Reconstructive Surgery Following Bisphosphonate-Related Osteonecrosis of the Jaws: Evolving Concepts

Giuseppe Spinelli, Francesco Arcuri, Domenico Valente, Mirco Raffaini, and Tommaso Agostini

1 Introduction

Bisphosphonates are synthetic analogues of the endogenous substance pyrophosphate (a normal constituent of the bone matrix), which inhibit bone resorption and thus have a hypocalcemic effect [1–3]. Bisphosphonates are a relatively novel class of agents that have been increasingly recommended for use in patients suffering osteoporosis, Paget's disease of bone, hypercalcemia of malignancy, osteolytic bone metastases, and osteolytic lesions of multiple myeloma [1–12]. Several medicines are available in the United States with different indications, dosage, administration, and potency (Table 1). Despite the benefits related to their use, osteonecrosis of the jaws represents a complication in a subset of patients receiving these treatments, especially when administered intravenously and following dentoalveolar surgery [8–22]. In this condition, the affected bones become friable, nonviable, and eventually exposed [22–37]. The oral complications can have negative impact on quality of life by affecting eating, speaking, and maintenance of oral hygiene [18]. The first complications were described in 2003, few years later their approval, and nowadays, although more than 950 articles have been published, pathophysiology remains to be well elucidated [23]. In 2003, Marx described 36 cases of exposed necrotic bone in patients suffering tumors who had been treated with intravenous bisphosphonates, and in 2004, Ruggiero reported further 63 cases [23, 24, 38, 39]. Several cells are implicated in bone metabolism including osteoblasts, osteoclasts, and osteocytes, and at this time osteoclasts represent the main cellular target; specifically bisphosphonates provide downregulation of osteoclasts thus repressing bone remodeling, but their effects on osteocytes remain controversial [12–24]. It is accepted that osteoblasts activity remains unalterated. The basic premise of this hypothesis is that the jaw has a high remodeling rate and bisphosphonates suppress remodeling [40–45]. It is also clear that remodeling within the intracortical envelope is considerably higher in the jaw compared with other skeletal sites. As a consequence the bisphosphonate-related osteonecrosis (BRON) follows the idea that since remodeling is higher in the jaw and bisphosphonates suppress remodeling, then this plays a role in the pathophysiology of osteonecrosis [45–50]. Intravenous bisphosphonate treatment seems to pose a greater risk of bisphosphonate-related osteonecrosis of the jaw (BRONJ) than oral administration, though oral treatment longer than 3 years may increase the risk [50–53]. Since dentoalveolar

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Recent Clinical Techniques, Results, and Research in Wounds (2018)
DOI 10.1007/15695_2017_70, © Springer International Publishing AG
Published Online: 07 June 2018

Table 1 Medicines available in the United States with different indications, dosage, administration, and potency

Active ingredient (Drug's name)	Indication to use	Nitrogen	Administration	Dose	Relative potency
Etidronate (Didronel)	Paget's Disease	No	Oral	300–750 mg daily for 6 months	1
Tiludronate (Skelid)	Paget's Disease	No	Oral	400 mg daily for 3 months	50
Alendronate (Fosamax)	Osteoporosis	Yes	Oral	10 mg/day 70 mg/week	1.000
Risedronate (Actonel)	Osteoporosis	Yes	Oral	5 mg/day 35 mg/week	1.000
Ibandronate (Boniva)	Osteoporosis	Yes	Oral	2.5 mg/day 150 mg/month	1.000
			Intravenous	3 mg every 3 months	
Pamidronate (Aredia)	Bone metastasis	Yes	Intravenous	90 mg/3 weeks	1.000–5.000
Zoledronate					10.000
(Zometa)	Bone Metastasis	Yes	Intravenous	4 mg/3 weeks	
(Reclast)	Osteoporosis	Yes	Intravenous	5 mg/year	

surgery is a precipitating factor, preventive measures include maintaining good oral hygiene and undertaking any necessary dental treatment before beginning a course of intravenous bisphosphonate treatment [30–35]. Some clinical guidelines recommend that people at risk of BRONJ should take a 3-month break from oral bisphosphonates before and after dental treatment [37–39]. Greater drug strength, longer duration of use, older age, and a history of inflammatory dental disease are associated with a higher risk of BRONJ. The true incidence of BRONJ is unknown. Reported rates range from 0.028% to 18.6% depending on indication for treatment, study population, and sample size [53]. Osteonecrosis is found more commonly in the mandible than the maxilla (2:1 ratio) and more commonly in areas with thin mucosa overlying bony prominences such as lingual and palatal tori, bony exostoses, and the mylohyoid ridge [1–7]. The following factors are thought to be risk factors for BRONJ: corticosteroid therapy, diabetes, smoking, alcohol use, poor oral hygiene, and chemotherapeutic drugs [53].

2 Diagnostic Criteria

According to the American Association of Oral and Maxillofacial Surgeons Position Paper, patients can be considered suffering BRONJ if all the following three characteristics are present at the same time:

1. Current or previous treatment with bisphosphonates
2. Exposed bone in the maxillofacial area persisting for more than 8 weeks
3. No history of radiotherapy to the jaws [1]

Differential diagnosis remains the main topic in order to identify the proper treatment, and in particular the following conditions must be excluded: alveolar osteitis, sinusitis, gingivitis/periodontitis, caries, periapical pathology, and temporomandibular joint disorders [1, 53]. BRONJ may be asymptomatic or present with pain, swelling, loose teeth, and altered sensation [1]. Other medications (denosumab, bevacizumab, cabozantinib, sunitinib) have also been associated with jaw osteonecrosis, the condition then being called medication-related osteonecrosis of the jaw (MRONJ) [53]. Beyond clinical assessment according to the above criteria, radiographic exams are necessary to stage the disease, and in particular orthopantomography, CT scans of the maxillofacial skeleton with contrast medium and magnetic resonance imaging are recommended [1–11].

3 Osteonecrosis Management

There is currently no "gold standard" of treatment for BRONJ [1, 53]. Interventions used to treat this complication are diverse, controversial, and largely empirical. Three broad categories of interventions have been described: classical

"wound-healing" conservative treatment, diverse surgical techniques, and different "add-on" treatments [1, 53]. These three approaches are often used in combination, either at the same time or in succession, and are elucidated in Table 2. Strategies for the management of patients suffering BRON have been defined by the American Association of Oral and Maxillofacial Surgeons in the Position Paper on Bisphosphonates-Related Osteonecrosis of the Jaw and approved by the Board of Trustees in September 2006 [1]. The position paper was developed by a task force appointed by the Board and composed of clinicians with extensive experience in treating these patients and basic science researchers. The knowledge base and experience in addressing BRON have expanded, thus requiring modifications and refinements to the original paper [1–4]. The task force was then called again in 2008 to revise the recommendations previously published in 2006. This update contains revisions to the diagnosis and staging and management strategies and highlights the status of basic science research (Table 3). Despite this, these recommendations are not widely followed, and several therapeutic strategies have been recommended in the literature according to the severity of this complication, ranging from strictly conservative to aggressive surgical approaches [53]. At-risk patients and asymptomatic patients have been identified including proper prophylactic measurements as listed in Tables 4 and 5, respectively. The treatment of BRONJ is still under debate, and most reports show different outcomes. For this reason, a systematic review of the available literature was made in order to assess which treatment has a higher success rate in patients diagnosed with BRONJ by Comas-Calonge and co-workers [53]. In this research the author considered the treatment successful when the patient improved the stage of the disease or when there was absence of bone exposure with proper healing and the patient remained asymptomatic without any clinical signs of infection. They referred several limitations including the lack of standardized success criteria and treatment protocols, the use of different surgical approach (sequestrectomy vs. bone resection), and the association of several antibiotics and antiseptics. Nonetheless the success rates of BRONJ surgical treatment vary between 58% and 100%. The main advantage of sequestrectomy is an expected superior healing process since unaffected periosteum is preserved. Tension-free closure of the wound and an adequate bone resection are key factors for the treatment prognosis [53]. Although it is extremely difficult to quantify the amount of bone that should be removed, bleeding is considered a sign of healthy bone [45–53]. Some authors proposed a more aggressive management, based in bone resections, to treat BRONJ patients, in the idea that, regardless of the stage of the disease, areas of the necrotic bone that are a constant source of soft tissue irritation should be removed in order to allow a proper healing [50–53].

Table 2 Three approaches often used in combination, either at the same time or in succession

Conservative treatments	Surgical treatments	Adjuvant non-surgical treatments
Disinfectant mouth rinses (saline, chlorhexidine, chlorine, peroxide)	Surgical debridement, sequestrum removal, surgical sinus drainage procedures (antrostomy)	Hyperbaric oxygen therapy
Antibiotic therapy (local, systemic, or both)	Extraction of teeth within osteonecrotic bone, management of implants	Pentoxifylline and tocopherol (vitamin E)
Antifungal therapy	Bone resection	Ozone therapy
	Surgical wound closure, reconstructive surgery, grafts	Low level laser therapy (LLLT) for biostimulation, pain relief anti-inflammatory treatment (erbium-doped yttrium aluminium garnet (Er:YAG); neodymium-doped yttrium aluminium garnet (Nd:YAG), natrium-doped yttrium aluminium perovskite (Nd:YAP), etc.
	Laser-assisted surgery	Platelet-rich plasma
	Fluorescence-assisted surgery	Parathyroid hormone and teriparatide
		Bone morphogenetic protein (BMP)

Table 3 Revisions to the diagnosis and staging and management strategies and highlights the status of basic science research

Bron stage[a]	Signs and symptoms	Management[b,c,d]
At risk	No apparent necrotic bone in patterns who have been treated with either oral or IV bisphosphonates	• No treatment indicated
		• Patient education
0	No clinical evidence of necrotic bone, but non-specific clinical findings and symptoms	• Systemic management, including the use of pain medication and antibiotics
1	Exposed and necrotic bone in patients who are asymptomatic and have no evidence of infection	• Antibacterial mouth rinse
		• Clinical follow-up on a quarterly basis
		• Patient education and review of indications for continued bisphosphonate therapy
2	Exposed and necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage	• Symptomatic treatment with oral antibiotics
		• Oral antibacterial mouth rinse
		• Pain control
		• Superficial debridement to relieve soft tissue irritation
3	Exposed and necrotic bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus in the mandible, maxilliary sinus and zygoma in the maxilla) resulting in pathologic fracture, extra-oral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible of sinus floor	• Antibacterial mouth rinse
		• Antibiotic therapy and pain control
		• Surgical debridement/resection for longer term palliation of infection and pain

[a]Exposed bone in the maxillofacial region without resolution in 8–12 weeks in persons treated with a bisphosphonate who have not received radiation therapy to the jaws

[b]Regardless of the disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone. The extraction of symptomatic teeth within exposed, necrotic bone should be considered since it is unlikely that the extraction will exacerbate the established necrotic process

[c]Discontinuation of the IV bisphosphonates shows no short-term benefit. However, if systemic conditions permit, long-term discontinuation may be beneficial in stabilizing established sites of BRONJ, reducing the risk of new site development, and reducing clinical symptoms. The risks and benefits of continuing bisphosphonate therapy should be made only by the treating oncologist in consultation with the OMS and the patient

[d]Discontinuation of oral bisphosphonate therapy in patients with BRONJ has been associated with gradual improvement in clinical disease. Discontinuation of oral bisphosphonates for 6-12 months may result in either spontaneous sequestration or resolution following debridement surgery. If systemic conditions permit, modification or cessation of oral bisphosphonate therapy should be done in consultation with the treating physician and the patient

Table 4 At-risk patients and management

	Risk stratification	Management
1	Patients who have taken oral bisphosphonates for less than three years and have no clinical risk factors (corticosteroid therapy, diabetes, smoking, alcohol use, poor oral hygiene, and chemotherapeutic drugs)	• No alteration or delay in the planned surgery is necessary
		• If implants are placed, informed consent should be provided related to possible implant failure and possible osteonecrosis of the jaws if the patient continues taking oral bisphosphonates
		• It is advisable to contact the practitioner who initially prescribed the oral bisphosphonate and suggest monitoring such patients and considering either alternate dosing of the bisphosphonate, drug holidays, or an alterative to bisphosphonate therapy
		• Implant patients should be on a regular recall schedule
2	Patients who have taken oral bisphosphonates for less than three years and have also taken corticosteroids concomitantly or have any of the other risk factors listed above	• The prescribing provider should be contacted to consider discontinuation of the oral bisphosphonate (drug holiday) for at least three months prior to oral surgery (if systemic conditions permit)
		• The bisphosphonate should not be restarted until osseous healing has occurred
3	Patients who have taken oral bisphosphonates for more than three years with or without concomitant steroid medication or other risk factors	• The prescribing provider should be contacted to consider discontinuation of the oral bisphosphonate for three months prior to oral surgery, if systemic conditions permit
		• The bisphosphonate should not be restarted until osseous healing has occurred
4	Patients with an established diagnosis of Bisphosphonate-Related Osteonecrosis of the Jaws (BRON)	• Treatment objectives are to eliminate pain, control infection of the hard and soft tissues, and minimize the progression or occurrence of bone necrosis
		• Surgical treatment is less predictable than with the established surgical algorithms for osteomyelitis or osteoradionecrosis; therefore, surgery should be delayed if possible
		• Areas of necrotic bone that are a constant source of irritation should be removed or recontoured without exposure of additional bone
		• Loose segments of bony sequestrum should be removed with exposed/necrotic bone in patients with pain
		• Patients should avoid elective dentoalveolar surgical procedures
		• The extraction of symptomatic teeth within exposed, necrotic bone should be considered since it is unlikely that the extraction will exacerbate the established necrotic process

Table 5 Asymptomatic patients and management

Type	Asymptomatic patient's status	Management
A	Patients about to initiate intravenous bisphosphonate therapy	• If systemic conditions permit, initiation of IV bisphosphonate therapy should be delayed until dental health is optimized
		• Non-restorable teeth and those with a poor prognosis should be extracted. Other elective dentoalveolar surgery necessary should be done at this time
		• Patients with full or partial dentures should be examined for areas of mucosal trauma (lingual flange, palatal or mandibular tori, or other exostoses). These areas should be treated if necessary prior to bisphosphonate therapy
		• If systemic conditions permit, bisphosphonate therapy should be delayed until the extraction site has mucosalized (14–21 days) or until there is adequate osseous healing. Dental prophylaxis, caries control, and conservative restorative dentistry on an ongoing basis are necessary to maintain functionally sound teeth
B	Asymptomatic patients receiving intravenous bisphosphonate treatment	• Procedures that involve direct osseous injury should be avoided. Non-restorable teeth may be treated by crown removal and endodontic treatment of the remaining roots
		• Placement of dental implants should be avoided in patients exposed to the more potent IV bisphosphonates (zoledronate "Zometa" and pamidronate "Aredia" on a frequent dosing schedule [4–12 times per year])
C	Asymptomatic patients receiving oral bisphosphonate therapy	• Appear to be at risk of developing Bisphosphonate-Related Osteonecrosis of the Jaws (BRON) to a much lesser degree than those people treated with IV bisphosphonates
		• BRON can develop spontaneously or after minor trauma
		• These patients seem to have less severe manifestations of necrosis, and respond more readily to stage specific treatment regimens
		• Elective dentoalveolar surgery does not seem to be contraindicated in this group
		• Patients should be informed of the small risk of compromised bone healing. The risk of BRON may be associated with increased duration of treatment with oral bisphosphonates, i.e., greater than three years, and other risk factors including concomitant use of corticosteroids, chemotherapy, diabetes, smoking, excessive alcohol use, and poor oral hygiene

4 Reconstructive Microsurgery

For the management of exposed necrotic bone, additional surgical debridement or sequestrectomy with primary mucosal closure seems to be effective in most cases [3–23]. If there are recurrences at the conservative treatment, then osteotomies should be considered as it seems to be more successful than wound debridement alone [33–43]. The reconstruction of subtotal mandibulectomy defects requires the vascularized bone to promote healing and provide adequate soft tissue support and oral competence [34]. Patients with reasonable life expectancy with regard to their malignant disease should be considered for microvascular tissue transfer after aggressive resection of the affected region [5]. The effect of the transferred flap with a new input of blood supply might be one of the reasons for the uneventful postoperative in all patients; moreover the cutaneous component provides additional health tissue useful to achieve successful reconstruction by establishing a tension-free closure of the intraoral defect [52]. Finally it gives also the opportunity of oral prosthetic rehabilitation using dental implants, as described by Ferrari et al. (2008) [15]. After an observation period of 12 months from microsurgical reconstruction of

the jaws, high survival rates can be expected with few recurrences of osteonecrosis [53]. This, in turn, means that vascularized fibula flap has been a well-accepted method to reconstruction, and despite the limited number of publications, this treatment appears to be practicable in BRONJ-resected patients and doesn't seem to influence the natural course of the primary disease [45–53].

According to the best of our knowledge, there have been 37 cases of stage III BRONJ treated with free-flap reconstruction in the published literature (Table 6). Radiographic imaging with CT, cone beam, and/or orthopantomogram was obtained during follow-up in all patients. Flap failure occurred in two cases from the fibula, and a second flap was constructed from additional tissue during a second procedure [44, 50]. Fistulas formed in four cases making it the most common complication observed across studies [44]; BRONJ recurred in the contralateral jaw in two cases [12, 30]. Nonunion as reported by Nocini et al. [30] can occur because the resected margins were not free of disease; this finding was not

Table 6 37 cases of stage III BRONJ treated with free-flap reconstruction in the published literature

Reference	Patients (n), years	Medical history	Pharmacological therapy	Bone involvement, reconstruction	Follow-up	Postoperative complications
Engroff and Kim (2007) [12]	2, 56.6 y	2 Breast cancer	1 Pz. IV Zoledronate 1 Pz. OS Pamidronate	Partially, FFF	12 months	– Postoperative hematoma – Contralateral BRONJ, managed conservatively
Ferrari et al. (2008) [15]	1, 66 y	1 Multiple myeloma	IV Pamidronate and Zoledronate	Totally, FFF	12 months	No
Mucke et al. (2009) [29]	1, 60 y	1 Multiple myeloma	IV Zoledronate	Partially, FFOCF	12 months	No
Nocini et al. (2009) [30]	7, 61 y	5 Breast cancer 1 1 Prostate cancer 1 1 Multiple myeloma	5 Pz. IV Pamidronate and Zoledronate; 2 Pz. IV Zoledronate	2 Partially, FFF 6 Totally, FFOCF	6–36 months	– 1 Shortterm recurrence at resection margin, managed conservatively
Seth et al. (2010) [44]	11, 61.3 y	5 Breast cancer 2 Prostate cancer 2 Multiple myeloma 2 osteoporosis	6 Pz. IV Zoledronate 2 Pz. OS Alendronate 2 Pz. OS Ibandronate 1 Pz. IV Etidronate	11 Partially, FFOCF	2 weeks to 31 months	4 Fistula 1 Infection 1 Flap loss
Bedogni et al. (2011) [50]	3, NA	NA	NA	Partially, FFF	NA	1 Flap loss
Ghazali et al. (2013) [49]	1,82 y	Osteoporosis	OS Alendronate	Partially, FFF	NA	No
Colletti et al. (2014) [48]	2, NA	NA	NA	Partially, FFF	NA	NA
Spinelli et al. (2014) [51]	8, 64.7 y	3 Breast cancer 1 Prostate cancer 4 Multiple myeloma	5 Pz. IV Pamidronate 6 Pz. IV Zoledronate	3 Partially, FFF 5 Totally, FFOCF	29 months	No
Neto et al. (2016) [53]	1, 54 y	Lung cancer	IV Zoledronate	Partially, FFF	48 months	No

evident during surgery and was found during histological evaluation of the resected tissue.

Some authors have stated that "aggressive" surgery, in this case resection and reconstruction with a free flap, is inappropriate because of the diminished life expectancy, poor general condition, and concomitant medications, such as steroids or chemotherapy, that can interfere with the postoperative result of patients with advanced BRONJ and the overall success of conservative measures and minimal surgical procedures [53]. Diminished life expectancy is certainly a theoretical concern given that most people who received intravenous bisphosphonates in our and others' reviews had metastatic cancer to the bone or malignancy-related hypercalcemia [52, 53].

The main concerns, just theoretical, regard the possible transfer of sicked tissue into the oral cavity in patients suffering disseminated disease, but this is not been described yet. Indeed, one patient in the Seth et al. series died 8 weeks after reconstruction surgery in consequence of cancer-related complications [50–53]. On the other hand, most patients among published reports survived at least 12 months and many for at least several years after surgery suggesting that health status alone should not be an absolute contraindication to this procedure.

5 Outcome Measurements

Primary outcomes of proper management include healing of the osteonecrosis as indicated by one or more of the six indicators listed in Table 7; secondary outcomes are important indicators and listed in Table VII. Patients need close follow-up every 3 months for monitoring intraoral or extraoral symptoms along with radiographic examination (Table 8).

Table 7 Primary and secondary outcomes

	Primary outcome	Secondary outcome
1	Improvement in the clinical grade of the lesions according to the American Academy of Oral and Maxillofacial Surgeons staging or BRONJ	Mortality rate and cause of death.
2	Wound healing (yes or no)	Pam: presence and level of pain, use of analgesia during the first two weeks after intervention, use of analgesics, duration of pain, per cent pain relief.
3	Improvement in exposed bone quality (judged clinically on inspection of the mouth by a dentist or a dental/oral surgeon as exposed bone that is less friable, less devitalised, less necrotic).	Improvement of pre-existing accompanying symptoms other than pain, such as mucosal oedema, super-infection. purulent discharges, fistulae to skin, or inflammatory reactions including fever.
4	Halt in bone disease progression as per imaging techniques such as: X-ray examination (improvement of sclerotic changes, mottling and bone fragmentation, improvement of formed sequestrum or persistent extraction sockets), computed tomography (CT) scan, magnetic resonance imaging (MRI) (surface area of the bone disease, localisation, evidence of bone marrow disease), positron emission tomography (PET)/CT imaging (decreased abnormal focal uptake)	Improvement in nutritional intake or in the ability of eating different types of food (normal diet, blended or pureed foods, liquid diets).
5	Halt in bone disease progression as visualised with doxycycline viable bone fluorescence (surface area of the bone disease, localisation, evidence of bone marrow disease)	Quality of life
6	Healing of sinus tract or deep periodontal pockets.	Health economic measures, such as effect on healthcare consumption, number or length of hospitalisations, health resource use.

Table 8 Symptoms of biphosphonate-related osteonecrosis

Intraoral	Extraoral
Pain, dental mobility, cutaneous fistula, halitosis, gingival recession, pathological fractures, oro-antral communication, dehiscence, phlogoses, decubitus, abscess	Abscess, edema, erythema, retraction, cervical mass, trismus, limited/extended sinusitis

6 Proposed Flowchart

Our flowchart to surgical management differs according to the mandible and maxilla (Fig. 1). For bisphosphonate-related osteonecrosis stage 0 and stage 1, we propose curettage, sequestrectomy, and marginal mandibulectomy according to the extension of bone resection, and this is applied both to mandible and maxilla. Stage 2 and stage 3 are managed according to site (maxillary/mandible) and patient's performance status; mandible bisphosphonate-related osteonecrosis stage 2 and stage 3 affecting patients with poor performance status are managed with segmental mandibulectomy without reconstruction (Figs. 2, 3, and 4); in case of good performance status, reconstruction is performed with free fibula flap for longer defects (Figs. 5, 6, and 7) and with medial femoral condylar flap for small defects (Figs. 7, 8, and 9). Maxillary stage 2 and

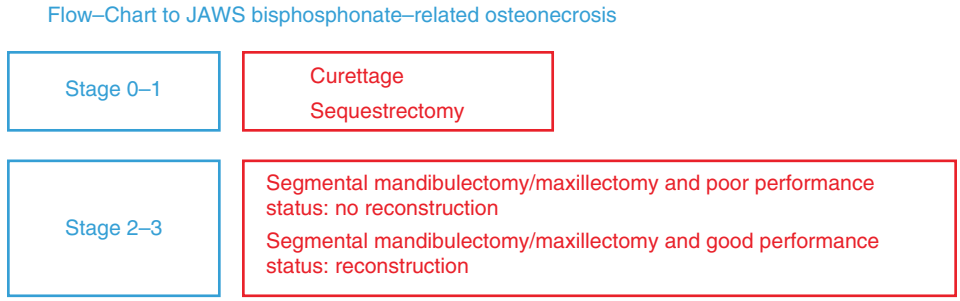

Fig. 1 Flowchart to bisphosphonate-related osteonecrosis

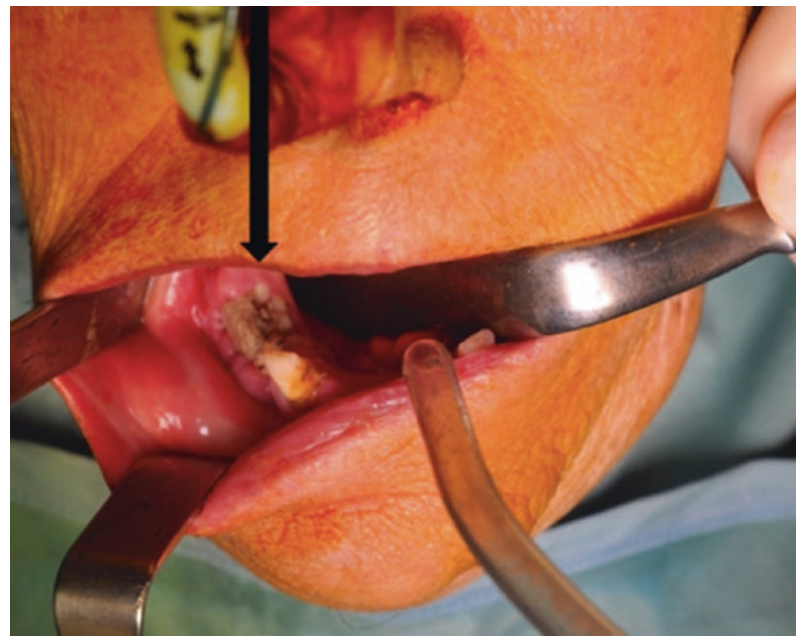

Fig. 2 A 78-year-old patient suffering breast cancer and right mandibular osteonecrosis (stage 2)

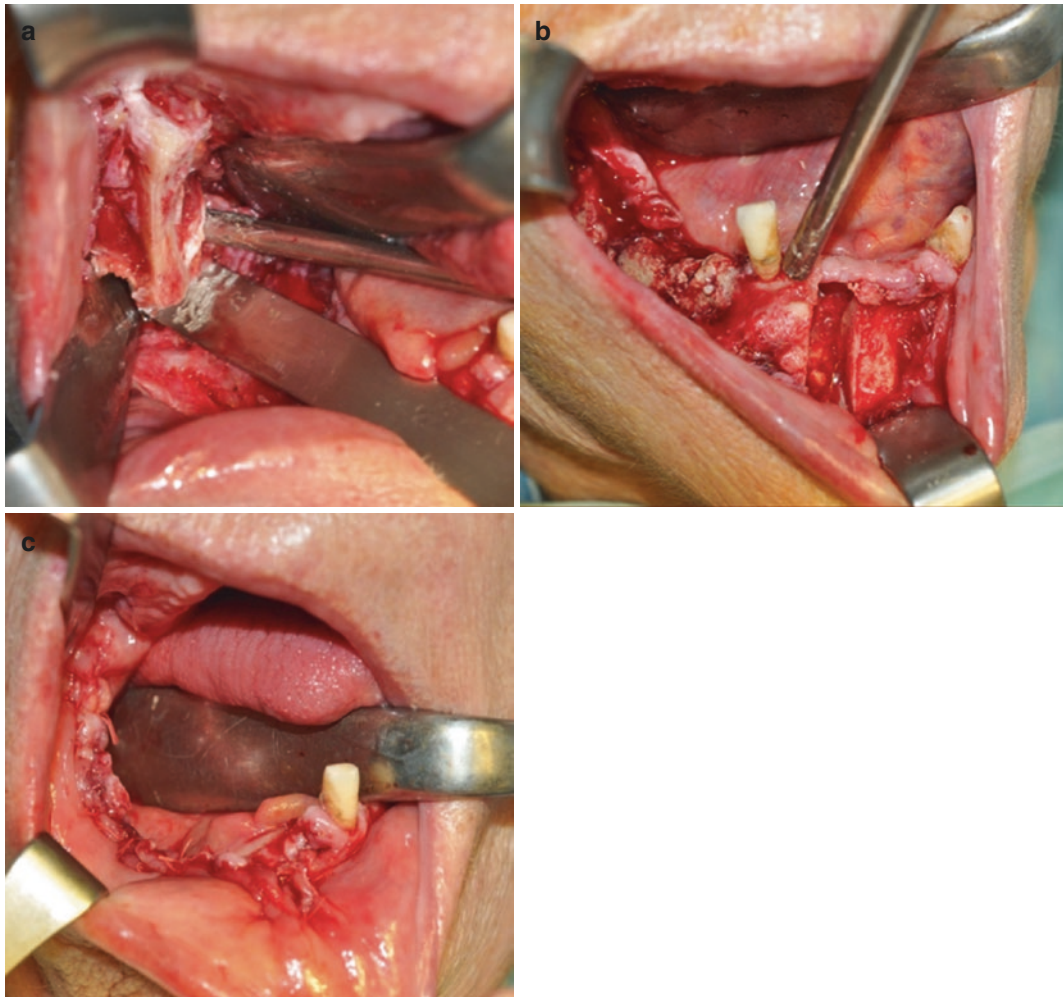

Fig. 3 (**a**–**c**) Due to poor performance status, she underwent right segmental mandibulectomy without reconstruction

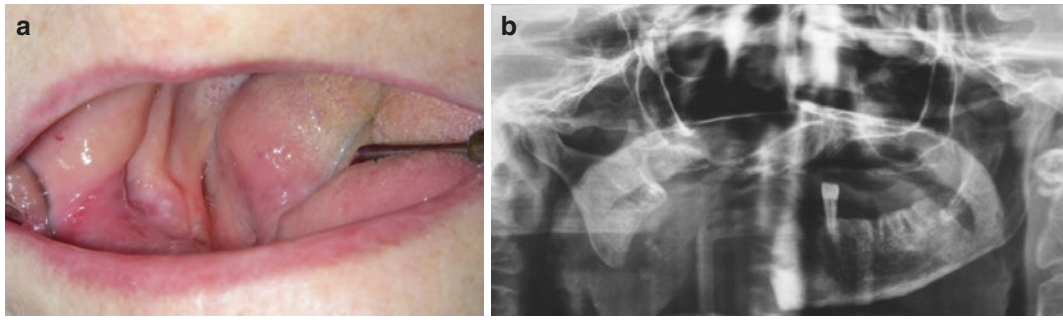

Fig. 4 (**a**, **b**) Postoperative control 6 months later showing good clinical and angiographic control

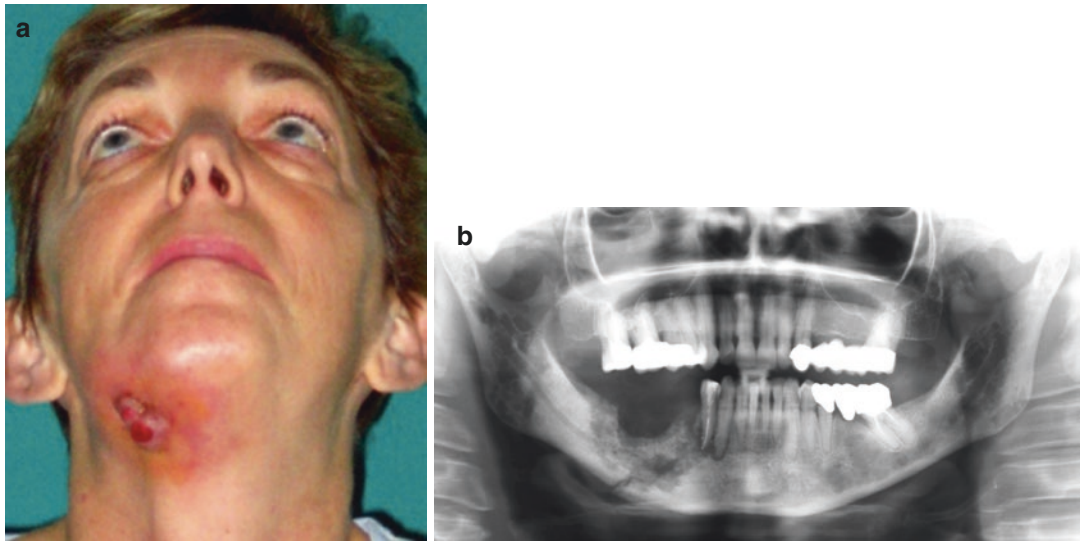

Fig. 5 (**a**, **b**) A 68-year-old patient suffering breast cancer and right mandibular osteonecrosis with cutaneous fistula (stage 3)

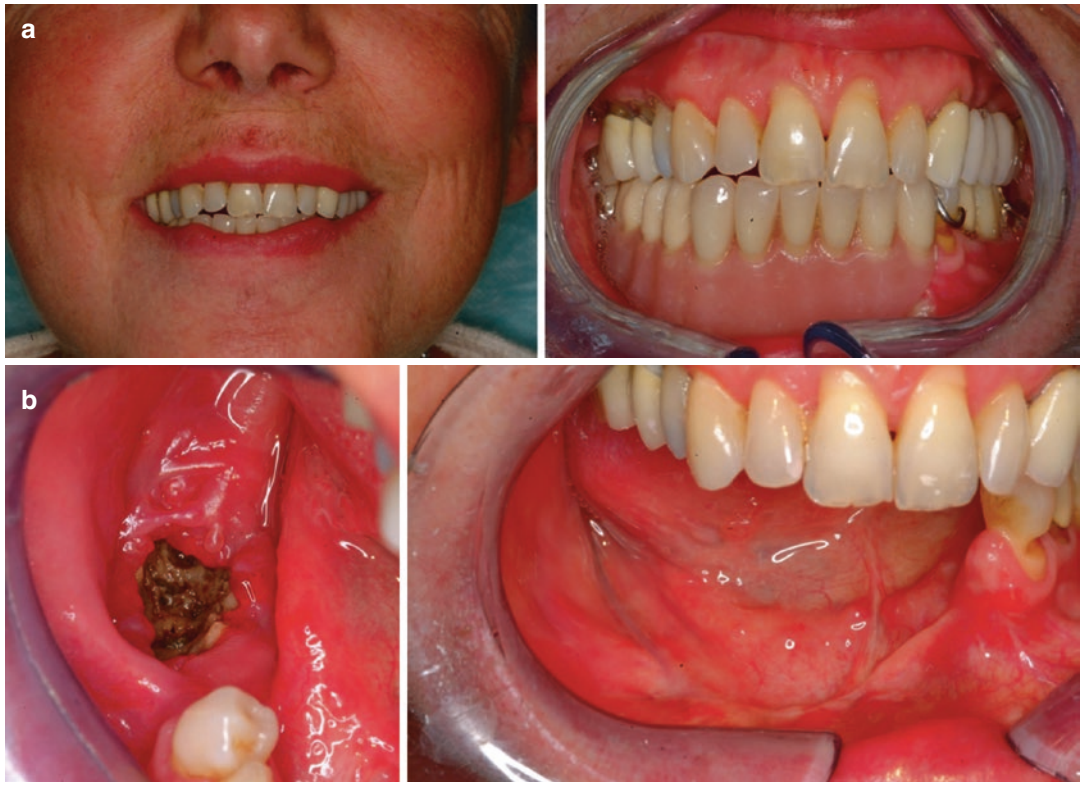

Fig. 6 (**a**, **b**) On the left the preoperative status and on the right the postoperative outcome after reconstruction. Due to good performance status, she underwent reconstruction with osteocutaneous fibula flap; the skin was used to restore the cervical skin

stage 3 are managed with hemimaxillectomy and Bichat fat flap/temporalis muscle flap in case of good performance status (Figs. 9 and 10).

7 Future Research

The National Institute of Health has provided fundings to researchers in order to elucidate the pathophysiology of bisphosphonate-associated osteonecrosis of the jaw. The researchers focused on different aspects of this entity including but not limited to (a) the effect of bisphosphonates on intraoral soft tissue healing, (b) alveolar bone hemostasis, (c) antiangiogenic properties of bisphosphonate, (d) pharmacogenetic research, and (e) risk assessment tools. Novel strategies to improve prevention and treatment of BRON need to be developed and discussed in a proper manner. In the meantime, the 2014 update favors the term medication-related osteonecrosis of the jaw instead of BRONJ to accommodate the growing number of osteonecrosis cases involving the maxilla and mandible associated with other antiresorptive (denosumab) and antiangiogenic therapies. Denosumab is an antiresorptive agent that exists as a fully humanized antibody against receptor activator of nuclear factor kappa B ligand and inhibits osteoclast function and associated bone resorption. It is administered subcutaneously every 6 months to decrease the risk of vertebral, nonvertebral, and hip fractures in osteoporotic patients and administered monthly in metastatic bone disease from solid tumors. Denosumab is superior to zoledronic acid in preventing complications for patients with bone metastases. However, further studies are still needed to assess longer-term safety and efficacy of denosumab [53].

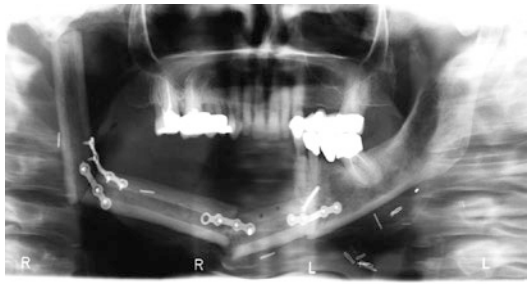

Fig. 7 Postoperative radiographic control a three months of the case presented in Figs. 5 and 6

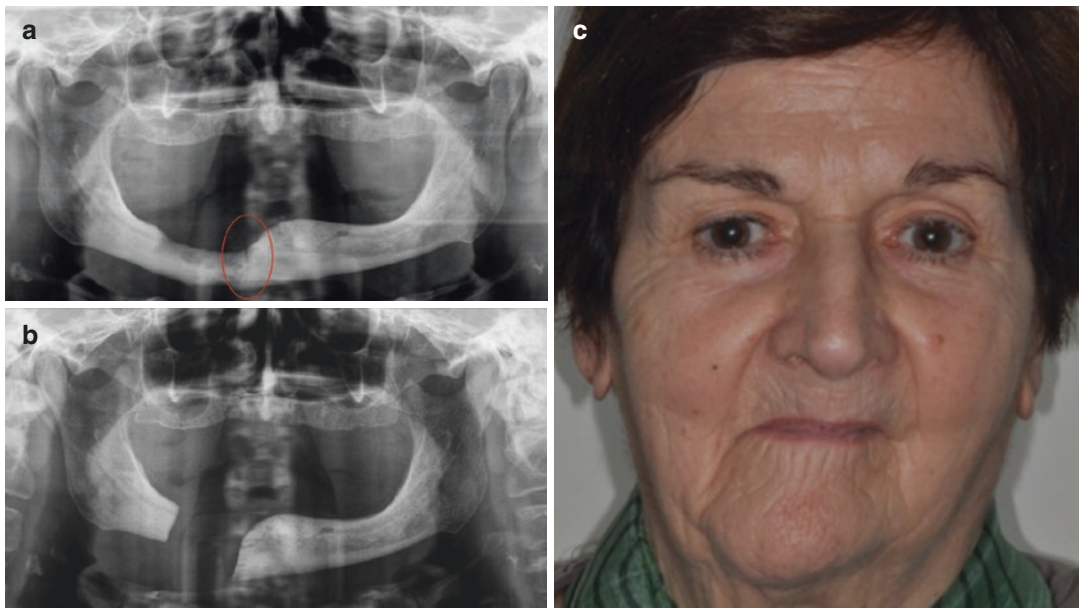

Fig. 8 (**a**–**c**) Preoperative radiographs showing pathological fracture on the right mandible (stage 3) of a 73-year-old patient suffering osteoporosis. She underwent segmental mandibulectomy without immediate reconstruction

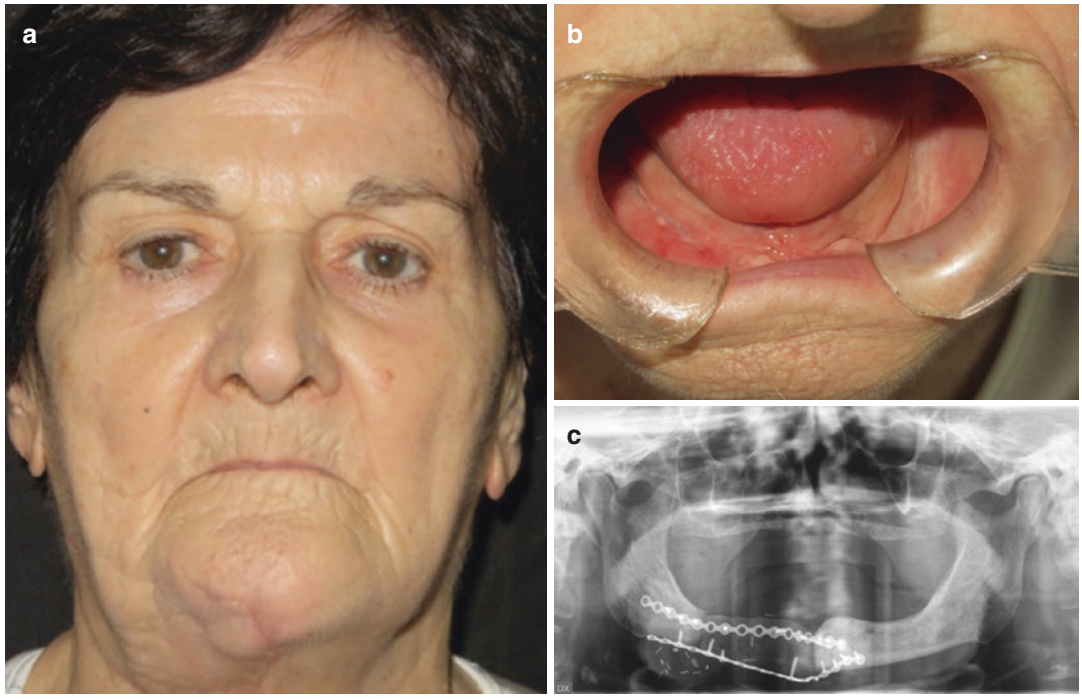

Fig. 9 (**a**–**c**) Postoperative outcome 6 months later showing symmetry, local disease control into the oral cavity, and good reconstruction outcome using a medial femoral condylar flap

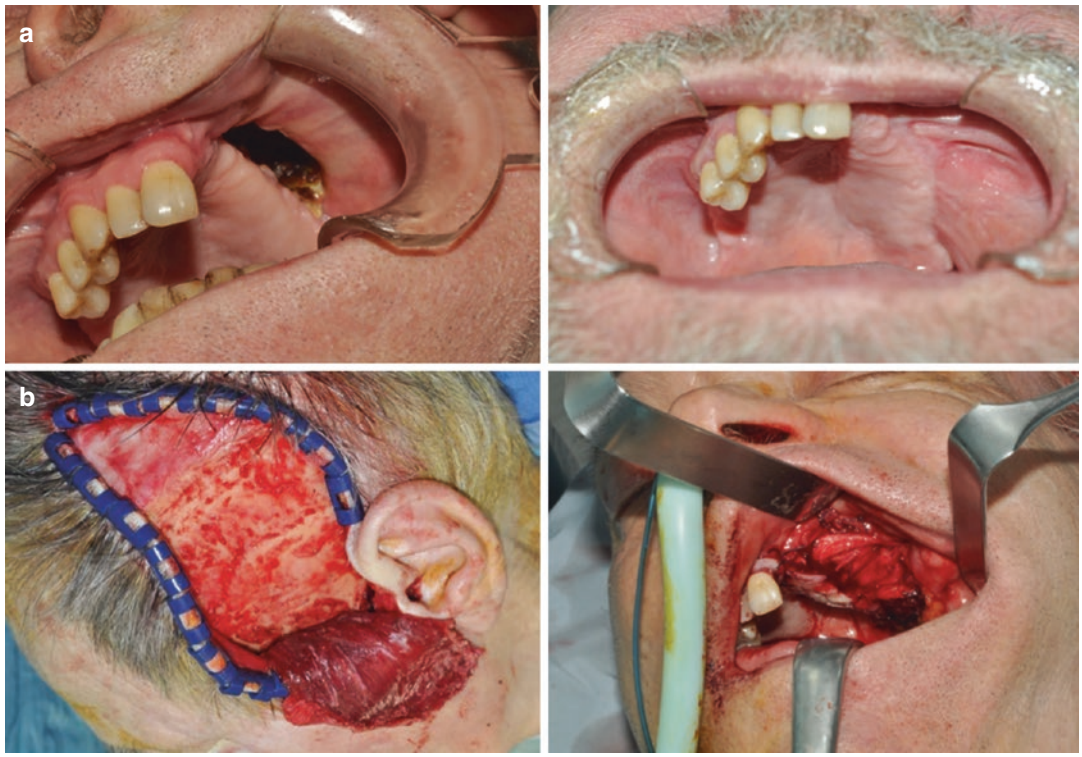

Fig. 10 (**a**, **b**) A 71-year-old patient suffering prostate cancer and left maxillary osteonecrosis with good reconstructive outcome after 3 months. He underwent reconstruction with a temporalis muscle flap due to good performance status

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