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CLINICAL INVESTIGATION **Head and Neck**

EARLY HYPERBARIC OXYGEN THERAPY FOR REDUCING RADIOTHERAPY SIDE EFFECTS: EARLY RESULTS OF A RANDOMIZED TRIAL IN OROPHARYNGEAL AND NASOPHARYNGEAL CANCER

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Purpose: Comparison of quality of life (QoL) and side effects in a randomized trial for early hyperbaric oxygen therapy (HBOT) after radiotherapy (RT).
Methods and Materials: From 2006, 19 patients with tumor originating from the tonsillar fossa and/or soft palate (15), base of tongue (1), and nasopharynx (3) were randomized to receive HBOT or not. HBOT consisted of 30 sessions at 2.5 ATA (15 msw) with oxygen breathing for 90 min daily, 5 days per week, applied shortly after the RT treatment was completed. As of 2005, all patients received validated questionnaires (*i.e.,* the European Organization for Research and Treatment of Cancer [EORTC] QLQ-C30, EORTC QLQ Head and Neck Cancer Module (H&N35), Performance Status Scale): before treatment; at the start of RT treatment; after 46 Gy; at the end of RT treatment; and 2, 4, and 6 weeks and 3, 6, 12, and 18 months after follow-up.
Results: On all QoL items, better scores were obtained in patients treated with hyperbaric oxygen. The difference between HBOT vs. non-HBOT was significant for all parameters: EORTC H&N35 Swallowing ($p = 0.011$), EORTC H&N35 Dry Mouth ($p = 0.009$), EORTC H&N35 Sticky Saliva ($p = 0.01$), PSS Eating in Public ($p = 0.027$), and Pain in Mouth (visual analogue scale; $p < 0.0001$).
Conclusions: Patients randomized for receiving hyperbaric oxygen after the RT had better QoL scores for swallowing, sticky saliva, xerostomia, and pain in mouth. © 2009 Elsevier Inc.

Hyperbaric oxygen, Radiotherapy, Oropharynx, Nasopharynx, Side effects, Xerostomia.

INTRODUCTION

The goal of treating head and neck cancer patients with radiotherapy (RT) is to deliver high doses of ionizing radiation to the cancer (target) aiming for control of the disease and to maximally spare the surrounding normal tissues. The parotid glands are frequently protected from radiation by applying intensity-modulated radiation therapy (IMRT) techniques. The quality of life (QoL) of oropharyngeal or nasopharyngeal cancer patients treated with such high doses of RT is influenced by acute side effects, such as painful mucositis (*e.g.,* leading to compromised food intake) and late sequelae, such as xerostomia, Grade 3/4 mucositis, trismus, and dysphagia. These non-life-threatening side effects frequently affect QoL. Recently, we have reported a dose–effect relationship for swallowing problems. Using the European Organization for Research and Treatment of Cancer (EORTC) Head and Neck Cancer Module (H&N35) QoL questionnaire and fiberoptic endoscopic evaluation of swallowing (FEES), a significant increase in swallowing problems was reported with increasing dose (1). Xerostomia or dry mouth syndrome results in medical and psychological problems and social distress. For example, the disorder can cause difficulties in speech, chewing, and swallowing, leading to social problems, nutritional problems, and potentially severe dental decay. Dry mouth syndrome is caused by a lack of saliva and a change in the quality of saliva by radiation damage to the major and minor salivary glands. Saliva is produced in both resting and under salivary glands stimulatory conditions. Eisbruch *et al.* (2), for example, have shown that limiting the mean parotid gland dose to approximately

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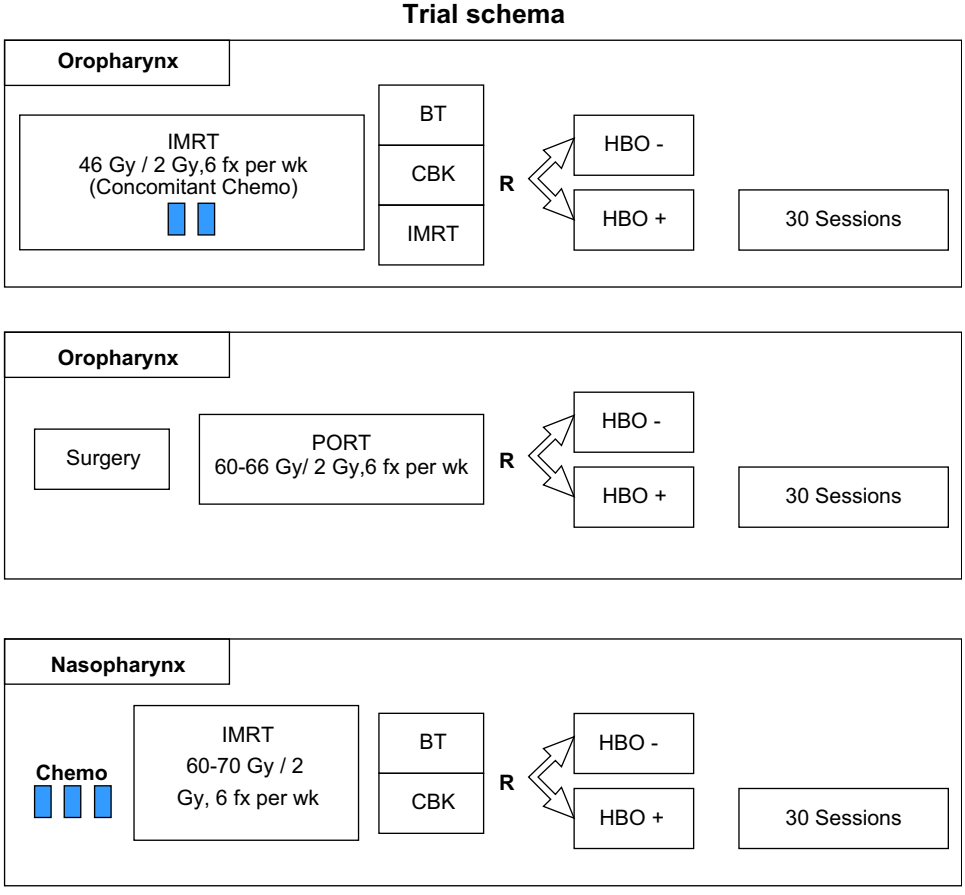
26 Gy can preserve the parotid gland function. Although the parotid glands contribute significantly to the saliva production under stimulatory conditions, they contribute only 20% of the total volume of saliva under resting conditions, whereas submandibular salivary glands contribute 65% (3). However, protecting the submandibular glands is far more difficult than protecting the parotid glands. Hyperbaric oxygen therapy (HBOT) is being used for treatment of late radiation tissue injury (4), but little is known whether HBOT shortly after radiotherapy can reduce radiation side effects. Recently Williamson (5) published an experimental study of the use of hyperbaric oxygen immediately after radiation treatment for malignant disease in a rat model. He reported that, in contrast to the non-HBOT rats, HBO-treated rats showed continued growth of teeth and maintenance of specialized tissues, such as salivary gland and bone in the histological sections. The potential benefit of HBOT in preventing and reducing side effects of RT or chemotherapy in oropharyngeal or nasopharyngeal cancers of the head and neck was the subject of this study. It focused on reduction of radiotherapy toxicity in treatment of oropharyngeal cancer patients with or without administration of HBOT after completion of a radiotherapy treatment schedule (Table 1). Our primary study objective was to determine whether adjuvant hyperbaric oxygen would reduced RT-related side effects in primary oropharyngeal and nasopharyngeal cancer of the head and neck treated by radiation therapy. The primary endpoint was toxicity: xerostomia, dysphagia, trismus, and QoL.

METHODS AND MATERIALS

Patients

Patients presenting at the Erasmus Medical Center (Rotterdam, The Netherlands) with oropharyngeal or nasopharyngeal cancer were eligible for the trial. Patients aged > 18 with histological proof of squamous cell carcinoma of mucous membranes of the oropharynx and nasopharynx who were to be treated with curative intent and who had Karnofsky Performance Status score of ≥ 70 were included. All patients underwent dental examination before radiotherapy. The total prescribed dose of RT to the planning target volume ranged from 46 to 70 Gy. Prescribed brachytherapy boost dose to the primary tumor ranged from 11 to 22 Gy, and prescribed Cyberknife boost dose ranged from 11.2 to 16.5 Gy. More detailed institutional treatment schedule has been described elsewhere (6, 7). The parotids received a mean dose of 6–67 Gy (median dose, 37 Gy). Written informed consent was obtained before the start of the treatment. The study was approved by the Erasmus Medical Center medical ethics board.

Table 1. Schema of the hyperbaric oxygen trial of oropharyngeal and nasopharyngeal cancer patients



Abbreviations: IMRT = intensity-modulated radiotherapy; BT = brachytherapy; CBK = Cyberknife; HBO = hyperbaric oxygen; PORT = postoperative radiotherapy.

Hyperbaric treatment procedure

In patients randomized for HBOT, HBOT was started within 2 days after completion of radiotherapy (and chemotherapy if applicable). HBOT was given at the specialized Institute for Hyperbaric Medicine in Rotterdam in a multiplace hyperbaric chamber. The chamber was pressurized with air over 10 min to a treatment pressure of 2.5 atmospheres absolute (ATA). At this pressure, 100% oxygen was delivered by oronasal mask in three episodes of 25 min, interrupted by 5 min of air breathing, followed by a final 15-min block of oxygen. Depressurization was done on air over 10 min, resulting in an overall treatment duration of 125 min with a total of 90 min of hyperbaric oxygen breathing. This treatment schedule was followed 5 working days per week for the duration of 6 weeks, adding up to 30 total sessions. During pressure changes, great care was taken to avoid barotraumas, particularly of the middle ear, which is the most common side effect of hyperbaric treatment.

Randomization

Patients were randomized by the trial office. This randomization took place directly after inclusion of the patients in the study by use of a block of several randomized sizes. Patients were stratified by tumor site (*i.e.,* oropharynx or nasopharynx) and treatment modality (*i.e.,* IMRT or Cyberknife/Brachytherapy or postoperative radiotherapy).

Quality of life

For QoL investigation, all patients were given the following questionnaires: (*1*) The EORTC core QoL Questionnaire (QLQ)-C30, (*2*) The EORTC QLQ-H&N35 (8), and (*3*) the Performance Status Scale (PSS) of List *et al.* (9) with the normalcy of diet item. Patients also used a visual analogue scale (VAS; 0–10) to rate their dry mouth and pain. At the time points 0 (before treatment), 1 (start of treatment), 2 (46 Gy), 3 (end of treatment), 4 (2 weeks posttreatment, 5 (4 weeks posttreatment), 6 (6 weeks posttreatment), 7 (3 months posttreatment), 8 (6 months posttreatment), 9 (12 months posttreatment), and 10 (18 months posttreatment), questionnaires were sent to the patients by mail. After scoring, the questionnaires were returned to the data manager (Table 2).

Statistical analysis

The sample size of this trial was based on a reduction of xerostomia of 50% to 25% at 1 year after starting treatment if HBOT was used, which meant that 2 × 66 patients (alpha = 0.05, two-sided; beta = 0.80) were needed to be included. A robust regression analysis was performed with the responses to the QoL questionnaires at the various time points (Table 2). Further, differences (p values) for the hyperbaric oxygen vs. control group were computed at time cohorts before radiotherapy ($t = 0$), at the end of radiotherapy and until 13 weeks posttreatment ($t = 3$ through $t = 7$), and during the time periods of 13 weeks until 78 weeks posttreatment ($t = 7$ until $t = 10$). At $t = 0$, a Mann-Whitney U test was used. For the other two time cohorts, regression analysis for each complaint variable vs. time (coded with dummy variables) and treatment factor (yes/no hyperbaric oxygen) were performed with the program xtreg in Stata. This was a regression analysis based on maximum likelihood estimation and incorporating the longitudinal character of the data. Stata 9 software was used for the statistical analysis (Stata Statistical Software, Release 9; StataCorp, College Station, TX).

Table 2. Time points corresponding to the quality of life list numbers

List number	Time point
0	Before treatment
1	Start treatment
2	Mid treatment (46 Gy)
3	End treatment
4	2 weeks posttreatment
5	4 weeks posttreatment
6	6 weeks posttreatment
7	3 months posttreatment
8	6 months posttreatment
9	12 months posttreatment
10	18 months posttreatment

RESULTS

Because of slow accrual and lack of financial support, the trial was stopped at a premature time point, with only 19 patients eligible to be studied for the effect of hyperbaric oxygen. All patients included in the trial were analyzed to this effect. Patient characteristics are shown in Table 3. At the censor date of March 1, 2008, with first patient included at the beginning of 2006, maximum follow-up time was 78 weeks. Results regarding xerostomia-related questionnaires are shown in Figs. 1–3. A significant difference in the HBOT group compared with the non-HBOT-treated control group was found for the sticky saliva and dry mouth items of the EORTC H&N35 questionnaires and the VAS dry mouth item. The mean scores for the VAS dry mouth item per time point are given in Table 4. The p values were calculated by dividing the sequence of toxic events in an

Table 3. Patient characteristics table

	HBO +	HBO –
Number	8	11
Tumor site		
Tonsillar fossa	6	9
Base of tongue	1	0
Nasopharynx	1	2
Male/Female	6/2	6/5
TNM stage		
T1	2	2
T2	5	3
T3	1	4
T4a	0	2
N0	3	3
N1	0	2
N2a	0	1
N2b	4	2
N2c	0	2
N3	1	1
Stage grouping		
I	0	1
II	3	2
III	4	6
IV	1	2
Chemotherapy	3	5
Boost		
No	3	6
Brachytherapy	4	2
Cyberknife	1	3
Bilateral neck	1	1

Abbreviation: HBO = hyperbaric oxygen.

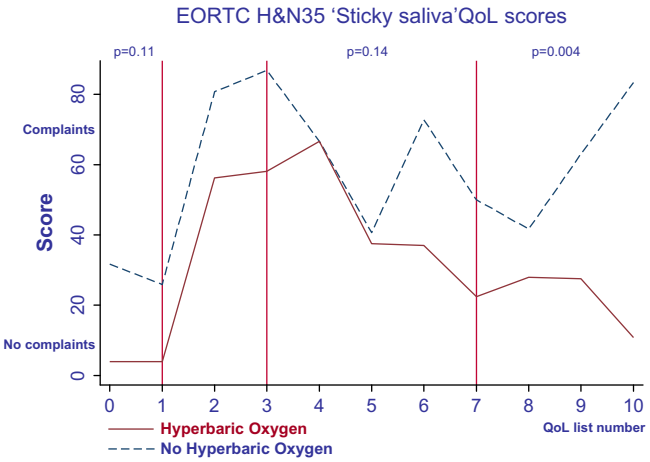


Fig. 1. European Organization for Research and Treatment of Cancer (EORTC) Head and Neck Cancer Module (H&N35) sticky saliva item scores between the hyperbaric oxygen–administered group of patients and the group that was not administered hyperbaric oxygen over an 18-month period. QoL = quality of life.

acute phase (end of radiation until 13 weeks posttreatment) and a late side effects phase (from 13 weeks until 78 weeks posttreatment). The differences in QoL scoring were not significant in the acute phase; however, late side effects were significantly reduced for the HBOT group (Fig. 1). For dysphagia-related questionnaires, there was also a significant difference in QoL between patients treated vs. not treated with hyperbaric oxygen (Figs. 4 and 5). The mean QoL scores for the EORTC H&N 35 swallowing item, per time point, are shown in Table 5. The VAS score for pain in mouth between the with- and without-HBOT groups was also significantly different, as shown in Fig. 6. The following p values were established for EORTC H&N35 sticky saliva (p = 0.01), EORTC H&N35 dry mouth (p = 0.009), EORTC H&N35 swallowing (p = 0.011), PSS eating in public (p = 0.027), and VAS Pain in mouth ($p < 0.0001$). HBOT side effects were limited in our patients. HBOT was well tolerated in this group of patients.

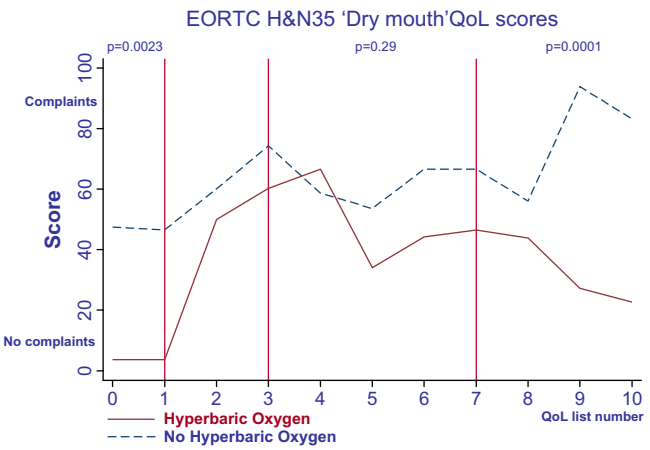


Fig. 2. European Organization for Research and Treatment of Cancer (EORTC) Head and Neck Cancer Module (H&N35) dry mouth item scores between the hyperbaric oxygen–administered group of patients and the group that was not administered hyperbaric oxygen over an 18-month period. QoL = quality of life.

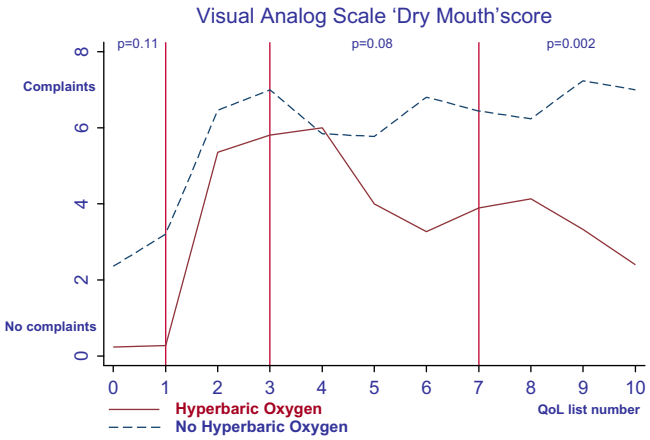


Fig. 3. Visual analog scale of the dry mouth between the hyperbaric oxygen–administered group of patients and the group that was not administered hyperbaric oxygen over an 18-month period. QoL = quality of life.

DISCUSSION

When radiation is used to treat cancer, it also (partly) affects a variety of critical surrounding normal tissues, which can become hypocellular, hypovascular, and hypoxic, frequently eluded to as "3 H tissue." The hypoxic status of tissues can be counteracted to some extent by oxygenation of normal cells with HBOT. The effects of hyperbaric oxygen can be briefly summarized as follows: short-term effects are enhanced by oxygen delivery, reduction of edema, and phagocytosis activation, as well as anti-inflammatory effects. Long-term effects are neovascularization, osteoneogenesis, and stimulation of collagen formation by fibroblasts (10).

It was recently found that a significant increase in mobilization of stem cells from the bone marrow occurs in the course of HBOT (4, 11). Wound healing and recovery of normal-tissue radiation injury are the end result (12–14). It has been demonstrated that hyperbaric oxygen administration reaches its optimal effect after 24–30 sessions for neo-angiogenesis, and stem cell mobilization is particularly prominent after 20 treatments (11). Therefore, in our study, we applied 30 sessions. It could be that 20 sessions are sufficient to reduce side effects. This remains to be elucidated in future studies.

Table 4. Mean quality of life score for visual analog scale dry mouth at the different time points

List number	HBO	No HBO	Total group
0	0	3	2
1	0	3	2
2	5	6	6
3	6	7	6
4	6	6	5
5	5	6	6
6	4	7	5
7	4	6	5
8	4	6	5
9	4	7	4
10	3	7	5

Abbreviation: HBO = hyperbaric oxygen.

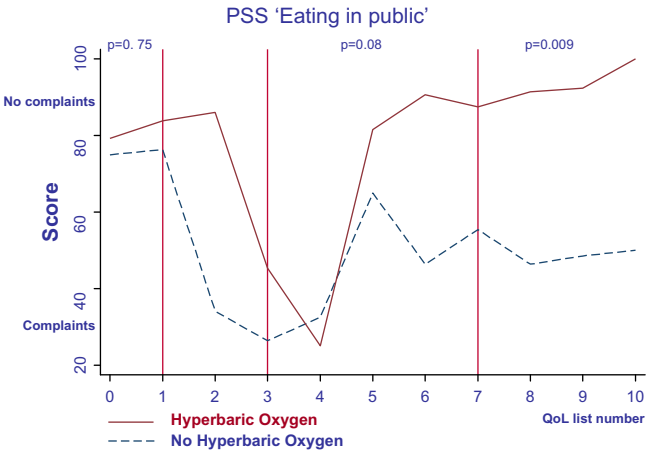


Fig. 4. Performance status scale (PSS) eating in public item scores between the hyperbaric oxygen–administered group of patients and the group that was not administered hyperbaric oxygen over an 18-month period. QoL = quality of life.

Clinically, hyperbaric oxygen has shown beneficial effects, for example, in hypoxic ulcers that result in severe wound-healing problems and in osteoradionecrosis (4). HBOT has been used for 40 years in combination with conservative treatment and radical surgery for necrotic soft tissues and bone that fail to heal. Although there are some conflicting experimental results (15), it is now believed that HBOT does not promote cancer growth (primary or metastasis). Moreover, according to Feldmeier *et al.* (16), no evidence indicates that hyperbaric oxygen is an initiator or promotor of cancer de novo. According to Schonmeyr *et al.* (17), no difference of cellular proliferation of squamous cell cancer in vitro was observed comparing hyperbaric oxygen–treated cells with controls. In a study by Marx *et al.* (18), HBO induced significantly angiogenesis, measurable after eight HBOT sessions. Recently, Gerlach *et al.* (19) published a retrospective study on the use of HBOT in clinic; they described 21 patients who received radiotherapy for oral or

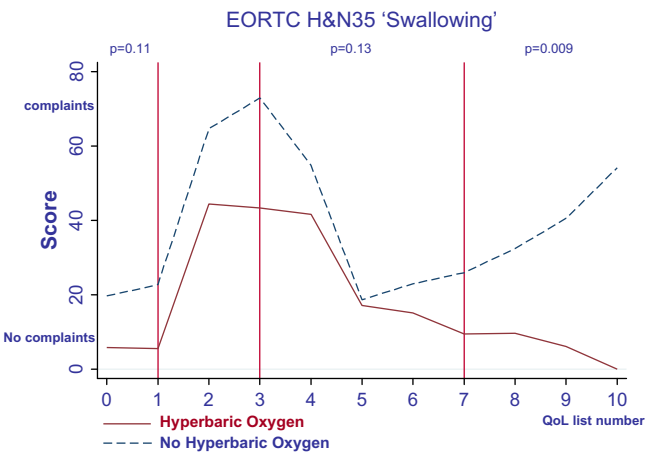


Fig. 5. European Organization for Research and Treatment of Cancer (EORTC) Head and Neck Cancer Module (H&N35) swallowing item scores between the hyperbaric oxygen–administered group of patients and the group that was not administered hyperbaric oxygen over an 18-month period. QoL = quality of life.

Table 5. Mean quality of life score for EORTC H&N35 swallowing item at the various time points

List number	HBO	No HBO	Total group
0	7	25	17
1	6	28	18
2	45	59	53
3	42	56	48
4	42	52	48
5	19	19	19
6	15	33	27
7	10	30	21
8	12	33	24
9	7	40	20
10	0	54	22

Abbreviations: EORTC = European Organization for Research and Treatment of Cancer; H&N35 = Head and Neck Cancer Module; HBO = hyperbaric oxygen.

oropharyngeal carcinoma in which swallowing-related problems significantly decreased with time. They also observed a subjective increase in saliva and an improvement in sense of taste. In a review by Bennett *et al.* (4), the authors concluded that there is some evidence that hyperbaric oxygen improves outcomes in late radiation tissue injury affecting bone and soft tissues of the head and neck, for proctitis, and to prevent the development of osteoradionecrosis following tooth extraction in an irradiated field. A large double-blind randomized study has shown the substantial benefit of HBOT on QoL in chronic refractory radiation proctitis (20). In contrast to our study, these publications are concerned with the use of HBOT in late radiation tissue damage. The possible preventive action of HBOT immediately after radiotherapy has not been addressed, which was the purpose for our study.

We found a significant difference in several QoL aspects between patients in whom early hyperbaric oxygen was administered vs. a non-HBOT group. Five to 18 patients responded to the questionnaires at each time point. Although there was variation in response to the questionnaires at each

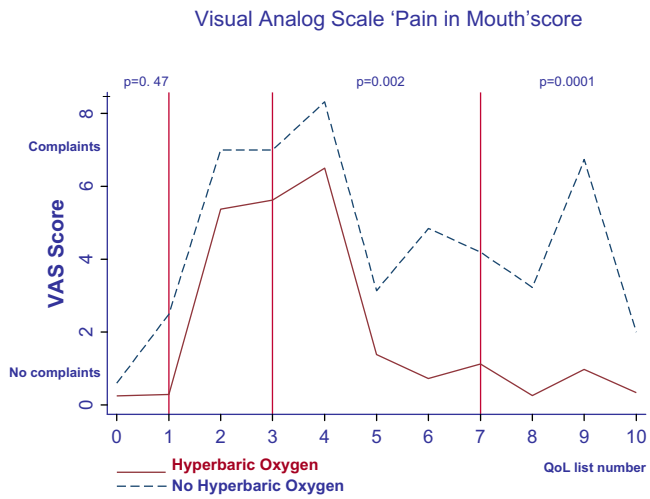


Fig. 6. Visual analog scale of the pain in mouth question between the hyperbaric oxygen–administered group of patients and the group that was not administered hyperbaric oxygen over an 18-month period. QoL = quality of life.

time point, comparison of the groups at the various time points appeared to be nonsignificant (Mann-Whitney U test; $p = 0.84$). Clearly, the QoL of patients is similar until the end of radiation or in the period within 2 weeks after radiation. The worst scores on the QoL items (patient complaints) were found at the end of radiation or in the period within 2 weeks after completion of radiation. A significant difference was observed for the EORTC H&N35 dry mouth question (Fig. 2), that is, baseline values for the patients treated with HBO and those not treated. However, we could not identify confounding factors to explain this difference. One possible reason for this is that some patients who knew they were not going to receive HBOT after radiation could argue that they must have a dry mouth to some extent because the purpose of the investigation was to investigate potential successful treatment of xerostomia with HBOT. Increased QoL in patients treated with hyperbaric oxygen showed a steep improvement beginning 2 weeks after finishing RT. This was found to be particularly true for the data in our study regarding xerostomia and dysphagia. Pain (VAS score) was also almost totally eliminated (no pain 6 weeks posttreatment). Of interest is the fact that no significant effect of hyperbaric oxygen was shown for early side effects (see Figs. 1, 4, and 5; time cohort 3 until 7 ($\leq$ 13 weeks) as opposed to the late side effects ($\geq$ 13 weeks posttreatment). Patients undergoing HBOT are probably aware that the treatment under study consisted of hyperbaric oxygen, with the reverse being true for those not receiving HBOT; however, we do not believe that patients filling in the questionnaires after 18 months maximum follow-up are biased by the treatment. Nevertheless, a placebo effect could not totally be disproved.

CONCLUSIONS

A significant difference was observed between the non-HBOT vs. HBOT groups in almost every QoL issue studied. Although this study is limited by the small numbers of patients, we feel that the data are of interest because they emphasize the potential beneficial effect of early hyperbaric oxygen. Several issues remain to be explored. It is of interest to determine the optimal commencement of HBOT after radiation therapy as well as the necessary number of treatments. Also, the mechanisms through which HBOT shortly after radiotherapy cause the demonstrated beneficial effects on QoL should be further explored. Because questions remain regarding HBOT after radiotherapy, a bigger randomized trial should be conducted to answer the remaining questions.

REFERENCES

1. Teguh DN, Levendag PC, Sewnaik A, *et al*. Results of fiberoptic endoscopic evaluation of swallowing vs. radiation dose in the swallowing muscles after radiotherapy of cancer in the oropharynx. *Radiother Oncol* 2008;89:57–63.
2. Eisbruch A, Ship JA, Dawson LA, *et al*. Salivary gland sparing and improved target irradiation by conformal and intensity modulated irradiation of head and neck cancer. *World J Surg* 2003;27: 832–837.
3. Schneyer LH. Source of resting total mixed saliva of man. *J Appl Physiol* 1956;9:79–81.
4. Bennett MH, Feldmeier J, Hampson N, *et al*. Hyperbaric oxygen therapy for late radiation tissue injury. *Cochrane Database Syst Rev* 2005;CD005005.
5. Williamson RA. An experimental study of the use of hyperbaric oxygen to reduce the side effects of radiation treatment for malignant disease. *Int J Oral Maxillofac Surg* 2007;36:533–540.
6. Teguh DN, Levendag PC, Voet P, *et al*. Trismus in patients with oropharyngeal cancer: Relationship with dose in structures of mastication apparatus. *Head Neck* 2008;30:622–630.
7. Teguh DN, Levendag PC, Noever I, *et al*. Treatment techniques and site considerations regarding dysphagia-related quality of life in cancer of the oropharynx and nasopharynx. *Int J Radiat Oncol Biol Phys* 2008;72:1119–1127.
8. Bjordal K, de Graeff A, Fayers PM, *et al*. A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. EORTC Quality of Life Group. *Eur J Cancer* 2000;36:1796–1807.
9. List MA, DAntonio LL, Cella DF, *et al*. The performance status scale for head and neck cancer patients and the functional assessment of cancer therapy head and neck scale—A study of utility and validity. *Cancer* 1996;77:2294–2301.
10. Marx RE, Ehler WJ, Tayapongsak P, Pierce LW. Relationship of oxygen dose to angiogenesis induction in irradiated tissue. *Am J Surg* 1990;160:519–524.
11. Thom SR, Bhopale VM, Velazquez OC, *et al*. Stem cell mobilization by hyperbaric oxygen. *Am J Physiol Heart Circ Physiol* 2006;290:H1378–H1386.
12. Mayer R, Hamilton-Farrell MR, van der Kleij AJ, *et al*. Hyperbaric oxygen and radiotherapy. *Strahlenther Onkol* 2005;181: 113–123.
13. Pasquier D, Hoelscher T, Schmutz J, *et al*. Hyperbaric oxygen therapy in the treatment of radio-induced lesions in normal tissues: A literature review. *Radiother Oncol* 2004;72:1–13.
14. van Merkesteyn R, Bakker DJ. Comment on ''Hyperbaric oxygen therapy for radionecrosis of the jaw: A randomized, placebo-controlled, double-blind trial from the ORN96 Study Group.'' *J Clin Oncol* 2005;23:4465–4466.
15. Bradfield JJ, Kinsella JB, Mader JT, Bridges EW. Rapid progression of head and neck squamous carcinoma after hyperbaric oxygenation. *Otolaryngol Head Neck Surg* 1996;114: 793–797.
16. Feldmeier J, Carl U, Hartmann K, Sminia P. Hyperbaric oxygen: Does it promote growth or recurrence of malignancy? *Undersea Hyperb Med* 2003;30:1–18.
17. Schonmeyr BH, Wong AK, Reid VJ, *et al*. The effect of hyperbaric oxygen treatment on squamous cell cancer growth and tumor hypoxia. *Ann Plast Surg* 2008;60:81–88.
18. Marx RE, Johnson RP, Kline SN. Prevention of osteoradionecrosis: A randomized prospective clinical trial of hyperbaric oxygen versus penicillin. *J Am Dent Assoc* 1985;111:49–54.
19. Gerlach NL, Barkhuysen R, Kaanders JH, *et al*. The effect of hyperbaric oxygen therapy on quality of life in oral and oropharyngeal cancer patients treated with radiotherapy. *Int J Oral Maxillofac Surg* 2008;37:255–259.
20. Clarke RE, Tenorio LM, Hussey JR, *et al*. Hyperbaric oxygen treatment of chronic refractory radiation proctitis: A randomized and controlled double-blind crossover trial with long-term follow-up. *Int J Radiat Oncol Biol Phys* 2008;72: 134–143.