

Surgical treatment protocol of bisphosphonate-related osteonecrosis of the jaws (BRONJ): long-term follow-up of 266 lesions

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Materials and methods



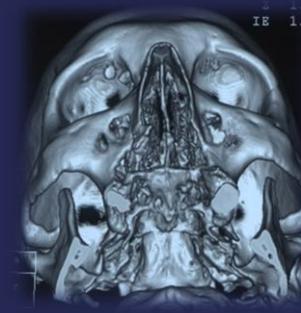
- ▶ From 2004 to 2013, 145 neoplastic and 58 osteoporotic patients with 266 BRONJ lesions referred to the Odontostomatology Unit of University of Bari.

- ▶ Our treatment protocol consisted of the following steps:

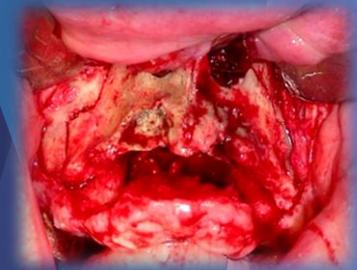
- radiographic evaluation
- suspension of BPs therapy if systemic conditions permit
- administration of ceftriaxone and metronidazole
- surgical debridement in minor lesions and marginal resection in major ones
- hyaluronic acid and amino acids application
- histopathological analysis
- BPs resume not before than 1 month after surgery
- clinical and radiological follow-up



Materials and methods



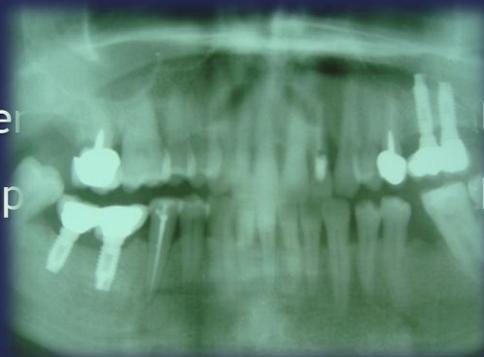
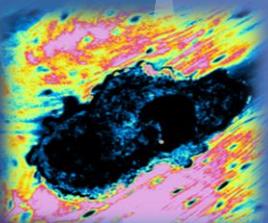
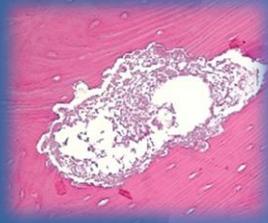
- ▶ The radiographic evaluation was made through OPT examination and multi-slices spiral CT with 3D reconstruction and all lesions were measured in centimetres to adequate the surgical treatment.
- ▶ When it was possible, BPs therapy was suspended at least 3 months before surgical procedure, and corticosteroids and chemotherapy were suspended, too
- ▶ At least 3 cycles of ceftriaxone (1g once a day i.m.) and metronidazole (500mg twice a day per os) were administered (8 days with 10 days of interruption after each cycle)
- ▶ The following treatments were performed:
 - Surgical debridement in lesions <2cm
 - Small open access surgery in lesions >2cm and <4cm
 - Wide open access surgery with extensive maxillary or mandibular resection, and Caldwell-Luc technique in lesions >4cm
- ▶ The marginal bone resection included at least 1 cm of vascularized bone tissue extended in depth and in all the sides. Surgery was complemented by piezosurgery for the osteoplastic of the residual resection margins.



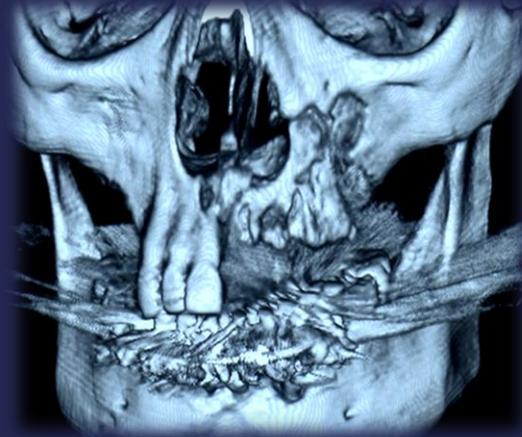
Materials and methods



- ▶ A gel compound made of hyaluronic acid and amino acids (glycine, leucine, lysine, and proline) was applied into the bone and upon the stitches to obtain a faster healing of both hard and soft tissues
- ▶ All the samples were sent to the Pathological Anatomy Unit of University of Bari and the histological examination was carried out using Nikon Eclipse E600 microscope allowing both optical and Confocal Laser Scanning Microscope (CLSM analysis)
- ▶ Patients could receive again BPs therapy after the complete soft tissues healing, at least 1 month after surgery
- ▶ Each patient underwent a clinical follow-up at 1, 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, 108, 114, 120 months and then clinical-radiographic follow-up at 120 months after surgery



Case



Clinical aspect and multi-slices spiral CT with 3D reconstruction of a III stage BRONJ involving the maxillary sinus, in a 74-years-old female patient with multiple myeloma, who underwent to zoledronic acid therapy



Complete bone and mucosal healing and multi-slices spiral CT with 3D reconstruction 13 months after surgery and intra-cavitary application of Aminogam® gel

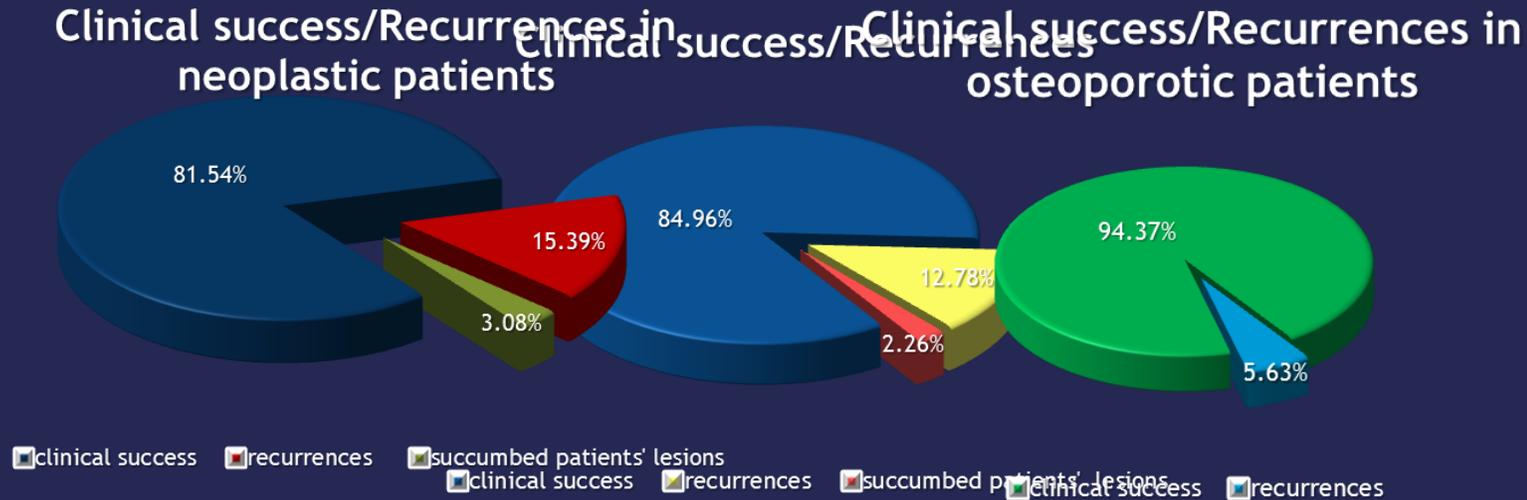
Case



Rehabilitation with social temporary removable prosthesis for aesthetic reasons with good stabilisation of the surgical sites

Results

- ▶ The 84.96% of lesions healed, whereas just the 12.78% of lesions recurred.



- ▶ Among the thirty-four lesions involving the maxillary sinus and treated by Caldwell-Luc technique, just the 14.7% recurred

Soft tissues healing time (days)		
	Stitches removal	Complete wound healing
Lesions <2 cm	7-9	9-12
Lesions >2 and <4 cm	12-15	14-21
Lesions >4 cm	15-21	25-28
Caldwell-Luc technique	20-23	40-45

Patient	Sex	Date of birth	Age	Date of surgery	Primary disease	Metastases	Osteonecrosis site	Specific site	Trigger	Pain	Suppuration	Paraesthesia	Maxillary sinus	Fistula	Size (cm)	N lesions	AOMS stage	SICMF-SIPMO stage	Biphosphonates	Dosage	Administration	Therapy duration	Therapy suspension	Treatment	Follow-up	Follow-up (months)	Other factors		
1	M	03/03/1951	53	17/03/2004	Multiple Myeloma	Spondyle, humerus	Mandible	44-46	Extraction	+	+	+	-	+	5	2	III	3	Zoledronate	4mg/month	iv	24	no	Antibiotic+Surgery	Recurrence	45	no		
				08/07/2004				Mandible	44-46	Extraction	+	+	+	-	+	5		III	3					24		Antibiotic+Surgery	Recurrence	41	
				27/10/2004				Mandible	43-45	Extraction	+	+	+	-	+	4		III	3					24		Antibiotic+Surgery	Recurrence	38	
				06/04/2005				Mandible	43-45	Extraction	+	+	+	-	+	3		III	3					24		Antibiotic+Surgery	Recurrence	32	
				18/05/2005				Mandible	42-32	Extracion	+	+	+	-	+	5		III	3					24		Antibiotic+Surgery	Recurrence	31	
				27/10/2005				Mandible	33-46	Extraction	+	+	+	-	+	8		III	3					24		Antibiotic+Surgery	Clinical success	26	
				14/12/2005				Mandible	32-42	Extraction	+	+	+	-	+	5		III	3					24		Antibiotic+Surgery	Clinical success	24	
2	F	ns	86	21/05/2004	Multiple Myeloma	Spondyle	Maxilla	23-25	Extraction	+	+	-	+	-	6.7	1	III	3	Zoledronate	4mg/month	iv	32	4	Antibiotic+Surgery	No data	no	Chemotherapy		
3	F	ns	88	26/05/2004	Breast cancer	Spondyle	Mandible	45-48	Spontaneous	+	+	+	-	+	6	1	III	3	Zoledronate	4mg/month	iv	25	4	Antibiotic+Surgery	No data	no	no		
4	M	02/01/1958	57	28/07/2005	Multiple Myeloma	Spondyle	Mandible	35-37	Extracion	+	+	+	-	+	6.2	2	III	3	Zoledronate	4mg/month	iv	28	5	Antibiotic+Surgery	Recurrence	34	Chemotherapy		
				22/11/2005				Mandible	44-47	Extraction	+	-	+	-	-	7		II	2b				28	9	Antibiotic+Surgery	Clinical success	31		
				18/01/2006				Mandible	36	Extraction	+	-	-	-	-	3.2		II	2b				28	11	Antibiotic+Surgery	Clinical success	29		
				22/02/2006				Mandible	35-36	Extraction	+	-	-	-	-	4		II	2b				28	12	Antibiotic+Surgery	Clinical success	28		
5	F	ns	56	25/06/2007	Uterus cancer	no	Mandible	44-45	Extraction	+	+	+	-	-	3.1	1	II	2b	Zoledronate	4mg/month	iv	22	4	Antibiotic+Surgery	No data	5	no		
6	F	ns	76	25/09/2007	Plasma cell Leukemia	no	Mandible	42-46	Spontaneous	+	-	+	-	+	6.2	1	III	2b	Zoledronate	4mg/month	iv	10	3	Antibiotic+Surgery	No data	No data	no		
7	F	14/08/1936	77	05/06/2012	Breast cancer	no	Maxilla	25-27	Spontaneous	+	+	-	+	-	2.8	4	III	3	Zoledronate	4mg/month	iv	14	5	Antibiotic+Surgery	Clinical success	22	Heart disease		
				17/12/2012				Mandible	43-48	Spontaneous	+	-	+	-	-	2.2		II	2b				20	14	Antibiotic+Surgery	Clinical success	16		
				17/12/2012				Maxilla	13-18	Spontaneous	+	-	+	-	-	1.3		II	2b				20	14	Antibiotic+Surgery	Clinical success	16		
				06/09/2013				Mandible	33-37	Spontaneous	+	-	+	-	-	2.4		II	2b				20	25	Antibiotic+Surgery	Incompleted Data			
8	F	08/07/1936	77	19/07/2013	Breast cancer	no	Mandible	35-37	Extraction	+	+	-	-	-	4.4	1	II	2b	Zoledronate	4mg/month	iv	120	5	Antibiotic+Surgery	Incompleted Data		no		
9	M	28/08/1938	74	03/09/2013	Lung cancer	Bone	Maxilla	25-27	Spontaneous	+	+	+	+	-	5	1	III	3	Zoledronate	4mg/month	iv	6	5	Antibiotic+Surgery	Incompleted Data		Chemotherapy Hipertension		
				01/10/2013				Mandible	46-47	Extraction	+	+	-	-	+	3	2		3				44	5	Antibiotic+Surgery	Incompleted Data		Chemotherapy	
10	F	02/11/1951	63	01/10/2013	Breast cancer		Mandible	46-47	Extraction	+	+	-	-	+	3	2		3				44	5	Antibiotic+Surgery	Incompleted Data		Chemotherapy		
				01/10/2013				Maxilla	26-27	Spontaneous	+	-	-	-	-	3			1b				44	5	Antibiotic+Surgery	Incompleted Data			
11	F	03/11/1947	66	22/10/2013	Breast cancer	no	Mandible	42-45 implant	Spontaneous	+	-	+	-	-	4	1	II	1b	Zolendronate	4mg/month	iv	23	13	Antibiotic+Surgery	Incompleted Data		no		

Conclusions

► This protocol could be a successful management strategy for BRONJ, considering the low recurrences rate and the good stabilisation of the surgical sites observed after a long-term follow up:

- BPs suspension is indicated even in the early stage of the disease because it could stabilize BRONJ site, reduce the risk of new lesions development, control symptoms, and improve post-surgical healing
- The three cycles of antibiotic association are mandatory remembering the BRONJ pathophysiology
- The surgical technique, characterized by the bone cortical preservation, improves the wound healing and implements the re-ossification, thanks to the scaffold function which is useful also for the gel application made of hyaluronic acid and amino acids

Since the dimensional problem in the resective surgery is important, the different treatment according to the lesions size allows to ensure a better patients management considering lesions from a surgical point of view

- The intra-cavitary intraoperative gel filling, followed by application of the same device upon the stiches, is effective in accelerating soft and hard tissues healing. It can improve angiogenesis, fibroblast and osteoblast proliferation, collagen biosynthesis, production of growth factors, enhancement of osteoblast differentiation, and regulation of the collagen matrix synthesis during osteogenesis¹⁻²

¹ Mariggio MA, Cassano A, Vinella A, Vincenti A, Fumarulo R, Lo Muzio L, Maiorano E, Ribatti D, Favia G. Enhancement of fibroblast proliferation, collagen biosynthesis and production of growth factors as a result of combining sodium hyaluronate and aminoacids. Int J Immunopathol Pharmacol. 2009 Apr-Jun; 22: 485-92

² Favia G, Mariggio MA, Maiorano F, Cassano A, Capodiferro S, Ribatti D. Accelerated wound healing of oral soft tissues and angiogenic effect induced by a pool of aminoacids combined to sodium hyaluronate (AMINOGAM). J Biol Regul Homeost Agents. 2008 Apr-Jun; 22: 109-16

Thanks for your attention

