



Original Article

Hyperbaric oxygen treatment of mandibular osteoradionecrosis: Combined data from the two randomized clinical trials DAHANCA-21 and NWHHT2009-1



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ABSTRACT

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

Methods and materials: Patients with ORN with indication for surgical treatment were randomised to either group 1: surgical removal of necrotic mandibular bone supplemented by 30 pre- and 10 postoperative HBO exposures at 243 kPa for 90 min each, 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. Ninety-seven were enrolled and 65 were eligible for the intent-to-treat analysis. The 33% drop-out was equally distributed between groups.

Results: In group 1, 70% (21/30) healed compared to 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. Due to insufficient recruitment, none of the endpoints reached a statistically significant difference between groups. ADL data could only be obtained from 50 patients.

Conclusion: Hyperbaric oxygen did not significantly improve the healing outcome of osteoradionecrosis after surgical removal of necrotic bone as compared to standard care (70% vs. 51%). This effect is not statistically significant due to the fact that the study was underpowered and is therefore prone to type II error.

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Abbreviations: ORN, Osteoradionecrosis; HBO, Hyperbaric Oxygen; HNC, Head and Neck Cancer; RT, Radiotherapy; CTCAE, Common Toxicity Criteria for Adverse Events; ADL, Activities of Daily Living; RCT, Randomised Clinical Trial; VIF, variance inflation factor; PROM, Patient reported outcome measure; AAP, Average Adjusted Predictions; AME, Average Marginal Effects.

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Worldwide, approximately 710,000 patients are diagnosed annually with head and neck cancer (HNC) [1,2].

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 of head and neck RT. It is defined as exposed bone after RT that fails to heal over a period of three months without evidence of persistent or recurrent cancer [3,4]. Recently, published data have indicated that the incidence is less than 5–6% of HNC patients treated with RT [5,6]. However, ORN remains a serious problem. Speech, eating, oral hygiene and dental rehabilitation are challenging, especially combined with xerostomia, dysphagia and trismus [7–9]. Hence, quality of life is often severely affected in ORN patients [10].

Hyperbaric oxygen (HBO) therapy is used adjunctively to surgical removal of ORN [11]. HBO stimulates angiogenesis, increases neovascularization, fibroblast and osteoblast proliferation, and collagen formation in irradiated tissues [12,13]. It is assumed to improve the conditions of the tissues that are marked by decreased vascularization, diminished oxygen supply, and decreased ability to recover after a minor trauma, such as tooth extraction.

However, the benefit of HBO in mandibular ORN remains controversial because of low evidence. Only one randomised clinical trial (RCT) has been conducted, while several cohort studies of variable quality have been published, reporting ORN recovery rates from zero to 100 percent [14–23,24–29]. 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 and the NWHHT2009-1 trial were initiated in a multicentre collaboration involving Danish, Dutch, British and Swedish Centres. The main primary and secondary endpoints of the trials were adjusted in a very early stage before accrual, to make it possible to merge the trials if the accrual rate would become a problem for both trials.

Patients and methods

Protocol design and patient eligibility

The study was a multicentre trial consisting of pooled data from two separate randomised trials with the same main primary endpoint. The secondary endpoints were partially adjusted. Data were pooled because of recruitment difficulties. DAHANCA-21 was conducted in Denmark (one site), Sweden (one site) and the United Kingdom (five sites), and NWHHT2009-1 in the Netherlands (five sites).

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 NWHHT2009-1 NCT 00989820).

Eligible participants were aged ≥ 18 years with osteoradionecrosis of the mandible requiring surgical removal of necrotic bone after RT 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 a pneumothorax, uncontrolled hypertension, uncontrolled epilepsy, or claustrophobia that could not be treated with medication. 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 centre. Patients in NWHHT2009-1 were not stratified.

Ninety-seven 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 Fig. 1.

Demographic data and follow-up.

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

Patient reported outcome measures (PROMs) 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, as judged by the treating clinician. Small necrotic lesions were treated by removal of small sequestrae, 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 vascularised bone graft.

HBO treatment

For the patients in the HBO arm, 100% oxygen was individually delivered through a hood or tight-fitting mask in a pressurised room at 243 kPa (2.4 atmospheres absolute) for 90 min in 40 daily sessions five days a week (30 pre- and 10 postoperative). The pressurisation protocol was equal to the standard treatment schedule used in most hyperbaric regimes [30].

Primary endpoints

The primary endpoint was healing of ORN after one year as evaluated by an adjusted version of the Common Toxicity Criteria of Adverse Events (CTCAE) v 3.0 [31], as shown in Table 1.

Secondary endpoints

Secondary endpoints measured in both trials were Quality of Life (EORTC QLQ-C30 and QLQ-H&N35), pain assessment (VAS scale and analgesics consumption) and smoking habits.

Other secondary endpoints that were measured by the DAHANCA-21 trial only were unstimulated and stimulated salivation rate (ml/min), xerostomia (UKU side effect rating scale [32]). Unstimulated whole saliva (UWS) was collected by the draining method in a pre-weighed cup for a period of 15 min. Stimulated whole saliva was collected for a period of 5 min 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 [33].

In DAHANCA-21, five questions were used to assess ADL. These 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

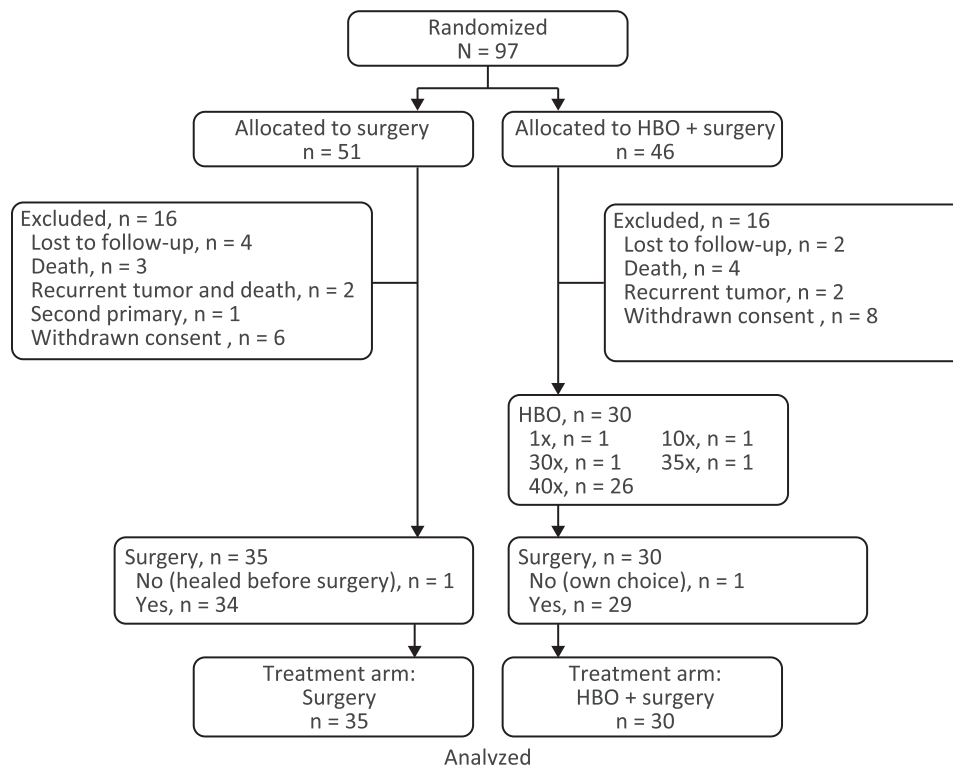


Fig. 1. Flowchart of patients included in the study.

Table 1
Primary clinical endpoint.

Grade*	Definition
0	No evidence of ORN, defined as mucosal coverage of the mandible and no radiologic evidence of ORN
1	Small (<2 mm), asymptomatic and radiographically undetectable bone exposures with no interference with ADL
2	Indication for minimal sequestrectomy, having symptoms with limited interference with ADL
3	Indication for larger sequestrectomy, yet above the mandibular canal and functional limitations interfering with ADL
4	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

* Staging of ORN based on CTCAE v 3.0. Grade 0 and 1 were only registered at evaluation of the primary endpoint at 1-year follow up, as all included patients had verified ORN and indication for treatment at inclusion.

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 ≥ 0) versus ‘Worsening’ (change < 0).

Xerostomia and dysphagia were assessed using an ordinal scale from 0 to 4 according to DAHANCA. Additional secondary endpoints in the DAHANCA21 trial were trismus (interincisal distance, or in edentulous patients, the distance between the alveolar ridges), and dysphagia (CTCAE v 3.0).

A secondary endpoint that was only measured in the NWHHT2009-1 trial was the amount of additional surgical interventions needed to treat the ORN lesion.

Statistics

Both trials were activated in 2008 and planned to include a total of 114 patients (DAHANCA-21) and 120 patients (NWHHT2009-1), 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 2 shows patient and treatment characteristics. 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 (Fig. 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 3). 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 (Supplementary Table 1). 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 (Supplementary Table 2). 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 Fig. 2. The predicted percentage of being healed 1 year after surgery increases when HBO is used with 14% (–3 to 31) for baseline grade 2, 22% (–2 to 46) for baseline grade 3/4, 14% (–4 to 33) for never smokers, and 23% (–2 to 47) for former/current smokers.

Similar results were obtained using ORN grades on an ordinal scale. Supplementary Table 3 shows the results of a univariate ordinal logistic regression analysis, and Supplementary Table 4 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 53 of the 65 patients, and the distribution of ADL scores at baseline was similar in the two treatment arms (Table 3). The changes in ADL score are illustrated in Fig. 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

Table 2
Patient and treatment characteristics.

	All		Surgery		Surgery + HBO		P value
	N	%	N	%	N	%	
<i>Number randomised</i>	97	100.0%	51	52.6%	46	47.4%	
DAHANCA-21	77	79.4%	40	41.2%	37	38.2%	
NWHHT 2009-1	20	20.6%	11	11.3%	9	9.3%	
<i>Number included in analysis</i>	65	100.0%	35	53.8%	30	46.2%	
DAHANCA-21	54	83.1%	30	46.2%	24	36.9%	
NWHHT 2009-1	11	16.9%	5	7.7%	6	9.2%	
<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
Marginal rim resection	33	50.8%	16	45.7%	17	56.7%	
Segmental resection 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 3
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%		

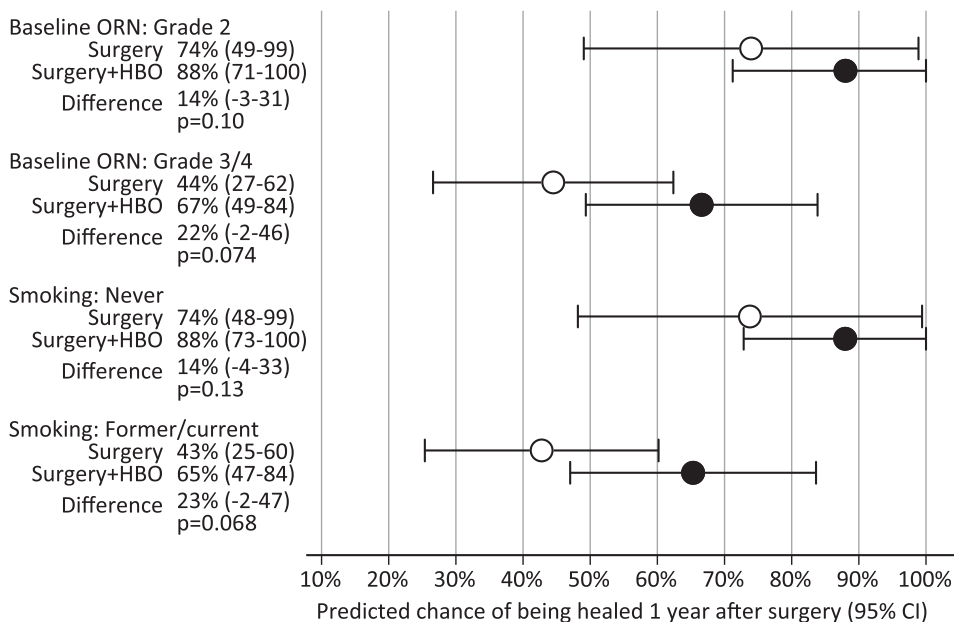


Fig. 2. Predicted chance of being healed 1 year after surgery based on multivariate binary logistic regression model including baseline ORN grade and smoking. Predictions are calculated as average adjusted predictions and differences are average marginal effects (with 95% CI).

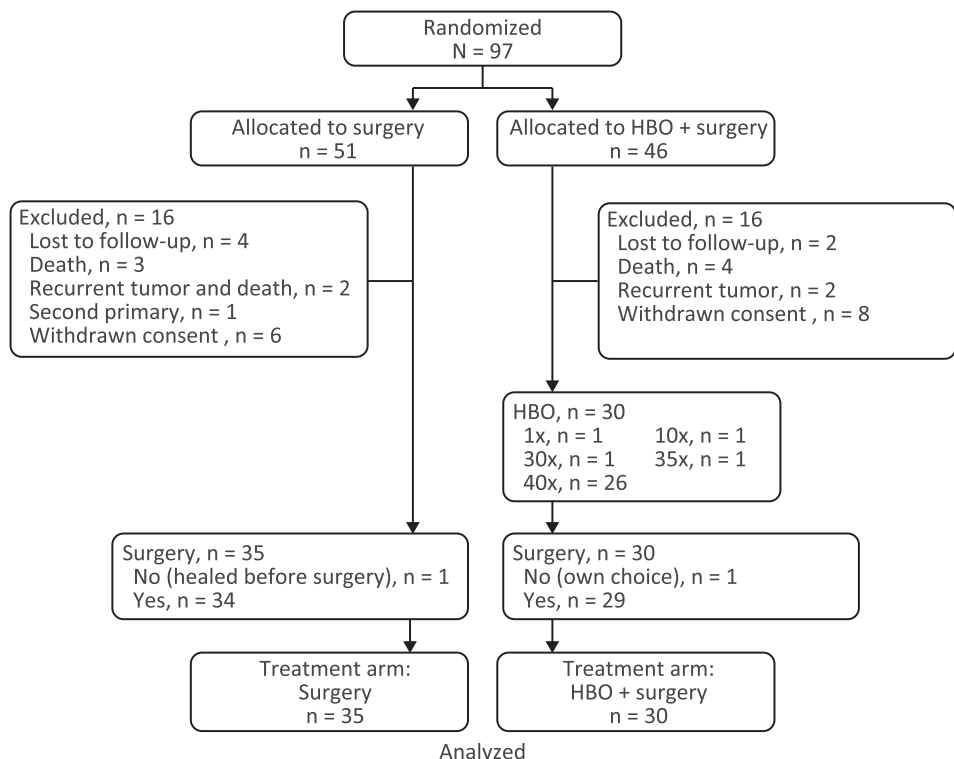


Fig. 3. Improvement in ADL score from baseline to 1 year after surgery by treatment arm. 0 indicates no change and positive numbers indicate improvement (ADL score is reduced).

(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 Fig. 1](#). Differences between treatment arms at each time point are listed in [Supplementary Table 5](#).

Several endpoints appeared to show beneficial effects over time for surgery + HBO compared to surgery alone. The surgery + HBO arm appeared to be more beneficial for xerostomia (DAHANCA), unstimulated whole saliva flow rates, and dysphagia (DAHANCA).

Nevertheless, none of the endpoints showed a significant difference due to the fact that the study was underpowered.

Discussion

DAHANCA-21 and NWHHT2009-1 are the first randomised, controlled trials of HBO + surgery treatment for ORN in head and neck patients investigating a standard HBO protocol with 30 pre-operative and 10 postoperative exposures delivered daily during a period of respectively 6 and 2 weeks.

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. Apparently, an increased chance of healing was observed after surgery + HBO independent of baseline ORN grade or smoking status. Multivariate regression analysis did not show a statistically significant difference between the two groups. Explanatory, the power calculation performed prior to trial initiation aimed at detecting a difference of 25%. Furthermore, the number of 114 cases for achieving adequate power was not obtained due to a low patient accrual rate in both trials. This is an obvious shortcoming 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 NWHHT2009-1. One possible explanation for this is the decreasing incidence of ORN due to improved RT techniques [5,34]. Additionally, a major reason was that the majority of patients who refused participation, did so because HBO was also offered without any requirement for trial participation. Others refused because they lacked mental or physical energy to complete 40 HBO treatments due to comorbidities or for other personal reasons. Some patients were not offered participation because it could not be ruled out that they had a recurrent or new primary cancer.

A minority of the participants randomised for surgery + HBO did not comply with the 40 treatments, mostly because of claustrophobia or malaise. 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. This could be explained by the compromised health status of many in this patient group due to a variety of comorbidities and sequelae from their previous cancer treatment.

In the light of the results of the statistical analysis it should be considered which extent of a clinical improvement will be sufficient to approve of a treatment modality. While planning both trials, we aimed at a 25% improvement to detect a significant difference in 114 patients. The 25% is, however, an arbitrary level. Although the beneficial effect was smaller than anticipated, and not statistically significant in this reduced subset of patients, there

was an increased chance of healing when HBO was used. This finding, although not statistically significant, was observed primarily in grade 3/4 ORN and in former or current smokers which seems in line with the theoretical effect of HBO on neovascularisation and oxygenation.

Further investigation should be encouraged because, besides this trial, only one French multicentre trial from 2004 by Annane and co-workers has been published [35]. 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 about the design of the trial regarding many factors such as diagnostic criteria, grading/classification of the ORN, lack of compliancy with standard HBO guidelines and lack of stratification. Overall, there are concerns regarding the validity of the conclusions regarding the effect of HBO as a mono-modality treatment of ORN in the Annane trial [36] instead of the HBO treatment additional to surgery.

Evaluation of secondary endpoints also showed a beneficial effect of HBO (as part of the combination HBO + surgery) on RT-induced xerostomia, unstimulated salivary flow rate, and dysphagia, although not statistically significant in multivariate analysis. Current literature reports that HBO has the potential to relieve various symptoms in ORN patients, such as hyposalivation and xerostomia (46–49), contributing to an overall improvement in quality of life [37].

Within the enrolment time of approximately 10 years, the accuracy of RT has continuously improved, leading to a more precise delivery of the RT treatment and potentially less toxicity of the surrounding normal structures [5,34,38–43]. Meanwhile, the incidence of head and neck cancer is increasing, as well as the five-year survival rate [44,45]. The onset of ORN occurs mainly within a couple of years after RT [46], but may occur many years later as well [5]. Consequently, treatment of ORN will remain a relevant issue despite ongoing improvements in cancer treatment.

As expected, we observed variable individual responses to the treatment modality HBO + surgery, as some participants did not benefit, whereas others healed successfully. It was, however, surprising that smoking status did not independently predict impaired healing on multivariate analysis ([Supplementary Table 2](#)). This may be explained by the small number of enrolled patients and due to the high healing potential in non-smokers 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 physiology 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 a negative effect primarily in grade 3/4 compared to grade 2 and in current/former smokers compared to the lifelong non-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, aesthetics and sensibility. Depending on the anatomical defect, primary closure may be difficult to obtain and the risk of infection and furtherly compromised healing will be present. This may be reinforced by individual comorbidities, increasingly impairing the healing potential. Finally, the variability in time span from RT to trial participation may affect the individual treatment response, as the RT-induced pathophysiological changes evolve over time. Thus, the timing of HBO may affect the individual response.

Sham treatment was considered in the planning phase of both DAHANCA-21 and NWHHT2009-1, but was abandoned mainly because of a potential hindering of recruitment. Another reason was of ethical nature. Having patients travel far and spend many hours in a HBO2 chamber while receiving only sham treatment

would not be approved by the ethical committees. 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 might increase the trial quality.

Currently, there are no well-documented alternatives to HBO in supporting bone healing combined with surgical intervention of ORN.

To conclude, 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. On the other hand, no recommendation can be done to abandon the use of HBO in the treatment of ORN based on this study as well. This would be a type II error due to the fact that the trial was underpowered and the results, therefore, are not significant. We encourage further research of the effect of HBO as well as relevant alternatives to HBO with regards to ORN.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2021.11.021>.

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.v144.810.1002/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] 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/idi.12318>.
- [4] 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>.
- [5] 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* 2019;58:1373–7. <https://doi.org/10.1080/0284186X.2019.1643037>.
- [6] 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>.
- [7] 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>.
- [8] Jensen K, Lambertsens 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>.
- [9] 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.icms.2012.01.011>.
- [10] 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>.
- [11] Bennett MH, Feldmeier J, Hampson NB, Smees 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>.
- [12] 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).
- [13] Thom SR. Hyperbaric oxygen: its mechanisms and efficacy. *Plast Reconstr Surg* 2011;127:1315–41S. <https://doi.org/10.1097/PRS.0b013e3181f6e2bf>.
- [14] Dieleman FJ, Phan TTT, van den Hoogen FJA, Kaanders JHAM, Merckx 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>.
- [15] 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>.
- [16] 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>.
- [17] 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>.
- [18] 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>.
- [19] 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.v38.5.10.1002/hed.23949>.
- [20] 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>.
- [21] 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>.
- [22] 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>.
- [23] Freiburger 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>.
- [24] Bui Q-C, Lieber M, Withers HR, Corson K, van Rijnsoever M, Elsahle 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>.
- [25] 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>.
- [26] 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>.
- [27] 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.
- [28] 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>.
- [29] 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>.
- [30] Moon RE. *Hyperbaric Oxygen Therapy Indications*. North Palm Beach, FL, USA: Best Publishing Company; 2019.
- [31] NCI. Common Terminology Criteria for Adverse Events v3.0 (CTCAE) 2006. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf (accessed April 21, 2020).
- [32] 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>.
- [33] 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>.
- [34] 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>.
- [35] 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>.
- [36] 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>.
- [37] 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>.
- [38] 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)Osteoradionekrose der Mandibula. Geringeres Risiko durch intensitätsmodulierte Radiotherapie (IMRT). *Strahlenther Onkol* 2006;182:283–8. <https://doi.org/10.1007/s00066-006-1477-0>.
- [39] 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>.
- [40] 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>.
- [41] 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>.
- [42] 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>.
- [43] 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).
- [44] 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* 2018;57:1143–51. <https://doi.org/10.1080/0284186X.2018.1438657>.
- [45] 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).
- [46] 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.