RADIONECROSIS

Introduction

To improve the quality of care, the European Committee for Hyperbaric Medicine (ECHM) regularly edits guidelines for hyperbaric oxygen therapy (HBOT) applications. These have been published in 1994 and 2004 and are to be reviewed for 2016 (Pasquier 2004).

HBOT has been applied to late radiation injury since the 60's and is nowadays one of the most frequently used applications (Hart 1976, Hampson 2012). A wide range of literature on the subject is still being published. An up-to-date synthesis of the evidence supporting the use of HBOT is required, however.

A literature search was performed on electronic databases (Pub Med), up to October 2015. The key word searched was 'hyperbaric oxygen', combined with all of the following terms: radionecrosis, osteoradionecrosis, radiation injury, radiation necrosis, radiation-induced injury, radiation-related injury, late radiation tissue injury, delayed radiation injury, radiation-induced late side effects, late radiation effects. Animal and human studies were selected and reviewed. The database search was accompanied by a manual search on items listed in bibliographies of the retrieved articles. The following discussion is mainly based on randomized controlled studies (RCT) and prospective studies, when available, and on retrospective case series if the former are unavailable.

The elaboration of new guidelines used the GRADE (Grading of recommendations, assessment, development and evaluations) method to report recommendations based on the evidence available (Atkins 2004). The following text is a report containing experts' opinions to help the jury reach final consensual recommendations.

General background on radio-induced lesions in normal tissues

Radiation-induced normal tissue injury may lead to severe, life-threatening, late side effects following radiation therapy (RT). This involves occasional damage to healthy tissues that have been adjacent to a tumor, within the irradiation area. In spite of all advances and precautions which are taken in the implementation of RT, the damage remains unavoidable, even though these lesions are few and rarely lead to a handicap. The damage is dose-related and may last for periods ranging from months to years following RT. The lesions are usually distinct from early radiation-induced injury, which can appear at the time of irradiation, but they can also be a continuum of the latter. An interindividual variation in healthy tissue tolerance is observed. The risk and severity of radiation-induced lesions depend on treatment-and patient-related factors (Stone 2003). Incidence is related to the total dose, field size and duration of RT. Predisposing factors include alcohol, smoking, diabetes, hypertension and the use of steroids. The lesions are usually asymptomatic, and some of them have a considerable impact on the quality of life for patients considered to be cured of their cancer. This may affect life prognosis.

Radiotherapeutic injury has been compared to a complex wound (Denham 2002). Various theories concerning the pathogenesis of radiation-induced lesions in normal tissues have been put forward: the stromal concept and the vascular concept. The possibility of an infectious process has been generally abandonned since the 80's, when Marx noted no presence of sepsis in histologic lesions of

osteoradionecrosis (Marx 1983). The vascular concept is based on Marx's theory of hypoxia, hypocellularity and hypovascularisation of radionecrosis. RT leads to cellular depletion, reduction of vascular density, rarefaction of small vessels, fibrosis and atrophy (Marx 1983, Marx 1987). A more recent concept has been developped by Delanian (Delanian 2004). This stromal concept involves a pathological fibrogenetic process including chemotaxis and fibroblast proliferation, metabolism secretion and regulation of extracellular matrix components. However, these two concepts are not necessarily mutually exclusive. This could explain the inefficiency of certain therapies based on oxygenation or anti-fibrotic drugs. Tissues undergo deterioration in microvascularity with accompanying fibrosis. This damage may eventually reach a critical point where tissue breaks down and an area of radionecrosis appears as a result. Infection and surgery may exacerbate this process.

Rationale for HBOT use for radiation injuries

The angiogenic properties of HBOT have been demonstrated in rabbit irradiated tissue with increased vascular density over both normobaric oxygen and air-breathing controls on microangiographic and histologic assessments (Marx 1990). Based on this neoangiogenesis, a progressive increase in the transmucosal oxygen tension was shown during a course of 30 HBOT sessions in irradiated oral tissues of patients with mandibular osteoradionecrosis (Thorn 1997). It did not reach the level of a reference point outside the radiation area and lasted at least 6 months (Svalestad 2014). HBOT affects many growth factors, as well as the recruitement and differenciation of circulating steam/progenitor cells to form vessels de novo (Sheikh 2000, Milovanova 2009). Collagen synthesis needed to form extra cellular matrix is proportional to hyperoxia (Hunt 1972). In an irradiated mouse model with HBOT prophylaxis, HBOT could reduce signs of radiation enteropathy, such as rigidy of harvested bowel segments, and could also affect the fibrosis aspect of radio-induced injuries (Feldmeier 1995). HBOT could therefore reverse hypoxia, hypovascularisation and hypocellularity, as demonstrated by Marx (Marx 1983). In the mouse model, Spiegelberg demonstrated that HBOT was able to partly reduce radiation-induced effects on microarchitectural parameters, resorption and bone viability at 24 weeks after RT (Spiegelberg 2015). In vitro, osteoclast formation has also been shown to be suppressed and osteoblast differentiation accelarated, leading to an increase in bone formation due to HBOT (Al Hadi 2013, Al hadi 2015). Williamson's experimental study involving the use of HBOT one week after completion of RT for a malignant disease in a rat model demonstrated that, in contrast to the non-HBOT rats, HBOT-treated rats showed continued growth of teeth and maintenance of specialised tissues, such as the salivary gland and bone in the histological sections (Williamson 2007). Spiegelberg recently backed the idea that HBOT was able to regenerate or protect salivary gland tissue and partly reduce radiation-induced effects on microarchitectural parameters, resorption and mandibule viability in a mouse model (Spiegelberg 2014, Spiegelberg 2015). Autogenous free bone grafts transplanted from the iliac crest to the mandibles of rabbits are enhanced with HBOT by accelarating the union of the grafts (Sawai 1996). HBOT prior to implant placement should improve blood flow in compromised areas and has been reported to increase bone mineralisation and histologic integration of implants, to increase biomechanical forces needed to unscrew titanium implants in irradiated bone tissue and to improve soft tissue wound healing (Nilsson 1988, Johnson 1993, Larsen 1993, Johnsson 1999, Chen 1999). These results are still debated because they have not been supported by another animal model where HBOT failed to enhance osseointegration of implants in irradiated bone (Nyberg 2013).

HBOT for radiation-induced necrosis of head and neck

In the case of radiation-induced necrosis of head and neck, osteoradionecrosis (ORN) should be distinguished from soft tissue radionecrosis.

Organ-preserving protocols where head and neck cancer patients are concerned have become more popular in the treatment of patients since the 1990's. RT was used with and without chemotherapy as a primary treatment. This combination is increasingly used, to preserve voice quality for example, and may increase incidences of complications following RT. Although Intensity-Modulated Radiation Therapy (IMRT) has reduced the risk of ORN, these lesions may still be still encountered (Freiberger 2009).

ORN classically presents itself as bone exposed through an opening in the overlying irradiated skin or mucosa, persisting as a non-healing wound for 3 months or more without evidence of tumor recurrence, though sometimes gingiva or mucosa are intact. ORN is, therefore, a non-healing, non-septic bone lesion which makes it impossible for bone volume and density to be maintened. ORN terminology and definitions can vary greatly across studies. The mandible is the most common site of radiation-induced tissue damage following treatment of head and neck cancer. Maxillary and other facial ORN cases are uncommon. Incidences of ORN ranges from 0.4 to 56% but nowadays appear to be less than 5% (Rice 2015, Robard 2014). It is most frequently noted in the first three years following completion of RT and is an avascular aseptic necrosis (Marx 1983, Marx 1987). Patients with ORN usually experience the full spectrum of collateral damage from RT (i.e xerostomia, trismus, dysguesia, dysphagia and decreased tongue mobility). They suffer from an impaired quality of life and poor social contact (inability to communicate, eat and join others). Recurrent or persistent cancer may look like ORN and may be ruled out. Antiseptic oral solution, better oral hygiene, avoidance of irritants (tobacco, alcohol, denture use), nutritional support, analgesics, corticosteroids, non-steroidal anti-inflammatory drugs and antibiotics are usued as conservative treatments prior to or together with surgical ORN treatment. In stable cases they may need to be continuated for years. Surgery relies on multiple debridements, sequestrectomy, resection and reconstruction, although historically the risks have been high and the outcomes poor. Usually multiple stage surgery modality is required with an intermediate stage for fixation between extirpation and reconstruction (Marx 1983). Thirty-five years ago, Marx developed a classification system (stage 1 to stage 3) for classifying ORN of the jaw (Marx 1982, Marx 1983). Patients undergo peri-operative HBOT at each stage (after 30 HBOT sessions per stage with 100% oxygen for 90 min. at 2.4 ATA) with 30 first sessions completed with 30 other if clinical improvement obtained. Patients who fail to respond are advanced to the next stage. Stage 1 patients have small amounts of necrotic bone usually debrided in the dental chair. Stage 2 patients have formal surgical debridement in the operating theatre (transoral alveolar sequestrectomy). Stage 3 patients suffer from severe ORN such as fistulae, pathologic fractures or extension of the necrosis to the inferior margin of the mandible. They undergo planned mandibular resections with a discontinuity defect, which is addressed with a planned reconstruction. They have 30 pre-operative daily HBOT sessions followed by 10 post-operative HBOT sessions. Patients requiring reconstruction return at a later date and, following reconstruction, undergo 10 additional HBOT sessions. Microvascular surgical techniques have recently improved tremendously (i.e microvascular free tissue transfer) and have enabled the development of single stage definitive resection and reconstruction, while in the Marx protocol, the primary modality of reconstruction was

a nonvascularized free bone graft (Jacobson 2013, Lee 2015). Nowadays, successful outcomes of microvascular free flaps have increased to a reported rate of 86-100% for the reconstruction for mandibular ORN without HBOT (Lee 2015). Reestablishment of bone continuity may ensure the foundations for future dental rehabilitation. Since the 1960's, the issue of HBOT in the treatment of mandibular ORN has been described as a perioperative treatment within a multimodality approach. It is also used as a prophylaxis for ORN (Mainous 1973, Tobey 1979, Mansfield 1981). The procedure is challenged nowadays, given that new surgical modalities allow for one stage resection and reconstruction, while anti-radiation fibrosis drugs (pentoxifylline, tocopherol and clodronate) have proved effective and safe in some cases of refractory mandibular ORN (Delanian 2011, Robard 2014, Lee 2015). These factors have led to many institutions doing away with perioperative HBOT (Gal 2003).

Two RCTs have been published on the subject of HBOT as a way to treat mandibular ORN (Table 1). In Tobey's study in 1979, only 12 patients were randomised. Patients treated at 2.0 ATA experienced significant improvement when compared to the group treated at 1.2 ATA. The study contains no data report on randomisation or information whether the 40 HBOT sessions were perioperative or not. Although it is presented as a double-blind study, nothing allows us to understand this methodology in a report of less than 20 lines. It is impossible to evaluate the reliability of their conclusion regarding the outcome of examining such a small sample of patients (Tobey 1979). The study is very poorly documented: given that 37 years ago methology was usually not as strict as it is nowadays, the accuracy of the conclusions of this study cannot be certain or at the same level as contemporary RTC standards; there is a high risk of bias. Annane failed to demonstrate any improvement associated with HBOT for cases of mild to moderate ORN in a double-blind RCT in 2004 (Annane 2004). Although well conducted, this trial was not in accordance with a multimodality approach in which HBOT is used peri-operatively. Two groups were graded before randomisation. Group A was composed of patients who did not need immediate surgery (area of exposed bone < 20 mm in diameter and no cutaneous fistula) and group B was composed of those who needed surgery (areas of exposed bone > 20 mm in diameter, cutaneous fistula). In the HBOT arm, HBOT was done according to the Marx protocol, with 30 sessions before surgery and 10 sessions after surgery for group B; group A, however, were only exposed to 30 HBOT sessions without surgery. Failure to heal without surgery in group A was viewed as a failure of HBOT. Failure to heal with HBOT and surgery in group B was also seen as a failure of HBOT. As it was presented, the study design is inconsistent with the standard of care of these patients: failure to heal with only HBOT should have advanced these patients to surgery with a final analysis following postsurgical re-initiation HBOT and surgery. The pertinence of analysing together these two groups in the HBOT arm is raised because HBOT is considered to be relevant of a multimodality approach. The study was stopped at the time of the second interim analysis, after 68 patients were enrolled out of the 222 initially expected due to potentially worse outcomes in the HBOT arm in a triangular test comparing the HBOT arm and the placebo arm (Annane 2004). Recovery rates 1 year later were 19% in the HBOT group and 32% in the placebo group. Finally, when assessing the utility of HBOT to improve healing after surgery (therefore excluding patients without surgery in both arms), only 42 patients were considered out of the 68 enrolled: a comparison of 20 patients who needed surgery in the HBOT arm to 22 in the placebo arm revealed no significant differences. These 42 patients, however, are considerably fewer than the number required to exclude a significant effect of HBOT. Patients presenting fractures or radiographic evidence of bone

reabsorption to inferior border were excluded from this study, and not included in its conclusion. The usefulness of HBOT without surgery is not supported by the results of the Annane study.

Out of a series of retrospective case series, there are biased reports which twist definite conclusions for ORN of the jaws (Table 1). First, HBOT use for prophylaxis or for treatment of ORN may be pooled and cannot be analysed for the subgroup in some studies (Bui 2004, Harding 2008) and includes sometimes ORN of facial bones in general and not only the jaws (Vudiniabola 2000). Second, the multimodality approach to surgery and adjunctive HBOT is not the rule. Some authors report results both with and without surgery, for example (David 2001, Bui 2004). Occasionally HBOT is done only before or after surgery (Maier 2000, McKenzie 1993). Other authors present results of free flap complications, but report on both non-comparable groups managed without the perioperative philosophy of HBOT (Gal 2003, Nolen 2014): Gal compared 9 patients with stage III Marx, 3 of whom had perioperative HBOT for microvascular reconstruction, to 21 patients who represented the failure of conservative management with HBOT and who had the same microvascular reconstruction without postoperative HBOT (Gal 2003). Nolen included patients after the initial failure of HBOT for ORN as a conservative treatment, but did not repeat HBOT sessions post surgery (Nolen 2014). The course of HBOT varies and is frequently a modified Marx protocol (Aitasalo 1998, Hao 1999, Vudiniabola 2000, Freiberger 2009). Older studies reported more than a hundred HBOT sessions (Hart 1976, Wood 1996). Third, inclusion and exclusion criteria may vary. In Hampson's report of a case involving 43 patients and using the multimodality approach, 19 other patients were excluded from the statistics for incomplete data or incomplete course of HBOT and no follow-up was done after the end of HBOT (Hampson 2012). On the other hand, London included all patients, even those having undergone only 1 session (London 1998). In a well-depicted consecutive cohort study by Freiberger, with planned HBOT and surgery where less intensive therapies often failed, there was no follow-up for 31% of patients out of 65. When excluded from final analysis at the time of follow-up, 82% of patients were resolved (53%) or improved (29%), and the intention to rectify this led to a resolved or improved percentage of 57% (Freiberger 2009). Fourth, the absence of randomisation led to a bias and no possibility of comparison between groups. When HBOT failed to improve the outcome, as seen in D'Souza's publication, we can understand from the discussion that HBOT patients were sicker (D'Souza 2007, Freiberger 2009). On the other hand, Sawhney compared patients with perioperative HBOT to a group of patients who could not have or not wished to have HBOT (Sawhney 2013). Fifth, results are presented either as 'improvement' for some authors or as 'success' (with complete healing) for others, and the relevancy to one another regarding patient life-span may be different. The addition of all these retrospective data show a positive outcome (whatever the end point: improvement or resolution) with HBOT (Feldmeier 2012). This is insufficient to draw a firm conclusion regarding HBOT interest because these data are not objective. For example, improvement with HBOT without surgery is usually rare and can vary from 6.5 to 15% (Freiberger 2009, Mounsey 1993, Marx 1983) but has been described to reach 95% (Davis 2001). These studies suggest that HBOT may be beneficial for patients with mandibular ORN, whether surgery is performed or not. Maier used HBOT as a salvage treatment for cases of failed operations for severe infected ORN (Maier 2000). All patients were given antibiotics and underwent surgery. HBOT sessions were done if the HBO unit was available after the surgery failed, but none had preoperative sessions. HBOT without new surgery was compared to a continuation of surgery procedures. HBOT failed to be beneficial when patients had to undergo surgery again. Maier

concluded that the Marx protocol involving perioperative HBOT should be respected and HBOT not usued as a rescue treatment (Maier 2000). It should be noted that HBOT has never been assessed in conjunction or versus anti-radiation fibrosis drugs such as PENTOCLO.

HBOT for head and neck radiation-induced injury is safe: few complications were described in the largest prospective study (Annane 2004). Although head and neck radiation have been considered as a risk factor for middle ear barotrauma, these occurred in 15% of 68 patients with mandibular ORN (Blanshard 1996, Fiesseler 2006, Annane 2004). No seizure arised from oxygen toxicity (Annane 2004). In retospective studies, side effects are usually not documented (Mounsey 1993, Marx 1983, V Merkensteyn 1995, Aitasalo 1998, Wong 1997, Hao 1999, Vudiniabola 2000, Maier 2000, David 2001, D'Souza 2007, Harding 2008). Middle ear barotraumas are also the main complication. They are usually rare and occur in less than 5% of cases (McKenzie 1993, Curi 2000, Freiberger 2009, Hampson 2012). However, up to 20-37% of patients have needed myringotomies and/or pressure equalizing tubes for otic barotrauma (Freiberger 2009, London 1998, Bui 2004). Regular but unusual well-known side effects of HBOT are also documented for patients with ORN: claustrophobia (McKenzie 1993, London 1998), blurred vision (McKenzie 1993, Bui 2004) and seizure (Freiberger 2009, Hampson 2012).

The specific aspect of HBOT cost to treat ORN or to prevent it has never been assessed in Europe and data from US is quite old (Marx 1985, Marx 1988, Vudiniabola 1999). HBOT was not universally applicable to all cases of ORN for fiscal limitations in North America (McKenzie 93, Wong 1997). The same authors considered availibility of HBO chambers as a limitation to general application and specially for travel logistics (Wong 1997, Hampson 2012).

The final GRADE score for treating mandibular ORN with HBOT is a Grade D (very low evidence of benefits) because of 2 RCT with conflincting results, with very serious limitation to study quality, inconsistency and some uncertainty about directness. Based on this grading system, we cannot suggest recommendations about the use of HBOT to treat ORN, although it cannot be excluded that HBOT could be beneficial.

HBOT is also used as **prophylaxis for mandibular ORN** (Table 2). RT damages small arteries, reducing the ability of irradiated bones to resist to trauma such as subsequent surgery, tooth extraction, biopsy or consecutive implant placement. When such procedures are necessary, perioperative HBOT could be planned to prevent ORN and have been used since the 80's (Kraut 1985, Marx 1985). This means of preventing ORN has been the subjet of much debate due to impact it can have on a patient's quality of life. The routine use of HBOT is being restricted by cost, limited availibility and conflicting reports regarding the safety of preirradiation and postirradiation extractions without HBOT, new radiation therapy modalities and new surgical techniques (Lambert 1997, Jacobson 2010, Clayman 1997).

Only one RCT assessed the use of HBOT to prevent ORN (Table 2). In 1985, Marx compared HBOT alone to systemic penicillin, the standard of care at the time, in 74 patients who required tooth removal in irradiated mandibles. HBOT group had 20 sessions before and 10 after tooth removal. Incidence ORN decreased significantly from 29.9% to 5.4% (Marx 1985). The risk of bias is not excluded because randomisation process was not reported. An occurrence rate, in 1985, of 29.9% of ORN in Marx's non-HBOT group may be questionnable today, given that the percentage of patients

with ORN who did not have prophylactic HBO in more recently treated cohorts is under 8.2% between 2000 and 2010 (Fritz 2010). No trial comparing modern surgical techniques against the same techniques plus HBOT have been found.

Few retrospective studies have been done (Table 2). For all these types of study, flaws prevent us from drawing definite conclusions despite good results for most of them. Although all HBOT courses involved 20 pre-extraction and 10 post-extraction sessions, many other variables remained uncontrolled, such as total maximum time at maximum atmospheric pressure, which can vary from 50 to 90 min (Heyboer 2013, Hampson 2012, Chavez 2001, Lambert 1997). It should be noted that HBOT results based on 50 min. at maximum atmospheric pressure of 2.5 ATA are the poorest published ones (Heyboer 2013). Aside from Hampson's report of 166 patients, others include only a small cohort of a maximum of 47 patients. ORN incidence varies from 0% to 15.8%. The follow-up is usually short (<1 year), especially in the largest cohort where evaluation is done immediately following completion of HBOT with no further follow-up (Hampson 2012). Quality of follow-up assessments may also be questionnable: Heyboer admitted that, despite hyperbaric physician documentation of mucosal healing at completion of HBOT, 4 (21%) of the patients were noted to have delayed mucosal healing upon later follow-up by their referring providers and 2 of these patients developped ORN (Heyboer 2013). Kaur had subjective endpoint assessed by patient telephone questionnaire about healing of tooth sockets (Kaur 2009). Zero percent ORN incidence is mainly encountered at the end of completion of an HBOT course in these studies, except in Lambert's, which involved 2.5 years of follow-up (Heyboer 2013, Hampson 2012, Lambert 1997). There is a lack of follow-up associated with more than 50% of patients, and these patients are not included in the analysis (Heyboer 2013, Hampson 2012, Lambert 1997). Lastly, the sole study with a controlled group had, in fact, a non-matched control group which consisted of patients who refused HBOT or had complications during the first session (claustrophbia, middle ear barotrauma) (Vudiniabola 1999).

The safety of the protocol 20 pre-extraction and 10 post-extraction HBOT cases has been specifically assessed in Chavez' prospective study, with 40 patients who were enduring severe radiation caries (Chavez 2001). No serious complication occurred (such as oxygen toxicity seizure, inner ear barotrauma, pneumothorax or arterial gaz embolism). Some degree of middle ear barotrauma occurred in 19 (47%) of the patients but were minor and no patients had to forego HBOT or required placement of pressure equalizing middle ear aeration tubes. Patient compliance with HBOT was very good but not reflected in the statistics (Chavez 2001).

The final GRADE score for preventing mandibular ORN with HBOT is a Grade C (low evidence of benefits) because of only one RCT is available with limitation to study quality, important inconsistency between observational studies and sparse data. Based on this grading system, it would be reasonable to recommand HBOT to prevent ORN when oral surgery in the field of irradiation is necessary.

Head and neck soft tissue radionecrosis is an heterogenous entity which involves major wounds that show no signs of healing, but also chronic fistulas, laryngeal necrosis and xerostomia. Local irrigation, humidification, wound debridement, steroids, antibiotics and analgesics represent the mainstay treatment, and prolonged observation is often required to avoid high-risk surgery, even with free or

pedicled flap. Since the 1960's, HBOT has been described to heal wounds in patients with radiation-induced soft tissue necrosis of head and neck (Greenwood 1973, Hart 1976, Farmer 1978, Davis 1979).

Regarding laryngeal radionecrosis, laryngeal edema or ulceration, skin damage, perichondritis and cartilage necrosis are the main complications; patients present skin erythema, pain, dysphagia, hoarseness, dyspnea, weight loss, fetor oris, dryness, aspiration and have a decreasing quality of life. It may become fatal in some cases, such as respiratory distress despite aggressive surgical treatment to remove necrotic tissue. Radical surgery such as partial or total laryngectomy and tracheostomy may sometimes be required. Symptoms and signs are similar to those seen in recurrent laryngeal carcinoma and they present a major diagnosis dilemma as well as make Positron Emission Tomography, laryngoscopy and biopsy essential. A grading system for qualifying the severity of radiation damage has been published by Chandler and is still used despite more recent ones by RTOG and EORTC (Chandler 1979).

Laryngeal radionecrosis studies are rare and usually retrospective cases, with very small cohorts of more than 10 patients. No RCT or prospective study has been reported (Table 3). One trial, found in a text book, is quoted as a RCT for soft tissue radionecrosis of the head and neck, but it has a poorly reported methodology and an unreliable peer-review process with a very high risk of bias (Marx 1994). Such a randomised aspect of this study has therefore been secondarily invalidated by other authors and may be in fact just a retrospective study with a non-matched control group (patients refusing HBOT or residing too far to HBOT chambers or experiencing financial problems) (Feldmeier 2002, Feldmeier 2012, Hoggan 2014). Unfortunately, this is the largest study to date, involving 160 patients while all other included a maximum of only 30 patients (table 3). This Marx study assessed 3 aspects of wound complications related to soft tissue flaps and wound healing: wound dehiscence, wound infection and delayed healing for 160 patients requiring a major soft tissue surgery or flap introduced into radiated tissue. Eighty patients had HBOT as a prophylactic treatment with 20 sessions before surgery and 10 sessions after surgery, while 80 had no HBOT. Results favour HBOT for all end points. No detail is provided about the randomisation process or about the comparability of groups at baseline. Outcomes such as follow-up periods are poorly reported (Marx 1994). Only one study is presented as a consecutive retrospective cohort (Neovius 1997). Neovius reports 15 patients who had HBOT for major infected wounds or chronic fistulas with no signs of healing at 3 weeks or longer after surgery in the irradiated head and neck (Neovius 1997). HBOT consisted in 31 oxygen sessions (20-42) at 2.5-2.8 ATA for 75 min. once or 2 times a day, each day of the week. This so-called consecutive retrospective study, however, excluded one patient who started HBOT but did not complete it. The 15 patients were compared to 15 previous patients without HBOT, reported 3 years earlier by the same institution. Twelve patients from the HBOT group healed completely, compared to only 7 of the historical group. No severe complications of HBOT were noted (Neovius 1997). All other published studies are retrospective case series and have unobjective interpretable results due to their small size (with only 4 groups exceding 15 patients) or other flaws (e.g. exclusion of patients with incomplete course of HBOT) (table 3).

The final GRADE score for treating head and neck soft tissue radionecrosis with HBOT is a Grade D (very low evidence of benefits) because of the lonely RCT has very serious limitations to study quality, high probality of reporting bias and observational studies are sparse data. Based on this

grading system, we cannot recommend HBOT to treat head and neck soft tissue radionecrosis, although it cannot be excluded that HBOT may be beneficial.

Radiation-induced **xerostomia** is one of the most common comorbidities of RT in patients with head and neck cancer and could have been presented with head and neck soft tissue necrosis but is presented apart because of many specific data. Affected patients have decreased salivary rates and viscous saliva. It contributes to difficulties with eating, speaking and swallowing, together with a decline in the overall quality of life. Biochemical properties of saliva are also altered, with a decrease in pH, bicarbonate concentration, immunoglobulins, lysozymes, peroxidases and, as a result, reduced buffer capacities. This oral environment is prone to infections and dental decay. Spontaneous recovery of xerostomia may be achieved up to 2 years after treatment. Different approaches have been applied to prevent radiation-induced salivary hypofunction and xerostomia such as optimisation of radiation techniques, e.g. IMRT and the administration of cytoprotective agents, e.g. amifostine. Futhermore, stimulation of residual capacity in radiation-damaged salivary gland tissue has been attempted by the administration of cholinergic muscarinic agonists (e.g. pilocarpine and bethanecol), masticatory and gustatory stimulation and acupuncture, or by the use of lubricating agents when saliva cannot be stimulated. None of these has been universally accepted and are only palliative treatment options. HBOT has been used since the early 70's (Greenwood 1973) with published series in early 90's (Fontanesi 1991). The main studies are reported in Table 4.

Teguh published a non-blind RCT in humans, assessing early HBOT for reducing RT side effects including xerostomia after RT in oropharyngeal and nasopharyngeal cancer to be treated with curative intent (Teguh 2009). Within 2 days following completion of RT (and chemotherapy if applicable), 30 HBOT sessions were applied for HBOT patients. Despite having to be stopped prematurely time with only 19 patients included, the preventive action of HBOT could be demonstrated. A significant difference favouring HBOT for EORTC H&N35 swallowing, EORTC H&N35 dry mouth, EORTC H&N35 sticky saliva, Performance Scale Status, eating in public and pain in mouth visual analog scale is shown at 18-month follow-up. No significant effect of HBOT was shown for early side effects as opposed to late side effects. A placebo effect could not be disproved completely because of non-blinding HBOT sessions. The small number of patients (19) limits definite conclusions (Teguh 2009). The effectiveness of early HBOT after RT to partly inhibit the progressive nature of radiation damage in the field of xerostomia symptoms is not fully validated in another prospective study (Gerlach 2008).

HBOT is used as a treatment of head and neck radiation-induced injury to improve quality of life (Irgens 2013). For this, xerostomia may be involved but has not been specifically studied. Consequently, in a prospective cohort, Irgens presented some significant improvement in social function with SF-36 scales for 54 patients with head and neck radiation injury, but nothing was significant for physical function, physical role, bodily pain, general health, vitality, emotional role and mental health with this SF-36 scale (Irgens 2013). Improvement in subjective end points have also been reported in prospective studies, such as Gerlach's, with a small cohort of 21 patients with only 12 assessed patients at end of follow-up (2 years) (Gerlach 2008). These patients had perioperative HBOT. Swallowing problems, taste and subjective saliva quantity may be improved, as opposed to dry mouth sensation, dental problems, subjective viscosity saliva, smell, conversation and thrist, which cannot (Gerlach 2008). These subjective reflections of a patient's problem with the

questionnaire, the absence of a control group and a short follow-up make it impossible to draw definite conclusions. Similarly, Harding showed that HBOT improved many aspects of quality of life with head- and neck-specific questionnaires in another prospective cohort of patients (Harding 2008). As in the Gerlach study, Harding could not exclude that improvement could be attributed to the concomitent surgery. To counter this hypothesis, the improvement of a few sub-items of the EORTC Core 30 or EORTC head and neck 35 questionnaires in another of Hardy's prospective studies on osteoradionecrosis without surgery suggested that HBOT could have itself positive physiologic and psychological effects on the quality of life (Harding 2012). These results have not been confirmed in a RCT about the effects of HBOT on rehabilitation of oral function in head and neck cancer patients after RT with implant-retained dentures (Schoen 2007). Schoen showed no differences between the HBOT group and the non-HBOT group at 1-year follow-up for clinical assessments, radiographics evaluation, quality of life, functional assessments and denture satisfaction in a rather small population (19 patients at end of follow-up for 26 included patients). Although these patients may represent a very specific subgroup of patients with radiation-induced xerostomia, this item was, again, not extensively studied (Schoen 2007). Objective parameters such as sialometry, functional scintigraphic assessment and histological study may warrant results. Cankar published significant positive results with HBOT on salivary secretion rate and salivary pH and a decreased Streptococcus mutans and Lactobacillus colony density for 16 patients with xerostomia, with concomitent improvement of xerostomia (Cankar 2011). This study was done less than 1 year after RT and spontaneous recovery could not be excluded due to the absence of a control group.

The final GRADE score for preventing or treating xerostomia with HBOT is a Grade D (very low evidence of benefits) because of RCT with very serious limitation to study quality, uncertainty about directness and inconsistency. Based on this grading system, we cannot suggest recommandations about the use of HBOT to treat or prevent xerostomia, although it cannot be excluded that HBOT may be beneficial.

In the field of prevention of radiation injuries in patients with head and neck cancer, HBOT is also used for **oral and facial rehabilitation using implant supported prosthesis** in irradiated bones following RT and mutilating surgery (Table 5). Osseointegrated implants, dental bridges and tissue prostheses can be anchored on retention elements attached directly to the craniofacial skeleton. The benefits are improved masticatory ability, less damage to oral mucosa, facilitated swallowing and speech functions, cosmetic and functional coverage and, more generally, better quality of life and social contact. The success of implant-supported restorations is associated with effective osseointegration of the implant, the health of peri-implant tissue and the reestablishment of function and aesthetics. They are related to material biocompatibilty, adequate quality of bone tissue that allows implantation, surgical technique and macrostructure and microstructure of the implant. An increased rate of implant loss in patients with irradiated jaws compared to non-irradiated ones has been demonstrated (Zheng 2014). A careful selection of patients may avoid complications and surgery should be performed at major craniofacial rehabilitation centres (Granstrom 1999). Mean survival rate of titanium implants in irradiated jaws (without HBOT) ranges from 40% to 100 % (Zheng 2014, Chambrone 2013). Impaired osseointegration and implant stability in some animal models, due to decreased bone vascularity and vitality in irradiated jaws, is debated (Chambrone 2013). HBOT has been used to prevent implants failure since the late 80's (Granstrom 2005). Nowadays, HBOT is

challenged by surgical techniques (which have very low incidence of ORN) and a prolonged healing period between RT and rehabilitation (that leads to a very good survival rate) (Zheng 2014).

In 2007, the only RCT assessing HBOT in the rehabilitation of the oral function with implant-retained lower dentures in head and neck cancer patients after radiotherapy failed to show any effects favouring HBOT after one year (Schoen 2007) (Table 5). This monocentre non blind study had a small sample size and included 26 patients (13 in each arms), 6 of whom were lost of follow-up. One hundred and three implants were inserted. All HBOT group patients had 20 HBOT sessions before surgery and 10 after surgery. Each arm was given peri-operative antibiotics and had one stage implants placement procedure by the same surgeon and, 6 months later, an implant-retained prosthese. Treatment outcome was assessed by the condition of peri implant tissues, implant survival, oral functioning and quality of life. Implants survival rate was 93.9% in the non-HBOT group and 85.2% in the HBOT group. A trend of better performance of patients not treated with HBO on almost every aspect led the authors to consider extra treatment encompassing 30 sessions on the quality of life (Schoen 2007).

An older case-controlled study included patients from the 1980's and early 1990's (Granstrom 1999). This population is quite different from Schoen's study. In this single-centre study, 78 patients had implants inserted not only in their lower dentures but in almost all other facial bones (orbit, temporal, nose, maxillar and mandible). They were divided into 3 groups (irradiated, non irradiated, irradiated plus HBOT) and a fourth group consisting of previously irradiated patients who had implants primarily installed without HBOT and later lost who were reoperated after HBOT. HBOT was planned for 20 pre- and 10 post-surgery sessions. Implants survival rate was significantly better with HBOT (91.9% in the HBOT group versus 46.3% in the irradiated non-HBOT group) even in re-treated patients with HBOT (88.1%). Follow-up periods of every group was greater than 3.4 years. The better outcome with HBOT was confirmed later on a similar but larger cohort even if HBOT use was less detailed (Granstrom 2005).

Retrospective data on osseointegration and HBOT are very few (Table 5). Some have been later reported in other larger cohorts (Granstrom 1993, Granstrom 1999, Granstrom 2005, Niimi 1997, Niimi 1998) or represent too small case series for sub group analysis as they are presented, separing mandible from maxillae implants for example and without information on why or not HBOT (Shaw 2005, Niimi 1998, Jisander 1997) or have no comparative group (Marx 1998). No objective analysis can be done.

The final GRADE score for HBOT to prevent loss of overall osseointegrated implants is a Grade D (very low evidence of benefits) because of one RCT not favourable, with important inconsistency and uncertainty about directness between studies. Based on this grading system, we can not suggest recommandations about use of HBOT to prevent loss of osseointegrated implants in irradiated tissue, although it cannot be excluded that HBOT may be beneficial.

HBOT for radiation cystic injury

Pelvic irradiation is an essential part of the treatment of pelvic malignancies, including prostate, rectal and gynecologic malignancies (Ribeiro 2015). Incidence of urinary bladder complications following RT is reported to be 5% to 15% (Oscarsson 2013). Radiation cystitis presents itself as

recurrent haematuria, frequent and/or imperative micturition, urine leakage, painfull micturition, pelvic pain, and leads to multiple, mostly emergency, admissions to hospitals. It can occurr from a few months to several years after RT (Degener 2005). Quality of life is impaired and vital prognosis sometimes engaged because of bleeding. These patients can also suffer from radiation proctitis (Degener 2015, Ribeiro 2015). Infectious haematuria is ruled out with urine cultures. Cystoscopy is performed to rule out urothelial carcinoma but biopsy for histology remains questionable due to bleeding and if obvious radiation changes are present, such as diffuse telangiectasia (Dellis 2014, Degener 2015). The primary modality for bleeding is hydration and bladder irrigation for clot evacuation. Oral or intravenous aminocaproic acid, tranexamic acid, oestrogens and sodium pentosanpolysulphate are used with limited success, as is intravesical treatment with alumsilver nitrate, prostaglandins, formalin or sodium hyaluronate. Electrocoagulation or Laser photocoagulation may also be used. Blood transfusion may be necessary. Selective embolisation of the hypogastric arteries, urinary diversion or cystectomy may be needed in the most severe cases when conservative measures fail (Payne 2013, Mendenhall 2015, Alesawi 2014). Cystectomy is associated with a high risk of perioperative morbidity and mortality. HBOT has been used since the 80's (Weiss 1985, Schoenrock 1985). The main studies are reported in Table 6.

A prospective randomised Chinese study comparing HBOT and intravesical hyaluronic acid (HA) instillation has been published (Shao 2012). Shao studied the overall component of hematuria, the frequency of voiding and the visual analogue scale of pelvic pain as a primary end point in 36 patients with radiation-induced hemorrhagic cystitis. The study consisted of 16 grade II patients (macroscopic hematuria) and 20 grade III patients (macroscopic hematuria with clots and/or anemia needing blood transfusion). There was no grade I (microscopic hematuria) or grade IV (life threatening bleeding not responding to treatment and necessitating surgical intervention) patients, and only 6 patients needed bladder irrigation. The HBOT group received 100% oxygen daily for 60 min at 2,5 ATA, 7 days a week, for a principle of 30 sessions. In the HA group, 40mg of HA was instilled weekly in the first month into the bladder through a Foley catheter which was clamped for 20 min. Subsequently, two other HA instillation were performed monthly. The respect of these protocols is not described. At 6, 12 and 18 months after treatment, an improvement was demonstrated, but without statistical difference between the two groups (Shao 2012). No specific data has been presented about hematuria, which is usually the primary end point in other studies.

Four prospective studies have also been published (Table 6) (Bevers 1995, Vilar 2011, Dellis 2014, Oscarsson 2013). In 1995, Bevers first reported a prospective non-controlled study of 40 patients with severe hematuria, most of them requiring blood transfusion (Bevers 1995). All patients suffered from haemorrhagic cystitis, had not responded to previous treatment, and there was no tumor recurrence in the bladder. They received 20 daily HBOT sessions (90 min. at 3 bar pressure 5 or 6 time a week), although 4 patients had 40 sessions due to persistant hematuria. Hematuria stopped in 30 patients with a follow-up of 29 months; 3 of them, however, suffered from recurrent bleeding during this period. Seven patients had persistant slight hematuria after HBOT with a 5-month follow-up and 4 of them had severe recurrence. HBOT had no effect on the remaining 3 patients. The treatment's failure was seen only in patients with very severe haemorrhagic cystitis and often led to a diagnosis of recurrence of bladder or prostate cancer. Bladder preservation was achieved in 36 patients (90%) with regard to cystectomy for recurrent severe hematuria, although 12.5% of patients had cystectomy completed (Bevers 1995). For these cases of severe hematuria, 30% of patients were

dead due to various reasons at end of the follow-up period (13 months). In a second similar prospective study, Vilar reported 38 patients who had an average of 31 sessions (10-48) at 2 to 2,5 ATA for 90 min. 5 time a week (Vilar 2011). It should be noted that 24 of the 38 patients had already received previous HBOT prior to this study. They were followed up for an average of 56 months (4-72) with annual RTOG scale and monthly telephone survey. Hematuria was resolved in 34 patients (89%). Results are poorly reported: RTOG scale was planned to establish the level of bladder disease but these results are not reported. Similarly, nothing is reported about previous HBOT sessions and results of this course of HBOT. Oscarsson prospectively studied the effect of 30 to 40 HBOT daily sessions (2-2.4 ATA, 90 min. 5 days weekly) on 39 patients with radiation induced cystitis and/or proctitis (Oscarsson 2013). Thirty-two of these patients had cystitis. Although these patients were lesser invalidated by hematuria than patients in other studies (none required transfusion), they had other debilitating urinary symptoms. The mean number of treatment was 36. Improvement on the EPIC (Expanded Prostate Index Composite) scale, a validated instrument to evaluate function and symptoms after prostate cancer, was demonstrated at 6- and 12-month follow-ups. If we review the fourth prospective study, Dellis published the only one which is a pilot-feasibility study on HBOT for radiation cystitis as a primary treatment for 11 patients (Dellis 2014). Patients had severe bleeding symptoms (grade IV radiation-induced cystitis according to RTOG/EORTC scale). None of them underwent any other treatment apart from bladder irrigation and blood transfusions before HBOT. They received oxygen for 90 min per day, 5 days a week at a 1.8 ATA, which is quite unusual in literature. 30 HBO sessions were scheduled but could be re-initiated until the hematuria was resolved. Nine out of 11 patients had complete responses, one had a partial response but succeed after an additionnal HBOT, and the last one had an initial partial response but experienced severe hematuria at 6 months and accepted cystectomy and urinary diversion. Although 100% of patients had complete or partial responses to initial HBOT, as authors presented their results, only 72.7% had a durable effect and one cystectomy had to be completed. Histologically normal mucosa was confirmed for the 7 patients who underwent a biopsy (Dellis 2014).

Numerous retrospective studies suggest that HBOT is a promising option in therapy-resistant radiation cystitis (Table 6). Studies with the largest number of HBOT sessions (>40) seem to have better results than those with fewer sessions (<30) (Mathews 1999, Nakada 2012). Success rate among hematuria in retrospective studies has usually been evaluated at between 50 and 100% (Rijkmans 1989, Norkool 1993, Weiss 1994, Lee 1994, Suzuki 1998, Mathews 1999, Miyazato 1998, Degener 2015, Chong 2005, Oscarsson 2013, Yoshida 2008, Corman 2003, Ribeiro 2015, Fuentes 2013, Liss 2013, Parra 2011, Neheman 2005, Safra 2008). A rate of 20-27%, however, has been published in studies involving a small population (respectively 10 and 11 patients) (Del Pizzo 1998, Mohamad Al Ali 2010). Other symptoms such as dysuria have been infrequently studied (Safra 2008). The retrospective study with the most significant numbers included 176 patients with an average follow-up of 12 months (0-108) (Ribeiro 2015). Hematuria occurred at an average of 55.72 months after RT and HBOT was done after an average of 13 months following the onset of hematuria. All patients were referred to HBOT after at least one conservative technique. A transfusion support was needed for 19.3% of patients before the HBOT was instituted. A mean of 37 HBOT sessions (7-179) was delivered. The success rate was 89.8% (67% complete, 22.7% partial). Two other important retrospective studies, from one single institution within the same period and probably concerning exactly the same patients (except 2), showed 86 and 80% overall or partial response on haematuria

at 12 months of follow-up from the end of HBOT (Corman 2003, Chong 2005). Favourable HBOT outcome was associated with younger age, higher radiation dose and treatment within 6 months from the onset of haematuria (Mathews 1999, Chong 2005, Dellis 2015). Although durable results have been published for up to 10 years, HBOT succes rates may drop from 73 to 27% as follow-up increases from 2,5 to 5 years (Weiss 1994, Del Pizzo 1998). The recurrence of hematuria has been described in up to 13.6% to 41% of patients at one year, but usually without requiring further intervention (Ribeiro 2015, Shilo 2013, Vilar 2011). When HBOT fails, underlying causes such as malignancy should be carefully examined (Dellis 2015, Rijkmans 1989, Norkool 1993). The need for cystectomy following HBOT failure is not systematically reported but regularly described (Bevers 1995, Dellis 2014, Shilo 2013). Numerous factors lead to flawed conclusions about HBOT efficacity in these studies. Groups can be too different and/or too small for adequate conclusions (Mohamad Al – Ali 2010). There is no unique way to describe late radiation cystitis for all these studies, which include CTCv3 (Fuentes 2013), ASTRO, LENT-SOMA Score, RTOG or EORTC classification (Liss 2013, Oliai 2012, Shilo 2013, Dellis 2015, Chong 2005, Degener 2015) or often personal classifications (Bevers 1995, Ribeiro 2015, Shao 2011). A lack of data on the frequency and severity of every hematuria episode that occurred before and after HBOT limits retrospective analysis (Chong 2005). Patients with insufficient data and/or incomplete follow-up are excluded (Degener 2015). Consequently, heterogeneity exists between retrospective studies. For example, in Degener's study, the patients included had radio- or chemotherapy-induced hemorrhagic cystitis but had not all been treated for a cancer-related disease (Degener 2015). HBOT sessions may vary between all these studies (1,8 to 3 ATA and 60 to 120 min) (Dellis 2014, Bevers 1995, Mohamad Al Ali 2010, Oliai 2012). The average number of HBOT sessions varies from one study to another from 14 to more than 60, and also in the same series with a trend toward an incremental over the last decades to 40 rather than 30 sessions (Mathews 1999, Nakada 2012). Prior and concomitant treatments vary widely from nothing before HBOT to multiple other modalities (Dellis 2011, Del Pizzo 1998). Some of these series may have been implemented from prior studies or come from the same centre (Norkool 1993, Corman 2003, Chong 2005, Hampson 2007, Hampson 2012). Patients with an incomplete course of therapy or an incomplete follow-up are frequently excluded, although not systematically (Hampson 2012, Hampson 2007, Degener 2015, Corman 2003). The condition most frequently found is haematuria but for some authors can also be a combination of problems or the need for vesical diversion (Hampson 2012, Ribeiro 2015). HBOT may have improved results in patients with milder hematuria and may be less succesful in cases of more severe hematuria, although there are discrepencies to this conclusion (Bevers 1995, Liss 2013, Ribeiro 2005). Follow-up periods vary from 0 to more than 10 years (Hampson 2007, Nakada 2012). A change of histopathological findings of the bladder mucosa after resolution of bleeding with HBOT has been demonstrated (Suzuki 1998).

Early application of HBOT after the onset of hematuria appears to produce favourable outcomes, no matter what the follow-up period is (1-11 years) (Chong 2005, Vilar 2011, Nakada 2012, Dellis 2014). This has not been confirmed in the largest study (Ribeiro 2005).

Side effects of HBOT are rare: reversible middle ear (10.6%) is the most common adverse effect and is an easily manageable risk (Hampson 2007, Tahir 2015, Degener 2015, Ribeiro 2015). Eardrum perforation, however, has been described in 4 out of 32 patients (12,5%) in Shilo's retrospective serie (Shilo 2013). The potential of HBOT for tumor growth has not been proved in specific animal or human studies (Feldmeier 2012, Chong 2004, Liss 2013).

There are too few studies on HBOT cost analysis to draw firm conclusions. Radiation cystitis treatment including HBOT compared favourably against surgical interventions in one case (Smart 2012) and both should compare favourably to multiple conservative treatments in the USA 25 years ago (Norkool 1994, Corman 2003).

HBOT may improve postoperative outcomes when given before planned open operations in patients with previous pelvic irradiation and a history of radiation-related complications. In 1998, a lonely series of 5 cases was presented as a preliminary experience and seemed promising with regard to subjective end points for planned pelvic or abdominal surgery (Pomeroy 1998).

The final GRADE score for treating radio-induced cystic injury with HBOT is a Grade C (low evidence of benefits for improvement with HBOT) because of only observational studies without conflicting results are available. Based on this grading system, it would be reasonnable to use HBOT for radio-induced bladder injury.

HBOT for radiation-induced proctitis

Radiation-induced proctitis develops following radiation therapy particularly in patients with prostate but also rectal, testicular or cervical cancer (Marshall 2007). Pelvic irradiation can cause small bowell obstruction, fistulas, bowel perforations, mucus rectal discharge and bleeding. Normal daily activities and quality of life is impaired. Up to 20% of patients are affected by serious complications requiring operative intervention within 20 years of RT (Abu Asi 2013, Fuentes 2013, Clarke 2008). Severe forms are life-threatening and could result in mortality rates of 2-8% (Clarke 2008). Various interventions have been tested to improve chronic proctopathy, particularly rectal bleeding, including corticosteroids, sulfasalazine, 5-amino-salycilates, amifostine, short chain fatty acid enemas, oral metronidazole, oral vitamins E and C, formalin, sucralfate topic applications, laser coagulation or argon plasma coagulation, radiofrequency ablation, cryoablation, endoscopic balloon dilation of strictures, diverting colostomy and other surgical repairs, but with unclear benefits (Jones 2006, Clarke 2008, Shadad 2013, Karamanolis 2013). Serious manifestations can necessitate high-risk surgery (leaks, mortality) as a last resort. HBOT has mainly been used to treat bleeding since the early 90's (Charneau 1991, Clarke 2008, Sidik 2007, Alvaro 2011, Woo 1997, Warren 2007, Gouello 1999, Jones 2006, Marshall 2007, Dall'Era 2006, Hampson 2012), but occasionally also for bowel obstruction (Neurath 1996, Abu Asi 2013), diarrhea, fistulae and pain (Feldmeier 1996, Woo 1997, Marshall 2007). The main studies are reported in Table 7.

Clarke, in a well-designed multicentre, double-blind, cross-over RCT examined HBOT for refractory radiation proctitis in 150 patients with long-term assessment (5 years) despite lost of follow-up at up to 2 years of > 50% (Clarke 2008). Patients had no response to therapies for at least 3 months before enrollment and were evaluated using the SOMA-LENT scale and bowel-specific quality of life assessment. The HBOT group was treated with 100% oxygen at 2 ATA pressure for 90 minutes once daily, 5 times a week; the control group was treated with 21% oxygen at 1.1 ATA for 90 minutes once daily, 5 times a week. Each group had 30 sessions. A significant proportion of HBOT patients demonstrated clinical responses in intention-to-treat analyses. A substantial improvement occurred when patients received HBOT after the initial allocation up to 5 years, and even after cross-over. An absolute risk reduction of 0.32 was generated (number requiring treatement: 3). A local recurrence was diagnosed for 45% of patients without HBOT response.

A second RCT, with 65 patients, had been published earlier, with two articles (Sidik 2007, Sidik 2007). The symptomatic treatment for the control group is not detailed. HBOT is also incompletely reported (min 18 sessions), and the study methodology and outcome reporting are poorly described. Improved quality of life (Karnofsky score) and decreased side effects of pelvic radiation were demonstrated at 6 months. A high risk of bias cannot be excluded due to the poor reporting of this study.

A third controlled trial with 31 patients compared HBOT to APC, without randomisation (Alvaro Villegas 2011). No significant differences for clinical and demographic data existed between these two groups. Patients were sent for either APC or HBOT by their primary care physician, according to resource availability at the time of referral. HBOT sessions were set at 2-2.5 ATA for 90min. Patients had 3.1 sessions for the APC group and 35+/-5 sessions for HBOT. These treatments had similar improved results at the end of the follow-up period (3 months) for control of rectal bleeding, reduction in number of transfusions and SOMA-LENT score, however clinical response was faster with APC (Alvaro Villegas 2011).

The improvement of radiation proctitis thanks to HBOT has also been advocated in many retrospective series (Gouello 1996, Woo 1997, Jones 2006, Dall'Era 2006, Marshall 2007, Hampson 2007, Hampson 2012, Fuentes Raspall 2012, Safra 2008). Some of them come from the same centre (Dall'Era 2006, Marshall 2007, Hampson 2007, Hampson 2012). The two largest series included 36 and 73 patients, with an improvement respectively of 66% and 63% (Gouello 1999, Hampson 2012). A minimum of 30 HBOT sessions were usually used, sometimes more than 40 (Hampson 2012, Gouello 1999) – the optimal dose is unknown. Patients referred to HBOT had usually failed to respond to previous treatments. They also had additionnal treatments to HBOT, sometimes in more than half of the cases (Marshall 2007). Patients with insufficient medical data for retrospective outcome scoring were excluded from the largest retrospective study (Hampson 2012).

Apart from bleeding, the experience of 5 patients with recurrent acute bowel obstruction after prior pelvic radiotherapy had been retrospectively described with success (Abu-Asi 2013). All cases were refractory to previous medical/or surgical interventions (laxatives, antibiotics, parenteral nutrition, surgical bypass). Forty to 60 HBOT sessions were completed.

The adverse effect of HBOT has not been reported in some prospective series (Sidik 2007, Alvaro Villegas 2011). No oxygen toxicity occurred at 2 ATA for 30 to 40 HBOT sessions in Clarke's study, but 15.8% of patients complained of ear pain or discomfort, 3.3% experienced transient myopia and 1.7% complained of confinement anxiety (Clarke 2008). In retrospective studies, one seizure and 7% to 16% of myopia is described for oxygen toxicity (Dell'Era2006, Jones 2006, Mayer 2001, Woo 1997). Minor barotraumatic accidents occured in up to 40% of cases, with the need for pressure equalizing tympanostomy tube placement in up to 11% of all patients (Jones 2006, Dell'Era 2006).

A single American retrospective study discusses the cost impact of HBOT for patients with gastrointestinal radiation injury (Marshall 2007). It states that HBOT should be limited to patients for whom less aggressive measures have failed.

Experience with HBOT of upper radiation-induced gastro-intestinal symptoms such as dysphagia and odynophagia is scarce, with poor results: 1 response of 14 patients (Bui 2004).

In an animal model, HBOT to prevent radiation-induced enteropathy was administered 7 weeks after radiation exposure. At 7 months, HBOT resulted in fewer gross signs of enteropathy, as well as less narrowing and less rigidity in their harvested bowel segments (Feldmeier 1995). These results agreed with histologic morphometry (Feldmeier 1998).

The final GRADE score for treating radiation proctitis with HBOT is a Grade A (high evidence of benefits) thanks to RCT and observational studies without conflicting results. Based on this grading system, we recommend to use HBOT for radiation-induced proctitis.

HBOT for radiation-induced neurologic injuries

RT is a mainline intervention for tumors, vascular malformations, pain, movement disorders and epilepsy (Kuffler 2012). External beam radiation, stereotactic radiosurgery and radioactive implants are prone to cause radiation-induced necrosis. The nervous system may be affected by radiation (Rahmathulla 2013). Myelitis, plexopathy, brain necrosis and optic neuropathy are described. The pathogenic mechanism is not fully understood (Rahmathulla 2013, Kuffler 2012). Symptoms develop months to years after radiation exposure and are usually progressive but irreversible. Diagnosis is difficult and biopsy or a PET scan should ideally be practised given that an MRI cannot distinguish between necrosis and recurrent tumor growth (Valadao 2014). No treatment demonstrated improvement, although steroids are often used and some studies advocate anticoagulation, barbituates and hypothermia (Wanebo 2009). Symptomatic therapies such as the resection of avascular necrotic debris are done when mass effect is still present after conservative therapies (Rahmathulla 2013).

Several potential mechanisms of HBOT have been advocated to treat cerebral edema, though none of them have been studied alongside cerebral radiation necrosis (Helms 2005, Kuffler 2012). HBOT increases tissue oxygen levels, which can facilitate cellular and vascular repair. It could reduce cerebral edema and maintain blood-brain barrier integrity in an ischemic brain (Lanse 1978, Mink 1995). In addition, the anaerobic condition of the brain can be improved, as demonstrated by the reduction of CSF lactate levels (Kapp 1982). Lastly, inflammation could be decreased at the site of necrosis (Helms 2005, Kuffler 2012). HBOT promotes antioxydant defenses, suppresses proliferation of macrophage and foam cells and prevents activated macrophages and astrocytes from releasing neurotoxic factors (Kuffler 2012). It has been used since the 1970's in the field of radiation-induced necrosis (Hart 1976). The main studies are reported in Table 8.

HBOT has been used for myelitis. A case report showed improvement with HBOT but the patient died of an unrelated cause at 3 months follow-up and another reported no improvement in symptoms or clinical and radiologic outcomes (Calabro 2000, Valadao 2014). Two retrospective series of 5 patients from 1966 to 1975 and 9 patients from 1982 to 1992 demonstrated no improvement in motor function for the former and a putative stabilization or improvement for the latter. Differents kinds of HBOT resulted in 9 to 197 sessions (Hart 1976, Angibaud 1995). In animals, a small pilot study did not demonstrate any clinically significant benefits of HBOT for radiation myelitis (Poulton 1985).

For radiation-induced brachial plexopathy, a double-blind randomised phase II study failed to demonstrate improvement, with 30 HBOT sessions on a warm sensory treshold for 34 patients at 12 months post treatment (Pritchard 2001). Similarly, no effect was registered at 5 years on pain and

general status for these patients (Yarnold 2005). A single case report with sacral plexopathy described discontinuation of opioid analgesics one year later, with a course of initial 30 HBOT sessions (Videtic 1999).

For optic neuropathy, conflicting results exist on case reports and small retrospective studies with few patients (2 to 13 patients), on both children and adults (Fontanesi 1991, Boschetti 2006, Guy 1986, Roden 1990, Miller 2004). The authors are pessimistic as to the effect of HBOT, though sometimes it could be considered to be better than the expected natural course (Borruat 1996, Liu 1992).

For brain necrosis, some case reports were not consistent with HBOT (Cirafisi 1999, Kohshi 2003), while others improved (Hart 1976, Leber 1998, Takenaka 2003, Tandon 2001, Perez-Espejo 2009, Wanebo 2009, Cihan 2009). Other concomitant treatments such as steroids are frequent and HBOT sessions varies from a few to more than 100. Small retrospective series have been published (Valadao 2014, Chuba 1997). Chuba published a study involving 10 children with 8 histologically proven cases of necrosis. He documented initial improvement or stabilisation of symptoms and /or imaging findings for all, but only 6 were still alive at an average of 7 months (3-36 months): 2 improved, 2 others stabilised and the 2 remaining with progressive lesions which had to be operated (Chuba 1997). The role of concomitant administration of corticosteroids or surgery and HBOT are unclear based on the data. The Valadao retrospective series reports 10 patients with post-radiation central nervous system injury: 7 patients with radiation necrosis, 2 with radiation encephalopathy and 1 with myelitis (Valadao 2014). Three out of 7 patients with radiation necrosis reported subjective improvement. Only one of these 3 patients had radiologic improvement. Data is incomplete for a clinical assessment but the condition of all patients with complete data worsened. Two patients with radiation encephalopathy did not improve clinically or radiologically. Concomitant chemotherapy (7 patients) and/or steroid treatment (5 patients) during HBOT may twist these results (Chuba 1997, Valadao 2014). A minimum of 20 to 30 HBOT sessions were used within these 2 series. For Hulshof, HBOT failed to significantly improve cognitive disorders in a comprehensive neuropsychological test battery for 7 patients after irradiation of the brain with 30 sessions of HBOT in a phase I-II study (Hulshof 2002). Only 1 patient out of 7 had benefited from the treatment. In Bui's retrospective serie only 1 out of 6 patients with neurologic radionecrosis was considered (minimally) responsive (Bui 2004).

The best timing for HBOT is questionnable. Some advocate early HBOT after the onset of radionecrosis. Early or delayed (3 months) treatment after diagnosis did not change the progression in a serie examining 7 patients (Hulshof 2002). Usually, HBOT is done after months of radiation injury progression. The minimum number of sessions should be 30 (Kuffler 2012, Perez Espejo 2009, Valadao 2014).

The adverse effect of HBOT for brain necrosis should be evaluated. Some authors decreased treatment pressure due to seizures that can be a symptom of either the disease or oxygen toxicity (Valadao 2014).

The cost impact of HBOT for radiation-induced neurologic injuries has never been studied.

Prophylactic HBOT for radiation-induced brain injury has been retrospectively evaluated for 78 patients after they underwent stereotactic radiosurgery (Ohguri 2007). Thirty-two patients with the best predictors of longer survival received HBOT one week after stereotactic radiosurgery while the other had no HBOT. White matter injury was less frequent with HBOT but not confirmed with multivariate analysis. Radiation necrosis did not appear to be different with or without HBOT respectively at 13.7 and 10.5 months follow-up periods (Ohguri 2007). In an animal model, HBOT as prophylaxis for radiation myelitis could be of value but answered the optimal timing for HBOT to produce a beneficial rather than detrimental effect (Feldmeier 1993). In a rat spinal cord model, prophylactic HBOT was not effective for radiation injury to the spinal cord (Sminia 2003).

The final GRADE score for treating radio-induced neurologic injuries with HBOT is a Grade D (very low evidence of benefits) because of observational studies with conflicting results and important inconsistency and uncertainty about directness. We can not recommend using HBOT in the field of radiation-induced neurologic injury.

HBOT for radiation-induced injuries after breast RT

HBOT has been used in other soft tissue sites with radiation-induced injuries, and especially in late breast cancer sequelae (Table 9). First, Carl reported a prospective study of 44 women with persistent pain, erythema and edema which impacted their quality of life following breast conservation therapy including RT (Carl 2001). These symptoms were scored according to modified SOMA-LENT criteria. Thirty-two patients were enrolled in a treatment protocol with HBOT and compared to 12 other women who refused HBOT. Follow-up periods were respectively of 11 and 7 months. After 25 HBOT sessions (7-60), a significant reduction in pain, erythema and edema was obsreved in the HBOT group. In a double-blind randomised phase II study about radiation-induced brachial plexopathy, Pritchard failed to demonstrate any improvement with 30 HBOT sessions on a warm sensory treshold for 34 patients at 12 months post-treatment; an improvement in arm lymphoedema was reported, however, although this was unplanned as an end point and was therefore not systematically assessed (Pritchard 2001). These results were only partially confirmed in a later non-randomised phase II trial (Gothard 2004). Radiation-induced arm lymphoedema was assessed in 21 patients by measuring its volume in an operator independant method. HBOT consisted of 30 sessions over a period of 6 weeks (Gothard 2004). Although a significant reduction of arm volume was noted, it was clinically modest and could not improve quality of life at 12 months follow-up (Gothard 2004). Furhter investigations were conducted in a randomised phase II trial by the same author (Gothard 2010). Fifty-eight women with up to 15% increase in arm volume after RT for breast cancer were randomised at a 2:1 ratio to the same HBOT protocol as published earlier and the best standard care. No evidence has been found of a beneficial effect of HBOT on arm lymphoedema as a primary end point, while quality of life could be misinterpreted in the absence of blinding (Gothard 2010).

The current final GRADE score for not treating arm lymphoedema as radiation-induced breast injury with HBOT is a Grade A (high evidence of absence of benefits). Based on this grading system, we cannot recommend using HBOT for lymphedema in radiation-induced breast injury, although it cannot be excluded that HBOT could be beneficial for treating other problems.

HBOT for radiation-induced injury of bones

There is little literature regarding ORN in other parts of the body. Even in the largest retrospective studies, few cases are reported (Hart 1976, Bui 2004, Hampson 2012, Tahir 2015). Feldmeier published the largest retrospective case series with 23 cases of chest wall ORN (Feldmeier 1995). A durable resolution of radiation-induced lesions was achieved only with adequate debridement and removal of necrotic bone, and HBOT can serve only as a useful adjunct (Granick 1993, Feldmeier 1995, Hart 1976). Based on the GRADE method, we cannot suggest recommendations on the use of HBOT to treat ORN in parts other than the jaws due to insufficient data.

HBOT for other radiation-induced injuries

HBOT has been used in a single case series of 17 radionecrosis of the extremities (Feldmeier 2000). Feldmeier retrospectively reviewed non-healing necrotic wounds of the extremities within a previously irradiated limb. These were cases of soft tissue necrosis. One to 95 HBOT sessions were done with an average number of 47 for the 11 patients who healed. 73% of healed patients required surgery (i.e debridement, skin grafting or myocutaneous flap). When excluding local or metastatic malignancy, 11 of 13 patients healed (Feldmeier 2000).

Soft tissue necrosis in other parts of the body has sometimes been treated with HBOT. Almost all case series included abdomen and pelvic injuries from gynaecologic cancer (Feldmeier 1996, Rud 2009, Fink 2006, Williams 1992). Interpretation is very difficult due to the small sample sizes and the wide heterogeneity of organs (abdominal wall, groin, vagina, pelvic bones, small or large bowel, perineum, skin, etc.) and symptoms (pain, fistula, wounds, etc.). Feldmeier retrospectively studied the wound healing of 44 patients (Feldmeier 1996). Rud conducted the sole existing prospective study. He was unable to demonstrate pain relief in 16 patients with gynaecologic cancer after a follow-up of 6 months with the use of HBOT for 21 consecutives days (Rud 2009). No recommandations based on GRADE method can be suggested from this data.

Conclusion:

These findings indicate that HBOT may offer a clinical benefit to patients suffering from late radiation-induced injuries. Despite a recent increase in the number of published comparative studies, this systematic review highlights the limitations of the available evidence justifying the use of HBOT. A cautious interpretation of unclear methodological issues undermines the strength of conclusions that can be made with actual guidelines such as the GRADE method. Results from studies in progress are awaited.

The levels of evidence (based on GRADE system) actually are:

Grade D (very low level) to support HBOT for treating mandibular ORN.

Grade C (low level) to support HBOT for preventing mandibular ORN.

Grade D (very low level) to support HBOT for treating head and neck soft tissue radionecrosis.

Grade D (very low level) to support HBOT for treating or preventing xerostomia.

Grade D (very low level) to support HBOT for preventing loss of osseointegrated implants in irradiated tissue.

Grade C (low level) to support HBOT for radiation cystitis.

Grade A (high level) to support HBOT for treating radiation proctitis.

Grade D (very low level) to support HBOT for treating radiation-induced neurologic injuries.

Grade A (high level) to recommend not to use HBOT for lymphedema after breast RT.

Grade D (very low level) to support HBOT for treating ORN in bones other than mandibules.

Grade D (very low level) to support HBOT for treating soft tissue radionecrosis in areas other than the head and neck.

Grade A (high level) to include data on the cost impact of HBOT and assessment of HBOT side effects in prospective studies.

Grade A (high level) to continue research into HBOT for late radiation tissue injury as a priority given the advances in recent years in surgical, medical and perioperative management of patients with radiation-induced injuries in fields other than hyperbaric medicine.

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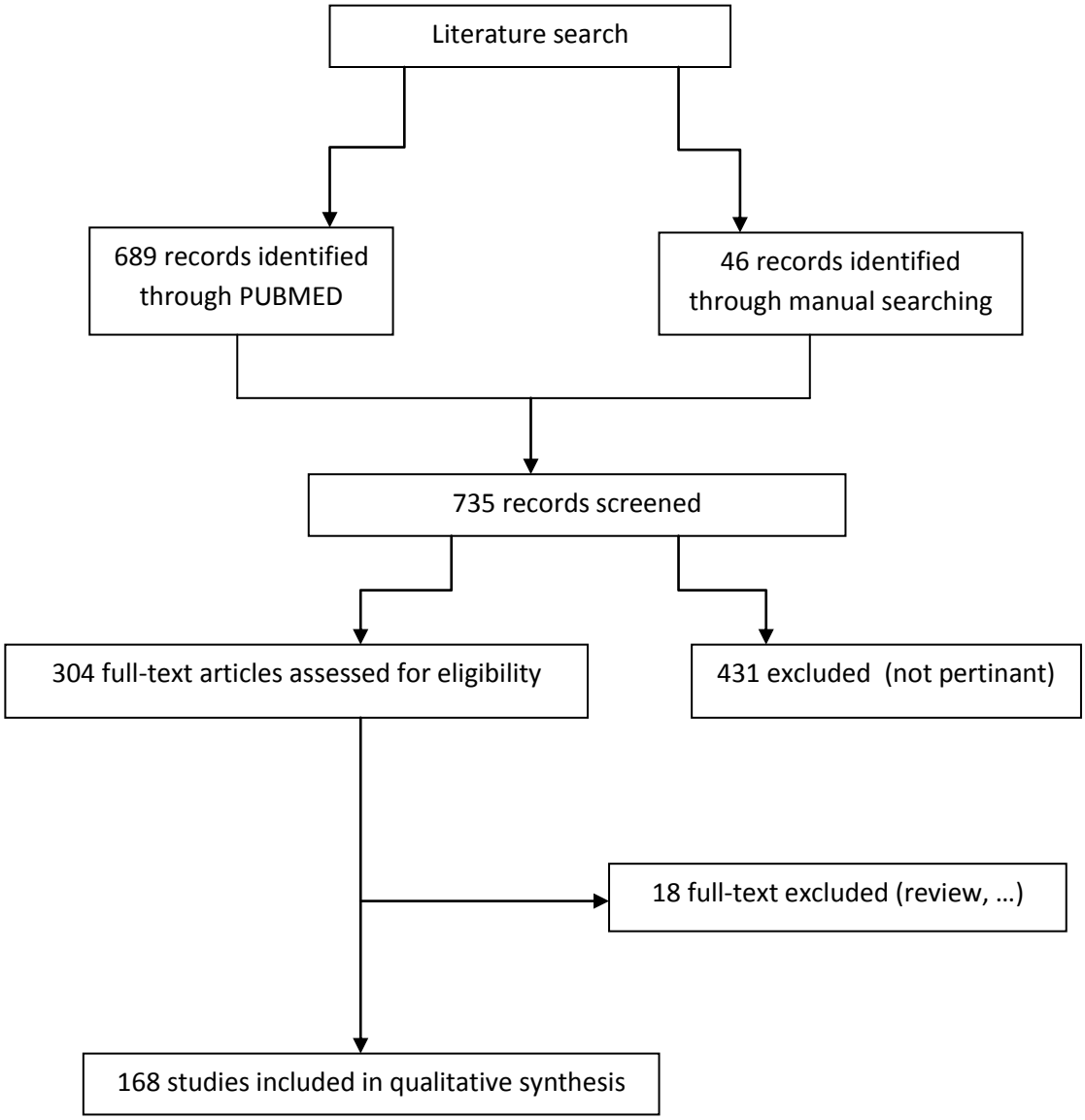
Literature search
689 records identified through PUBMED
46 records identified through manual searching
735 records screened
304 full-text articles assessed for eligibility
431 excluded (not pertinant)
18 full-text excluded (review, …)
168 studies included in qualitative synthesis

Table 1: Overt osteoradionecrosis of the jaws (prospective studies or retrospective studies with ≥ 15 patients)

Study (authors, year)	Type	Nb patients	Aim(s) / Evaluation criteria	Inclusion / Exclusion criteria	HBO protocol (pressure, time, nb of sessions/ week and mean total)	Results/ Follow-up	Conclusion / comment
Nolen D et al. 2014 (including Cannady SB et al. 2011)	Multi site retrospective	89 (39 with prior failure of HBOT as a conservative therapy/ 50 without HBOT)	Surgical complications of free flap reconstruction/ wound breakdown, fistula, flap necrosis, infection, flap failure	Free flap reconstruction for ORN of the mandible	Not reported (No data on when, how and why HBOT was done) But no new sessions after free flap	No difference in overall complications with or without previous HBOT Follow-up not reported	Case series. No evidence for HBOT efficacy
Sawhney R et al. 2013	Retrospective	37 (26 with HBOT/ 11 without HBOT for insurance issue or patient wishes)	Management of fracture with osteocutaneous free tissue transfer/ Flap loss, nonbony union, Skin paddle loss	Pathologic fracture of ORN of the mandible	Not reported (Planned 20 pre operative sessions and 10 post operative sessions)	No complications with HBOT 2 skin paddle loss and 4 bony non unions in non HBOT group 4,5 years of follow-up (10 months-12 years)	Case series. No evidence for HBOT efficacy
Hampson NB et al. 2012	Retrospective	43	HBOT in multimodality therapy/ Combined retrospective objective and subjective findings	Established ORN of the jaw	2.4 ATA 90 min. 5-11/week 40 (30-60)	73% resolved 21% improved No follow up	Case series. No evidence for HBOT efficacy
Freiberger JJ et al. 2009	Retrospective	65	HBOT in multimodality therapy/ Lesion grade and Epstein classification	ORN of the mandible with multimodality surgical and HBOT management	2 ATA 120 min. (planned HBOT: 2 sessions/day with 30 before and 10 post surgery) 36 (19-55)	88% resolved or improved immediately after HBOT 57% improvement at 56 months of follow up	Case series. No evidence for HBOT efficacy

D'Souza J et al. 2007	Retrospective with non matched controlled group	23 (16 with HBOT, 7 without HBOT)	HBOT alone or with surgery/ Lesion grade (Notani classification)	ORN of the mandible (stage I to III)	Not reported ("not all patients received HBOT in accordance to Marx protocol")	"it seems that HBOT was of little benefit"	Case series. No evidence for HBOT efficacy
Annane D et al. 2004	Double blind Randomized Controlled Trial	68 (31 HBOT, 37 placebo)	HBOT (alone for group A with no need a priori surgery or perioperatively for group B who need surgery) / Recovery of ORN	Mild to moderate form of ORN of the mandible (without fracture or bone reabsorption to inferior border)	2.4 ATA 90 min. 10/week 30 for group A 30 before surgery and 10 after surgery for group B Full range of the number of sessions not reported	Lower recovery in HBOT group 1 year follow-up	Against HBOT in mild to moderate ORN Moderate level of evidence Methodology flaw (inadequate multimodality Therapy approach)
Bui QC et al. 2004	Retrospective	31	HBOT alone or with surgery/ RTOG grade based on telephone questionnaire	Established ORN of Head and neck cancer patients and prophylactic HBOT for ORN	Not reported	Improvement in overall Follow-up not reported	Case series. No evidence for HBOT efficacy
Gal TJ et al. 2003	Retrospective	30 (9 who never had HBOT, 21 with prior HBOT and debridement which failed to heal ORN)	Complications following microvascular reconstruction +/- peri operative HBOT/ Clinical resolution of ORN, perioperative complications	ORN of the mandible with Marx III stage	Not reported	More wound infections and overall complications in HBOT Follow-up not reported	Case series. No evidence for HBOT efficacy
David LA et al. 2001	Retrospective	51	HBOT alone or with surgery/ Bone exposure/ fistula/ symptomatic status	Overt ORN of the mandible	2.4 ATA 60 min. Number/ week and total Not reported	Success in 70% 1.8 years of follow-up	Case series. No evidence for HBOT efficacy
Curi MM et al. 2000	Retrospective	18	Peri operative HBOT/ Not reported	Refractory ORN of the jaws	2.4 ATA 120 min. 1/day Not reported	78% healed and 17% improved 24.8 months follow-up (12-68)	Case series. No evidence for HBOT efficacy

Maier A et al. 2000	Retrospective with non matched controlled group	41 (21 surgery alone because HBOT non available/ 20 surgery plus HBOT)	Post operative HBOT as salvage treatment after failed operation/ Not reported	Severe infected ORN of the mandible	2.5 ATA 60 min. ?/week 29 (15-57)	13 success/20 patients in HBOT group 13 success/21 patients in control group Follow-up: 18 months in HBOT group and 59 months in non HBOT group	Case series. No evidence for HBOT efficacy
Hao SP et al. 1999	Prospective	26 (10 HBOT/ 16 non HBOT)	Management of ORN (including non systematically pre operative HBOT)/ Not reported	Head and neck ORN	2.5 ATA 120 min. ?/week Planned 40 sessions Mean total not reported	Controlled ORN in 77% (HBOT results not detailed) Follow-up not reported	Case series. No evidence for HBOT efficacy
London SD et al. 1998	Retrospective	16	Peri operative HBOT/ Patient score Physician score Pain, fracture	Head and neck ORN	2.5 ATA 90 min. ?/week 24 (1-70)	Improvement for all patients (although it may be slight) 15 months Follow-up	Case series. No evidence for HBOT efficacy
Aitasalo K et al. 1998	Retrospective	36	Peri operative HBOT/ Not reported	Mandibular or maxillar ORN	2.5-2.8 ATA 90-120 min. 5-6/week Not reported (10-14)	92% success 34 months follow-up (10 months-6 years)	Case series. No evidence for HBOT efficacy
Van Merkesteyn JPR et al. 1995	Retrospective	29 (27 HBOT/ 2 non HBOT)	Peri operative HBOT/ Not reported ("resolution of ORN")	ORN of the mandible	3 ATA 90 min. ?/week (Planned 30 pre operative and 10 post surgery) Total Not reported	69% healed 16 months of follow-up (3-84)	Case series. No evidence for HBOT efficacy
McKenzie MR et al. 1993 (and Epstein J et al. 1997)	Retrospective	26	HBOT with multimodality approach/ Epstein classification Mucosal and cutaneous coverage	ORN of the mandible	2.5 ATA 90 min. ?/week 35 (9-84)	50% healed 31% improved 38 months follow-up (8-156)	Case series. No evidence for HBOT efficacy

Marx RE 1994	Non blind randomized Controlled Trial	104 (52 HBOT/ 52 non HBOT)	Peri operative HBOT / achievement of continuity, restoration of alveolar bone height, restoration of osseous bulk, restoration of arch form, maintenance of bone for 18 months, restoration of facial contour	Hemi-mandibular jaw reconstructions in irradiated bed	2.4 ATA 90 min. ?/week Planned 20 sessions before surgery and 10 post surgery Final total number not reported	100% success Follow-up not reported	Favors HBOT low level of evidence (Methodology not described High risk of bias)
Mounsey RA et al. 1993	Retrospective	41	HBOT/ Size of exposed bone, relief of symptom, closing of fistula.	ORN of the mandible	2 ATA 120 min. 1/day Not reported	83% improvement Follow-up not reported	Case series. No evidence for HBOT efficacy
Marx RE 1983	Retrospective	58	Peri operative HBOT/ Marx Criteria	"Refractory" ORN of the mandible	2.4 ATA 90 min. 5/week Not reported (60-72)	100% healed (with 85% needing surgery) 18 months follow-up min.	Case series. No evidence for HBOT efficacy
Davis JC et al. 1979	Retrospective	23	Adjunct HBOT to surgery and antibiotics/ Response not detailed	No detailed description of ORN of the mandible	2.4 ATA 90 min. 1/d 45 (29-90)	96% recovery Follow-up not detailed (1-24 months)	Case series. No evidence for HBOT efficacy
Tobey RE et al. 1979	Double blinded randomized Controlled Trial	12 (how many into each group?)	HBOT with multimodality approach / Clinical signs, symptoms and x-ray	ORN of the mandible	2 ATA versus 1.2ATA 120min. 5/week Planned for 8 weeks (mean total number of HBOT not documented)	"significant improvement" (no quantitative data) Follow-up not reported	Favors HBOT Low level of evidence Poor methodology report with high risk of bias (randomization/ outcome not stated)
Hart GB et al. 1976 (including Mainous EG et al. 1975)	Retrospective	46	Multimodality therapy with HBOT/ Not described	Refractory ORN of the mandible	2 ATA 120 min. Planned series of 60 daily sessions at 6 and 12 months followed by 10 annual sessions	80% free of symptoms at end of first HBOT serie Follow-up not reported	Case series. No evidence for HBOT efficacy

ORN : Osteoradionecrosis, HBOT : Hyperbaric Oxygen Therapy, RTOG : Radiation Therapy Oncology Group

Table 2: Prophylaxis of ORN of the jaws with HBOT (Prospective studies or retrospective studies with > 10 patients)

Study (authors, year)	Type	Nb patients	Aim(s) / Evaluation criteria	Inclusion / Exclusion criteria	HBO protocol (pressure, time, nb of sessions/week and mean total)	Results/ Follow-up	Conclusion / comment
Heyboer M et al. 2013	Retrospective	40	Peri operative HBOT/ Healing at completion of HBOT (clinical evaluation) and at 6 months (mailing)	Dental extractions in previously irradiated head and neck	2.5 ATA 50 min. Sessions/week Planned 20/10 protocol but final mean total number not reported	0% ORN at end HBOT 15.8% ORN at 6 months follow-up	Case series. No evidence for HBOT efficacy
Hampson NB et al. 2012	Retrospective	166	Perioperative HBOT/ Combined retrospective objective and subjective findings	Oral surgical procedures involving jaw bone within a previously irradiated field	2.4 ATA 90 min. 5-11/week 30 (23-40)	92% resolved 8% improved No follow up	Case series. No evidence for HBOT efficacy
Kaur J et al. 2009	Retrospective	26	Perioperative HBOT/ Telephone interview (pain, healing of tooth sockets)	Dental extractions in previously irradiated jaws	2.4 ATA 90 min. 5/week Planned 20/10 protocol but final mean total number not reported	96% healed Follow-up not reported	Case series. No evidence for HBOT efficacy
David LA et al. 2001	Retrospective	24	Perioperative HBOT/ "Post-operative complications"	Dental extractions for "patients at risk of developing ORN"	2.4 ATA 60 min. Number/ week and total Not reported	98% healed uneventfully No ORN 10.3 months of follow-up (6 months-2.3 years)	Case series. No evidence for HBOT efficacy

Chavez JA et al. 2001	Prospective	40	Perioperative HBOT/ Healing of extraction site, mucosal coverage, Safety of HBOT	Dental extraction in previously irradiated mandible	2.4 90 min. 5/week Planned 20/10 protocol but final total number of sessions not reported	98.5% healed No serious complications 47% with minor middle ear barotrauma 1 year follow-up	Case series. No evidence for HBOT efficacy but evidence for HBOT safety
Vudiniabola S et al. 1999	Retrospective with unmatched controlled group (contraindication, no consent, early complication of HBOT course)	36 (29 HBOT 7 Non HBOT)	Perioperative HBOT/ Oral status and radiographic	Oral surgery in irradiated jaws	2.4 ATA 90 min. 6/week Planned 20/10 protocol but final mean total number not reported (8-53)	4% ORN with HBOT Versus 15% without HBOT Follow-up unknown	Case series. No evidence for HBOT efficacy
Lambert PM et al. 1997	Retrospective	47	Perioperative HBOT/ "outcome" not described	Dental extraction in previously irradiated jaws	2.4 ATA 90 min. ?/week Planned 20/10 protocol but final mean total number not reported	0% ORN 2.9 years of follow-up (2 months-7.5 years)	Case series. No evidence for HBOT efficacy
Marx RE et al. 1985	Non blind Multi centre randomized controlled trial	74 (37 patients/ 156 teeth with HBOT and 37 patients/ 135 teeth without HBOT)	Prophylactic perioperative HBOT/ Exposed bone in a study sockets	Dental extraction in previously irradiated mandible (≥60 Gy)	2.4 ATA 90 min. 5-6/week Planned 20/10 protocol but final mean total number not reported	Significant reduction of ORN incidence 6 months Follow-up	Favors HBOT Moderate level of evidence Methodology poorly reported with risk of bias

HBOT : Hyperbaric Oxygen Therapy

Table 3: Head and neck soft tissue radio-induced necrosis (prospective studies or retrospective studies ≥ 15 patients)

Study (authors, year)	Type	Nb patients	Aim(s) / Evaluation criteria	Inclusion / Exclusion criteria	HBO protocol (pressure, time, nb of sessions/ mean total)	Results/ Follow-up	Conclusion / comment
Dequanter D et al. 2013	Retrospective	16	HBOT/ Not described (clinical examinations)	Soft tissue radio-induced necrosis with major infected wounds or chronic fistulas with no signs of healing after surgery	2.5 ATA 90 min. 7/week 24 (20-30)	87.5% healed Follow-up not reported	Case series. No evidence for HBOT efficacy
Hampson NB et al. 2012	Retrospective	27	HBOT/ Combined retrospective objective and subjective findings	Soft tissue radionecrosis of the larynx	2.4 ATA 90 min. 5-11/week 40 (28-60)	4% healed 78% responders >50% 15% responders <50% No follow-up	Case series. No evidence for HBOT efficacy
Filntisis GA et al. 2000	Retrospective	18	HBOT/ Chandler's grading system	Severe radionecrosis of the larynx > 3 months	2 ATA 120 min. 6/week 41 (6-80)	72% improvement 28% failure (total laryngectomy) Follow-up 22 months	Case series. No evidence for HBOT efficacy
Neovius EB et al. 1997	Consecutive Retrospective With historical reference group	30 (15 HBOT 15 non HBOT)	HBOT/ Clinical examination (not detailed)	Infected wounds or chronic fistulas after surgery for irradiated head and neck patients without ORN	2.5-2.8 ATA 75 min. 7-14/w 31 (20-42)	80% healed with HBOT 47%healed without Follow-up not reported	Case series. No evidence for HBOT efficacy

Marx RE 1994	Non blind randomized controlled trial	160 (80 HBOT 80 non HBOT)	Surgery vs surgery and prophylactic HBOT/ Wound infection Wound dehiscence Delayed healing	Hemimandibular jaw reconstructions in tissue bed radiated ≥ 64 Gy	2.4 ATA Not reported	Improvement in all criterias Follow-up not reported	Favors HBOT Moderate level of evidence Methodology poorly reported with high risk of bias
Davis JC et al. 1979	Retrospective	16	Adjunct HBOT to surgery and antibiotics/ Response not detailed	No detailed description of Soft tissue radionecrosis of the head and neck	2.4 ATA 90 min. 1/d 45 (29-90)	94% recovery Follow-up not detailed (2 months-2 years)	Case series. No evidence for HBOT efficacy

HBOT : Hyperbaric Oxygen Therapy

Table 4: Radio-induced xerostomia (prospective studies or retrospective studies with ≥ 15 patients)

Study (authors, year)	Type	Nb patients	Aim(s) / Evaluation criteria	Inclusion / Exclusion criteria	HBO protocol (pressure, time, nb of sessions/ week and mean total)	Results/ Follow-up	Conclusion / comment
Tahir ARM et al. 2015	Retrospective cohort	50	HBOT on xerostomia/ CTCAE grading system	Chronic radiation induced toxicity with xerostomia	2.4 ATA 70 min. 7/week Not reported	64% improvement (mainly minor) Follow-up not reported	Case series. No evidence for HBOT efficacy
Irgens A et al. 2013	Prospective cohort	54	HBOT on quality of life/ SF-36	Head and neck radiation injury	2.4 ATA 90 min. 5/week ? (19-60)	Improvement only in Social Function (no item specifically dedicated to xerostomia) 1 year follow-up	Favors HBOT Low level of evidence
Harding SA et al. 2012	Prospective cohort	18	HBOT on quality of life/ EORTC C 30 EORTC HN 35 SF-36	Spontaneous ORN in head and neck cancer patients	2.2 ATA 90 min. 10/week 34 (29-49)	Improvement in few items including xerostomia (social eating and teeth) follow-up at completion of HBOT	Favors HBOT Low level of evidence
Forner L et al. 2011	Retrospective cohort	80	HBOT on xerostomia/ Visual Analog Scale Salivary flow rate	Prevention or treatment of ORN of the mandibule	2.4 ATA 90 min. 5/week 30	Improvement in salivary flow rate and xerostomia No follow-up (at completion of HBOT)	Case series. No evidence for HBOT efficacy
Cankar et al. 2011	Prospective cohort	16	HBOT on xerostomia/ Xerostomia grade, Salivary flow rate, Buffer capacity, Saliva pH, Colony density	Head and neck cancer with radiation therapy	2.5 ATA 90 min. 5/week 20	Improvement in all end point except buffer capacity, Follow-up at completion of HBOT	Favors HBOT Low level of evidence
Teguh DN et al. 2009	Non blind randomized controlled trial	19 (8 HBOT / 11 non HBOT)	Prevention of radiation induced injury with HBOT/ Visual Analog Scale EORTC C30 EORTC HN 35 PFS	Oropharyngeal and nasopharyngeal cancer with radiotherapy	2.5 ATA 90 min. 5/week 30	Improvement in QoL scores for swallowing, sticky saliva, xerostomia and pain in mouth 18 months follow-up	Favors HBOT moderate level of evidence (stopped at premature point: slow accrual and lack of financial support)

Harding SA et al. 2008	Prospective cohort	66	Peri operative HBOT on quality of life/ EORTC HN 35 EORTC C30 SF-36 HADS UW-QOL	Prevention (38 patients) or treatment (28 patients) of ORN	2.2 ATA 90 min. 5/week 26 prior surgery (14-40) and 16 post surgery (6-23)	Improvement in EORTC C30 and EORTC HN35 (including items on Xerostomia) No improvement in UW-QOL, HADS, SF-36 No follow-up	Favors HBOT Low level of evidence
Gerlach NL et al. 2008	Prospective cohort	21	Peri operative HBOT on quality of life/ EORTC HN 35	Prevention or treatment of ORN of the mandibule or soft tissue necrosis	2.5 ATA 95 min. 5/week (Planned 20-30 preoperative and 10 post operative) Mean total not reported	Improvement in swallowing problems, taste, and subjective saliva quantity No improvement in dental problems, dry mouth sensation, smell, conversation, 2 years follow-up	Favors HBOT Low level of evidence
Schoen PJ et al. 2007	Non blinded randomized controlled trial	26 (13 peri operative antimicrobial prophylaxis/ 13 peri operative antimicrobial prophylaxis and HBOT)	HBOT for prosthodontic rehabilitation/ Dental status, oral condition, prosthetic rehabilitation, Radiographic, EORTC C30, EORTC HN35, Oral health impact profile questionnaire, Denture satisfaction, Subjective chewing ability, Impact on Social activities	Edentulous patients treated for first malignancy in head and neck region with lower denture functioning problems and implant placement	2.5 ATA 80 min. ?/week 20 sessions before implant surgery and 10 sessions after	No difference in QoL (including few items on Xerostomia) 12 months follow-up	Not favors HBOT Low level of evidence (high risk of bias)

CTCAE grading system: Common Terminology Criteria for Adverse Events v3.0 grading system. HADS: Hospital Anxiety and Depression Scale. SF-36: Medical Outcomes Short Form 36. UW-QOL: University of Washington Quality of Life Version 4 Questionnaire. EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Core questionnaire. EORTC HN35: European Organization for Research and Treatment of Cancer Head and Neck Quality of Life questionnaire. PFS: Performance status scale

Table 5: HBOT for irradiated bones who require osseointegrated implants (prospective studies or series with > 20 patients).

Study (authors, year)	Type	Nb patients	Aim(s) / Evaluation criteria	Inclusion / Exclusion criteria	HBO protocol (pressure, time, nb of sessions/ week and mean total)	Results/ Follow-up	Conclusion / comment
Schoen PJ et al. 2007	Single centre randomized controlled trial Not blinded	26 patients/ 103 implants (13 pre and post-surgery HBOT, 13 non HBOT)	Peri operative HBOT/ Dental status, oral condition, prosthetic rehabilitation, Radiographic, EORTC C30 EORTC HN35 Oral health impact profile questionnaires, Denture satisfaction, Subjective chewing ability Impact on social activities	Prosthodontic rehabilitation with implant-retained lower denture in irradiated head and neck cancer	2.5 ATA 80 min. ?/week Planned 20 pre and 10 post surgery sessions (total non-reported)	No improvement of Implant survival rate, peri implant health, quality of life at 1 year follow-up	Not favors HBOT Moderate level of evidence
Granstrom G et al. 2005 (including Granstrom G et al. 1999 and Granstrom et al 1993)	Retrospective single centre case-controlled study	207 patients [107 irradiated patients (631 osseointegrated implants in which 340 had HBOT)/ 100 non irradiated patients (614 osseointegrated implants)]	Peri operative HBOT/ Implants failure	Osseointegrated implants in irradiated and non-irradiated patients	2.5 ATA 90 min; ?/week Planned 20 pre and 10 post surgery sessions Mean total not reported	Implant survival improved in irradiated field with HBOT (91,5% vs 59,8%)	Favors HBOT low level of evidence

Shaw RJ et al. 2003	Retrospective	77 patients (386 implants)/ (16 HBOT patients/ 77 implants and 61 non HBOT patients/309 implants)	Peri operative HBOT/ ORN and implant functional osseointegration (not detailed)	Implant-based oral rehabilitation (in irradiated or non irradiated bones and with or without HBOT	2.4 ATA 90 min. (Planned 20 pre and 10 post operative sessions)	No benefit from HBOT on rates of implant loss (19% vs 18%) or ORN (2 vs 0) in irradiated bones 3.5 years follow-up (0.3-14)	Case series. No evidence for HBOT efficacy
Marx RE et al. 1998	Retrospective	748 implants	Peri operative HBOT/ ORN and implant functional osseointegration (not detailed)	Osseointegrated implants in irradiated bones	2.5 ATA 90 min. 5/week (Planned 20 pre and 10 post operative sessions)	ORN: 0.5% functional implants: 83% 5 years follow-up	Case series. No evidence for HBOT efficacy
Niimi et al. 1998 (including Niimi et al. 1997)	Retrospective multi site	44 patients (228 implants)/ (14 HBOT patients/67 implants and 30 non HBOT patients/ 161 implants)	Peri operative HBOT/ Implants survival rate	Osseointegrated implants in irradiated maxillae and mandibles	Not detailed (generally 20 pre operative and 10 post operative sessions of 90 min. at 2.4 ATA)	Overall survival rate of 89,4% without HBOT versus 93,4% with HBOT Mean follow-up not reported	Case series. No evidence for HBOT efficacy

HBOT : Hyperbaric Oxygen Therapy, EORTC C30 : European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire, EORTC HN35 : European Organisation for Research and Treatment of Cancer Quality of Life Head and Neck cancer Module

Table 6: Radio-induced cystitis (prospective studies and retrospective studies ≥ 30 patients)

Study (authors, year)	Type	Nb patients	Aim(s) / Evaluation criteria	Inclusion / Exclusion criteria	HBO protocol (pressure, time, nb of sessions/ week mean total)	Results/ follow-up	Conclusion / comment
Ribeiro de Oliveira TM et al. 2015	Retrospective case series	176	HBOT/ Macroscopic hematuria	Radiation-induced cystitis	2.5 ATA 90 min. 5/week 37 (7-179)	67% complete initial resolution 23% partial initial resolution 12 months follow-up (0-108) with 15% recurrence	Case series. No evidence for HBOT efficacy
Dellis A et al. 2014	Prospective pilot-feasibility study	11	HBOT/ Hematuria (RTOG/ EORTC score)	Grade IV radiation-induced haemorrhagic cystitis without prior treatment	1.8 ATA 90 min. 5/week 32 (27-44)	73% complete or partial response with durable effect 18 months follow-up (3-34)	Favors HBOT Low level of evidence
Oscarsson N et al. 2013	Prospective cohort study	39	HBOT/ Urinary domain of EPIC Score	Late radiation induced cystitis and/or proctitis (without requirement of blood transfusion)	2-2.4 ATA 90min. 5/week 36 (28-40)	Improvement for 76% of patients 1 year follow-up	Favors HBOT Low level of evidence
Shilo Y et al. 2013	Retrospective case series	32	HBOT/ Hematuria	Hemorrhagic radiation-induced cystitis	2 ATA 90 min. 5/week Not reported	84% resolved initially 12 months follow up (5-74) with 41% recurrence	Case series. No evidence for HBOT efficacy
Shao Y et al. 2012	Randomized Controlled Study	36 (20 HBOT / 16 Hyaluronic Acid)	HBOT vs intravesical HA instillation/ Symptoms of hematuria, frequency of voiding, VAS of pelvic pain	Radiation-induced hemorrhagic cystitis	2.5 ATA 60 min. 7/week Number of sessions not reported	No improvement in frequency of voiding HBOT = HA for hematuria and pelvic pain (Improvement rates not interpretable because combined) 18 months follow-up	Favors HBOT low level of evidence HBOT = HA for improvement HA cheaper and more convenient Lack of methodology/ results reporting

Nakada T et al. 2012	Retrospective case series	38	HBOT/ modified SOMA scale	Radiation-induced cystitis	2 ATA 90min. 6/week 62 (39-92)	Improvement of ratios of objective and subjective findings 11.6 years follow up (7-19)	Case series. No evidence for HBOT efficacy
Hampson N et al. 2012 (including part of Hampson et al. 2007)	Retrospective case series	44	HBOT/ Combined objective and subjective findings	Radiation-induced cystitis	2.4 ATA 90 min. 5-11/week 42 (34-60)	57% resolved 32% responders >50% 5% responders < 50% Follow up not reported	Case series. No evidence for HBOT efficacy
Vilar DG et al. 2011	Prospective study	38 (14 de novo HBOT, 24 with previous HBOT)	HBOT/ Hematuria (RTOG, telephone survey)	Radiation-induced hemorrhagic cystitis	2-2.5 ATA 90 min. 5/week 31 (10-48)	Poorly reported (just hematuria) 89% healed initially 76% at end follow up 56 months (4-72)	Favors HBOT Low level of evidence Insufficient reported data
Hampson NB et al. 2007 (including Chong KT et al. 2005, Corman JM et al. 2003 and part of Hampson NB et al. 2012)	Retrospective case series	94	HBOT (1 vs 2 daily sessions)/ Combined objective and subjective findings	Radiation-induced cystitis	2.4 ATA 90 min. 2-12/week 30 (4-60)	40% complete healing 43% partial healing 17% failure	Case series. No evidence for HBOT efficacy
Bevers RFM et al. 1995	Prospective study	40	HBOT/ Recurrence of hematuria, cystectomy, death	Severe haemorrhagic radio-induced cystitis not responding to previous treatment	3 ATA 90 min. 6/week Planned 20-40 sessions mean total not reported	92% healed 13 months follow-up with 22.5% recurrence 12,5% cystectomy 30% death	Favors HBOT low level of evidence

HBOT : Hyperbaric Oxygen Therapy, RTOG : Radiation Therapy Oncology Group , EORTC : European Organization for Research and treatment of Cancer, EPIC score : Expanded Prostate Index Composite score, VAS: Visual analogue scale. HA: Hyaluronic Acid.

Table 7: Radio-induced proctitis (prospective studies or retrospective studies with ≥ 10 patients)

Study (authors, year)	Type	Nb patients	Aim(s) / Evaluation criteria	Inclusion / Exclusion criteria	HBO protocol (pressure, time, nb of sessions/ week and mean total)	Results/ Follow-up	Conclusion / comment
Fuentes-Raspall R et al. 2013	Retrospective case series	14	HBOT/ Rectal symptoms CTCv3, SOMA LENT Toxicity grading SF36	Rectal toxicity CTCv3 grade ≥2 with rectal bleeding (+/- bladder toxicity)	Not described	93% healed Follow-up not reported	Case series. No evidence for HBOT efficacy
Hampson N et al. 2012	Retrospective case series	73	HBOT/ Combined objective and subjective findings	Any forms of radiation proctitis or enteritis	2.4 ATA 90 min. 5-11/week 42 (26-60)	25% healed 38% responders ≥50% 25% responders <50% Follow-up not reported	Case series. No evidence for HBOT efficacy
Alvaro Villegas JC et al. 2011	Prospective non randomized	31 (17 HBOT/ 14 APC)	HBOT vs Argon Plasma Coagulation (APC)/ Hb level, transfusions, SOMA LENT	Radiation-induced proctitis with Rectal bleeding	2-2.5 ATA 90 min. ?/week 35 +/-5	Improvement in both group APC = HBOT at 3 months follow up Faster response with APC	Favors HBOT Moderate level of evidence
Clarke RE et al. 2008	Double blind Multicentre cross over Randomized Controlled Trial	120 (75 HBOT/ 75 sham)	HBOT/ SOMA LENT, Bowel function, QoL	Radiation proctitis≥ 3 months not responder to other therapies	2 ATA 90 min. 5/week 30 or 40	SOMA-LENT improvement at 1 to 5 years (end of follow-up) Bowel specific QoL improvement	Favors HBOT Number needed to treat of 3 High level of evidence
Sidik S et al. 2007a (including Sidik S et al. 2007b)	Non blind Monocentre Randomized Controlled Trial	65 (32 HBOT/ 33 controls)	HBOT/ SOMA LENT Karnofsky score	Not clear (gynaecologic cancer with pelvic radiation)	Not reported 18 sessions min.	Improvement in QoL and side effects 6 months follow up	Favors HBOT Moderate level of evidence (Lack of methodology reporting)

Marshall GT et al. 2007	Retrospective case series	54	HBOT/ Clinical records (not reported)	Radiation proctitis	2.4 ATA 90 min. 7/week Not reported	39% healed 26% partially healed 23 months follow up (1-70)	Case series. No evidence for HBOT efficacy
Dell'Era MA et al 2006	Retrospective case series	27	HBOT/ RTOG/endoscopy	Prostate cancer RTOG acute grade≥3 or RTOG chronic grade ≥2	2.4 ATA 90 min. 5-7/week 36 (29-60)	Overall 67% partial to good response 13 months follow up (1-60)	Case series. No evidence for HBOT efficacy
Jones K et al. 2006	Retrospective case series	10	HBOT/ SOMA-LENT scale	Prostate cancer Radiation proctitis	2-2.5 ATA 90 min. 5/week 40 (36-41)	80% responders 25 months follow up (6-43)	Case series. No evidence for HBOT efficacy
Mayer R et al. 2001	Retrospective case series	10	HBOT/ Modified RTOG	Radiation-induced gastro intestinal disorders(+/- cystitis)	2.2-2.4 ATA 60 min. 7/week	90% responders 15.3 months follow up	Case series. No evidence for HBOT efficacy
Woo TCS et al. 1997	Retrospective case series	18	HBOT/ Bleeding, pain, incontinence, diarrhoea	Radiation proctitis	2 ATA 105min. 6/week 24 (12-40)	11% completely healed 44% partial improvement 14 months follow up (3-65)	Case series. No evidence for HBOT efficacy
Warren DC et al. 1997	Retrospective case series	14	HBOT/ Medical records (not described) and telephone questionnaire	Radiation proctitis	2-2.4 ATA 90-120min. 5-6/week 40 (20-63)	64% responders (57% healed) 17 months follow up (5-35)	Case series. No evidence for HBOT efficacy
Gouello JP et al. 1996	Retrospective case series	36 (25 proctitis, 11 bowel)	HBOT/ SOMA-LENT	Chronic radiation-induced digestive disorders	2.5 ATA 90min. 7/week 67 (12-198)	25% healed 33% partial response 52 months follow up (+/- 41)	Case series. No evidence for HBOT efficacy

HBOT : Hyperbaric Oxygen Therapy, CTCv3 : Common Terminology for Critical Adverse Events version 3.0, SOMA LENT : Subjective Objective Management Late Effect on Normal Tissue grading, SF36 : Short Form (36) health study, Qol : Quality of Life, RTOG : Radiation Therapy Oncology Group

Table 8: Radio-induced neurologic injuries (prospective studies or retrospective studies ≥ 10 patients)

Study (authors / year)	Type	Nb patients	Aim(s) / Evaluation criteria	Inclusion / Exclusion criteria	HBO protocol (pressure, time, nb of sessions/week and mean total)	Results/ follow-up	Conclusion / comment
Valadao J et al. 2014	Retrospective case series	10	HBOT/ Karnofsky performance status scale ECOG performance status scale Radiology	Post radiation central nervous system injury	2-2.4 ATA 90 min. ?/week 40 (19-90)	No statistics clinical data not fully reported 4-74 months follow-up	Case series. No evidence for HBOT efficacy
Ohguri T et al. 2007	Retrospective case series	78 (32 HBOT with predictors of longer survival/ 46 non HBOT)	Prophylactic effect of HBOT/ neurologic examination, imaging findings	Stereotactic radiosurgery for brain metastases	2.5 ATA 60 min. 5/week Planned 20 sessions one week after stereotactic radiosurgery Total not reported	Non-significant on Radiation-induced brain injury 10.5-13.7 months follow-up	Case series. No evidence for HBOT efficacy
Pritchard J et al. 2001	Double blind randomized controlled trial	34 (17 HBOT/ 17 sham)	HBOT/ Warm sensory threshold, pain, quality of Life	Radiation-induced brachial plexopathy	2.4 ATA 100 min. 5/week 26 (15-30)	No significant response. 12 months follow-up	Against HBOT. Moderate level of evidence
Chuba PJ et al. 1997	Retrospective multicentre case series	10	HBOT/ Symptoms	Children (4-24 years) Radiation-induced necrosis of central nervous system	2-2.4 ATA 90-120 min. ?/week 28 (20-40)	70% initially improved 30% initially stabilized 40% improved and 40% dead at 7 months follow up (3-36)	Case series. No evidence for HBOT efficacy

HBOT : Hyperbaric Oxygen Therapy, ECOG : Eastern Cooperative Oncology Group

Table 9: Radio-induced injuries after breast cancer

Study (authors, year)	Type	Nb patients	Aim(s) / Evaluation criteria	Inclusion / Exclusion criteria	HBO protocol (pressure, time, nb of sessions/ week and total)	Results/ Follow-up	Conclusion / comment
Pritchard J et al. 2001	Double blind randomized controlled trial	34 (17 HBOT/ 17 sham)	Warm sensory threshold/ Pain/ Quality of Life	Radiation-induced brachial plexopathy	2.4 ATA 100 min. 5/week 26.6 (15-30)	No significant response at 1 year follow-up.	Against HBOT. High level of evidence
Carl UM et al. 2001	Prospective with non-matched controlled group	44 (32 HBOT/ 12 refusing HBOT)	HBOT/ Modified SOMA-LENT criteria	Persisting symptomatology after breast-conserving surgery and radiation	2.4 ATA 90 min. 5/week 25 (7-60)	Improvement in pain, edema and erythema, no improvement in telangiectasia and fibrosis at 7 and 11 months Follow-up	Case series. No evidence for HBOT efficacy
Gothard L et al. 2004	Prospective	21	HBOT/ Volume of the arm, Lymphoscintigraphy, photographic appearance and palpable induration, patient self-assessment of arm swelling, physical functioning	Chronic arm lymphedema (≥30%) after radiotherapy for cancer	2.4 ATA 90 min. 5/week 30	Improvement in arm volume and lymphoscintigraphy 1 year follow-up	Case series. No evidence for HBOT efficacy
Gothard L et al. 2010	Randomized phase II Trial	58 (38 HBOT/ 20 non HBOT)	HBOT/ Volume of the arm, Lymphoscintigraphy, di-electric constant measurements, patient self-assessment of arm swelling, physical functioning	Chronic arm lymphedema (≥15%) after radiotherapy for cancer	2.4 ATA 90 min. 5/week 30	No improvement with HBOT compared to standard care 1 year follow-up	Not favors HBOT. High level of evidence