



UNIVERSITY OF LEEDS

This is a repository copy of *Hyperbaric oxygen treatment of mandibular osteoradionecrosis: Combined data from the two randomized clinical trials DAHANCA-21 and NWHHT2009-1*.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/180909/>

Version: Accepted Version

---

**Article:**

Forner, LE, Dieleman, FJ, Shaw, RJ et al. (16 more authors) (2021) Hyperbaric oxygen treatment of mandibular osteoradionecrosis: Combined data from the two randomized clinical trials DAHANCA-21 and NWHHT2009-1. *Radiotherapy and Oncology*. ISSN 0167-8140

<https://doi.org/10.1016/j.radonc.2021.11.021>

---

© 2021, Elsevier. This manuscript version is made available under the CC-BY-NC-ND 4.0 license <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

**Reuse**

This article is distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs (CC BY-NC-ND) licence. This licence only allows you to download this work and share it with others as long as you credit the authors, but you can't change the article in any way or use it commercially. More information and the full terms of the licence here: <https://creativecommons.org/licenses/>

**Takedown**

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing [eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk) including the URL of the record and the reason for the withdrawal request.



[eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk)  
<https://eprints.whiterose.ac.uk/>

## **Hyperbaric oxygen treatment of mandibular osteoradionecrosis: Combined data from two randomized clinical trials.**

\*Lone E Forner<sup>1,2</sup>, \*Francois Dieleman<sup>3,4</sup>, Richard J Shaw<sup>5</sup>, Anastasios Kanatas<sup>6</sup>, Christopher J Butterworth<sup>7</sup>, Göran Kjeller<sup>8</sup>, Jan Alsner<sup>9</sup>, Jens Overgaard<sup>9</sup>, Søren Hillerup<sup>1</sup>, Ole Hyldegaard<sup>2</sup>, Per Arnell<sup>10</sup>, Christian von Buchwald<sup>11</sup>, Johannes HAM Kaanders<sup>12</sup>, Ludi E Smeele<sup>13</sup>, Lena Specht<sup>14</sup>, Jørgen Johansen<sup>15</sup>, §Thijs MAW Merckx<sup>4</sup> and §Erik C. Jansen<sup>2</sup>.

\* Primary investigators, shared first authorship: Lone E Forner and Francois Dieleman

§ Shared last authorship: Erik Jansen og Thijs Merckx

- 1) Department of Oral and Maxillofacial Surgery, Center of Head and Orthopedics, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark.
- 2) Department of Anaesthesia, Center of Head and Orthopedics, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark.
- 3) Department of Head and Neck Surgical Oncology, UMC Utrecht Cancer Center, University Medical Center, Utrecht, Utrecht, The Netherlands.
- 4) Department of Oral and Maxillofacial Surgery, Radboud University Medical Center Nijmegen, Nijmegen, The Netherlands.
- 5) Department of Head and Neck Surgery, Aintree University Hospital, Liverpool, UK.
- 6) Oral & Maxillofacial Surgery Department, Leeds Teaching Hospitals NHS Trust, Leeds, UK.
- 7) Maxillofacial Prosthodontics, Department of Maxillofacial Surgery, Aintree University Hospital, Liverpool, UK.
- 8) Department of Oral and Maxillofacial Surgery, Institute of Odontology, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.
- 9) Experimental Clinical Oncology, Department of Oncology, Aarhus University Hospital, Aarhus, Denmark.
- 10) Department of Anaesthesiology and Intensive Care Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden.
- 11) Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark.
- 12) Department of Radiation Oncology, Radboud University Medical Center Nijmegen, Nijmegen, The Netherlands.
- 13) Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute, Amsterdam, The Netherlands.
- 14) Department of Oncology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark.
- 15) Department of Oncology, Odense University Hospital, Odense, Denmark.

Corresponding author: Lone Forner <loneforner@outlook.dk>

Keywords: osteoradionecrosis, hyperbaric oxygen treatment, randomized, head and neck cancer

## **Abstract**

**Purpose:** Osteoradionecrosis (ORN) of the mandible is a serious complication to head and neck radiotherapy. This study aims to investigate the effect of hyperbaric oxygen (HBO) treatment on ORN in two randomized, controlled multicenter trials.

**Methods and materials:** Patients with ORN with indication for surgical treatment were randomized to either group 1: surgical removal of necrotic mandibular bone supplemented by 30 pre- and 10 postoperative HBO exposures at 243 kPa for 90 minutes each during a period of eight weeks or group 2: surgical removal of necrotic bone only. Primary outcome was healing of ORN one year after surgery evaluated by a clinically adjusted version of the Common Toxicity Criteria of Adverse Events (CTCAE) v 3.0.. Secondary outcomes included xerostomia, unstimulated and stimulated whole salivation rates, trismus, dysphagia, pain, Activities of Daily Living (ADL), and quality of life according to EORTC. Data were combined from two separate trials. 97 were enrolled and 65 were eligible for the intent-to-treat analysis. The 33% drop-out was equally distributed within the groups.

**Results:** In group 1, 70% healed (21/30) compared with 51% (18/35) in group 2. HBO was associated with an increased chance of healing independent of baseline ORN grade or smoking status as well as improved xerostomia, unstimulated whole salivary flow rate, and dysphagia. However, none of the endpoints reached a statistically significant difference between groups. ADL data could only be obtained from 50 patients.

**Conclusion:** The attrition rate to HBO after surgery for osteoradionecrosis of the mandible, as well as acquisition of patient reported outcomes, was modest in this multinational, multicenter clinical trial. Hyperbaric oxygen did not significantly improve the healing outcome of osteoradionecrosis after surgical removal of necrotic bone, and no recommendations for HBO after surgery for ORN of the mandible may be proposed from this study.

## Introduction

Worldwide, approximately 710,000 patients are diagnosed annually with head and neck cancer (HNC) [1,2]. The incidence is increasing, and so is the number of survivors [3,4], causing a growing need for treatment of side effects after head and neck cancer.

Radiotherapy (RT) plays a major role in the treatment of HNC, either alone or in combination with chemotherapy and/or surgery. Osteoradionecrosis (ORN) is a serious complication to head and neck radiotherapy. It is defined as exposed bone after RT that fails to heal over a period of three months without evidence of persistent or recurrent disease [5,6]. Due to improved radiotherapy techniques such as intensity-modulated radiation technique (IMRT) and volumetric modulated arc therapy (VMAT), the incidence of ORN has decreased [7–14]. Recently, published data have indicated that the incidence is less than 5-6% of HNC patients treated with radiotherapy [14,15]. Despite this decrease, ORN remains a serious problem. Speech, eating, oral hygiene, and dental rehabilitation are challenging, especially when ORN is accompanied by other sequelae such as xerostomia, dysphagia, and trismus [16–18]. Hence, quality of life is often severely affected in ORN patients [19].

ORN is treated conservatively or surgically. Hyperbaric oxygen (HBO) therapy can be used as a supplement to surgical removal of necrotic bone [20]. HBO stimulates angiogenesis, increases neovascularization, cellular levels of oxygen, fibroblast and osteoblast proliferation, and collagen formation in irradiated tissues [21,22]. It is assumed to improve the conditions of the irradiated normal tissues that are marked by decreased vascularization, diminished oxygen supply, and decreased ability to recover after trauma.

However, the impact of HBO in mandibular ORN remains controversial because of lack of confirmation of its efficacy. Only one randomized clinical trial (RCT) has been conducted, showing improved recovery in the placebo group (32%) compared with the HBO group (19%) [23]. Several cohort studies of variable quality have been published, reporting ORN recovery rates from zero to 100 percent [24–33][34–39] (Mendeley cannot handle more than 10 references at a time, citation numbers will be merged just before submission). The studies are hardly comparable due to variation in the application of HBO, as well as variability of the study designs, classification, and severity of ORN. Consequently, there has been a need for further investigation of the clinical effect of HBO on ORN. For this purpose, the DAHANCA-21 trial was initiated in a multicenter collaboration involving Danish, British and Swedish Centers. Due to a low patient accrual rate, a further collaboration with centers in the Netherlands was instigated and the combined data are

reported here. Due to this collaboration that started very early after the initiation of both studies, it was possible to merge the results of the DAHNACA 21 trial with the Dutch NWHHT 2009-1 trial.

## **Patients and methods**

### *Protocol design and patient eligibility*

The study was a multicenter trial consisting of pooled data from two separate randomized trials with comparable endpoints. The reason for pooling of data was recruitment difficulties. DAHANCA-21 was conducted in Denmark, Sweden and the United Kingdom, while NWHHT2009-1 was conducted in the Netherlands.

Both studies were randomized, controlled phase 3 trials. The patients and the investigators were unblinded. The trials were conducted in one Danish, five Dutch, five British, and in one Swedish site.

The DAHANCA-21 trial was granted ethics approval by the Regional Ethics Committee of the Capital Region of Denmark (H-A-2008-031). Approval was obtained from The Danish Medicines Health Agency (EudraCT no. 2007-007842-36). The NWHHT2009-1 trial was granted ethics approval by the Dutch Central Committee on Research Involving Human Subjects (CCMO NL20963.091.08 EudraCT no. 2008-001972-55). Both studies were conducted in accordance with Good Clinical Practice (DAHANCA-21 NCT 00760682 and NWHHT 2009-1 NCT 00989820).

Eligible participants were aged  $\geq 18$  years with osteoradionecrosis of the mandible requiring surgical removal of necrotic bone after radiation treatment for head and neck cancer (any site). Patients were considered non-eligible if they were previously treated with HBO, had active cancer or contraindications to HBO such as uncontrolled hypertension, epilepsy, or claustrophobia. Participants were randomly assigned (1:1) to receive or not to receive HBO supplemental to surgical removal of necrotic mandibular bone. Allocation of treatment was unblinded to patients and investigators.

In DAHANCA-21, participants were stratified according to ORN grade and geographic location. Patients in NWHHT 2009-1 were not stratified.

97 patients were enrolled and 65 were included in the statistical analysis. The dropout rate was 33%. Of the 32 patients who dropped out, the distribution was 16 in each group. Reasons for drop out is shown in Figure 1.

Demographic data and follow-up.

Baseline demographic patient data included treatment center, gender, age, smoking, BMI, pain, dental status, and baseline ORN. The surgical procedure and number of HBO treatments were recorded.

Patient reported outcome (PRO) included xerostomia, dysphagia, ability to take liquids, trismus, and quality of life measures according to EORTC QLQ-C30 and Activities of Daily Living measures (ADL).

Patients were followed for one year after planned surgery for evaluation of the primary endpoints. Secondary endpoints were evaluated at 3 months after planned surgery.

### *Surgical treatment*

Surgery was performed according to the extent of the bone necrosis. Small necrotic lesions were treated by removal of small sequestrums, while larger necrotic lesions were treated with larger resections with or without discontinuation of the mandible. Some patients with discontinuation of the mandible were reconstructed with a free vascularized fibular bonegraft.

### *HBO treatment*

For the patients in the HBO arm, 100% oxygen was delivered through a hood at 243 kPa (2.4 atmospheres absolute) for 90 minutes in 40 daily (30 pre- and 10 postoperative treatments). The pressurization protocol was equal to the standard treatment schedule used in most hyperbaric regimes [40].

*Primary endpoints* The primary endpoint was healing of ORN as evaluated by an adjusted version of the Common Toxicity Criteria of Adverse Events v 3.0 [41].

- Patients with no evidence of ORN, defined as intact mucosal coverage of the mandible and no radiologic evidence of ORN, were characterised as grade 0.
- Patients with small (<2 mm), asymptomatic and radiographically undetectable bone exposures with no interference with Activities of Daily Living (ADL) were characterised as grade 1.

- Patients with an indication for minimal sequestrectomy, having symptoms with limited interference with ADL, were characterised as grade 2.
- Patients with an indication for larger sequestrectomy, yet above the mandibular canal and functional limitations interfering with ADL, were characterised as grade 3.
- Patients with invalidating ORN, defined as an indication for resection with disruption of continuity or bone necrosis with extension below the mandibular canal, severely interfering with ADL, were characterised as grade 4.

In this study, only patients with verified ORN and indication for surgical treatment were included, and thus, grade 0 and 1 were only registered at evaluation of the primary endpoint at 1-year follow-up.

### *Secondary endpoints*

In DAHANCA-21, five questions were used to assess ADL. This included denture wear, tooth brushing, eating, eating with others and being with others, as evaluated by use of an ordinal scale from 0 to 4 (0=no problems, 1=slightly problematic, but do not need to refrain from, 2=sometimes problematic, must seldom refrain from, 3=problematic, must often refrain from, and 4=not possible to do). The registered ADL score for each participant was the highest score achieved among all five questions.

Changes in ADL at 1 year were calculated as the number of points lower than at baseline, i.e. positive numbers indicate improvement. ADL improvement was dichotomized as 'No change or improvement' (change  $\geq 0$ ) versus 'Worsening' (change  $< 0$ ).

Xerostomia and dysphagia were assessed using an ordinal scale from 0 to 4 according to DAHANCA.

Secondary endpoints measured in both trials were Quality of Life (EORTC QLQ-C30 and QLQ-H&N35) and pain assessment (VAS scale and analgetics consumption). Other secondary endpoints that were measured by the DAHANCA trial alone were unstimulated and stimulated salivation rate (ml/min), xerostomia (UKU side effect rating scale [42]). Unstimulated whole saliva (UWS) was collected by the draining method in a pre-weighed cup for a period of 15 minutes. Stimulated whole saliva was collected for a period of 5 minutes while chewing a piece of paraffin wax (1 g). Salivary flow rates were estimated by dividing the saliva volume (1 g of saliva equals 1 mL) by the collection time [43].

Additional secondary endpoints were pain assessment (VAS scale and analgesics consumption), trismus (interincisal distance, or in edentulous patients, the distance between the alveolar ridges), and dysphagia (CTCAE v 3.0).

### *Statistics*

Both trials were activated in 2008 and planned to include a total of 114 patients (DAHANCA-21) and 120 patients (NWHHT 2009-1), respectively, and the trials were powered to detect a difference of 25% between the two treatment groups.

Differences in patient and treatment characteristics were evaluated by Fisher's exact test (ordinal data) and t-test or Wilcoxon rank-sum test (continuous data). Frequency distributions and Q-Q-plots were used for checking normality visually.

Differences in frequencies (1 year after surgery) of patients healed were evaluated by Chi-squared test and expressed as odds ratio.

Factors affecting ORN healing 1 year after surgery were evaluated in an exploratory univariate logistic regression analysis of protocol, baseline ORN grades, treatment type, smoking, sex, and age. Collinearity was assessed by the variance inflation factor (VIF). All variables had VIFs <1.6, however, baseline ORN grades and treatment types were correlated, with higher baseline grades being associated with more intensive treatment ( $p < 0.001$ , Chi-squared test).

The final multivariate model included baseline ORN values and smoking (never versus former/current). Compared to a model with treatment type instead of baseline ORN values, the AIC (Akaike Information Criterion) was 88 for the model with baseline values and 85 for the model with treatment type, and the coefficients for protocol were similar (test for equality,  $p = 0.81$ ).

Probabilities of healing in non-smokers versus former/current smokers was calculated as AAPs (Average Adjusted Predictions) and AMEs (Average Marginal Effects). Factors affecting ORN grade 1 year after surgery were evaluated likewise using an exploratory univariate logistic regression analysis and a final multivariate model including baseline ORN values and smoking (never versus former/current).

The effect of HBO on changes in ADL grade were evaluated by Wilcoxon rank-sum test for changes from baseline to 1 year after surgery and by Fisher's exact test for binary groups.

Secondary endpoints were evaluated using mixed-effect models with time of visit (baseline, 3 months follow-up, 1 year follow-up), treatment arm, interaction between visit and treatment arm, and smoking (never versus former/current) as fixed effects and patient as random effect. BMI, dysphagia (EORTC H&N35), pain (VAS), and global health status (EORTC QLQ-C30) were evaluated by linear mixed-effects regression models using an unstructured covariance matrix. The remaining secondary endpoints were evaluated by mixed effects binary logistic regression models. Predicted scores and differences between treatment arms were calculated as AAPs and AMEs.

The analyses were performed using Stata 16.1 (StataCorp, Texas, USA).

## **Results**

### *Patient and treatment characteristics*

Table 1 shows patient and treatment characteristics for the 65 patients included in the analysis. No differences were observed for age, sex, smoking status, type of surgery, or ADL between patients treated with surgery or surgery+HBO. Of the 30 patients in the HBO arm, 26 (87%) received 40 treatments (Figure 1).

### *Effect of HBO on ORN healing*

The primary clinical endpoint was healing of ORN 1 year after surgery. First, healing was defined as a binary outcome with healed (grade 0-1) versus not healed (grade 2-4). One year after surgery, healing was observed in 18 out of 35 patients (51%) treated with surgery alone and in 21/30 patients (70%) treated with surgery+HBO ( $p=0.13$ ) with an odds ratio for being healed of 2.2 (95% CI: 0.7-7.0) (Table 2). Second, the effect of protocol, baseline ORN grades, treatment type, smoking, sex, and age were tested in an exploratory univariate binary logistic regression analysis using ORN healing as endpoint (Table 3). With only 65 patients included, and with missing values for some of the factors, caution must be taken when interpreting the results in a multivariate analysis. With these reservations, a final model was constructed with baseline ORN grades (grade 2 vs grade 3 or 4) and smoking (never versus former or current) as covariates, resulting in an adjusted odds ratio of 2.7 (0.9-8.0,  $p=0.083$ ) for healing when using HBO (Table 4). Tests for interaction for protocol and baseline grade ( $p=0.99$ ) and protocol and smoking ( $p=0.88$ ) indicate that HBO is associated with an increased chance of healing independent of

baseline ORN grade or smoking status.

Predictions for frequency of patients healed are shown in Figure 2. The predicted percentage increases of being healed 1 year after surgery with HBO are 14% (-3-31) for baseline grade 2, 22% (-2-46) for baseline grade 3/4, 14% (-4-33) for never smokers, and 23% (-2-47) for former/current smokers.

Similar results were obtained using ORN grades on an ordinal scale. Supplementary Table 1 shows the results of a univariate ordinal logistic regression analysis, and Supplementary Table 2 shows the results of the final model, resulting in an adjusted odds ratio of 1.8 ( $p=0.23$ ) for having a lower grade after 1 year when using HBO. Tests for interaction were performed for protocol and baseline grade ( $p=0.58$ ) and protocol and smoking ( $p=0.83$ ).

### *Effect of HBO on change in activities of daily living*

The primary PROM was change in ADL from baseline to 1 year after surgery. ADL data were available from 50 of the 65 patients, and the distribution of ADL scores at baseline was similar in the two treatment arms (Table 1). The changes in ADL score are illustrated in Figure 3, where zero indicates no change and positive values indicate improvement in ADL score (the score is reduced). Overall, the changes in ADL score were not significantly different ( $p=0.29$ ). If changes in ADL score were reduced to a binary outcome, no change or improvement vs. worsening, there were 17 patients (59%) experiencing no change or improvement with surgery alone vs. 19 (79%) with surgery+HBO ( $p=0.15$ ).

### *Secondary endpoints*

Secondary endpoints were evaluated using mixed-effect models. Predicted outcomes at baseline, 3 months follow-up, and 1 year follow-up are shown in Supplementary Figure 1. Differences between treatment arms at each time point are listed in Supplementary Table 3.

Several endpoints showed trends for improvements over time with surgery + HBO compared to surgery alone. The strongest trends for improvement with surgery + HBO was for xerostomia (DAHANCA), unstimulated whole saliva flow rates, and dysphagia (DAHANCA).

## Discussion

DAHANCA-21 and NWHHT 2009-1 are the first randomized, controlled trials of HBO treatment for ORN in head and neck patients investigating a standard HBO protocol with 30 preoperative and 10 postoperative exposures delivered daily during a period of eight weeks. Due to low accrual in both trials, despite being offered in several academic centers, the studies joined forces to gather utmost information and knowledge about HBO in this serious condition.

Seventy percent of participants in the present study showed successful recovery when HBO was administered as a supplement to surgical removal of necrotic bone. Correspondingly, this was the case for 51% of the participants who received surgical treatment only. An increased chance of healing after surgery + HBO was observed independent of baseline ORN grade or smoking status, but multivariate regression analysis did not show a statistically significant difference between the two groups. There may be two explanations for the lack of significance. First, the power calculation performed prior to trial initiation aimed at detecting a difference of 25%. Second, the number of 114 cases for achieving adequate power was not obtained due to a low patient accrual rate in both trials. These are obvious shortcomings which must be considered when interpreting the results of the analysis.

Although low patient accrual was expected, it was surprisingly low in both DAHANCA-21 and NWHHT 2009-1. One possible explanation for this is the decreasing incidence of ORN due to improved radiotherapy techniques [13,14]. Additionally, a major reason was that the majority of patients who rejected participation, did so because HBO was offered without any requirement for trial participation. Others rejected because they lacked mental or physical energy to complete 40 treatments due to comorbidities or logistics, including transport challenges. Some patients were not offered participation because it could not be completely ascertained that they were free of cancer. No alternative treatments to HBO and surgery were offered.

A minority of the participants randomized to HBO did not comply with the 40 treatments. Mostly, this was because of claustrophobia or lack of mental or physical energy. Except for one participant who declined due to barotrauma, none of the non-compliant participants were subject to any harm caused by HBO treatment.

The dropout rate was 33%, which was higher than expected, and another shortcoming of the study. The health status of these patients is compromised due to several potential

comorbidities and sequelae to their previous cancer treatment. With this impact on quality of life, the motivation and physical ability to participate in 40 hyperbaric treatment sessions is obviously impaired and, consequently, the dropout rate is high.

In the light of the result of the statistical analysis it should be considered which extent of a clinical improvement that is sufficient to give a treatment modality the seal of approval. While planning both trials, we aimed at a 25% improvement in order to detect a significant difference in 114 patients. The 25% is, however, an arbitrary level. Although the beneficial effect was smaller than required, and not statistically significant in this reduced subset of patients, there was trend towards an increased chance of healing when HBO was used. This finding, though not statistically significant, was observed primarily in grade 3/4 ORN and in former/current smokers which seems in line with the theoretical effect of HBO on vasculature and oxygenation, hence, we encourage future research. Secondly, because ORN is a potentially disabling condition with severe consequences for function and aesthetic appearance, even a smaller chance of healing may be acceptable to the individual patient.

Another reason why further investigation should be encouraged is that besides this trial, only one French multicenter trial from 2004 by Annane and coworkers has been published [23]. The results from this trial showed significantly higher recovery (32%) in the placebo arm than in the HBO arm (19%). However, major concerns were raised regarding the design of the trial. Firstly, the diagnosis, stage and distribution of patients with ORN have been criticized for an imprecise definition of ORN, indicating that not all participants with certainty had ORN. Moreover, advanced stages of ORN were excluded from the trial; another factor that limits the usefulness of its findings. Another concern was that stratification was not used, potentially creating an uneven distribution of severe ORN cases within the two arms. Finally, the trial did not follow standard HBO protocol as two daily exposures were used instead of one daily exposure. Hence, the duration of the full treatment course was shorter than recommended in standard protocols, limiting the potential benefit of the treatment and leading to invalid conclusions. Furthermore, HBO was used without sequestrectomy, which may have falsely led to the conclusion that HBO had no effect, as HBO cannot revitalize necrotic bone. Overall, there are concerns regarding the validity of the conclusions regarding the effect of HBO on ORN in the Annane trial [44].

Evaluation of secondary endpoints also showed a trend towards a beneficial effect of HBO on radiotherapy-induced xerostomia, unstimulated salivary flow rate, and dysphagia, although not statistically significant in multivariate analysis. Hence, it is possible that HBO has the potential to relieve various symptoms in ORN patients, contributing to an overall improvement in quality of life [45]. Other reports have shown improvement in salivation rate and xerostomia [46–49]. Thus, HBO may still be a potential treatment modality for head and neck indications other than ORN, and should be investigated further.

The enrollment time for DAHANCA-21 was 10 years and two months. The enrollment time for NWHHT 2009-1 was 6 years and six months. Within this period, the accuracy of radiotherapy has continuously improved, leading to more precise delivery of the radiation treatment and less toxicity of the surrounding normal structures [7–14]. However, the incidence of head and neck cancer is increasing, and so is five-year survival rate [3,4]. The onset of ORN occurs mainly within a couple of years radiotherapy [50], but may occur years after [14]. Consequently, treatment of ORN will remain a relevant issue despite ongoing improvements in cancer treatment.

As expected, we observed variable individual responses to HBO treatment, as some participants did not benefit, whereas others healed successfully. It was, however, surprising that smoking status did not independently predict healing on multivariate analysis (Table 4). This may be explained by the small number of enrolled patients and due to the high healing potential in nonsmokers after surgery irrespectively of HBO (74%) rendering it unlikely that any intervention would be able to demonstrate an effect of a considerable value. Due to the nature of the treatment it was expected that smoking would influence the delivery of oxygen to the tissues. As alluded to above, there was a trend of effect primarily in grade 3/4 compared to grade 2 and in current/former smokers.

Another explanation for the individual response is the complexity of the surgical intervention, which may as well influence the response to treatment. The anatomy of the defects varies considerably with regards to size, dimension and proximity to critical structures with potential implications for oral function, esthetics and sensibility. Depending on the anatomical defect, primary closure may be difficult to obtain and the risk of infection and further compromised healing will be present. This may be reinforced by individual comorbidities, increasingly impairing the healing potential. Finally, the variability in time span from radiotherapy to trial participation may affect the individual treatment response,

as the radiotherapy-induced pathophysiological changes evolve over time. Thus, the timing of HBO may affect the individual response.

Sham treatment was considered both in the planning phase of DAHANCA-21 and NWHHT2009-1, but was abandoned mainly because of a potential hindering of recruitment. Moreover, creating a realistic scenario for sham treatment would require additional financial support, which was unrealistic to obtain. We are aware, though, that sham treatment would increase the trial quality.

Currently, there are no suitable alternatives to HBO in supporting bone healing after surgical intervention of ORN. Despite the statistically insignificant impact of smoking in this study, the trend towards a detrimental effect of tobacco and documentation from the literature, mean smoking cessation should be enforced in this patient population.

Investigation of pentoxifylline has shown some effect on ORN in prospective as well as retrospective studies, but no randomized trials have been conducted [51–58].

Consequently, pentoxifylline treatment of ORN is not sufficiently evidence-based and at least at this point should not be recommended.

Four animal studies have investigated the effect of stem cell transplantation to osteoradionecrotic defects [59–62]. While the results are promising, the effect in humans is only presented as two case reports [63,64]. Thus, neither of these treatments should be offered outside clinical trial.

As of HBO in ORN of the mandible, the present data have only shown a trend for a positive effect on bone healing after surgery as well as on a few other late effects after radiation treatment of head and neck cancer. The compiled data from DAHANCA and NWHHT2009-1 were not able to demonstrate a significant impact of HBO as a supplement to surgery, and thus, no firm recommendations for HBO after surgery for ORN of the mandible may be drawn from this study.

To conclude, the combined DAHANCA-21/ NWHHT2009-1 studies demonstrated a trend towards an increased chance of healing independent of baseline ORN grade or smoking status when used adjunctively to surgery, although this effect was not statistically significant. Moreover, there was a trend towards a beneficial effect of HBO on xerostomia, unstimulated salivary flow rate and dysphagia. We encourage further research of the effect of HBO as well as relevant alternatives to HBO with regards to ORN.

## **Acknowledgements**

This research was supported by the Danish Cancer Society, the National Institute for Health Research (NIHR) infrastructure at Leeds (DenTCRU), Danish Cancer Research foundation, Danish Dental Association, Doctor Sofus Carl Emil and Wife Olga Doris Friis' Foundation. We wish to thank members of the Hyperbaric Unit staff Martin Forchhammer, Annet Schack von Brockdorff, Paul Banks, Gillian Dukanovic for their help. The views expressed are those of the author(s) and not necessarily those of any funders or national health institutions. **PLEASE ADD YOUR ACKNOWLEDGEMENTS HERE**

## References

- [1] Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer* 2019;144:1941–53. <https://doi.org/10.1002/ijc.31937>.
- [2] Simard EP, Torre LA, Jemal A. International trends in head and neck cancer incidence rates: Differences by country, sex and anatomic site. *Oral Oncol* 2014;50:387–403. <https://doi.org/10.1016/j.oraloncology.2014.01.016>.
- [3] Jakobsen KK, Grønhøj C, Jensen DH, Karnov KKS, Agander TK, Specht L, et al. Increasing incidence and survival of head and neck cancers in Denmark: a nation-wide study from 1980 to 2014. *Acta Oncol (Madr)* 2018;57:1143–51. <https://doi.org/10.1080/0284186X.2018.1438657>.
- [4] Cancer Research UK. Head and neck cancers incidence statistics 2020. <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/head-and-neck-cancers/incidence#ref-2> (accessed March 3, 2020).
- [5] Chronopoulos A, Zarra T, Ehrenfeld M, Otto S. Osteoradionecrosis of the jaws: definition, epidemiology, staging and clinical and radiological findings. A concise review. *Int Dent J* 2018;68:22–30. <https://doi.org/10.1111/idj.12318>.
- [6] Store G, Boysen M. Mandibular osteoradionecrosis: clinical behaviour and diagnostic aspects. *Clin Otolaryngol Allied Sci* 2000;25:378–84. <https://doi.org/10.1046/j.1365-2273.2000.00367.x>.
- [7] Studer G, Studer SP, Zwahlen RA, Huguenin 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. <https://doi.org/10.1007/s00066-006-1477-0>.
- [8] Eisbruch A, Harris J, Garden AS, Chao CKS, Straube W, Harari PM, et al. Multi-Institutional Trial of Accelerated Hypofractionated Intensity-Modulated Radiation Therapy for Early-Stage Oropharyngeal Cancer (RTOG 00-22). *Int J Radiat Oncol* 2010;76:1333–8. <https://doi.org/10.1016/j.ijrobp.2009.04.011>.
- [9] Gomez DR, Zhung JE, Gomez J, Chan K, Wu AJ, Wolden SL, et al. Intensity-Modulated Radiotherapy in Postoperative Treatment of Oral Cavity Cancers. *Int J Radiat Oncol* 2009;73:1096–103. <https://doi.org/10.1016/j.ijrobp.2008.05.024>.
- [10] Huang K, Xia P, Chuang C, Weinberg V, Glastonbury CM, Eisele DW, et al. Intensity-modulated chemoradiation for treatment of stage III and IV oropharyngeal carcinoma. *Cancer* 2008;113:497–507. <https://doi.org/10.1002/cncr.23578>.
- [11] Ben-David MA, Diamante M, Radawski JD, Vineberg KA, Stroup C, Murdoch-Kinch C-A, et al. Lack of Osteoradionecrosis of the Mandible After Intensity-Modulated Radiotherapy for Head and Neck Cancer: Likely Contributions of Both Dental Care and Improved Dose Distributions. *Int J Radiat Oncol* 2007;68:396–402. <https://doi.org/10.1016/j.ijrobp.2006.11.059>.
- [12] Claus F, Duthoy W, Boterberg T, De Gerssem 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. [https://doi.org/10.1016/S1368-8375\(01\)00111-7](https://doi.org/10.1016/S1368-8375(01)00111-7).
- [13] Nguyen NP, Vock J, Chi A, Ewell L, Vos P, Mills M, et al. Effectiveness of intensity-modulated and image-guided radiotherapy to spare the mandible from excessive radiation. *Oral Oncol* 2012;48:653–7.

<https://doi.org/10.1016/j.oraloncology.2012.01.016>.

- [14] Aarup-Kristensen S, Hansen CR, Forner L, Brink C, Eriksen JG, Johansen J. Osteoradionecrosis of the mandible after radiotherapy for head and neck cancer: risk factors and dose-volume correlations. *Acta Oncol (Madr)* 2019;58:1373–7. <https://doi.org/10.1080/0284186X.2019.1643037>.
- [15] Shaw RJ, Butterworth CJ, Silcocks P, Tesfaye BT, Bickerstaff M, Jackson R, et al. HOPON (Hyperbaric Oxygen for the Prevention of Osteoradionecrosis): A Randomized Controlled Trial of Hyperbaric Oxygen to Prevent Osteoradionecrosis of the Irradiated Mandible After Dentoalveolar Surgery. *Int J Radiat Oncol* 2019;104:530–9. <https://doi.org/10.1016/j.ijrobp.2019.02.044>.
- [16] Mortensen HR, Overgaard J, Specht L, Overgaard M, Johansen J, Evensen JF, et al. Prevalence and peak incidence of acute and late normal tissue morbidity in the DAHANCA 6&7 randomised trial with accelerated radiotherapy for head and neck cancer. *Radiother Oncol* 2012;103:69–75. <https://doi.org/10.1016/j.radonc.2012.01.002>.
- [17] Jensen K, Lambertsen K, Grau C. Late swallowing dysfunction and dysphagia after radiotherapy for pharynx cancer: Frequency, intensity and correlation with dose and volume parameters. *Radiother Oncol* 2007;85:74–82. <https://doi.org/10.1016/j.radonc.2007.06.004>.
- [18] López-Jornet P, Camacho-Alonso F, López-Tortosa J, Palazon Tovar T, Rodríguez-Gonzales MA. Assessing quality of life in patients with head and neck cancer in Spain by means of EORTC QLQ-C30 and QLQ-H&N35. *J Cranio-Maxillofacial Surg* 2012;40:614–20. <https://doi.org/10.1016/j.jcms.2012.01.011>.
- [19] Rogers SN, D'Souza JJ, Lowe D, Kanatas A. Longitudinal evaluation of health-related quality of life after osteoradionecrosis of the mandible. *Br J Oral Maxillofac Surg* 2015;53:854–7. <https://doi.org/10.1016/j.bjoms.2015.07.008>.
- [20] 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. <https://doi.org/10.1002/14651858.CD005005.pub4>.
- [21] 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. [https://doi.org/10.1016/S0002-9610\(05\)81019-0](https://doi.org/10.1016/S0002-9610(05)81019-0).
- [22] Thom SR. Hyperbaric Oxygen: Its Mechanisms and Efficacy. *Plast Reconstr Surg* 2011;127:131S–141S. <https://doi.org/10.1097/PRS.0b013e3181f8e2bf>.
- [23] Annane D, Depondt J, Aubert P, Villart M, Géhanno P, Gajdos P, et al. Hyperbaric Oxygen Therapy for Radionecrosis of the Jaw: A Randomized, Placebo-Controlled, Double-Blind Trial From the ORN96 Study Group. *J Clin Oncol* 2004;22:4893–900. <https://doi.org/10.1200/JCO.2004.09.006>.
- [24] Dieleman FJ, Phan TTT, van den Hoogen FJA, Kaanders JHAM, Merks 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. <https://doi.org/10.1016/j.ijom.2016.12.004>.
- [25] Niezgoda JA, Serena TE, Carter MJ. Outcomes of Radiation Injuries Using Hyperbaric Oxygen Therapy. *Adv Skin Wound Care* 2016;29:12–9. <https://doi.org/10.1097/01.ASW.0000473679.29537.c0>.
- [26] Tahir ARM, Westhuyzen J, Dass J, Collins MK, Webb R, Hewitt S, et al. Hyperbaric

oxygen therapy for chronic radiation-induced tissue injuries: Australasia's largest study. *Asia Pac J Clin Oncol* 2015;11:68–77. <https://doi.org/10.1111/ajco.12289>.

- [27] Skeik N, Porten BR, Isaacson E, Seong J, Klosterman DL, Garberich RF, et al. Hyperbaric Oxygen Treatment Outcome for Different Indications from a Single Center. *Ann Vasc Surg* 2015;29:206–14. <https://doi.org/10.1016/j.avsg.2014.07.034>.
- [28] 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. <https://doi.org/10.1016/j.ijom.2007.05.007>.
- [29] Chen J-A, Wang C-C, Wong Y-K, Wang C-P, Jiang R-S, Lin J-C, et al. Osteoradionecrosis of mandible bone in patients with oral cancer-associated factors and treatment outcomes. *Head Neck* 2016;38:762–8. <https://doi.org/10.1002/hed.23949>.
- [30] Gupta P, Sahni T, Jadhav GK, Manocha S, Aggarwal S, Verma S. A Retrospective Study of Outcomes in Subjects of Head and Neck Cancer Treated with Hyperbaric Oxygen Therapy for Radiation Induced Osteoradionecrosis of Mandible at a Tertiary Care Centre: An Indian Experience. *Indian J Otolaryngol Head Neck Surg* 2013;65:140–3. <https://doi.org/10.1007/s12070-013-0640-z>.
- [31] 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. <https://doi.org/10.1002/cncr.26637>.
- [32] Oh H-K, Chambers MS, Martin JW, Lim H-J, Park H-J. Osteoradionecrosis of the Mandible: Treatment Outcomes and Factors Influencing the Progress of Osteoradionecrosis. *J Oral Maxillofac Surg* 2009;67:1378–86. <https://doi.org/10.1016/j.joms.2009.02.008>.
- [33] Freiberger JJ, Yoo DS, de Lisle Dear G, McGraw TA, Blakey GH, Padilla Burgos R, et al. MultiModality Surgical and Hyperbaric Management of Mandibular Osteoradionecrosis. *Int J Radiat Oncol* 2009;75:717–24. <https://doi.org/10.1016/j.ijrobp.2008.11.025>.
- [34] Bui Q-C, 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* 2004;60:871–8. <https://doi.org/10.1016/j.ijrobp.2004.04.019>.
- [35] 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. <https://doi.org/10.1054/ijom.2002.0332>.
- [36] Notani K-I, 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. <https://doi.org/10.1002/hed.10171>.
- [37] David LA, Sándor 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.
- [38] Curi MM, Dib LL, Kowalski LP. Management of refractory osteoradionecrosis of the jaws with surgery and adjunctive hyperbaric oxygen therapy. *Int J Oral Maxillofac Surg* 2000;29:430–4. <https://doi.org/10.1034/j.1399-0020.2000.290607.x>.

- [39] 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. <https://doi.org/10.1054/bjom.1999.0285>.
- [40] Neuman T, Thom S. *Physiology and Medicine of Hyperbaric Oxygen Therapy*. 1st ed. Philadelphia, PA, USA: Saunders; 2008.
- [41] NCI. Common Terminology Criteria for Adverse Events v3.0 (CTCAE) 2006. [https://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/ctcae3.pdf](https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf) (accessed April 21, 2020).
- [42] Lingjærde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K. The UKU side effect rating scale: A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatr Scand* 1987;76:1–100. <https://doi.org/10.1111/j.1600-0447.1987.tb10566.x>.
- [43] Navazesh M, Christensen CM. A Comparison of Whole Mouth Resting and Stimulated Salivary Measurement Procedures. *J Dent Res* 1982;61:1158–62. <https://doi.org/10.1177/00220345820610100901>.
- [44] Shaw RJ, Dhanda J. Hyperbaric oxygen in the management of late radiation injury to the head and neck. Part I: Treatment. *Br J Oral Maxillofac Surg* 2011;49:2–8. <https://doi.org/10.1016/j.bjoms.2009.10.036>.
- [45] Harding SA, Hodder SC, Courtney DJ, Bryson PJ. Impact of perioperative hyperbaric oxygen therapy on the quality of life of maxillofacial patients who undergo surgery in irradiated fields. *Int J Oral Maxillofac Surg* 2008;37:617–24. <https://doi.org/10.1016/j.ijom.2008.04.004>.
- [46] Forner L, Hyldegaard O, von Brockdorff AS, Specht L, Andersen E, Jansen EC, et al. Does hyperbaric oxygen treatment have the potential to increase salivary flow rate and reduce xerostomia in previously irradiated head and neck cancer patients? A pilot study. *Oral Oncol* 2011;47:546–51. <https://doi.org/10.1016/j.oraloncology.2011.03.021>.
- [47] Cankar K, Finderle Z, Jan J. The Effect of Hyperbaric Oxygenation on Postradiation Xerostomia and Saliva in Patients with Head and Neck Tumours. *Caries Res* 2011;45:136–41. <https://doi.org/10.1159/000324811>.
- [48] Teguh DN, Levendag PC, Noever I, Voet P, van der Est H, van Rooij P, et al. Early Hyperbaric Oxygen Therapy for Reducing Radiotherapy Side Effects: Early Results of a Randomized Trial in Oropharyngeal and Nasopharyngeal Cancer. *Int J Radiat Oncol* 2009;75:711–6. <https://doi.org/10.1016/j.ijrobp.2008.11.056>.
- [49] Sherlock S, Way M, Tabah A. Hyperbaric oxygen treatment for the management of radiation-induced xerostomia. *J Med Imaging Radiat Oncol* 2018;62:841–6. <https://doi.org/10.1111/1754-9485.12789>.
- [50] Matras R, Forner LE, Andersen EV, Specht L, Hillerup S. Osteoradionecrosis: Patient characteristics and treatment outcome in a cohort from Copenhagen University Hospital 1995-2005. *J Cranio-Maxillary Dis* 2013;2:105–13.
- [51] Lyons A, Osher J, Warner E, Kumar R, Brennan PA. Osteoradionecrosis—A review of current concepts in defining the extent of the disease and a new classification proposal. *Br J Oral Maxillofac Surg* 2014;52:392–5. <https://doi.org/10.1016/j.bjoms.2014.02.017>.
- [52] Delanian S, Chatel C, Porcher R, Depondt J, Lefaix J-L. Complete Restoration of

Refractory Mandibular Osteoradionecrosis by Prolonged Treatment with a Pentoxifylline-Tocopherol-Clodronate Combination (PENTOCLO): A Phase II Trial. *Int J Radiat Oncol* 2011;80:832–9. <https://doi.org/10.1016/j.ijrobp.2010.03.029>.

- [53] Delanian S, Depondt J, Lefaix J-L. Major healing of refractory mandible osteoradionecrosis after treatment combining pentoxifylline and tocopherol: A phase II trial. *Head Neck* 2005;27:114–23. <https://doi.org/10.1002/hed.20121>.
- [54] Patel V, Gadiwalla Y, Sassoon I, Sproat C, Kwok J, McGurk M. Use of pentoxifylline and tocopherol in the management of osteoradionecrosis. *Br J Oral Maxillofac Surg* 2016;54:342–5. <https://doi.org/10.1016/j.bjoms.2015.11.027>.
- [55] Hayashi M, Pellecer M, Chung E, Sung E. The efficacy of pentoxifylline/tocopherol combination in the treatment of osteoradionecrosis. *Spec Care Dent* 2015;35:268–71. <https://doi.org/10.1111/scd.12124>.
- [56] 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. <https://doi.org/10.1016/j.bjoms.2014.01.003>.
- [57] Robard L, Louis M-Y, Blanchard D, Babin E, Delanian S. Medical treatment of osteoradionecrosis of the mandible by PENTOCLO: Preliminary results. *Eur Ann Otorhinolaryngol Head Neck Dis* 2014;131:333–8. <https://doi.org/10.1016/j.anorl.2013.11.006>.
- [58] Mcleod NMH, 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. <https://doi.org/10.1016/j.bjoms.2010.11.017>.
- [59] Janus JR, Jackson RS, Lees KA, Voss SG, Wilson ZC, Remmes NB, et al. Human Adipose-Derived Mesenchymal Stem Cells for Osseous Rehabilitation of Induced Osteoradionecrosis: A Rodent Model. *Otolaryngol Neck Surg* 2017;156:616–21. <https://doi.org/10.1177/0194599816688647>.
- [60] Park HS, Lee J, Kim J-W, Kim HY, Jung SY, Lee SM, et al. Preventive effects of tonsil-derived mesenchymal stem cells on osteoradionecrosis in a rat model. *Head Neck* 2018;40:526–35. <https://doi.org/10.1002/hed.25004>.
- [61] Xu J, Zheng Z, Fang D, Gao R, Liu Y, Fan Z, et al. Mesenchymal Stromal Cell-Based Treatment of Jaw Osteoradionecrosis in Swine. *Cell Transplant* 2012;21:1679–86. <https://doi.org/10.3727/096368911X637434>.
- [62] Jin IG, Kim JH, Wu H-G, Kim SK, Park Y, Hwang SJ. Effect of bone marrow-derived stem cells and bone morphogenetic protein-2 on treatment of osteoradionecrosis in a rat model. *J Cranio-Maxillofacial Surg* 2015;43:1478–86. <https://doi.org/10.1016/j.jcms.2015.06.035>.
- [63] Mendonça JJ, Juiz-Lopez P. Regenerative Facial Reconstruction of Terminal Stage Osteoradionecrosis and Other Advanced Craniofacial Diseases with Adult Cultured Stem and Progenitor Cells. *Plast Reconstr Surg* 2010;126:1699–709. <https://doi.org/10.1097/PRS.0b013e3181f24164>.
- [64] Manimaran K, Sankaranarayanan S, Ravi VR, Elangovan S, Chandramohan M, Perumal SM. Treatment of osteoradionecrosis of mandible with bone marrow concentrate and with dental pulp stem cells. *Ann Maxillofac Surgery* 2014;4:189–92. <https://doi.org/10.4103/2231-0746.147130>.

**Table 1.** Patient and treatment characteristics.

	All		Surgery		Surgery + HBO		P value
	N	%	N	%	N	%	
<i>Number</i>	65	100.0%	35	53.8%	30	46.2%	
<i>Age (years)</i>							
Median (range)	61	(49-80)	61	(49-80)	60	(51-78)	0.80
<i>Sex</i>							
Female	10	15.4%	5	14.3%	5	16.7%	1.00
Male	55	84.6%	30	85.7%	25	83.3%	
<i>Smoking</i>							
Never	15	23.1%	7	20.0%	8	26.7%	0.14
Former	30	46.2%	20	57.1%	10	33.3%	
Current	20	30.8%	8	22.9%	12	40.0%	
<i>Surgery</i>							
Minor sequestrectomy	11	16.9%	7	20.0%	4	13.3%	0.83
En bloc resection	33	50.8%	16	45.7%	17	56.7%	
Resection with discontinuation of the mandible	19	29.2%	11	31.4%	8	26.7%	
None	2	3.1%	1	2.9%	1	3.3%	
<i>Baseline activities of daily living (ADL)</i>							
Grade 0	3	4.6%	2	5.7%	1	3.3%	0.35
Grade 1	7	10.8%	4	11.4%	3	10.0%	
Grade 2	11	16.9%	9	25.7%	2	6.7%	
Grade 3	28	43.1%	12	34.3%	16	53.3%	
Grade 4	5	7.7%	3	8.6%	2	6.7%	
Unknown	11	16.9%	5	14.3%	6	20.0%	

**Table 2.** ORN healing 1 year after surgery.

	All (N=65)		Surgery (N=35)		Surgery + HBO (N=30)		P value	OR (95% CI)
	N	%	N	%	N	%		
ORN healed (grade 0-1)	39	60%	18	51%	21	70%	0.13	2.2 (0.7-7.0)
ORN not healed (grade 2-4)	26	40%	17	49%	9	30%		

**Table 3.** Univariate binary logistic regression analysis with ORN healing as outcome.

	OR (95% CI)*	P value	N
Protocol			65
Surgery (reference)	1.00		35
Surgery +HBO	2.20 (0.79-6.14)	0.13	30
Baseline ORN grade			65
2 (reference)	1.00		12
3	0.38 (0.09-1.63)	0.19	34
4	0.57 (0.11-2.84)	0.49	19
Baseline ORN grade			65
2 (reference)	1.00		12
3/4	0.43 (0.11-1.79)	0.25	53
Surgery†			63
Minor sequestrectomy(reference)	1.00		11
En bloc resection	0.24 (0.04-1.26)	0.092	33
Resection with discontinued mandible	0.48 (0.08-2.95)	0.43	19
Surgery†			63
Minor sequestrectomy(reference)	1.00		11
En bloc resection	0.30 (0.06-1.54)	0.15	52
Smoking			65
Never (reference)	1.00		15
Former	0.29 (0.07-1.22)	0.091	30
Current	0.31 (0.07-1.43)	0.13	20
Smoking			65
Never (reference)	1.00		15
Former/Current	0.29 (0.07-1.17)	0.082	50
Sex			65
Female (reference)	1.00		10
Male	1.62 (0.42-6.27)	0.49	55
Age			65
<55 (reference)	1.00		13
55-60	1.25 (0.28-5.53)	0.77	18
61-65	0.49 (0.11-2.16)	0.34	16
>65	1.25 (0.28-5.53)	0.77	18
Age			65
Continuous	1.00 (0.93-1.07)	0.98	65

\* Odds ratios reflect odds of being healed.

† Excluding 2 patients where surgery was not performed.

**Table 4.** Multivariate binary logistic regression analysis with ORN healing as outcome (N=65).

	OR (95% CI)*	P value
Protocol		
Surgery (reference)	1.00	
Surgery +HBO	2.65 (0.88-8.02)	0.083
Baseline ORN grade		
2 (reference)	1.00	
3/4	0.26 (0.06-1.18)	0.081
Smoking		
Never (reference)	1.00	
Former/Current	0.25 (0.06-1.04)	0.057

\* Odds ratios reflect odds of being healed.

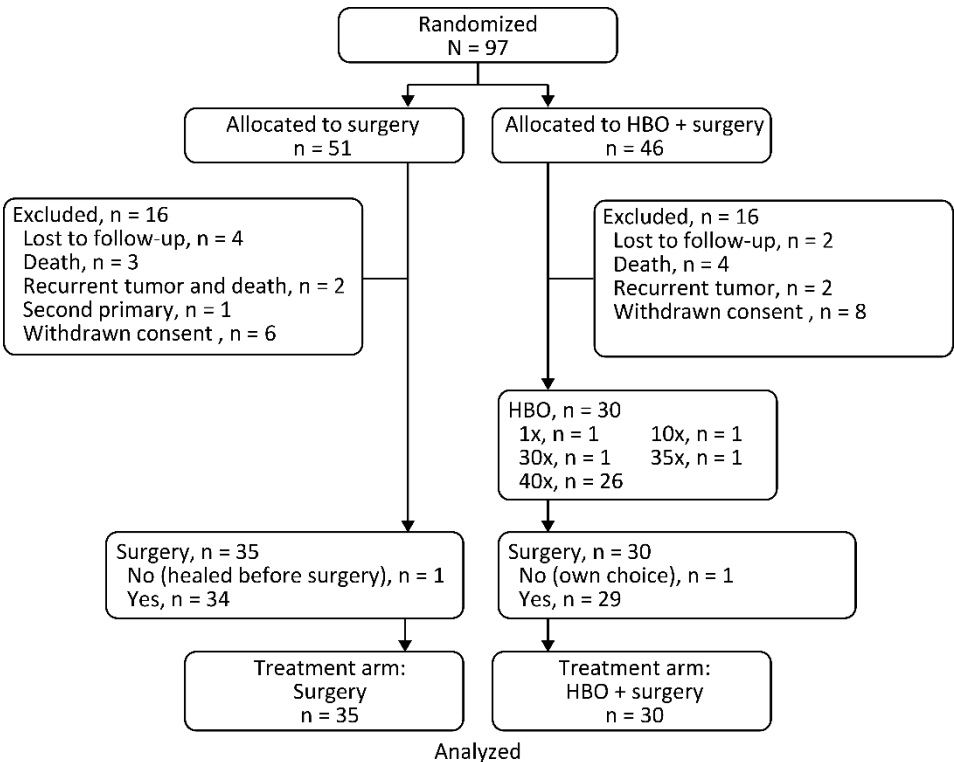
## Figure legends

**Figure 1.** Flowchart of patients included in the study.

**Figure 2.** Predicted chance of being healed 1 year after surgery based on multivariate binary logistic regression model including baseline ORN grade and smoking. Predictions are calculated as average adjusted predictions and differences are average marginal effects (with 95% CI).

**Figure 3.** Improvement in ADL score from baseline to 1 year after surgery by treatment arm. 0 indicates no change and positive numbers indicate improvement (ADL score is reduced).

Figure 1



**Figure 2**

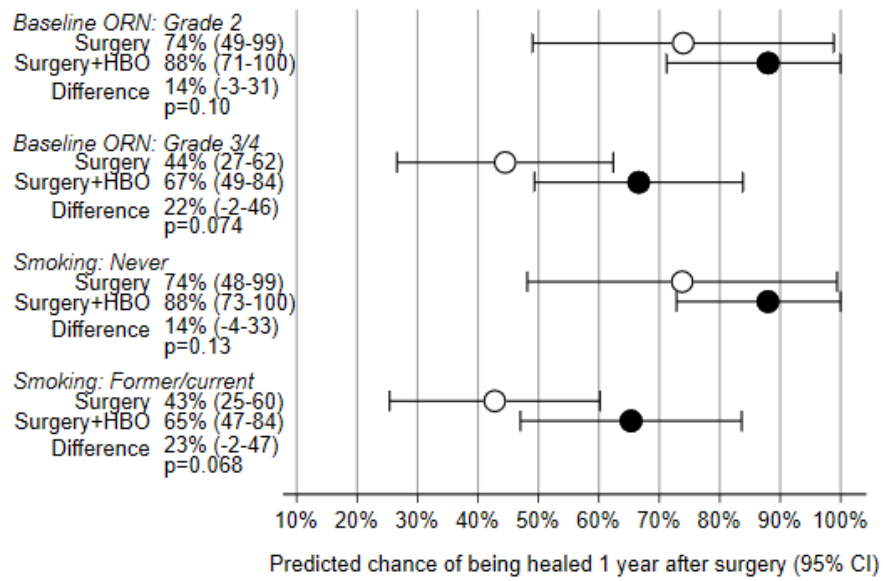
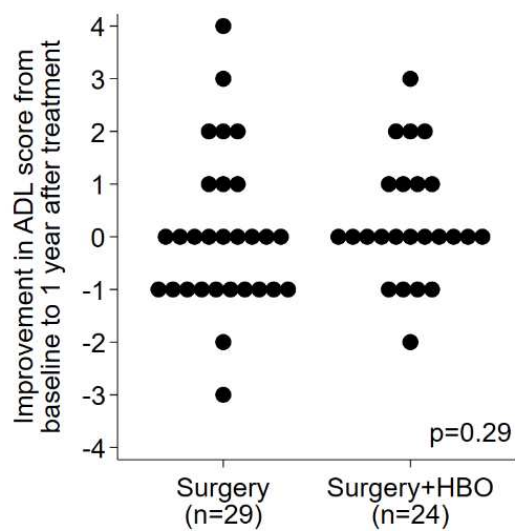
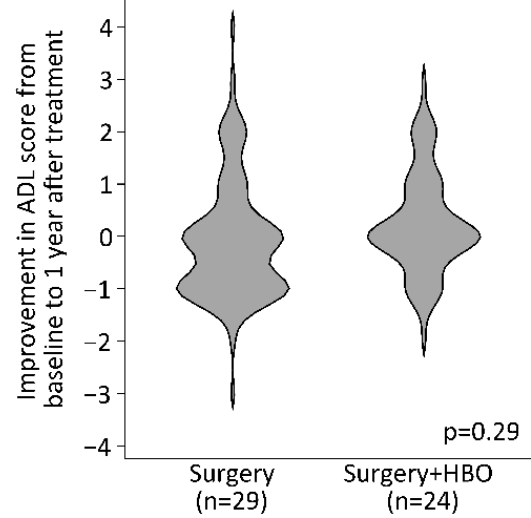


Figure 3



OR



## Supplementary Material

### Hyperbaric oxygen treatment of mandibular osteoradionecrosis: Combined data from two randomized clinical trials

*Lone E Forner, Francois Dieleman, Richard J Shaw, Anastasios Kanatas, Christopher J Butterworth, Göran Kjeller, Jan Alsner, Jens Overgaard, Søren Hillerup, Ole Hyldegaard, Per Arnell, Christian von Buchwald, Johannes HAM Kaanders, Ludi E Smeele, Lena Specht, Jørgen Johansen, Thijs MAW Merkx and Erik Jansen*

#### Supplementary Table 1

Page

Univariate ordinal logistic regression analysis with ORN grades as outcome..... 1

#### Supplementary Table 2

Multivariate ordinal logistic regression analysis with ORN grades as outcome ..... 2

#### Supplementary Table 3

Secondary endpoints, differences between treatment arms at baseline, 3 months follow-up,  
and 1 year follow-up based on mixed effects models ..... 3

#### Supplementary Figure 1

Secondary endpoints, predicted chance of scores based on mixed effects models ..... 4

**Supplementary Table 1.** Univariate ordinal logistic regression analysis with ORN grades as outcome.

	OR (95% CI)*	P value	N
Protocol			65
Surgery (reference)	1.00		35
Surgery +HBO	1.76 (0.69-4.47)	0.24	30
Baseline ORN grade			65
2 (reference)	1.00		12
3	0.76 (0.23-2.54)	0.66	34
4	1.17 (0.29-4.69)	0.83	19
Baseline ORN grade			65
2 (reference)	1.00		12
3/4	0.87 (0.27-2.77)	0.82	53
Surgery†			63
'Minor sequestrectomy (reference)'	1.00		11
'En bloc resection'	0.40 (0.10-1.52)	0.18	33
'Resection with discontinuation of the mandible'	0.90 (0.19-4.14)	0.89	19
Surgery†			63
'Minor sequestrectomy (reference)'	1.00		11
'En bloc resection'	0.51 (0.14-1.87)	0.31	52
Smoking			65
Never (reference)	1.00		15
Former	0.45 (0.13-1.57)	0.21	30
Current	0.44 (0.12-1.65)	0.23	20
Smoking			65
Never (reference)	1.00		15
Former/Current	0.44 (0.14-1.44)	0.18	50
Sex			65
Female (reference)	1.00		10
Male	0.90 (0.27-3.06)	0.87	55
Age			65
<55 (reference)	1.00		13
55-60	0.83 (0.21-3.32)	0.79	18
61-65	0.56 (0.14-2.22)	0.41	16
>65	0.91 (0.21-3.87)	0.90	18
Age			65
Continuous	0.99 (0.93-1.06)	0.85	65

\* Odds ratios reflect odds of being healed.

† Excluding 2 patients where surgery was not performed.

**Supplementary Table 2.** Multivariate ordinal logistic regression analysis with ORN grades as outcome (N=65).

	OR (95% CI)*	P value
Protocol		
Surgery (reference)	1.00	
Surgery +HBO	1.80 (0.69-4.66)	0.23
Baseline ORN grade		
2 (reference)	1.00	
3/4	0.70 (0.21-2.28)	0.55
Smoking		
Never (reference)	1.00	
Former/Current	0.44 (0.13-1.45)	0.18

\* Odds ratios reflect odds of being healed.

**Supplementary Table 3.** Secondary endpoints, differences between treatment arms at baseline, 3 months follow-up, and 1 year follow-up are based on mixed effects models and calculated as average marginal effects.

	Difference (with 95% CI) between surgery alone and surgery + HBO					
	Baseline	P value	3 months follow-up	P value	1 year follow-up	P value
BMI (kg/m <sup>2</sup> )	-0.2 (-1.8-1.5)	0.82	-0.2 (-1.9-1.5)	0.82	0.3 (-1.4-2.0)	0.73
Xerostomia, DAHANCA (frequency of grade >1)	8.6% (-12.8%-30.0%)	0.43	-3.1% (-26.8%-20.7%)	0.80	-24.6% (-51.7%-2.5%)	0.076
Xerostomia, EORTC H&N35 (frequency of grade >2)	20.0% (-1.6%-41.6%)	0.070	13.0% (-9.1%-35.1%)	0.25	6.1% (-11.9%-24.0%)	0.51
Unstimulated whole saliva flow rate (frequency of <0.1 ml/min)	4.3% (-10.0%-18.6%)	0.55	-9.0% (-17.2%--0.8%)	0.032	-13.8% (-26.0%--1.6%)	0.027
Dysphagia, DAHANCA (frequency of grade >1)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Dysphagia, EORTC H&N35 (symptom scale)	19.6% (-3.9%-43.1%)	0.10	-6.8% (-34.1%-20.4%)	0.62	-11.8% (-39.9%-16.2%)	0.41
Pain (frequency of regular use of non-morphine or use of morphine)	-0.5 (-13.5-12.5)	0.94	-8.0 (-20.9-4.8)	0.22	-8.7 (-22.9-5.5)	0.23
Pain (VAS)	-11.1% (-33.4%-11.2%)	0.33	-10.6% (-32.6%-11.3%)	0.34	-6.1% (-27.9%-15.8%)	0.59
Global health status, EORTC C30 (function scale)	0.8 (-0.3-1.9)	0.17	-0.5 (-1.8-0.8)	0.46	-0.4 (-1.9-1.1)	0.62

**Supplementary Figure 1.** Secondary endpoints. Predicted chance of scores are based on mixed effects models and calculated as average adjusted predictions.

