)	36 (25.35)
Non-Surgical Bone Interventions, n (%)	57 (40.14)

Legend: TKI = Tyrosine Kinase Inhibitor, FU = Follow-Up, AR = Anti-Resorptive, SD = Standard Deviation, IQR = Interquartile Range

3.2 MRONJ clinical manifestations

Table 3 shows the clinical characteristics of the MRONJ sites at T0 (time of the enrollment) and over the follow-up. A total of 142 MRONJ sites were detected, 39 (27.46%) in the osteoporotic group and 103 (72.54%) in the oncologic group. Only one MRONJ lesion had a follow-up less than 12 months and was therefore excluded from the subsequent analyses. One-hundred-ten (85.94%) patients presented one site of MRONJ, while 18 (14.06%) of patients presented with two MRONJ sites involved. In 10 (55.56%) patients, the two MRONJ sites were already present at the enrollment, while in 8 (44.44%) the second site involvement occurred after the enrollment **(Table 5**). 102 (71.83%) MRONJ sites were localized at the mandible (79.49% in osteoporotic patients and 68.93% in oncologic patients). Triggers of MRONJ were found in almost all the patients: 61 (42.96%) had dental/periodontal infections triggering the osteonecrosis, 60 (42.25%) and 21 (14.79%) tooth/teeth extractions and implant placement respectively, while in 5 (3.52%) no trigger was found. With respect to the MRONJ clinical manifestations, during the follow-up, exposed bone was mainly registered in oncologic patients (61.17%) than in osteoporotic patients (41.03%) ($p = 0.038$). Pain, intraoral soft tissue swelling, and loosen teeth occurred primarily in oncologic patient (pain: 67.96%; intraoral soft tissue swelling: 38.83%; loosen teeth: 33.01%) than in osteoporotic patients (pain: 43.59%, $p = 0.012$; intraoral soft tissue swelling: 17.95%, $p = 0.027$; loosen teeth: 7.69%; $p = 0.002$). Notably, spontaneous bony sequestrum exfoliation occurred in 33 (23.23%) cases, 6 (4.22%) were already present at the enrollment while 27 (19.01%) occurred over the follow-up. All the other clinical variables are listed in **table 5** and did not show any significant difference between the two subgroups.

Table 5 - MRONJ clinical manifestations					
		All Sample	Osteoporotic pts	Oncologic pts	*p-value*
Number of sites involved		142	39 (27.46%)	103 (72.54%)	
Site of MRONJ					
Mandible		102 (71.83)	31 (79.49)	71 (68.93)	0.296
Maxilla		40 (28.17)	8 (20.51)	32 (31.07)	
Number of sites involved					
One site		110 (87.30)	33 (91.67)	77 (85.56)	0.000
Two sites		16 (12.70)	3 (8.33)	13 (14.44)	
Time of second site involvement					
Already present at enrollment		10 (55.56)	2 (66.67)	8 (60.00)	0.114
During follow-up		8 (44.44)	1 (33.33)	7 (40.00)	
Exposed Bone	T_0	72 (50.70)	17 (43.59)	55 (53.40)	0.349
	FU	79 (55.63)	16 (41.03)	63 (61.17)	0.038
Probing Bone through a sinus tract	T_0	55 (38.73)	20 (51.28)	35 (33.98)	0.082
	FU	76 (53.52)	24 (61.54)	52 (50.49)	0.263
Pain	T_0	31 (21.83)	9 (23.08)	22 (21.36)	0.823
	FU	87 (61.27)	17 (43.59)	70 (67.96)	0.012
Pus Discharge	T_0	67 (47.18)	19 (48.72)	48 (46.60)	0.852
	FU	62 (43.66)	13 (33.33)	49 (47.57)	0.135
Intraoral Soft Tissue Swelling	T_0	49 (34.51)	14 (35.90)	35 (33.98)	0.845
	FU	47 (33.10)	7 (17.95)	40 (38.83)	0.027
Odontogenic Abscess	T_0	6 (4.23)	3 (7.69)	3 (2.91)	0.346
	FU	0 (0.00)	0 (0.00)	0 (0.00)	NA
Extra-oral Fistula	T_0	7 (4.93)	3 (7.69)	4 (3.88)	0.393
	FU	14 (9.86)	5 (12.82)	9 (8.74)	0.531
Nasal Leaking	T_0	2 (1.41)	0 (0.00)	2 (1.94)	1.000
	FU	4 (2.82)	0 (0.00)	4 (3.88)	0.575
Facial Swelling	T_0	22 (15.49)	6 (15.38)	16 (15.53)	1.000
	FU	17 (11.97)	3 (7.69)	14 (13.59)	0.401
Trismus	T_0	3 (2.11)	1 (2.56)	2 (1.94)	1.000
	FU	1 (0.70)	0 (0.00)	1 (0.97)	1.000
Halitosis	T_0	44 (30.99)	11 (28.21)	33 (32.04)	0.691
	FU	32 (22.54)	6 (15.38)	26 (25.24)	0.264
Mandible Asymmetry	T_0	8 (5.63)	0 (0.00)	8 (7.77)	0.107
	FU	24 (16.90)	5 (12.82)	19 (18.45)	0.616
Vincent's Sign	T_0	12 (8.45)	1 (2.56)	11 (10.68)	0.180
	FU	26 (18.31)	4 (10.26)	22 (21.36)	0.151
Loosen teeth	T_0	17 (11.97)	2 (5.13)	15 (14.56)	0.154
	FU	37 (26.06)	3 (7.69)	34 (33.01)	0.002
Preternatural Mobility	T_0	0 (0.00)	0 (0.00)	0 (0.00)	NA

	FU	3 (2.11)	2 (5.13)	1 (0.97)	0.183
Non-healing post-extraction socket	T_0	31 (21.83)	8 (20.51)	23 (22.33)	1.000
	FU	23 (16.20)	5 (12.82)	18 (17.48)	0.615
Spontaneous Bony Sequestrum	T_0	6 (4.23)	2 (5.13)	4 (3.88)	0.666
	FU	27 (19.01)	9 (23.08)	18 (17.48)	0.477
Triggers					
Dental/periodontal infection		61 (42.96)	18 (46.15)	43 (41.75)	
Tooth Extraction		60 (42.25)	16 (41.03)	44 (42.72)	0.904
Implant Placement		21 (14.79)	5 (12.82)	16 (15.53)	
Trigger Not Found		5 (3.52)	1 (2.56)	4 (3.88)	NA

Legend: FU = Follow-Up, NA = Not-Applicable, SD = Standard Deviation, IQR = Interquartile Range

3.3 Clinical outcomes

3.3.1 Primary outcome: Pain

Pain (mild-moderate-severe pain) was recorded in 112 (79.43%) sites. Specifically, 80 (56.74%) sites presented with pain at the enrollment, while 61 (43.26%) with no pain. Out of these 61 (43.26%), 32 (22.53%) sites developed pain during follow-up, whereas 29 (11.82%) did not develop any painful symptoms over the observational period. Pain was mainly observed in sites of oncologic patients (85.29%) than in those of osteoporotic patients (64.10%) ($p = 0.009$). 109 (97.32%) out of 112 sites with pain, achieved complete pain remission after, on average, 7.49 ± 9.12 months. 43 (39.45%) did not experienced any further pain, while in 63 (57.80%) sites 1-3 relapses occurred within on average 7.71 ± 7.11 months, and in 3 (2.75) sites relapses occurred ≥ 4 times. For 53 (81.54%) sites with relapse, a second remission was observed within 8.43 ± 11.77 months. Overall, out of 141 sites, 51.1% (n=72) of the MRONJ lesions had never experienced pain or relapses after the first pain remission, while in 46.8% (n=66) relapses were successfully treated with medical therapy. Only in the 2.1% (n=3) pain was persistent **(Table 6).**

Table 6 – Pain (Primary Outcome)				
	All Sample (n = 141)	**Osteoporosis pts (n = 39)**	**Oncologic pts (n = 102)**	**P-value**
At enrollment	80 (56.74)	18 (46.15)	62 (60.78)	0.132
Onset	112 (79.43)	25 (64.10)	87 (85.29)	0.009
First Remission	109 (97.32)	25 (100.00)	84 (96.55)	1.000
Time of 1° remission, Mean (SD) **Median (IQR) (months)**	7.49 (9.12) (1-52) 4.5 (2-10.5)	7.04 (6.89) (1-24) 5 (1-11)	7.62 (9.69) (1-52) 4 (2-10)	0.780
Num. Relapses				
None	43 (39.45)	7 (28.00)	36 (42.86)	0.475
1-3 times	63 (57.80)	18 (72.00)	45 (53.57)	
≥ 4 times	3 (2.75)	0 (0.00)	3 (3.57)	
First relapse	65 (59.63)	17 (68.00)	48 (57.14)	
Time 1° relapse, Mean (SD) **Median (IQR) (months)**	7.71 (7.11) (1-33) 5 (2-11)	9.47 (7.72) (1-22) 9 (3-18)	7.08 (6.86) (1-33) 5 (2-11)	0.237
Second Remission	53 (81.54)	13 (76.47)	40 (83.33)	0.717
Time of 2° remission, Mean (SD) **Median (IQR) (months)**	8.43 (11.77) (1-48) 4 (1-8)	13.08 (16.82) (1-48) 4 (2-13)	6.93 (9.39) (1-43) 4 (2-7.5)	0.102

3.3.2 Secondary outcomes

3.3.2.1 Signs of infection

Signs of infection were reported in 118 (83.69%) sites without any statistically significant difference between sites of oncologic and osteoporotic patients. Specifically, 89 (63.12%) sites presented with signs of infection at the enrollment, while 52 (36.88%) with no signs of infection. Out of these 52 (36.88%), 29 (20.56%) sites developed signs of infection during the follow-up, whereas 23 (16.31%) did not developed any painful symptoms over the observational period. 109 (97.32%) out of 118 (83.69%) sites achieved complete remission of signs of infection on an average of 6.44 ± 8.85 months.

41 (37.61%) did not experienced any further infection, while in 67 (61.47%) sites 1-3 relapses occurred within 10.16 ± 13.58 months, and only in one case (0.92%) relapses occurred ≥ 4 times. A second remission was reported for 53 (79.10%) sites after the first relapse within on average 5.60 ± 7.17 months (Table 5). Overall, out of 141 sites, the 49.64% (n=70) of the MRONJ lesions had never experienced signs of infection or

relapses after the first remission, while in 47.51% (n=67) relapses were treated with medical therapy. In the 6.38% (n=9) instead infection was persistent. **(Table 7).**

Table 7 – Sign of Infection				
	All Sample (n = 141)	**Osteoporosis pts (n = 39)**	**Oncologic pts (n = 102)**	**p-value**
At enrollment	89 (63.12)	27 (69.23)	62 (60.78)	0.436
Onset	118 (83.69)	29 (74.36)	89 (87.25)	0.077
First Remission	109 (92.37)	29 (100.00)	80 (89.89)	0.110
Time of 1° remission, Mean (SD) **Median (IQR) (months)**	6.44 (8.85) (1-45) 3 (1-7)	7.27 (9.40) (1-40) 3 (1-10)	6.14 (8.69) (1-45) 3 (1-7)	0.555
Num. Relapses				
None	41 (37.61)	17 (58.62)	24 (30.00)	0.053
1-3 times	67 (61.47)	12 (41.38)	55 (68.75)	
≥ 4 times	1 (0.92)	0 (0.00)	1 (1.25)	
First relapse	67 (61.47)	12 (41.38)	55 (68.75)	1.000
Time 1° relapse, Mean (SD) **Median (IQR) (months)**	10.16 (13.58) (1-88) 5 (1-12)	9.33 (8.56) (1-25) 6.5 (3-16)	10.35 (14.51) (1-88) 5 (2-88)	0.817
Second Remission	53 (79.10)	8 (66.67)	45 (81.82)	0.232
Time of 2° remission, Mean (SD) **Median (IQR) (months)**	5.60 (7.17) (1-36) 3 (2-7)	9.00 (10.83) (1-36) 8 (2-9)	4.93 (6.17) (1-33) 3 (2-5)	0.121

3.3.2.2 Complete remission of signs of infection and pain

One-hundred-twenty-five sites (88.65%) presented with pain and signs of infection over the follow-up, while 16 (11.34%) did not develop any symptoms/infection. Out of 125 (88.65%) sites, a first remission was observed in 113 (89.60%) sites within on average 9.12 ± 12.09 months with no difference between oncologic and osteoporotic patients, while 12 (8.5%) did not experience any remission over the follow-up. Out of 113 sites which achieved remission, 41 (36.28%) remained free form pain and infection, whereas 68 (60.17%) sites were subject to 1-3 relapses during follow-up. The first relapse occurred on average within 8.00 ± 8.47 months. A second remission was observed for 53 (74.65%) sites (time of second remission: 7.23 ± 9.05 months). Overall, out of 141 sites, about 40% (n=57) of the MRONJ lesions had never showed pain/infection or relapses after the first

remission, while about 48% (n=68) of the sites periodically presented with relapses which indicate that medical therapy is effective in treating acute infection/pain but that is not effective in preventing further recurrences in almost half of the patients. In 8% (n=12) pain/infection was persistent **(Table 8).**

Table 8 – Complete Remission of signs of infection and pain

	All Sample (n = 141)	**Osteoporosis pts (n = 39)**	**Oncologic pts (n = 102)**	**p-value**
At enrollment	101 (71.63)	29 (74.36)	72 (70.59)	0.835
Onset	125 (88.65)	31 (79.49)	94 (92.16)	0.042
First Remission	113 (89.60)	30 (96.77)	83 (87.23)	0.291
Time of 1° remission, Mean (SD) **Median (IQR) (months)**	9.12 (12.09) (1-75) 5 (2-11)	9.37 (10.63) (1-50) 5.50 (2-13)	9.04 (12.64) (1-75) 4 (1-11)	0.899
Num. Relapses				
None	41 (36.28)	14 (46.67)	27 (32.53)	0.357
1-3 times	68 (60.17)	15 (50.00)	53 (63.85)	
≥ 4 times	4 (3.57)	1 (3.33)	3 (3.61)	
First relapse	71 (62.83	16 (53.33)	55 (66.27)	1.000
Time 1° relapse, Mean (SD) **Median (IQR) (months)**	8 (8.47) (1-38) 4 (2-10.5)	9.13 (7.93) (1-22) 6 (3-19)	7.68 (8.66) (1-38) 4 (2-9.5)	0.551
Second Remission	53 (74.65)	10 (62.50)	43 (78.18)	0.335
Time of 2° remission, Mean (SD) **Median (IQR) (months)**	7.23 (9.05) (1-38) 4 (2-10.5)	9.8 (13.73) (1-22) 6 (3-22)	6.63 (7.69) (1-38) 4 (2-9.5)	0.323

3.3.2.3 Mucosal coverage status

Exposed bone or bone that can be probed was noted in 138 (97.87%) sites, especially in oncologic patients (99.02%) than in osteoporotic patients (94.87%), although without statistically significant difference. Specifically, 122 (86.52%) sites presented with signs of bone exposure at the enrollment, while 19 (13.47%) with intact mucosa. Out of these 19 (13.47%), 16 (11.34%) sites developed bone exposure or sinus tracts during the follow-up, whereas 3 (2.12%) continued to manifest complete mucosal coverage over the

observational period. 102 (72.34%) out of 138 (97.87%) sites achieved complete mucosal coverage within on average 15.85 ± 15.39 months, while 36 (25.55%) did not show remission. The percentage of remission was mainly reported in sites of osteoporotic patients (91.89%) than in those of oncologic patients (67.33%) (p = 0.004). 61 (59.80%) sites did not report a second relapse, while 41 (40.20%) sites registered amid 1 and 3 relapses during follow-up within 10.54 ± 9.86 months without statistically significant difference between the two groups. After the first relapse, a second remission was reported for 26 (63.41%) of sites within 9.35 ± 9.75 months.

Overall, out of 141 sites, about 45% (n=64) of the MRONJ lesions had never showed exposed bone or probing bone through a sinus tract or relapses after the first remission, while about 40% (n=41) of the sites periodically presented with relapses which indicate that mucosal closure may not be stable over the time in a subset of patients. In 25.5% (n=36) bone exposure was persistent (Table 9).

Table 9 – Mucosal coverage status: Exposed Bone or bone that can be probed through a sinus tract)

	All Sample (n = 141)	**Osteoporosis pts (n = 39)**	**Oncologic pts (n = 102)**	**p-value**
At enrollment	122 (86.52)	37 (94.87)	85 (83.33)	0.098
Onset	138 (97.87)	37 (94.87)	101 (99.02)	0.185
First Remission	102 (73.91)	34 (91.89)	68 (67.33)	0.004
Time of 1° remission, Mean (SD) **Median (IQR) (months)**	15.85 (15.39) (1-90) 13 (6-19)	15.94 (13.69) (1-59) 15 (6-18)	15.81 (16.28) (1-90) 13 (5-19)	0.968
Num. Relapses				
None	61 (59.80)	19 (55.88)	42 (61.76)	0.570
1-3 times	41 (40.20)	15 (44.12)	26 (38.24)	
≥ 4 times	0 (0.00)	0 (0.00)	0 (0.00)	
First relapse	41 (40.20)	15 (44.12)	26 (38.24)	1.000
Time 1° relapse, Mean (SD) **Median (IQR) (months)**	10.54 (9.86) (1-41) 8 (3-13)	10.93 (9.86) (2-41) 9 (4-13)	10.31 (10.04) (1-39) 6.50 (3-13)	0.848
Second Remission	26 (63.41)	8 (53.33)	18 (69.23)	0.482
Time of 2° remission, Mean (SD) **Median (IQR) (months)**	9.35 (9.75) (1-41) 8 (3-13)	11.38 (13.96) (1-42) 5.50 (3.50-15.0)	8.44 (7.54) (1-30) 7.50 (3-12)	0.491

3.2.2.4 Complete clinical remission of MRONJ

During follow-up, complete clinical remission was reported in 96 (68.09%) sites within 15.38 ± 14.87 months with a statistically significant difference between the osteoporotic patients (35/39 sites, 89.74%) and the oncologic patients (61/102 sites, 59.80%) p-value=0.001. 45 (46.88%) sites did not show any further clinical signs of MRONJ over the follow-up. On the contrary, 51 (53.13%) sites experienced relapses between 1- and 3-times during follow-up (time of 1° relapse: 12.12 ± 13.79 months). About 61% percent of these sites reported a second remission within 11.55 ± 15.51 months **(Table 10)**. Overall, 32.62% (n=45) of the MRONJ lesions achieved a complete clinical remission and without any further relapse; on the other side, almost half of the sites (53.13%, n=51) showed periodic recurrences, while 32.62% (n=45) did never achieve complete clinical remission.

At the end of the observational period, 28 (19.7%) of the patients were still on ongoing follow-up while 53 (37.3%) were lost to follow-up. Instead, 18 (12.7%) exit from the follow-up after 1 year of complete clinical and radiological remission) and 32 (22.5%) oncologic patients died for the malignancy. Unfortunately, in 11 (7.7%) pain and/or local infection could not be controlled by the non-surgical therapy and were therefore treated with surgical resection/ sequestrectomy.

Table 10 – Complete Clinical remission of MRONJ				
	All Sample (n = 141)	**Osteoporosis pts (n = 39)**	**Oncologic pts (n = 102)**	**p-value**
At enrollment	134 (95.04)	39 (100.00)	95 (93.14)	0.190
Onset	141 (100.00)	39 (100.00)	102 (100.00)	1.000
First Remission	96 (68.09)	35 (89.74)	61 (59.80)	0.001
Time of 1° remission, Mean (SD) **(range)** **Median (IQR) (months)**	15.38 (14.87) (1-90) 12 (5-19.5)	15.57 (13.70) (1-59) 13 (6-18)	15.26 (15.62) (1-90) 11 (4-20)	0.923
Num. Relapses				
None	45 (46.88)	15 (42.86)	30 (49.18)	0.614
1-3 times	51 (53.13)	20 (57.14)	31 (50.82)	
≥ 4 times	0 (0.00)	0 (0.00)	0 (0.00)	
First relapse	51 (53.13)	20 (57.14)	31 (50.82)	
Time 1° relapse, Mean (SD) **Median (IQR) (months)**	12.12 (13.79) (1-82) 8 (3-15)	13.95 (18.31) (1-82) 9.50 (3.5-13.0)	10.94 (10.04) (1-36) 8 (3-16)	0.451
Second Remission	31 (60.78)	11 (55.00)	20 (64.52)	0.565
Time of 2° remission, Mean (SD) **Median (IQR) (months)**	11.55 (15.51) (1-78) 8 (3-12)	9.73 (13.34) (1-46) 5 (3-8)	12.55 (16.82) (1-78) 8 (5-12)	0.636

3.4 AAOMS and SICMF-SIPMO Staging systems

The AAOMS stage **(Table 11)** was 0a/0s/1/2/3 respectively in 5 (3.52%) /12 (8.45%) /41 (28.87%)/75 (52.82%)/9 (6.34%) sites. The SICMF- SIPMO stage was 1A/1B/2A/2B/3A/3B in 15 (12.10%)/19 (15-32)/22 (17.74)/44 (35.48%)/22 (17.74%)/1 (0.81%) sites **(Table 12).** With respect to the latter, out of 141 sites, 124 had complete CT scan records. During the follow-up, variation of the stage evaluated by the AAOMS staging system was observed in 95.07% of sites, while SICMF- SIPMO variation occurred in 63.41% of sites. In AAOMS, comparing the stage at the enrollment with the stage at the last follow-up, clinical progression (up-staging) occurred in 11.97% of sites, down-staging was observed in 69.72%, while 18.31% of sites reported at the last follow-up the same stage registered at enrollment.

Table 11 – AAOMS Stages				
	All Sample (n = 142)	**Osteoporotic pts (n = 39)**	**Oncologic pts (n = 103)**	**p-value**
AAOMS Stage at T0				
0a	5 (3.52)	0 (0.00)	5 (4.85)	0.624
0s	12 (8.45)	2 (5.13)	10 (9.71)	
1	41 (28.87)	13 (33.33)	28 (27.18)	
2	75 (52.82)	21 (53.85)	54 (52.43)	
3	9 (6.34)	3 (7.69)	6 (5.83)	
AAOMS Variation during Follow-Up	135 (95.07)	38 (97.44)	97 (94.17)	0.674
AAOMS Last Follow-Up				0.409
0a	71 (50.00)	25 (64.10)	46 (44.66)	
0s	13 (9.15)	3 (7.69)	10 (9.71)	
1	29 (20.42)	6 (15.38)	23 (22.33)	
2	16 (11.27)	3 (7.69)	13 (12.62)	
3	13 (9.15)	2 (5.13)	11 (10.68)	
Stage at last follow-Up vs. T0				
Improved	99 (69.72)	33 (84.62)	66 (64.08)	0.064
Unchanged	26 (18.31)	4 (10.26)	22 (21.36)	
Worsened	17 (11.97)	2 (5.13)	15 (14.56)	

Different percentages were observed according to the SICMF-SIPMO staging system: clinical progression occurred in 17.07% of sites, down-staging was observed in 44.72% of sites, and 18.31% of sites did not report any variation (Table 11).

Table 12 – SICMF-SIPMO Stage				
	All Sample (n = 124)	**Osteoporotic pts (n = 32)**	**Oncologic pts (n = 92)**	**p-value**
SICMF at T0				
0	0 (0.0)	0 (0.0)	0 (0.0)	
1A	15 (12.10)	7 (21.88)	8 (8.70)	0.516
1B	19 (15.32)	6 (18.75)	13 (14.13)	
2A	22 (17.74)	4 (12.50)	18 (19.57)	
2B	44 (35.48)	10 (31.25)	34 (36.96)	
3A	22 (17.74)	5 (15.62)	17 (18.48)	
3B	1 (0.81)	0 (0.00)	1 (1.09)	
Not Reported	1 (0.81)	0 (0.00)	1 (1.09)	
SICMF Variation during Follow-Up	78 (63.41)	21 (65.62)	57 (62.64)	0.833
SICMF Last Follow-Up				
0	32 (26.02)	9 (28.12)	23 (25.27)	0.177
1A	13 (10.57)	7 (21.88)	6 (6.59)	

1B	1 (0.81)	1 (3.12)	0 (0.00)	
2A	27 (21.95)	6 (18.75)	21 (23.08)	
2B	25 (20.33)	4 (12.50)	21 (23.08)	
3A	22 (17.89)	5 (15.62)	17 (18.68)	
3B	1 (0.81)	0 (0.00)	1 (1.10)	
Not Reported	2 (1.63)	0 (0.00)	2 (2.20)	
Stage at last follow-Up vs. T0				
Improved	55 (44.72)	16 (50.00)	39 (42.86)	
Unchanged	47 (38.21)	11 (34.38)	36 (39.56)	0.825
Worsened	21 (17.07)	5 (15.62)	16 (17.58)	

3.5 Subgroup Analysis

In an additional analysis executed using a subgroup of 48 patients with follow-up visits at 6, 12, 18 and 24 months (Table 12), several improvements were reported for all the outcomes during follow-up. Pain was reported in 56.25% of sites at baseline with a continuous percentage decrease during the whole follow-up. Pain was present in 63.64% of sites of oncologic patients at baseline. After six months, only 21.21% of these sites reported pain. At 18 and 24 months, only 12.12% of sites of oncologic patients reported pain respectively. The same trend did not emerge in sites of osteoporotic patients.

About 60.24% of sites reported signs of infection at baseline. After six months, 31.25% of sites registered still signs of infection, while at 12 months, a slight percentage increase emerged (39.58%). At 18 and 24 months, only 25% and 21% of sites reported signs of infection. Sites of both subgroups of patients reported a similar percentage of signs of infection at baseline (osteoporotic patients: 60%; oncologic patients: ~ 61%). At six months, only sites of oncologic patients reported a percentage decrease of signs of infection (24.24%), while in sites of osteoporotic patients, the percentage decrease was slightly higher than 10%. After 18 and 24 months, sites of oncologic patients reported a percentage decrease (signs of infection in 24.24% and 21.21%, respectively), while a substantial reduction emerged only after 24 months in sites of osteoporotic patients.

Bone exposure (or bone that can be probed through a sinus tract) was observed in 83.33% of sites at baseline in both groups. After 18 and 24 months, a substantial decrease emerged in sites of osteoporotic patients (18 months: 53.33%; 24 months: 46.67%). A percentage reduction was observed in oncologic patients after 24 months (baseline: 75.76%, 24 months: 45.45%).

With respect of complete clinical remission of MRONJ, after 18 months, 62.50% of sites still presented no complete clinical remission, with a higher prevalence in sites of oncologic patients (66.67%) than in those of osteoporotic patients (53.33%). After 24 months, 56.25% of sites continued not to show complete clinical remission (sites of osteoporotic patients: 53.33%, sites of oncologic patients: 57.58%).

Signs of infection along with pain were observed in 70.83% of sites at baseline. After six months, about 44% of sites continued to show signs of infection/pain. At the third follow-up (12 months), a slight increase of sites without complete clinical remission of infection/pain was observed (52.08%). At 18 months, only one-third of sites (31.25%) showed no complete clinical remission of infection/pain from baseline. At 24 months, only the 27.08% of the patients still presented signs of infection/pain, while the 82.92% were free from infection and pain.

Table 13 – Subgroup analysis: Outcome at baseline, 6, 12, 18, 24 months				
		All Sample (n = 48)	**Osteoporotic ptz (n = 15)**	**Oncologic ptz (n = 33)**
Pain presence	Baseline	27 (56.25)	6 (40.00)	21 (63.64)
	6 months	12 (25.00)	5 (33.33)	7 (21.21)
	12 months	13 (27.08)	3 (20.00)	10 (30.30)
	18 months	8 (16.67)	4 (26.67)	4 (12.12)
	24 months	5 (10.42)	1 (6.67)	4 (12.12)
Sign of infection	Baseline	29 (60.42)	9 (60.00)	20 (60.61Six
	6 months	15 (31.25)	7 (46.67)	8 (24.24)
	12 months	19 (39.58)	6 (40.00)	13 (39.39)
	18 months	12 (25.00)	4 (26.67)	8 (24.24)
	24 months	10 (20.83)	3 (20.00)	7 (21.21)
Mucosal stutus (Exposed bone or bone that can be probed through a sinus tract)	Baseline	40 (83.33)	15 (100.00)	25 (75.76)
	6 months	35 (72.92)	12 (80.00)	23 (69.70)
	12 months	33 (68.75)	10 (66.67)	23 (69.70)
	18 months	26 (54.17)	8 (53.33)	18 (54.55)
	24 months	22 (45.83)	7 (46.67)	15 (45.45)
No Complete Clinical Remission of MRONJ	Baseline	45 (93.75)	15 (100.00)	30 (90.91)
	6 months	40 (83.33)	12 (80.00)	28 (84.85)
	12 months	37 (77.08)	10 (66.67)	27 (81.82)
	18 months	30 (62.50)	8 (53.33)	22 (66.67)
	24 months	27 (56.25)	8 (53.33)	19 (57.58)
No Complete Clinical Remission of signs of infection and pain	Baseline	34 (70.83)	11 (73.33)	23 (69.70)
	6 months	21 (43.75)	8 (53.33)	13 (39.39)
	12 months	25 (52.08)	7 (46.67)	18 (54.55)
	18 months	15 (31.25)	6 (40.00)	9 (27.27)
	24 months	13 (27.08)	4 (26.67)	9 (27.27)

Subgroup Analysis Graphs

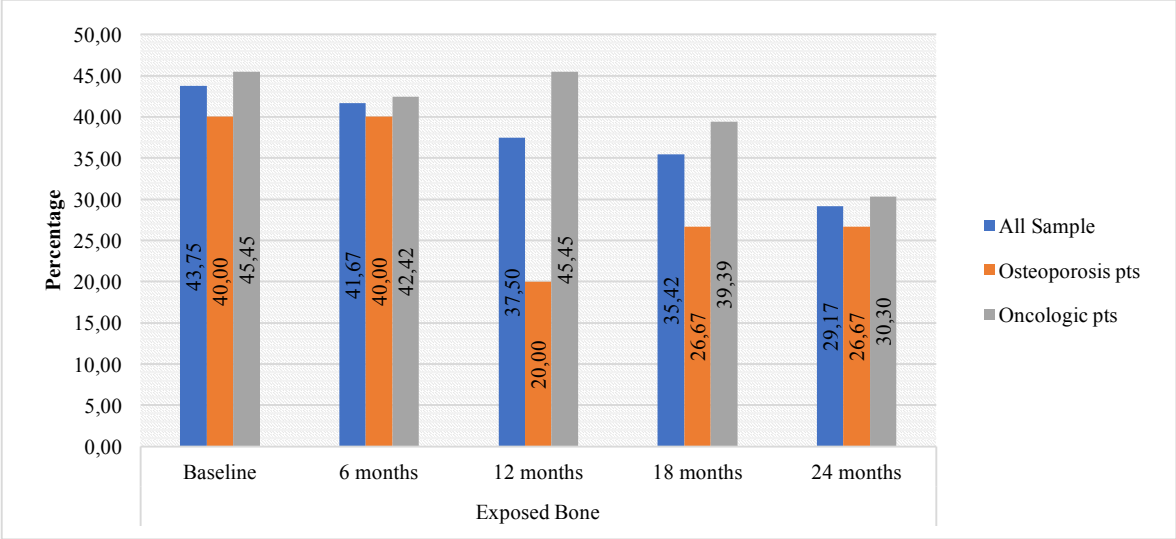

Figure 1 – Exposed Bone

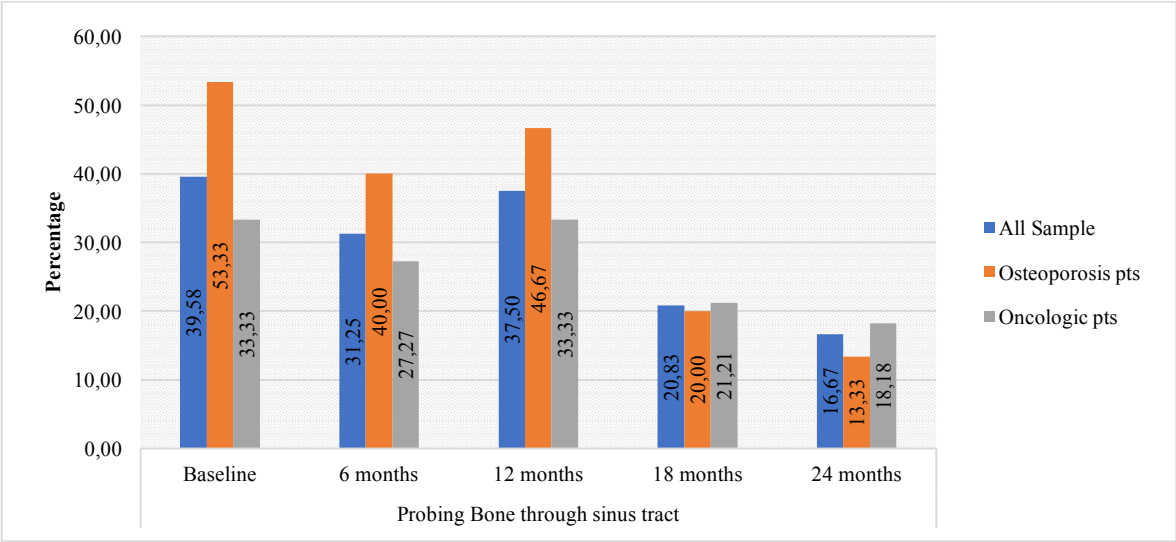

Figure 2 – Probing Bone through sinus tract

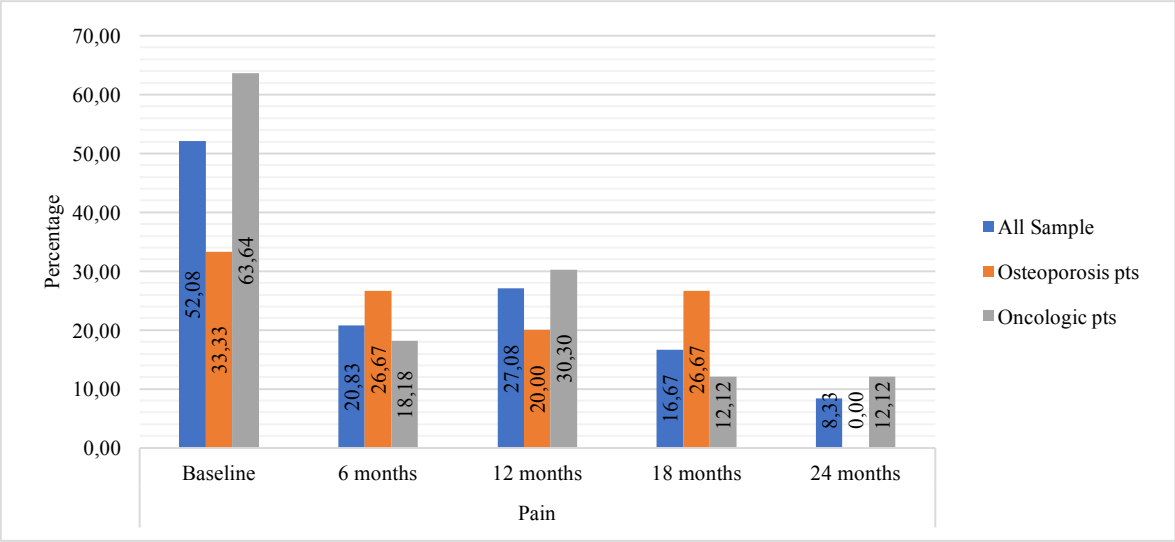

Figure 3 – Pain

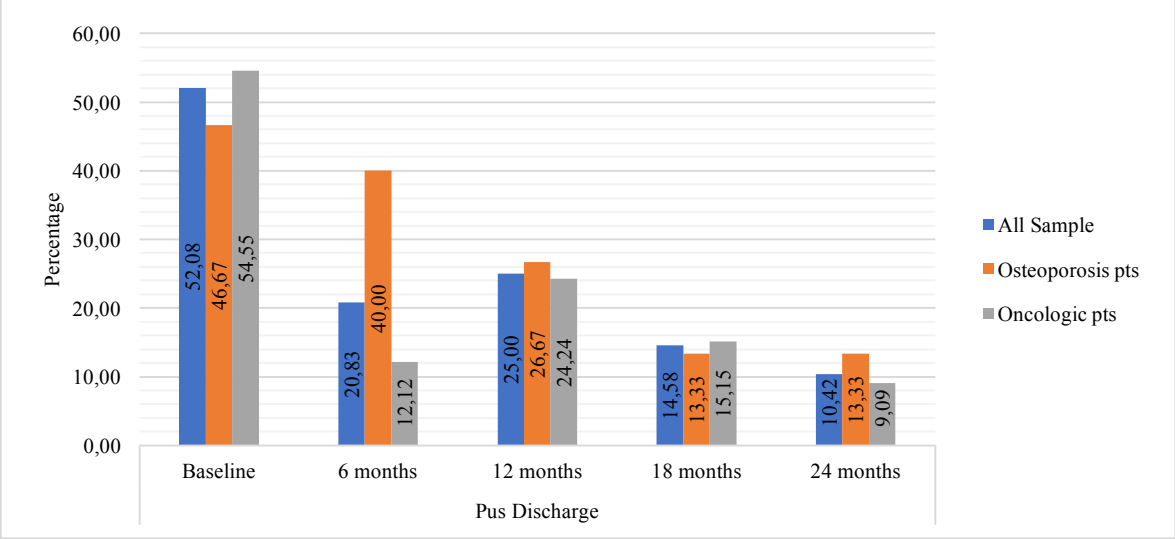

Figure 4 – Pus Discharge

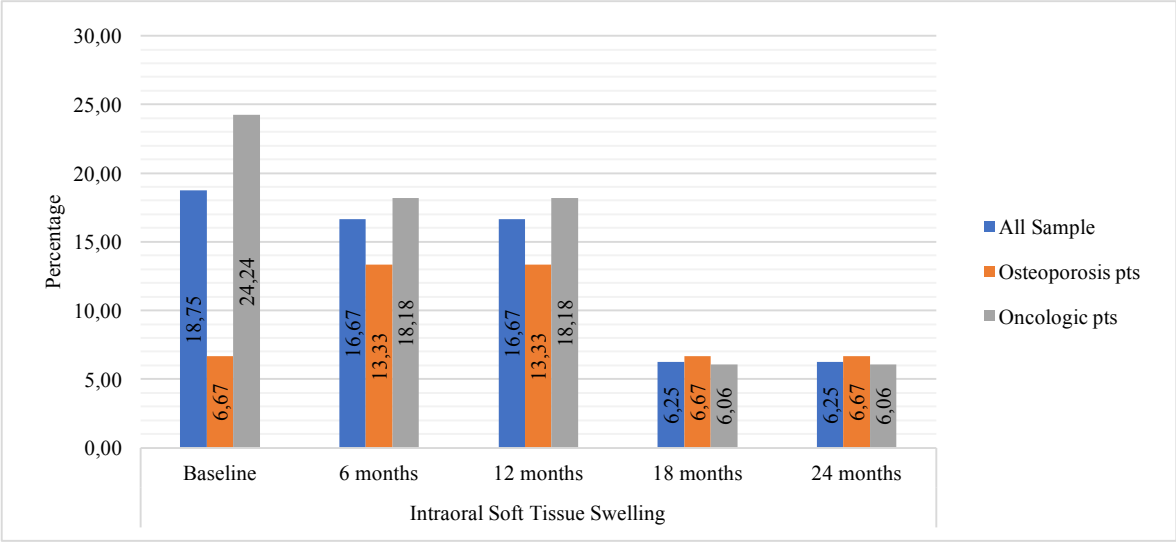

Figure 5 – Intraoral Soft Tissue Swelling

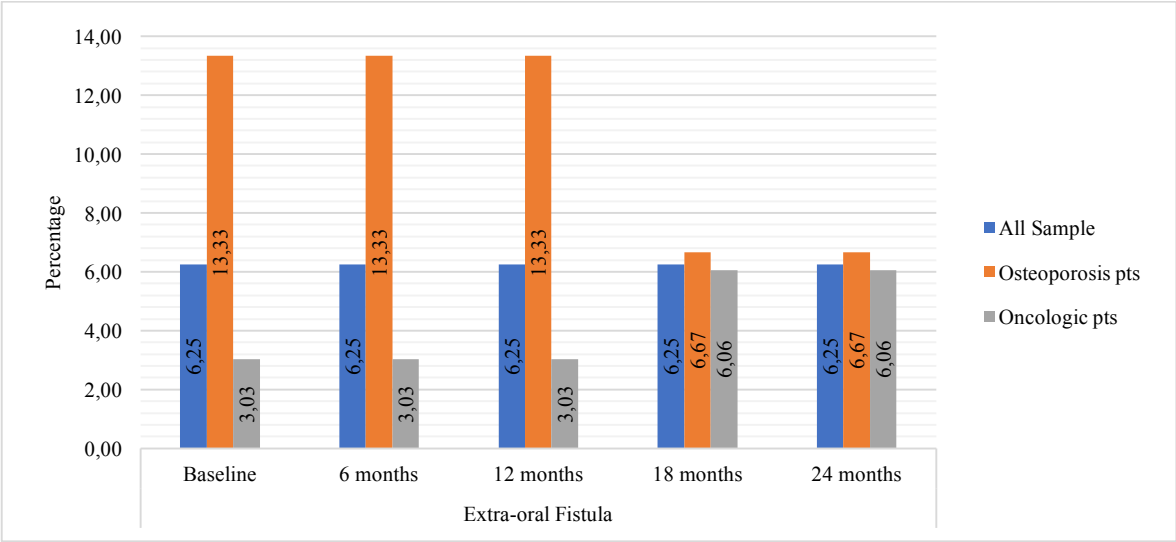

Figure 6 – Extra-oral Fistula

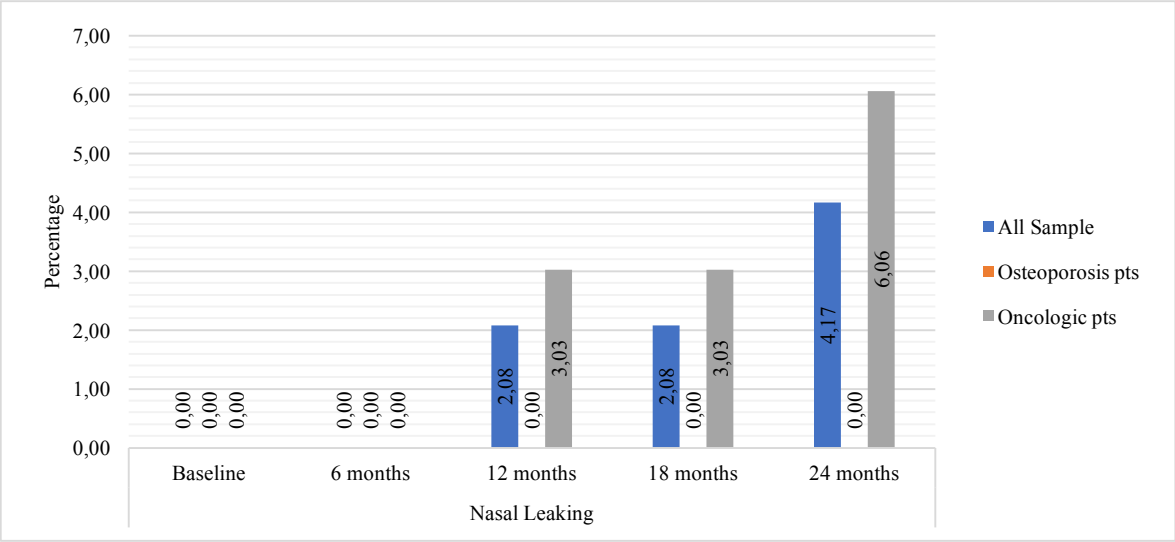

Figure 7 – Nasal Leaking

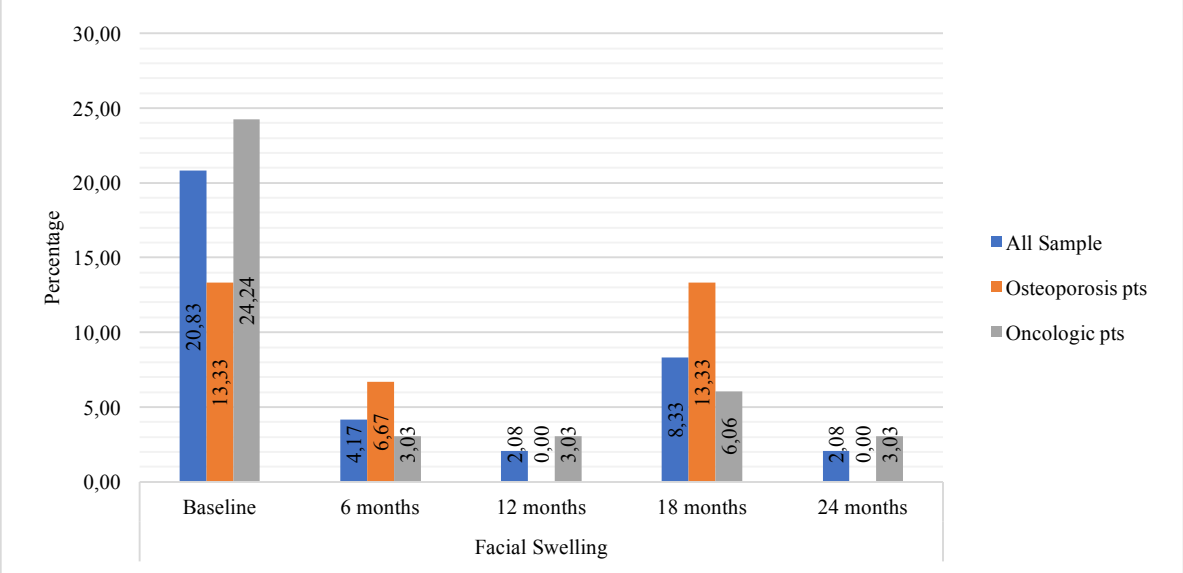

Figure 8 – Facial Swelling

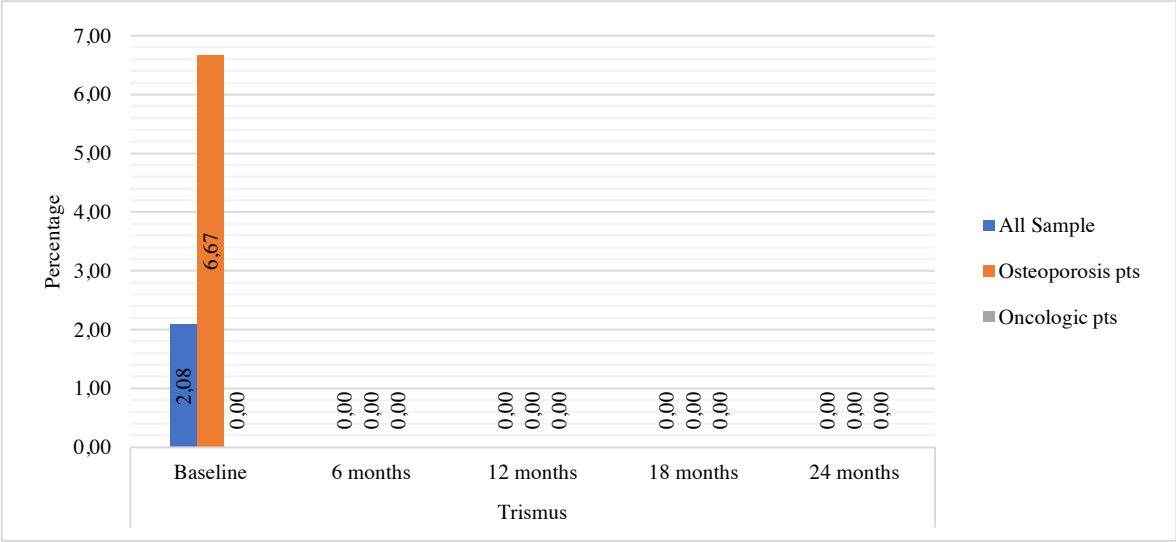

Figure 9 – Trismus

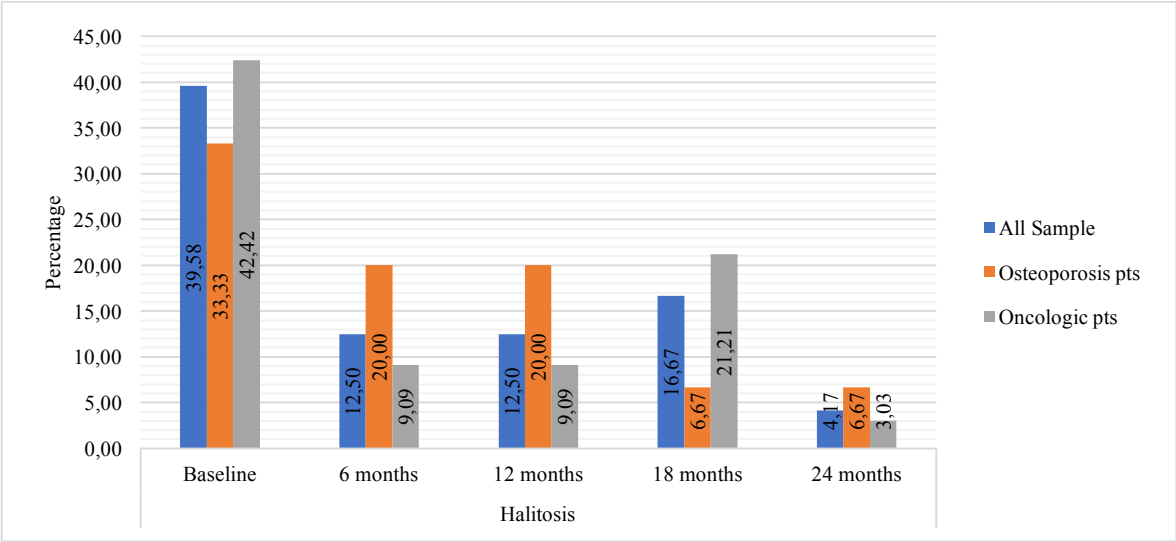

Figure 10 – Halitosis

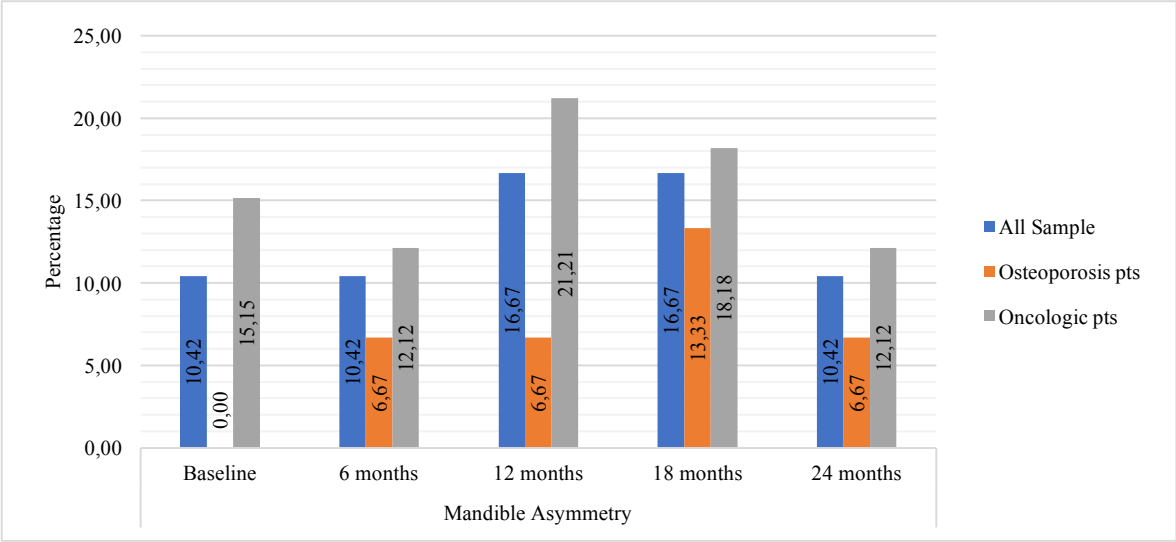

Figure 11 – Mandible Asymmetry

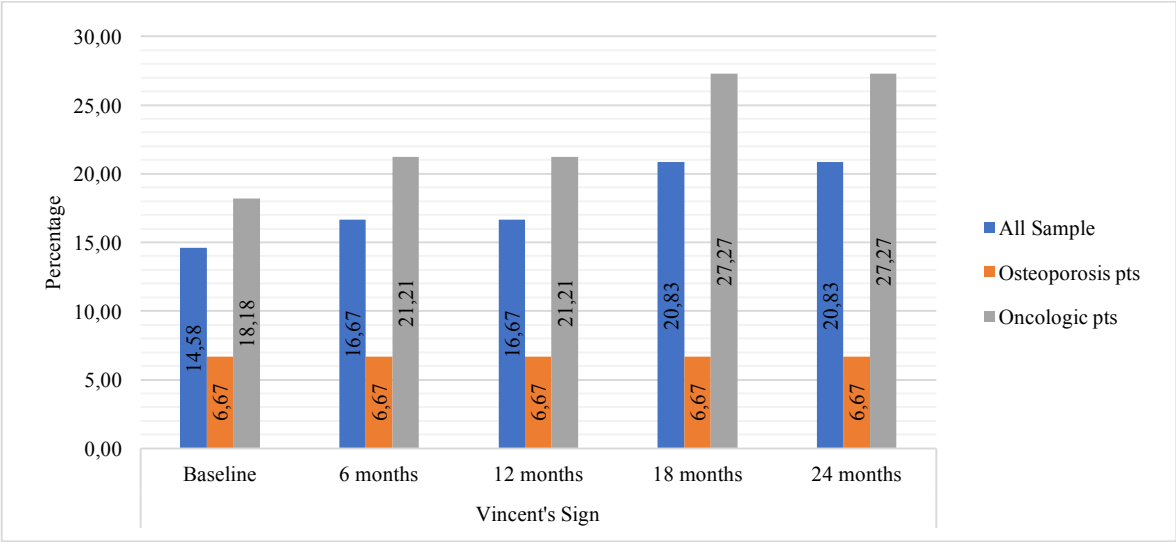

Figure 12 – Vincent's Sign

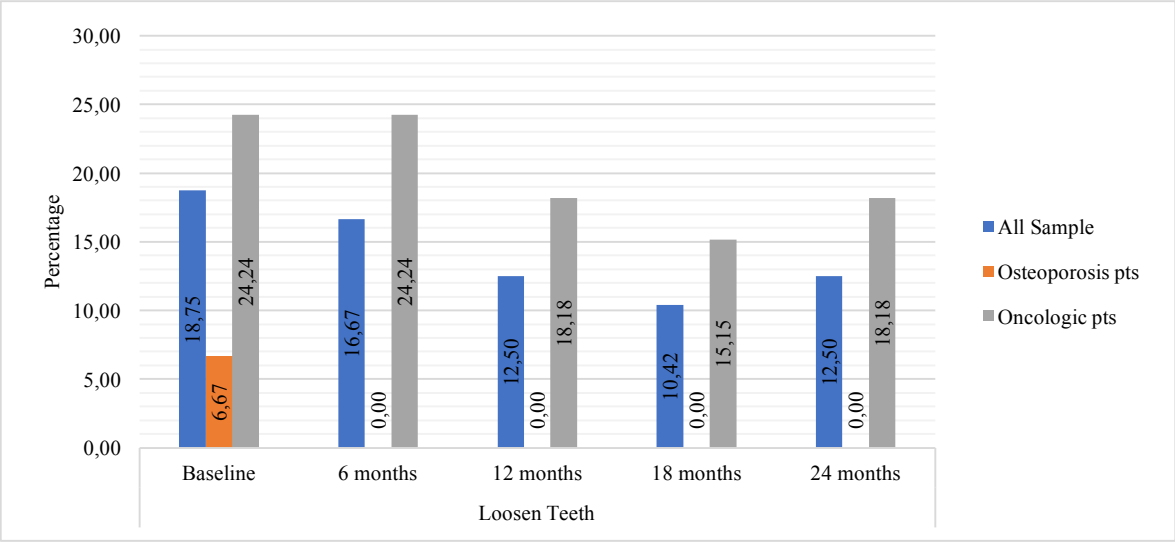

Figure 13 – Loosen teeth

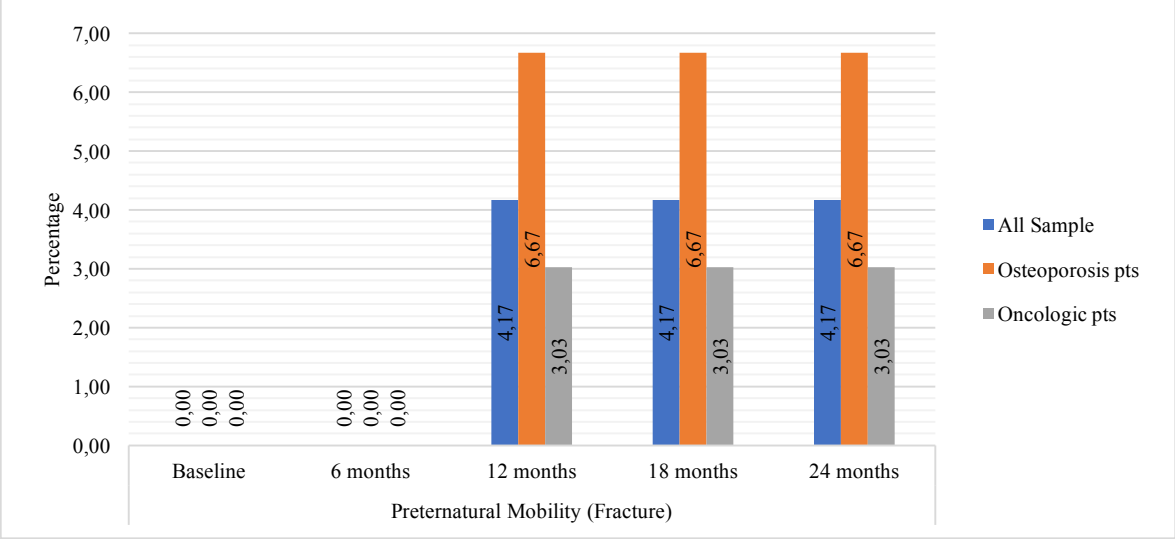

Figure 14 – Preternatural Mobility (Fracture)

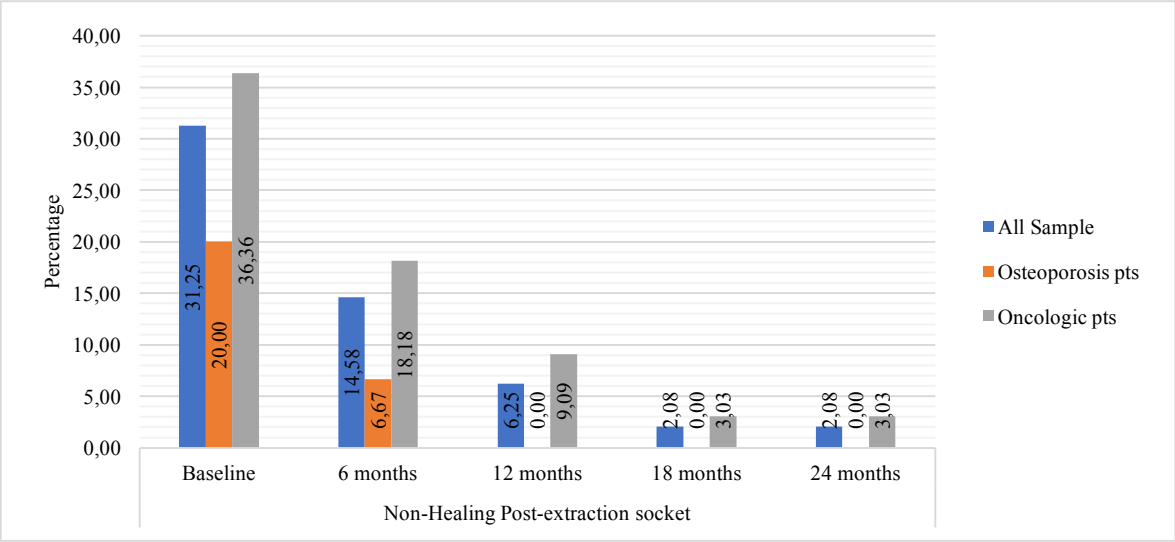

Figure 15 – Non-healing post-extraction socket

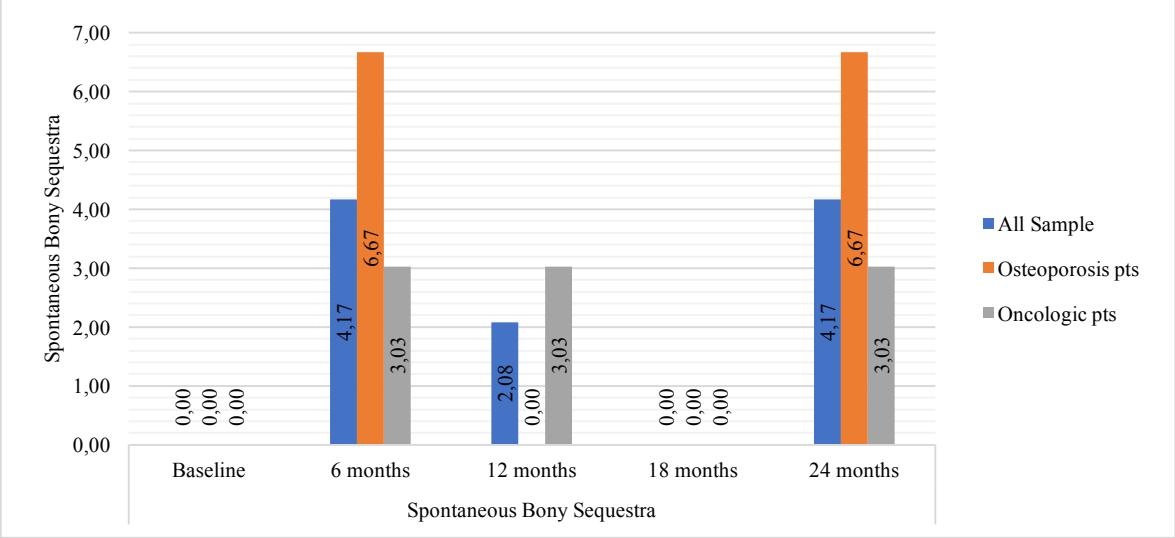

Figure 16 – Spontaneous Bony Sequestrum

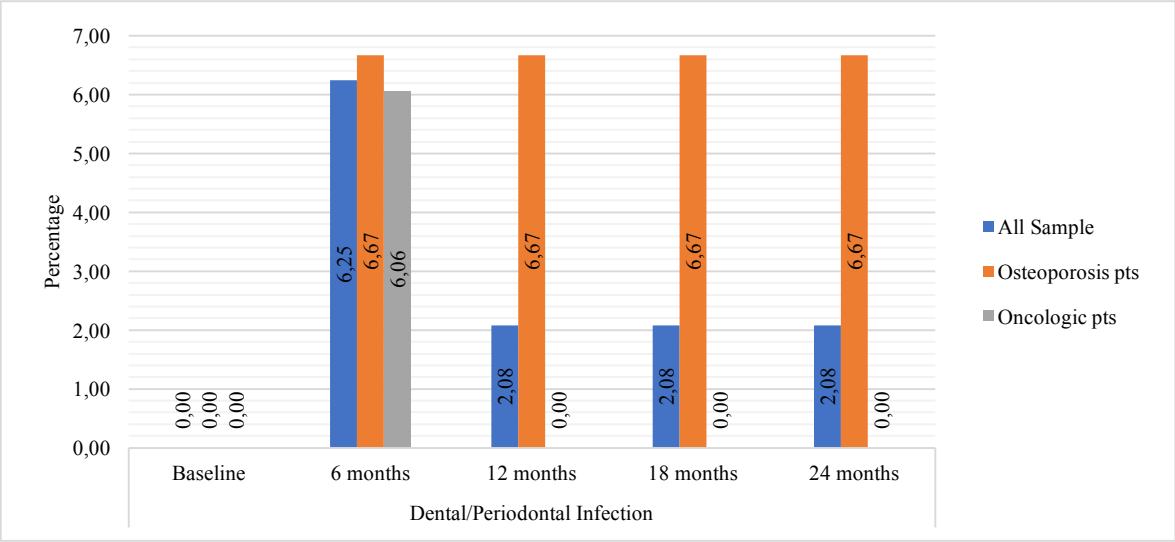

Figure 17 – Dental/Periodontal Infection

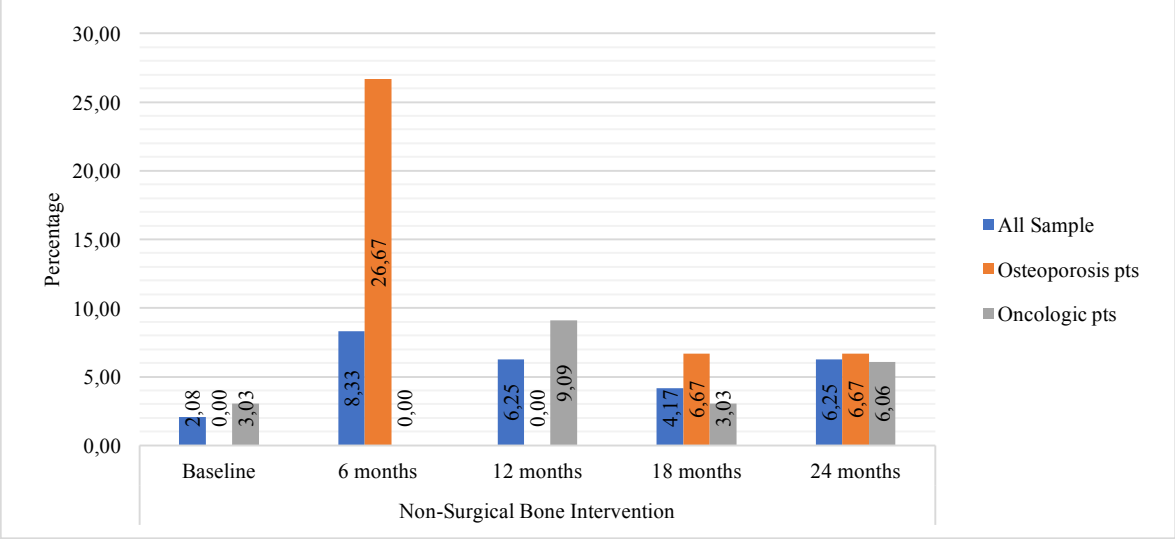

Figure 18 – Non-Surgical Bone Intervention

4. DISCUSSION

Treatment of MRONJ patients remains challenging and controversial, since consensus standard protocol has not yet been established (Moraschini *et al*, 2021). Published treatment recommendations are based on consensus opinion and not on randomized controlled trials, and most retrospective or prospective studies included only small numbers of subjects. Management of MRONJ has historically centered on minimizing symptoms and eliminating infection (Moretti *et al*, 2011; Ruggiero *et al*, 2014). According to the guidelines of the AAOMS, indeed, treatment strategies of MRONJ 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. Therapeutic options vary from pharmacological supportive approach with antibiotics and antiseptics to extensive surgical resection of necrotic bone (Ruggiero *et al*, 2014). Basically, treatment strategies can be categorized as nonsurgical or conservative (Van den Wyngaert *et al*, 2009; Moretti *et al*, 2011; Lerman *et al*, 2013) and surgical approaches (Carlson and Basile, 2009; Wilde *et al*, 2011) Nonsurgical treatment includes a combination of antiseptic mouth rinses, antimicrobial chemotherapy, when inflammation occurs, and non-surgical sequestrectomy and/or debridement (Montebugnoli *et al*, 2007; Van den Wyngaert *et al*, 2009; Alsehimy, 2014; Melea *et al*, 2014; Ikeda *et al*, 2015; Rugani *et al*, 2015; Bodem *et al*, 2015; Coropciuc *et al*, 2017). On the other hand, surgical treatments range from the minimally invasive to the more invasive bone resection with or without reconstructions (Yamada *et al*, 2018; Marcianò *et al*, 2020).

Recently, there have been a growing number of studies demonstrating the superiority of the surgical interventions on the conservative ones especially for early MRONJ stages (Nisi *et al*, 2018; Giudice *et al*, 2020) in terms of mucosal healing. However, a great

proportion of MRONJ patients, particularly those affected by malignancies, may not be eligible for the surgical treatments, either because of their short life expectancy, or their poor health status, and may benefit from the non-surgical management which has been proved to be effective in controlling pain and infection, therefore improving their quality of life (Marcianò *et al*, 2020).

By now, the majority of the studies evaluating the non-surgical treatments' outcomes have been conducted on small samples or on patients with follow-up ranging between few months to several years (Montebugnoli *et al*, 2007; Van den Wyngaert *et al*, 2009; Alsehimy, 2014; Melea *et al*, 2014; Ikeda *et al*, 2015; Rugani *et al*, 2015; Bodem *et al*, 2015; Coropciuc *et al*, 2017).

To the best of our knowledge, the present study is the first to have evaluated the long-term outcomes of the conservative non-surgical treatment on a big sample of patients, all having a minimum follow-up of at least 12 months.

Moreover, although it has been recommended that the first aim of MRONJ treatment should be to control pain and infection (Ruggiero *et al*, 2014), few studies, if any, have assessed these two parameters as separate or combined outcomes, having the majority being focused on the mucosal healing (Montebugnoli *et al*, 2007; Van den Wyngaert *et al*, 2009; Alsehimy, 2014; Melea *et al*, 2014; Ikeda *et al*, 2015; Rugani *et al*, 2015; Bodem *et al*, 2015; Coropciuc *et al*, 2017). Indeed, the mucosal healing has been one of the most used outcome measures for assessing the effectiveness of a specific treatment although it has been established that, as MRONJ is a chronic bone disease, the mere mucosal integrity does not necessarily match with the MRONJ lesion healing. Indeed, the exposed bone can be interpreted as the "tip of the iceberg" seen from the outside (Haviv *et al*, 2021). Furthermore, the inconsistency and variability of the outcome measures and the different timing of the measurements adopted make extremely difficult to compare results among

the published studies.

For the all above reasons, we aimed at evaluating the presence of pain as patient-reported outcome, and the presence of signs of infection (which has never been properly investigated until now), and the presence of mucosal coverage, separately, as clinical outcomes. In addition, by combining these outcomes, we have also assessed together the absence of pain and infection, which would reflect the primary goal of the MRONJ treatment according to the Position Paper, and the complete clinical remission, defined as the absence of pain/infection and the presence of mucosal integrity. By doing this, we have provided more insight on the clinical chronic course of MRONJ patients treated by non-invasive means.

This retrospective study is one of the largest to-date on MRONJ patients treated by exclusive non-surgical therapy and the first to have evaluated long-term outcomes not only by comparing the first and the last follow-up visits but also by analyzing the chronic clinical course over the entire follow-up. Moreover, patients were followed up for a minimum of 12 months (median follow-up 39 months, range 12-150). All the patients included were considered not eligible for surgical treatment mostly because of the poor health systemic conditions due to the underlined oncological disease or because patients were willing to continue the conservative treatment and refused any invasive procedure. The findings of this study demonstrated favorable outcomes using a combination of topical antiseptics such as chlorhexidine oral rinses, antibiotics, non-surgical bony sequestrum removal in the majority of the patients.

Our sample comprises a population of 126 MRONJ patients, predominantly females, and 71% of oncologic patients, mostly affected by breast cancer (60%) or multiple myeloma (35%). Demographic data of this study is in accordance with the present literature, since

the oncologic population presents a higher prevalence of MRONJ compared to the osteoporotic one, due to the higher dosage and potency of antiresorptive drugs used for treating the underlined malignancies and the possible associations with antiangiogenic molecules (Vescovi, Merigo, *et al*, 2012).

The majority of the patients had been treated with antiresorptive drugs, mostly bisphosphonates (95%) and only few with denosumab (5%). Moreover, about the 8% were additionally treated with antiangiogenics or TKI. The most prescribed antiresorptive drug was zoledronate among the oncologic population (Vescovi, Merigo, *et al*, 2012; Ruggiero and Kohn, 2015), while alendronate in the osteoporotic one (Manfredi *et al*, 2011) (Manfredi et al., 2011) for a median duration of 39 months. This data reflects the changes in the oncological treatment protocols, as in the recent years we have been assisting to an increasing number of MRONJ cases in patients treated with both antiresorptive and monoclonal antibodies and also in naïve-antiresorptive patients (Pimolbutr *et al*, 2018).

With respect to the role of the drug-holiday, the controversy exists in the literature as to whether drug-holiday affect healing and clinical resolution. While some physicians recommend interrupting treatment with bisphosphonates or denosumab for 2–3 months (i.e. a drug holiday) to allow local treatment and healing following surgery, there is no evidence to support the optimal timing or the effectiveness and safety of this approach (Otto *et al*, 2018). Besides, in some conditions, such as multiple myeloma a drug holiday is not recommended due to the risk of progression of disease and hence it is left to the clinician's recommendations whether the AR suspension is warranted (Terpos *et al*, 2021). Indeed, as the AAOMS Position Paper states, the aim is to prioritize and support the continued oncologic treatment in patients receiving IV AR and antiangiogenic

therapy, so that the decision of the suspension is strictly related to the health status of the patient (Ruggiero *et al*, 2014). In the present study, we have found a great variability when analyzing the drug-holiday patterns. In fact, 41 patients were still on the AR therapy at enrollment, and 32 of them would have suspended AR treatment during the follow-up over a wide range of time (mean time for suspension 19.27 ± 18.56 months). On the other side, 85 patients had already suspended the AR therapy at the time of the enrollment (with a time between AR suspension and first follow-up of 10.31 ± 18.92 months), and only 7 restarted AR treatment during the follow-up after a mean time of 15.67 ± 13.44 months. This great heterogeneity in the AR treatments, in term of type of drugs, duration and suspension patterns, reflects the long-term pharmacological history of the patients, especially the oncologic ones, and did not allow further statistical analysis in order to better understand how the drug-holiday can influence the clinical outcomes.

With respect to MRONJ clinical manifestations, we found that almost the 71% of MRONJ sites were localized at the mandible, as also largely reported in the literature (Ruggiero and Kohn, 2015). MRONJ clinical manifestations were more severe in the oncologic group who presented mainly the exposed variant of MRONJ ($p = 0.038$), were more symptomatic ($p = 0.012$) and presented more signs of infection compared to the non-oncologic group.

Triggers of MRONJ were found in almost all the patients: 61 (42.96%) had dental/periodontal infections triggering the osteonecrosis, 60 (42.25%) and 21 (14.79%) tooth/teeth extractions and implant placement respectively, while in 5 (3.52%) no trigger was found. Accordingly, several studies found dento-alveolar surgery and dental infections as the main risk factors for MRONJ (Ruggiero, 2011; Schiodt *et al*, 2019). The European task force believes that a proportion of MRONJ cases were triggered by

extractions due to the presence of an underlying non-exposed variant of MRONJ that has formed due to the presence of a pre-existing periodontal or dental infection. Therefore, it is recommended that patients on antiresorptive therapy should not be declined surgical dental intervention in the presence of an infection if which may trigger the bone necrosis (Schiodt *et al*, 2019).

According to recent guidelines and recommendations, systemic antibiotic treatment is a key component in the treatment of all stage 2 and 3 MRONJ patients (Ruggiero *et al*, 2014). All the patients included in the present study were treated by conservative non-surgical means. Typically, asymptomatic patients (stage 0a or 1) were managed with observation (generally including chlorhexidine); symptomatic patients (stage 0s, 2, or 3) were generally treated with antibiotics, for the management of pain/infection. Antibiotic regimens used in this study largely varied depending on the local and systemic status of the patients. However, the most used molecules were from the group of the penicillin and metronidazole. This clinical behavior was in accordance with the majority of the studies focused on MRONJ medical therapies (Montebugnoli *et al*, 2007; Van den Wyngaert *et al*, 2009; Angiero *et al*, 2009; Nicolatou-Galitis *et al*, 2011; Thumbigere-Math *et al*, 2012), although different schemes were reported. Only the minority of the studies on MRONJ non-surgical treatments have reported the use of adjuvant novel therapies in addition to antibiotics, such as Low Level Laser Therapy, Hyperbaric Oxygen Therapy, Teriparatide, Pentoxifylline and alfa-tocopherol (Elad *et al*, 2006; Vescovi *et al*, 2007; Epstein *et al*, 2010; Kakehashi *et al*, 2015). A recent retrospective analysis of bacterial colonization of necrotic bone and testing the antibiotic resistance, have found out that bacterial species resistant against β-lactamase inhibitors were present in at least 70% of all patients. Therefore, the authors suggested that the empiric choice of antibiotics in

MRONJ patients should consider the high rate of gram-negative bacteria and resistance against β-lactam antibiotics. In light of this evidence they further recommended using fluoroquinolones for empiric treatment and emphasized the use of bacterial cultivation and susceptibility testing to enable an effective antibiotic treatment (Ewald *et al*, 2021). However, the lack of randomized clinical trial on specific non-surgical therapeutic protocols are lacking, and therefore the choice of the most appropriate medical therapy still relies on the clinician's experience (Moraschini *et al*, 2021).

Nonetheless, although the majority of the studies investigating the clinical outcomes from the application of non-surgical therapies are predominantly retrospective in nature and conducted on small samples, findings suggest that the medical therapy is effective in controlling pain and infection in a great number of cases.

The pain from MRONJ has somatic, ischemic, and neuropathic elements, with intermittent infective inflammatory components (Poon *et al*, 2010). Yet sometimes the areas of exposed necrotic bone in the jaws may remain asymptomatic for long periods of time. Lesions tend to become symptomatic, especially when the surrounding soft tissue is inflamed (Haviv *et al*, 2021). Inflammation and related pain usually have an infectious etiology, thus antimicrobial therapy to fight infection also reduces the associated inflammatory pain (Naik and Russo, 2009). This somatic pain is usually mild to moderate but may become severe when irritated (Abdalla-Aslan *et al*, 2016). Pain due to infection and inflammation in the oral cavity is usually acute, and while it can be of high intensity, it is usually short term and nociceptive in nature. In contrast, MRONJ lesions are long standing (can remain for months to years), more resistant to therapy, and when not effectively treated may cause significant suffering (Haviv *et al*, 2021).

In the present study, approximately 79% of the patients experienced pain. Similarly, a recent paper reported that the 64.5% of the patients suffered from painful symptoms especially those with a longer bone-modifying-agent/antiangiogenic history (p=0.045) (Haviv *et al*, 2021). Moreover, they found that moderate-to-severe pain had a better prognosis over two months follow-up than mild pain after antibiotic treatments possibly due to the neuropathic nature of the mild pain. In our study, we evaluated the presence of the pain rather than the intensity due to the retrospective design of the study. However, by assessing the pain perception over a long follow-up we could demonstrate that only in 2% of the patients pain was resistant to the treatment, while approximately the 51% of the patients had never experienced pain or relapses after the first pain remission and in 46% recurrences of symptoms were successfully treated with medical therapy. In the series from Scoletta et al on 37 patients, at 18 and 24 months, pain score had a high statistical improvement in the 78% of the cases and patients reported a significant enhancement in quality of life when they were treated using medicine only (Scoletta *et al*, 2010). Similar findings were also reported in a study from Moretti et al, were non-surgical therapy was effective in controlling pain in 32 out of 34 patients who had a complete remission of pain (Moretti *et al*, 2011). Overall, the evidence suggest that MRONJ symptomatic patients may benefit from the medical/palliative therapy as they experience either complete pain remission or pain relief (Marcianò *et al*, 2020).

In addition to pain remission, we also demonstrated that even signs of infection and their recurrences were effectively managed by antibiotics cycles in almost 94% of the cases (a mean of 2.1 ± 2.49 antibiotics cycles) and that only in a small proportion of cases (6%) infection was persistent. Consequently, by combining pain and infection, we observed that 92% of the patients were free from any signs of acute inflammation or symptoms or

experienced complete remission after recurrences.

Moreover, looking at the complete clinical remission of MRONJ as defined above, we observed a complete resolution in almost 68% of the cases over a mean time of 15.38 ± 14.87 months predominantly in osteoporotic patients (89%) than in the oncologic group (59%) p-value=0.001. We further confirmed that, as per the chronic behavior of the MRONJ, approximately the 32% could achieve a stable complete resolution, while almost the half (53%) experienced intermittent period of complete remission followed by recurrences. Overall, our findings are promising as in almost 93% of the cases patients achieve either complete clinical healing of the lesions (32%), or experienced pain/signs of infection remission presenting a clinical stable disease (61%). Only the 7% resistant to treatments patients needed to be treated by surgical intervention in order to achieve a better pain/infection control. These findings are in line with those of one of the largest —in terms of patients—retrospective study by Lerman et al. In this study on 97 MRONJ patients, 71–80% of the cases, treated conservatively improved or remained asymptomatic and stable and 23% showed complete re-epithelialization (Lerman *et al*, 2013). Instead, in the study from Melea et al, 63% of the patients achieved complete mucosal healing, at a higher rate compared to that found in our study possibly because the conservative protocol consisted, besides the medical therapy, also in the minimally-invasive surgical procedures which were not considered as "non-surgical" in our report (Melea *et al*, 2014). Similarly, to our findings however, even Melea et al reported the need of major surgical interventions in 5.2% of the patients because of failure of the conservative treatment (Melea *et al*, 2014). Another report from Van den Wyngaert et al. suggest that strictly conservative treatment in low stages of MRONJ can lead to healing in about 53%, to a stable disease in 37%, while to bone necrosis progression in 10% (Van den Wyngaert *et al*, 2009). Moreover, the outcomes of a review by Kuhl et al. showed

that, when comparing the results of conservative and surgical treatment ONJ, 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 ONJ after conservative treatment is only successful in low stages (Kühl *et al*, 2012).

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, while surgical intervention should be performed only in cases of failure of the above strategies.

According to Scoletta et al, the surgical treatment of MRONJ probably cannot achieve better results because the entire bone is affected in bisphosphonate-induced bone necrosis, and therefore necrotic bone cannot be completely debrided to a definitely viable bone margin (Scoletta *et al*, 2010). Surgery should be considered only in limited symptomatic cases when antimicrobial management has failed to control the disease. Moreover, many of the MRONJ patients have a compromised systemic condition that is usually not compatible with more radical treatments, as well as a low life expectancy, or may decline surgery, as a treatment option. For these reasons, obtaining a reasonable quality of life can be considered as the most favorable goal (Scoletta *et al*, 2010; Marcianò *et al*, 2020). Besides, if the patient fails multiple courses of antibiotic therapy and is in constant pain substantially affecting the patient's quality of life, and is medically stable, surgery may be an important and viable option (Lerman *et al*, 2013).

Nevertheless, a recent report by Varoni E et al have suggested that the combined protocol consisting in a first pharmacological phase promoting the progressive isolation of the bone sequestrum, and followed by a minimally invasive surgical intervention, has a potentially higher rate of long-term success than major surgical resection since the removal of necrotic tissue is feasible without undue sacrifice of healthy bone. Progressive

isolation of necrotic bone and its spontaneous exfoliation throughout the pharmacologic phase was also observed in the 23% of our sample and led to mucosal healing in the majority of the cases (Varoni *et al*, 2021).

Finally, another interesting finding of the present study was the poor correspondence between the two staging systems used. According to the AAOMS staging system, clinical progression (up-staging) occurred in 12% of sites, improvement (down-staging) was observed in 70%, while stable disease was observed in 18%. On the other side, based on the SICMF-SIPMO staging system, clinical progression occurred in 17% of sites, down-staging was observed in 45% of sites, and 38% of sites did not report any variation (Table 11). This discrepancy may reflect the different criteria on which these two staging systems are based: the AAOMS system takes into account principally clinical manifestations, while the second the bone necrosis extension. Indeed, according to the AAOMS staging system, patients with stage 1 disease may become symptomatic and develop stage 2 disease but will return to stage 1 disease after a few weeks of antibiotics. Similarly, patients with stage 2 disease may become asymptomatic and relapse to stage 2 or even progress to stage 3. The period that each patient stays in each stage is also variable and unpredictable (Lerman *et al*, 2013). This typical clinical behavior of this chronic condition makes the clinical staging system not fully reliable for assessing the severity of the disease. On the contrary, we believe that the radiological staging system would be more reliable as it is based on TC scan findings and can better reflect the degree of the MRONJ severity.

5. LIMITATION

The results from this study should be cautiously interpreted in light of some limitations. The main limitation of this retrospective study is the use of medical records not specifically designed for the aim of the study. Further limitations include the lack of a standardize non-surgical treatment protocols, especially with regard to the antibiotic's regimens along with the lack of calibration among the specialists of the three different outpatients' departments. Moreover, the varying lengths of follow-up of patients and intervals between two consecutive follow-up visits made difficult to detect specific outcomes' patterns and prevented the possibility of performing the time-to event analyses (through the Kaplan- Meier curves). The role of comorbidities in the prognosis of MRONJ has not been considered and would be of relevance in the evaluation of the pathogenesis of MRONJ and the prognosis.

The variability of the clinical characteristics among the patients (for instance the drug-holiday patterns, the different sample sizes of the oncologic and non-oncologic groups etc.) and the different lengths of follow-up prevented the chance to perform regression analyses with the aim to detect any potential confounder factors predicting a specific outcome. Finally, patient reported outcome in relation to quality of life was not evaluated. Therefore, an assumption of the quality of life was made in regard to absence of pain and infection. It would have been beneficial to include the overall quality of life according to the patients' experience.

6. CONCLUSION

The present study is a retrospective medical record review of 126 patients diagnosed with MRONJ. 93% of the cases patients achieved either complete clinical healing of the lesions (32%), or a clinical stable disease (61%) experiencing pain and signs of infection remission. Only 7% of the patients were refractory to the non-surgical treatment and needed surgical interventions in order to achieve a better pain/infection control. This is consistent with the findings of previous studies and confirms that a combination of antimicrobial rinses, antibiotic therapy, nonsurgical sequestrectomy, is an appropriate and effective approach for management of MRONJ. Prospective multicenter, controlled trials are necessary to better determine the relative effectiveness of the non-surgical treatment for a more evidence-based approach to management of MRONJ.

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