Review Article

Management of osteoradionecrosis of oral cavity

Nivedhaa Chezhian[1], Dhanraj Ganapathy[1], Ashish R. Jain[1]*

ABSTRACT

The treatment of head and neck cancer remains a challenge. Despite advances in surgical reconstructive techniques, most patients will require adjuvant therapy in the form of radiotherapy or chemoradiotherapy to improve locoregional control. The short- and long-term side effects of radiotherapy can be difficult to treat. The initial effects of radiotherapy to the oral tissues such as mucositis and loss of taste are troublesome but short-lived resolving within a few weeks. Xerostomia may be more persistent but can be managed with supportive therapy such as sialogogues and artificial saliva. Osteoradionecrosis (ORN) is the long-term and most serious side effect of radiotherapy. ORN develops as irradiation diminishes the bone's ability to withstand trauma and avoid infection, and it can be facilitated by poor nutrition and hygiene. ORN usually occurs in the mandible and causes chronic pain and surface ulcerations. All patients who require extraction of teeth in a previously irradiated field should be considered at risk of developing ORN.

KEY WORDS: Osteoradionecrosis, Radiotherapy, Xerostomia

INTRODUCTION

The treatment of head and neck cancer remains a challenge. Despite advances in surgical reconstructive techniques, most patients will require adjuvant therapy in the form of radiotherapy or chemoradiotherapy to improve locoregional control.[1,2] Radiation treatment is an as often as possible utilized treatment methodology for head and neck disease, either as a remain solitary choice or in blend with medical procedure (adjuvant or neoadjuvant radiotherapy) or potentially chemotherapy. A standout among the most all-around reported entanglements of radiation treatment in the head and neck area is osteoradionecrosis (ORN).[3] The short- and long-term side effects of radiotherapy can be difficult to treat.[4] The initial effects of radiotherapy to the oral tissues such as mucositis and loss of taste are troublesome but short-lived resolving within a few weeks. Xerostomia may be more persistent but can be managed with supportive therapy such as sialogogues and artificial saliva.[5] ORN or bone death of the facial skeleton is the long-term and most serious side effect of radiotherapy. The clinical appearance of Osteoradionecrosis is that of necrotic bone present in the oral pit.[6] Marx characterizes ORN as "a region more prominent than 1 cm of uncovered bone in a field of illumination that had neglected to demonstrate any confirmation of recuperating for not less than a ½ year."[7] ORN comes about because of the traded-off bloodstream to the mandible optional to radiation instigated vascular harm. This diminished bloodstream debilitates the typical recuperating limit of the bone after even the scarcest affront. It likewise inclines to optional disease of the bone. This inconvenience of radiation treatment is once in a while announced in the jaws of youngsters and hence would not be talked about further here.[8] In any case, ORN limits the essence of the sore to 3 months and peruses there after: ORN is a condition portrayed by bone that moves toward becoming devitalized and uncovered through the overlying skin or mucosa, without mending for 3 months tumor report has been discounted. This condition occurs in 3–10% of patients.[9] ORN usually occurs in the mandible and causes chronic pain and surface ulcerations. The difference between its blood supply and anatomical structure may make it be more affected than maxilla.[10,11] This review will discuss about the etiology, the various treatment option, and the prevention of ORN a serious complication of oral and maxillofacial radiotherapy.

Access this article online

Website: jprsolutions.info | ISSN: 0975-7619

Etiology

The cause of ORN is radiation-induced tissue damage. This damage is compounded by the fact that the mandible is essentially an end-artery system supplied by the

Department of Prosthodontics, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India

***Corresponding author:** Dr. Ashish R. Jain, Department of Prosthodontics, Saveetha Dental College and Hospital, Saveetha University, Poonamalle High Road, Chennai – 600127, Tamil Nadu, India. Phone: +91-9884233423. E-mail: dr.ashishjain_r@yahoo.com

Received on: 19-08-2018; Revised on: 16-09-2018; Accepted on: 25-10-2018

inferior alveolar artery, with minor supply from the bony attachments.[12] The incidence of ORN after radiotherapy for head and neck cancers has been reported to be due to the loss of soft tissue, which naturally recovers, and the exposure of necrotic bone for over 6 months.[13] Trauma to the soft tissue overlying bone in the oral cavity induces bacteria to enter the underlying demineralized bone and leads to osteomyelitis.[14] The radiation destroys some of the very small blood vessels within the bone. These blood vessels carry both nutrients and oxygen to the living bone. Tissue breakdown and chronic non-healing wounds are sequelae of endarteritis that results in tissue hypoxia, hypocellularity, and hypovascularity. A reduction in these vessels correlates to a reduction in the bone's ability to heal itself.[15] In an irradiated field, minor insult such as periodontal disease, pulpal infections, and procedures such as dental extractions can result in delayed healing and in some cases develop into ORN.[16] Remodeling cells such as fibroblasts, osteoblasts, and osteoclasts will show changes when they try to divide, such as during healing.[1] Damage to the microvasculature results in initial hyperemia, followed by endarteritis, thrombosis, and eventual obliteration. This results in the 3 "H"s or hypocellularity, hypoxia, and hypovascularity. Intraoral tissues are damaged by irradiation, which causes mucositis and xerostomia. These conditions, in combination with poor dental care or a poorly fitting tissue-borne prosthesis, will give rise to odontogenic and periodontal infections. This again can lead to ORN.[17,18]

This hypothesis depends on the idea that osteoclasts endure radiation harm sooner than the improvement of vascular changes.[19,20] In like manner, the key occasion in the movement of ORN is the actuation and dysregulation of fibroblastic action that prompts atrophic tissue inside a formerly illuminated zone.[19] The histopathologic periods of the improvement of ORN incorporate the prefibrotic stage, the constitutive sorted out stage, and the late fibroatrophic stage. In the underlying prefibrotic stage, changes in endothelial cells prevail, alongside the intense fiery reaction; in the constitutive composed stage, anomalous fibroblastic movement prevails and there is complication of the extracellular grid; in the late fibroatrophic stage, tissue rebuilding happens alongside the development of delicate recuperated tissues that convey a genuine characteristic danger generally reactivated aggravation in case of nearby damage.[21]

Meyer proposed a hypothesis including radiation, injury, and contamination and detailed that oral microbiological verdure attacks the fundamental lighted bone after damage.[19] Endothelium, bone, and periosteum are extremely imperative tissues that have been appeared to end up hypoxic, hypocellular, and hypovascular because of ORN.[20] With this hypothesis, the great succession of radiation, injury, and contamination can be supplanted by an arrangement of metabolic and cell changes as cell demise and collagen lysis surpass combination and cell replication, bringing about incessant non-recuperating wounds.[21]

Management

Hyperbaric oxygen (HBO) and ORN

When ORN develops, tissue destruction devolves into the breakdown of overlying tissues and symptomatic destruction of bone. During this process, the response to antibiotics can be poor. In many cases, the situation can be improved with the use of HBO therapy.Once in a while, foundational anti-infection agents will be required if ORN creates. In fact, it is anything but a contamination of bone but instead a non-healing hypoxic wound.[22] Systemic antimicrobials are of restricted an incentive to the mandible itself due to the diminished vasculature and consequent poor medication conveyance to the site. No endeavor ought to be made at first to acquire essential delicate tissue conclusion of bone since most injuries under 1 cm or less will mend in weeks to a long time without careful mediation other than expelling sequestrum.[23] For expansive imperfections in the jaw, medical procedure will be required with bony and delicate tissue remaking with the helper of pre-operative and post-operative HBO. HBO has been shown to be more effective than penicillin. HBO therapy is a mode of treatment in which a patient breathes 100% oxygen intermittently while the treatment chamber's pressure is increased above 1 atmosphere absolute. HBO therapy for radiation damaged tissue was introduced in 1973 by Greenwood and Gilchrist and Mainous *et al*.[24,25] It is known that HBO increases the amount of oxygen in tissue fluids by a 10-fold factor.[26] In addition, the HBO stimulates angiogenesis in the healing tissue. It can produce angiogenesis in previously irradiated tissue.[27] A series of treatment using pentoxifylline, tocopherol, and Vitamin E are sometimes used as an alternative.[28] HBO therapy is a relatively safe treatment. If pressures within the chamber are kept below 3 times of normal atmospheric pressure and if sessions last no longer than 2 h, complications can be minimized.[29] At the end of an HBO session, patients often feel light headed and tired, but more serious problems can occur. Milder problems associated with HBO therapy include claustrophobia (in monoplace chambers), fatigue, and headache. More serious complications include myopia (short-sightedness) that can last for weeks or months, sinus damage, ruptured middle ear, and lung damage. Oxygen toxicity, a major complication, can result in convulsions, fluid in the lungs, and even respiratory failure.[30]

Pentoxifylline and Vitamin E

Pentoxifylline is a tri-substituted methylxanthine derivative chemically designated as 1-(5-oxohexyl)-3,7-dimethylxanthine and is a hemorrheologic agent,

unlike theophylline. Pentoxifylline is a white to creamy white crystalline powder. It is freely soluble in chloroform and methanol, soluble in water, sparingly soluble in ethanol, sparingly soluble in toluene, and slightly soluble in ether. It has a melting point of 104–107°C, within a 3°C range.[31] Pentoxifylline exerts an antitumor necrosis factor-α effect, increases erythrocyte flexibility, vasodilates, inhibits inflammatory reactions *in vivo*, inhibits human dermal fibroblast proliferation and extracellular matrix production, and increases collagenase activity *in vitro*.[32] Pentoxifylline and its metabolites improve blood flow by decreasing its viscosity. Tissue oxygen levels have also been shown to increase significantly with therapeutic doses of pentoxifylline in patients with peripheral arterial disease.[33,34] Pentoxifylline has been used concurrently with antihypertensive drugs, β-blockers, digitalis, diuretics, and antiarrhythmics. If needed, dosage of antihypertensive agents should be reduced.[35] Concomitant administration of pentoxifylline and theophylline-containing drugs leads to increased theophylline levels and theophylline toxicity in some individuals.[36]

Tocopherol

Tocopherols are a class of organic chemical compounds consisting of various methylated phenols, many of which have Vitamin E activity. Tocotrienols are related compounds that also have tocopherol activity. All of these derivatives with vitamin activity may correctly be referred to as "Vitamin E."[37] Tocotrienols have the same methyl structure in its ring and the same Greek letter-methyl-notation but differ from tocopherols due to the presence of three double bonds in the hydrophobic side chain. Whereas tocopherols have three centers and eight possible stereoisomers per structural formula, the unsaturation of tocotrienol tails has only a single stereoisomeric carbon and, thus, two possible isomers per structural formula, one of which occurs naturally.[38] Vitamin E exists in eight different forms, four tocopherols and four tocotrienols. All feature a chromane ring, with a hydroxyl group that can donate a hydrogen atom to reduce free radicals and a hydrophobic side chain that allows for penetration into biological membranes. Each form has different biological activiies; the unnatural l-isomers of tocotrienols lack almost all vitamin activity, and half of the eight possible isomers of the tocopherols, those with 2S chirality at the ring-tail junction, also lack vitamin activity. Both the tocopherols and tocotrienols occur in α (alpha), β (beta), γ (gamma), and δ (delta) forms, determined by the number and position of methyl groups on the chromanol ring.[39]

Mandibular reconstruction

Bony reconstruction of the jaws in cancer-related deformities presents several unique problems that have historically produced low success rates and high morbidity. Large spans of discontinuity, soft tissue deficiency, irradiated tissue, and extreme scarring with bony displacement are some of the more obvious problems. Particular goals of reconstruction are to restore the function of the jaw bone, especially with regard to food processing, swallowing, and intelligible speech production, and to restore the appearance of the lower face.[40] It has been generally accepted that wide, radical resection of necrotic bone with immediate free flap reconstruction is often the only and best option for the treatment of advanced ORN.[41,42] In addition, perioperative adjunctive HBO therapy is often given, although it has not been conclusively proven to be of benefit. Furthermore, it should be realized that ORN affects surrounding soft tissue and is not only a disease of the bone.[43,44] Several free flaps such as the scapula bone flap (in combination with either a parascapular skin island or partial latissimus dorsi muscle), iliac crest flap, or soft tissue only flaps (rectus abdominis and latissimus dorsi myocutaneous flaps) have been used, but the osteocutaneous fibula free flap is generally considered the workhorse flap. Furthermore, the donor-site morbidity is generally minimal and compares favorable to the iliac crest flap.[45] Sometimes, after radical ORN resection, composite through-and-through defects exist, which require a second free flap for the reconstruction of the external skin defect of the lower face or neck. As already mentioned, recipient vessel identification and dissection in a previously operated and irradiated neck can be tedious. It often requires more delicate dissections, sometimes with the aid of a microscope.[46]

Prevention

The patient should have a full dental evaluation. This should include radiographs to show all the teeth as well as the jaws to check for unerupted teeth and any bony pathology. Preventive measures are vital to avoid the need for dental intervention such as extractions and may have led to a significant decline in rates of ORN over the past few decades.[47] However, even with adequate care, the extraction of diseased teeth may become inevitable. A minimal trauma technique is, especially, indicated in the irradiated patient, and therefore, experienced clinicians should perform the procedure. A panoral radiograph should be a minimum, but ideally, periapical views of all the teeth should be taken. All the teeth should be meticulously charted for caries and periodontal pocketing.[48] Each tooth should be given an individual prognosis and a treatment plan completed and discussed with the patient. It is important to educate the patient regarding meticulous oral hygiene and the need for lifelong regular follow-up. All teeth should be cleaned and scaled. The patient should be encouraged to rinse with a fluoride and antibacterial mouthwash on a regular

basis and high-risk patients should have custom trays made to assist in regular fluoride treatment.[49,50] Patients with no teeth are easier to treat but should still have a baseline radiographic evaluation to check for buried teeth. Dentures should be inspected for fitting to ensure minimal trauma to the tissues. The timing of extractions is controversial, but 2–3 weeks before radiotherapy are advised to ensure timely healing. The extractions should be carried out in a non-traumatic manner with minimal damage to the surrounding tissues. Teeth with questionable prognosis should be carefully discussed with the patient. During radiotherapy, the patient will experience mucositis and xerostomia. Regular review with the dentist is essential to minimize discomfort. The xerostomia will cause dryness of the mouth due to lack of saliva, which is essential to wash away debris and dilute the plaque. Regular mouthwashes and meticulous oral hygiene are essential during this period.[51-53]

CONCLUSION

Head and neck cancer patients continue to pose a challenge for surgeons and oncologists. ORN can be a cruel blow to patients and their families who have already had to endure treatment for cancer. Improved radiotherapy protocols, multidisciplinary preventive care, and reconstructive surgery can help to improve the quality of their lives. ORN of craniofacial skeleton is a severe complication of head and neck radiotherapy and may be acute or appear later. Main complications observed were exposure of synthesis material, extraoral fistula, relaxation, and loss of fixation screws. The advantage of the organization of diagnosis and treatment through the protocol established by Marx is in its ability to select those patients who present conditions to undergo less aggressive treatments and less oxygenotherapy sessions, besides preparing patients for reconstruction, thus keeping facial contour and avoiding collapse of cervical-mandibular soft tissues.

REFERENCES

1. Samant S, Kumar P, Wan J, Hanchett C, Vieira F, Murry T, *et al*. Concomitant radiation therapy and targeted cisplatinum chemotherapy for the treatment of advanced pyriform sinus carcinoma: Disease control and preservation of organ function. Head Neck 1999;21:595-601.
2. Robbins KT, Kumar P, Wong FS, Hartsell WF, Flick P, Palmer R, *et al*. Targeted chemoradiation for advanced head and neck cancer: Analysis of 213 patients. Head Neck 2000;22:687-93.
3. Chrcanovic BR, Reher P, Sousa AA, Harris M. Osteoradionecrosis of the jaws--a current overview--part 1: Physiopathology and risk and predisposing factors. Oral Maxillofac Surg 2010;14:3-16.
4. Jones AS, Fish B, Fenton JE, Husband DJ. The treatment of early laryngeal cancers (T1-T2 N0): Surgery or irradiation? Head Neck 2004;26:127-35.
5. Sciubba JJ, Goldenberg D. Oral complications of radiotherapy. Lancet Oncol 2006;7:175-83.
6. Ruggiero SL. Bisphosphonate-related osteonecrosis of the jaw: An overview. Ann N Y Acad Sci 2011;1218:38-46.
7. Spanos WJ, Shukovsky LJ, Fletcher GH. Time dose, and tumor volume relationships in irradioation of squamous cell carcinomas of the base of the tongue. Cancer 1976;37:2591-9.
8. Bagan JV, Jiménez Y, Hernández S, Murillo J, Díaz JM, Poveda R, *et al.* Osteonecrosis of the jaws by intravenous bisphosphonates and osteoradionecrosis: A comparative study. Med Oral Patol Oral Cir Bucal 2009;14:e616-9.
9. Beumer J, Harrison R, Sanders B, Kurrasch M. Osteoradionecrosis: Predisposing factors and outcomes of therapy. Head Neck Surg 1984;6:819-27.
10. Bagan J, Scully C, Sabater V, Jimenez Y. Osteonecrosis of the jaws in patients treated with intravenous bisphosphonates (BRONJ): A concise update. Oral Oncol 2009;45:551-4.
11. Assael LA. New foundations in understanding osteonecrosis of the jaws. J Oral Maxillofac Surg 2004;62:125-6.
12. Epstein JB, Hatcher DC, Graham M. Bone scintigraphy of fibro-osseous lesions of the jaw. Oral Surg Oral Med Oral Pathol 1981;51:346-50.
13. Scarborough WL. Osteoradionecrosis in intra-oral cancer. Am J Roentgenol Radiat Ther 1938;40:524-34.
14. Marx RE. Osteoradionecrosis: A new concept of its pathophysiology. J Oral Maxillofac Surg 1983;41:283-8.
15. Komisar A, Silver C, Kalnicki S. Osteoradionecrosis of the maxilla and skull base. Laryngoscope 1985;95:24-8.
16. Herskind C, Bamberg M, Rodemann HP. The role of cytokines in the development of normal-tissue reactions after radiotherapy. Strahlenther Onkol 1998;174 Suppl 3:12-5.
17. Bensadoun RJ, Magné N, Marcy PY, Demard F. Chemotherapy- and radiotherapy-induced mucositis in head and neck cancer patients: New trends in pathophysiology, prevention and treatment. Eur Arch Otorhinolaryngol 2001;258:481-7.
18. Lyons A, Ghazali N. Osteoradionecrosis of the jaws: Current understanding of its pathophysiology and treatment. Br J Oral Maxillofac Surg 2008;46:653-60.
19. Mainous EG, Hart GB. Osteoradionecrosis of the mandible; treatment with HBO. Arch Otolarynol 1975;101:173-277.
20. Jacobson AS, Buchbinder D, Hu K, Urken ML. Paradigm shifts in the management of osteoradionecrosis of the mandible. Oral Oncol 2010;46:795-801.
21. Delanian S, Lefaix JL. The radiation-induced fibroatrophic process: Therapeutic perspective via the antioxidant pathway. Radiother Oncol 2004;73:119-31.
22. Greenwood TW, Gilchrist AG. Hyperbaric oxygen and wound healing in post-irradiation head and neck surgery. Br J Surg 1973;60:394-7.
23. Mainous EG, Boyne PJ, Hart GB, Terry BC. Restoration of resected mandible by grafting with combination of mandible homograft and autogenous iliac marrow and postoperative treatment with HBO. Oral Surg 1973;35:134-20.
24. Bassett BE, Bennette PB. Introduction to the physical and physiological bases of hyperbaric therapy. In: Davis JC, Hunt TK, editors. Hyperbaric Oxygen Therapy. Bethesda, MD: Undersea and Hyperbaric Medical Society; 1977. p. 11-24.
25. 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.
26. Hunt TK, Zederfeldt BH, Goldstick TK. Oxygen and healing. Am J Surg 1969;118:521-5.
27. Peters E, Lovas GL, Wysocki GP. Lingual mandibular sequestration and ulceration. Oral Surg Oral Med Oral Pathol 1993;75:739-43.
28. Peterson L, Ellis E, Hupp J, Tucker M. Contemporary Oral and Maxillofacial Surgery. Cha. 14. St. Louis: C.V. Mosby Company; 1988. p. 113-5.
29. Kinghton DR, Hunt TK. Regulation of Wound Angiogenesis-Effect of Oxygen Gradients and Inspired Oxygen Concentrations. Hershey (PA): Presented to the Society of University Surgeons; 1981.
30. McLeod NM, Pratt CA, Mellor TK, Brennan PA.

Pentoxifylline and tocopherol in the management of patients with osteoradionecrosis, the portsmouth experience. Br J Oral Maxillofac Surg 2012;50:41-4.
31. Epstein MS, Wicknick FW, Epstein JB, Berenson JR, Gorsky M. Management of bisphosphonate-associated osteonecrosis: Pentoxifylline and tocopherol in addition to antimicrobial therapy. An initial case series. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;110:593-6.
32. Inyang AF, Schwarz DA, Jamali AM, Buchman SR. Quantitative histomorphometric assessment of regenerate cellularity and bone quality in mandibular distraction osteogenesis after radiation therapy. J Craniofac Surg 2010;21:1438-42.
33. D'Souza J, Lowe D, Rogers SN. Changing trends and the role of medical management on the outcome of patients treated for osteoradionecrosis of the mandible: Experience from a regional head and neck unit. Br J Oral Maxillofac Surg 2014;52:356-62.
34. 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.
35. Hutchinson IL. Complications of radiotherapy in the head and neck: An orofacial surgeon's view. In: Tobias JS, Thomas PR, editors. Current Radiation Oncology. London: Arnold; 1996. p. 144-77.
36. Harris M. The conservative management of osteoradionecrosis of the mandible with ultrasound therapy. Br J Oral Maxillofac Surg 1992;30:313-8.
37. Epstein JB, Wong FL, Stevenson-Moore P. Osteoradionecrosis clinical experience and a proposal for classification. J Oral Maxillofac Surg 1987;45:104-10.
38. Balogh JM, Sutherland SE. Osteoradionecrosis of the mandible: A review. J Otolaringol 1989;18:245-50.
39. Chiapasco M, Biglioli F, Autelitano L, Romeo E, Brusati R. Clinical outcome of dental implants placed in fibula-free flaps used for the reconstruction of maxillo-mandibular defects following ablation for tumors or osteoradionecrosis. Clin Oral Implants Res 2006;17:220-8.
40. 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.
41. Buchbinder, D, Hilaire H. The use of free tissue transfer in advanced osteoradionecrosis of the mandible. J Oral Maxillofac Surg 2006;64:961-4.
42. Ang E, Black C, Irish J, Brown DH, Gullane P, O'Sullivan B, *et al.* Reconstructive options in the treatment of osteoradionecrosis of the craniomaxillofacial skeleton. Br J Plast Surg 2003;56:92-9.
43. Chang DW, Oh HK, Robb GL, Miller MJ. Management of advanced mandibular osteoradionecrosis with free flap reconstruction. Head Neck 2001;23:830-5.
44. Yazar S, Wei FC, Chen HC, Cheng MH, Huang WC, Lin CH, *et al.* Selection of recipient vessels in double free-flap reconstruction of composite head and neck defects. Plast Reconstr Surg 2005;115:1553-61.
45. Cordeiro PG, Disa JJ, Hidalgo DA, Hu QY. Reconstruction of the mandible with osseous free flaps: A 10-year experience with 150 consecutive patients. Plast Reconstr Surg 1999;104:1314-20.
46. Sulaiman F, Huryn JM, Zlotolow IM. Dental extractions in the irradiated head and neck patient: A retrospective analysis of memorial sloan-kettering cancer center protocols, criteria, and end results. J Oral Maxillofac Surg 2003;61:1123-31.
47. Hao SP, Chen HC, Wei FC, Chen CY, Yeh AR, Su JL, *et al.* Systematic management of osteoradionecrosis in the head and neck. Laryngoscope 1999;109:1324-7.
48. Beumer J 3rd, Harrison R, Sanders B, Kurrasch M. Preradiation dental extractions and the incidence of bone necrosis. Head Neck Surg 1983;5:514-21.
49. Fowler JF. Is there an optimum overall time for head and neck radiotherapy? A review with new modeling. Clin Oncol (R Coll Radiol) 2007;19:8-22.
50. 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.
51. Reuther T, Schuster T, Mende U, Kübler 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.
52. Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws; American Association of Oral and Maxillofacial Surgeons. American association of oral and maxillofacial surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 2007;65:369-76.
53. Chuang SK. Limited evidence to demonstrate that the use of hyperbaric oxygen (HBO) therapy reduces the incidence of osteoradionecrosis in irradiated patients requiring tooth extraction. J Evid Based Dent Pract 2012;12 3 Suppl:248-50.

Source of support: Nil; Conflict of interest: None Declared