

**HYPERBARIC OXYGEN THERAPY IN THE TREATMENT OF
RADIO-INDUCED LESIONS IN NORMAL TISSUES**

CONSENSUS CONFERENCE

Long Version

Jointly held by:

EUROPEAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY

AND

EUROPEAN COMMITTEE FOR HYPERBARIC MEDICINE

*October 19-20th, 2001
Lisbon – Portugal*

Introduction

Format of the Conference

Conference Report

Question 1:

What are the incidence and the cost of the radio-induced lesions in normal tissues?

Question 2:

What tissue changes induced by radiotherapy lead to impaired healing in radio-injured normal tissues?

Question 3:

What is the rationale for Hyperbaric Oxygen Therapy in the treatment of radio-induced lesions in normal tissues?

Question 4:

What are the locations of radio-induced lesions where hyperbaric oxygen therapy has shown efficacy?

Question 5:

May hyperbaric oxygen therapy play any role in the prevention of radio-induced tissue lesions?

Question 6:

Is hyperbaric oxygen therapy cost effective in these indications?

Future Research

Introduction

Surgery, radiation therapy and cytotoxic chemotherapy are the principal methods employed in the treatment of cancer. Although all have achieved considerable advances in the attainment of cure all are associated with a risk of morbidity and mortality. Radiation therapy differs from the other two modes of treatment in that its most serious associated morbidity tends to occur months and commonly years after treatment when management is often difficult and unsatisfactory.

It has been estimated that within the European Union there are five million people alive at five years or more after having received radiation therapy as the principal or as an adjuvant method of treatment. Although the large majority are fit and well with little or nothing to relate to the treatment given, troublesome symptoms may be present in up to 5% due to late radiation changes. Perhaps as many as 1%, that is, 50,000 people, may have serious problems, which are resistant to simple methods of treatment. Major surgery may be required as well as prolonged hospital care. Personal and social problems may be very distressing and commonly those affected are unable to pursue gainful employment.

Because a dominant feature of post-radiation change is the obliteration of small blood vessels leading to hypoxia, hyperbaric oxygen has been employed in the care of these patients. In the past forty years there have been many publications reporting benefit in studies, which have included some thousands of patients.

Because the literature is dominated by case series containing modest numbers and by case reports and because there have been few randomised trials, there is considerable uncertainty as to the place of hyperbaric oxygen in the management of radiation morbidity. The importance of the problem led the European Society of 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.

Format of the Conference

After listening to evidence, a jury drawn from authorities in the areas of medicine concerned, were asked to answer six questions covering the field of concern.

The jury and those attending the conference were informed by two highly detailed literature reviews:

- (i) **Radio-Induced Lesions in Normal Tissues: Incidence, Risk Factor and Conventional Treatment.**
Dr David Pasquier, Centre Oscar Lambret, Lille, France
- (ii) **Hyperbaric Oxygen Therapy in Radionecrosis (A review of the literature).**
Dr Jorg Schmutz, Hyperbaric Center, Basel, Switzerland

Nine experts prepared written reviews often with the assistance of colleagues and gave presentations which extended through the whole of the first day of the conference:

- (iii) **Professor Michael Baumann**
Carl Gustav Carus, Dresden, Germany
Incidence, risk factors and cost of radio-induced lesions in normal tissues.
Written review by: Baumann, M. Holscher, T.
- (iv) **Professor Bernard Dubray**
Centre Henri Becquerel, Rouen, France
Pathophysiological basis of radiation-induced lesions in normal tissues.
Written review by: Dubray, B. Lefaix, J-L. Martin, M. Delanian, S.
- (v) **Professor Gosta Granstrom**
Goteborg Universitat, Goteborg, Sweden
Pathophysiological basis for HBO in the treatment of healing disorders in radio-injured normal tissues.
Written review by: Granstrom, G.
- (vi) **Professor Johannes Van Merkesteyn**
Leiden University Medical Center, The Netherlands
Hyperbaric oxygen therapy in the treatment of osteo-radionecrosis.
Written review by: Van Merkesteyn, J
- (vii) **Professor A J Van der Kleij**
Academic Medical Center, Amsterdam, The Netherlands
Hyperbaric oxygen therapy in soft tissue radionecrosis. Radio-induced cystitis.
Written review by: Van der Kleij, A J. De Rijke, T. Hulshof, M.
- (viii) **Dr F Roque**
Hospital da Marinha, Lisboa, Portugal
Hyperbaric oxygen therapy for late radio-induced intestinal lesions.
Written review by: Roque, F. Saraiva, A. Simao, G. Sousa, A. Torres, P. Sampaio, J.
- (ix) **Professor J Yarnold**
Institute of Cancer Research, Sutton, Surrey, UK
Hyperbaric oxygen therapy in soft tissue radionecrosis: Radiation-induced myelitis and plexopathy.
Written review by: Yarnold, JR. Gothard, L.
- (x) **Professor John Feldmeier**
Medical College of Ohio, USA
Hyperbaric oxygen: Does it have a cancer causing or growth enhancing effect?

- Written review by: Feldmeier, J.
- (xi) **Dr A Marroni**
Centro Iperbarico Ravenna, Italy
A cost-benefit evaluation of hyperbaric oxygen use in tissue radio-induced lesions.
Written review by: Marroni, A. Longobardi, P. Cali Corleo, R.

After each presentation there was a vigorous discussion amongst the 150 attendees who were physicians and surgeons with an interest in hyperbaric oxygen or radiation oncologists.

On the second morning there was a three-hour session of the jury. The members were:

Stanley Dische, President

Professor in Oncology – Centre for Cancer Treatment – Mount Vernon Hospital – UK

Dirk Bakker

Professor of Surgery – Academic Medical Center – Amsterdam – The Netherlands

Karl Hartmann

Department of Radiation Oncology – University of Dusseldorf – Germany

Ferran Guedea

Head of the department of Radiation Oncology – Institut Catala d'Oncologia – Barcelona – Spain

Joaquim Gouveia

Director Hospital Cuf-Descobertas/Former Director Instituto Portugues de Oncologia – Lisboa - Portugal

Eric Lartigau, ESTRO General Secretary

Professor in Radiation Oncology – Centre Oscar Lambret – Lille – France

Daniel Mathieu, ECHM General Secretary

Professor in Critical Care Medicine – Centre Hospitalier Universitaire – Lille – France

Advising the jury were –

David Pasquier

Centre Oscar Lambert – Lille – France

Jorg Schmutz

Hyberbaric Center – Basel – Switzerland

After the meeting of the jury there was an immediate report to the conference by the President of the Jury. A written report was drafted by the President and circulated to all members of the jury for comment, addition and deletion before presentation for publication.

Conference Report

The jury discussed all the evidence put before it and came to recommendations for clinical practice. In assessing the quality of the evidence, the scale: 1 (strong), 2 (convincing evidence), 3 (existing but weak evidence) and 4 (anecdotal evidence) was employed (Table 1).

The jury were grateful to the eleven reviewers who worked so hard to collect and analyse the evidence, which they had considered. These valuable reviews, which were at a high standard of scholarship, will be published on the web of ESTRO (www.estro.be), so as to be generally available. In this report the reviews will be referred to by the Roman numbers as noted above.

Question 1:

What are the incidence and the cost of the radio-induced lesions in normal tissues?

The jury was grateful to Professor Michael Baumann for his review of the subject. It was the modification of the late effects by use of hyperbaric oxygen that was the concern of the meeting and the incidence was much influenced by the definition and grading of the late changes. There was unfortunately no internationally agreed grading system but the greatest experience was with the RTOG/EORTC system available for over thirty years and the LENT-SOMA, which was developed from it and published in 1995. Other systems such as the Franco Italian glossary and the dictionary approach had been proven of value in randomised clinical trials. International agreement as to the definition of morbidity would advance knowledge in the field. The Mitre Meeting held in Brussels in December 2000 effectively reviewed systems, which might be employed in routine practice. There was to be a meeting in Florida in April 2002 to try to make further advance in this field. The Conference gave its encouragement towards the pursuit of agreement in this area.

The hardest evidence as to the incidence of morbidity is contained in reports of randomised controlled clinical trials but some can be gained from reports of consecutive series. These have been reviewed by Dr Pasquier ^[1] and the incidence figures varied very widely according to definition and site. Even with one site a common range was from less than 1% to over 30%. There was no doubt that the incidence of late damage using the older techniques of radiotherapy, particularly the use of ortho-voltage apparatus, was considerable and has reduced with the employment of high energy equipment, with improvements in patient immobilisation, the introduction of precise planning using simulators and with greater precision in dose definition and delivery. Further improvements, such as advanced planning so that treatment is "conformal" to the tumour target volume and the use of intensity modulated radiotherapy, should spare normal tissue damage.

There were, on the other hand, developments in oncology, which might reverse this trend. "Conformal" radiotherapy has encouraged the attainment of higher tumour doses and inevitably some normal tissues will be included. The concomitant administration of cytotoxics where an adjuvant effect is likely to increase the incidence of late damage and the quantitative importance of these drug radiation interactions are difficult to predict. An increasing use of major surgery for restoration of function or for salvage of advanced recurrent disease is also associated with a high risk of morbidity when a heavily irradiated area is operated upon.

The maximum tolerable radiation dose is often set as that which produces an incidence of 5% of moderate or severe late damage. The number of patients with severe damage that is resistant to simple measures is likely in actual fact to be much

smaller. However, a prevalence of 1% does represent a very large number of patients in need of care.

The risk factors are similar over all sites and include the total radiation dose, the overall time, the biological effective dose which takes into account fraction size and the overall time, the volume irradiated, the use of a combination of external beam with an implantation or intracavity procedure, a high dose rate with brachytherapy, tumours adjacent to or involving bone, the presence of infection, the use of surgery and the occurrence of trauma.

Although we need better data concerning the incidence of late damage due to radiotherapy in routine practice the level of evidence to support the observations about incidence which we have made is extensive and certainly can be regarded as being at level 1/2.

Professor Baumann could find very little useful evidence to answer the question concerning the cost of morbidity. Dr Marroni, in his contribution ^[xi] concerned with cost effectiveness, has reviewed two papers from the United States concerned with mandibular radionecrosis where the average yearly costs of care reached \$140,000. Much of the cost was due to hospitalisation and drugs and these figures did not include costs due to loss of work and care at home. Dr Marroni presented data from Italian hospitals suggesting that over 3000 patients in the year 2000 were discharged with a diagnosis of "radio-lesions of the mandible and soft tissues» and these did seem to represent a high cost to the Italian Health Service. Dr Marroni also gave some evidence suggesting that hyperbaric oxygen treatment would considerably reduce the cost. The jury had some uncertainty about the reliability of this data but it did give some support to the view that the costs of care for radionecrosis were extremely high and that these might be reduced with the use of hyperbaric oxygen. Overall the current evidence was regarded to be at level 3, that is, weak.

Question 2:

What tissue changes induced by radiotherapy lead to impaired healing in radio-injured normal tissues?

When heavily irradiated tissues are examined at an interval of months or years after treatment the characteristic findings are a cellular depletion, fibrosis and a reduction in vascular density with marked narrowing of the small blood vessels. There is therefore hypoxia due to the vascular changes. . Professor Granstrom ^[j] described the changes, which may be observed in irradiated tissue.

Professor Bernard Dubray reviewed the subject and stressed the inter-relationship between these three types of change. The exact mechanism of production of these changes is undoubtedly complex and incompletely understood. Molecular biology has shown that hypoxia could trigger altered gene expression leading to a whole range of effects. Use of hyperbaric oxygen in these circumstances may also lead to complex changes, which may not all be favourable.

There is laboratory and clinical evidence that interstitial fibrosis and necrosis can, at least in part, be reversed by drugs such as exogenous SOD or a combination of Pentoxifylline and vitamin E. The mechanism whereby the benefit is gained remains obscure and Professor Dubray expressed the need for better knowledge of radiation induced late damage in normal tissues

The jury felt that there was some level 4 and considerable level 3 evidence to support the views expressed.

Question 3:

What is the rationale for Hyperbaric Oxygen Therapy in the treatment of radio-induced lesions in normal tissues?

This subject was fully reviewed by Professor Granstrom (v). He considered papers, which gave evidence that there could be an increase in vascular density in irradiated skin and soft tissues after treatment with hyperbaric oxygen. There was further evidence using bone densitometry that new bone formation capacity could be increased. In a controlled study in rabbits where implants had been performed there was evidence of a significant increase in the force necessary to unscrew implants. In another animal study hyperbaric oxygen increased the capacity for osseointegration. Further it has been found that hyperbaric oxygen could stimulate bone maturation.

Experimental studies of animals with myocutaneous flaps showed significantly increased vascularity with hyperbaric oxygen. It was found that steep oxygen gradients stimulated macrophage angiogenesis factor and macrophage derived growth factor. Bone healing in mice was enhanced.

There was evidence at a similar level which suggested that in patients, hypoxia was a major component of delayed wound healing because a reduced fibroblast activity and less efficient production of collagen. Hyperbaric oxygen inducing a temporary increase in the oxygen supply stimulated angiogenesis and modified fibrosis.

The jury considered there was a real rationale for hyperbaric oxygen to be used in radiation-induced morbidity as gained from these studies. The evidence was at level 1 and level 2.

Question 4:

What are the locations of radio-induced lesions where hyperbaric oxygen therapy has shown efficacy?

Mandibular osteo-radionecrosis:

Here there was a large body of evidence [i,ii & vi].

The conservative management combines the use of antiseptic solutions, analgesics, oral hygiene, systemic antibiotics and simple sequestrectomy. Lesions less than 1cm in maximum diameter commonly heal but larger lesions tend to be refractory, however very varied healing rates are reported in the literature [1].

When conservative measures fail then surgery, often mandibulectomy with complex reconstructive work becomes indicated. These procedures tend to be followed by post-operative complications, which tend to be great when a large area of heavily irradiated bone must be incised.

Hyperbaric oxygen has been used in the management of osteo-radionecrosis for forty years and it has often been employed with radical surgery, benefit rates of 30-100% have been reported but the situation is complex because surgery is also employed in a number of the published series.

There is no randomised controlled trial of the use of hyperbaric oxygen in this area. However, impressive margins healing have been reported when comparison has been made with previously treated cases. There were seven studies recorded since 1993 with improvements noted in 70-92% of the cases included in each series (ii).

In this situation where conservative treatment for gross mandibular radionecrosis can achieve at best a minimal healing and where commonly there may be progression of the process the results achieved in the management of consecutive cases can be given considerable importance. The proportion of cases showing improvement in many of the series was impressive. The jury felt that there was a considerable body of evidence to support a view that hyperbaric oxygen was effective in improving osteo-radionecrosis of the mandible and that it should be considered as part of management when conservative measures fail to allow healing to take place (level 2 evidence).

There was a wide variety of clinical presentation of osteo-radionecrosis of the mandible and the use of hyperbaric oxygen alone or in combination with surgery would need to be decided according to the features of a particular case.

Osteo-radionecrosis at other sites:

There was a body of literature concerned with the treatment of bone necrosis at other sites and these included the maxilla, spine and pelvic bones. Many of the contributions to the literature were anecdotal and the tendency for publication to be of positive results and lack of interest in publishing negative results must lead to some reservation. However, with the evidence for benefit in osteo-radionecrosis of the mandible, hyperbaric oxygen therapy could be considered as a possible method to employ in refractory cases of osteo-radionecrosis at other sites than the mandible³).

Radionecrosis of the larynx:

Here there was some evidence of benefit. Five papers reporting a total of 45 cases with publication dates between 1976 and 2000 were available (ii). In general the majority of the patients appeared to benefit, however, the evidence must be regarded as weak and at level 4. Hyperbaric oxygen could be employed in this situation.

Radiation cystitis:

Here there was a considerable literature and fifteen papers reporting a total of 256 cases have been published since 1989 (ii). Haematuria was a dominant symptom, one which was relieved in many cases. Frequency and incontinence was also reported as improved in some cases. Professor Van der Kleij gave us a full review of the subject. Radiation cystitis occurred after radiotherapy for pelvic tumours, with incidence figures varying from less than 1 to over 30%. However, much depended on the radiotherapy given and the criteria for reporting the complications.

Conservative treatment included antibiotic therapy, corticosteroids, blood transfusion, bladder irrigation and Tocopherol.

Intervention included irrigation of the bladder with alum and installation of formalin solution. These measures can be effective but the use of formalin may be associated with major complications. Limited cysto-diathermy and laser photocoagulation may also be employed in the management of small areas of bladder where the sites of bleeding can be demonstrated.

Surgery in the form of a urinary diversion, an ileo-cystoplasty or a cystectomy with diversion may be employed. Operations performed in the heavily irradiated pelvis are associated with a high risk of further morbidities.

A recent literature review from Oxford identified 309 references where many different forms of treatment were employed. They concluded in the absence of randomised studies that it is impossible to set definite rules for treatment.

The jury were however impressed that in patients resistant to conservative treatment and where the only measure to be considered was cystectomy, there was a high rate of response to hyperbaric oxygen; while recurrence of bleeding did occur in some, there were a considerable number where the improvement was maintained long term. The jury therefore considered that there was convincing evidence (level 2) that in this situation hyperbaric oxygen should be employed in management.

There was possibly a place for hyperbaric oxygen at an earlier stage when the simplest methods of treatment had failed to gain a response. Further this was a logical development but its adoption must depend upon the result of a randomised controlled clinical trial.

Radiation-induced proctitis and enteritis:

Here there was a considerable literature which had been gathered [i, ii & vi] for review by the conference and the jury. Fifteen papers reporting 256 cases treated with hyperbaric oxygen were found and there were 10 papers reporting 116 cases from 1993 to 2000 (i,ii). The majority of the cases were reported as either cured or improved with regard to the symptoms and/or clinical findings. In their review Dr Roque and his colleagues found 13 papers reporting 107 cases between 1990 and 2000, and gained an even greater impression of improvement (viii). The symptoms and findings in these cases were obviously complex, making assessment difficult.

The jury concluded that hyperbaric oxygen could be employed in the management of radiation proctitis and enteritis, however the evidence must be regarded as at level three (weak).

Radiation plexopathy:

The review by Dr Yarnold assisted by Mrs Gothard reviewed radiation induced myelitis and plexopathy. A randomised controlled trial involving 31 patients with brachial plexopathy performed by Dr Yarnold and his colleagues had yielded no evidence for benefit but the study, though performed with great care, was considerably underpowered. There were, in addition, a number of anecdotal reports concerning the use of hyperbaric oxygen for brain necrosis and radiation myelitis, however the evidence was unconvincing. There was therefore considerable uncertainty as to the place of hyperbaric oxygen in the treatment of radio necrosis in central nervous system and we could therefore come to no recommendation as regards its place in management.

Other sites

Evidence was presented concerning the use of hyperbaric oxygen at other sites, which included skin, the subcutaneous tissues, the eye and breast. The largest body of evidence was with regard to the breast where there may be a place for hyperbaric oxygen however the evidence must be regarded as weak (level three)

Question 5:

May hyperbaric oxygen therapy play any role in the prevention of radio-induced tissue lesions?

a) Tooth extraction in irradiated tissues

Here there was considerable evidence gathered by our reviewers [eye^{ii,v} & vi]. Included was a randomised controlled trial performed by Marks [v, p.87] and the result was supported by other studies reporting consecutive cases where a comparison was made with cases managed without hyperbaric oxygen. The jury felt that there was convincing evidence (levels 1 and 2) that in a situation where teeth extraction was planned in an area of mandible or maxilla which had

received high dose radiotherapy, hyperbaric oxygen importantly reduced the risk of osteo-radionecrosis. However some evidence was presented that the risk of tooth extraction in irradiated tissue was normally so low that hyperbaric oxygen was unnecessary as a preventative measure. It was however felt by the jury that in this report case selection may have played a role in that the radiation doses may have been moderate and so the risk may have been so low as to make hyperbaric oxygen unnecessary. This was obviously an area where radiation oncologist and surgeon must collaborate together to assess the site, volume and radiation dose so as to determine the indication. It was also obviously an area for further randomised studies.

b) Surgery in irradiated tissue

Considerable evidence was brought before the jury that post operative complications could be reduced by the use of hyperbaric oxygen when major surgery was planned in previously irradiated patients. Wound infections and dehiscence were significantly reduced as well as delayed wound healing reported as serious. No randomised controlled study has however taken place. The jury felt it was an area where hyperbaric oxygen may well have a place but the evidence remained weak in the absence of a randomised controlled trial published in peer-reviewed journals, which is always necessary when a measure for prevention is being assessed.

c) Implants in irradiated tissues

There is an increasing use of implantation of metal prostheses into heavily irradiated tissue as restorative surgery is increasingly used in patients who have extensive resections and radiotherapy for advanced tumours. There was evidence suggesting that hyperbaric oxygen could have a role but it must be regarded as weak and again a need for a randomised controlled clinical trial was clear.

Question 6

Is hyperbaric oxygen therapy cost effective in these indications?

An important consideration in a patient with malignant disease was the possibility that there could be a harmful effect of hyperbaric treatment. Professor Feldmeier gave us a most interesting review of this subject. The question first arose over forty years ago when patients were being treated by radiotherapy in hyperbaric oxygen chambers. Dr Feldmeier effectively reviewed the subject and showed that the evidence that hyperbaric oxygen disseminated tumour and led clinically to a higher incidence of distant metastasis was extremely weak and the jury were convinced that this was not a problem. In patients who suffered post-radiation phenomenon the large majority were, of course, free of tumour so this was not a problem to even consider.

The evidence produced in reviews (iii) and (xi) has already been considered. The jury felt that there was so little hard evidence in this field that it was not possible to reach a conclusion. Costs of hyperbaric therapy could be measured but even here it was necessary to consider the personal and social costs as well as that of the actual treatment. The cost of radiation morbidity itself is obviously high but until real data was available it was not possible to determine whether hyperbaric oxygen would truly have a cost-saving effect. Their impression was that this would be the case but presently this could not be substantiated by hard evidence.

Future Research

The Consensus Conference did reveal many areas where research was required in order to advance knowledge and to lead to evidence-based decisions as to the place of hyperbaric oxygen in the management of late radiation morbidity.

The jury felt that data should be gathered concerning:

1. The incidence of post-radiation morbidity in routine practice. An internationally agreed simple system for recording such morbidity would be an essential prerequisite
2. Cost of radiation morbidity.

The jury felt that randomised controlled clinical trials were indicated in the clinical situations:

1. Where tooth extraction is planned in areas, which have received radiotherapy, but where the post-radiation change is not gross so as not to be included in the group where the jury felt that hyperbaric oxygen was already indicated.
2. In patients who are planned for extensive restorative surgery and/or prosthetic implantation after large volume radiotherapy to tumourcidal dosage.
3. Patients with irradiation cystitis after simple methods of management had failed but before the stage at which cystectomy/urinary diversion had become indicated.

The jury felt that these were all areas where, on a European basis, in a close collaboration between physicians and surgeons concerned with hyperbaric oxygen and radiation oncologists, together with surgeons called on to operate in post-radiation situations, trials could be established, performed at a high standard and recruit sufficient numbers of patients.

Table I : Scale used to assess the evidence presented.

Level	Grade	Definition
Level 1	Strong evidence of beneficial action.	At least 2 concordant, large, double-blind, controlled randomised studies with no or only weak methodological bias.
Level 2	Convincing evidence of beneficial action.	Existence of double-blind controlled, randomised studies but with methodological bias, or concerning only small sample, or only a single double-blinded, controlled, randomised study.
Level 3	Evidence of beneficial action but weakly supported.	Only uncontrolled studies : historic control group, cohort study, ...
Level 4	Anecdotal evidence of beneficial action	Case report only or methodological or interpretation bias preclude any conclusion.

Table II : Indications of HBO in the treatment of radio-induced lesions in normal tissues

Recommendation grade	Indication
Level 2 – convincing evidence	<p>Radionecrosis of the mandible Radiation Cystitis of the bladder resistant to conservative measures Tooth extraction in irradiated tissues (preventive action)</p>
Level 3 - Evidence of beneficial action but weakly supported.	<p>Radionecrosis of other bones Radiation-induced proctitis and enteritis Radiation-induced lesions of soft tissues Surgery and implants in heavily irradiated tissues (preventive action)</p>
Level 4 – anecdotal evidence	<p>Radiation-induced lesions of the larynx Radiation-induced lesions of the central nervous system.</p>
No evidence to support	Radiation-induced plexopathy