A Systematic Review of the Literature Reporting The Application of Hyperbaric Oxygen To the Prevention and Treatment Of Delayed Radiation Injuries: An Evidence Based Approach

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Abstract:

The treatment of delayed radiation injuries (soft tissue and bony radiation necrosis) is one of the thirteen indications approved by the Hyperbaric Oxygen Therapy Committee of the Undersea and Hyperbaric Medical Society as an appropriate intervention for hyperbaric oxygen. This paper is designed to provide a systematic review of the literature reporting the results of hyperbaric oxygen therapy in the treatment and/or prophylaxis of delayed radiation injury. Since 1992 with the introduction of the concept of evidence based medicine, the medical community at large has set out to apply more critical and stringent standards in evaluating published support for therapeutic interventions. Evidence based medicine is designed to discover and apply in daily practice the best evidence available for developing a treatment plan for the individual patient. The preferred level of evidence is the randomized controlled trial. However, other evidence has merit as well. Sixty-four publications reporting the results in applying hyperbaric oxygen as treatment or prevention against radiation injuries are presented in this review. These are subjected to scrutiny in an evidence based fashion by applying three established systems of evaluation. All but seven of these publications report a positive result when hyperbaric oxygen is delivered as treatment for or prevention of delayed radiation injury. These results are even more impressive if we consider alternatives for intervention. Treatment without hyperbaric oxygen often requires radical surgical intervention, which is itself likely to result in additional complications. Other alternatives for intervention including various drug trials are rare and anecdotal and for the most part have not been the subject of randomized controlled trials. Based on this review, hyperbaric oxygen is recommended for delayed radiation injury as a routine component of management except for neurologic injuries where in subsets of neurologic injury either further study is required or it is not indicated based on the presently available evidence.

Introduction:

Approximately 1.2 million new cases of invasive cancer will be diagnosed this year in the United States and approximately one half of these patients will receive radiation therapy as part of the management of their malignancy.[1] About one half of patients treated for cancer become long term survivors. Radiation complications are rare but typically occur in up to about 5% of those patients receiving therapeutic radiation.[2] These complications characteristically occur after a latent period of that may vary from several months to several years. The etiology of delayed radiation injury is not fully understood though most would agree that endarteritis, tissue hypoxia and fibrosis are consistently seen and are certainly major contributors to its pathogenesis.[2]

Historically the conservative management of delayed radiation injuries including frank radionecrosis has been unsatisfactory. Radiation injuries may be life threatening and may significantly reduce quality of life under certain circumstances. Definitive treatment may require surgical resection or bypass of the affected part. In a patient who has likely already survived an aggressive course of therapy including chemotherapy and surgery in addition to radiation in many cases, the prospect of further radical treatment to possibly include major surgical intervention is most unwelcome. Additionally surgical intervention in a heavily radiated field may result in delayed wound healing, dehiscience or infection. These post-operative complications may be life threatening in their severity.

Mandibular radiation necrosis has been treated with hyperbaric oxygen for sometime with consistently positive results. Hyperbaric oxygen therapy has been applied now with increasing frequency to radiation injuries and necrosis of other tissues and at other anatomic sites. It is felt to be effective by enhancing angiogenesis and in so doing providing oxygen to meet the metabolic demands of these radiation impaired tissues.

This paper is intended to review and critically assess the literature in radiation injury as one of 13 indications approved as appropriate for therapeutic intervention with hyperbaric oxygen by the Undersea and Hyperbaric Medical Society.[3] It reviews the published literature reporting the use of hyperbaric oxygen (HBO_2) in the comprehensive treatment, or prophylaxis of delayed radiation injury. A major drawback in this effort is the paucity of randomized controlled clinical trials, which are available to support or refute this intervention. Although randomized controlled trials are indeed the gold standard for establishing the efficacy of a therapeutic intervention, other evidence including pre-clinical studies and retrospective case series have merit.[4] The literature presented herein will be critiqued by applying three previously published review schemes. These have been designed to critically evaluate the strength of literature in support of employing a therapeutic intervention. The first of these has been developed by the American Heart Association.[4,5] The second is the system developed and utilized by the National Cancer Institute's PDQ Editorial Board in their presentation of ongoing reviews of cancer treatment information.[6] The third is an adaptation of the approach developed by the BMJ Publishing Group and used by them in the publication, Clinical Evidence.[7]

Three Models for Literature Assessment:

In 1995, the American Heart Association (AHA) published a scheme to evaluate and subsequently to recommend to the Federal Drug Administration (FDA) and to the Health Care Finance Administration or HCFA (now CMS) the value of therapeutic interventions.[4] In 1998, the AHA updated and further defined and clarified this system.[5]. Table 1 specifies levels of evidence as defined and applied by this system to interventions. Randomized controlled trials are given the most weight and historical acceptance given the lowest weight. Human case series and animal studies are given intermediate weighting. Table 2 demonstrates the principles of the AHA system as applied to specific therapeutic interventions and as related to assessing the evidentiary support for such interventions.

After a review of the published evidence for a particular therapy, the AHA system assigns interventions into categories according to the strength of the evidence supporting their use. Interventions designated as Category I, IIa or IIb are recommended for application to clinical practice while category III interventions are not supported. Therapeutic interventions assigned to the "Indeterminate Category" are judged to require additional investigation prior to recommendation for or against their application.

The National Cancer Institute (NCI) provides PDQ (Physicians' Data Query) as an Internet-accessible summary of current treatment and diagnostic standards for the therapeutic management and discovery of common childhood and adult malignancies. Through the NCI, summaries are available to the clinician, and separate summaries are available to the lay person in the appropriate language and at the appropriate educational level for comprehension by an inquiring patient or family member. Recently, the PDQ Editorial Board has begun to include assessments of the level of supporting evidence for a particular intervention utilizing their own quantitative system. The system is summarized in Table 3. This system is a two-tiered system. The first or numeric portion is assigned in the following fashion:

Level 1 represents evidence supported by a randomized controlled trial(s) (RCT). This numeric grade is further modified so that 1i represents a double-blinded study and 1ii represents an RCT that is not blinded. Meta-analyses of RCT's are given level 1 status with the suffix modifier applied in the same fashion in regard to blinding as a single RCT.

Level 2 represents non-randomized but controlled clinical trials. This group would include trials in which the allocation of a patient to the treatment or control group is set by birth date, day of clinic appointment, bed availability or any other determinant which would make allocation known to the investigator prior to obtaining informed consent.

Level 3 are case series. Category 3i is a series, which is consecutive and population based. Category 3ii is a case series reporting consecutive but not population based cases. Category 3iii reports cases which are neither consecutive nor population based.

The PDQ grading system includes a secondary component based on the "strength of the end points." For Category A, the end point is total mortality. For Category B, the end point is disease specific mortality. Category C represents quality of life outcome measures and Category D reports other surrogate measures of outcome such as disease-free survival and tumor response rate. The second set of categorizations of PDQ evidence is more or less specific to cancer treatment and will not be adapted strictly to our efforts in reviewing the evidence available supporting hyperbaric oxygen for radiation injuries. However, it should be noted that unresolved serious delayed radiation injuries can cause death under certain circumstances and certainly lead to a decreased quality of life in most circumstances.

The PDQ system evaluates individual papers in regard to the strength of evidence but does not numerically sum the evidence in a formal fashion to assign an overall assessment of the strength of the evidence for any particular therapeutic modality in a given circumstance.

In Clinical Evidence, the editors seek to provide the practicing clinician with a handy, pocketbook reference providing evidence based reviews of interventions for common conditions seen in primary care and hospital practice. This publication, which is updated every six months, begins each section by asking a question about available therapies for a particular clinical problem. For example, in the section on metastatic breast cancer, a question asked is "what are the effects of treatment for bone metastases". Then, following the statement of the question, individual therapies are discussed in terms of "Benefits", "Harms" and "Comments".

The "Benefits" sections first presents published evidence from systematic reviews and randomized controlled trials. These are the preferred levels of evidence. If randomized controlled trials are not available for a given question, other published evidence supporting a therapeutic strategy is presented and discussed to develop arguments supporting that intervention. A discussion of potential

complications and side effects follows and is included in “Harms” so that the adverse effects can be compared to the evidence in favor of therapy and decision making based on risk to benefit considerations can be made by the clinician.

In “Comments”, the editors present additional considerations, amplifying or modifying information to clarify further the application of a particular therapy in a given circumstance.

As we apply the “Clinical Evidence” approach to hyperbaric oxygen for radiation injuries, the recent reports of Plafki et al[8] and Sheffield and Desautels[9] are constantly considered in regard to “Harms”. Both of these publications demonstrate the hyperbaric oxygen therapy is a very safe modality and unlikely to be accompanied by significant morbidity if properly delivered. For this particular application, concern has been previously voiced that hyperbaric oxygen may increase the likelihood of recurrent cancer. The review by Feldmeier et al[10] in 1994 has failed to demonstrate an increased risk of cancer recurrence or progression for patients treated for radiation injuries. In applying the “Clinical Evidence” approach, as we review each of the individual anatomic sites or tissues involved by injury, we are asking the question, “Is hyperbaric oxygen effective in resolving or palliating this disorder?”

The BMJ scheme actually assigns a verbal description of the strength of support for a particular modality in a given circumstance based on a compilation of all evidence available in that particular circumstance. For the purpose of illustrating these principles in Tables 4. Through 11., we have slightly modified the system to assign a verbal description of the strength of the evidence for each paper. We will then combine these to give an overall strength for a particular indication within the discussion portion for each indication.

Application of the Three Models to Hyperbaric Oxygen Intervention for Radiation Injury: Site Specific Summaries:

For the discussion of the evidence-based models in regard to their application to radiation injury, we will follow the discussion site by site in the same order as used in Tables 4 through 11 . For ease in reading the Table, negative studies are entered in bold italics and the author’s name is underlined. Single case reports are considered a case series of “one” for classification and entry into Tables 4 through 12. Papers discussing the application of hyperbaric oxygen to the treatment or prevention of the various radiation injuries were sought by searching several internet accessible search engines including “Pubmed” and “Cancerlit”. Once a paper was found, its references were manually reviewed to search out additional appropriate references.

I. Prophylaxis of Mandibular Osteoradionecrosis

able 4. summarizes the literature in which hyperbaric oxygen has been applied to the prevention of mandibular osteoradionecrosis (ORN). Robert E. Marx, D.D.S. has published the results of a randomized controlled trial reporting the successful use of hyperbaric oxygen in preventing mandibular radiation necrosis by giving a course of hyperbaric oxygen before and after dental extractions. This report provides us with AHA and NCI level 1 evidence.[11] Two additional clinical series present their results in the prophylactic treatment of 53 additional patients (AHA level 4 or 5 and NCI level 3ii evidence). If we combine the patients from all three reports, we find an incidence of osteoradionecrosis (ORN) in 4.5% (4 of 90) of the HBO_2 prophylaxis group (2 of 37 Marx; 1 of 29 Vudiniabola[12]; and 1 of 24 David[13]). In Marx’s control group, the incidence of osteoradionecrosis was 29.9% (11 of 37).

The AHA therapeutic intervention classification for ORN prophylaxis merits a designation as a “Class Ia” indication for HBO_2.

The BMJ Clinical Evidence review of this indication would be “Beneficial” based on the randomized controlled trial and the low incidence of “Harms”.

II. Treatment of Existing Osteoradionecrosis of the Mandible:

For the second entity reviewed, manifest mandibular osteoradionecrosis (ORN), we have summarized the literature in Table 5. [13--26] A total of 14 publications are reviewed. One very small randomized controlled trial by Tobey et al[17] is positive. Only 12 patients were studied. These patients were randomized to 100% oxygen at 1.2 vs 2.0 ATA. The authors state that those patients treated at 2.0 ATA “experienced significant improvement” compared to the group receiving oxygen at 1.2 ATA. No details are given regarding randomization or outcome determination. In fact we cannot tell how many patients were assigned to each group. The study is randomized and doubly blinded in that neither the patient nor the clinician assessing the patient knew which therapy the patient was receiving. Even though it is a small study, it does present level 1 evidence. This study is therefore assessed an AHA 1B and a NCI 1ii level of evidence classification.

In addition to Tobey’s trial, thirteen additional reports are listed in Table 5. All of these trials present AHA Level 5 evidence and NCI Level 3ii evidence. Twelve of the 13 trials are positive. Only the report by Maier et al fails to show an advantage for hyperbaric oxygen in the treatment of existing ORN. In this paper, hyperbaric oxygen is given only after an attempt is made at surgical correction. No hyperbaric oxygen was given prior to surgery. Marx has previously established the importance of pre-operative HBO prior to surgical wounding in irradiated tissues. This principle has been widely accepted by those applying HBO_2 to the treatment of ORN.

If all of the cases reported in Table 5 are combined (excluding those reported by Tobey and noting that Marx’s second report includes the 58 patients reported earlier), we have a total of 371 reported cases of mandibular ORN. Improvement is reported in 310 cases or 83.6%. Resolution would certainly be a better endpoint. However, especially in the earlier reports, hyperbaric oxygen was not combined with aggressive extirpation of necrotic bone or with surgical reconstruction of bony discontinuity. Certainly, Marx[21] has reported the best results. Marx has identified the need for optimizing surgery and sequencing HBO_2 and surgery to include and emphasize the pre-surgical application of HBO_2. Marx reports 100% success, but his successful treatment includes mandibulectomy and reconstruction in 73% of his patients. Dr. Marx also sets high standards for successful intervention in those patients requiring mandibulectomy and reconstruction. Marx requires not only the successful re-establishment of bony continuity but also requires functional success in that these patients must be able to support a denture for cosmesis and mastication.

Based on the one small single RCT and the consistent experience otherwise reported in case series, we should consider HBO_2 as treatment for ORN as an AHA class IIa indication (Acceptable and Useful Based on Very Good Evidence). Applying the BMJ standards, the treatment of ORN by HBO is “Likely to be Beneficial” once again recognizing the low likelihood of “Harms” and the consistent reports of success.

III. Treatment of Soft Tissue Radiation Necrosis of the Head and Neck Including Laryngeal Necrosis:

Table 6. includes 6 published reports of hyperbaric oxygen applied to soft tissue injuries of the head and neck.[18, 27-31] Marx’s chapter in the textbook, Hyperbaric Medicine Practice[29] reports his experience in a prospective controlled but not randomized study. Those patients who refused hyperbaric oxygen or for whom treatment was not practical due to having homes distant from a hyperbaric chamber or other financial reasons were assigned to the control group. These cohorts of patients were treated

concurrently and all other aspects of their treatment were identical. This study is therefore considered as presenting AHA level 3 evidence and NCI level 2 evidence. In his report of 160 patients receiving hyperbaric oxygen in support of surgical resection or flap reconstruction in heavily irradiated patients comparing wound infection, wound dehiscence and delayed wound healing, Marx reports the incidence of complications in the HBO_2 group versus the control group in the following fashion: 1. Wound infection: 6% versus 24%; 2. Wound dehiscence: 11% versus 48%; and 3. Delayed wound healing: 11% versus 55%. Applying the Chi square test to these results we obtain P values of 0.004, less than 0.0001 and less than 0.0001 respectively. This study resulted in statistically decreased likelihood of wound infection, dehiscence and wound healing delay in patients receiving HBO versus those not receiving HBO in support of major soft tissue surgery or flaps. These patients received 20 pre-operative HBO treatments followed by 10 post-operative treatments at 2.4 ATA.

In addition to the large controlled trial reported by Marx, five additional publications reporting case series are listed in Table 6. These consistently report a positive outcome in patients treated with HBO for soft tissue radionecrosis of the head and neck. In 1997 Neovius[36] and colleagues reported a series of 15 patients treated with hyperbaric oxygen for wound complications within irradiated tissues. They compared this group to a historical control group from the same institution. Twelve of the 15 patients in the hyperbaric group healed completely with improvement in 2 and only 1 without benefit. In the control group only 7 of 15 patients healed. Two patients in the control group developed life-threatening hemorrhage and 1 of these did exsanguinate. Any practitioner experienced in caring for head and neck cancer patients has experienced at least one patient in his or her career that exsanguinated as the result of a soft tissue necrosis of the neck which progressed to erode into the carotid artery or other major vessel.

The effects of HBO on chondroradiation necrosis of the larynx are reported by 3 authors from 3 separate institutions. The majority of these patients had severe (Chandler's Grade III or IV necrosis). Most patients with severe laryngeal chondroradionecrosis will require laryngectomy.[32-35] If the results from these 3 trials are combined, only 6 of 35 patients underwent laryngectomy. The rest maintained their larynx with most patients having good voice quality after HBO.

The case series by Davis et al reports success in 15 of 16 patients treated for soft tissue radionecrosis of the head and neck. Many of these patients had large chronic soft tissue wounds as a result of their radiation injury. Such patients can progress to life threatening complications. Erosion into the carotid artery and death due to exsanguination may result if this process is allowed to progress unchecked.

Based on the Marx controlled trial and the consistent outcome in the reported case series, we should consider soft tissue radiation injury of the head and neck as an AHA category IIb (acceptable and useful based on fair to good evidence). Applying the BMJ system, the application of hyperbaric oxygen to soft tissue radiation injuries of the head and neck would be rated "likely to be beneficial" based again on the consistently positive outcome and a low likelihood of any substantial side effects or "harms".

IV. Treatment of Radiation Cystitis

Table 7. lists 14 published reports detailing results of HBO_2 interventions in the treatment hemorrhagic radiation induced cystitis.[36-49] These publications are all case series. The report by Bevers[45], which includes the largest number of patients, was a prospective but not a controlled trial. In the final report by Weiss et al[43], the earlier patients reported by the same author were included. If we combine all those patients reported in these 14 publications, we find a total of 136 patients treated with HBO_2 with 112 patients or 82.4% resolving when treated with hyperbaric oxygen.

Many of the patients reported in the hyperbaric experience had already failed conservative management including irrigation and the instillation of alum or formalin. Severe hemorragic radiation cystitis is unquestionably a life threatening and quality of life limiting disorder. Cheng and Foo[50] have reported their experience in managing 9 serious refractory cases of hemorrhagic radiation cystitis without hyperbaric oxygen. Six patients were treated with bilateral percutaneous nephrostomies. Three patients required ileal loop diversions of their urinary stream. Four of nine (44%) patients ultimately died in spite of these aggressive treatments. Similarly, Sun and Chao[51] have reported a 3.7% mortality due to bladder injury in their review of 378 patients treated with radiation for cervical cancer.

A success rate of 82.4% with hyperbaric oxygen is all the more impressive when results with other more aggressive interventions are considered. It is also noteworthy that 13 of 14 publications listed in Table 3 are positive reports. Patients listed in Table 3 represent patients treated in several different countries on 3 different continents with consistent benefit seen in a large majority of patients in each study except that reported by Del Pizzo.[45]

Although there are no randomized controlled trials supporting this indication for hyperbaric oxygen, the results of the case series reviewed are so consistent that we can justify a Class IIa AHA designation (Acceptable and Useful) and a BMJ designation of "Likely to be Beneficial" for radiation cystitis.

V. Treatment of Radiation Induced Chest Wall and Breast Injury

Four publications related to HBO_2 treatment of chest wall and breast radiation injury are listed in Table 8.[16, 52-54] These would all be considered AHA level 5 or NCI level 3ii evidence with the exception of the second publication by Carl[54] which has a non-randomized control group treated concurrently and would therefore be considered an AHA level 4 study.

In the first of these, Hart[16] reports the use of hyperbaric oxygen as an adjunct to skin grafting with all patients experiencing graft take. In the second series, Feldmeier[52] reports a total of 23 cases: eight with soft tissue only necrosis and 15 with a combination of bone and soft tissue necrosis. Resolution in those with soft tissue involvement only was 75% while those with a component of bone necrosis had resolution in 53% and all of these patients required resection of necrotic bone.

In a case report Carl and Hartmann[53] in 1998 published their results in treating a patient with long standing symptomatic breast edema following lumpectomy and irradiation. The patient received 15, 90 minute HBO_2 treatments at 2.4 ATA. The patient had complete resolution of pain and edema.

Carl and his associates[54] in 2001 reported the outcome of 44 patients who suffered complications following lumpectomy and irradiation for early breast cancers. These patients were found to have pain, edema, fibrosis and telengectasias. Each patient experienced these complications in various combinations. The severity of symptoms was assessed a score for each patient based on a modified LENT-SOMA score. Only patients with at least grade 3 pain (persistent and intense) or a summed LENT-SOMA score of 8 were studied. Each patient was assessed a score from 1 to 4 in the severity of symptoms in the categories of pain, edema, fibrosis/ fat necrosis and telangectasia/erythema. Thirty-two patients agreed to undergo hyperbaric oxygen treatment while 12 women refused HBO_2 and constituted the control group. Hyperbaric oxygen treatments resulted in a statistically significant reduction in the post treatment SOMA-LENT scores in women receiving hyperbaric oxygen compared to those who did not. Fibrosis and telangectasia were not reduced. Women in the control group continued to demonstrate symptoms at the completion of the trial with no improvement in pain or edema. Seven women in the hyperbaric group had complete resolution of their symptoms at the end of the trial.

Based on the information discussed above and delineated in Table 3, hyperbaric oxygen for radiation induced chest wall or breast injury would be considered an AHA level IIB (Acceptable and Useful based on Fair to Good Evidence) indication. In the BMJ scheme it would be considered "Likely to be Beneficial."

VI. Treatment of Radiation Proctitis and Enteritis

Table 9 lists 11 publications reporting experience in applying hyperbaric oxygen as treatment for radiation enteritis and proctitis.[56-66] The first paper is a single case report detailing the successful treatment of a single patient with hemorrhagic proctitis. An additional 8 case series reports are detailed in Table 3. Of the 105 cases reported in these 9 publications, thirty-four (32%) resolved and 67 (64%) improved.

The animal studies by Feldmeier[57,62] demonstrate a decrease in fibrosis and an improvement in compliance in the small bowel of animals receiving hyperbaric oxygen before frank necrosis was evident. In these studies enough time was allowed to elapse to for the vascular changes and fibrosis associated with late radiation injury to be established prior to animal sacrifice. Characteristically, a latent period of several months to years is observed to occur between the completion of radiation and the clinical expression of radiation damage.[58]

The case reports all represent AHA level 5 evidence and the 2 controlled animal studies present AHA level 6 evidence. In the NCI models, the case reports are level 3ii evidence and the animal studies are not given a categorization.

Based on the consistency of the findings, an AHA IIb indication category is assigned (Fair to good evidence provides support). Applying the BMJ scheme hyperbaric oxygen would be deemed to "Likely to be Beneficial" for this indication.

VII. Miscellaneous Abdominal Wall and Pelvic Injuries

Farmer and his colleagues[16] in 1978 as part of a report, which included radiation injuries to many sites, reported a single case of vaginal necrosis. This necrosis resolved with HBO_2. Williams and his associates[66] reported their results in treating 14 patients with vaginal radiation necrosis in 1992. Thirteen of 14 patients had resolution of their necrosis with hyperbaric treatment. One patient required 2 courses of HBO_2. In 1996 Feldmeier and colleagues[57] reported a series of 44 patients treated with various abdominal and pelvic injuries. The results in treating small and large bowel injuries have already been discussed above. Twenty-six of 31 patients who experienced injuries to the abdominal wall, groin, perineum, vagina or pelvic bones and who received at least 20 hyperbaric treatments had complete resolution with treatment. This group included 6 patients with vaginal necrosis, all of whom experienced complete resolution with treatment. If we total the results reported in these 3 papers we find complete resolution in 40 of 46 patients (87%). All but one patient of the 21 reported in all three papers with soft tissue vaginal necrosis were treated successfully.

All three publications in this section are AHA category 5 and NCI category 3ii. Based on the consistent positive outcome in treating pelvic injuries, an AHA category IIb is assessed to this indication. Applying the BMJ system, we determine that hyperbaric oxygen is "Likely to be Beneficial" for miscellaneous pelvic and abdominal injuries. Additional support for treating these injuries is found by reviewing the response of pathologically similar injuries at other anatomical sites including bowel, bladder and soft tissue injuries of the head and neck.

VIII. Neurologic Injuries

Table 11. lists 12 publications wherein hyperbaric oxygen has been applied to radiation-induced neurologic injuries.[17, 67-75] These injuries include radiation myelitis of the spinal cord, radiation necrosis of the brain, optic nerve injury and brachial plexopathy.

Hart and Mainous[15] in 1976 reported 5 cases of myelitis treated with hyperbaric oxygen without significant improvement. Glassburn and Brady[67] have reported 9 cases of myelitis in which patients received hyperbaric oxygen. Six of these 9 patients improved, including improvement in motor function. In 2000 Calabro and Jinkins[75] reported a single case of myelitis in which the patient demonstrated progressive improvement including imaging documentation by MRI after treatment with hyperbaric oxygen. Feldmeier and his colleagues[71] have reported a statistically significant delay in the onset of transverse myelitis in mice who received hyperbaric oxygen in a prophylactic fashion. The clinical papers present AHA category 5 and NCI category 3ii evidence. The animal study presents AHA category 6 evidence.

There are no other known successful treatments for radiation induced transverse myelitis and the consequences of myelitis are permanent paralysis and loss of sensation below the level of involvement. The published experience reviewed above shows improvement in 7 of 15 patients. Based on the evidence available this indication would be considered “Indeterminate” by the AHA scheme and of “Unknown Effectiveness” in the BMJ model. In this desperate circumstance with a low likelihood of harms and no other effective treatment, intervention based on humanitarian considerations would appear to be justifiable if hyperbaric oxygen therapy could be initiated promptly.

Table 11. includes 4 publications in which hyperbaric oxygen has been applied to the treatment of brain necrosis. In the publication by Hart and Mainous[15], a single case of brain necrosis is presented and this patient had improvement after treatment. In the paper by Chuba and associates[72], hyperbaric oxygen treatment led to temporary improvement initially in all 10 pediatric patients treated. Ultimately, four patients died as a result of their malignancy. At the time of their publication, five of the surviving 6 patients had maintained their improvement. Leber and his colleagues[73] reported the results in delivering hyperbaric oxygen to 2 patients suffering from radiation necrosis as a result of radiosurgery for arteriovenous malformations. Both patients had shrinkage of their lesions by imaging studies and 1 had complete resolution. In the paper by Cirafisi and Verderamae[75] presents a case report of a single patient who failed to respond to hyperbaric oxygen. The patient also failed to respond to steroids and anti-coagulants. All four of these publications represent AHA level 5 and NCI level 3ii evidence. If we combine the results from these 4 publications, we find that 8 of 14 patients reported had a positive therapeutic outcome with hyperbaric oxygen. No other treatments short of surgical resection of the necrotic focus have been effective. Based on the evidence available this indication would be considered “Indeterminate” by the AHA scheme and of “Unknown Effectiveness” in the BMJ model. As in radiation myelitis under these desperate conditions with a low likelihood of harms and no other effective treatment, intervention based on humanitarian considerations should be considered.

Table 11. also includes four publications reporting the results in applying hyperbaric oxygen to the treatment of radiation induced optic neuritis. Again all four of these publications are case series including the single case report by Fontanesi.[69] Only four of the 19 patients reported in these publications had visual improvement. Guy and Schatz[67] report in their series that hyperbaric oxygen must be initiated promptly. In their series, two patients had complete restoration of their sight when they began hyperbaric treatment within 72 hours of loss of their sight. The other 2 patients who began hyperbaric oxygen at 2 weeks and 6 weeks after loss of vision had no improvement. In the paper by Borruat et al[71], a single patient with bilateral radiation-induced optic neuritis had complete resolution in the more recently affected eye and improvement in the eye first affected. These results also suggest the importance of early intervention in order to obtain a positive outcome.

Based on these 4 publications, the indication of hyperbaric oxygen would be considered “Indeterminate” in the AHA scheme and “Unknown Effectiveness” in the BMJ scheme. No other effective therapy exists for radiation-induced optic neuritis. In this desperate circumstance where

permanent blindness is likely to occur, a trial of hyperbaric oxygen intervention would appear to be justified based on humanitarian considerations. This therapy must be promptly initiated.

Finally, in regard to neurologic injury treated by hyperbaric oxygen, Table 11. includes the randomized controlled trial conducted by Pritchard and colleagues[76] which investigates the effect of HBO_2 in the treatment of radiation-induced brachial plexopathy. This is a negative trial and fails to demonstrate a therapeutic advantage for HBO_2. The median time from onset of symptoms until enrollment into the trial was 11 years. As noted above, in some neurologic disorders, a positive outcome for hyperbaric oxygen requires prompt intervention. Patients in the hyperbaric arm did demonstrate less post study deterioration in neurologic function compared to the control group. This decrease in rate of deterioration was statistically significant. Six patients in the hyperbaric arm also experienced a reduction in symptomatic lymphedema of the affected arm. Based on the presently available evidence, we would consider this indication for hyperbaric oxygen to be "Not Acceptable" in the AHA scheme and "Unlikely to be Beneficial" in the BMJ scheme.

IX. Radiation Necrosis of the Extremities

Hyperbaric oxygen has also been reported as a useful therapy in radiation necrosis of the extremities. Table 12. Contains the two studies discovered which discuss hyperbaric oxygen results in treating radiation injuries of the extremities. In the report previously discussed by Farmer and his colleagues[16] a single case of foot injury did not respond to hyperbaric oxygen (AHA level 5 evidence and NCI level 3ii evidence). In a series reported by Feldmeier and associates[77], seventeen patients with necrosis of the extremities treated with hyperbaric oxygen were reported (AHA level 5 and NCI level 3ii evidence). Sixteen of the 17 patients had only soft tissue necrosis. Eleven of 17 had resolution with HBO_2. Actually if we restrict our analysis to those patients in whom follow-up was available and in whom there was no evidence of recurrent cancer, eleven of 13 (85%) had resolution.

Although based on limited evidence in terms of patient numbers, this indication is considered an AHA level IIb and by the BMJ system "Likely to be Beneficial". This determination is made in part based on successful intervention in soft tissue and bony radiation necrosis at other sites as reported above.

Discussion:

Although few randomized controlled trials have been completed to investigate the efficacy of hyperbaric oxygen in treating delayed radiation injuries, the consistent outcome of publications reporting lower levels of evidence supports its application for this indication. Positive reports have been generated in multiple anatomic sites and in multiple tissue/organ types and from multiple investigators from a number of different countries and continents. A characteristic of valid scientific methodology is the consistency of reproducibility of outcome by other investigators in other venues. Tables 4 through 12. contain 64 studies (some included in more than 1 section). Of these 64 publications, all but 7 give positive results for intervention with hyperbaric oxygen. Four of the negative reports are related to intervention with hyperbaric oxygen in neurologic injuries where the pathophysiology is certainly unique and where the promptness of intervention with HBO_2 is critical.

Although experts are not in complete agreement as to the exact pathophysiology of delayed radiation injuries, there is a general consensus that endarteritis and resultant tissue hypoxia are consistent findings and contribute substantially to its etiology.[78-83] Hyperbaric oxygen has been shown to enhance neovascularization at the microscopic level and to improve tissue oxygenation. The mechanisms whereby hyperbaric oxygen offers a positive therapeutic effect have been revealed in the animal studies of Robert Marx and his associates and by John J. Feldmeier and his collaborators. Marx et al[82] have shown a dose dependent increase in vascular density in irradiated rabbits treated with hyperbaric oxygen. Feldmeier and co-workers[57,62] have shown evidence of decreased fibrosis in the pelvic and

abdominal organs of mice receiving whole abdominal irradiation and then receiving post-irradiation hyperbaric oxygen as compared to those receiving the same course of radiation but without the hyperbaric oxygen. Quantitative morphometry identifying and contrasting the relative percentages of collagenous vs non-collagenous components in small and large bowel and kidney in these animals confirm the success in reducing tissue fibrosis in animals receiving hyperbaric oxygen 7 weeks after their radiation exposure. [61,84,85]

For the purpose of this review, published materials have been divided into anatomic or organ system categories. Perhaps more properly, from a pathophysiologic perspective, it is appropriate to divide tissues broadly into soft tissue and bony injuries. The response to and mechanisms of response to hyperbaric oxygen in soft tissue wounds resulting from radiation necrosis from the head and neck to the abdominal wall to the groin to the perineum to the extremities is not likely to be different. Just as the response to antibiotics in cellulitis affecting soft tissues at many anatomic sites is unlikely to be different as long as the therapeutic substance can be delivered in adequate dose to the site of pathology. Similarly, the response to hyperbaric oxygen in treating bone necrosis in the mandible is unlikely to be different from treating radiation necrosis in a rib, or pelvic bone or long bone of the extremities as long as large and medium sized arteries are available to allow transport of the oxygen to the site of radiation injury.

Damage to the nervous system, especially the central nervous system, certainly presents a special case and the mechanisms whereby hyperbaric oxygen might be effective in the treatment of CNS injuries is not likely to be as simplistic as enhancing neovacularization. Although some have recently challenged the concept that ischemic injury of the CNS is absolutely irreparable, no one would deny that the repair of central nervous system tissues as the result of ischemic insult is very limited and that only through very innovative research including stem cell transplantation are we likely to see any substantial incremental improvement in ischemic injury of the CNS.

The systematic review presented herein would certainly be stronger if large numbers of collaborating randomized clinical trials or meta-analyses of these trials were available to substantiate the conclusions made. In the process of preparing this review, the author did not discover large numbers of randomized controlled trials supporting other interventions for radiation injuries. A recent meeting convened at the National Cancer Institute designed to examine strategies for reducing radiation injuries presented the results of several pre-clinical studies but only identified a very few ongoing clinical trials for FGF7 (a fibroblast growth factor).[86] In an area of research, which appears promising based on pre-clinical study, maneuvers designed to block the renin-angiotensin system, no clinical trials are underway. A number of published trials are now in the medical literature reporting some success in preventing radiation damage with Amifostine given during therapy as a radioprotector.[87-91] Two papers have presented very early information from a pilot study and a small retrospective review suggesting that pentoxifylline may have efficacy in the treatment of some delayed radiation injuries.[92,93]

In the absence of type 1 evidence we must make do with the evidence available. The Baromedical Research Foundation is currently sponsoring the HORTIS trials, a series of eight randomized blinded placebo-controlled trials investigating the effects of hyperbaric oxygen on a variety of delayed radiation injuries.[94] Seven of the eight trials are designed to investigate the effects of hyperbaric oxygen on existing injuries in a variety of tissues. The final trial is designed to investigate the efficacy of hyperbaric oxygen as a prophylaxis against radiation injuries in a group of patients at high risk. When these studies are completed and analyzed, we will have type 1 evidence elucidating the effects of hyperbaric oxygen for a broad range of radiation injuries. The HORTIS trial design makes use of the SOMA/LENT system.[95,96] This system for quantifying the severity of radiation injuries was the result of a cooperative project jointly developed by the RTOG, an NCI sponsored, cooperative research group, and the EORTC, the corresponding multi-national European radiation research cooperative group. These criteria for reporting the severity of radiation injuries should be applied in any future report of radiation toxicity or treatment of toxicity. In the SOMA/LENT system, for each organ the severity of injury is assigned a numerical grade. If a therapeutic modality is applied, its effects can be quantified by comparing pre-treatment and post-treatment scores.

A recent publication by Bennett et al[97] in the dermatologic literature presents an evidence-based evaluation of the use of oral steroids in the treatment of infantile cutaneous hemangiomas . Dr. Bennett and colleagues base their review entirely on case series and review 10 of these with a total of 184 patients. Based on a consistently positive result, the authors do not hesitate to recommend oral steroids for this condition.

In the BMJ publication, Clinical Evidence[7], the editors do not refuse to review therapies when no randomized controlled trials are available. For example in the section reviewing treatment of cerebral metastases secondary to metastatic breast cancer, the editors state, "We found no systematic review and no RCT's comparing one form of treatment with another…Non-randomized evidence suggests that symptoms from cerebral metastases can be successfully controlled with radiotherapy." The editors deem radiotherapy "Likely to be Beneficial" for breast cancer metastatic to the brain. This is indeed the standard treatment virtually anywhere in the world in spite of the absence of type 1 evidence. Radiation oncologists are not challenged to present type 1 evidence prior to initiating radiation therapy to a patient with brain metastases.

Sackett and associates state that evidence-based medicine is the use of the best current evidence in making decisions about the care of individual patients.[98] The best current evidence for hyperbaric oxygen in the treatment of radiation injury is presented in this paper in a systematic fashion. This evidence includes 2 randomized controlled trials, 2 prospective cohort controlled trials, numerous case series and several animal studies. The overwhelming majority of these papers are positive in their support of hyperbaric oxygen for delayed radiation injury. The associated harms are few and generally of minor consequence. The NCI model judges the strength of evidence with an eye to the severity of the problem and the consequences of effective treatment, especially when the treatment is life saving or enhances quality of life in a highly significant fashion.[6] It is therefore appropriate to judge the success of hyperbaric oxygen for delayed radiation injury as even more notable when the alternative is death, radical surgery in an already compromised patient or severe limitation of quality of life if treatment is unsuccessful.

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Table 1.

AHA Emergency Cardiovascular Care Levels of Evidence

Level 1: Statistically significant randomized controlled trials (RCT's).

- **1A:** Meta-analysis of multiple positive RCT's.
- **1B:** One or more positive RCT's with statistically positive results
- **1C:** Meta-analysis with inconsistent but significant results

Level 2: Statistically insignificant RCT's

- **2A:** Meta-analysis of positive RCT's but not statistically significant
- **2B:** One or more positive RCT's; not statistically significant
- **2C:** Meta-analysis of inconsistent RCT's; not statistically significant

Level 3: Prospective, controlled, but not randomized cohort studies

Level 4: Historic, non-randomized cohort or case-control studies

Level 5: Human case series

Level 6: Animal or mechanical model studies

Level 7: Reasonable extrapolations from existing data; quasi-experimental designs

Level 8: Rational conjecture (common sense); historical acceptance as standard practice

Table 2.

The American Heart Association System

Class I: Definitely Recommended. Excellent evidence provides support.

Class II: Acceptable and Useful.

IIa: Very good evidence provides support.

IIb: Fair-to-good evidence provides support.

Class III: Not Acceptable, Not Useful, May be Harmful.

Indeterminate: A Continuing Area of Research; no recommendation until further research is available.

Table 3.

National Cancer Institute: Physicians Data Query (PDQ)
Level of Evidence

1. ***Evidence Supported by Randomized Controlled Trials (RCT)***
   1i is a Double Blinded RCT
   1ii is an RCT that is not blinded

2. ***Evidence Supported by Controlled but Non-Randomized Trials***
   (e.g. allocation to a given group is determined by birth date or day of week enrolled)

3. ***Evidence is Supported by Case Studies***
   3i is a case series that is population based and consecutive
   3ii is a case series which is consecutive but not population based
   3iii is a case series which is neither population based nor consecutive

Table 4.

Published Reports of Hyperbaric Oxygen for Prevention of Mandibular Necrosis

Author	Type of Report	AHA Grade	NCI Grade	Clinical Evidence	Comments
Marx (1985)[11]	RCT-74 patients	1B	1ii	Beneficial	5.4% ORN in HBO Group 29.9% in non-HBO Group
Vudiniabola (1999)[12]	Case Series-37 patients	4	3ii	Likely to be Beneficial	1 of 29 HBO and 7 of 8 non-HBO developed ORN
David (2001)[13]	Case Series-24 patients	5	3ii	Likely to be Beneficial	1 of 24 developed ORN

Table 5.

Published Reports of Hyperbaric Oxygen as Treatment for Mandibular Necrosis

Author	Type of Report	AHA Grade	NCI Grade	Clinical Evidence	Comments
Mainous (1975)[14]	Case Series-14 patients	5	3ii	Likely to beBeneficial	Relief of pain and resolution of sinus tracts in all patients
Hart (1976)[15]	Case Series-46 patients	5	3ii	Likely to be Beneficial	37 of 46 Resolved
Farmer (1978)[16]	Case Series-13 patients	5	3ii	Likely to be Beneficial	Radiographic Improvement in 10 of 13 patients
Tobey (1979)[17]	RCT-12 patients 100% O2 at 1.2 vs 2.0 ATA	1B	1ii	Beneficial	Significant improvement in those at 2.0 vs 1.2 ATA
Davis (1979)[18]	Case Series-23 patients	5	3ii	Likely to be Beneficial	20 of 23 resolved
Marx (1983)[19]	Case Series-58 patients	5	3ii	Likely to be Beneficial	100% resolution with HBO and aggressive surgery
Marx (1984)[20]	Case Series-70 patients	5	3ii	Likely to be Beneficial	100% resolution with HBO and aggressive surgery

Mounsey (1993)[21]	Case Series-41 patients	5	3ii	Likely to be Beneficial	34 of 41 had significant improvement
McKenzie (1993)[22]	Case Series-26 patients	5	3ii	Likely to be Beneficial	18 of 26 pertsistent mucosal and epithelial healing
van Merkesteyn (1995)[23]	Case Series-29 patients	5	3ii	Likely to be Beneficial	20 of 29 patients resolved
Epstein[24]	Case Series-20 patients with long term followup	5	3ii	Likely to be Beneficial	12 of 20 resolved with long term followup
Maier (2000)[25]	***Case Series-41 patients***	***3***	***2***	***Not Beneficial***	***A negative trial of hyperbaric compared to historic controls; 13 of 20 HBO resolved***
Curi (2000)[26]	Case Series-18 patients	5	3ii	Likely to be Beneficial	14 of 18 resolved
David (2001)[13]	Case Series-51 patients	5	3ii	Likely to be Beneficial	48 of 51 showed improvement

Table 6.

Hyperbaric Oxygen as Treatment for Soft Tissue Radiation Injury of the Head and Neck

Author	Type of Report	AHA Grade	NCI Grade	Clinical Evidence	Comments
Davis (1979)[19]	Case Series-16 patients	5	3ii	Likely to be Beneficial	15 of 16 resolved
Ferguson (1987)[28]	Case Series-8 patients with laryngeal necrosis	5	3ii	Likely to be Beneficial	Dramatic improvement in 7 of 8
Feldmeier (1993)[29]	Case Series-9 patients with laryngeal necrosis	5	3ii	Likely to be Beneficial	Resolution in all 9 patients
Neovius (1997)[30]	Case series of 15 patients compared to historical control group	5	3ii	Likely to be Beneficial	Healing in 12 of 15 patients; 2 improved; 1 non-healing; compared to 7 of 15 healed in the control group with 1 fatal bleed
Marx (1999)[31]	Prospective controlled but not randomized study of 160 patients	3	2	Likely to be Beneficial	Statistically significant reduction in wound infection, dehiscience and delayed healing in HBO group
Filntisis (2000)[31]	Case Series-18 patients with laryngeal necrosis	5	3ii	Likely to be Beneficial	13 of 18 had major improvement

Narozny (2001)[32]	Case Series-2 patients soft tissue necrosis including larynx and pharynx	5	3ii	Likely to be Beneficial	Resolution in both patients

Table 7.
Hyperbaric Oxygen as Treatment for Radiation Cystitis

Author	Type of Report	AHA Grade	NCI Grade	Clinical Evidence	Comments
Weiss (1985)[36]	Case Series-3 patients	5	3ii	Likely to be Beneficial	3 of 3 resolved
Schoenrock (1986)[37]	Single Case Report	5	3ii	Unknown Benefit	1 of 1 resolved
Weiss (1989)[38]	Case Series-8 patients	5	3ii	Single positive case Likely to be Beneficial	7 of 8 resolved
Rijkmans (1989)[39]	Case Series-10 patients	5	3ii	Likely to be Beneficial	6 of 10 resolved
Norkool (1993)[40]	Case Series-14 patients	5	3ii	Likely to be Beneficial	8 of 14 resolved
Lee (1994)[41]	Case Series-20 patients	5	3ii	Likely to be Beneficial	16 of 20 resolved
Akiyama (1994)[42]	Case Series-2 patients	5	3ii	Likely to be Beneficial	2 of 2 resolved
Weiss (1994)[43]	Case Series-13 patients	5	3ii	Likely to be Beneficial	12 of 13 resolved
Bevers(1995)[44]	Prospective non-randomized trial of 40 patients	5	3ii	Likely to be Beneficial	37 of 40 resolved
Del Pizzo (1998)[45]	***Case-Series-11 patients***	***5***	***3ii***	***Not likely to be Beneficial***	***3 of 11 resolved***
Miyazato (1998)[46]	Case Series-10 patients	5	3ii	Likely to be Beneficial	7 of 10 resolved
Suzuki (1998)[47]	Case Series-3 patients	5	3ii	Likely to be Beneficial	3 of 3 resolved
Mathews (1999)[48]	Case Series-17 patients	5	3ii	Likely to be Beneficial	11 of 17 resolved
Mayer (2001)[49]	Case Series-8 patients	5	3ii	Likely to be Beneficial	6 of 8 resolved

Table 8.

Hyperbaric Oxygen as Treatment for Radiation Injury of the Chest Wall and Breast

Author	Type of Report	AHA Grade	NCI Grade	Clinical Evidence	Comments
Hart (1976)[15]	Case Series-6 patients	5	3ii	Likely to be Beneficial	HBO2 as adjunct to skin graft into irradiated bed all 6 grafts successful
Feldmeier (1995)[52]	Case Series-23 patients-8 soft tissue-15 bone+ soft tissue necrosis of chest wall	5	3ii	Likely to be Beneficial	6 of 8 soft tissue resolved 8 of 15 soft tissue+bone resolved
Carl (1998)[53]	Case Report Single positive case	5	3ii	No category for single case report	Resolution of breast edema and pain
Carl (2001)[54]	Case Series-44 patients 32 received HBO;12 control	4	2	Likely to be Beneficial	Statistically significant improvement in pain, erythema and edema of breast in HBO group compared to control

Table 9.

Hyperbaric Oxygen for Radiation Enteritis and Proctitis

Author	Type of Report	AHA Grade	NCI Grade	Clinical Evidence	Comments
Nakada (1993)[55]	Single Case Report	5	3ii	Unknown Effectiveness Single Positive Case	Single patient with successful treatment of hemorrhagic proctitis
Feldmeier (1995)[56]	Animal Study	6	Not Clinical	Not Clinical but Positive Study	Reduced Fibrosis and reduced gross appearance of enteritis in murine ileum
Feldmeier (1996)[57]	Case Series-8 patients: 7 proctitis/colitis; 1 enteritis	5	3ii	Likely to be Beneficial	4 of 7 proctitis/colitis resolved; 1 enteritis did not resolve
Woo (1997)[58]	Case Series-18 patients	5	3ii	Likely to be Beneficial	2 patients had complete resolution; 8 partial and no change in 8
Warren (1997)[59]	Case Series-14 patients	5	3ii	Likely to be Beneficial	7 patients complete resolution; 2 improved 5 patients non-responders
Bredfelt (1998)[60]	Case Series-19 patients	5	3ii	Likely to be Beneficial	Complete resolution in 47%; 37% improved 16% non-responders

Feldmeier (1998)[61]	Animal Study	6	Not Clinical	Not Clinical but Positive Study	Quantitative morphometry showed decreased Collagen in Bowel Wall
Carl (1998)[62]	Case Series-2 patients	5	3ii	Likely to be Beneficial	One patient completely resolved;the other stopped at 38 treatments without improvement
Gouello (1999)[63]	Case Series-36 patients	5	3ii	Likely to be Beneficial	2/3's of patients followed long term were improved or cured; 1/3 failed to improve
Bem (2000)[64]	Case Series-2 patients	5	3ii	Likely to be Beneficial	Both patients with anorectal ulcers resolved
Mayer (2001)[49]	Case Series-10 patients	5	3ii	Likely to be Beneficial	5 of 5 with rectal bleeding resolved; Statistically significant decrease in late morbidity score

Table 10.

Hyperbaric Oxygen as Treatment for Delayed Miscellaneous Radiation Injuries of the Abdomen and Pelvis

Author	Type of Report	AHA Grade	NCI Grade	Clinical Evidence	Comments
Farmer (1978)[16]	Single Case Report	5	3ii	Unknown Effectiveness	Single case of vaginal necrosis resolved
Williams (1992)[65]	Case Series-15 patients	5	3ii	Likely to be Beneficial	13/14 patients with vaginal necrosis resolved
Feldmeier (1996)[57]	Case Series-37 patients	5	3ii	Likely to be Beneficial	26/31 who received at least 20 HBO sessions resolved including 1of 2 with pelvic osteoradionecrosis

Table 11.

Hyperbaric Oxygen as Treatment for Radiation Injuries of the Nervous System

Author	Type of Report	AHA Grade	NCI Grade	Clinical Evidence	Comments
Hart (1976)[15]	***Case Series-5 myelitis pa- tients and 1 with brain necrosis***	***5***	***3ii***	***Unknown Effectiveness (mixed result)***	***Sensory but no motor improvement for myelitis patients; brain patient improved***
Glassburn (1977)[66]	Case Series-9 patients with Myelitis	5	3ii	Likely to be Beneficial	6 of 9 improved
Guy (1986)[67]	Case Series-4 patients optic nerve	5	3ii	Likely to be Beneficial (if initiated within 72hrs)	2 of 2 improved if started within 72 hrs; if beyond 72 hrs, neither responded
Roden (1990)[68]	***Case Series-13 patients optic nerve injury***	***5***	***3ii***	***Not likely to be Beneficial***	***No patient had improvement in vision***
Fontanesi (1991)[69]	Single Case Report optic nerve	5	3ii	Unknown Effectiveness Single Positive Case	Visual acuity significantly improved in spite of persistent tumor
Feldmeier (1993)[70]	Animal Study of Myelitis	6	Not Clinical	Not Clinical but Positive Study	Onset of myelitis delayed for 9 weeks in a statistically significant fashion for animals treated prophylactically

Borruat (1993)[71]	Single Case Report	5	3ii	Unknown Effectiveness	Single patient with bilateral optic neuritis; resolution in more recently affected eye; slight improvement in earlier affected eye
Chuba (1997)[72]	Case Series-10 patients brain necrosis	5	3ii	Likely to be Beneficial	All ten initially improved; 4 died from tumor; 5 of remaining 6 still improved
Leber (1998)[73]	Case Series-2 patients brain necrosis	5	3ii	Likely to be Beneficial	One lesion disappeared; the other was reduced in size
Calabro (2000)[74]	Single Case report of radiation myelitis	5	3ii	Unknown Effectiveness Single Positive Case	Progressive improvement following HBO
Cirafisi (2000)[75]	***Single Case Report of rhombencephalopathy***	***5***	***3ii***	***Unknown Effectiveness Single Negative Case***	***No improvement with HBO, steroids or anticoagulants***
Pritchard (2001)[76]	***RCT: Brachial Plexopathy***	***1B***	***1ii***	***A Negative Study: No Benefit***	***No improvement in brachial plexopathy 6 patients with lymphedema had significant reduction***

Table 12.

Hyperbaric Oxygen as Treatment for Radiation Injuries of the Extremities

Author	Type of Report	AHA Grade	NCI Grade	Clinical Evidence	Comments
Farmer (1978)[17]	***Single Case Report***	***5***	***3ii***	***Unknown Effectiveness Single Negative Case***	***1 of 1 failed to respond***
Feldmeier (2000)[78]	Case Series-17 patients	5	3ii	Likely to be Beneficial	11 of 17 resolved; 11 of 13 if those lost to followup or with active cancer are excluded