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Review

Hyperbaric oxygen in the management of late radiation injury to the head and neck. Part II: prevention

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Abstract

Osteoradionecrosis (ORN) of the jaws is a feared complication of treatment for head and neck cancer, and understandably much attention has been given to its prevention; good oral hygiene, careful preventative dental care, and extractions done before radiotherapy have been highlighted by many authors. Such necessary dental extractions when the healing capacity of the bone is normal will, it is hoped, reduce the incidence of subsequent ORN. This review considers the optimal dental management of patients before radiotherapy as well as the evidence base for treatment with hyperbaric oxygen (HBO) before extractions in patients who have had radiotherapy.

Keywords: Osteoradionecrosis; Dental extraction; Hyperbaric oxygen; Randomised controlled trials

Minimising the risks of ORN before cancer treatment

Preoperative dental assessment

With the advent of the NICE guidelines[1] for the management of head and neck cancer in 2004, the inclusion of a consultant in restorative dentistry and oral rehabilitation was advocated to assist in the management of these complex patients. Effective integration of consultant specialists before, during, and after active cancer treatment should be the aim for modern head and neck cancer practice to ensure optimal outcomes for patients. Every dentate patient with head and neck cancer should have a preoperative dental assessment with input from the restorative consultant where decision making on the dentition is not clear-cut. Ideally, this assessment should be done before admission for general anaesthetic assessment, examination under anaesthetic, or surgical treatment, as dental extractions should be done early in the treatment pathway to maximise the length of time for healing before the commencement of radiotherapy. Where possible, patients are seen before examination under anaesthetic, particularly for oropharyngeal cases where chemoradiation is being considered as a possible primary treatment. The majority of other dental extractions are done at the time of primary surgery, thus allowing approximately six weeks for the socket to heal before the commencement of radiotherapy.

Decision making protocol

There are several published papers that explore decision making protocols for dental extractions in head and neck cancer, including the suggestion of complex tooth-by-tooth algorithms.[2]

We have approached the assessment in a tripartite way with consideration of general factors associated with the patient,

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Fig. 1. Severe radiation caries. The dentition was in excellent condition before cancer treatment but is now at serious risk of osteoradionecrosis after extractions.

dental factors, and those associated with the tumour and its treatment.

General factors concerning the patient are extremely important when considering an extraction protocol. Factors such as smoking and alcohol misuse are risks for dental and periodontal disease. After radiotherapy (particularly chemoradiotherapy), salivary hypofunction magnifies these effects and often leads to rapid deterioration in the dentition (Fig. 1). The patient's motivation is also of prime importance if functional dentition is to be effectively maintained after radiotherapy. Dental follow-up studies have shown that among this patient population many do not attend the dentist after treatment. In one study[3] of 334 dentate patients 51% were lost to follow-up within 7 months of completing radiotherapy. Unfortunately many patients also present with high levels of dental anxiety and phobia, and almost 50% are not currently registered with a primary care dental practitioner. This single factor is highly likely to predict future problems, and is an indication for management of the dentition in conjunction with cancer treatment. The wishes and desires of the patient also fall into this category and may have some influence on the overall pattern of extractions proposed.

The common indications for dental extraction in this group of patients have been well described,[4] and for many the choice is obvious (Table 1). Teeth with serious dental disease and those where there is considerable doubt about their future prognosis, should be removed. Teeth that are likely to be non-functional or inaccessible after other extractions, or because of the effects of cancer treatment should also be removed to reduce the future burden of care for patients and their dentists.

Table 1
Dental factors indicating removal.

Indications for dental extraction
Gross caries
Retained roots
Teeth with apical pathology
Mobile teeth
Teeth associated with tumour
Periodontally involved teeth
Non-functional teeth
Teeth close to osteotomy cuts
Inaccessible teeth
Prophylactic removal for other reasons

Factors associated with staging of the presenting tumour, its biological aggression, subsequent management (surgery, radiotherapy, chemotherapy), as well as the overall prognosis for the patient have major implications for the plan of dental intervention. Patients with a limited prognosis should not generally be subjected to radical dental intervention unless the presenting condition is extremely poor. In general terms, if cure is unlikely then symptomatic teeth only, or those with a very poor prognosis should be extracted.

On the whole, where treatment is with curative intent, management of the dentition needs to take into account the site and stage of the tumour. The use of the concept of the shortened dental arch as initially described by Witter et al.[5] is a useful approach.

The hypothesis that much ORN could be prevented by dental care before radiotherapy has been challenged. Chang et al.[6] reported on the dental management of 413 patients undergoing radiotherapy to the oral cavity and oropharynx. Their clinical findings are less positive in regard to extractions before radiotherapy. Although this is a non-randomised retrospective case series with many potential sources of bias, those patients having extractions before irradiation were not found to have a lower risk of ORN than those treated expectantly. Those with poor teeth in the field of radiation who had extractions before radiotherapy had a higher incidence of ORN (16%) than those who did not have extractions (6%). Even for patients with healthy teeth in the radiation field, the 5-year incidence of ORN in those who had extractions before radiation was 15% compared with 2% for those who did not have extractions. The incidence of ORN was very high (28%) in those having brachytherapy, or radiotherapy over 70 Gy (10%); some would comment that subjecting the mandible to either of these is unnecessary in modern head and neck practice. However, this study adds weight to a rather nihilistic view that those with poor dental health or who have extractions may have a high risk of ORN irrespective of the timing of the treatment. This evidence highlights the fact that many patients remain at high risk despite our best efforts, and effective treatments to prevent ORN are needed.

Even with the best possible dental advice before cancer treatment, there are always patients whose dental condition deteriorates to the point that they require extractions. Survival in oral cancer is in excess of 55%,[7] and many survivors will live for several decades during which their risk of ORN does not diminish. The chances of "at risk" surgical procedures such as dental extractions or placement of implants are serious for these long-term survivors.

Next we consider the evidence base for the use of hyperbaric oxygen (HBO) with an emphasis on a critical appraisal of evidence from existing clinical trials.

Randomised controlled trials in the prevention of ORN

Marx et al. published the only randomised controlled trial of HBO in the preventative setting in 1985.[8] Seventy-four

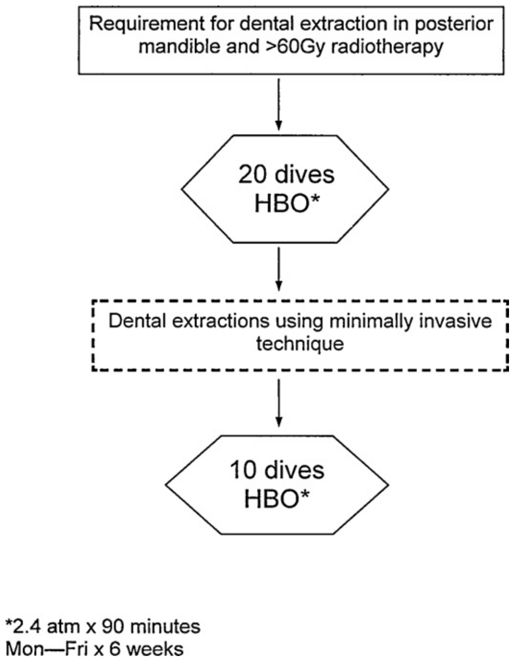

Fig. 2. Hyperbaric oxygen protocol used for the prevention of osteoradionecrosis in the irradiated mandible requiring dental extractions (after Marx et al.[8]).

patients were randomised equally into two arms, one according to the protocol in Fig. 2 with 20 and 10 HBO dives, and the "control" arm with 10 days of penicillin. No details of the methods of randomisation or stratification were mentioned. The potentially attractive experimental arm both with antibiotics and HBO was not employed. The primary endpoint was a clinical diagnosis of ORN that was defined as the presence of exposed bone in the study socket after 6 months. The trial was carried out in three centres, although it is not clear how the diagnosis was standardised. If any observers were blinded to the selected arm it was not mentioned. In the group treated with penicillin, the rate of ORN was 30%/patient and 23%/extraction socket. In the HBO group the corresponding rates were 5%/patient and 3%/socket. The excess incidence of ORN in the penicillin arm was significant ($p = 0.005$), and the number who needed to be treated with HBO to prevent a single case of ORN was four. In the 11 cases of ORN in the penicillin group, three resolved at stage II in the Wilford Hall protocol[9] and required transoral alveolar sequestrectomy, but eight resolved at stage III and required more aggressive resection. Both cases of ORN in the HBO arm resolved at stage II. Based on these limited data the authors stated that the severity of ORN was greater in the penicillin arm, and their simple health economics assessment found in favour of prophylactic HBO in this setting. In a retrospective cohort without randomisation, Vudiniabola et al.[10] showed that one of 29 patients (3%) who were given HBO before extraction, and one of seven (14%) who were not, developed ORN. On the basis of these studies, many dentists and surgeons have prescribed prophylactic HBO to prevent ORN in patients having extractions after radiotherapy. Prophylactic treatment with HBO has become the "treatment of choice"; the "optimum management" for the prevention of ORN.[11–13]

Despite this simple and convincing trial, many clinicians seem either unwilling or unable to prescribe HBO before extraction in irradiated patients. A postal questionnaire[15] of UK practice showed that, in the management of an "at risk" extraction of a lower molar in an irradiated mandible, 33% "never", 41% "sometimes", and 26% "usually" or "always" prescribe prophylactic HBO. This highlights the current state of equipoise in the UK, with expert opinion remaining undecided on the need for HBO.[16] Questionnaires about attitude to randomised controlled trials for HBO[14] showed that 93% of responders would wish to recruit such patients into a national trial with an appropriate infrastructure and governance. Nearly 25 years since Marx's landmark paper, why does such controversy remain?

Treatment with HBO is a time-consuming and relatively costly process (more than £3000 /course of 30 dives, excluding patients' costs such as transport and loss of income). The typical protocol calls for 30 h of preoperative treatment in twenty 90-min sessions in a hyperbaric chamber, followed by 15 h of postoperative treatment in ten 90-min sessions. A doctor, medical assistant, and technical staffs are required for each session, and there are risks associated with the treatment. One study of 90 HBO patients[17] recorded serious adverse events including seizure (3%), stroke (1%), and myocardial infarction (1%). There were also cases of Eustachian tube dysfunction that required myringotomy (2%). The overall incidence of complications was 8%. Subsequent series have, however, reported lower complication rates, and this impression has been confirmed by more reassuring safety data from the British Hyperbaric Association. The most comprehensive recent review[10] cited 33 research papers and estimated that the risks were temporary visual problems ("common"), Eustachian tube problems (2%), claustrophobia (2%), and seizure (<0.01%); myocardial infarction and stroke were not considered to be risks. Transient visual disturbance because of the temporary increase in the refractive index of the lens occurred in 34%[11] of patients treated at 2.4 atm, although recovery was complete. There is a theoretical risk of decompression sickness if decompression is not controlled, and a risk of explosion both from the oxygen-rich environment of the hyperbaric chamber and the pressure of the chamber itself. With modern and accredited HBO chambers, these complications are fortunately very rare indeed.In addition to the potential for adverse events associated with HBO, retrospective evidence gives contradictory data regarding any protective benefits. Sulaiman et al.[18] reviewed a series of 180 consecutive dental extractions without the use of HBO in a 3-year period among the irradiated population of Memorial Sloan-Kettering. They reported only four cases of ORN (2%), although it is important to note that the favourable socioeconomic profile, oral hygiene, and compliance of that particular population is likely to be atypical of the general population with squamous cell carcinoma of the head and neck. This issue with retrospective series is recurrent; the numerator

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(that is some cases of ORN following extraction) may be defined with certainty. It is less clear how many cases they are selected from, and to what extent this denominator is skewed from the overall population who need extractions after radiotherapy by prevailing factors in that institution. A simple pooling by Wahl[19] of eight published retrospective studies of dental extractions without HBO from 1986–2005 found 16 cases of ORN from 461 extractions (4%), and advised that prophylactic HBO should be reconsidered. Further randomised trials are needed to clarify this issue.

The incidence of ORN among patients who have had radiotherapy is not certain, but may have declined[20] with the improvement in radiotherapy techniques in recent decades. The most recent changes in the delivery of radiotherapy, in particular the rise in the popularity of organ preservation, concomitant chemoradiotherapy, and intensity-modulated radiotherapy (IMRT) may effect the rate of ORN in future.[21] Previous reliance on megavoltage and cobalt units resulted in high accumulated doses to the facial skeleton, which may explain the very high incidence of ORN after extraction that was seen in the study by Marx et al.[8] An incidence of 30% ORN has rarely been reported since this paper, and this may be one of the most important factors serving to reduce the impact of this trial on modern practice. Another factor in the reduction of overall risk over the last few decades may be the greatly reduced enthusiasm for the use of primary radiotherapy or chemoradiotherapy in cancers of the oral cavity. Even within the "halo effect" of clinical trials by the few remaining enthusiasts for primary non-surgical management of oral cancer, the incidence of ORN remains unacceptably high. In a 2009 report that accumulated 38 such patients treated by IMRT, 20% of those who completed treatment and survived developed spontaneous ORN.[22] The standard of care for locally advanced oral cancer now constitutes primary surgery, simultaneous microvascular free-flap reconstruction, and postoperative radiotherapy in selected cases.[7] In such series the overall rates of ORN seem to be around 5%,[23] but this incidence is not known with certainty. Further trials based on intention to treat with HBO would also give a valuable guide to the magnitude of risk caused by modern protocols of radiotherapy.

HBO and the placement of implants in the irradiated field

With regard to the placement of implants, the case for HBO is made both on the basis of ORN, and a potential beneficial effect on implant survival. Schoen et al.[24] reported on 26 patients, 13 of whom were given HBO. In the HBO group loss of implants was actually higher (15% compared with 6%) and there was one case of ORN. In contrast, Granström[25,26] reported in a case-controlled study of irradiated bone that HBO significantly improved survival of implants from 34 losses out of 43 implants to 5 losses out of 42 ($p = 0.008$). Further work by Granström that reinforced these earlier data found that treatment with HBO reduced the rate of implant failure. His work seems to suggest more evidence for the use of HBO in extraoral sites in the head and neck before placement of implants in than in intraoral sites.

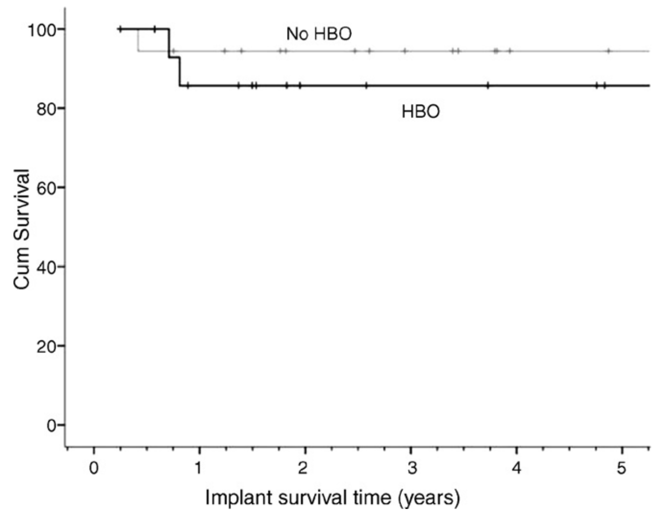

Fig. 3. Shaw et al.[27] series with implant cohorts with and without hyperbaric oxygen (HBO). Five-year survival of implants without HBO (94%), and with HBO (86%). Kaplan–Meier analysis ($p = 0.21$).

A published retrospective series[27] of 364 osseointegrated implants placed intraorally in 77 head and neck cancer patients was done with loss of implants, and ORN as endpoints. As the unit's standard practice changed halfway through the series because of the availability of funding for HBO, the cohort was divided into two subgroups with radiotherapy available for comparison; those treated with, and those treated without HBO. The use of radiotherapy before placement, notably, was *not* associated with a higher rate of implant loss ($p = 0.34$). Loss of implants was not influenced by HBO (19% were lost by patients treated with, and 18% by those treated without HBO, $p = 0.21$) as shown in Fig. 3. Potential confounding variables between the groups were explored but were not biased. ORN was seen in two patients (6%), which is probably typical of similar patients managed without implants with comparable doses of radiotherapy.[28] In this series both cases of ORN occurred in patients treated with HBO, although numbers are small and prescription bias is possible.

Summary

Recent Cochrane reviews[29] and Scottish Intercollegiate Guidelines Network (SIGN) guidelines[30] have urged the need for greater quality research into the value of HBO for the prevention of ORN of the jaws. In particular, the paucity of randomised trials carried out in the modern era is notable. Without doubt, improved dental management of head and neck patients remains a priority, but clinicians will continue to be faced with decisions about failing dentitions in irradiated fields. Resources should be diverted into the generation of better evidence to inform these difficult decisions.

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Conflict of interest

RJS is Chief Investigator on CR-UK HOPON trial and UK Principal Investigator on DAHANCA-21 trial. CB is a co-investigator on CR-UK HOPON trial.

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