Oral Oncology 47 (2011) 420–424

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Long-term outcomes of surgical resection of the jaws in cancer patients with bisphosphonate-related osteonecrosis

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ARTICLE INFO

Article history:
Received 23 December 2010
Received in revised form 22 February 2011
Accepted 25 February 2011
Available online 24 March 2011

Keywords:
Osteonecrosis
Jaw
Bisphosphonate
Surgery

SUMMARY

Surgical treatment of bisphosphonate-related osteonecrosis of the jaw (BRONJ) is controversial. Current recommendations contraindicate aggressive surgery because its results are unpredictable and may trigger disease progression. In this prospective study, we assessed the effectiveness of surgical resection of the jaws in cancer patients with BRONJ.

Between June 2004 and July 2009, 30 cancer patients with refractory BRONJ underwent surgical resection of the jaws at our Units. They were followed-up weekly for the first month, at 3-month intervals up to 1 year, and at 6-month intervals up to 2 years. Panoramic radiographs and CT-scan were obtained at 3, 6, 12, 18 and 24 months. Primary outcomes were the 24-month recurrence rate of BRONJ and the 24-month mortality rate. Secondary outcomes were post-operative complications, duration of hospital stay after surgery, time to return to oral diet, and degree of oral pain.The 30 patients had a median age of 66 years and were mostly females (80%). Twenty-eight underwent a single resection and two had both jaws resected, for a total of 32 resected jaws. The cumulative recurrence rate of BRONJ in resected jaws 3.1% and 9.4% at 3 and 6 months, respectively. All the jaws with recurrent BRONJ had osteomyelitis at the margins of bone resection. The cumulative incidence of death was 3%, 12% and 16% at 12, 18 and 24 months.Surgical resection of BRONJ was highly effective, with few post-operative complications and were not associated with long-term mortality.

Introduction

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a rare but severe complication of the treatment with nitrogen-containing bisphosphonates (NBP). Since the first report of BRONJ in 2003,[1] many series of patients with BRONJ have been published, but the pathogenesis and treatment of this disease are still controversial. Current recommendations favor palliative nonsurgical treatments because BRONJ involves the entire jawbone and viable bone margins are difficult to obtain with surgery.[2–4] Moreover, surgical injury may trigger osteonecrosis and worsen symptoms.[5,6] We performed a 24-month follow-up study to evaluate the effectiveness of surgical resection of the jaw in cancer patients with BRONJ.

Materials and methods

Study design

A prospective study was conducted at the Units of Maxillofacial Surgery of Verona University and Padova University (Italy) between June 2004 and July 2009 to evaluate the long-term effectiveness of surgical resection of the jaws in a group of cancer patients with established BRONJ. All subjects gave written informed consent.

Patients

BRONJ patients with multiple myeloma or metastatic cancer were consecutively enrolled into the study if they had: (1) BRONJ refractory to previous medical and/or minimally invasive surgical treatment; (2) no clinical or radiological evidence of metastatic disease or multiple myeloma of the jawbones; (3) no evidence of progression of the underlying cancer, as determined by the caring oncologist. The clinical, drug, and dental history of the patients was

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doi:10.1016/j.oraloncology.2011.02.024

collected at the first visit. Oral pain was measured using a visual analog scale (VAS) ranging from 0 (absent) to 10 (unbearable) by steps of 1. All patients underwent panoramic radiography and spiral computed tomography (CT). Because no accepted diagnostic criteria for BRONJ were available until 2006,[3] a running definition of BRONJ was adopted and maintained during the study. We defined BRONJ as the presence of non-healing exposed bone in the oral cavity, during NBP treatment for metastatic bone disease or multiple myeloma, in the absence of previous radiation therapy of the jaws. Patients with oral lesions other than exposed bone received a diagnosis of non-exposed BRONJ[7] if they had signs of bone involvement at CT. The clinical and CT signs used to diagnose non-exposed BRONJ are listed in Table 1.[8–10] Refractory BRONJ was defined as the occurrence of multiple infections and severe pain not responding to medical and/or minimally-invasive surgical treatments (debridement and sequestrectomy).

Pre-surgical treatment

NBP were discontinued immediately before surgery if they had not already been withdrawn because of the diagnosis of BRONJ. The choice to discontinue NBP was always taken together with the caring oncologist. Thirty sessions of hyperbaric oxygen therapy (HBO) were performed before surgery, except in patients with unresected primary tumor or metastatic invasion of organs other than bone, because of the risk of inducing tumor growth.[11] CT and magnetic resonance (MR) imaging were used preoperatively to assess the degree of jawbone involvement and to define the margins of resection.[8,12] All patients underwent a 10-day intra- and post-operative cycle of intravenous Sulbactam-Amoxicillin 1.5 g *tid* and intravenous Metronidazole 500 mg *tid*. Patients with known allergy to penicillin were given intravenous Lincomycin 500 mg *bid* for 10 days.[5,13]

Surgical treatment

Segmental resection of the diseased jawbone with inclusion of the periosteal layer was performed in all patients. The resection margins were located 1 cm beyond the affected bone.[8] Bone defects were reconstructed with titanium plates, microvascular bone flaps and local soft-tissue flaps, depending on the site and the extent of jawbone resection.

Post-surgical treatment

After surgery, 30 sessions of HBO were performed and NBP treatment was resumed on the basis of a tailored decision taken together with the caring oncologist.

Table 1
Running definition of non-exposed BRONJ.

Clinical signs other than bone exposure	Radiological signs (CT)
Mucosal sinus tracks	Trabecular thickening
Purulent discharge	Osteosclerosis
Delayed mucosal healing of post-extraction socket	Osteolytic areas
Vincent's sign[a]	Cortical bone erosions
Cutaneous fistula	Maxillary sinusitis
Spontaneous tooth loss	Bone sequestration
Abscess	Periosteal reaction
Trismus	Pathologic fracture
Gross mandibular asymmetry	

Non-exposed BRONJ was diagnosed when one or more clinical signs were associated with one or more radiological signs.

[a] Hypoesthesia or paresthesia of the lips due to involvement of the inferior alveolar nerve or infraorbital nerve.

Histopathology

Surgical bone specimens were analyzed by the same pathologist to confirm BRONJ and to rule out concurrent metastatic jawbone disease. The resection margins were examined separately to disclose signs of osteomyelitis or osteonecrosis. A resection margin was considered normal when its bone architecture was preserved and there were no signs of necrosis or inflammation. Presence of osteomyelitis in the resection margins was evaluated as predictor of BRONJ recurrence.[10]

Follow-up

Patients were followed-up weekly for the first month, at 3-month intervals up to 1 year, and at 6-month intervals up to 2 years. At each visit, a VAS score for oral pain was obtained, and the oral mucosa was inspected for early signs of BRONJ (Table 1). Photographs of the oral cavity were taken at all visits and panoramic radiographs and CT-scans were performed at 3, 6, 12, 18 and 24 months.

Study outcomes

The primary outcomes were the 24-month recurrence rate of BRONJ and the 24-month all-cause mortality rate. BRONJ recurrence was defined as the appearance of exposed or non-exposed bone, this latter diagnosed as specified in Table 1, in the treated jaw. The secondary outcomes were the number and severity of postoperative complications, the duration of hospital stay after surgery, the time needed to return to oral feeding, and the degree of oral pain.

Statistical analysis

Thirty patients and 32 bones were available for analysis. Descriptive statistics were calculated on a per-patient basis ($n = 30$). Continuous variables are reported as median and minimum and maximum values, because of skewed distributions. Categorical variables are given as the number or percentage of patients with the characteristic of interest. Inferential statistics were calculated on a per-bone basis ($n = 32$). Because death and loss to follow-up are "competing risks" for BRONJ, i.e., events whose occurrence could alter the probability of BRONJ, we take them into account by using non-parametric competing risk regression analysis (main outcome = BRONJ; competing outcome 1 = death; competing outcome 2 = loss to follow-up).[14] Exact logistic regression was used to evaluate the association between osteomyelitis (yes vs. no) and BRONJ recurrence with and without correction for sex (male vs. female) and age (dichotomized at 60 years).[15] Because of the low number of events, we were not able to account for the fact that two subjects contributed both maxillary and mandibular bones to the analysis (correlated observations). Statistical analysis was performed using Stata 11 (Stata Corp, College Station, TX, USA) and LogXact 9 (Cytel Inc., Cambridge, MA, USA).

Results

Description of the patients

Between June 2004 and July 2009, a total of 112 BRONJ patients were diagnosed and treated at our Surgical Units. Thirty (27%) of them had refractory BRONJ and were enrolled into the study (Table 2). They were mostly females (80%) and had a median age of 66 years. Breast cancer was the most common

Table 2
Descriptive statistics of the 30 patients (and 32 resected bones).

Age (years)	66 (46–80)
Sex	
Male	6
Female	24
Involved bone[a]	
Maxilla	17
Mandible	15
BRONJ stage[a]	
0	10
1	1
2	9
3	12
Cancer	
Breast cancer	13
Multiple myeloma	10
Prostate cancer	3
Lung cancer	2
Thyroid cancer	1
Acute myeloid leukemia	1
Predisposing factor	
Tooth extraction	21
Periodontal infection	3
Prosthesis	5
Spontaneous	2
Dental implant infection	1
Zoledronate	
Yes	26
No	4
Cumulative dose (mg)	64 (4–144)
Pamidronate	
Yes	15
No	15
Cumulative dose (mg)	2160 (720–6120)
Alendronate	
Yes	1
No	29
Cumulative dose (mg)	2520

Values of continuous variables are given as median and minimum and maximum values (between parentheses). Values of categorical variables are given as the number of subjects with the characteristic of interest.

[a] Two patients had involvement of both maxilla and mandible.

diagnosis, and tooth extraction the most common predisposing factor (70%). Zoledronate (87%) and pamidronate (50%) had been the most commonly used NBP (11 patients on pamidronate had been shifted to zoledronate.) The median oral pain as detected by VAS was four (range 0–10).

Treatment

Five patients with unresected primary cancer or metastatic organ involvement were excluded from pre-operative and post-operative HBO. Twenty-eight patients underwent resection of a single jawbone and two had both jaws resected, for a total of 32 jaw resections (15 maxillae and 17 mandibles).

Histopathology

The histological analysis of resected bone confirmed BRONJ in all cases. Concurrent metastatic jawbone disease was detected in three patients (one with breast cancer, one with thyroid cancer and one with prostate cancer) who had no clinical and radiological preoperative evidence of such disease. The margins of resection showed normal histology in 29 jaws and chronic osteomyelitis in three jaws.

Secondary outcomes

Three patients had postoperative complications that did not require preoperative surgery (Table 3). One patient had a failure of the microvascular bone flap and developed a salivary duct fistula 2 days after subtotal resection and maxillary reconstruction; direct soft-tissue closure of the maxillary defect was obtained with flap removal and salivary fistula repair. One patient developed a mucosal wound breakdown that required surgical repair under local anesthesia. Oral feeding was resumed within a median of 1 day (range 1–26 days) and the median hospital stay after surgery was 5 days (range 1–32 days). Table 3 stratifies secondary outcomes on the basis of the surgical intervention performed. Most patients showed consistently better profiles of oral pain during the study (Fig. 1).

Primary outcomes

BRONJ recurred at 3 months in one maxilla and at 6 months in two mandibles of three women aged 56, 67 and 79 years. According to current criteria, these patients had stages 2, 1 and 0 of BRONJ.[2] The cumulative recurrence rate of BRONJ was 3.1% and 9.4% at 3 and 6 months, respectively (Table 4). All the jaws with recurrent BRONJ had histological signs of chronic osteomyelitis at one margin of bone resection ($n = 3$). The odds of BRONJ was higher for the jaws with osteomyelitis than for those without it (Odds ratio (OR) = 64.3, exact 95%CI = 4.0 to ∞, exact p-value = 0.004) and persisted after correction for age and sex (OR = 26.0, exact 95%CI = 1.94 to ∞, exact p-value = 0.016). Because of the low number of patients with BRONJ recurrence ($n = 3$), we could not do any evaluation of other potential predictors of recurrence besides age and sex.

The cumulative incidence of all-cause death was 3%, 12% and 16% at 12, 18 and 24 months, respectively (Table 4). Two patients who failed to present at the 18 or 24-month follow-up visit respectively were contacted by phone and were found to be alive and well. Living in Southern Italy, they were apparently not motivated to reach our Centers located in Northern Italy.

NBP were resumed between 1 and 14 months after surgery in seven patients because of progression of the underlying disease. The three patients with recurrent BRONJ had restarted intravenous NBP treatment before the occurrence of clinical or radiological signs of disease. The remaining four patients who resumed NBP treatment were free of BRONJ at 24 months.

Table 3
Secondary outcomes.

Postoperative complications	
Free flap loss	1
Salivary gland fistula	2
Neck hematoma	1
Miniplate fracture	1
Partial wound dehiscence	2
Hospital stay	
Maxillectomy and soft-tissue closure	3 [1–28]
Hard palate resection	7 ($n = 1$)
Mandibulectomy + titanium plate reconstruction	4 [4–6]
Mandibulectomy/maxillectomy and bone flap reconstruction	17 [14–32]
Time to resumption of oral feeding	
Maxillectomy and soft-tissue closure	1 [1–26]
Hard palate resection	7 ($n = 1$)
Mandibulectomy and titanium plate reconstruction	1 [1–1]
Mandibulectomy and bone flap reconstruction	14 [12–26]
Resumption of NBP treatment	
Yes	7
Zoledronate (monthly)	5
Pamidronate (monthly)	1
Alendronate (weekly)	1
No	23

Values of continuous variables are given as median and minimum and maximum values (between parentheses). Values of categorical variables are given as the number of subjects with the characteristic of interest.

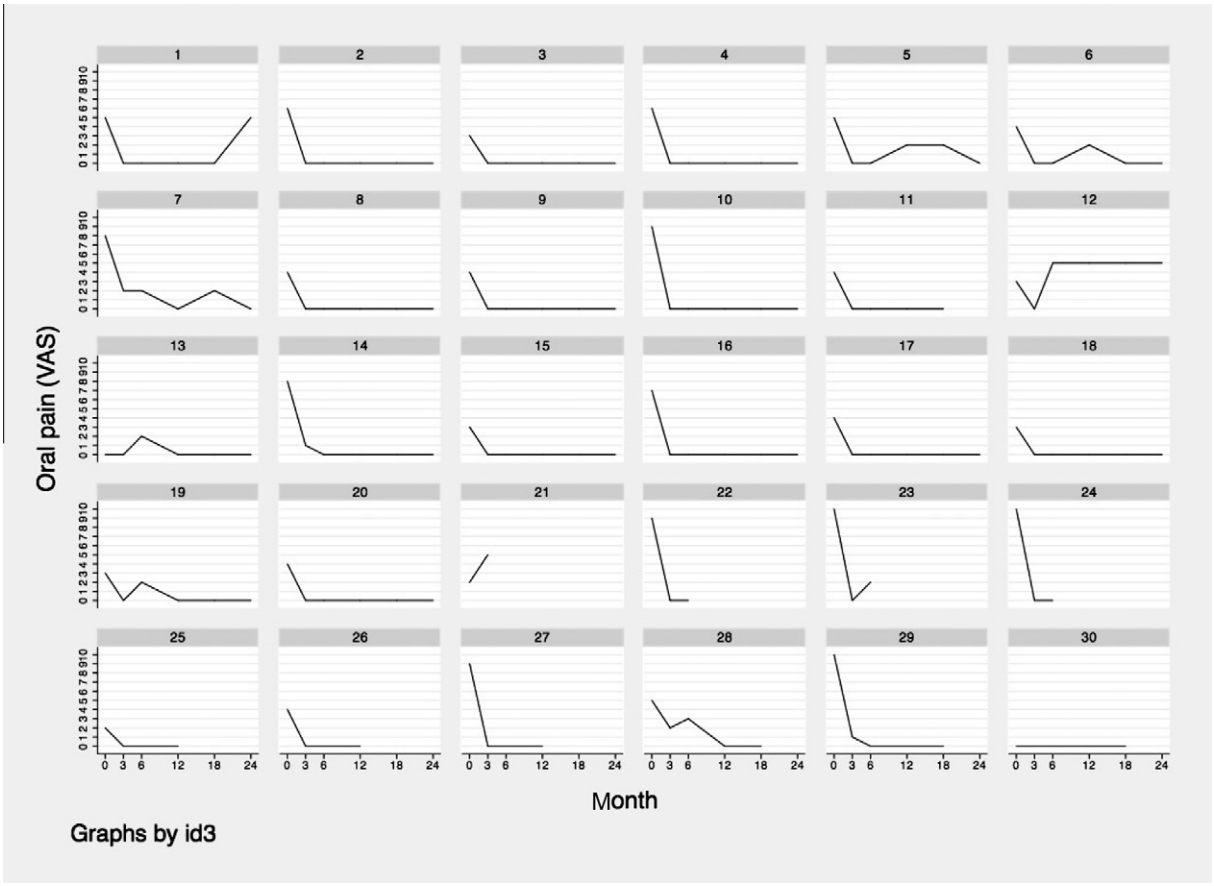

Figure 1 Profile plots of oral pain during the study. Changes in oral pain during the study as detected by a visual analog scale (VAS) ranging from 0 (absent) to 10 (unbearable) by steps of 1.

Table 4
Cumulative incidence of BRONJ.

	BRONJ (main outcome)		Death (concurrent outcome 1)		Loss to follow-up (concurrent outcome 2)	
	n	Cum. inc. (95%CI)	*n*	Cum. inc. (95%CI)	*n*	Cum. inc. (95%CI)
3rd month	1	0.031 (0.002 to 0.137)	0	–	0	–
6th month	2	0.094 (0.024 to 0.223)	0	–	0	–
12th month	0	–	1	0.031 (0.002–0.137)	0	–
18th month	0	–	3	0.125 (0.039–0.262)	1	0.031 (0.002–0.137)
24th month	0	–	1	0.156 (0.057–0.300)	1	0.062 (0.011–0.181)

The analysis was done on a per-bone basis ($n = 32$) using non-parametric competing risk regression (see text for details). Abbreviations: Cum. inc. = cumulative incidence; 95%CI = 95% confidence intervals; *n* = number of incident cases at given time-point.

Discussion

In the present study, we evaluated the effectiveness of surgical resection of the jaws in cancer patients with BRONJ. Although a standardized surgical approach to BRONJ has been proposed, the presently available series of surgical patients do not provide robust evidence as they are heterogeneous in terms of the underlying disease (cancer vs. osteoporosis), bisphosphonate use and route of administration (intravenous vs. oral), and type of surgery (marginal vs. segmental resection).[16–19] Moreover, these series lack detailed and long-term follow-up data, which are essential as BRONJ may recur in surgical patients up to 14 months of follow-up.[20] To control for these potential confounders, we selected only cancer patients treated with intravenous NBP, performed the same surgery and followed them regularly for 24 months.

It should be pointed out that we assessed the margins and the extent of bone resection using MR and CT and used CT to evaluate bone healing during follow-up.[12,21] We consider this a major strength of our study, as BRONJ is primarily a bone disease, despite the fact that it is often evaluated only on clinical grounds.[16,17,22] Clinical judgment may underestimate the extent of bone involvement, as we have previously observed that, in cancer patients, BRONJ may extend well beyond the exposed bone in the oral cavity.[8] In addition, clinical judgment may underestimate the amount of bone resection during surgery and diseased, albeit vascularized, bone left in place may become later evident as "new" foci of BRONJ, even at distant sites.[23] In this way, "new" foci may actually be "recurrent" foci and this possibility has to be taken into account when interpreting the available studies.[16–19] Most of our patients were in BRONJ stages 2 or 3. However, one third of them were in stage 0, as they would be classified using current criteria.[2] Our data show that also stage 0 patients (non-exposed BRONJ) can have refractory disease similarly to more advanced stages and this is the reason why

patients with different stages of BRONJ underwent the same treatment in the present study.

We used histological analysis of bone margins to evaluate the appropriateness of bone resection as they were determined preoperatively only on the basis of CT and MR. Importantly, the presence of osteomyelitis at one margin of resection was a predictor of BRONJ recurrence. It seems clear that clinical and radiological healing depend on the presence of healthy bone at the margins of resection. In fact, all patients that relapsed during the follow-up had osteomyelitic involvement of the margins of resection. BRONJ recurrences in our study may be attributed to preoperative CT and MRI artifacts that did not allow us to establish realistic margins of resection. We also found that CT signs of recurrent disease are apparent within 6 months after surgery and precede clinical manifestations of BRONJ.

Researchers who oppose to surgical resection of BRONJ do so on the basis that the life expectancy of these patients is low and their quality of life is negatively impacted by major surgery.[9] However, our study shows that a reasoned selection of patients and interventions can lead to very good results, which may actually improve the quality of life. Two thirds of the patients underwent a resection limited to one side of the maxilla or mandible. Expectedly, they had a quicker recovery than who underwent subtotal jaw resection and reconstruction with vascularized bone. However, post-operative morbidity, duration of hospital stay and rehabilitation times of the latter were comparable to those of patients undergoing microvascular jaw reconstruction because of osteoradionecrosis.[24] We used pain as a patient-oriented outcome of successful surgical resection. A sudden decrease of pain was detected in all patients after surgery. Most patients with normal bone histology at baseline maintained low VAS pain scores. However, pain gradually increased in the patients who had osteomyelitis and BRONJ recurrence. A limitation of this study is that, because of the low number of events, we could not assess the influence of a number of potential risk factors on BRONJ recurrence rate (e.g., NBP type and dosage).

In conclusion, our study shows that jawbone surgical resection might cure BRONJ, with little morbidity and good survival, provided that a cautious selection of patients is performed and an accurate diagnosis is made pre-operatively. The fact that only 27% of the patients evaluated during the study period underwent jawbone resection shows that this treatment cannot and should not be offered to all BRONJ patients. An histopathological assessment of the resection margins may be useful to predict BRONJ recurrence but needs further confirmation.

Funding

Funded by a research grant from the Italian Public Health Ministry, (PRIN 2007LT5X87_004).

Conflict of interest statement

None declared.

Acknowledgements

We are grateful to Mrs. Vincenza Guzzardo for her assistance in the preparation of bone specimens.

References

1. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 2003;**61**(9):1115–7.
2. Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B. American Association of Oral and Maxillofacial Surgeons. American association of oral and maxillofacial surgeons position paper on bisphosphonate-related osteonecrosis of the jaws–2009 update. *J Oral Maxillofac Surg* 2009; **67**(Suppl. 5):2–12.
3. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsnberg D, et al. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American society for bone and mineral research. *J Bone Miner Res* 2007;**22**(10):1479–91.
4. Khan A. Osteonecrosis of the jaw: new developments in an old disease. *J Rheumatic* 2008;**35**(4):547–9.
5. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. *J Oral Maxillofac Surg* 2005;**63**(11):1567–75.
6. Madrid C, Bouferrache K, Abarca M, Jaques B, Broome M. Bisphosphonate-related osteonecrosis of the jaws: how to manage cancer patients. *Oral Oncol* 2010;**46**(6):468–70.
7. Fedele S, Porter SR, D'Aiuto F, Aljohani S, Vescovi P, Manfredi M, et al. Nonexposed variant of bisphosphonate-associated osteonecrosis of the jaw: a case series. *Am J Med* 2010;**123**(11):1060–4.
8. Bedogni A, Blandamura S, Lokmic Z, Palumbo C, Ragazzo M, Ferrari F, et al. Bisphosphonate-associated jawbone osteonecrosis: a correlation between imaging techniques and histopathology. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008;**105**(3):358–64.
9. Lazarovici TS, Yahalom R, Taicher S, Elad S, Hardan I, Yarom N. Bisphosphonate-related osteonecrosis of the jaws: a single-center study of 101 patients. *J Oral Maxillofac Surg* 2009;**67**(4):850–5.
10. Saia G, Blandamura S, Bettini G, Tronchet A, Totola A, Bedogni G, et al. Occurrence of bisphosphonate-related osteonecrosis of the jaw after surgical tooth extraction. *J Oral Maxillofac Surg* 2010;**68**(4):797–804.
11. Daruwalla J, Christophi C. Effect of hyperbaric oxygen in the treatment of malignancy: a review. *World J Surg* 2006;**30**:2112–31.
12. Bisdas S, Chambron Pinho N, Smolarz A, Sader R, Vogl TJ, Mack MG, et al. Biphosphonate-induced osteonecrosis of the jaws: CT and MRI spectrum of findings in 32 patients. *Clin Radiol* 2008;**63**(1):71–7.
13. Bamias A, Kastritis E, Bamia C, Moulopoulos LA, Melakopoulos I, Bozas G, et al. Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. *J Clin Oncol* 2005;**23**(34):8580–7.
14. Coviello V, Boggess M. Cumulative incidence estimation in the presence of competing risks. *Stata Journal* 2004;**4**:103–12.
15. Corcoran C, Mehta C, Patel N, Senchaudhuri P. Computational tools for exact conditional logistic regression. *Stat Med* 2001;**20**(17–18):2723–39.
16. Wutzl A, Biedermann E, Wanschitz F, Seemann R, Klug C, Baumann A, et al. Treatment results of bisphosphonate-related osteonecrosis of the jaws. *Head Neck* 2008;**30**(9):1224–30.
17. Carlson ER, Basile JD. The role of surgical resection in the management of bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg* 2009;**67**(5 Suppl):85–95.
18. Stockmann P, Vairaktaris E, Wehrhan F, Seiss M, Schwarz S, Spriewald B, et al. Osteotomy and primary wound closure in bisphosphonate-associated osteonecrosis of the jaw: a prospective clinical study with 12 months follow-up. *Support Care Cancer* 2010;**18**(4):449–60.
19. Mucke T, Koschinski J, Deppe H, Wagenpfeil S, Pautke C, Mitchell DA, et al. Outcome of treatment and parameters influencing recurrence in patients with bisphosphonate-related osteonecrosis of the jaws. J Cancer Res Clin Oncol; 2010 Oct 7. Epub ahead of print.
20. Kyrgidis A, Koloutsos G, Vahtsevanos K. Treatment protocols of bisphosphonate-related osteonecrosis of the jaws. *Head Neck* 2009;**31**(8): 1112–3 Author reply 1113–4.
21. Chiandussi S, Biasotto M, Dore F, Cavalli F, Cova MA, Di Lenarda R. Clinical and diagnostic imaging of bisphosphonate-associated osteonecrosis of the jaws. *Dentomaxillofac Radiol* 2006;**35**(4):236–43.
22. Williamson RA. Surgical management of bisphosphonate induced osteonecrosis of the jaws. *Int J Oral Maxillofac Surg* 2010;**39**(3):251–5.
23. Abu-Id MH, Warnke PH, Gottschalk J, Springer I, Wiltfang J, Acil Y, et al. "Bisphossy jaws" – high and low risk factors for bisphosphonate-induced osteonecrosis of the jaw. *J Cranio Maxillofac Surg* 2008;**36**(2):95–103.
24. Buchbinder D, St Hilaire H. The use of free tissue transfer in advanced osteoradionecrosis of the mandible. *J Oral Maxillofac Surg* 2006;**64**(6):961–4.