Hyperbaric Oxygen and Radiotherapy

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Background: Hyperbaric oxygen (HBO) therapy is the inhalation of 100% oxygen at a pressure of at least 1.5 atmospheres absolute (150 kPa). It uses oxygen as a drug by dissolving it in the plasma and delivering it to the tissues independent of hemoglobin. For a variety of organ systems, HBO is known to promote new vessel growth into areas with reduced oxygen tension due to poor vascularity, and therewith promotes wound healing and recovery of radiation-injured tissue. Furthermore, tumors may be sensitized to irradiation by raising intratumoral oxygen tensions.
Methods: A network of hyperbaric facilities exists in Europe, and a number of clinical studies are ongoing. The intergovernmental framework COST B14 action "Hyperbaric Oxygen Therapy" started in 1999. The main goal of the Working Group Oncology is preparation and actual implementation of prospective study protocols in the field of HBO and radiation oncology in Europe.
Results: In this paper a short overview on HBO is given and the following randomized clinical studies are presented:
a) reirradiation of recurrent squamous cell carcinoma of the head and neck after HBO sensitization;
b) role of HBO in enhancing radiosensitivity on glioblastoma multiforme;
c) osseointegration in irradiated patients; adjunctive HBO to prevent implant failures;
d) the role of HBO in the treatment of late irradiation sequelae in the pelvic region.
The two radiosensitization protocols (a, b) allow a time interval between HBO and subsequent irradiation of 10–20 min.
Conclusion: Recruitment of centers and patients is being strongly encouraged, detailed information is given on *www.oxynet.org*.

Key Words: Hyperbaric oxygen therapy · Radiation-induced lesions · Radiosensitization · Radiotherapy · Clinical protocols

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Hyperbare Oxygenation und Strahlentherapie

Hintergrund: Unter „hyperbarer Sauerstofftherapie", auch „hyperbare Oxygenation" (HBO) genannt, versteht man die Atmung von 100% Sauerstoff bei einem Druck von mindestens 1,5 ATA (absolute Atmosphären; 150 kPa). Bei der HBO wird das Medikament Sauerstoff durch erhöhten Umgebungsdruck physikalisch im Plasma gelöst und unabhängig vom Hämoglobin in das Gewebe transportiert. Die HBO unterstützt in schlecht durchbluteten bestrahlten Geweben mit verringerter Sauerstoffspannung die Gefäßneubildung und trägt zur Wundheilung und Erholung des bestrahlten Gewebes bei. Andererseits kann Sauerstoff unter hyperbaren Bedingungen – während oder kurz vor der Strahlentherapie verabreicht – durch Erhöhung der intratumoralen Sauerstoffspannung als Radiosensitizer eingesetzt werden.
Methodik: In Europa existiert ein Netzwerk von Druckkammern, an denen klinische Studien laufen. Im Jahr 1999 wurde das europäische Projekt COST B14 „Hyperbare Sauerstofftherapie" gestartet. Das Hauptziel der Arbeitsgruppe „Onkologie" ist die Vorbereitung und Implementierung klinischer Studienprotokolle, die sich mit dem Thema „HBO und Strahlentherapie" beschäftigen.

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Ergebnisse: Die vorliegende Arbeit gibt einen kurzen Überblick über die Grundlagen und Wirkweise der HBO und stellt folgende zur Rekrutierung offenen randomisierten klinischen Studien vor:
a) erneute Bestrahlung rezidivierter Plattenepithelkarzinome im Kopf-Hals-Bereich nach HBO-Sensibilisierung;
b) HBO zur Erhöhung der Strahlensensibilität des Glioblastoma multiforme;
c) Osseointegration nach Bestrahlung im Hopf-Hals-Bereich – adjuvante HBO zur Verhinderung der Implantatabstoßung;
d) HBO bei radiogenen Spätfolgen im Beckenbereich.
Die zwei Protokolle zur Strahlensensibilisierung (a, b) erlauben einen Zeitabstand zwischen HBO und nachfolgender Bestrahlung von 10–20 min.
Schlussfolgerung: Interessierte Zentren werden eingeladen, sich aktiv an den Studien zu beteiligen (Details s. *www.oxynet.org*).

Schlüsselwörter: Hyperbare Sauerstofftherapie · Radiogene Spätfolgen · Strahlensensibilisierung · Strahlentherapie · Klinische Protokolle

Introduction

Hyperbaric Oxygen Therapy

Hyperbaric oxygen (HBO) therapy is the inhalation of 100% oxygen at elevated pressure > 1.5 atmospheres absolute (ATA; 150 kPa), typically 2–3 ATA (200–300 kPa). The hyperbaric chamber is the medical tool that provides those conditions to apply very high doses of oxygen in amounts that cannot be reached by any other means.

During HBO, oxygen is dissolved physically in the blood plasma. At an ambient pressure of 2.8 ATA, the amount of plasma-dissolved oxygen is approximately 6 vol.%, equivalent to basic oxygen metabolic needs, and the paO_2 in the arteries can reach 2,000 mmHg. With a normal lung function and tissue perfusion, a pO_2 > 1,000 mmHg could be reached. The physiological effects of HBO include short-term effects like vasoconstriction and enhanced oxygen delivery, reduction of edema, and phagocytosis activation, and it has an anti-inflammatory effect [25, 71]. Long-term effects are neovascularization [53], osteoneogenesis as well as stimulation of collagen production by fibroblasts. The clinical results are, therefore, wound healing and recovery of radiation-injured tissue. Extensive evidence is available [16] now to preclude any tumor-enhancing effect of HBO. A different aspect is that tumors may be sensitized to irradiation by raising intratumoral oxygen tensions. For irradiation sensitization it is aimed for euoxic conditions, which may persist for some time after leaving the pressure chamber, even if the high level oxygenation has been exhaled.

HBO in radiation oncology was discussed at the ESTRO (European Society for Therapeutic Radiology and Oncology) – ECHM (European Committee for Hyperbaric Medicine) Consensus Meeting in Lisbon 2001 [46]. It was concluded that, according to evidence-based medicine criteria, the effect of HBO on neoangiogenesis and osteogenesis was graded level 1. The aim of the present project is to obtain clinical data that meet this evidence.

The Hyperbaric Treatment

Each patient is examined by the hyperbaric physician regarding their suitability for the treatment. Before HBO treatment patients may have spirometry and a chest X-ray, to exclude severe lung disease, and an investigation by the ear-nose-throat (ENT) specialist confirming their ability to equalize pressures in the middle ear. Contraindications for HBO therapy are listed in Table 1.

Apart from monoplace chambers (Figure 1) which are pressurized with 100% oxygen, multiplace chambers (Figure 2) are much more comfortable for patients. Today, HBO is frequently applied in multiplace chambers. Patients are pressurized in air while oxygen is administered through a personal breathing system which is sealed off from the air in the chamber. For safety reasons, it is advised to have a medical attendant inside the chamber. In all HBO facilities there is a control panel outside the chamber, operated by

Table 1. Contraindications to hyperbaric oxygen therapy.

Tabelle 1. Hyperbare Sauerstofftherapie – Kontraindikationen.

Absolute contraindications
Untreated pneumothorax
Simultaneous administration of
• Doxorubicin
• Bleomycin
• Disulfiram
• Cisplatinum
• Mafenide acetate
Previous administration of bleomycin
Relative contraindications
Claustrophobia
Seizure disorders
Pyrexia (severe)
Upper respiratory tract infections
Chronic sinusitis
Chronic lung disease with CO_2 retention
History of spontaneous pneumothorax
History of thoracic surgery
Asymptomatic pulmonary lesions on chest X-ray
History of surgery for otosclerosis
History of optic neuritis
Viral infections
Congenital spherocytosis
Pregnancy

Figure 1. The monoplace HBO chamber. The atmosphere in the chamber consists of 100% oxygen.

Abbildung 1. Einpersonenkammer zur hyperbaren Sauerstofftherapie. Die Atmosphäre in der Kammer besteht aus 100% Sauerstoff.

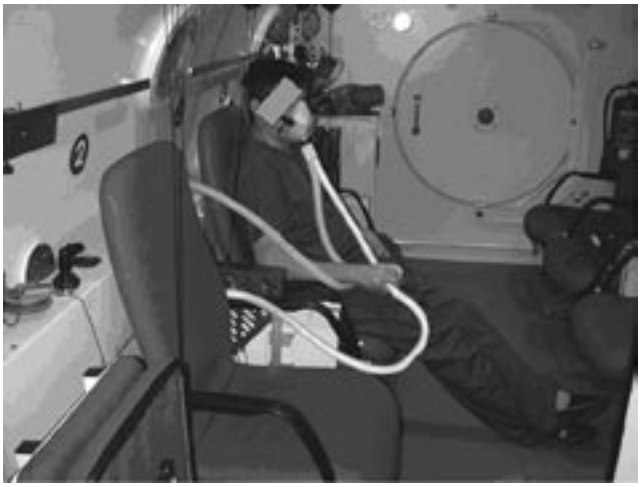

Figure 2. Oxygen-breathing patient in a multiplace HBO chamber. The atmosphere in the chamber consists of air. Oxygen is taken up through a breathing-mask system.

Abbildung 2. Patient mit Sauerstoffmaske in einer begehbaren Mehrpersonenkammer. Die Atmosphäre in der Kammer besteht aus Luft. Sauerstoffaufnahme erfolgt über ein Maskensystem.

trained staff members, taking care that the chamber is pressurized or depressurized within the safety limits. A communication system allows contact with the patients inside the chamber.

Hyperbaric Oxygen Therapy in Europe

In Europe, there are many hyperbaric facilities (c.f., *www.oxynet.org*). They vary in capacity and in patient dependence, although some are able to treat critically ill patients requiring

Table 2. Clinical trials of radiotherapy and hyperbaric oxygen (HBO) in head and neck tumors. SCC: squamous cell carcinoma.

Tabelle 2. Klinische Studien – Radiotherapie und hyperbarer Sauerstoff (HBO) bei Kopf-Hals-Tumoren. SCC: Plattenepithelkarzinom.

Author	Patients (n)	Tumor localization	Radiotherapy	HBO sessions ATA	HBO sessions Number	Results	Follow-up (months)
Henk 1986 [35] Prospective controlled trial	104	SCC head and neck	a) 35 Gy/10 fx under HBO b) 60 Gy/30 fx in air	4	10	a) 5-year survival 60% (sign. better) 5-year local control 63% (sign. better) b) 5-year survival 30% 5-year local control 30%	not detailed
Sealy et al. 1986 [67]	130	SCC head and neck (locally advanced)	a) 36 Gy/6 fx + misonidazole under HBO b) 63 Gy/30 fx in air	3	6	a) 1-year local control 43% b) 1-year local control 28%	not detailed
Haffty et al. 1999 [30] Randomized trial	48	SCC of head and neck (locally advanced)	a) 23 Gy/2 fx under HBO separated by 21 days b) 25.3 Gy/2 fx in air separated by 21 days	4	2	a) 21 of 25 clinical response 5-year local control 29% (sign. better) b) 13 of 25 clinical response 5-year local control 16% (sign.) No difference in overall survival High late complication rate due to extreme form of hypofractionation	20 years (all pts. died)
Haffty et al. 1999 [31] Retrospective trial	45	Advanced laryngeal carcinoma without prior surgery	22 Gy/2 fx under HBO separated by 21 days	4	2	Complete clinical response in 87% 10-year local control for all patients 58% 10-year local control for responders 69% 10-year voice preservation in responders 55% 5-year actuarial complication rate 42%	not detailed

Table 3. Clinical trials of radiotherapy and hyperbaric oxygen (HBO) in brain tumors. NA: not available.
Tabelle 3. Klinische Studien – Radiotherapie und hyperbarer Sauerstoff (HBO) bei Hirntumoren. NA: nicht angegeben.

Author	Patients (n)	Tumor localization	Radiotherapy	Additional therapy	HBO sessions ATA	HBO sessions Number	Results	Follow-up (months)
Kohshi et al. 1999 [43] Non-randomized trial	29	Glioblastoma (a = 10, b = 11) Anaplastic astrocytoma (a = 5, b = 3)	a) 57.8 ± 5.7 Gy 15–30 min after HBO b) 57.8 ± 5.7 Gy	*Concurrent radiochemotherapy a) and b)* Nitrosurea 75 mg/m² day 1 and 5–6 weeks after radiotherapy	2.5	20–30	a) 73% tumor regression > 50 % median survival 24 months b) 29% tumor regression > 50% median survival 12 months	2–76
Ogawa et al. 2003 [60] Prospective trial	21	Glioblastoma (15) Anaplastic astrocytoma (1) Anaplastic oligodendroglioma (5)	60 Gy/2 Gy < 15 min after HBO	*Concurrent radiochemotherapy* Procarbazine 90 mg/m² (day 1–14) ACNU 80 mg/m² (day 1) Vincristine 0.5 mg/m² (day 1 and 8) *Adjuvant chemotherapy post RT* 3-month interval max. 4 courses	2.8	30	Median time to progression 15 months 1-year progression-free survival 58% 2-year progression-free survival 38%	Mean 14.2 4.4–27.9
Beppu et al. 2003 [4] Phase II study	35	Supratentorial malignant glioma	60 Gy/2 Gy < 15 min after HBO	*Concurrent radioimmunochemotherapy* Interferon-β 3 million IU/m² (3 times per week) ACNU 80 mg/m² (day 1 and 36)	2.8	30	Median time to progression: Glioblastoma 38 weeks Anaplastic astrocytoma 56 weeks Overall 43 weeks	NA

multisystem support, including artificial ventilation. Some are integral to a university institute, and some are located within public hospitals. It is estimated that about 500 patients a year are treated in European hyperbaric facilities for radiation-induced injuries, the majority with disease in the head and neck. There is a limited number of HBO centers positioned in the proximity of radiation oncology departments. As a matter of course, studies on the use of HBO as radiosensitizer are restricted to those institutes.

All facilities are medically accompanied. The physician is responsible for the safety and appropriate treatment of patients, together with medical nursing and technical staff who are trained to a high standard. Each country has its own standards of care, including health and safety. European normalization has been started and will be available in the coming year. Concerning the cost-benefit ratio in the treatment of normal tissue damage following radiation treatment, different aspects should be considered. The costs of reduced quality of life are difficult to quantify. However, the health-economic costs resulting from frequent consultation of physicians as well as socioeconomic costs from disability or early retirement are slightly easier to estimate. Although HBO treatment is limited to dedicated centers, its use might contribute to cost reduction in the care of long-term survivors of malignancy.

Hyperbaric Oxygen and Tumor Induction and Recurrence

Feldmeier et al. [16] reviewed preclinical and clinical data providing strong evidence that intermittent HBO has no enhancing effect on cancer growth (primary or metastatic). Also, there is no credible evidence that HBO is an initiator or promoter of cancer de novo. Animal studies specifically designed to study the impact of HBO on malignant tumor growth and metastasis failed to demonstrate a tumor growth-enhancing effect. A large number of studies (mostly controlled) including > 3,000 patients enrolled in trials designed to investigate HBO as a radiosensitizer demonstrated either a neutral or cancer-inhibitory effect.

Hyperbaric Oxygen and Radiotherapy

Regarding the combination of HBO and radiotherapy, we are faced with two applications in clinical practice: (1) HBO as radiosensitizer: hyperbaric oxygen is then applied simultaneously with or prior to irradiation with the aim of sensitizing hypoxic tumor cells and thereby increasing tumor cure probability; (2) HBO as therapeutic agent: once late radiation-induced normal tissue side effects have become manifest, HBO is used to dissolve or reduce the severity of symptoms [1, 3, 4, 6, 8–12, 15, 17–24, 26–29, 33, 42, 46–49, 51, 52, 54–59, 62–66, 72, 73, 75, 77–79, 82, 83].

Hyperbaric Oxygen as Radiosensitizer

Most tumors contain nutrient- and oxygen-deprived compartments. Sterilization of hypoxic tumor cells requires a three

times higher radiation dose than for cells at normal oxygen tension (e.g., [61, 74]. HBO therapy is an effective approach to cope with the phenomenon of hypoxia by increasing the oxygen load of the tumor [2, 5, 34, 41], and therewith to enhance the response to irradiation [7, 34, 60]. First clinical data were obtained by the British Medical Research Council (MRC). In a clinical trial with HBO and radiotherapy, a significant advantage in local tumor control and survival was reported for carcinoma of the cervix [76]. However, in a next randomized controlled trial with long follow-up, HBO therapy showed no therapeutic benefit, while morbidity was increased [14]. However, in the radiation and HBO treatment arm of the study, doses per fraction up to 7 Gy were used in pelvic irradiation whereas the control radiation treatment arm consisted of standard fractionation. Hence, the actual setup rather than HBO might have been responsible for the disappointing outcome. A second MRC trial of HBO and radiotherapy for bladder carcinoma showed HBO not to be better than misonidazole additional to radiotherapy, while carbogen inhalation resulted in a significantly increased bladder tumor local control and overall survival [36]. A meta-analysis of randomized clinical trials of radiotherapy with any hypoxic cell modifier including HBO [61] demonstrated that, in particular in carcinoma of the head and neck, significant improvement of overall survival and local tumor control could be obtained. However, all early clinical trials had practical difficulties, i.e., the simultaneous application of HBO and radiation [30, 31, 35, 67]. Besides the complicated technical aspects, an increase in normal tissue side effects was noticed with this approach (Table 2). The increase in tumor control was partly negated by an increase in normal tissue side effects [13]. With regard to brain tumor treatment, recent Japanese data showed the feasibility of a treatment setup with HBO applied prior to radiotherapy [4, 43, 60] (Table 3). With this strategy, tumor control and patients' survival were significantly improved, with no increase in normal tissue side effects. Due to postponed oxygen saturation and washout kinetics, tumors remain well oxygenated for some time after leaving the chamber [41]. The two radiosensitization treatment protocols presented here allow a time interval between HBO and subsequent irradiation of 10–20 min.

Hyperbaric Oxygen as Therapeutic Modality for Radiation Sequelae

The goal of radiation treatment is to eradicate tumors with minimal, if any, adverse effects on normal tissue [69, 80]. Despite all efforts in preventative measures, radiation-induced lesions in normal tissue occur which may result in permanent injury. The turnover time of injured functional cells determines the appearance and time of the response. Different types of injury may develop sequentially in one organ, due to the depletion of the critical target cells. In a number of tissues, an early wave of damage (weeks or months after exposure) may be followed by a later wave of injury (months or years after exposure). Late effects are often considered irreversible and may lead to severe, even life-threatening, complications after therapeutic use of irradiation [39, 44, 70, 81]. HBO seems to be able to overcome progressive loss of the microvasculature resulting in chronic tissue hypoxia present in radiation-induced changes; repetitive HBO sessions gradually induce regrowth of connective tissue, and thereby of capillaries and epithelium [37, 38, 40]. The following organ-specific summary gives a short overview on experiences with HBO in the management of radiation-induced normal tissue side effects.

Radionecrosis of the mandible and improvement of osseointegration in previously irradiated tissues. HBO therapy for radiation-damaged tissues was introduced in 1973 by two principal studies [29, 49] and since then, numerous studies have attested to the value of HBO for the treatment of osteoradionecrosis of different bone tissues [26–29, 51]. Using a standardized protocol including surgery, antibiotics and HBO, Marx [50] showed the efficacy of HBO. After treatment, tissues were permanently stabilized. A randomized, prospective clinical trial using HBO and penicillin in previously irradiated jaws demonstrated that HBO significantly reduced the development of osteoradionecrosis after tooth removal [54]. The authors also discussed that HBO may prevent from development of osteoradionecrosis by pressure from tissue-borne appliances, periodontal surgery, endodontic instrumentation, mucosal grafts, skin grafts and secondary excisional biopsies. The value of HBO has also been demonstrated in the management of radiation-induced injury of the nose, floor of the mouth and temporal bone [15, 45].

HBO therapy produces sufficient oxygen partial pressures in poorly perfused tissues to allow fibroblastic activity and collagen production, creating a matrix for capillary budding and neovascularization. The daily elevation of oxygen tension in hypoxic bone and soft tissues results in the ingrowth of capillaries [38], fibroblastic proliferation and collagen synthesis [37] and capillary angiogenesis [40]. HBO has been reported to improve reconstruction attempts in the maxillofacial area due to mentioned mechanisms [52]. To date, this is the only known technique that can be used to oppose the negative tissue effects induced by radiotherapy.

In the study of Marx et al. [54] it was shown that HBO-induced angiogenesis became measurable after eight HBO sessions, rapidly progressed to a plateau at 80–85% of nonirradiated tissue vascularity by 20 sessions and remained at that level without further improvement with additional HBO. With a follow-up of 3 years, HBO therapy patients had tissue pO_2 levels at or within 90% of their values recorded directly after treatment. Hence, HBO-induced angiogenesis is permanent.

Chondronecrosis of the larynx [18, 22, 33, 48]. This is a debilitating disease associated with respiratory obstruction, dysphagia, pain and, in severe cases, the patient may require tracheostomy or laryngectomy. In 1987, Ferguson et al. [21] reported, that signs and symptoms of radionecrosis were dramatically ameliorated in seven of eight patients, while one patient, despite subjective improvement, eventually required

Table 4. Hyperbaric oxygen (HBO) for radiation-induced late effects following pelvic radiotherapy (including radiation proctitis; single-case reports excluded). GI: gastrointestinal; NA: not available.

Tabelle 4. Hyperbarer Sauerstoff (HBO) zur Therapie radiogener Spätfolgen nach Beckenbestrahlung (inkl. radiogene Proktitis; Fallberichte nicht berücksichtigt). GI: gastrointestinal; NA: nicht angegeben.

Author	Patients (n)	Symptoms and lesions	Cancer localization	Details of HBO treatment sessions ATA	Duration	Number	Results (months)	Follow-up (months)
Williams et al. 1992 [79]	14	Vaginal necrosis/fistula	Not detailed	2.0	90 min daily	Average 44	13 of 14 improved or healed	minimum 9
Feldmeier et al. 1996 [20]	7	Rectovaginal fistula ± necrotic wound	Cervix (7)	2.4	90 min	Mean 24 3–50	Fistula resolved (2) Fistula resolved (+ surgery) (2) Inadequate, patients deceased early (3)	NA
Warren et al. 1997 [75]	14	Proctitis	Prostate (12) Uterus (2)	2.0–2.36	90–120 min q.d.	Mean 45	Complete resolution (8) Substantial resolution (1) No change (5)	Mean 17 5–35
Woo et al. 1997 [82]	18	Hemorrhagic proctitis	Prostate (14) Anus (1) Bladder (1), Cervix (1)	2.0	105 min	Mean 24 (12–40)	Complete resolution (2) Partial resolution (8) No change (8)	Mean 14 3–65
Gouello et al. 1999 [24]	36	Failing healing (9) Rectal bleeding (19) Profuse diarrhea (9) Recurrent anal abscess (1)		2.5	90 min	Mean 67	Complete resolution (9) Improvement (12) No change (11)	Mean 52 (32)
Carl et al. 1998 [9]	2	Hemorrhagic proctitis	Prostate (1) Anus (1)	2.4	90 min 5 days/week	40 (in 8 weeks) 38 (in 12 weeks)	→ Complete resolution (1) → No change (1)	8
Williams & Clarke 1999 update [78]	44	Vaginal necrosis/fistula	Not detailed	2.0	90 min daily	NA	37 of 46 improved or healed	NA
Bem et al. 2000 [3]	2	Nonhealing anal ulcer	Anus (2)	NA	NA	NA	Complete resolution (2 of 2)	10
Kitta et al. 2000 [42]	4	Hemorrhagic proctitis	Prostate (4)	2.0	60 min 5 days/week	Mean 37 (30–60)	Complete resolution (1) Substantial resolution (2) No change (1)	11–13
Mayer et al. 2001 [56]	9	(Hemorrhagic) proctitis Modified RTOG/EORTC late GI morbidity score grade 2 (3), grade 3 (6)	Prostate (9)	2.2–2.4	60 min daily tx	Mean 30 (18–60)	Rectal bleeding resolved (5 of 5) Late GI morbidity score statistically sign. improved	Mean 14.4 8.6–26.9

Table 5. Hyperbaric oxygen (HBO) for radiation-induced cystitis (single-case reports excluded). GU: genitourinary; NA: not available.
Tabelle 5. Hyperbarer Sauerstoff (HBO) bei radiogener Zystitis (Fallberichte nicht berücksichtigt). GU: urogenital; NA: nicht angegeben.

Author	Patients (n)	Symptoms and lesions	Cancer localization	Details of HBO treatment sessions ATA	Duration	Number	Results	Follow-up (months)
Rijkmans et al. 1989 [65]	10	Hemorrhagic cystitis	Prostate (2) Bladder (8)	3	90 min	20	Hematuria resolved (6) Hematuria improved (4) = all patients with residual/ recurrent bladder cancer	2–24
Norkool et al. 1993 [59]	14	Hemorrhagic cystitis		NA	90 min	Mean 28 (9–58)	Hematuria resolved (8) Hematuria improved (2) Hematuria unchanged (4) = 3 patients with recurrent malignancy	10–42
Weiss et al. 1994 [77]	13	Hemorrhagic cystitis		2.0	120 min	60	Hematuria resolved (12) Hematuria improved (1)	mean 30
Lee et al. 1994 [47]	20	Hemorrhagic cystitis		2.5	100 min	Mean 40	Hematuria resolved (16) Hematuria improved (3) Hematuria unchanged (1)	mean 14 (5–41)
Bevers et al. 1995 [6] Prospective study	40	Hemorrhagic cystitis	Prostate (10) Bladder (20) Gynecologic tumors (10)	3	90 min 5–6 days/week	Mean 21 (20–40)	Hematuria resolved (30) Hematuria improved (7) Hematuria unchanged (3)	mean 23.1 (1–74)
Del Pizzo et al. 1998 [12]	11	Hemorrhagic cystitis	Prostate (4) Bladder (1) Uterus (4) Cervix (2)	2.0	90 min 5 days/week	Mean 40 (28–64)	Hematuria resolved (3) Recurrent hematuria after long FU (8)	Median 5.1 year (3.2–8.5 years)
Suzuki et al. 1998 [72]	3	Hemorrhagic cystitis		NA	NA	NA	Hematuria resolved (3)	NA
Miyazato et al. 1998 [57]	10	Hemorrhagic cystitis	Cervix (8) Vagina (1) Vulva (1)	2.0	75 min	20	Hematuria resolved (7) Hematuria improved (3)	NA
Peusch-Dreyer et al. 1998 [62]	3	Severe urge incontinence	Gynecologic tumors	2.4	90 min	20–40	Symptoms improved (3)	NA
Mathews et al. 1999 [55]	17	Hemorrhagic cystitis	Prostate (11) Bladder (3) Uterus (1) Cervix (1) Rectum (1)	2–2.5	90 min 5 days/week	Mean 14	Hematuria resolved (13) Hematuria improved (2) Hematuria unchanged (2)	mean 21 (9–60)
Mayer et al. 2001 [56]	11	(Hemorrhagic) cystitis Modified RTOG/EORTC late GU morbidity score grade 2 (2), grade 3 (6), grade 4(2)	Prostate (10)	2.2–2.4	60 min daily tx	Mean 25 (2–30)	Hematuria resolved (6) Hematuria unchanged (2) Late GI morbiditiy score statistically sign. improved	mean 15.3 (2.2–51.6)
Corman et al. 2003 [11]	57	Hemorrhagic cystitis	Prostate Bladder	2.4	90 min 5–7 days/week	Mean 33 (9–68)	Hematuria resolved (21) Hematuria improved (28) Hematuria unchanged (8)	10–120

Table 6. Hyperbaric oxygen (HBO) for late sequelae following breast cancer radiotherapy (single-case reports excluded). NA: not available.
Tabelle 6. Hyperbarer Sauerstoff (HBO) zur Therapie von radiogenen Spätfolgen nach Bestrahlung von Patientinnen mit Mammakarzinom (Fallberichte nicht berücksichtigt). NA: nicht angegeben.

Author	Patients (n)	Symptoms and lesions	Cancer localization	Details of HBO treatment sessions			Results	Follow-up (months)
				ATA	Duration	Number		
Hart & Mainous 1976 [33]	6	Radiation necrosis (chest wall)	Breast (6)	2	120 min	20–40	Adjunct to skin graft into irradiated bed All grafts successful	NA
Feldmeier et al. 1995 [19]	23	Soft-tissue necrosis (8) Soft-tissue + bone necrosis (15)	Breast (23)				Resolution in soft tissue involvement in 75% Resolution in soft-tissue + bone involv. in 53% All patients required resection of necrotic bone	
Pritchard et al. 2001 [64] Randomized trial	34	Brachial plexopathy	Breast (34)	2.4	100 min	30	No improvement of brachial plexopathy Reduction of lymphedema (6)	12–24
Carl et al. 2001 [8] Prospective observation	HBO (32) control (12)	Symptomatic breast edema	Breast (44)	2.4	90 min	Median 25 (7–60)	Compelete resolution (7 of 32) Pain, erythema, edema stat. sign. reduced 12 of 12 (control group) persistent symptoms	Median 11 (HBO) Median 7 (controls)
Gothard et al. 2004 [23]	21	Arm lymphedema and tissue fibrosis	Breast (21)	2.4	100 min	30	Stat. sign. reduction in arm volume at 12 months Mean percentage reduction: 7.68% (2.65–12.72) mean percentage reduction: Lessening of induration (8/15)	12

laryngectomy. Also, encouraging results were reported in 2000 by Filntisis et al. [22] with 13 out of 18 patients having a major improvement after HBO. Five patients failed to have a good response, however; one of them presented with local recurrence, three had significant concurrent medical problems, and one patient had received an insufficient number of HBO sessions.

Radiation-induced pelvic late effects and radiation-induced proctitis [3, 9, 20, 24, 42, 56, 73, 75, 79, 82, 83]. Table 4 displays an overview of published data on HBO treatment for late effects of pelvic irradiation treatment. Williams et al. [79] obtained healing of vaginal necrosis in 13 out of 14 patients as well as Feldmeier & Hampson [17], who reported encouraging results, particularly in patients who had received a sufficient number of HBO sessions. Radiation proctitis, mostly obtained following prostate cancer irradiation, is very disabling for the patients with symptoms like local pain, urgency, rectal discharge or bleeding. Most patients of the reported series had been unsuccessfully treated by one or more conventional treatment attempts or had required blood transfusion to control rectal bleeding. With 40 HBO fractions the number of treatments seems to be higher than necessary in other indications. Patients should be informed that it might be possible that rectal bleeding increases during the first three to six sessions [56]. The reason might be the induction of neovascularization prior to the formation of firm connective tissue and reepithelization.

Radiation-induced cystitis [6, 11, 12, 47, 55–57, 59, 62, 65, 72, 77]. Details are given in Table 5. In 2003, Corman et al. reported a series of 62 patients which comprised the largest group of patients reported to date [11]. The authors observed a response rate of 81%, which is according to the response rate of 82% reported in the world literature. As observed, HBO should not be delayed too long, as in case of extensive bladder shrinkage significant improvement of symptoms seems hard to achieve [56].

Late radiation sequelae to the breast [8, 19, 23, 33, 64, 69]. Table 6 shows five papers dealing with late sequelae of breast cancer radiotherapy encompassing late effects like breast and arm lymphedema, brachial plexopathy as well as soft-tissue and bone necrosis of the chest wall. While results in cases with radiation-induced necrosis of the chest wall were encouraging, no improvement of brachial plexopathy could be observed. However, although not a defined endpoint of this randomized trial, a reduction of lymphedema was obtained. A statistically significant reduction of lymphedema was also reported by two other trials, one prospective observation and one retrospective analysis published recently [8, 23].

See Schmutz [66] and Feldmeier & Hampson [17] for a comprehensive review of the literature.

COST B14 Initiative

The COST (European intergovernmental framework COST [European CO-operation in the field of Science and Tech-

nology research]) B14 action "Hyperbaric Oxygen Therapy" started in 1999. The action is managed by appointed experts in HBO from a number of European institutes, who officially represent their country [32, 68]. After its first year of operation, different working groups were composed, each coordinating a specific subject. The Working Group Oncology is concerned with the role of HBO in oncology, in particular the linkage with radiation oncology. The main goal of the working group is preparation as well as actual implementation and follow-up of European clinical randomized studies in the field of HBO and radiation oncology. The activities of the working group include:

(1) elaboration, adoption and approval of protocols;
(2) implementation and follow-up of protocols;
(3) advisory board for studies on HBO in oncology;
(4) actively providing information on HBO to radiation oncologists;
(5) bibliography.

Clinical Protocols with Hyperbaric Oxygen as Radiosensitizer

Reirradiation of Recurrent Squamous Cell Carcinoma of the Head and Neck after HBO Sensitization

The objective of the study is to evaluate whether HBO enhances tumor radiosensitivity in patients with previously irradiated histologically proven recurrent head and neck cancers, using a conventionally fractionated treatment schedule. All irradiation fractions should be preceded by HBO treatment, 2.5 ATA (2.4–2.6) for 60 min. Each irradiation fraction must be given within 10–20 min after HBO treatment. Endpoints of the study include: tumor recurrence rate and disease-free survival, overall survival, early and late normal tissue morbidity.

Role of HBO in Enhancing Radiosensitivity on Glioblastoma Multiforme: a Clinical Study

The objective of the study is to evaluate the efficacy of HBO on median survival when applied in combination with conventionally fractionated radiotherapy. Patients with pathologically verified glioblastoma multiforme are to be included in the study. Standardized HBO treatment are to be given prior to irradiation. This treatment setup is based on the Japanese studies listed in Table 3.

Clinical Protocols for Hyperbaric Oxygen Therapy of Radiation Sequelae

Two protocols, implemented and supported by the working group, are focused on the effectiveness of HBO as therapeutic modality in previously irradiated patients.

Osseointegration in Irradiated Patients – Adjunctive HBO to Prevent Implant Failures

This is a randomized, single-blinded study of patients intended for rehabilitation with the osseointegration concept. According to the osseointegration principle, implants of titanium can be installed in the skeleton and used to anchor fixed dental bridges or prostheses intra- or extraorally. In former cancer patients, the technique can be used to cover craniofacial defects created by tumor surgery. However, higher implant failures have been reported if the patient has been irradiated prior to implant surgery. The survival of the implants is depending on several factors including type and design of the implant, the surgical technique, the host bone, pharmacological and physiological affects. Radiotherapy has been shown to be the single most aggravating factor for implant failures. Despite basic and clinical research for many years, there is no general agreement that patients should be given presurgical HBO in conjunction with implant installation. The objectives of the study are to establish whether (1) osseointegrated implant failure rates are higher in previously irradiated tissues, and (2) HBO can be used to reduce implant failure rates in irradiated tissues. Standardized HBO treatments will be given both pre- and postoperatively. All centers working with rehabilitation of former cancer patients using the osseointegration concept are cordially invited to participate in this multicenter study.

The Role of HBO in the Treatment of Late Irradiation Sequelae in the Pelvic Region

This is a prospective randomized controlled clinical cross-over multicenter study. The objective of this study is to evaluate the extent to which HBO plays a role in the treatment of symptoms due to late radiation injuries induced by curative pelvic radiotherapy for malignancies. At the onset of the HBO treatment and during follow-up, organ-related parameters are to be assessed using the EORTC grading system, as well as other parameters (applying to all patients) such as health-related quality of life as scored in the SF-36 questionnaire.

Conclusion

Randomized clinical studies on HBO and radiation oncology are initiated and supported by the Working Group Oncology of the COST B14 action "Hyperbaric Oxygen Therapy". The protocols have been considered in detail and are approved by the COST action B14. They have been subjected to extensive peer review and amendment, and may be regarded as consistent with best practice in the field of hyperbaric medicine. All protocols are presented in detail on the website of the COST B14 action (www.oxynet.org). At present, they are open for enrollment of patients. The final outcome of the clinical studies will provide data on the efficacy of HBO therapy of late radiation injuries and on the therapeutic efficacy of HBO used as radiosensitizer.

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