Original Article

Radiation effects in head and neck and role of hyperbaric oxygen therapy: An adjunct to management

ABSTRACT

Background: Radiotherapy is considered an essential treatment modality in cancers, especially head and neck cancers. Radiotherapy can be given as a definitive, supportive, or adjuvant therapy for various cancers. Radiation damage is an avoidable complication in many patients, after or during radiotherapy. It may be either dose-related, duration-related, or frequency-related. The effects of radiation damage are mainly caused by ischemic necrosis, and once settled it is difficult to manage due to the low vascularity of the affected area.

Aim: To find out the effectiveness of hyperbaric oxygen therapy (HBOT) in the management of radiation damage in the head and neck region.

Materials and Methods: Retrospective data of patients attending the HBOT clinic for postradiotherapy changes were recorded in an Excel sheet and analyzed in this study. Statistical analysis was done.

Result: Our study showed that HBOT is effective in postradiation trismus, xerostomia, discharge, foul smell, discharging sinus, etc., However, it was not found to be significant in the closure of fistula with exposed bone.

Conclusion: HBOT is an effective adjunct modality for the management of postradiation changes in the head and neck region.

Keywords: Hyperbaric oxygen therapy, oro-cutaneous fistula, osteoradionecrosis, radiation damage, sub-mucous fibrosis

INTRODUCTION

Radiation therapy is an essential part of the management of many cancers. It may be introduced in various forms, like as an adjuvant, definitive of palliative forms. Effects of radiation therapy develop in reversible or irreversible ischemia and present as unstable scars, discharging sinus, fistula, necrosis, bony infection, osteomyelitis, etc., The occurrence of osteoradionecrosis (ORN) as a sequelae of radiation therapy in head and neck cancer is not very uncommon. ORN may develop during or after the completion of radiotherapy. ORN is associated with devastating complaints like pain, inflammation, inability to feed, malnutrition, dribbling of saliva, reduced mouth opening, poor hygiene, and poor quality of life.[1,2]

Clinical features of ORN include necrosis, ulceration, discharge, sinus, fistula, exposed bone, bone necrosis, trismus, xerostomia, etc., Neurological symptoms include pain, para-aesthesis, dysgeusia, etc., Radiological features include osteolytic areas, sequestrum, pathological fracture, mixed radio-opaque and radiolucent lesions, cortical interruptions, etc., in orthopantomogram. Magnetic resonance imaging shows abnormal marrow signal with cortical destruction and irregular enhancement.[3,4]

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Dental causes of ORN include periodontal disease, repeated trauma induced by ill-fitting dentures, infection following tooth extraction, etc., Hence dental evaluation is a must before starting radiotherapy regimen.[5]

ORN following head and neck cancer: Head and neck cancer is the seventh most common cancer worldwide, with a trend of fifth most common cancer in the male population and twelfth most common cancer in the female population. Incidence is higher in Asia as Asia contributes 57.5% to global head and neck cancer. Among all Asian countries, India has 30% of all head and neck cancers. In India, oral cancer poses a significant burden and it is increasing trends because of various factors like tobacco chewing, consumption of pan masala, smoking, poor awareness, etc., A study by Decker *et al.* documented tobacco as a risk factor in 80–90% of oral cancers.[6,7]

Head and neck cancer can be treated by various modalities, which include surgery, radiotherapy, chemotherapy, immunotherapy, gene therapy, etc., They can be used either individually or in combination. The choice of techniques depends on various factors like tumor factors, patient factors, availability of facilities, financial status, etc., However, definitive margin-free surgery is a widely accepted and well-established treatment modality in suitable cancers. The introduction of radiotherapy and chemotherapy has revolutionized the treatment of oral cancers. It can be used as a primary modality or as an adjuvant modality of treatment. Radiotherapy is considered a major role in the management of head and neck cancer, mostly in the postoperative period. The aim is to prevent recurrence and micrometastasis. Complications following radiotherapy include wound dehiscence, dermatitis, fibrosis, xerostomia, dysphagia, poor oral hygiene, discharging sinus, fistula, exposure of bone, osteomyelitis, ORN, etc.[8]

Owing to the increased availability and use of radiotherapy, the incidence of radiation damage to the tissues has also increased. Mandible is commonly affected bone to undergo radiation necrosis following radiotherapy of head and neck cancers. ORN is a devastating complication of radiotherapy, which often needs a second surgical procedure. However, the severity of the problem depends on the dose, duration, and frequency of radiotherapy. If a patient has received high-dose radiation, the risk of developing ORN persists lifelong.[9]

As the name suggests, hyperbaric oxygen contains oxygen at higher pressure, and hyperbaric oxygen therapy (HBOT) provides 100% oxygen at more than atmospheric pressure, i.e., 1 ATA. Although HBOT was discovered and used very early, in 1620, Drebbel designed a diving bell for HBOT. Later Henshaw designed another chamber called domicilium. In 1928, Orville Cunningham designed another multi-chambered, multi-storied delivery system, which could deliver oxygen at 3 ATA.[10]

A rapid rise in the use of hyperbaric oxygen began in 1937, and it was invented as an effective treatment modality for decompression sickness by Behnke and Shaw. In the modern era, there are numerous indications of HBOT, which are approved by the Undersea and Hyperbaric Medicine Society (UHMS) British Hyperbaric Association. Various indications of HBOT are air embolism, CO poisoning, arterial insufficiencies, Crush injury, compartment syndrome, compromised skin grafts and flaps, necrotizing fasciitis, burn injuries, radiation-induced damage, chronic osteomyelitis, sensory neural hearing loss, etc.

Although HBOT is a relatively safe procedure, there are various contraindications of HBOT, which include untreated pneumothorax, sinus infection, upper respiratory infection, pulmonary lesions on chest X-ray, high fever (>39°C), history of chest or ear surgery, any convulsive disorder, middle ear infection, pregnancy, acute hypoglycemia, etc.[11,12]

HBOT is used by many physicians for the management of ORN since it stimulates angiogenesis and increases neovascularization, fibroblast and osteoblast proliferation, and collagen formation in irradiated tissues. Hence tissues that are compromised as a result of decreased vascularization, diminished oxygen supply, and decreased ability to recover after a minor trauma, such as tooth extraction, are benefitted by HBOT.[13,14]

The role of HBOT in radiation-induced damage or ORN is not widely known due to limited research in this field. Dieleman conducted a study on the use of HBOT in ORN and found that HBOT is an effective modality for the management of ORN.[15]

Another study was done by D'Souza *et al.*[16] on the effect of HBOT on the outcomes of ORN. They also concluded that HBOT is effective in improving outcomes; however, a larger controlled trial is required to draw a definitive conclusion.

Hampson *et al.* conducted a study on 411 patients with chronic radiation-induced damage treated with HBOT. They also found promising results of HBOT. Various other cohort studies also have shown promising results of HBOT, when used for radiation-induced damage, ORN, etc.[17-19]

Our study is a retrospective study done on patients undergoing radiation therapy for various reasons.

MATERIALS AND METHODS

The present study is a retrospective study done in patients with radiation-induced damage, who underwent treatment by HBOT at our institute. Ethical committee approval was obtained from the institute. Ethical clearance ref-2924/ethics/2024, dated 16-01-2024. The study was done from January 2022 to August 2023.

Inclusion criteria: Patients with radiation damage who were treated by HBOT.

Exclusion criteria: Patients with contraindications of HBOT like middle ear pathology.

A total of 42 patients with radiation damage who visited the departmental outpatient department (OPD) and who underwent HBOT were included in the study. The procedure was explained to the patient and attendants. Patients were thoroughly examined to rule out contraindications of HBOT. The presence of any systemic diseases or degenerative diseases affecting hearing was also ruled out. A detailed psychiatric evaluation was done on all patients. Detailed ear including tympanic membrane assessment was done. Fitness for HBOT was obtained in all patients. Informed consent was obtained from all patients for the procedure, photography, as well as publication. Patients were given a trial session of pressure of 1.5 ATA for 15–20 min and were observed for any discomfort. If they tolerated the trial session then regular sessions were started from the next day onward. The pressure of the HBOT chamber was increased gradually from 1.5 ATA to a maximum of 2.5 ATA, depending on their tolerance. The duration of the session was also increased gradually up to 60 min. Patients were subjected to the treatment daily on an OPD basis [Figure 1]. All patients were given HBOT for 12 weeks. Patient data was collected after completion of the therapy. Hospital records, patient files, OPD sheets, telephonic communication, etc., were used to collect data. All data were entered into an Excel sheet for statistical analysis, and the following outcome parameters were analyzed.

- Demographic features like age, gender, etc.
- Presence or absence of comorbidity
- Comparison of pre-HBOT session and post-HBOT session findings (mouth opening, xerostomia, discharge, discharging sinus, oro-cutaneous fistula, foul smell, bone exposure, osteomyelitic changes, requirement of further surgical procedure, etc.).

Figure 1: Patient being shifted to HBOT chamber

RESULT

Statistical analysis

Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA) for Windows program (26.0 version). The continuous variables were evaluated by mean (standard deviation) or range value when required. The dichotomous variables were presented in number/frequency and analyzed using Chi-square or Fisher's Exact test. For comparison of the means between the two groups, analysis by Student's *t*-test with a 95% confidence interval was used. A *P*- value of <0.05 or 0.001 was regarded as significant.

Age: A total of 42 patients were treated by HBOT who underwent radiotherapy for various causes. Most of the patients (61.90%) belonged to the elderly age group, between 49 and 57 years [Figure 2].

Gender: Most of the patients in our study were males (71.43%) as compared to females (28.57%). Sex preponderance also correlates with the increased incidence of head and neck cancer in the male population leading to exposure to radiation [Figure 3].

Chemoradiotherapy: Out of 42 patients, 24 patients underwent chemotherapy, however, 41 out of 42 patients underwent radiotherapy prior. One patient who did not undergo radiotherapy developed mandibular necrosis as a result of wound dehiscence and an exposed implant was used for mandibular fixation during tumor resection.

Comorbidity status, diabetes mellitus, hypertension:

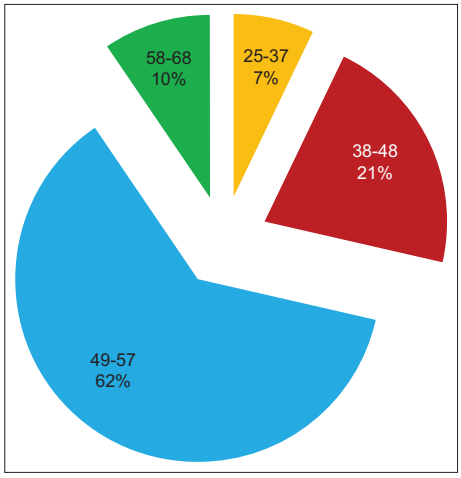

Figure 2: Age distribution among cases

Comorbidity was not found to be associated significantly. Only 10 patients had diabetes mellitus, however, only 10 patients had hypertension [Figure 4].

Duration of complaints: Duration of complaints was recorded in weeks as mean ± SD. Patients presented at 4.86 ± 1.96 weeks for HBOT [Table 1].

Mouth opening

Mouth opening was measured by finger insertion method. In all patients, pre-session mouth opening was recorded. Out of 42 patients, 34 patients presented with an associated complaint of reduced mouth opening of less than 3 finger breadth (80.95%). Post-session mouth opening was recorded in all patients. Most of the patients showed satisfactory improvement in mouth opening during and after completion of HBOT. The pre and post-session assessments yielded significant improvements in mouth opening (Finger) from a mean of 1.81 ± 0.85 to 2.68 ± 0.55 ($t = 5.569$, $P < 0.0001$) [Figure 5].

Xerostomia: Xerostomia was also one of the major associated complaints in many patients. HBOT was found to be effective in improvement of xerostomia in most of the patients. Pre and post-HBOT xerostomia were compared. None of the patients complained of xerostomia after HBOT, and the results were found to be significant, with a *P*- value <0.05.

Discharge from the wound: Most of the patients complained of discharge, either serous, seropurulent, or saliva, from their wound, at the time of presentation. Discharge was found to be reduced in all the patients undergoing HBOT. Hence HBOT was found to be highly effective in the prevention of post-radiation discharge. *P* value was found to be highly significant, i.e. <0.0001.

Foul smell: Out of 42 patients, 34 patients presented with complaints of foul smell from the mouth due to reduced mouth opening and persistent discharge. Foul smell from the mouth was relieved in all patients after completion of HBOT, and the *P*- value was found to be <0.0001.

Table 1: Demographic and clinical details of the patients

	Number	Percentage
Age (years)		
25–37	3	7.14
38–48	9	21.43
49–57	26	61.90
58–68	4	9.52
Gender		
Female	12	28.57
Male	30	71.43
Chemotherapy		
No	18	42.86
Yes	24	57.14
Radiotherapy		
No	1	2.38
Yes	41	97.62
Diabetes		
No	32	76.19
Yes	10	23.81
HTN		
No	32	76.19
Yes	10	23.81
Duration of complaints (weeks)		
Mean±SD	4.86±1.96	

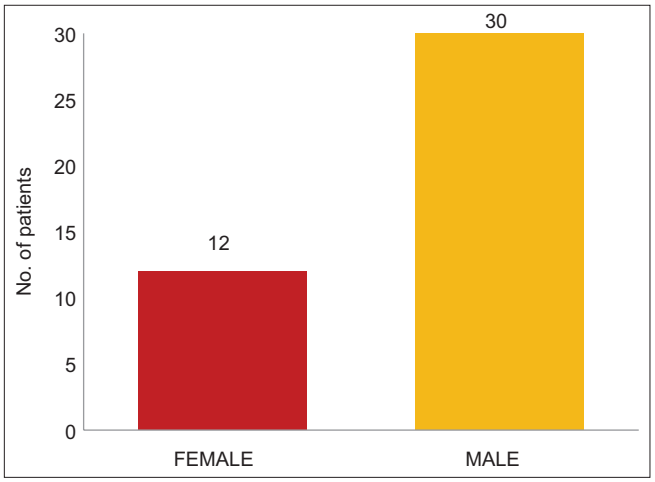

Figure 3: Gender distribution among cases

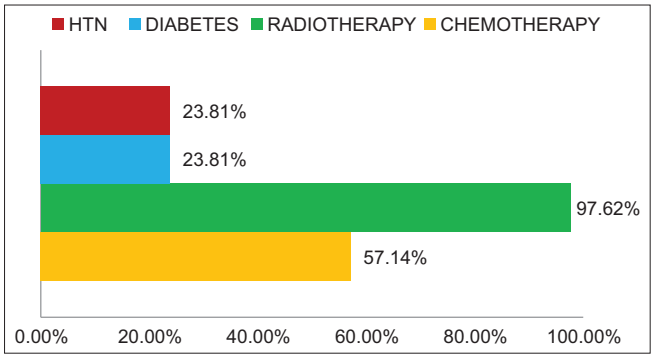

Figure 4: Comorbidities and chemoradiotherapy among cases

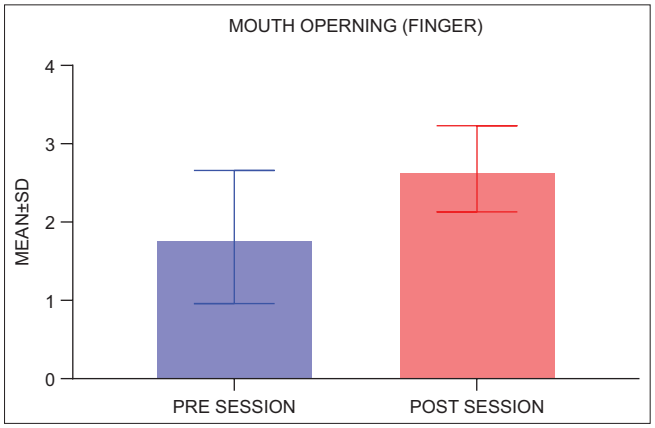

Figure 5: Pre and post-HBOT mouth opening

Discharging sinus: Discharging sinus was found to be present in 33 patients, and in all patients, sinus was found to be either reduced or absent. On comparison of pre-HBOT and post-HBOT, discharging sinus was found to be highly improved, $P < 0.0001$.

Oro-cutaneous fistula: A total of 27 patients (64.28%) presented with complaints of oro-cutaneous fistula before HBOT. Although patients showed clinical improvement after HBOT, the *P*- value was not significant and many patients required further procedures for fistula closure.

Exposed bone: In our study, 20 patients had bone exposure at the time of presentation. In a few patients, HBOT reduced the size of exposed bone, but a complete reduction of bone exposure was not seen in any patient. They required further surgical procedures to cover the bone [Figure 6].

Radiological bony findings: Osteomyelitic changes were found in 19 patients on orthopantomogram (OPG). Although few patients showed improvement, the results were not found to be significant [Table 2].

Complications of HBOT: None of the patients reported complications after HBOT.

DISCUSSION

HBOT is known to cause increased vascularity, which reduces ischemic damage to the tissues. Marx 1990 assessed the angiogenic properties of normobaric oxygen (100% oxygen at 1 ATA for 90 min daily) and hyperbaric oxygen (100% oxygen at 2.4 ATA for 90 min daily for 20 days), as compared with air-breathing controls. Results indicated that normobaric oxygen had no angiogenic properties above the normal revascularization of irradiated tissue than air-breathing controls ($P = 0.89$). Hyperbaric oxygen demonstrated an eight-to-nine-fold increased vascular density over both normobaric oxygen and air-breathing controls.[20]

A study done by Kivisaari and Niinikoski[21] suggested that HBOT might be of benefit in chronic ulcers, complicated wounds, and non-healing diabetic ulcers. Apart from chronic wounds, HBOT is shown to be effective in various other situations like failing flaps and grafts, burns, etc.[22,23]

In many cancers of the head and neck, radiotherapy plays an integral role. However, apart from damaging cancerous cells, radiation damage to normal cells is a universal complication associated with radiotherapy. ORN is a serious complication of radiotherapy and should always be considered based on risk versus benefit principle. ORN was first described in 1922 by Regaud. He described osteoradionecrosis as post-radiation exposed bone for 3 months in the absence of residual or recurrent tumor.[20]

Later Ewing, in 1974, used the term "radiation osteitis," which was later named "septic osteoradionecrosis" by Guttenberg in 1974. Later Marx gave a detailed and complete

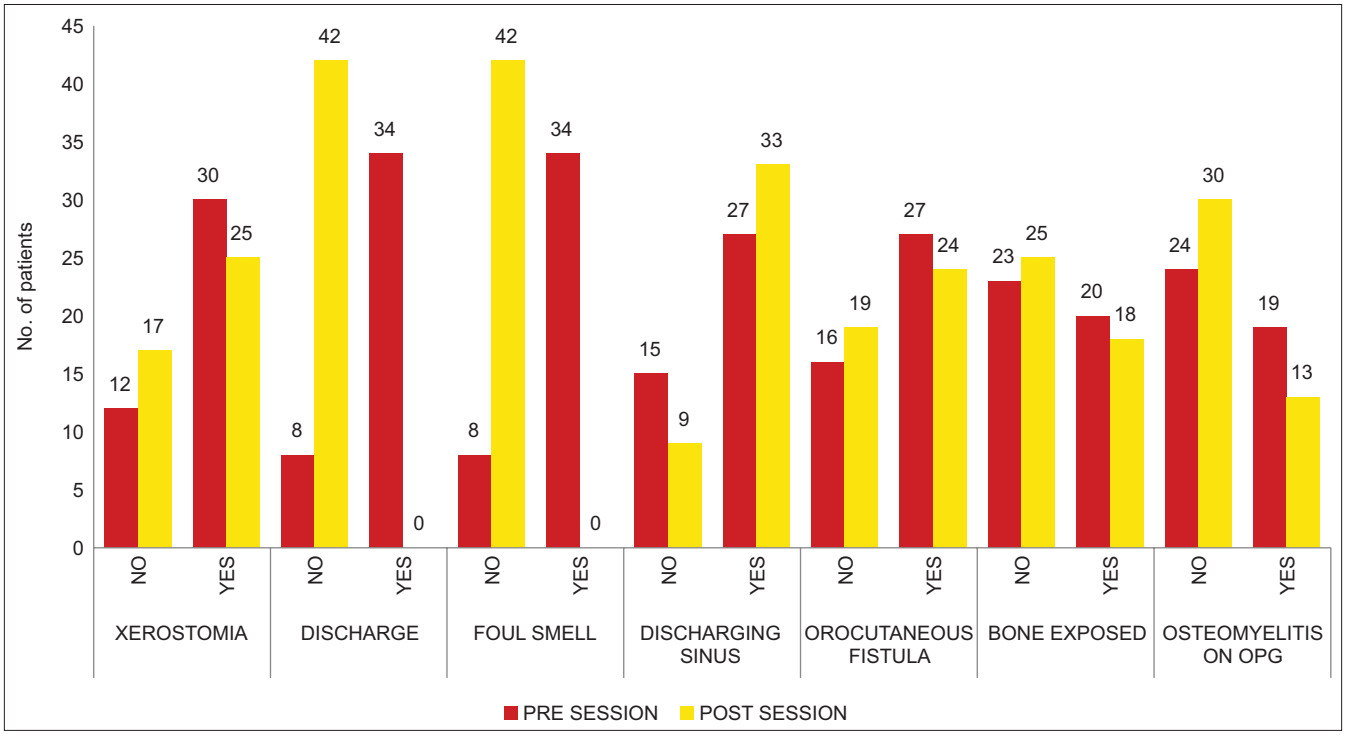

Figure 6: Comparison of various parameters, before and after HBOT

Table 2: Clinical outcomes with statistical analysis

	Pre-session		Post-session		*P*
	Mean	SD	Mean	SD	
Mouth opening (finger)	1.81	0.85	2.68	0.55	t=5.569, P<0.0001*
Xerostomia					
No	12	28.57%	42	100.00%	χ=41.317, P<0.05
Yes	30	71.43%	0	18.52%	
Discharge					
No	8	19.05%	42	100.00%	χ=57.12, P<0.0001*
Yes	34	80.95%	0	0.00%	
Foul smell					
No	8	19.05%	42	100.00%	χ=57.12, P<0.0001*
Yes	34	80.95%	0	0.00%	
Discharging sinus					
No	10	23.80%	42	100.00%	χ=44.716, P<0.0001*
Yes	33	76.19%	0	0.00%%	
Orocutaneous fistula					
No	16	37.21%	19	44.19%	χ=0.4336, P=0.5102
Yes	27	62.79%	24	55.81%	
Bone exposed					
No	23	53.49%	25	58.14%	χ=0.1886, P=0.6641
Yes	20	46.51%	18	41.86%	
Osteomyelitis on OPG					
No	24	55.81%	30	69.77%	χ=1.792, P=0.1807
Yes	19	44.19%	13	30.23%	

*Values are significant

definition of ORN, according to him, "a nonhealing wound of more than 6 month duration with exposure of more than 1 cm of bone" is known as ORN.[24]

Although the exact etiology and pathogenesis of radiation damage are not known, several factors like hypoxia, apoptosis, tissue ischemia, radiation arteritis, and reduced wound healing contribute to its occurrence. Intraoral exposure of bone was first noted by Epstein *et al.*[25] According to him a discontinuity in the mucous membrane with exposed bone for more than 3 months is known as ORN.

ORN is almost always associated with radiological findings. Many times bony changes are present, even in the absence of exposed bone. Hence it is not necessary for ORN to always have exposed bone. In 2000, Store and Boysen described the diagnostic criteria for ORN. According to them presence of bony erosion is always associated with ORN, and is a confirmatory feature, even in the absence of exposed bone.[26]

According to previous literature, the definition of ORN may be defined as "post radiation chronic wound with ischaemic changes in bone, with or without exposure of bone for more than three months." Since the occurrence of ORN is multifactorial and largely dependent on dose, duration, exposed area, etc., its prevalence is wide and ranges between 4% and almost 56%. The most common age presenting with ORN is the elderly age group, more than 55 years of age. In our study also most common presentation was the elderly age group.[27,28]

Watson *et al.*[27] reported that approximately 20% of patients of ORN, who do not respond to conservative management, are found to have either tumor recurrence or a second primary tumor responsible for ORN. However, in our study, none of the patients showed either recurrence or second primary on histopathological examination.

Classification of ORN: Various classifications have been proposed to date for ORN, which divides ORN into minor and major or minor moderate major. However, these classifications are largely subjective and observer-biased.[29,30]

The staged classification of ORN, given by Marx, in 1983 appears to be more accurate. Stage 1 defines ORN with the exposed bone for at least 6 months, without cutaneous fistula, osteolysis of the mandible, or pathological fracture. Stage 2 ORN includes the features of Stage 1 along with bony resorption and necrosis. Stage 3 includes ORN with a large amount of bony necrosis, cutaneous fistula, pathological fracture, etc., In their study, most of the patients responded well to HBOT, however, Stage 2 patients required minor

surgical procedures like debridement, tooth extraction, wound closure, etc., along with HBOT. Stage 3 patients require major surgical procedures along with HBOT.[31]

Another classification was introduced by Clayman L.[31] They divided ORN into two types, type 1 and type 2. Type 1 includes ORN with intact gingiva, whereas type 2 includes ORN with mucosal defect causing secondary contamination. According to them most cases of type 1 respond to conservative management, whereas cases of type 2 require surgical intervention.

The most recent classification, which includes both clinical as well radiological findings, was given by Schwartz and Kagan[32] and Notani *et al*.[33] According to them, Grade 1 ORN is limited to the alveolar bone, and Grade 2 ORN extends up to the mandible, above the level of mandibular alveolar canal. Grade 3 ORN involves extension above the level of mandibular alveolar canal, with or without pathological fracture and skin fistula.

CONCLUSION

Post-radiation changes are devastating complications of radiotherapy. HBOT is found to be effective in improvement of post-radiation changes like mouth opening, xerostomia, discharge, foul smell, discharging sinus, etc., However, it was not found to be significant in the closure of fistula with exposed bone.

Abbreviations

- HBOT = Hyperbaric oxygen therapy
- ORN = Osteoradionecrosis
- Competing interest = None of the authors have competing interests.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Nabil S, Samman N. Incidence and prevention of osteoradionecrosis after dental extraction in irradiated patients: A systematic review. Int J Oral Maxillofac Surg 2011;40:229–43.
2. 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.
3. Niebel HH, Neeman EW. Dental aspects of osteoradionecrosis. Oral Surg Oral Med Oral Pathol 1957;10:1011-24.
4. Epstein JB, Wong FLW, Dickens A, Szasz I, Lepawsky M. Bone and gallium scans in postradiotherapy osteonecrosis of the jaw. Head Neck 1992;14:288-92.
5. Margalit DN, Losi SM, Tishler RB, Schoenfeld JD, Ann Fugazzotto J, Stephens J, *et al.* Ensuring head and neck oncology patients receive recommended pretreatment dental evaluations. J Oncol Pract 2015;11:151–4.
6. Decker AM, Taichman LS, D'Silva NJ, Taichman RS. Periodontal Treatment in Cancer Patients: An Interdisciplinary Approach. Curr Oral Health Rep 2018;5:7-12.
7. Kulkarni MK. Head and neck cancer burden in India. Int J Head Neck Surg 2013;4:29–35.
8. Shah JP. Current concepts in management of oral cancer – surgery. Oral Oncol 2009;45:394–401.
9. Kojima Y, Yanamoto S, Umeda M, Kawashita Y, Saito I, Hasegawa T, *et al*. Relationship between dental status and development of osteoradionecrosis of the jaw: A multicenter retrospective study. Oral Surg Oral Med Oral Pathol Oral Radiol 2017;124:139–45.
10. Sahni T, Hukku S, Jain M, Prasad A, Prasad R, Singh K. Recent advances in hyperbaric oxygen therapy. Medicine update. Assoc Physicians India 2004;14:632–9.
11. Camporesi EC, editor. Current Diseases Approved for Treatment, Hyperbaric Oxygen Therapy: A Committee Report. Undersea and Hyperbaric Medical Society UHMS.
12. Doctor N, Pandya S, Supe A. Hyperbaric oxygen therapy in diabetic foot. J Postgrad Med 1992;38:112–4.
13. Bennett MH, Feldmeier J, Hampson NB, Smee R, Milross C. Hyperbaric oxygen therapy for late radiation tissue injury. Cochrane Database Syst Rev 2016;2016:CD005005.
14. 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.
15. Dieleman FJ, Phan TTT, van den Hoogen FJA, Kaanders JHAM, Merkx MAW. The efficacy of hyperbaric oxygen therapy related to the clinical stage of osteoradionecrosis of the mandible. Int J Oral Maxillofac Surg 2017;46:428–33.
16. 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.
17. Hampson NB, Holm JR, Wreford-Brown CE, Feldmeier J. Prospective assessment of outcomes in 411 patients treated with hyperbaric oxygen for chronic radiation tissue injury. Cancer 2012;118:3860–8.
18. Curi MM, Dib LL, Kowalski LP. Management of refractory osteoradionecrosis of the jaws with surgery and adjunctive hyperbaric oxygen therapy. Maxillofac Surg 2000;29:430–4.
19. 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.
20. Marx RE. Radiation injury to tissue. In: Kindwall EP, editor. Hyperbaric Medicine Practice. Flagstaff, AZ: Best, 1994. p. 447–503.
21. Kivisaari J, Niinikoski J. Effects of hyperbaric oxygen and prolonged hypoxia on the healing of open wounds. Acta Chir Scand 1975;141:14–9.
22. Zamboni WA, Roth AC, Russell RC, Nemiroff PM, Casas L, Smoot EC. The effect of acute hyperbaric oxygen therapy on axial pattern skin flap survival when administered during and after total ischemia. J Reconstr Micro 1989;5:343.
23. Korn HN, Wheeler ES, Miller TA. Effect of hyperbaric oxygen on second degree burn wound healing. Arch Surg 1977;122:732–7.
24. Teng MS, Futran ND. Osteoradionecrosis of the mandible. Curr Opin Otolaryngol Head Neck Surg 2015;13:217-21.
25. Epstein JB, Rea G, Wong FL, Spinelli J, Stevenson-Moore P. Osteonecrosis-study of the relationship of dental extractions in patients receiving radiotherapy. Head Neck Surg 1987;10:48-54.
26. Store G, Boysen M. Mandibular osteoradionecrosis: Clinical behavior and diagnostic aspects. Clin Otolaryngol 2000;25:378-84.

27. Watson WL, Scarborough JE. Osteoradionecrosis in intraoral cancer. Am J Roentgenol1938;40:524-34.
28. Grötz KA, Riesenbeck D, Brahm R, Seegenschmiedt MH, al-Nawas B, Dörr W, *et al*. Chronic radiation effects on dental hard tissue (radiation caries). Classification and therapeutic strategies. Strahlenther Onkol 2001;177:96-104.
29. Coffin F. The incidence and management of osteoradionecrosis of the jaws following head and neck radiotherapy. Br J Radiol 1993;56:851-85.
30. Morton ME, Simpson W. The management of osteoradionecrosis of the jaws. Br J Oral Maxillofac Surg 1986;24:332-41.
31. Clayman L. Management of dental extractions in irradiated jaws: A protocol without hyperbaric oxygen therapy. J Oral Maxillofac Surg 1997;55:275-81.
32. Schwartz HC, Kagan AR. Osteoradionecrosis of the mandible: Scientific basis for clinical staging. Am J Clin Oncol 2012;25:168-71.
33. 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.