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The efficacy of hyperbaric oxygen therapy related to the clinical stage of osteoradionecrosis of the mandible

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Abstract. This study aimed to evaluate the success of hyperbaric oxygen therapy (HBOT) and surgery in the treatment of mandibular osteoradionecrosis (ORN) in relation to the extent of the ORN. Twenty-seven patients with ORN were identified from a total of 509 patients with a history of primary oral or base of the tongue cancer; these patients had been treated with radiation therapy with curative intent between 1992 and 2006, with a radiation dose to the mandible of ≥50 Gy. The ORN was staged according to the classification of Notani et al. The time from completion of radiation therapy to the development of ORN varied (median 3 years). Forty HBOT sessions were offered. After HBOT alone, 3 of 11 stage I lesions, 0 of 8 stage II lesions, and 0 of 8 stage III lesions had healed ($P = 0.0018$). An absolute incidence of 5.3% ORN was found in this population. Of all sites irradiated in this study, the floor of the mouth was most associated with ORN (8.6%), whereas the cheek was least associated (0%). Based on the results of this study, HBOT can be recommended for stage I and II ORN and for selected cases of stage III ORN.

Key words: hyperbaric oxygen therapy; mandible; osteoradionecrosis; radiation therapy.

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Osteoradionecrosis (ORN) of the mandible is a serious complication after radiation therapy for head and neck cancer. It can be defined as a non-healing condition in which the irradiated necrotic bone becomes exposed through dehiscence of the overlying mucosa or skin. The first description of ORN of the mandibular bone after radiation therapy was given by Regaud in 1922.[1] The incidence of ORN varies widely, with an estimated incidence of between 1.2% and 15% in head and neck oncology patients treated with radiation therapy.[2–7] In a review of studies, Clayman reported an overall incidence of ORN of 11.8% before 1968 and

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5.4% after 1968,[8] due to changes in the way radiotherapy was applied. However, it should be noted that in most studies, the absolute incidences were given without correction for the reduction in number of patients at risk over time. Therefore these studies underestimated the real, actuarial incidence of ORN.

The severity of mandibular ORN in head and neck cancer patients varies widely from exposed bone with a loss of soft tissue to pathological fractures due to necrotic bone.[4] The interval between radiation therapy and the onset of ORN varies between 4 months and as much as 20 years,[9] with a peak incidence at 2–4 years and a remaining lifelong risk, albeit to a lesser degree.[8] The main cause of ORN is a high radiation dose to the mandible, sometimes (but not necessarily) followed by a trauma.[3,10–16] Although chemotherapy, because of its potential to induce vascular damage, could theoretically contribute to ORN, no significant association has been shown in clinical studies.[17,18] Late stage ORN is observed several years after radiation therapy and is often directly related to trauma to the irradiated tissue.[3,10,19]

The optimal treatment for ORN of the mandible remains a matter of debate. Patient- and therapy-related factors such as poor oral hygiene, trauma, alcohol and tobacco use, and a low body mass index (BMI), may influence the onset and progression of the disease.[18,20–22]

The outcome of the treatment of ORN is usually assessed clinically. Several staging systems have been suggested for the assessment of the severity of mandibular ORN.[2,23,24] These range from simple datasets of limited radiological features, with or without some clinical parameters, to extensive datasets with many clinical parameters as well as radiological features. The staging system used in this study was described by Notani et al. and is based on a radiological description of the extent of the ORN lesion in the mandibular bone.[25] Patients are divided into three categories: those with lesions of stage I, II, or III. Some staging systems come with guidelines for the purpose of guiding the clinician to make more standardized decisions on the treatment of ORN.[24,25]

In 1983 Marx suggested combined hyperbaric oxygen (HBO) and surgical treatment for ORN.[19,23] His four criteria for success were the absence of pain, mandibular salvage or reconstruction, restoration of mandibular function, and survival of the overlying oral mucosa.[26] This approach has since been adopted by others, but there is a lack of high-level evidence for the efficacy of HBO therapy (HBOT) in the treatment of ORN due to an absence of well-designed randomized trials. Many studies advocate the use of HBOT, whereas several recent studies have questioned the added value of its use.[3,7,20,26–33] Concern about the possibility that HBOT could promote tumour growth lacks evidence.[34,35]

The objective of the present study was to evaluate the effect of an HBOT–surgery protocol related to the stage of ORN of the mandible according to the staging system of Notani et al. The emphasis of this study was on the clinical outcome.

Patients and methods

Patient and tumour characteristics

ORN was defined as a wound-healing problem due to bone necrosis after radiation therapy, which failed to heal over a period of 6 months.[3,23]

A total of 509 patients treated during the period 1992–2006 with primary or adjuvant radiation therapy for an oral or base of the tongue tumour, with the mandible in the high volume area, were evaluated. Within this patient group, 134 patients had a carcinoma of the border of the tongue, 133 had a tumour of the base of the tongue, 128 had a tumour of the floor of the mouth, 53 had a tumour of the retromolar trigone, 31 had a tumour of the cheek, and 30 had a tumour of the inferior alveolar process (Table 1). Patients with tumours of the oral cavity mostly underwent surgery with postoperative radiotherapy, whereas oropharyngeal tumours were generally treated with primary radiotherapy. Of these 509 patients, 27 had one episode of histologically proven ORN of the mandible and received HBOT in combination with surgery as necessary. Their data were retrieved from the databases of the radiation oncology department of the university medical centre and the hyperbaric treatment facilities.

Patients with ORN at locations other than the mandible were excluded. Of the 27 patients included, 11 had a floor of the mouth carcinoma, nine had a base of the tongue carcinoma, five had a border of the tongue carcinoma, one had a retromolar trigone carcinoma, and one had an inferior alveolar process carcinoma (Table 1).

The ORN classification was determined both clinically and radiologically. A panoramic radiograph was used for the radiological assessment. A biopsy was taken for histopathological confirmation and to exclude malignancy.

Treatment

All patients underwent radiation therapy as a primary or adjuvant therapy after surgery for a primary oral or base of the tongue carcinoma with curative intention, with the mandible in the target area. All patients underwent clinical and radiological dental screening prior to radiation; if necessary, focal infections were eliminated. Radiotherapy was started after confirmed healing of the treated dentoalveolar focus site. During radiotherapy, patients received instructions from an oral hygienist who also followed them up and treated them.

The radiation dose to the ORN site varied between 50 Gy and 70 Gy. Three patients were re-irradiated for a recurrence or secondary primary tumour in the same

Table 1. Absolute incidence of osteoradionecrosis per tumour site.

Site	Number	ORN	Incidence (%)
Border of the tongue	134	5	3.7
Base of the tongue	133	9	6.8
Floor of the mouth	128	11	8.6
Retromolar trigone	53	1	1.9
Cheek	31	0	0
Inferior alveolar process	30	1	3.3
Total	509	27	5.3

ORN, osteoradionecrosis.

Table 2. Radiation therapy dose related to osteoradionecrosis stage at the time of diagnosis.

Radiation therapy dose, Gy	Number	ORN stage		
		I	II	III
50–60	2	1	1	0
60–70	21	9	4	8
>70	4	1	3	0

ORN, osteoradionecrosis.

area. These three patients, together with a fourth patient who had no recurrence, received a cumulative physical total dose to the mandible higher than 70 Gy (Table 2).

ORN classification and treatment

In this study, ORN was categorized into three stages using the classification of Notani et al., based on the extent of the ORN lesion.[25] Stage I is defined as ORN confined to the alveolar bone. Stage II is ORN limited to alveolar bone and mandible above the mandibular canal. Stage III is ORN extending to the mandible under the level of the mandibular canal, with a skin fistula and/or pathological fracture. Panoramic radiographs were used for the radiological assessment.

All 27 patients received 30 pre-surgical and 10 post-surgical sessions of HBOT in accordance with the Wilford Hall guidelines.[23,26,29] The 30 pre-surgical sessions of HBOT were followed by surgical debridement and antibiotics, and subsequently followed by another 10 sessions of HBOT if the lesion had not healed after HBOT alone. Simple removal of a small piece of sequestrum in the gingival area that had detached from the mandibular bone, or the removal of debris, was not recorded as a surgical procedure.

Follow-up

Follow-up during HBOT was scheduled on a fortnightly or monthly basis. After ORN treatment had been completed and a stable clinical situation had been achieved, follow-up was scheduled every 3–6 months. Radiological follow-up was done when indicated by clinical appearance. The endpoint was defined as the stable absence of pain, fistulation, and mucosal dehiscence of bone at the former ORN site for a period of 2 years. Functional restoration of the mandible was not feasible in several patients due to co-morbidities.

Statistics

The data obtained were correlated and analyzed statistically using Fisher's exact test. SAS 9.2 software (SAS Institute, Cary, NC, USA) was used for this analysis.

Results

Twenty-seven patients with ORN of the mandible, treated between 1992 and 2006 at the university medical centre, were identified. Eighteen of the 27 patients underwent surgery for their primary tumour, with postoperative radiation therapy. Nine patients were treated with radiation therapy alone. The time interval from completion of radiotherapy to the onset of ORN ranged from 1 to 8 years (median 3 years). All patients underwent dental screening prior to the radiation therapy and were supervised and instructed by a dental hygienist.

Table 3. Tumour stage related to osteoradionecrosis stage.

Tumour stage	Number	ORN stage		
		I	II	III
I	1	0	0	1
II	8	4	2	2
III	8	3	4	1
IV	10	4	2	4

ORN, osteoradionecrosis.

Table 4. Additional causes of osteoradionecrosis.

Cause of ORN	Number	%
Unknown/spontaneous	8	30%
Extractions post RT	6	22%
Extractions pre RT	1	4%
Related to prosthetics	6	22%
Tumour-related surgery	3	11%
Periodontal disease	3	11%
Total	27	100%

ORN, osteoradionecrosis; RT, radiotherapy.

There was no association between the radiation dose and the stage of ORN (Table 2). No significant correlation between the tumour stage and the stage of ORN was found (Table 3). No factor provoking the development of the ORN was identified for eight cases. Extractions and prosthesis-related complaints were an additional cause of the ORN in seven and six cases, respectively. Tumour-related surgery (three cases) and periodontal disease (three cases) were also associated with the development of ORN (Table 4).

Eleven of the 27 ORN cases were Notani stage I, eight were stage II, and eight were stage III. All of the initial stage I lesions healed, all of the initial stage II lesions healed, and seven of the eight initial stage III lesions healed (Table 5). The patient with an initial stage III ORN that did not heal refused further treatment with stable stage I disease. The difference in outcome between the initial ORN stage I and III patients after HBOT alone was significant ($P = 0.0018$).

In this retrospective study, segmental resection was the most common primary surgical treatment for ORN,[23] followed by sequestrectomy and decorticalization of the mandible. Three patients healed after HBOT alone and did not need surgery. With regard to secondary surgical treatment, five segmental resections were needed to treat refractory ORN. Fourteen

Table 5. Correlation between osteoradionecrosis stage and the effect rate of treatment with hyperbaric oxygen therapy and surgery. The effect rate is defined as the absence of mucosal dehiscence of bone at the former osteoradionecrosis site.

	Primary ORN stage		
	I ($n = 11$)	II ($n = 8$)	III ($n = 8$)
ORN stage after HBOT alone			
0	3	0	0
I	4	2	0
II	2	5	0
III	2	1	8
% improved	27%	25%	0%
% healed	27%	0%	0%
% deteriorated	36%	12%	0%
ORN stage after primary therapy			
0	8	2	5
I	0	3	2
II	1	1	1
III	2	2	0
% improved	73%	63%	100%
% healed	73%	25%	63%
% deteriorated	27%	25%	0%
ORN stage after subsequent surgery			
0	11	8	7
I	0	0	1
II	0	0	0
III	0	0	0
% improved	100%	100%	100%
% healed	100%	100%	87%
% deteriorated	0%	0%	0%

ORN, osteoradionecrosis; HBOT, hyperbaric oxygen therapy.

patients did not need secondary surgery to heal. The initial ORN stage and the response to therapy are shown in Table 5.

Fifteen cases healed after primary treatment for ORN (HBOT and surgery). The other 12 cases needed subsequent surgery. In one case, the patient had stable disease.

In this study, the primary tumour site with the highest absolute incidence of ORN was the floor of the mouth (8.6%), whereas the cheek had the lowest absolute incidence (0%). An average of 5.3% was found for all sites (Table 1).

Discussion

An important finding of this study is that all patients with stage I and II ORN were successfully treated with primary therapy including HBOT, and if needed, subsequent surgery. An overall absolute incidence of ORN of 5.3% was found in this patient population, and the floor of the mouth tumour site was the site most associated with ORN. A significant difference in outcome between the initial ORN stage I and III patients was found after HBOT alone ($P = 0.0018$). Three patients with a stage I ORN lesion healed after HBOT alone. The highest cure rate for stage III ORN is attained with extensive surgery, including segmental mandibulectomy and reconstruction with a free vascularized osteocutaneous flap.[25] HBOT seemed to be useful for stages I and II ORN, but might be less useful for bone healing in stage III ORN. In stage III ORN, a segmental resection, removal of the mandibular bone in the high-dose radiation field, and reconstruction with a free vascularized osteocutaneous flap has been shown to be the most effective treatment.[36] HBOT does not seem to be effective for bone healing in this stage.[37] HBOT may, however, improve the surrounding soft tissues and so may have a positive effect on wound healing after reconstructive surgery for ORN.[38] Healing followed secondary surgical treatment in almost all cases. One ORN lesion did not heal. This patient had stable disease and refused further treatment.

Many factors such as tumour characteristics, drinking and smoking habits, oral hygiene, and traumatic events, such as surgery, have been mentioned in the literature as factors in the development of ORN.[18,20–22] The overall stage, tumour size, and proximity to bone have been correlated with the occurrence of ORN.[18,20] ORN stage and tumour size was not correlated in this study.

It is known that a high external radiation dose and brachytherapy are risk factors for the development of ORN. In this study, no correlation was found between the radiation dose and the stage of ORN.

Developments in the delivery of radiation therapy, such as intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT), have increased the conformality of the high-dose distribution, thereby sparing larger volumes of mandible and the salivary glands.[39,40] Preliminary reports have suggested that the use of IMRT may reduce the incidence of ORN.[36,39,41,42] These studies reported that although the prevalence of ORN following IMRT was lower than that following conventional radiotherapy, additional studies are needed to determine whether this difference is clinically significant.

The classification of Notani et al. was used in this study, because it describes the bone involvement (assessed radiologically) in three stages and is easy to use.[25] Due to the retrospective nature of this study, soft tissue involvement could not reliably be assessed. Many of the clinical studies on HBOT for ORN have followed the Wilford Hall guidelines for both ORN staging and treatment.[10,31,38,43] In these guidelines, the proposed type of treatment is related to the stage of ORN.

In 1983, Marx introduced combined HBOT–surgical staging as the standard treatment for ORN of the jaw into the Wilford Hall guidelines.[23] Several researchers support the use of this protocol, despite the retrospective nature of their studies and a lack of statistically supported evidence.[7,13,41,44–46] However, others have failed to find a beneficial effect of HBOT, whether or not used according to the Wilford Hall guidelines, and have suggested that it might delay definite therapy.[9,47,48] The staging system in these guidelines seems more appropriate for clinical use rather than research purposes, because of the selection bias due to relating the therapy to the stage.

The floor of the mouth was the tumour site most related to ORN in the present study. Others have reported the tongue to be the most related tumour site.[30,47,49] The influence of the primary tumour site on the onset of ORN has been discussed.[2,31,32,50] Some authors have found a positive relationship between ORN and the primary tumour site.[20,42,50] Curi and Dib reported that oral cancers treated with radiotherapy had the highest incidence of ORN, especially those of the tongue, floor of the mouth, and retromolar region.[20]

A double-blind, randomized clinical trial published by Annane et al. in 2004 failed to show the benefits of HBOT.[28] The authors concluded that HBOT should not be recommended for patients with overt mandibular ORN. A discussion arose regarding the reliability of the methodology of that study. Some authors criticized the study protocol, stating that the clinical and radiographic criteria barely corresponded to a known ORN classification, which raised doubts as to whether all the treated lesions could be classified as ORN.[51] The use of a twice daily HBOT regimen was also in contrast with the majority of reported studies, in which HBOT once daily was the standard treatment.[52] Therefore, this patient population may not have been representative of patients with ORN of the mandible treated with HBOT according to the standard guidelines.

A recent systematic review of clinical evidence concluded that HBOT should not be recommended for the routine treatment of patients with mandibular ORN, except when resection/reconstruction surgery is needed.[37] Van Merkesteyn et al., however, showed that lesions that do not respond to conservative treatment are best treated with combined surgical debridement, antibiotics, and HBO.[32] In 2004, Delanian and Lefaix proposed a new theory for the pathogenesis of ORN.[53] The assumption that bone damaged by radiation is mainly the result of radiation-induced fibrosis,[54] led to the development of a triple-drug therapy to reduce radiation-induced fibrosis and bone destruction and to stimulate osteogenesis via an antioxidant pathway.[55,56] Treatment with pentoxifylline combined with tocopherol and clodronate led to complete recovery in most patients at 6 months.[57,58]

In conclusion this study showed a beneficial effect of HBOT for the lower ORN stages (I and II). Stage III ORN usually requires a segmental resection of the affected part of the mandible. With this treatment, the segment of mandible in the target area of the radiation therapy is removed and the region reconstructed. It is unclear what the added value of HBOT is to the bone in cases of extensive ORN. If the soft tissues surrounding the ORN lesion are in a poor state, HBOT could be recommended to promote revascularization and support wound healing after free flap reconstruction.

Based on the results of this study, although performed on a limited number of patients and without a control group, HBOT can be recommended for stage I and II ORN and for selected cases of stage III ORN, for example those with a poor state of the surrounding soft tissues.

The management of ORN is challenging and no study reporting the ultimate solution to the problem of ORN – reversing the damage of ORN or controlling its course – has been published. New theories on the pathological basis of ORN may lead to a better understanding of this difficult condition. The treatment protocol proposed recently by Delanian et al., based on antioxidant products such as pentoxifylline, tocopherol (vitamin E), and bisphosphonates, might be promising.[54,57–59] More research is needed to better understand the course of the pathological changes occurring during the development of ORN and to identify the correct treatment for early intervention in the pathological pathway of ORN.

The efficacy of HBOT as reported in the literature remains uncertain: several negative case series and one negative randomized clinical trial have been reported,[16,28,60] but there have been many retrospective reports of successful treatment of ORN with HBOT. More well-designed systematic research is required to determine whether HBOT has a significant impact on the treatment of ORN.

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Competing interests

None.

Ethical approval

Exempted.

Patient consent

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References

1. Regaud C. Sur la necrose des os attenté par un processus cancereux et traites par les radiaions. *Compt Rend Soc Biol* 1922;**87**:478.
2. Epstein JB, Wong FL, Stevenson-More P. Osteoradionecrosis: clinical experience and a proposal for classification. *J Oral Maxillofac Surg* 1987;**45**:104–10.
3. Marx RE. Osteoradionecrosis. A new concept in its pathophysiology. *J Oral Maxillofac Surg* 1983;**41**:282–8.
4. Wong JK, Wood RE, McLean M. Conservative management of osteoradionecrosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997;**84**:16–21.
5. Murray CG, Daly TE, Zimmerman SO. The relationship between dental disease and radiation necrosis of the mandible. *Oral Surg Oral Med Oral Pathol* 1980;**49**:99–104.
6. Morrish Jr RG, Chan E, Silverman Jr S, Meyer J, Fu KK, Greenspan D. Osteonecrosis in patients irradiated for head and neck carcinoma. *Cancer* 1981;**47**:1980–3.
7. Vudiniabola S, Pirone C, Williamson J, Goss AN. Hyperbaric oxygen in the therapeutic management of osteoradionecrosis of the facial bones. *Int J Oral Maxillofac Surg* 2000;**29**:435–8.
8. Clayman L. Clinical controversies in oral and maxillofacial surgery: part two. Management of dental extractions in irradiated jaws: a protocol without hyperbaric oxygen therapy. *J Oral Maxillofac Surg* 1997;**55**:275–81.
9. Celik N, Wei FC, Chen HC, Cheng MH, Huang WC, Tsai FC, et al. Osteoradionecrosis of the mandible after oromandibular cancer surgery. *Plast Reconstr Surg* 2002;**109**:1875–81.
10. Marx RE, Johnson RP. Studies in the radiobiology of osteoradionecrosis and their clinical significance. *Oral Surg Oral Med Oral Pathol* 1987;**64**:379–90.
11. Bras J, de Jonge HK, van Merkesteyn JP. Osteoradionecrosis of the mandible: pathogenesis. *Am J Otolaryngol* 1990;**11**:244–50.
12. Store G, Boysen M. Mandibular osteoradionecrosis: clinical behaviour and diagnostic aspects. *Clin Otolaryngol* 2000;**25**:378–84.
13. Mounsey RA, Brown DH, O'Dwyer TP, Gullane PJ, Koch GH. Role of hyperbaric oxygen therapy in the management of mandibular osteoradionecrosis. *Laryngoscope* 1993;**103**:605–8.
14. Thorn JJ, Hansen HS, Specht L, Bastholt L. Osteoradionecrosis of the jaws: clinical characteristics and relation to the field of irradiation. *J Oral Maxillofac Surg* 2000;**58**:1088–93.
15. Epstein J, Meij E, McKenzie M, Wong F, Lepawsky M, Stevenson-Moore P. Postradiation osteoradionecrosis of the mandible: a long-term follow study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997;**83**:657–62.
16. Marx Re. Ehler WJ, Tayapongsak P, Pierce LW. Relationship of oxygen dose to angiogenesis induction in irradiated tissue. *Am J Surg* 1990;**160**:519–24.
17. Glanzmann C, Gratz KW. Radionecrosis of the mandible: a retrospective analysis of the incidence and risk factors. *Radiother Oncol* 1995;**36**:94–100.
18. Jereczek-Fossa BA, Orecchia R. Radiotherapy-induced mandibular bone complications. *Cancer Treat Rev* 2002;**28**:65–74.
19. Marx R. Radiation injury to tissue. In: Kindwall EP, Whelan HT, editors. *Hyperbaric medicine practice*. Flagstaff, AZ: Best Publishing; 1999. p. 665–723.
20. Curi MM, Dib LL. Osteoradionecrosis of the jaws: a retrospective study of the background factors and treatment in 104 cases. *J Oral Maxillofac Surg* 1997;**55**:540–4.
21. Kluth EV, Jain PR, Stuchell RN, Frich Jr JC. A study of factors contributing to the development of osteoradionecrosis of the jaws. *J Prosthet Dent* 1988;**59**:194–201.
22. Beumer J, Harrison R, Saunders B, Kurasch M. Osteoradionecrosis: predisposing factors and outcome of therapy. *Head Neck Surg* 1984;**6**:819–27.
23. Marx RE. A new concept in the treatment of osteoradionecrosis. *J Oral Maxillofac Surg* 1983;**41**:351–7.
24. Schwartz HC, Kagan AR. Osteoradionecrosis of the mandible: scientific basis for clinical staging. *Am J Clin Oncol* 2002;**25**:168–71.
25. Notani K, Yamazaki Y, Kitada H, Sakakibara N, Fukuda H, Omori K, et al. Management of mandibular osteoradionecrosis corresponding to the severity of osteoradionecrosis and the method of radiotherapy. *Head Neck* 2003;**25**:181–6.
26. Marx RE, Ames JR. The use of hyperbaric oxygen therapy in bony reconstruction of the irradiated and tissue-deficient patient. *J Oral Maxillofac Surg* 1982;**40**:412–20.
27. Johnson RP, Marx RE, Buckley SB. Hyperbaric oxygen in oral and maxillofacial surgery. In: Worthington P, Evans JR, editors. *Controversies in oral and maxillofacial surgery*. Philadelphia: WB Saunders Co; 1992. p. 107–26.
28. Annane D, Depondt J, Aubert P, Villart M, Gehanno P, Gajdos P, et al. Hyperbaric oxygen therapy for radionecrosis of the jaw: a randomised, placebo-controlled, double-blind trial from the ORN96 study group. *J Clin Oncol* 2004;**22**:4893–900.
29. Pitak-Arnnop P, Sader R, Dhanuthai K, Masaratana P, Bertolus C, Chaine A, et al. Management of osteoradionecrosis of the jaws: an analysis of evidence. *Eur J Surg Oncol* 2008;**34**:1123–34.
30. Oh HK, Chamber MS, Martin JW, Lim HJ, Park HJ. Osteoradionecrosis of the mandible: treatment outcomes and factors influencing the progress of osteoradionecrosis. *J Oral Maxillofac Surg* 2009;**67**:1378–86.
31. Mainous EG, Hart GB. Osteoradionecrosis of the mandible. Treatment with hyperbaric oxygen. *Arch Otolaryngol* 1975;**101**:173–7.
32. Van Merkesteyn JP, Bakker DJ, Borgmeijer-Hoelen AM. Hyperbaric oxygen treatment of osteoradionecrosis of the mandible: experience in 29 patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995;**80**:12–6.
33. Wood GA, Liggins SJ. Does hyperbaric oxygen have a role in the management of osteoradionecrosis? *Br J Oral Maxillofac Surg* 1996;**34**:424–7.
34. Feldmeijer J, Carl U, Hartmann K, Sminia P. Hyperbaric oxygen: does it promote growth or recurrence of malignancy? *Undersea Hyperb Med* 2003;**30**:1–18.

35. Shi Y, Lee CS, Wu J, Koch CJ, Thom SR, Maity A, et al. Effects of hyperbaric oxygen exposure on experimental head and neck tumor growth, oxygenation, and vasculature. *Head Neck* 2005;**27**:269–362.
36. Gal TJ, Yueh B, Futran ND. Influence of prior hyperbaric oxygen therapy in complications following microvascular reconstruction for advanced osteoradionecrosis. *Arch Otolaryngol Head Neck Surg* 2003;**129**: 72–6.
37. Bessereau J, Annane D. Treatment of osteoradionecrosis of the jaw: the case against the use of hyperbaric oxygen. *J Oral Maxillofac Surg* 2010;**68**:1907–10.
38. D'Souza J, Goru J, Goru S, Brown J, Vaughan ED, Rogers SN. The influence of hyperbaric oxygen on the outcome of patients treated for osteoradionecrosis: 8 year study. *Int J Oral Maxillofac Surg* 2007;**36**:783–7.
39. Studer G, Studer SP, Zwahlen RA, Huquenin P, Grätz KW, Lütolf UM, et al. Osteoradionecrosis of the mandible: minimized risk profile following intensity modulated radiation therapy (IMRT). *Strahlenther Onkol* 2006;**182**:283–8.
40. Studer G, Gratz KW, Glanzmann C. Osteoradionecrosis of the mandibula in patients treated with different fractionations. *Strahlenther Onkol* 2004;**180**:233–40.
41. Claus F, Duthoy W, Boterberg T, de Gersem W, Huys J, Vermeersch H, et al. Intensity modulated radiation therapy for oropharyngeal and oral cavity tumors: clinical use and experience. *Oral Oncol* 2002;**38**:597–604.
42. Van den Broek GB, Balm AJ, van den Brekel MW, Hauptmann M, Schornagel JH, Rasch CR. Relationship between clinical factors and the incidence of toxicity after intra-arterial chemoradiation for head and neck cancer. *Radiother Oncol* 2006;**81**:143–50.
43. Peleg M, Lopez EA. The treatment of osteoradionecrosis of the mandible: the case for hyperbaric oxygen and bone graft reconstruction. *J Oral Maxillofac Surg* 2006;**64**:956–60.
44. David LA, Sandor GK, Evans AW, Brown DH. Hyperbaric oxygen therapy and mandibular osteoradionecrosis: a retrospective study and analysis of treatment outcomes. *J Can Dent Assoc* 2001;**67**:384–90.
45. Bui QC, Lieber M, Withers HR, Corson K, van Rijnsoever M, Elsaleh H. The efficacy of hyperbaric oxygen therapy in the treatment of radiation-induced late side effects. *Int J Radiat Oncol Biol Phys* 2004;**60**:871–8.
46. Chang DW, Oh HK, Robb GL, Miller MJ. Management of advanced mandibular osteoradionecrosis with free flap reconstruction. *Head Neck* 2001;**23**:830–5.
47. Reuther T, Schuster T, Mende U, Kubler A. Osteoradionecrosis of the jaws as a side effect of radiotherapy of head and neck tumour patients—a report of a thirty year retrospective review. *Int J Oral Maxillofac Surg* 2003;**32**:289–95.
48. Niewald M, Barbie O, Schnabel K, Engel M, Schedler M, Nieder C, et al. Risk factors and dose–effect relationship for osteoradionecrosis after hyperfractionated and conventionally fractioned radiotherapy for oral cancer. *Br J Radiol* 1996;**69**:847–51.
49. Lee IJ, Koom WS, Lee CG, Kim YB, Yoo SW, Keum KC, et al. Risk factors and dose–effect relationship for mandibular osteoradionecrosis in oral and oropharyngeal cancer patients. *Int J Radiat Oncol Biol Phys* 2009;**75**:1084–91.
50. Murray CG, Herson J, Daly TE, Zimmermans S. Radiation necrosis of the mandible: a 10 year study. Part I. Factors influencing the onset of necrosis. *Int J Radiat Oncol Biol Phys* 1980;**6**:543–8.
51. Van Merkesteyn R, Bakker DJ. Comment on ''Hyperbaric oxygen therapy for radionecrosis of the jaw: a randomized, placebo-controlled, double-blind trial from the ORN96 study group''. *J Clin Oncol* 2005;**23**:4465–6.
52. Lee IJ, Koom WS, Lee CG, Kim YB, Yoo SW, Keum KC, et al. Risk factors and dose–effect relationship for mandibular osteoradionecrosis in oral and oropharyngeal cancer patients. *Int J Radiat Oncol Biol Phys* 2009;**75**:1084–91.
53. Delanian S, Lefaix JL. The radiation-induced fibroatrophic process: the therapeutic perspective via the antioxidant pathway. *Radiother Oncol* 2004;**73**:119–31.
54. Ansher M. The irreversibility of radiation-induced fibrosis: fact or folklore? *J Clin Oncol* 2005;**23**:8551–2.
55. Delanian S, Lefaix JL. Current management for late normal tissue injury: radiation-induced fibrosis and necrosis. *Semin Radiat Oncol* 2007;**17**:99–107.
56. Maier A, Gaggl A, Klemen H, Santler G, Anegg U, Fell B, et al. Review of severe osteoradionecrosis treated by surgery alone or surgery with postoperative hyperbaric oxygenation. *Br J Oral Maxillofac Surg* 2000;**38**:173–6.
57. Delanian S, Depondt J, Lefaix JL. Major healing of refractory mandible osteoradionecrosis after treatment combining pentoxifylline and tocopherol: a phase II trial. *Head Neck* 2005;**27**:114–23.
58. Delanian S, Chatel C, Porcher R, Depondt J, Lefaix JL. Complete restoration of refractory mandibular osteoradionecrosis by prolonged treatment with a pentoxifylline–tocopherol–clodronate combination (PENTOCLO): a phase II trial. *Int J Radiat Oncol Biol Phys* 2011;**80**:832–9.
59. Delanian S, Lefaix JL. Complete healing of severe osteoradionecrosis by treatment combining pentoxifylline, tocopherol and clodronate (case report). *Br J Radiol* 2002;**75**:467–9.
60. Myer RA, Marx RE. Use of hyperbaric oxygen in postradiation head and neck surgery. *NCI Monogr* 1990;**9**:151–7.

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