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Review article

Hyperbaric oxygen therapy in the treatment of radio-induced lesions in normal tissues: a literature review

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Abstract

Late complications are one of the major factors limiting radiotherapy treatment, and their treatment is not codified. Hyperbaric oxygen (HBO) has been used in combination with radiotherapy for over half a century, either to maximise its effectiveness or in an attempt to treat late complications. In this latter case, retrospective trials and case reports are prevailing in literature. This prompted European Society for Therapeutic Radiotherapy and Oncology and European Committee for Hyperbaric Medicine to organise a consensus conference in October 2001, dealing with the HBO indications on radiotherapy for the treatment and prevention of late complications. This updated literature review is part of the documents the jury based its opinion on. A systematic search was done on literature from 1960 to 2004, by only taking into account the articles that appeared in peer review journals. Hyperbaric oxygen treatment involving complications to the head and neck, pelvis and nervous system, and the prevention of complications after surgery in irradiated tissues have been studied. Despite the small number of controlled trials, it may be indicated for the treatment of mandibular osteoradionecrosis in combination with surgery, haemorrhagic cystitis resistant to conventional treatments and the prevention of osteoradionecrosis after dental extraction, whose level of evidence seems to be the most significant though randomised trials are still necessary. The other treatment methods are also outlined for each location.

Keywords: Hyperbaric oxygen; Radiotherapy; Late complications

1. Introduction

Hyperbaric oxygen (HBO) was introduced into radiation oncology by Gray et al. in 1953 when they showed in an animal tumour model that breathing oxygen at 3 atmospheres pressure could overcome the radioresistance of hypoxic tumour cells [81,188]. It was Churchill-Davidson who first used a hyperbaric chamber in the treatment of patients by radiotherapy and showed promising results [36]. A series of controlled trials, some on a multicentre basis where performed and significant improvement in local tumour control was demonstrated in some [88,162]. Improvement in local tumour control and survival was demonstrated in less advanced laryngeal tumours [88]. Concerning locally advanced carcinomas of the cervix, a recent analysis of the randomised trial conducted by the Medical Research Council from 1971 to 1980 did not show any benefits in the use of HBO [53], and there was evidence for some increase in late morbidity [53,201]. The method was abandoned as other ways of overcoming hypoxia became favoured.

Hyperbaric oxygen has however been applied to the treatment or prevention of late complications after radiation therapy and many papers have now been published reporting its use. Because the literature is dominated by case series containing modest numbers and case reports, and

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because there have been few randomised trials of hyperbaric oxygen used for this purpose, there is considerable uncertainty on the place of hyperbaric oxygen in the management of radiation morbidity. Indeed, when evaluating the efficacy of a treatment, the highest level of evidence is based on the results of controlled, randomised trials. Furthermore, the majority of retrospective studies we discuss do not record the complications according to the RTOG/EORTC or SOMA/LENT scales, nor are the HBO response criteria and the duration of this response defined, thereby making their interpretation a delicate issue.

The importance of the problem led the European Society for Therapeutic Radiology and Oncology and the European Committee for Hyperbaric Medicine to jointly organise a Consensus Conference, so that the evidence could be reviewed and guidance drawn up as to clinical practice. The results of this first consensus conference—hyperbaric oxygen therapy in the treatment of radio-induced lesions in normal tissue—held in Lisbon October 2001 are displayed in this issue. This paper records an updated review of the literature performed for the purposes of the consensus conference and presented to it at its first session.

2. Materials and methods

A systematic search for controlled randomised trials, non-controlled trials, retrospective studies and case reports from 1960 to 2004 was done on PubMed, Cancerlit and Medline by using the MeSH headings: hyperbaric oxygenation, radiotherapy, radiation injuries, complications, osteoradionecrosis, necrosis, soft tissues injuries, proctitis, cystitis, nervous system, myelitis, brachial plexus neuropathies, optic nerves injuries, tooth extraction, dental implants, and other text words. Only the articles that appeared in the peer review journals were retained, while abstracts, proceeding books and trials published as book chapters were not considered. Relevant articles identified by the literature search, found in personal files or cited in papers and reviews were retrieved and reviewed.

3. Incidence of late effects

In radiotherapy the volume of normal tissues included in the planning target volume is often considerably larger than the gross tumour volume. Even larger volumes are irradiated with less than prescribed dose. Radiation therefore is associated with a broad spectrum of normal-tissue reactions and it is impossible to cure a tumour by radiotherapy without any risk of normal tissue injury. The degree of changes related to the biological dose and the volume irradiated [11].

By definition late effects occur at least 90 days and commonly many months or years after start of radiotherapy [43]. In contrast to early reactions, typical late injuries are irreversible and often progressive. In general there is no correlation between the expression of early and late normal tissue damage in individual patients. However very severe early reactions may result in consequential late effects. This can be observed for skin, soft tissue or bone, especially after severe mucosal reactions in head and neck cancer patients. While it was initially thought that consequential late effects develop from early effects without healing, evidence is now accumulation that consequential late effects may occur after complete disappearance of early reactions. It has been suggested that the radiobiological characteristics of consequential late effects are similar to early rather than to late normal tissue effects [11,54,199].

There are many systems which have been used for recording late effects and incidence figures will vary according to the system which has been employed. Among the systems which have been widely used are the RTOG/EORTC [43], the LENT/SOMA system [151,152,171,172] or the European, developed by Dische [52]. Comparison between these different recording systems is not always possible.

Secondly, many publications reported no actuarial analysis of late normal tissue morbidity but used crude data. If only crude data of radiation damage is noted, especially if survival is short, late occurring complications are considerably underestimated [16,153]. Long-term follow-up of patients is mandatory for a better evaluation of late radiation induced complications [57]. When analysing data from the literature, Jung et al. concluded that there might be a lifelong risk of developing late complications [99].

Factors influencing the incidence and severity of late normal tissue damage can be broadly divided into two categories: therapy related and patient related. Therapy related factors include total dose, dose per fraction, time interval between reactions, overall treatment time, irradiated volume, and combination with other modalities (chemotherapy, surgery, hormonal therapy, hyperthermia, HBO). Host related factors could be age, gender, smoking, alcohol consumption, anaemia, atherosclerosis, collagen vascular diseases, infections, pre-existing functional disease or genetic syndromes [10,15]. Commonly accepted is an estimated complication rate of 5% of treated patients (tolerance dose concept). For experimental therapy (e.g. dose modification/escalation, chemotherapy intensification) however the risk to develop late injury could be higher.

4. Pathophysiological mechanisms of HBO-treatment

Late onset radiation injuries may lead to cellular depletion, reduction of vascular density, rarefication of small vessels, fibrosis, atrophy. All of these factors might result in hypoxia [62,125,128]. Hypoxia is a major component of delayed wound healing because of a reduced

fibroblast activity and less efficient production of collagen. Secondary infection, injury, surgery contribute finally to worsening late morbidity.

Chronic hypoxia in irradiated tissues has been highlighted by several authors. Thorn et al. [189] measured transmucosal oxygen tension in irradiated or not irradiated gingiva. In the previous 2–4 years, the 10 treated patients had received 64–66 Gy for a cancer of the oral cavity. The mean oxygen tension of healthy and irradiated gingiva were, respectively, 40.5 and 20.4 mmHg (from 16.6 to 23.2 mmHg). Marx et al. [127] measured transcutaneous oxygen tension in irradiated tissues. The mean values were, respectively, 100 and 30 mmHg in non-irradiated and irradiated tissues.

HBO stimulates angiogenesis, fibroblast and osteoblast proliferation as well as collagen formation in irradiated tissues, and increases cellular levels of oxygen. In an animal model, 20 sessions at 2.4 atmospheres absolute (ATA) pressure, 90 min each day, significantly increased angiogenesis and cellular density in irradiated mandibles versus normobaric oxygen and air breathing control ($P = 0.001$) [129]. In an human model, transmucosal oxygen tension in irradiated gingiva increases from 50 to 86% of the oxygen tension of healthy gingiva after 30 sessions (90 min/day at 2.4 ATA) [189]. Another study showed that angiogenesis rapidly progresses to plateau values of 80 to 85% of non-irradiated tissue vascularity after 20 HBO sessions; transcutaneous oxygen measures remained at that level during several years [127]. Improvement of angiogenesis and cellular density has been histologically proven too [125,127,128]. Hyperoxia could paradoxically enhance production of growth factors, including VEGF [178].

5. Treatment

5.1. Head and neck

5.1.1. Osteoradionecrosis

The reported incidence of osteonecrosis (ORN) ranges from 1 to 37.5% [12,17,39,45,59,80,91,137,140,156,166,190,191,206]. Comparison of the different reports is difficult because of differences between the studied populations (radiotherapy alone, technique of radiation, brachytherapy, post-operative radiotherapy, policy of dental management…). Overall the incidence has decreased over the last 20 years.

Conservative measures are often the first stage of treatment. In most series such treatment consists of local application of antiseptic, analgesics if necessary, oral hygiene, systemic antibiotics, possibly sequestrectomy and smoothing of bony projections [8,19,21,22,39,44,60,85,166,182,190,208]. Conservative measures result in healing of the lesion in 15–100% of the cases without the adjunct application of hyperbaric oxygen therapy, however, on average it takes several months before improvement occurs [12,18,20–22,44,45,59,80,137,141,163,166,208]. Mandibular resection is necessary in 12–40% of patients initially treated with conservative measures without hyperbaric oxygen therapy [12,20–22,45,80,141,149,156,182]. Most of the authors reserve radical surgery to the following indications: intractable pain, fistulae, pathological fracture, no response to conservative treatment [1,8,12,22,39,44,106,141,163,182,208]. Surgery tends to be followed by post-operative complications which often are severe when large areas of irradiated bone must be excised.

Owing to the principally ischemic mechanism of osteoradionecrosis, there are many theoretical reasons to use HBO in its treatment. Furthermore, HBO alone is bactericidal for certain anaerobes [89], bacteriostatic for some species of escherischia [24], and increases the rate of killing of bacteria by phagocytosis [118].

HBO has been used in the management of ORN since the 1960s. Hart and Mainous suggested as early as 1976 that its action may be due to an enhancement of vascular proliferation [85]. Several investigators have reported the use of HBO in addition to the conservative treatment or to radical surgery in non-controlled trials. The modalities of HBO and conservative measures are variable. The rates of healing range from 30 to 100%; these studies favour the use of HBO [1,6,22,46,59,60,84,85,98,116,138,190,193].

Marx [126] established a protocol to combine surgery and HBO, consisting of three stages. In stage I, after 30 HBO sessions (100% oxygen, 2.4 ATA, 90 min/day, 5 day/week), the wound is reexamined: in case of improvement, the patient completes a full course of 60 sessions. If there is no improvement, the patient advances to stage II: a sequestrectomy with primary closure is accomplished, with HBO if healing progresses without complication. If the wound dehisces, the patient treated according to stage III: a resection is accomplished. In a patient whose initial presentation includes pathologic fracture, orocutaneous fistulae, or radiographic evidence of resorption to the inferior border of the mandible, an initial course of 30 sessions is given, and the patient directly enters stage III. In stage III-R, 10 weeks after resection, the patient is given an additional 20 sessions in preparation for bone graft reconstruction. With this technique, resolution was achieved in stage I for 15%, in stage II for 14%, and in stage III (radical surgery) for 70% of the patients (total = 58). More recently the same rates were achieved with 268 patients [142]. London et al. [116] using the same protocol, showed clinical improvement with decreased pain in all sixteen patients. Marx proposed HBO as an adjuvant treatment to bone graft reconstruction in a non-controlled trial [124].

Although most of the reports on osteoradionecrosis in the literature concern lesions of the jaws, other sites of clinical significance are the skull, extremities, and pelvis and case reports of benefit have been reported [6,69,115,116,195,197].

There is no randomised controlled trial of the use of hyperbaric oxygen in any of these areas, which does not help to attribute it with the highest evidence level.

Nevertheless, the significant number and proportion of patients who improved in the retrospective series suggest that HBO could be effective in the treatment of mandibular osteoradionecrosis, while the conservative measures prove insufficient.

5.1.2. Laryngeal chondronecrosis

Laryngeal chondronecrosis is a rare complication of radiotherapy that occurs in less than 1% of all patients treated with conventional daily fractions of 2 Gy to total doses of 70 Gy [58,73,86,134,181]. The conventional treatment of this lesion includes analgesics, steam, corticosteroids, antibiotics, temporary or permanent tracheostomy, and even laryngectomy.

Several investigators have studied the effect of adding HBO to the conventional treatment of chondronecrosis. Farmer et al. reported the case of a patient improved due to HBO [64]. Hart et al. [85] utilised HBO in five patients; all had cutaneous fistulae. Improvement was present in four of them. Ferguson et al. [71] found an improvement in seven of 8 patients. Feldmeir et al. [65] obtained the following results in nine patients: three patients with tracheostomies were able to be decannulated. All nine patients maintained their voice, seven without hoarseness. None required laryngectomy. In 1998, London et al. [116] published the results of a retrospective study. Five patients have been treated with 15 to 25 HBO sessions at 2.5 ATA for 90 min; additional sessions were given depending on clinical response. All the patients had advanced disease and were tracheostomy dependent; two were decannulated, and none required laryngectomy. In the largest study published, Filntisis et al. [72] presented 18 patients treated with HBO. They received a mean number of 41 sessions (2 ATA, 2 h, twice a day, 6 days a week). Thirteen patients (72%) had a major improvement; all of them maintained their voice. Five underwent total laryngectomy.

All of these studies suggest that HBO has a beneficial effect in the management of laryngeal necrosis. There is no controlled trial and the number of patients in the retrospective series are small.

5.1.3. Soft tissue necrosis of the head and neck

The incidence of soft tissue necrosis is very variable and depends on the specifics of the irradiation schedule and technique applied. Pernot et al. [156] in a serie of 1134 patients treated by external irradiation and/or brachytherapy for cancers of the oral cavity and the oropharynx, found 18% of small superficial ulceration disappearing within 2 or 3 months, 4% of persisting necrosis and 1% or deep ulceration requiring usually surgery or repeated hospitalisation. The median duration of these soft tissues necrosis was 3, 8 and 11 months, respectively. Beumer et al. [17] reported 6.5% of soft tissue necrosis of the oral cavity, with an increased risk after brachytherapy; 83% of the lesions healed spontaneously.

Current treatment of soft tissue necrosis includes local irrigation, wound debridment, antibiotics, analgesics and often prolonged observation. Surgery is rarely required. Hyperbaric oxygen therapy was reported to contribute to wound healing in some patients treated for oral cavity cancer [102]. Some cases of successfully treated soft tissue necrosis have been reported [47,64,145]. Farmer et al. [64] reported two cases of nose and floor of the mouth necrosis, which were improved with HBO. Davis et al. [47] reported recovery in 15 out of 16 patients following HBO (2.4 ATA, 90 min daily, 45 sessions in average) used as an adjunct to surgery and antibiotic treatment. The characteristics of patients were never described in detail. Neovius et al. [145] published the results obtained in 15 patients treated with radiotherapy pre-operatively at the dose of 64 Gy for oral, pharyngeal or laryngeal cancers. These patients presented with soft tissue necrosis, some of which also had fistula, free flap necrosis or chronic infections. Patients were treated with 30 or 40 sessions of 75 min, once or twice a day at 2.5 or 2.8 ATA. Twelve of 15 patients healed completely, and 2 healed partially within 1–5 months after the introduction of HBO. Three patients had fewer sessions than planned (21, 26 and 20 sessions) because of rapid improvement. Overall, only a few retrospective studies support the use of HBO for this indication, thereby leading to a poor level of efficacy evidence.

5.2. Pelvis

5.2.1. Rectum

Late rectal morbidity may be observed in patients treated with radiotherapy using curative doses for cervical, prostate and rectal cancers. The actuarial incidence of severe complications in most of the modern series is less than 5% [9,25,26,57,75,83,107,120,154,155,173,177,180].

Conventional treatment includes rectal steroids, sucralfate, formalin, short chain fatty acid, laser, electrocoagulation, and surgery for the most severe cases. Few controlled trials have been published, all including a small number of patients, and optimal treatment is not still defined [49,96,104,158,186].

In 1991 the first reported case of haemorrhagic radiation proctitis was published [32]. Since then other retrospective trials favouring the use of HBO have been reported [30,68,77,103,133,136,144,200,209]. However, most of them do not use a toxicity scale and the number of patients was small; the largest studies are subsequently described. Warren et al. [200], in 14 patients, found complete resolution of symptoms in 8, and one had improvement (median follow-up of 17 months). Another published trial included 18 patients with radiation proctitis, most of them had been treated for prostate carcinoma. Previous therapies with steroids ($n = 13$) and formalin ($n = 1$) had failed to improve symptoms in most of the patients. The average number of session was 24 (2 ATA, 105'/session, 6 days a week). Before HBO 17 patients complained bleeding: in 4 of these it stopped completely, partial improvement was

observed in further three patients. Overall improvement of the symptoms (bleeding, incontinence, diarrhoea, pain) was achieved in about 50% of the patients [209]. The largest study included 36 patients; toxicity was recorded with the SOMA–LENT system. The score was 1 in 1 patient, 2 in 11 patients, 3 and 4 in 16 and 8 patients. Complete response was defined as the disappearance of symptoms and endoscopic lesions, while partial response was defined as a decrease of at least one point to the SOMA LENT score and failure was described as a stagnant or worsened score. The long-term results were able to be evaluated in 32 patients. With a mean follow-up of 52 months, a complete or partial response was observed in 21 patients [77]. Nevertheless, no controlled study was published and the level of evidence of HBO beneficial action is weakly supported.

5.2.2. Bladder

As for rectal complications, actuarial incidence of severe late effects is less than 5% [9,57,75,83,107,120, 154,155,177,180].

Haematuria is a dominant symptom, and its optimal treatment is not defined. Conventional treatment includes bladder irrigation, antibiotic therapy, corticosteroids, blood transfusion, aluminous salts or formalin instillation [13,51,108,112–114,117,119,139,179,194]. These measures can be effective but the use of formalin may be associated with major complications [7,13,35,63,119,164,179,194]. Cysto-diathermy and laser photocoagulation may also be employed in the management of bleeding [165]. If conservative measures fail surgery (urinary diversion, ileo-cystoplasty, cystectomy) may be employed. Interruption of internal iliac or vesical arteries may be considered. Operations performed in the heavily irradiated pelvis are associated with a high risk of further morbidities [121,175]. A recent literature review concluded that in the absence of randomised controlled studies it is impossible to set definite rules for treatment [50].

Several authors have studied the use of hyperbaric oxygen in patients with radiation cystitis [23,48,87,111,131, 133,135,143,148,157,167,176,184,203,204]. These publications are all retrospective series except one. Bevers et al. [23] reported a prospective non-controlled study in 40 patients; most of them required transfusion. Before HBO the patients had received unsuccessful treatments: clot evacuation, electrocoagulation, aluminous salts, fibrinolytic inhibitor. The patients received 20 HBO sessions with 100% oxygen at 3 bar for 90 min, 5 or 6 times a week. In 4 patients, 40 sessions were given because of persistence of symptoms. Haematuria stopped in 30 patients; occasional slight haematuria persisted in 7 patients; with a median follow-up of 23 months, in 9 patients haematuria recurred. The severity of initial haematuria appeared to influence the response to hyperbaric oxygen; failure of treatment was seen only in patients with a very severe haemorrhagic cystitis (3 patients with a mean blood transfusion need of 26 units). The retrospective study with the most significant numbers included 62 patients, with a follow-up of 10–120 months. Of the 57 patients to be evaluated, 49 (86%) presented with a complete disappearance or a notable improvement of their haematuria [40]. Lee et al. [111] reported a retrospective study of 20 patients. They received an average of 44 HBO sessions (2.5 ATA, 100 min/session). Bleeding stopped in 16 patients, and markedly decreased in 2, with a mean follow-up of 14 months. However Del Pizzo et al. [48] reported less impressive results with a long term follow-up. With a median follow-up of 2.5 years, 8 of 11 patients were asymptomatic (3 had required urinary diversion), but with a median follow-up of 5 years only 3 had complete resolution of their symptoms (8 had been treated with surgery). The toxicity of HBO is weak, with no significant side effects recorded in neither the Bevers et al. retrospective study nor the largest retrospective study [23,40]. The largest trials are listed in Table 1. The majority of these studies do not use a toxicity scale, which renders their comparison difficult. Although there is no randomised study, the results of a prospective study and the retrospective studies suggest that HBO is effective, leads to a high rate of bladder preservation and has few side effects. These conclusions tally with those of the recently published literature review by Feldmeier et al. [70]. However, these results should be verified with controlled, randomised trials to obtain the highest level of evidence level.

5.3. Other sites

HBO has been used in the management of breast and chest wall injury [31,67,76,85]. Carl et al. [31] prospectively reported outcome in 44 patients presenting with pain, edema, erythema, fibrosis and telangiectasia after lumpectomy and radiotherapy for early breast cancers. Complications were scored using modified LENT–SOMA criteria. Only patients with at least grade 3 pain or a summed LENT–SOMA score of 8 were studied. Thirty-two patients received a median of 25 sessions with 100% oxygen at 2.4 ATA for 90 min, 5 times per week. Patients who received HBO had a significant reduction of pain, erythema and edema compared to those who refused HBO; however fibrosis and telangiectasia were not significantly reduced. Recently Gothard et al. [76] reported a phase II trial in patients with chronic arm lymphoedema. The twenty-one patients received 30 sessions with 100% oxygen at 2.4 ATA for 100 min over a period of 6 weeks. Arm volumes were measured in an operator-independent method using a perometer. There was a statistically significant but clinically modest reduction in arm volume at 12 months follow-up; a controlled randomised trial is under development.

In a few retrospective studies, HBO has been successfully used to treat rectal and duodenal ulcerations [14,55], and pelvic necrosis with or without fistula [64,68,85,207].

Table 1
Results of hyperbaric oxygen therapy in the treatment of radiogenic bladder complications

	No. patients	Symptoms	No. sessions	Mode	Results	Follow-up
Corman et al. [40]	62	Haemorrhagic cystitis	33 (mean)	2.4 ATA, 90 min/session, 5 to 7 sessions/week	Complete response: 21 patients. Partial response: 28 patients. Failure: 8 patients	
Mayer et al. [133]	11	Radiation cystitis (macroscopic hematuria in 8 patients), Grade 2:2 patients, Grade 3:6 patients, Grade 4:2 patients (RTOG/EORTC)	26 (median)	2.4 ATA, 60 min/session, 7 sessions/week	Grade 0:2 patients, Grade 1:4 patients, Grade 2:2 patients, Grade 3:1 patient, Grade 4:1 patient. ($P = 0.004$)	18 months (mean)
Hendricks et al. [87]	20	Radiation cystitis	35	2 ATA	Complete response: 14 patients, failure: 6 patients	13 months
Mathews et al. [131]	17	Haemorrhagic cystitis (blood transfusion in 8 patients)	14 (mean)	2 to 2.5 ATA, 90 min/session, 5 sessions/week	Complete response: 11 patients, partial response: 2 patients, microscopic haematuria: 2 patients, failure: 2 patients	21 months (mean)
Del Pizzo et al. [48]	11	Haemorrhagic cystitis (blood transfusion in all patients)	40 (mean)	2 ATA, 90 min/session, 5 sessions/week	Complete response: 3 patients, complete response followed by recurrence: 5 patients, failure: 3 patients	5.1 years (median)
Bevers et al. [23]	40	Haemorrhagic cystitis (blood transfusion in 30 patients)	20 (40 sessions in 4 patients)	3 ATA, 90 min/session, 5 to 6 sessions/week	Complete or partial response: 37 patients	23 months (mean)
Lee et al. [111]	20	Haemorrhagic cystitis in 19 patients, radiation cystitis without haematuria in 1 patient	44 (mean)	2.5 ATA, 100 min/session	Complete response: 16 patients, partial response: 2 patients, failure: 1 patient, radiation cystitis without haematuria: complete response	14 months (mean)
Weiss et al. [204]	13	Haemorrhagic cystitis (blood transfusion in 9 patients)	60	2 ATA, 120 min/session, 7 sessions/week	Complete response: 12 patients	2.5 years (mean)
Nakada et al. [143]	6	Haemorrhagic cystitis	45	2 ATA	Complete response: 5 patients	
Rijkmans et al. [167]	10	Haemorrhagic cystitis	20	3 ATA, 90 min/session	Complete response: 6 patients	7 months

ATA, Atmosphere absolute.

5.4. Nervous system

5.4.1. Myelitis

Marcus and Million [122] have shown that at 45 Gy, applied with conventional fractionation, the incidence of radiation myelitis is less than 0.2%. The administration of corticosteroids allows a transient improvement of neurologic symptoms. No treatment has shown to be effective in the long term. In animals studies, HBO showed no benefit in the treatment [160], but could be of value in prevention however [66,70]. HBO has only been reported as beneficial in one case report [29] and one retrospective trial [85] and has not shown to be of interest in controlled trials.

5.4.2. Plexopathy

Narcotics, corticosteroids, physiotherapy and surgical procedures such as neurolysis but with none is there convincing evidence of benefit. A case report of successfully treated patient with HBO has been published [195]. Recently a double blind placebo-controlled randomised trial (34 patients) showed no evidence that HBO slows or reverses brachial plexopathy (12 months follow-up), in spite of improvements in sensory threshold in some [161].

5.4.3. Optic neuropathy

Only retrospective studies are available, having included a total of 18 patients with three presenting improvement to their vision. In the Guy et al. series, the two patients who regained normal eyesight were treated within 72 h following the appearance of symptoms; likewise, Borruat et al. suggest the importance of early treatment [27,82,168].

5.4.4. Brain necrosis

In adults, positive results were reported in 5 out of a total 6 patients treated with HBO; in the case reported by Takenaka et al., the patient had nevertheless benefited from previous surgery [37,85,105,110,185]. Hulshof et al. prospectively evaluated the relevance of HBO in patients presenting with cognitive problems following cerebral

radiotherapy: only 1 out of 7 patients presented significant improvement [92].

Chuba et al. [34] retrospectively reported 10 cases of children presenting with a brain necrosis. Their median age was 12 years old (4–23 years old). All patients received external beam radiotherapy at the dose of 24–70.4 Gy, with fractional doses of 1.17–1.8 Gy; 4 patients were treated according to a hyperfractionated regimen. Three children received interstitial brachytherapy, and another three stereotaxic radiosurgery. Finally, chemotherapy was administered in 6 children. The 10 patients presented a deficient, new or worsened neurological symptomatology. Necrosis was histologically proven in 8 of the patients, of which 2 also presented with a persistent tumour. MRI provided the diagnosis in the 2 other patients. The delay between radiotherapy and diagnosis of necrosis stretches out from 2 to 14 months. The treatment consisted of a minimum of 20 sessions from 2 to 2.4 ATA, from 90 min to 2 h. Initial improvement or stabilisation of symptoms, including cases with ataxia, cranial nerve palsies, dysphasia, hemiparesis, seizures and headaches were reported in all patients. In the 6 patients alive at the time of reporting a median of 7 months (3–36 months) after HBO, 2 cases were documented as having completely resolved (hemiparesis) or stabilised (severe ataxia). Nevertheless, it only concerns retrospective data, and the authors were unable to determinate the difference between the effect of HBO and that of administered corticosteroids.

The data from the literature concerning the efficacy of HBO in the treatment of neurological side effects in radiotherapy is scarce (cases reports and one small randomised clinical trial). The negative result of this randomised study does not therefore recommend its use in the treatment of plexopathy [161]. The level of evidence of efficacy in the treatment of complications of the central nervous system is very weak.

6. Prevention of surgery complications

6.1. Tooth extraction in irradiated tissues

One of the most important risk factor of osteoradionecrosis is dental extraction after radiotherapy [21,22,44,94,127,141,156,166,169]. Therefore, prevention of dental extractions is of the utmost importance. Dental management has been a topic of debate, and the practices have dramatically changed since 20 years. Before, all teeth or all teeth in the radiation field were extracted. This ‘aggressive‘ management is a risk factor for osteoradionecrosis; extraction of only unsalvageable teeth with primary closure, restoration of remaining teeth as needed, and daily fluoride application is the most appropriate practice [12,19,20,22,45,91,94,95,140,166]. There is no relationship between the time elapsed between the end of radiotherapy and extraction, with the incidence of osteoradionecrosis [21,128]. Measures of transcutaneous oxygen pressure in irradiated tissues show a continuous decrease; there is no spontaneous revascularisation with time [128].

Marx et al. [127] in a randomised trial showed that hyperbaric oxygen therapy before and after teeth removal in irradiated patients versus penicillin significantly decreases osteoradionecrosis (increasing angiogenesis and cellular density). For this study, osteoradionecrosis was defined as the presence of exposed bone after 6 months. Seventy-four patients having received irradiation to doses of 60 Gy or greater were randomised in two groups. One group of 37 patients, in whom a total of 135 teeth had to be removed, received 1 million units of penicillin G intravenously just before surgery and 500 mg of phenoxymethyl penicillin four times daily for 10 days after surgery. The other group of 37 patients, in whom a total of 156 teeth had to be removed, received no antibiotics but twenty sessions of hyperbaric oxygen before tooth removal and 10 sessions after tooth removal. Session of HBO (2.4 ATA, 90’ each session) was conducted once daily, 5 or 6 days each week. In the penicillin group eleven patients (29.9%) developed osteoradionecrosis, whereas in the HBO group only two patients (5.4%) developed osteoradionecrosis. This difference is statistically significant, however the incidence of osteoradionecrosis in non-HBO group seems high.

Clayman [38] in a literature review estimates that the incidence of post-extraction osteoradionecrosis is relatively low: 5.8% for studies published since 1968, and 2.1% for studies published between 1986 and 1995. Indeed some authors have demonstrated that post-radiation extraction without hyperbaric oxygen could be safe, with very strict precautions [90,100,132,166,183]. Horiot et al. [90] reported one osteoradionecrosis in 22 patients who required post radiation dental extractions (with peri antibiotic coverage, alveolectomy, primary closure). In Maxymiv’s study [132] no osteoradionecrosis occurred (196 removed teeth included within the treatment volume in 72 patients).

Using a similar protocol of hyperbaric oxygen therapy (20 sessions before, 10 sessions after teeth extraction), Lambert et al. [109] in a retrospective study found no osteoradionecrosis in 75 patients, however follow-up data were only obtained for 47 of them. Vudiniabola et al. [196] in a prospective non-randomised trial showed that prophylactic HBO treatment reduced the risk of osteoradionecrosis following surgery to irradiated jaws. In the retrospective series of David et al., 1 out of 24 patients presented with osteoradionecrosis [46]. Chavez and Adkinson [33] reported a low incidence of osteoradionecrosis after dental extractions of 1.5% in 40 consecutive patients treated with this HBO protocol.

The randomised trial by Marx et al. [127] showed the efficacy of HBO in the prevention of osteoradionecrosis following dental extractions in the irradiated territory. Indications should nevertheless be considered for each individual case and could be reserved for patients with the most significant risk. Indeed, the literature [38,90,100,132,166,183] shows

that the incidence of osteoradionecrosis following dental extraction with precaution, alveolectomy and primary closure, appears to be lower (2–5%) than that described in the non-HBO arm of the Marx trial (29.9%) [127]. It nevertheless concerns retrospective data and the hypothesis of a selection bias (patients having received weak doses of radiotherapy) is possible.

6.2. Dental implants

Several reports show an increased rate of implant loss when implants are placed in irradiated maxilla or mandibular bones [78,93,150], whereas other reports show no increase of implant loss in irradiated bones [2,4,56,74,97,101,198]. Implant survival in irradiated bones range from 58 to 100% [3,4,28,74,79,123,146,170,174,198,202,205]. Unfortunately data on radiation doses are not always specified.

The use of HBO to reduce implant loss has been reported in a number of series [3,5,61,78,79,97,130,147,187,192]; implant survival ranged from 83 to 100%. Granstrom et al. [79] in a case controlled study showed that HBO (20 pre-operative and 10 post-operative sessions) reduced the failure rate in irradiated bone (53.7 vs 8.1%, $P < 0.05$). In a multicenter study, Niimi et al. [147] found that HBO improved implant survival only in maxilla, due to good results normally obtained in the management of mandibular implants.

The use of HBO to reduce implant loss in irradiated jaws is not clearly defined. We agree with the recently published Cochrane Database review, in that no randomised trials are available and there is a need for controlled trials to assert the effectiveness of HBO in this indication [41,42].

6.3. Surgery in irradiated tissues (except dental implant and extractions)

Very few trials are available. In a report, post-operative complications seems fewer after pre operative HBO in patients with previous pelvic radiotherapy [159].

7. Conclusion

As we can notice, few controlled trials are available. Moreover, in the great majority of studies, the complications are often not assessed with either the RTOG/EORTC or SOMA/LENT scales, the duration of symptoms improvement is not specified and the endpoints are not clearly defined. Equally, a small number of studies have reported facts about the quality of life. So, it makes it difficult to draw a guiding principle. Nevertheless, few indications could have a higher evidence level than others due to the presence of prospective studies and the significant number of positive retrospective studies: the treatment of mandibular osteoradionecrosis combined with surgery, the haemorrhagic cystitis resistant to conventional treatments and the prevention of osteoradionecrosis after dental extraction. This does not concern the highest level of evidence based on several randomised trials. In future, a prospective collection of toxicities using a common scale and the setting up of multicentric controlled trials to compensate for the impact of the scarcity of these complications may bring an answer to these issues. This will require a close collaboration between physicians concerned with hyperbaric medicine and radiation oncologists.

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