



WORKING GROUP ON ACUTE PURCHASING

The Use of Hyperbaric Oxygen in the Management of Patients with Oral Cancer

May 2000

GUIDANCE NOTE FOR PURCHASERS 00/03
Series Editor: Nick Payne

Trent Development and Evaluation Committee

The purpose of the Trent Development and Evaluation Committee is to help health authorities and other purchasers within the Trent Region by commenting on expert reports which evaluate changes in health service provision. The Committee is comprised of members appointed on the basis of their individual knowledge and expertise. It is chaired by Professor Sir David Hull.

The Committee recommends, on the basis of evidence provided, priorities for:

- the direct development of innovative services on a pilot basis;
- service developments to be secured by health authorities.

The statement that follows was produced by the Development and Evaluation Committee at its meeting on 11 April 2000 at which this Guidance Note for Purchasers (in a draft form) was considered.

THE USE OF HYPERBARIC OXYGEN IN THE MANAGEMENT OF PATIENTS WITH ORAL CANCER

AUTHORS: Ward SE, Thomas N, Mander C, Brook I. Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield 2000. Guidance Note for Purchasers: 00/03.

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(The recommendations made by the Committee may not necessarily match the personal opinions expressed by the experts)

DECISION: The Committee recommended that hyperbaric oxygen (HBO) in the treatment of oral cancer is only used in the context of a clear statement of clinical practice, fully informed consent, comprehensive patient information and the collection of clinical data that allows analysis of benefits and risks. Patients should only receive HBO from a unit which has the necessary quality controls, both in respect of the pressure used and patient observation.



TRENT DEVELOPMENT & EVALUATION COMMITTEE

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MANAGEMENT OF PATIENTS WITH ORAL CANCER**

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Trent Institute for Health Services Research
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Conflict of Interest

None of the authors of this document has any financial interests in the drug or product being evaluated here.

ABOUT THE TRENT INSTITUTE FOR HEALTH SERVICES RESEARCH

The Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield with support from NHS Executive Trent.

The Trent Institute:

- undertakes Health Services Research (HSR), adding value to the research through the networks created by the Institute;
- provides advice and support to NHS staff on undertaking HSR;
- provides training in HSR for career researchers and for health service professionals;
- provides educational support to NHS staff in the application of the results of research;
- disseminates the results of research to influence the provision of health care.

The Directors of the Institute are: Professor R L Akehurst (Sheffield);
Professor M Clarke (Leicester); and
Professor H Williams (Nottingham).

Professor Clarke currently undertakes the role of Institute Co-ordinator.

A Core Unit, which provides central administrative and co-ordinating services, is located in Regent Court within The University of Sheffield in conjunction with The School of Health and Related Research (SchARR).

FOREWORD

The Trent Working Group on Acute Purchasing was set up to enable purchasers to share research knowledge about the effectiveness and cost-effectiveness of acute service interventions and determine collectively their purchasing policy. The Group is facilitated by The School of Health and Related Research (SchARR), part of the Trent Institute for Health Services Research, the SchARR Support Team being led by Professor Ron Akehurst and Dr Nick Payne, Consultant Senior Lecturer in Public Health Medicine.

The process employed operates as follows. A list of topics for consideration by the Group is recommended by the purchasing authorities in Trent and approved by the Health Authority And Trust Chief Executives (HATCH) and the Trent Development and Evaluation Committee (DEC). A public health consultant from a purchasing authority leads on each topic assisted by a support team from SchARR, which provides help including literature searching, health economics and modelling. A seminar is led by the public health consultant on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy. The guidance emanating from the seminars is reflected in this series of Guidance Notes which have been reviewed by the Trent DEC, chaired by Professor Sir David Hull.

In order to share this work on reviewing the effectiveness and cost-effectiveness of clinical interventions, The Trent Institute's Working Group on Acute Purchasing has joined a wider collaboration, InterTASC, with units in other regions. These are: The Wessex Institute for Health Research and Development and The University of Birmingham Department of Public Health and Epidemiology.

Professor R L Akehurst

Chairman, Trent Working Group on Acute Purchasing

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SUMMARY

The use of hyperbaric oxygen therapy (HBO) has been undertaken for the last three decades as part of the management of patients with oral cancer. HBO involves a patient breathing 100% oxygen whilst inside a treatment chamber at a pressure greater than sea level pressure (i.e. greater than one atmosphere). The patient must receive the oxygen by inhalation within a pressurised chamber.

HBO has been used for a number of different therapeutic aims:

- to prevent the occurrence of osteoradionecrosis (ORN);
- to treat established cases of ORN;
- to aid wound healing;
- prior to the placement of endosseous implants in order to facilitate implant survival.

Although the impact of oral cancer upon a person's physical and psychological well-being is great, the number of patients who may benefit from therapy is small. There are around 20 new cases of oral cancer per year for a health authority with a population of 500,000 and only a proportion of these patients may benefit from HBO. There is potential to double the number of patients by including people affected by head and neck cancer as well as those with oral cancer. In addition, there is a wider pool of patients who may benefit from the use of endosseous implants. Current funding of this reconstructive procedure is limited.

At present, the service provided does not allow equitable access across the Trent Region. A recent survey in the Region has shown that approximately one third of head and neck surgeons prescribe hyperbaric oxygen. Trent residents have been referred to a wide number of chambers including those at Plymouth, Bangor, Peterborough, Hull, Sheffield and Lincoln. In some units, a physician is not present when the treatment is given.

The evidence for the use of HBO in the treatment of oral cancer is limited. Whilst there is some research evidence available, much is still unknown and there is a need for further research. In relation to the treatment of ORN, the weight of evidence supports the effectiveness of HBO but suggests that it might not be necessary for all patients. For the prevention of ORN, the evidence is unclear. Management protocols based on careful wound care and surgical technique may minimise the risk of ORN. The use of HBO should not be used as a substitute for the high quality management of patients. There is limited evidence to support the use of HBO prior to the placement of endosseous implants, but further

evidence is required.

There is a need for better information systems pertaining to the diagnosis and management of people with head and neck cancer. There appears to be a lack of criteria for the use of HBO and work at a local and national level is required in order to produce clinical consensus on treatment. As this procedure is not without risk, patients need to have access to comprehensive information and this is difficult in the absence of agreed clinical guidance.

In summary, it is recommended that HBO in the treatment of oral cancer is used in the context of a clear statement of clinical practice, fully informed consent, comprehensive information and the collection of clinical data that allows the analysis of benefits and risks. Patients should only receive HBO from a unit, which has the necessary quality controls both in respect to the pressure used and patient observation.

ABBREVIATIONS

BHA	British Hyperbaric Association
CRC	Cancer Research Campaign
COM	Chronic osteomyelitis
ECHM	European Committee for Hyperbaric oxygen
HBO	Hyperbaric Oxygen Therapy
ORN	Osteoradionecrosis
RCT	Randomised Controlled Trial
TO	Transmuscosal Oxygen
UHMS	Underseas and Hyperbaric Medicine Society

1. AIM OF THE REVIEW

The use of hyperbaric oxygen therapy (HBO) has been undertaken for the last three decades as part of the management of patients with oral cancer.

Hyperbaric oxygen therapy involves a patient breathing 100% oxygen whilst inside a treatment chamber at a pressure greater than sea level pressure (i.e. greater than one atmosphere). The patient must receive the oxygen by inhalation within a pressurised chamber.

HBO has been used for a number of different therapeutic aims:

- to aid wound-healing;
- to prevent the occurrence of osteoradionecrosis (ORN);
- to treat established cases of ORN;
- prior to the placement of endosseous implants in order to facilitate implant survival.

Initially, HBO was used primarily for the prevention and treatment of ORN. It was proposed in the management of ORN, a condition characterised by endarteritis with tissue hypoxia and secondary fibrosis. A paucity of nutrient vessels and fibroblastic cells exists in the irradiated mandible. HBO was proposed for the management of ORN specifically because it has been shown to enhance neovascularisation in irradiated and other hypoxic tissues.

These properties fall into two categories:

- Leucocyte utilisation of hydrogen peroxide, and other reduced oxygen components as part of their bacterial activity; and
- Oxygen itself as an inhibitor of gram positive and gram negative growth.

With changes in radiation therapy dosage schedules, the incidence of ORN is falling. There are now increasing pressures to move towards HBO prior to the placement of endosseous implants. Some clinicians argue that this therapy is an essential part of a post-surgical reconstructive regime, and its use will lengthen implant survival.

In this instance, it is proposed that HBO will enhance osteogenesis, collagen formation and angiogenesis, prolonging implant survival.

Other clinicians believe that HBO is not essential for implant survival. The published literature reflects these differences in opinion with regard to the benefits and role of HBO in the treatment of patients with oral cancer.

The Centre for Health Services and Policy Research (Canada) undertook a review of the issue in 1992.¹ At that time, no conclusions regarding the use of HBO were possible. A number of additional reviews and case studies have since been published allowing the issue of HBO to be assessed further. This Guidance Note re-examines the literature evidence base regarding the use of HBO in the management of oral cancer. The objective is to address the following primary questions:

- Is the use of HBO effective in the prevention of osteoradionecrosis?
- Is the use of HBO effective in the treatment of osteoradionecrosis?
- Is HBO effective in promoting wound healing?
- Can the use of HBO prior to the placement of endosseous implants improve implant survival rates?
- Can the wider use of HBO lead to NHS resource saving (real or notional) through:
 - reduced demand for in-patient hospitalisation relating to osteoradionecrosis;
 - reduced length of in-patient stay for the treatment of failure to heal wounds;
 - improved implant survival rate and reduced demand for repeat procedures/prostheses.

2. BACKGROUND

2.1 DESCRIPTION OF THE UNDERLYING DISEASE

Oral Cancer is defined by ICD10 codes as: C00 (lip); C02 (tongue); C03 (gum); C05 (hard palate); C06 (floor of the mouth and other unspecified areas). The majority of cancers in and around the mouth are squamous cell carcinomas of the mucous membrane.

2.1.1 Incidence

As with malignant tumours of other sites, oral cancer is a disease which is more common in advancing age. It shows a sharp rise in incidence after the age of 40 years. Incidence in younger patients, however, is increasing, highlighting the important need for a satisfactory long-term cure and optimal restoration of function. More recent reports^{2,3} have suggested that there may be a rising trend in incidence in young men. Oral cancer is more common in men than women. It is largely preventable, the principal risk factors being the use of tobacco (primarily cigarette smoking) and the consumption of alcohol. In combination, alcohol and tobacco show a synergistic relative risk.

There is a time lag in obtaining reliable data. In 1993 there were 1,918 new cases of oral cancer registered in England and Wales, giving an incidence of 3.73 per 100,000 population.⁴ Regional incidence varies throughout the United Kingdom, with higher rates seen in the Northern Regions. The incidence and mortality rates from oral cancer are higher in Scotland than in England and Wales. In Scotland there is no clear pattern of occurrence, but in England and Wales there is a distinct North/South gradient for cancer of the mouth in males, with a higher rate in the North of the country.⁵ Registrations in the Trent Region for the period 1990-1998 are shown in Table 1.

The number of cases which would be registered per year for a health authority with a population of 500,000 is in the order of 19.

Table 1 Registrations of Oral Cancer in the Trent Region 1990 - 1998

Sex	Health Authority	1990	1991	1992	1993	1994	1995	1996	1997	1998
F	NORTH DERBYSHIRE	4	3	5	4	4	3	2	4	2
	SOUTHERN DERBYSHIRE	4	3	5	8	9	5	11	9	9
	LEICESTERSHIRE	11	10	20	7	8	13	20	16	7
	LINCOLNSHIRE	11	8	6	9	7	4	9	10	4
	NORTH NOTTINGHAMSHIRE	4	3		3	4	1	7	10	10
	NOTTINGHAM	9	5	10	4	6	5	10	7	9
	BARNLEY	4	2	1	3	4	1	4	7	1
	DONCASTER	4		6	3	2	2	3	3	4
	ROTHERHAM	2	3	1	3	3	8	2	6	1
	SHEFFIELD	11	3	7	6	1	5	5	7	3
F Total		64	40	61	50	48	47	73	79	50
M	NORTH DERBYSHIRE	5	9	8	8	11	14	5	6	3
	SOUTHERN DERBYSHIRE	10	8	9	12	9	13	12	12	20
	LEICESTERSHIRE	15	18	17	20	13	16	16	17	8
	LINCOLNSHIRE	5	18	10	11	12	7	12	12	9
	NORTH NOTTINGHAMSHIRE	6	8	9	15	10	8	6	3	3
	NOTTINGHAM	7	14	13	12	12	11	16	19	19
	BARNLEY	4	7	4	1	5	2	7	6	3
	DONCASTER	12	8	4	9	10	7	8	3	9
	ROTHERHAM	8	6	4	6	10	8	7	9	4
	SHEFFIELD	13	14	7	14	10	6	12	16	14
M Total		85	110	85	108	102	92	101	103	92
Grand Total		149	150	146	158	150	139	174	182	142

2.1.2 Prognosis and Mortality

Binnie and Rankin⁶ have reviewed survival rates for oral cancer. Their analysis suggests that there has been little or no change in the five-year relative survival rate for oral cancer since 1950.

Mortality rates differ according to site; with cancer of the lip showing the lowest rates. Mortality in the Trent Region for the period 1990 - 1998 is shown in Table 2.

Table 2 Deaths from Oral Cancer by District of Residence in the Trent Region

Sex	Health Authority	1990	1991	1992	1993	1994	1995	1996	1997	1998
F	NORTH DERBYSHIRE	1	1	4	0	0	1	0	1	1
	SOUTHERN DERBYSHIRE	2	3	1	1	1	6	2	4	4
	LEICESTER	8	6	3	10	8	6	5	8	5
	LINCOLN	2	4	6	2	4	4	5	5	0
	NORTH NOTTINGHAMSHIRE	1	2	0	3	1	2	4	3	0
	NOTTINGHAM	5	5	2	2	2	3	2	6	3
	BARNSLEY	3	0	1	1	0	3	1	2	1
	DONCASTER	0	4	0	2	2	0	0	0	3
	ROTHERHAM	1	0	1	1	0	2	3	2	2
	SHEFFIELD	3	4	4	2	2	5	3	8	1
		SOUTH HUMBER							0	3
F Total		26	29	22	24	20	32	25	42	21
M	NORTH DERBYSHIRE	2	3	6	4	4	3	3	4	2
	SOUTHERN DERBYSHIRE	5	0	5	3	5	4	4	9	6
	LEICESTERSHIRE	5	7	5	6	9	7	8	7	7
	LINCOLNSHIRE	1	3	5	4	5	5	5	5	5
	NORTH NOTTINGHAMSHIRE	4	3	3	5	3	3	4	3	1
	NOTTINGHAM	2	9	3	3	8	2	9	9	9
	BARNSLEY	1	0	1	0	1	0	0	4	5
	DONCASTER	6	1	3	6	7	4	1	1	3
	ROTHERHAM	8	6	4	6	10	8	7	9	4
	SHEFFIELD	0	1	3	0	1	3	2	3	4
		SOUTH HUMBER							4	6
M Total		28	31	42	34	52	33	44	60	53
Grand Total		54	60	64	58	72	65	69	102	74

2.1.3 Histology

Lip cancer and intra oral cancer have different risk factors and prognosis and should be considered separately.

2.1.4 Lip Cancer

The majority of carcinomas of the lip occur in males who work outdoors, who are fair skinned and exposed to excess sunlight.⁷ They are well differentiated and 90% occur on the lower lip. They tend to be less aggressive tumours and the nature of their site may lead to their early detection. Spread to surrounding tissues can occur and there is a potential for spread to local lymph nodes and distant sites.

Although lip cancer is virtually unknown in individuals younger than forty years, its incidence in men increases sharply with age. Overall lip cancer incidence, however, has diminished during the last two decades.

2.1.5 Intra Oral Cancer

A range of intra oral sites may be affected. The development of the primary site is not clearly understood, but widespread dysplastic mucosa (field change) may exist. A certain percentage of oral cancer patients develop multiple primary tumours. Additional primary tumours are most likely to be seen in patients with gingival, floor of the mouth, lingual or buccal carcinomas. Retrospective studies of head and neck cancer have demonstrated an incidence of between 7% and 20% for multiple primaries. The outlook after the diagnosis of a second primary is very poor. Intra oral cancer also has the potential for local, regional and metastatic spread. Between 28% and 83% of patients have been reported as developing a local recurrence at the primary site. Of those individuals who do suffer a recurrence, 90% will do so in the first two years post initial diagnosis. The presence of a secondary cancer is associated with a significant reduction in survival time. The sites of predilection for secondary tumours are elsewhere in the oral cavity, the hypopharynx and the larynx. The risk is higher in those who do not change their original tobacco habit than in those who reduce or discontinue smoking.

The site and size of the primary growth mainly influence the chance of metastatic spread. Cancers of the tongue and floor of the mouth show a higher tendency to local and regional metastasis than cancers of the lower lip. In midline or near midline cancers, contralateral and bilateral lymphatic spread is not uncommon.

The average duration of symptoms is usually around four to five months, ranging from a few weeks to up to one year.⁸ The majority of squamous cell carcinomas grow rather slowly. Occasionally, however, such cancers behave in a very aggressive way.

Some oral cancers arise de novo and present without any prior mucosal changes. However, there are a number of lesions which may precede oral cancer. The following oral lesions are considered to carry a potential for malignant change:

- Leukoplakia;
- Erythroplakia;
- Chronic hyperplastic candidiasis.

Erythroplakia is defined as 'any lesion of the oral mucosa that presents as bright red velvety plaques which cannot be characterised clinically or pathologically as any other recognisable condition'.⁹

Oral leukoplakia has been defined 'as a predominantly white lesion of the oral mucosa that cannot be characterised as any other definable lesion; some oral leukoplakias will transform into cancer'.¹⁰ Leukoplakias may occur either as a single, localised change of the oral mucosa, or as diffuse, often multiple lesions. The surface may be smooth or wrinkled. Many lesions are crossed by cracks or fissures. The site distribution shows world-wide differences, that are partly related to gender and tobacco habits. The percentage of malignant transformation also varies world-wide, probably as a result of the same factors.

Candida albicans is a normal oral commensal. Under certain conditions the organism may produce acute or chronic infection. In chronic hyperplastic candidiasis, dense chalky plaques are formed. Cawson¹¹ has drawn attention to the high incidence of malignant transformation in these lesions.

Other conditions have been considered as possible pre-malignant lesions and these include erosive and atrophic Lichen Planus, Oral Submucous Fibrosis, and Discoid Lupus Erythematosus. However, it is not clear what proportion of these lesions may proceed to malignant transformation.

2.1.6 Risk and Protective Factors for Oral Cancer

The possibility of an individual developing oral cancer depends upon his/her genetic predisposition and exposure to risk factors. There are a number of established and possible risk factors. The two major factors responsible for oral cancer are tobacco and alcohol consumption. It is well established that the use of tobacco whether chewed or smoked is an important risk factor for oral cancer and cancer of other extra-oral sites. Case control studies have demonstrated a dose response relationship for cigarette, cigar and pipe smoking as well as for alcohol consumption.¹² The carcinogenic effects of tobacco and alcohol are synergistic rather than additive.¹³

Poor oral hygiene and nutritional deficiencies have been cited as further risk factors.^{6,14} Iron deficiency has been shown to be linked to mucosal atrophy, which in its severest form is expressed as Plummer-Vinson Syndrome. Other risk factors such as candidiasis, herpes simplex or human papilloma virus infection have also been implicated in the aetiology of oral cancer. Other studies have shown a protective effect with the intake of vegetables and fish.¹⁵ The interaction of the implicated etiological factors and the host susceptibility is a complex one. The extent to which these factors exert a direct effect on the oral mucosa, or make it more responsive to other carcinogens is unclear.

2.1.7 Pathology

A clinical diagnosis of oral cancer must always be confirmed histopathologically. Malignant tumours of the oral squamous epithelium are intraepithelial carcinoma (carcinoma in situ), squamous cell carcinoma and variants of squamous cell carcinoma (verrucous carcinoma, spindle cell carcinoma and lymphoepithelioma).

The pathologist's ability to make a diagnosis of squamous cell carcinoma, is dependent on the receipt of an adequate oral mucosa biopsy specimen.

2.1.8 Prognosis and Mortality

Relative survival by district of residence within Trent is shown in Table 3.

Recurrence rates vary considerably. For those individuals who do suffer a recurrence, 90% will do so in the first two years post primary diagnosis. The presence of a secondary neoplasm is associated with a significant reduction in survival time. The presence of a node or metastasis is also associated with poor prognosis. Between 17% and 47% of patients

who appear to be free of nodal disease go on to develop positive nodes following treatment. The salvage rate of previous treatment failures is poor.

Table 3 Relative Survival for all Cases of Oral Cancer by District of Residence within Trent

Years Since Diagnosis	0	1	2	3	4	5
Trent (587 Cases) % Relative Survival 95% CL	100 (100.0-100.0)	73.5 (69.8-77.1)	64.5 (60.6-68.5)	59.9 (55.8-63.0)	56.9 (52.9-60.9)	53.3 (49.2-57.3)
N. Derbyshire (45 Cases) % Relative Survival 95% CL	100 (100.0-100.0)	68.6 (54.8-82.4)	60.5 (46.0-74.9)	57.4 (42.9-72.0)	56.2 (41.5-70.8)	50.2 (35.7-64.7)
S. Derbyshire (59 Cases) % Relative Survival 95% CL	100 (100.0-100.0)	83.3 (73.4-93.3)	65.8 (53.5-78.1)	65.3 (52.8-77.7)	55.4 (42.7-68.2)	49.8 (37.1-62.5)
Leicestershire (114 Cases) % Relative Survival 95% CL	100 (110.0-100.0)	76 (67.0-84.0)	65.6 (56.7-74.5)	61.2 (52.1-70.3)	61.1 (52.0-70.2)	59 (49.8-68.2)
Lincolnshire (78 Cases) % Relative Survival 95% CL	100 (100.0-100.0)	78.1 (68.6-87.6)	73.6 (63.3-83.8)	65 (54.1-75.9)	57.9 (46.8-69.0)	58.8 (47.7-69.9)
N. Notts (45 Cases) % Relative Survival 95% CL	100 (100.0-100.0)	64.8 (50.6-79.0)	59 (44.5-73.5)	55.7 (41.1-70.3)	55.3 (40.7-69.9)	49.5 (35.1-63.9)
Nottingham (73 Cases) % Relative Survival 95% CL	100 (100.0-100.0)	64.9 (53.8-75.9)	54.7 (43.3-66.2)	49.3 (37.8-60.7)	48.3 (37.0-59.7)	47.1 (35.9-58.3)
Barnsley (26 Cases) % Relative Survival 95% CL	100 (100.0-100.0)	79 (62.8-95.2)	68.2 (50.0-86.5)	65.8 (47.1-84.5)	63 (44.0-82.0)	62.8 (43.8-81.8)
Doncaster (43 Cases) % Relative Survival 95% CL	100 (100.0-100.0)	67 (52.7-81.2)	65.6 (51.2-80.1)	62.3 (47.5-77.0)	63.5 (48.8-78.3)	52.2 (37.3-67.1)
Rotherham (33 Cases) % Relative Survival 95% CL	100 (100.0-100.0)	84 (70.8-97.2)	79.2 (64.6-93.8)	71.7 (55.6-87.8)	70.8 (54.4-87.2)	66.5 (49.7-83.4)
Sheffield (71 Cases) % Relative Survival 95% CL	100 (100.0-100.0)	70.6 (59.8-81.3)	59.1 (47.5-65.0)	53.4 (41.7-65.0)	48 (36.5-59.6)	43.1 (31.9-54.4)

2.1.9 Treatment Modalities

Early diagnosis of oral cancer should lead to better treatment results. A high proportion of the population attends the dentist and the oral cavity is easily examined. Yet, between 27% and 50% of patients present for treatment with late lesions. Scully¹⁶ analysed this delay in diagnosis and notes that many patients are elderly and delay visiting their doctor or dentist. Many wear dentures and ascribe ulceration to their dentures. Practitioners may have a low

index of suspicion and initially treat a lesion with antibiotics or steroids. Finally, oral cancer is not usually painful in the initial stages.

Treatment options include surgery, radiation therapy, cryosurgery, CO₂ laser surgery and, more recently, photodynamic therapy. Chemotherapy is reserved primarily as adjunctive therapy. Traditionally, the main treatment approaches for oral cancer are:

- surgery alone;
- surgery combined with radiotherapy; or
- radiotherapy.

Current activity data do not allow the proportion of patients currently receiving each of these options to be determined, since no out-patient radiotherapy data are available. The elective management of the neck at the time of the operation is a controversial matter. The value of elective neck dissection in improving survival has not yet been shown clearly.

2.1.10 Surgery

Excision and reconstruction together form the basis of the surgical management of oral cancer. Following surgery, the patients with advanced cancers are, in general, given adjuvant radiotherapy within six weeks. A small proportion of patients require the provision of suitable prosthetic rehabilitation which may require the surgical insertion of osseointegrated implants as part of combined surgical/prosthetic rehabilitation. In oral cancer cases, implants are often the only way in which a patient can be rehabilitated satisfactorily with an oral prosthesis.

2.1.11 Radiotherapy

There are two different methods of delivering radiotherapy. Teletherapy, or external beam irradiation, delivers a beam or irradiation to the tumour from a machine. In brachytherapy, the source of radiation is placed within or near to the tumour.

Radiotherapy may be used as the only treatment for oral cancer, or in combination with other treatment modalities. It may be used pre- or post-surgery.

ORN is a serious medical condition which can develop as a result of radiation therapy for oral cancer. The majority of all trauma-induced osteoradionecrosis of the mandible is caused by tooth extraction in the radiated jaw. ORN has been described as the

development of a hypovascular hypoxic, hypocellular state due to progressive radiation-induced fibrosis.¹⁷ In practical terms it refers to exposed bone in a field of irradiation which has failed to heal for at least six months. Conventional treatment of ORN, generally referred to as 'conservative treatment', includes avoidance of local irritants, irrigation with a wide variety of agents, antibiotics and superficial sequestrectomies. If the disease does not respond, reconstructive surgery is undertaken.¹⁸

The incidence of ORN has declined since the 1970s. Clayman¹⁹ extensively reviewed the literature on ORN and reported that prior to 1968 the incidence of ORN was 11.8%, falling to 5.4% after that date. In addition, Clayman reported that the five most recent studies reported a prevalence of ORN of only 1.1% in 424 patients who had teeth removed after radiotherapy. These patients received aggressive preventative dental care and the extractions were performed by experienced oral and maxillofacial surgeons. Brown²⁰ also reports a decline in incidence levels, resulting from the more efficient use of radiation and improved dental care and follow-up.

2.2 CURRENT SERVICE PROVISION

Research in the Trent Region has shown that approximately one third of head and neck surgeons prescribe HBO. A survey of ENT, oral and maxillofacial surgeons in Trent showed that 12 out of the 16 respondents did refer patients for hyperbaric oxygen. There were 32 referrals in the last 12 months from consultants in the Region who responded to the survey.

Table 4 **Number of Trent Patients Referred by Consultants Responding to Survey**

No. of Patients Referred	Consultants Referring
0	1
1	5
2	3
3	1
4	2
10	1
Unknown	1

More detailed results of the survey are shown in Appendix A.

The majority of responses (13 of 16) to the Trent survey were from Maxillofacial consultants, suggesting that the majority of patients with ORN are treated within this specialty. Consultants in the Trent Region refer patients for the treatment of osteoradionecrosis (11 of 12 respondents), pre- and post-radiation therapy in order to prevent osteoradionecrosis (4 of 12), pre- and post-surgery in order to promote wound healing (5 of 12), and prior to the placement of endosseous implants in order to improve implant survival (7 of 12).

Trent residents have been referred to a wide number of chambers including chambers at Plymouth, Bangor, Peterborough, Hull, Sheffield and Lincoln.

The number of Trent residents attending the HBO facility at Plymouth over the last 2 years was as follows:

Table 5 Number of Trent Patients Receiving Treatment at Plymouth Chamber Since 1998

Patient	Year	Area	No of 'Dives'
1	1998	Head	38
2	1998	Head	35
3	1998	Mandibular	13
4	1998	Jaw	39
5	1998	Mandibular	38
6	1998	Jaw	42
7	1998	Mandibular	33
8	1999	Skull	40

The numbers of patients attending the HBO facility at Peterborough since 1997 were:

1997	3
1998	6
1999	4

This comprised patients from Leicestershire, Nottingham and Lincolnshire Health Authorities.

It is not known how many patients have been referred to local chambers run by the Multiple Sclerosis Society.

2.2.1 The British Hyperbaric Association

The British Hyperbaric Association (BHA) provides information regarding the availability of hyperbaric oxygen facilities in Britain. The BHA provides lists of the 25 member chambers which each offer emergency hyperbaric therapy. This list includes the chambers at Hull, Plymouth and Peterborough.

A document entitled 'A code of good working practice for the operation and staffing of hyperbaric chambers for therapeutic purposes'²¹ has been adopted by members of the Association. The code has been accepted by the UK Department of Health.

Table 6 Number of Patients Receiving Hyperbaric Therapy at BHA Chambers in Great Britain

	1994	1995	1996	1997
Diving Related Emergencies	262	270	258	349
Hyperbaric Oxygen Emergency Cases	315	343	385	352
Hyperbaric Elective Cases	346	425	639	673

Table 7 Indications for Hyperbaric Therapy in Patients in 1997 at BHA Chambers

	Number	Percentage
Decompression Illness	349	25.4%
Carbon Monoxide Poisoning	352	25.6%
Gas Embolism (Non-diving)	0	0%
Soft Tissue Infections	32	2.3%
Post Radiotherapy	112	8.2%
Other ECHM or UHMS indications	271	19.7%
Research	37	2.7%
Other Indications	592	35.8%
Total		100%
ECHM = European Committee for Hyperbaric Oxygen		
UHMS = Underseas and Hyperbaric Medicine Society		

2.3 THE DELIVERY OF HYPERBARIC OXYGEN

There are four conditions where hyperbaric oxygen is used following radiotherapy for oral cancer. They are:

- the treatment of osteoradionecrosis;
- prophylactically before and after surgery to prevent osteoradionecrosis;
- the promotion of wound-healing;
- before and after placement of implants.

The use of HBO for the treatment and prevention of ORN has been advocated by some clinicians since the early 1970s.

2.3.1 Criteria for Treatment

The referral of patients in these categories varies widely; apparently, this is dependent on the lead surgeon involved with the case. Many individuals treated for oral cancer receive adjunctive radiotherapy. When the mandible is in the path of irradiation then well-described changes in the blood-supply to the bone cells occur.¹⁷ This results in an impaired ability for oxygen to reach the bone being regenerated. Regardless of its specific type, radiotherapy causes a decrease in the vascular supply of all tissues and compromises many other factors responsible for wound healing.^{22,23} As radiation dosage increases, fibroblast activity diminishes, and there is a progressive obliteration of tissue capillaries resulting in a decrease in their total number. Costantino et al.¹⁷ emphasised that radiation-damaged tissues cannot reverse these changes over time without therapeutic intervention. The irradiated bone loses its capacity to replace normal collagen and cellular components. When the bone breaks down from routine wear, it does not have the capacity to repair itself fully, owing to limitations imposed on it by the radiation-induced hypoxic, hypovascular state. The resultant bone and wound are incapable of increasing their metabolic requirements and nutrient supply to the point at which healing can occur.

The blood supply to the mandible is of such a type as to make radiation damage most important. The dominant blood supply to the mandible varies with the region of the bone. The area of the posterior part of the mandible has a blood supply from the surrounding musculature, but that to the body of the mandible is largely from the inferior alveolar artery²⁴. Severing this supply as would happen during surgery in this area, concomitant with stripping the periosteum from the bone, can reduce greatly the blood supply to the bone distal to the site of the osteotomy. In addition, it has been shown that there are age-related

changes in the intramedullary blood supply of the mandible.²⁵ A significant proportion of adults over 55 have no functional intramedullary blood supply to the anterior part of the mandible. This is of significance as the incidence of oral cancer in the UK is greatly skewed towards the elderly.²⁶

Because of these changes in the blood supply, some surgeons chose to improve the regeneration of arterioles by using hyperbaric oxygen²⁷ and prolonged courses of intravenous antibiotics.

2.3.2 The Theory of Hyperbaric Oxygen Useage

In a normal uncomplicated non-radiated wound, there is a steep oxygen gradient between the normal and the damaged tissue. A steep oxygen gradient appears necessary for the regeneration of blood capillaries and their penetration of the hypovascular area.²⁸ In the normal wound this may be 0 to 5mm Hg in the centre, with levels of 50 to 60 mm Hg in the adjacent normal tissue, as measured by needle electrode or transcutaneous oximetry. In radiation damage, steep gradients are not found.²⁹

Marx et al.³⁰ have shown that the oxygen tensions in the centre of an uncomplicated radiation-damaged area are about 5 to 10 mm Hg. They found a gradual improvement at 1 cm intervals from the centre to the edge of the irradiated field which showed a gradual improvement in tissue oxygen tensions until the normal values of 55 to 60 mm Hg were found at the edge. During exposure of the tumour to hyperbaric oxygen at 2.4 atmospheres they found a 7 to 10 fold increase in oxygen tension at each 1 cm increment. This rise was also seen in the non-irradiated tissue outside the irradiated field. The shallow oxygen gradient previously found was magnified into a step gradient at each increment. This happened increasingly after repeated exposure to hyperbaric oxygen, until after 20 to 24 treatments, the oxygen gradients at the increments were largely eliminated.³⁰

The mechanism for hyperbaric oxygen to enhance revascularisation of irradiated tissues is through the creation of steep oxygen gradients which are present normally in non-irradiated wounds. This is said to stimulate the process of tissue angiogenesis. A controlled study has shown that 100% oxygen at normal atmospheric pressure does not produce angiogenesis in irradiated tissue. Results were no different from those seen in air-breathing controls.³¹

Kindwall argues that this mechanism demonstrates that there will be no effect until significant damage has already occurred. For this reason, complete prophylaxis would not appear to be feasible. He points out that more research is necessary to determine at which

point post-radiation HBO becomes useful, where vascular damage has not yet posed a clinical problem such as ulceration or osteoradionecrosis.²⁹

2.3.3 The Delivery of Hyperbaric Oxygen

There are two types of HBO chambers in use, reflecting its different uses. The principal development has been for treating divers with decompression sickness (the 'bends'), and multiplace chambers (see figure 1) most commonly exist in well-established centres for diving, such as Plymouth, Bangor (North Wales), Aberdeen and Hull. The large chamber is pressurised with compressed air and the patients receive oxygen from a face-mask or hood, which is a tightly-sealed head tent. The chamber pressure can be brought up to 2.4 atmospheres, which is sufficient for treatment involving osteoradionecrosis. An attendant is present inside the chamber and, at some centres, a physician is present also. There can be problems of claustrophobia for some patients, but an advantage of the multiplace chamber is that ill patients requiring nursing or close supervision can be treated. Patients sent to a multiplace centre usually require bed and breakfast accommodation to be arranged and funded.

The other type of chamber is the monoplace one (see figure 2). These are present in many cities in the UK, and many are owned and operated by the Multiple Sclerosis Therapy Centre, a charitable organisation, for use by sufferers of Multiple Sclerosis. If the facility is within reasonable travelling distance, the patient can return home between 'dives'.

The unit comprises a small plastic chamber which is filled with oxygen under pressure of 2 to 2.4 atmospheres. These units are small and are run by nurses or other workers and are not supervised by a physician. They can cause greater claustrophobia than the multiplace chambers.

Treatment Regime

The treatment regime in both types of chamber is the same. The Marx Protocols³⁹, which combine HBO and surgery in the prevention and management of osteoradionecrosis have become the standard of care. For the prevention of osteoradionecrosis, the 20/10 protocol is advocated: 20 'dives' of 90 minutes each pre-operatively, followed by 10 'dives' post-operatively. For the treatment of established osteoradionecrosis, the 30/10 protocol is advocated with 30 initial 'dives' (See Appendix B for further details).

Figure 1 **Example of Monoplace Chamber**

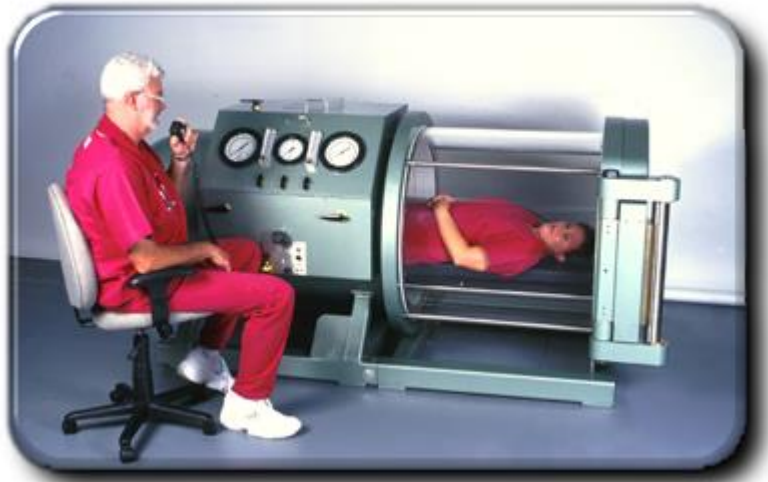


Figure 2 **Example of Multiplace Chamber**



2.3.4 Length of Benefit

The effects of hyperbaric oxygen are usually evident after eight treatments and a plateau is reached after about 20-24, beyond which no further benefit is observed. Kindwall²⁹ found that the level of angiogenesis four years after completion of the hyperbaric protocol was the same as at the completion of the protocol. Further studies were required to ascertain the full extent of benefit.

2.3.5 Cost

Detailed costs of treatment are available, and three examples are given:

a) *Medically Supervised at the Diving Diseases Research Centre at Plymouth*

20 sessions 2.4 atmospheres per day pre-op.
10 sessions 2.4 atmospheres per day post-op.

@ £55 per session = £1,650
Accommodation @ £50 per day = £1,500
Total = £3,150.

b) *Medically Supervised at the Peterborough District General Hospital*

The total cost is around £4,500. A breakdown of costs has been requested.

c) *Non-medically Supervised, at Sheffield Multiple Sclerosis Therapy Centre*

20 sessions 2.4 atmospheres per day pre-op.
10 sessions 2.4 atmospheres per day post-op.

@ £17 per session = £510
Accommodation = nil
Total = £510.

2.3.6 Side-effects of HBO

The use of HBO is not without complications, risks or contraindications. These complications may arise from environmental or therapeutic factors.

2.3.6.1 Environmental

Patients receiving HBO enter a specialised environment. HBO chambers may be monoplace (patient only enters chamber) or multiplace (patient and provider enter chamber). There are potential changes within and without the chamber - the oxygen rich air may become explosive; sudden loss of pressure can result in decompression.

2.3.6.2 Therapeutic

There are a number of medical conditions and contraindications for the use of HBO. These are:

- Pneumothorax;
- Severe chronic obstructive pulmonary disease;
- Optic neuritis;
- Acute viral infection;
- Upper respiratory infection;
- Pregnancy;
- Congenital Spherocytosis;
- Patients with psychiatric problems;
- Patients with prior thoracic or middle ear surgery.

2.3.6.3 Complications

Most of the complications arising from HBO therapy result from barometric pressure changes or oxygen toxicity. Some of the possible complications associated with HBO therapy are detailed below:

- Eustachian tube dysfunction;
- Tympanic membrane rupture;
- Oxygen toxicity;
- Ear, sinus or tooth pain;
- Pneumothorax;
- Middle ear haemorrhage;

- Deafness;
- Changes in vision;
- Nausea, fatigue, claustrophobia.

Middle ear barotrauma is the most common side-effect of HBO. It may be prevented by teaching autoinflation techniques or by the use of tympanostomy tubes for individuals who are unable to autoinflate their middle ear compartment.

Progressive myopia has been observed in some patients undergoing prolonged periods of daily HBO. It usually reverses within a period of a few days to several weeks after the last therapy.

A complete medical history and physical evaluation of the patient and knowledge of potential problems is essential.

2.3.7 Side-effects

A particular problem resulting from the administration of HBO is the feeling of claustrophobia which may result. For some patients this feeling is unacceptable and they are unable to complete the course of therapy.

In general, whilst side-effects may occur, the benefits of HBO therapy are such that the potential for side-effects can be considered to be an acceptable risk. However, patients should be provided with information relating to risk as part of their informed consent for HBO therapy.

Evidence on side-effects is reported in Table 8.

Table 8 Evidence on Adverse Events Related to HBO

Author Date Country	Aims of Study	Patient Population	Study Design	Intervention	Outcome Measures	Results	Comments
Giebfried et al. ³² 1986 USA	Case series – review of complications post HBO.	101 patients.	Retro-spective.	HBO for head and neck disease.	15 year retrospective.	3 patients developed serious complications; (all 3 experienced seizures; 1 developed a stroke and 1 sustained myocardial infarction). 2 patients developed minor complications (eustachian tube dysfunction).	
Foster ³³ 1992 USA	To discuss the contraindications for, and complications resulting from, the use of HBO.			HBO.			Contra indications and complications discussed overall safety observed.
Headley et al. ³⁴ 1991 USA	To study the effect of HBO on the growth of human squamous cell carcinoma Xenograft.	Xenografts transplanted In nude mouse host.	3 mouse groups: HBO given to half mice in each group.	HBO.	Xenografts growth.	Xenograft growth almost linear in all mice. No statistical difference between mice given HBO or control mice.	Study suggests that HBO has no effect on established tumour xenograft growth.
Blanshard et al. ³⁵ UK 1996	To measure the incidence and severity of middle ear barotrauma in patients undergoing HBO.	82 Patients.	Pro-spective.	HBO.	The incidence of otalgia 1 hr; 19 hours after treatment.	24 patients required insertion of ventilation tubes for intractable otalgia.	
Ross et al. ³⁶ 1996 USA	To examine the effect of HBO on myopia.	8 subjects receiving out-patient HBO (all had mandibular ORN or non healing soft tissue necrosis).	Pro-spective.	Vision tested prior to, at the mid point and end of HBO therapy. Keratometry undertaken.	Myopia as at days 1, 10, 20.	2 of the eight subjects showed increased myopia.	Previous studies had examined patients who had 40 sessions of HBO; this study looked at patients receiving 20 sessions of HBO.

3. EFFECTIVENESS

3.1 METHODS FOR REVIEWING EFFECTIVENESS

3.1.1 Search Strategy

Initial topic searches for the use of HBO, identified very limited randomised controlled trial (RCT) evidence on its efficacy. Therefore, a series of systematic searches have been undertaken to identify published evidence relating to trials and case series studies of the use of HBO and the health economics of HBO therapy.

The searches involved subject searches of the following medical and health databases: MEDLINE; EmBASE; COCHRANE, and SCIENCE CITATION INDEX, together with examination of the relevant health technology assessment agency resources: such as web sites, booklets etc.

3.2 RESULTS

3.2.1 Quantity and Quality of Research Available

Initial searching revealed a large number of research papers relating to hyperbaric oxygen for the prevention and treatment of ORN, wound healing and dental implants. Studies were limited to those reported in English on human patients.

The presence of only a very small number of RCTs in the reported results of the studies substantially weakens the quality of evidence.

3.2.2 Assessment of Effectiveness

(a) Treatment of Osteoradionecrosis

Case Studies

The evidence provided by case studies is summarised in Table 9. It comprises a relatively small number of retrospective case studies, published since 1975. Much of the work was carried out in the 1970s and 1980s. Due to the nature and incidence of the disease they

tend to comprise small numbers of patients over long time periods. Many of the studies suffer from inadequate detail on methodology and inconsistent endpoints.

The evidence from these case studies does offer some support for the use of HBO in the management of ORN. Some cases of ORN may respond to conservative treatment.^{37,38} However, where conservative treatment has failed, HBO, as an adjunct to antibiotic and surgical therapy, may offer additional benefits to some patients.^{39,40,41} However, the strength of the evidence is weakened by the lack of RCTs.

Health Technology Assessment Reviews

Two Canadian Health Technology Assessment reviews of hyperbaric oxygen treatment have been carried out. The conclusions are summarised below:

Sheps British Columbia Office of Health Technology Assessment Discussion Paper¹

This paper concluded that 'Given the complexity of the post-radiation ORN from a physiological and clinical perspective, and since there would seem little else you could offer the patient, HBO may well be a useful adjunct in this situation'. The authors' review of the evidence concluded that HBO for ORN of the mandible did seem to have some support, but that further work comparing treatments, with and without HBO, was required.

Mitton Health Technology Assessment Publication - Hyperbaric Oxygen Treatment in Alberta⁴²

This report considered the application of HBO for 12 conditions, one of which was ORN. It concluded that 'although results are promising, further studies are required to provide a clear picture of the effectiveness of HBO for this condition.'

Other Reviews

Myers and Schnitzer⁴³

Myers (Chairman of the Department of Hyperbaric Medicine at the Maryland Institute for Emergency Medical Services Systems) and Schnitzer report radiation necrosis as a condition for which HBO is known to be successful, referencing Greenwood and Gilchrist⁴⁴ and Marx and Ames.²⁷

Balogh and Sutherland⁴⁵

This review concludes that conservative management of ORN is recommended unless the disease is advanced or progressive. Treatment by HBO is 'complex and time-consuming

and results are confounded by the concurrent use of local antiseptic/antibiotic measures and surgery.'

***Grim et al.*⁴⁶**

This review reports on evidence from Marx⁴⁷, Farmer⁴⁸ and Davis⁴⁹ and concludes that 'the role of HBO as an adjunctive therapy in the treatment and prevention of osteonecrosis has been impressively documented.'

***Myers and Marx*⁵⁰**

This is an overview of Marx's work outlining the Marx Protocol and detailing the cost analysis of Marx and Johnson 1988.⁵¹

***Tibbles and Edelsberg*⁵²**

This is a review of the mechanisms of action and evidence of clinical efficacy. It concludes that the prevention and treatment of ORN is one of the uses of HBO for which the 'discovery of beneficial cellular and biochemical effects has strengthened the rationale for administering hyperbaric oxygen as primary therapy...' Osteoradionecrosis is listed as one of the diseases for which 'the weight of scientific evidence suggests that hyperbaric oxygen may be helpful'.

Table 9 (a) Evidence of the Effectiveness of HBO for the Treatment of Osteoradionecrosis

Author, Date Country	Aims of study	Patient population	Study design / period	Intervention	Outcome measures	Results	Comments
London et al. ⁵³ 1998 USA	Review use of HBO in management of ORN of the head and neck.	16 patients with ORN.	Retrospective study.	HBO alone or HBO and surgery.	Patient and physician grading scores.	All patients showed clinical improvement with decreased pain following HBO therapy.	
Wong et al. ⁵⁴ 1997 Canada	To determine effectiveness of nonsurgical/ nonhyperbaric oxygen conservative management. Correctly define ORN.	32 patients with mandibular ORN, seen between Aug 1960 and Sept 1995. Mean age 64, range 46-92.	Retrospective records analysis.	Conservative management and resection, HBO therapy or both were initiated in cases of pain, failure to respond to conservative measures and progressive deterioration.		2/32 died before final analysis; of those alive 65.5% patients were spared resection, 48.3% had lesions resolved, 3.4% improved, and 13.8% asymptotically stabilized. Sequestrum production allowing 'gentle' removal predicted a more favourable clinical course when managed conservatively compared with nonsequestering lesions (p<0.05). Of 11 patients receiving combination radiotherapy, 5 had resolution, 3 went on to resection and HBO, 2 had lesions stabilize and 1 died with ORN. Complete resolution 48% of 29 patients.	HBO is not universally applicable to all ORN cases for fiscal and physical limitations.
Aitasalo et al. ⁵⁵ 1998 Finland	Evaluate effectiveness of surgical decortication and free periosteal transplantation combined with antibiotics as well as pre-and post-operative HBO in treatment of ORN and chronic osteomyelitis (COM).	69 patients: 36 patients with ORN, 33 patients with COM of mandible or maxilla. Aged 7 – 72, mean 54 yrs. Median follow-up time = 34 months, min of 10 months. 1981-1998.	Retrospective study.	HBO and surgical therapy (decortication of affected bone). Periosteal transplantation and antibiotics.	Symptom-free success rates.	33 ORN patients (92%) and 26 COM patients (79%) remained symptom-free after first treatment period. 3 failed ORN patients were successfully treated with a free microvascular flap. The seven failed COM patients were retreated, and 5 of them have occasional clinical symptoms.	A combination of HBO and decortication with periosteal grafting is successful treatment for ORN and COM. Combination used in study allowed HBO to be reduced, and, therefore, costs too.
Thorn et al. ⁵⁶ 1997 Denmark	Measure effect of HBO on transmucosal oxygen tension in irradiated human oral mucosa.	10 patients with mandibular osteoradionecrosis. 4 women, 6 men. Aged 46-72.	Physiological study.	HBO, three also had sequestrial surgery after 20 'dives', one of which did not heal after that.	Level of gingival surface transmucosal oxygen tension. Patients measured against 5 healthy control individuals.	Transmucosal oxygen (T.O.) tension increased significantly after 5 'dives'. P < .05 compared with pretreatment values. After 30 'dives', the increases were from a mean of 50% to a mean of 86% of the T.O. tension of a normal healthy gingiva. Smallest increase was from 41%-69%. This patient did not heal after sequestromy. Maximal increase range was 53% to 100%.	Patients with subschaemic tissues, e.g. study pop. with post-irradiation mucosal and osseous necrosis, may benefit from HBO.

Epstein et al. ³⁸ 1997 Canada	Assess long-term progress of patients who experienced ORN of the jaw.	20 live patients (out of original 26 patients) with ORN of the mandible.	Long-term follow-up study of patients treated between 1975 and 1988.		% resolved, chronic persisting (unresolved) or active progressive.	Recurrence occurred in 10% of patients alive at end of 5 year follow-up 60% (12/20) remained resolved 10% (2/20) improvement in clinical staging 20% (5 of 20) chronic persistent ORN (stage II).	Paper supports treatment of chronic non-progressive ORN without HBO intervention.
Wood and Liggins ⁴¹ 1996 UK	Does HBO have role in management of ORN?	12 episodes of ORN treated with HBO in 11 patients over 8 years. All patients have previously received conservative treatment.	Retrospective study.	HBO – Marx Protocol.	% cure rate.	100% cure, with 83% of cases requiring surgery to remove necrotic bone.	
van Merkesteyn et al. ⁵⁷ 1995 Netherlands		29 patients with ORN of the mandible, 26 of whom had previously received conservative treatment or surgery.	Retrospective case study.	HBO, surgical debridement and antibiotics in 27 of 29 cases 24 of 27 HBO patients : 30/10 protocol.	% resolved % patients experiencing loss of continuity of the mandible.	69% (20 of 29) patients resolved Resection necessary in 23 patients 31% loss of continuity.	
Mounsey et al. ⁵⁸ 1993 USA	To establish whether HBO is beneficial in management of ORN, and to define clearly the role in which HBO is most valuable.	41 patients with mandibular ORN from 1980 to 1985.	Retrospective analysis.	HBO in addition to a combination of oral hygiene regimens, dental therapy, antibiotics and surgery.	Exposed bone, closure of fistulous tract, complete relief of symptoms, especially pain.	83% of patients had significant improvement with HBO therapy, judged by at least 50% decrease in the size of exposing of fistulous tract, or complete relief of symptoms. 6 patients (15% of 83 %) showed complete resolution of ORN. 17% of them did not benefit from HBO; all 7 patients had evidence of dead bone. Surgery was combined with HBO in 35 cases, 85%.	HBO is of benefit. Cases of mild ORN will heal with HBO alone, severe cases require surgery to remove dead bone. Authors suggest regular follow-up, in order to detect ORN at time when HBO can arrest disease.
McKenzie et al. ⁵⁹ 1993		26 patients with ORN of the mandible treated with HBO.		HBO.		69% (18 of 26) resolution of first episode of ORN. 12% (3 of 26) improvement in staging 19% (5 of 26) no improvement.	

Marx and Johnson ³⁰ 1988	The role of HBO in oral and maxillofacial surgery.	268 patients with refractory ORN. Protocol for ORN, 3 stages combining HBO and surgery. Over 8 yr period.		HBO and surgery.	1. Freedom from pain, 2. Retention/ reconstruction of mandibular continuity. 3. Restoration of mandibular function and wearing of dental appliances, if required. 4. Maintenance of intact mucosa and skin over the bone.	196/268 which had been unresponsive under other institutions were resolved under this scheme. Resolution in Stage I for 38 (14%), in Stage 2 48, (18%), Stage III 182, (68%).	Not much more expensive compared to conventional practice when one looks at all hidden costs. Resolution rate is higher over years and remaining quality of life is higher. NB. HBO used in majority of cases where other treatments have already failed.
Beumer et al. ³⁷ 1984 USA		70 patients suffering from 83 episodes of ORN, radiation-induced bone necrosis of head and neck, maxilla (5), mandible (78). 11 yr. period, ending July 1982. Follow-up for 1 yr. at least.		Saline irrigations, antibiotics, antiseptic/biotic dressings. If disease progressed, HBO and surgical sequestrectomy.	Healed, worse, mandibular resection necessary.	22/83: postirradiation extractions. 19/83: periodontal disease. 17/83 preradiation extractions. Mandibular resection rate was 44% in bone necroses where external radiation dose to affected bone exceeded 7000 Rad. Overall mandible resection = 23/78. 31 episodes healed, 15 were stable or improving with conservative treatment, 37 patients required the more aggressive therapy. Of these 24/37 had HBO, 13/37 had radical resection. 9 patients received HBO before and after sequestrectomy. Of these in 7/9 infection was controlled without loss of mandibular continuity. 4 patients had sequestrectomy without HBO; all 4 required resection of the mandible.	HBO is useful adjunct to therapy, particularly if combined with surgical sequestrectomy, for large exposures extending beyond the mucogingival junction.
Marx ³⁹ 1983 USA	Investigation into effect of HBO and combination of HBO and surgery.	58 patients with refractory osteoradionecrosis.	Investigatory HBO protocol based on pathophysiology elucidated in previous report. 3 Stages: I = HBO, II = surgery further HBO, III = surgery further HBO.	HBO and aggressive surgery.	Resolution criteria: 1. Freedom from pain. 2. Retention or reconstruction of mandibular continuity. 3. Restoration of mandibular function. 4. Maintenance of intact mucosa over all bone for length of follow-up min 18 months.	Resolution achieved in Stage I for 9 patients, 15%. 8 patients in Stage II 14%, and 41 patients in stage III 70%. 41/58 required partial mandibulectomy. All discontinuous mandibles were reconstructed and function restored in all patients. HBO enhances healing, but without aggressive surgery will not resolve disease process alone, (only 15% responded in stage I).	Results suggest HBO and surgery should be primary treatment. Need to get right timing, patient, disease state and combination of HBO and surgery.

Davis et al. ⁴⁹ 1979	Test HBO therapy as adjunctive therapy.	52 cases radiation necrosis; 39 of head and neck, 23 ORN of mandible. 16 soft-tissue radionecrosis of head and neck.	1-23 months follow-up so far, 24 months follow-up in total.	HBO, (surgery and antibiotics).	Wound healing enhancement. Arrested/ failed.	22/23 ORN of mandible excellent initial response. 1-23 months, 17/20 arrested, 3/20 failed. At 24 months 3/20 arrested. 15/16 soft-tissue radionecrosis, good response.	Recommend use of HBO as soon as possible after such a wound begins to deteriorate.
Farmer et al. ⁴⁸ 1978	Investigate effects of HBO therapy in management of radiation necrosis.	13 cases of refractory mandibular radionecrosis. 3 cases of head and neck radionecrosis. 3 others: radionecrosis of foot, hip and vagina. Age range 43-68.	Pilot study Follow-up 1-27 months.	HBO.	Improvement in: Pain, Soft tissue disease, X-ray changes.	Of 13 cases: Soft tissue disease: 7 cases complete healing, 11-27 months. Transient healing in 3, moderate-marked improvement in 3. Marked pain relief in 6, moderate in 4, slight in 1. Radiographic improvement, slight to moderate in 10, none in 3. 3 cases head/neck, significant improvement in lesions. Extra 3 only good results in vagina case.	HBO is beneficial adjunctive treatment in radiation necrosis of bone and soft tissue, particularly of head and neck. Although potentially expensive and complex.
Hart and Mainous ⁶⁰ 1976	Investigate treatment of radiation necrosis with HBO.	69 patients with radiation necrosis: of mandible 46, of chest 6, of pelvis and lumbar areas 6, CNS 6, larynx 5.	Jan. 1969 through Aug. 1975.	HBO (surgery and antibiotics).	1. Intractable pain 2. Exposed bone, 3. Orocutaneous fistula, 4. Pathological fracture.	Mandible 46 patients: 2% had 1 only, 43% had 1 and 2, 13% had 1, 2 and 3. 22% had 1, 2 and 4. 20% had 1, 2, 3 and 4. Chest wall: all grafts healed primum. Pelvis and Lumbar.	HBO supports the healing of ischemic tissues, however, it does not relieve clinician of necessity of surgery or admin. of antibiotics.
Mainous and Hart ⁶¹ 1975		14 patients intractable ORN of mandible.	Follow-up 1-8 yrs	HBO.	Intractable pain and exposed bone.	All 14 healed.	Very favourable changes in the healing environment.

Table 9 (b) Evidence of the Use of HBO in the Prevention of Osteoradionecrosis

Author Date Country	Aims Of Study	Patient Population	Study Design	Intervention	Outcome Measures	Results	Comments
Maxymiw et al. ⁶² 1991 Canada	To assess surgical techniques for the management of post radiation dental extractions without HBO.	72 patients who had extractions after head and neck radiation therapy.	Prospective.	Prophylactic antibiotic (Penicillin V) coverage 1 hour prior to surgical procedure and then 600 mg qds for 1 week. Low concentration local anaesthetic (prilocaine) atraumatic surgical technique.	Healing; No ORN.	No ORN	
Stofka and Liang ⁶³ 1994 USA	Review and case report.	15 year old girl.	Case report.	HBO prior to dental treatment.		Uneventful recovery post dental treatment.	Recommends HBO in post irradiated patients prior to dental treatment.
Kraut ⁶⁴ 1985 USA	To assess the prophylactic use of HBO.	3 cases - male.	Case Study.	Prophylactic HBO prior tooth extraction.	Healing without ORN.	Healed – no complications.	
Marx et al. ⁶⁵ 1985 USA	To evaluate the use of HBO in the prevention of ORN.	74 patients who had an indication for removal of one or more teeth from a segment of irradiated mandible.	RCT.	HBO Compared with prophylactic penicillin.	Development of ORN; 3 weeks; 6 months.	2 patients (HBO Group) developed ORN (5.4%). 11 patients (non HBO) developed ORN (29.9%).	Not clear whether observers were blinded. The study is now 'out of date' since the incidence of ORN has now fallen dramatically.

Table 9 (c) Evidence of the Effectiveness of HBO for Implants

Author Date Country	Aims of study	Patient Population	Study Design	Intervention	Outcome Measures	Results	Comments
Granstrom et al. ⁶⁶ 1999 Sweden	Report of 78 cancer patients.	78 cancer patients rehabilitated using osseointegrated implants.	Case control Study.	Irradiated non-irradiated, irradiated and HBO.	Review of success of individual implants.	In irradiated-only patients, implant failure was 54%. In non-irradiated patients it was 14%. In irradiated and HBO patients, it was 8%.	This study showed that although implant insertion in irradiated bone is associated with a higher failure rate, HBO treatment can reduce the failures.
Jisander et al. ⁶⁷ 1997 Sweden	Report of 17 oral cancer patients.	17 patients with oral cancer were treated by irradiation. Implants were placed for rehabilitation.	Case control study.	HBO in 7 patients All received implants. 8 patients received more than 50 Gy and 9 less than 50 Gy.	Patient follow-up for average of 21 months.	103 implants were placed. There was a 92% survival rate in the maxilla and 97% in the mandible.	The paper concluded that the risk of implant failure might be reduced by adjunctive HBO treatment. It also concluded that the successful placement of implants in patients receiving more than 50 Gy was probably the result of HBO therapy.
Marker et al. ⁶⁸ 1997 Denmark	Report of 12 oral cancer patients.	12 patients with oral cancer involving the mandible were treated by radiation and/or surgery. 19 implants were placed.	Case control study.	HBO was not used. Radiation dosages of 40-50 Gy were used.	Patient follow-up from 14 to 44 months. Implant success was determined.	All 19 implants were successful, and osseo-integrated without signs of infection or osteoradio-necrosis.	The paper concluded that patients who have been irradiated can successfully receive titanium implants. The use of HBO appears unnecessary with radiation doses of up to 50 Gy.
Arcuri et al. ⁶⁹ 1997 U.S.A.	Report of 4 oral cancer patients.	4 patients with oral cancer involving the mandible. 18 implants were placed.	Retrospective follow-up study.	HBO was used for all patients. No radiation dosage was given.	Patient follow-up from 1-5 years.	17 implants were successful. One failed to show osseo-integration.	This small study suggests that titanium endosseous implants placed in previously irradiated mandibles in conjunction with HBO therapy may be successful. Further research is required.

Esser and Wagner ⁷⁰ 1977 Germany	Report of 221 implants in mandibles, following oral cancer.	60 patients with oral cancer involving the mandible between 1985 and 1995.	Retrospective follow-up study.	HBO was not used for any patient. Radiation dosages of 60 Gy were given.	Patient follow-up up to 5 years.	2 patients suffered osteoradionecrosis and 1 soft tissue necrosis. 18 implants failed to osseointegrate and 15 lost osseointegration over a 30 month period.	The report considered that the incidence of osteoradionecrosis was low. The use of HBO had not been considered then. The report speculated that the use of HBO could prevent soft-tissue necrosis or improve healing. In patients at risk of osteoradionecrosis, HBO could be useful.
Taylor and Worthington ⁷¹ 1993 USA	Report of 21 implants placed in 4 irradiated patients.	4 patients with oral cancer treated by surgery, and irradiation.	Case control Study.	HBO in 3 patients. Radiation doses of more than 60 Gy were used.	Patient follow-up 3-7 years to review success of implants.	No implants lost. The patient without HBO experienced soft-tissue breakdown, but healed and implants successful.	A clear effect of HBO was not demonstrated in this small study. The study did demonstrate the successful placement of implants in mandibles which were irradiated with doses of more than 60 Gy.

Table 9 (d) Review of Evidence of the Effectiveness of HBO for Wound Healing

Author Date Country	Aims of Study	Patient Population	Study Design	Intervention	Outcome Measures	Results	Comments
Neovius et al. ⁷² 1997 Sweden	Review of the literature and a report of 15 consecutive patients.	15 patients with soft-tissue wounds without signs of healing after surgery in 64 Gy irradiated head and neck regions.	Consecutive retrospective study.	HBO and adjuvant therapy.	Follow-up at various intervals.	In HBO group, 12 of 15 patients healed completely, 2 partially within 1-5 months, 1 did not heal. In non-HBO group, 7 of 15 patients healed, 2 had massive acute bleeding, 5 required further surgery.	The study was on 15 irradiated ENT patients. None had osteoradionecrosis of the mandible. This small study tends to support the role of HBO in soft-tissue wound-healing.
Kindwall ²⁹ 1993 USA	A study of incidence of wound dehiscence with and without HBO.	160 patients divided into 2 groups of 80.	Randomised prospective controlled trial.	HBO.	Follow-up at 3 weeks.	Control group had 15% minor and 33% major wound dehiscence. In the hyperbaric group there was 7.5% minor and 3.5% major wound dehiscence.	The study relates only to soft-tissue flap surgery, but demonstrates a significant effect of HBO therapy on soft tissue wound healing.

(b) Prevention of Osteoradionecrosis

Evidence relating to the efficiency of HBO for the prevention of ORN is equivocal. There is a lack of appropriate RCTs which makes assessment of the use of HBO for the prevention of ORN difficult. Those studies, which indicate a positive role for this therapy, tend to have taken place in the 1980s. The only RCT, undertaken by Marx et al.⁶⁵ compared two groups of patients, one having HBO and one having penicillin before their extractions. The study found a significant reduction in ORN in the HBO group from 29.9% to 5.4%. Clayman¹⁹ notes that there is a particularly high overall rate of ORN, 35%, in these patients. The applicability of this study to the general population of patients in whom the ORN rate is less than 6% is certainly open to question.

A more recent study⁶² has shown that an atraumatic surgical technique, combined with prophylactic antibiotics and lowered dose of radiotherapy significantly reduces the incidence of ORN after surgery to the irradiated mandible/maxilla. If low rates of ORN can be achieved without HBO, the use of HBO is unlikely to be cost-effective.

(c) Dental Implants

The absence of any RCTs in the reported results of the studies weakened the evidence, but the studies reported gave a consistent result with respect to levels of radiation given. The evidence from the clinical cases reflected the theoretical benefits of HBO in the regeneration of bone, necessary for successful osseointegration of titanium implants. A RCT is needed to establish conclusively the level of radiation beyond which HBO therapy would be necessary to ensure successful osseointegration.

(d) Wound Healing

Most of the studies on wound healing related to areas unconnected with the head and neck, or were covered in the other three parts of this study. Only a small number of studies related specifically to soft-tissue wound-healing following cancer of the head and neck. The study by Marx⁷³ provided evidence at the RCT level involving 160 patients (80 HBO, 80 control) that there were significantly fewer or less severe complications of wound healing in the HBO group. Greenwood and Gilchrist⁴⁴ and Neovius et al.⁷² reported evidence from small case-controlled studies in support of the hypothesis that HBO therapy had a clinically significant effect on initiation and acceleration of healing processes in irradiated soft tissues. Further study is required to establish the efficacy of HBO in soft tissue wound healing following irradiation of the mandible.

The evidence supports the use of HBO in the treatment of refractory anaerobic or mixed bacterial soft tissue infections. HBO therapy should be integrated within a treatment protocol comprising adequate surgical and antibiotic therapy.

3.2.3 Summary and Conclusions

The value of HBO therapy for the treatment of ORN remains controversial. There are a number of studies which lend support to the use of HBO. However, these are generally retrospective case studies of small numbers of patients over long time periods. They are often poorly described in terms of methodology, making it difficult to draw any clear conclusions. In addition, many of the studies date back to the 1970s and 1980s. Since this time many factors have changed, including improved dental care and follow-up and more efficient use of radiation, resulting in a decline in the incidence of ORN.²⁰

Treatment protocols based on careful wound care and scrupulous surgical technique, such as that proposed by Schwartz⁷⁴, suggest that ORN can often be successfully managed without HBO. Schwartz⁷⁴ comments that he is aware of 'numerous ORN cases, treated with HBO protocols, who have failed to do as well as Marx's patients' and suggests the quality of the surgery, rather than HBO, may be the key. Maxymiw⁶² reported no cases of ORN among 72 patients based on the use of nonlidocaine local anaesthetics, antibiotics and conservative surgery following dental extraction. However, these protocols are also based on empirical evidence alone.

Conservative measures of therapy appear to control a reasonable proportion of bone exposures, particularly in patients receiving less than 65 Gy to the affected bone.³⁷ It seems likely, however, that there is a sub-set of patients for whom HBO offers benefits. It is not possible to define precisely the characteristics of the patients who make up this sub-set.

There is an urgent need for data to support the use of HBO as a treatment modality which prolongs implant survival.

In conclusion, the existing evidence does not provide a clear direction for policy. Further studies are required to provide a more definite picture of the effectiveness of HBO.

A properly designed clinical trial would answer a number of important questions:

1. Does the use of HBO result in improved outcomes?
2. For which sub-groups of patients?

3. What is the recommended protocol - how many 'dives' and at what pressure?

4. ECONOMIC ANALYSIS

4.1 METHODS FOR ECONOMIC ANALYSIS

A 'typical' health authority would expect to see less than 20 patients per year with oral cancer. Local clinical opinion suggests that around 50% of these patients receive radiotherapy, although this figure may vary on a local basis. Incidence rates of ORN have declined as a result of more efficient use of radiation and improved surgical techniques and dental care. The current incidence of ORN is not known with certainty, but is assumed to be around 5%. Therefore, the number of patients likely to experience ORN at any time after radiotherapy is expected to be less than one per year per health authority.

The use of HBO prior to implants is the most likely area of future demand for HBO. It is estimated that only around 5 - 10% of oral cancer patients who have radiotherapy currently receive implants, although this figure may vary nationally. Therefore, a 'typical' health authority would currently expect to have only one or two oral cancer patients per year receiving implants. Given that up to 25% of oral cancer patients who have radiotherapy may benefit from implants, this number could rise to around five patients per health authority. There is also a pool of patients, of unknown size, treated in earlier years who might benefit from implants. (Brook - Personal Communication, 2000).

4.1.1 Treatment of ORN

The resource implications in relation to the treatment of ORN are, therefore, small and likely to remain so.

A detailed cost-benefit analysis has not been undertaken. The results of two previously reported non-UK cost-effectiveness analyses of the treatment of ORN are summarised and reviewed.

Dempsey et al.¹⁸ Cost-effectiveness Analysis of Hyperbaric Therapy in Osteoradionecrosis

The paper by Dempsey et al. presents cost-effectiveness analysis of hyperbaric therapy from a societal perspective. The aim is to determine whether hyperbaric therapy is more cost-effective than the conservative therapy treatment for osteoradionecrosis. The incremental costs and effects of HBO are compared with the more traditional treatment of conservative therapy. The analysis supports the cost-effectiveness of HBO. The

methodology employed appears reasonable. However, the results are highly dependent on the length of stay assumptions used for which no references are provided. In addition, the 100% success rate for HBO treatment reported in this study is not replicated in other HBO studies.

Methodology

Dempsey assesses the cost-effectiveness of HBO by comparing 21 HBO patients with 21 hypothetical 'conservative therapy' patients. The costs and effects of the hypothetical group were calculated based on the expected outcome obtained from the literature.

Dempsey defines two types of treatment, 'conservative therapy' and the Marx University HBO protocol. The paper identifies five steps used in conservative therapy. Step 1 involves the patient avoiding local irritants; step 2 involves the irrigation of the area with a variety of agents; step 3 involves the prescription of antibiotics; step 4 involves superficial sequestrectomies and reconstructive surgery (step 5) is the last resort. Dempsey states that 'the resolution rate after the first four steps of this therapy ranges from 8% to 75%.' Reconstructive surgery, Step 5, only has a reported success rate of 66%.

The Marx University HBO protocol combines the treatment of HBO with specific surgery. Marx claims 100% success rate. There are four stages in the Marx University HBO treatment. All patients except those suffering from orocutaneous fistulae, pathological fracture and extensive bone resorption enter stage 1. However, the HBO protocol was modified in this study to allow the physician to use his discretion.

Stage 1 involves 30 HBO exposures at 2.4 atmospheres for 90 minutes each. Saline rinses are used to maintain wound care. If the patient shows signs of clinical improvement he/she undergoes 10 additional exposures. If the patient shows no signs of improvement he/she is considered a non-responder and advances to stage 2.

Stage 2 involves a local surgical debridement. If the patient shows signs of improvement he/she undergoes 10 additional exposures. If no improvement is evident, the patient advances to stage 3 as a non-responder.

Stage 3 involves a partial jaw resection and 10 additional HBO exposures. Patients then advance into stage 3-R which involves a bony reconstruction, 10 additional HBO 'dives' and eight weeks' jaw fixation. 'If further surgery is not required, the patient may enter prosthetic rehabilitation one month after fixation is released.'

The costs of the 21 HBO patients were compared to the costs of the 21 hypothetical 'conservative therapy' patients. Data presenting the costs of HBO were obtained from the Hamilton Civic Hospital, Ontario and from the relevant literature. Costs were presented in 1995 Canadian Dollars and were calculated for medications, sequestrectomy, dental extractions, out-patient visits, hyperbaric therapy, in-patient days and reconstructive surgery. Indirect costs such as lost earnings were not included in the analysis.

Results

In the HBO group, 57% healed during stage 1; 34% healed during stage 2 and 9% healed in stage 3. In the hypothetical 'conservative therapy' group, 65% of patients healed before reconstructive surgery, 23% healed after reconstructive surgery and 12% remained unhealed.

The cost per patient of treating the 21 hypothetical patients by conservative therapy was \$63,211. This figure includes the cost of one round of Marx therapy for the three patients who were not cured by conservative means. The cost per patient of treating the HBO patients was \$10,064. The cost of HBO was, therefore, less expensive. In addition, three more cases were resolved than with conservative therapy. Patients who underwent HBO treatment also enjoyed greater pain reduction and increased sleep while requiring fewer narcotics.

A sensitivity analysis was performed to address any problems concerning the validity of the data collected from the hospitals or from the literature. The variables, conservative therapy effectiveness, cost per in-patient day and the cost of reconstructive surgery were varied in the sensitivity analysis. The sensitivity analysis suggested that the key cost driver for both treatments of osteoradionecrosis is the number of days each patient spends in hospital.

Marx and Johnson - Problem Wounds in Oral and Maxillofacial Surgery. The Role of HBO⁵¹

This study reports on the cost of 300 osteoradionecrosis patients in America. Once again, the analysis concludes that HBO is the cheaper treatment. However, the results should be viewed with caution. The results are based on a study of patients treated in the early 1980s. The use of a 100% successful treatment rate for HBO and 8% for conservative treatment are not representative of the range of evidence available, and strongly influence the results in favour of the HBO option. The evidence of healing as a result of 'conservative treatment' of ORN of the mandible was reviewed by Clayman 1997,⁷⁵ who reported healing in 58.7% of

cases. Clayman 1997⁷⁵ reported that the average effectiveness of HBO from a range of studies was around 80%.

Methodology

Costs were calculated by the addition of the total course of treatment, all office visits, hospital care, surgery, medication and hyperbaric oxygen. This total was then normalised to the average prevailing fee. Indirect costs such as lost earnings were not included in the calculation of total costs.

Results

Marx and Johnson state that, in 1985, the average 1-year cost of treating osteoradionecrosis by 'conservative therapy' was \$31,000. As only 8% resolved their disease in the first year, treatment continued for several years in most cases. The average total cost of treating osteoradionecrosis by conservative therapy is \$102,000. (This figure could be even larger, as most of those not treated may have left the institutions reviewed and gone on to accumulate costs elsewhere.)

The 1-year cost of treating osteoradionecrosis by HBO without surgery was calculated at \$20,000. However, as 83% of cases required retreatment, the total cost of treatment rose to \$62,000.

The average 1-year cost of treating osteoradionecrosis with the Marx University protocol is \$35,000. The resolution rate for this type of treatment is given as 100%. This suggests that it is, in fact, cheaper, as the total cost remains the same as the 1-year cost. This form of treatment also reduces pain and improves quality of life. Narcotics dependency is also reduced by this form of treatment.

The 1-year cost of treating osteoradionecrosis by Marx's protocol, but in a private practice, was estimated at \$32,000. Again, a 100% resolution rate yields a total cost equal to the 1-year cost.

Discussion of Non-UK Cost-effectiveness Studies

The two studies demonstrate that prolonged 'conservative treatment' may be an expensive option. However, it cannot be concluded that all patients with ORN should be treated with HBO. Some patients respond well to conservative treatment and for these patients the use of HBO is not necessary. The use of HBO may be appropriate for a sub-group of patients who do not respond to conservative treatment.

4.1.2 Prevention of ORN

Many reviews have reported a high incidence of ORN after pre-radiation therapy extraction and post-radiation therapy extractions. Marx et al.⁶⁵ recommended the use of HBO prophylactically before postradiation dental extractions. However, since this time the incidence of ORN has declined as a result of the more efficient use of radiation and improved surgical techniques and dental care, reducing the justification for prophylactic treatment.

Two reviews have considered more recently the management of dental extractions in irradiated jaws. Clayman¹⁹ argued in favour of a protocol without HBO, whilst Lambert et al.⁷⁶ argued in favour of a protocol with HBO. Neither of the reviews provides a detailed cost-effectiveness analysis.

Clayman¹⁹

This review considers whether the use of adjunctive HBO is justified before extracting teeth in irradiated mandibles. It examines the literature for evidence on the incidence of ORN, the success rates of conservative therapy, and the likelihood of one of the most severe complications of ORN, loss of continuity of the mandible. It concludes that, given declining rates of ORN and the relatively low rates of loss of continuity of the mandible, the evidence does not support the mandatory use of HBO before removing teeth in irradiated mandibles.

Lambert⁷⁶

This paper argues that HBO should be used prophylactically for all patients requiring dental extraction on the basis that the cost of treating ORN is extremely high. In severe cases of ORN which may result in a pathologic fracture of the mandible, these costs may include HBO, partial mandibular resection, myocutaneous flap resurfacing of the neck and floor of

the mouth, and bone and skin grafting. Patients are likely to experience severe pain, long periods of hospitalisation and multiple surgical episodes.

Modelling of Cost-effectiveness of the Prevention of ORN

Modelling work has been undertaken to provide a crude indication of the cost-effectiveness of HBO in the prevention of ORN following dental extractions. The data on which these calculations are based is severely limited. The figures generated are intended to illustrate broad orders of magnitude only.

Assumptions

The following assumptions have been made:

- Patients who undergo dental extractions following radiotherapy can follow one of two pathways: either they receive a course of HBO prior to the extractions or they undergo the extractions without additional intervention.
- The incidence of ORN following extraction is 5.8%.
- The effectiveness of HBO in the prevention of ORN is 80%.
- The cost of HBO is £3,150, the current cost of treatment at the Diving Disease Research Centre in Plymouth.
- Patients who develop ORN fall into two groups: group A patients are treated successfully by a single course of HBO, group B patients progress to the 'worst case' scenario. The worst case scenario is that the patient develops ORN and suffers a pathological fracture of the mandible. The patient suffers from constant pain, discharge and inability to take anything by mouth.
- For patients who develop ORN, the probability of advancing to the worst case scenario is 55%.
- The cost of treating the 'worst case' patients is not known with any degree of certainty. It is assumed that patients, at a minimum, will require HBO treatment (£3,150) and surgery (approx. £15,000), at a minimum total cost of approximately £20,000. These patients will be very ill and, therefore, will also require other medication and additional hospital care.

Based on these assumptions, approximately five patients in a 'typical' health authority of 500,000 will require dental extractions. If these patients follow the HBO pathway, the cost of the treatment is dominated by the cost of HBO treatment (around £14,500). The number of patients developing ORN is extremely small (less than one patient every 10 years) and, therefore, associated costs are negligible. If these patients follow the non-HBO pathway, the number of patients developing ORN is higher but still small (one patient every four years). It

is assumed that 55% of these patients develop the worst case scenario (approximately one patient every eight years). The relative cost of the HBO and non-HBO options is dependent on the cost of treating the worst case scenario. At a cost of £20,000, the expected cost per annum of the HBO pathway is four times that of the expected cost of the non-HBO pathway. The cost of treating the worst case scenario would need to be £100,000 for the cost of both options to breakeven.

Sensitivity Analysis

Due to the uncertainty surrounding the value of the parameters used in the modelling, a number of sensitivity analyses were undertaken. The impact of the sensitivities on the breakeven cost of the treatment of the worst case scenario is shown in Table 10.

Table 10 The Breakeven Cost of the Treatment of the ORN (Worst Case Scenario) under Different Assumptions

Basecase and Sensitivities	Breakeven Cost
Basecase	£100,000
Sensitivities	
(a) Incidence of ORN: 29.5% without HBO, 5.4% with HBO	£17,500
(b) Probability of patients progressing to worst case scenario: 100% without HBO , 100% with HBO	£70,000
100% without HBO , 0% with HBO	£55,000
(c) Effectiveness of HBO: 100%	£95,000
50%	£127,500

(a) The Incidence of ORN

The reported incidence of ORN varies widely. Marx et al. reported the incidence of ORN to be 29.5% in patients without HBO and 5.4% in patients with HBO.⁶⁵ This alters substantially the expected costs. The breakeven cost of treatment of the worst case scenario would be approximately £17,500. However the incidence rate of 29.5% appears to be extreme, with most recent estimates falling well below this value. In fact, Maxymiw et al. reported no cases

of ORN among 72 patients following dental extraction.⁶² The lower the incidence of ORN, the higher the cost of treating the worst case ORN scenario needs to be to make the HBO option cost-effective.

(b) The Probability of the Patients who Develop ORN Progressing to the Worst Case Scenario

If the proportion of the patients with ORN who progress to the worst case scenario is assumed to be 100% for both HBO and non-HBO patients, the cost of the worst case scenario needs to be around £70,000 for the HBO option and non-HBO option to break even. It is likely that the probability of HBO patients developing the worst case scenario is lower due to revascularisation of the irradiated tissue. However, the exact difference is difficult to estimate. If it is assumed that the proportion of the HBO patients with ORN who progress to the worst case scenario is 0%, whilst the proportion of non-HBO patients remains at 100%, the breakeven cost is approximately £55,000.

(c) The Effectiveness of HBO

Assuming the effectiveness of HBO is 100% makes little difference to the expected cost of the HBO option. The breakeven cost of treatment for ORN would be £95,000. If the effectiveness of HBO was reduced to 50% the breakeven cost of treatment would be £127,500.

This analysis suggests that the cost of treating the worst case scenario must reach £100,000 per patient in order for the option of offering HBO to be less expensive. Initial estimates of this cost suggest that it is unlikely to be high. However, more detailed evidence on these costs would be useful. This analysis does not take account of the quality of life of patients with ORN. These patients are in considerable pain, are unable to take anything by mouth and their quality of life is severely impaired. The addition of quality of life information would be useful in the debate.

4.1.3 Wound Healing

It is not possible to estimate the number of oral cancer patients who receive HBO for wound healing, but numbers are expected to be small. No analysis has been undertaken.

4.1.4 Dental Implants

The use of HBO may reduce the proportion of implants which fail. Granstrom et al.⁶⁶ showed that the use of HBO resulted in a significant reduction in the number of implants lost:

- Irradiated jaw with no HBO 53.7% of implants lost
- Irradiated jaw with HBO 8.1%% of implants lost.

The cost of HBO treatment varies according to treatment location from £500 for patients receiving treatment at local chambers run by the MS society, to £4,500 for patients receiving treatment at Peterborough.

Cost savings resulting from the reduction in implant failures include the additional resources used as a result of implant failure. If the implants fail, a patient is likely to have one or two operations under local anaesthetic and around 12 out-patient visits. The quality of life for the patient is obviously reduced. Patients who develop ORN suffer from a high degree of pain. Additional costs to them include social costs of pain, analgesic dependence and loss of productivity.

5. IMPLICATIONS FOR OTHER PARTIES

5.1 QUALITY OF LIFE

The role of HBO in the treatment or prevention of osteoradionecrosis in the mandible is important because of the characteristics of the disease itself. Although mandibular osteoradionecrosis was originally viewed as infected osteomyelitis secondary to radiation, Marx³⁹ showed it to be an aseptic necrosis. Nevertheless, it is an unpleasant disease with marked necrosis of the bone of the mandible, often leading to pathological fractures. Often these fractures cannot heal without surgical intervention. The patient suffers protracted pain and disfigurement. In addition, soft tissue radionecrosis can be dangerous when the possibility of erosion into the carotid artery exists.²⁹ Every effort should be made to prevent the development of osteoradionecrosis.

Eighty-nine per cent of all trauma-induced osteoradionecrosis of the mandible is caused by tooth extraction in the radiated jaw.²⁹ (The proportion of trauma-induced ORN relative to non-trauma-induced ORN is not known) Therefore, it is commonplace to extract all doubtful teeth in the site of the radiation, and to extract sound teeth where the condition of the patient is such that good oral hygiene could not be relied on to keep those teeth healthy. If HBO could reduce the necessity for tooth extraction in the years following radiation, more teeth could be preserved. This is a clear benefit for the patient, as sound natural teeth are far more efficient than the most perfectly-fitting dentures. Kindwall²⁹ has also proposed that the extraction sockets in irradiated mandibles do not remodel as they do in the non-irradiated mandible, leaving sharper edges on the alveolar ridge. This can cause problems for subsequent denture-wearing.

Similarly, restoration of the irradiated mandible with titanium osseointegrated implants is an important issue in the quality of life. Successful placement of functional implants allows a far superior restoration of lost tooth tissue than does conventional dentures. If HBO can increase measurably the success rate for osseointegrated implants, then it can contribute positively to an increased quality of life for the patient. Failed implants can jeopardise a fixed prosthesis or bridge which affects the whole jaw and, thus, reasonable mastication for the future.

5.2 FINANCIAL IMPLICATIONS FOR PATIENTS AND OTHERS

It is obvious that HBO must be supplied from purpose-built equipment. This can be in large dedicated centres, such as the Diving Diseases Research Centre in Plymouth, or at one of the numerous facilities in cities and large towns run by the Multiple Sclerosis Therapy Trust. The direct costs for both the patient and the NHS differ for each type, and these have been shown elsewhere. The indirect costs for the patient are concerned with the amount of time required for therapy. A typical protocol for HBO, developed by Marx, is the 20/10 ratio, involving in total 30 'dives' of approximately 90 minutes each. It is usual to undergo one 'dive' per day, so the patient must be available for 30 days, in two blocks. If the patient is employed, this could lead to considerable loss of income, apart from the travel and subsistence costs. In addition, if they are sent to a remote site, even if the NHS pays for the bed and breakfast accommodation, it is still a greater expense to feed oneself away from home. These factors must be considered in the choice of HBO facility to which the patient is referred and, indeed, if the therapy is necessary, rather than just preferable.

5.3 ETHICAL ISSUES

The effectiveness of HBO in the applications mentioned in this paper has ethical implications. If the therapy is clearly effective in its described role, then it would be unethical not to provide it in those circumstances. Similarly, if it were not effective, it would be unethical to prescribe it routinely for all patients, as it has financial, time and other constraints, which would be wrong for a patient to bear if he/she cannot benefit.

There is another ethical issue in the use of a RCT to determine exactly which patients would benefit from the therapy. Many people have called for this as a gold-standard in evidence (Schwartz - Personal Communication 2000). Whilst it would be invaluable for putting the case for HBO beyond dispute, the ethical issue of denying a treatment, believed by many, and established in a number of case-controlled studies, to be effective in the prevention and treatment of osteoradionecrosis, is problematical. It is small wonder that no-one seems willing to run such a trial at present.

5.4 SOCIAL AND LEGAL IMPLICATIONS

The social implications of HBO use are as described above - cost, inconvenience and time for therapy, set against possible protracted pain, jaw fracture, additional surgery and diminished quality of life if not used. The balance must be found between the two, so that a protocol can be developed and accepted whereby those patients who would clearly benefit from HBO therapy, and only those, receive it.

The legal implications are not so clear. Research in the Trent Region has shown, as reported in this paper, that only a small proportion of head and neck surgeons appear to prescribe HBO. Therefore, it cannot be accepted yet as a routine procedure. To the knowledge of the authors, the position of a Trust, Health Authority or Health Board denying such therapy to a patient has not been tested in the U.K. courts. However, as the use of HBO therapy continues to increase, it may in time be seen as a patient's right. Such a position would increase the chance of a successful prosecution if an aggrieved patient were to challenge legally a refusal of therapy. Again, the existence of some harder evidence in the form of further RCTs clearly would assist in such a position. The dilemma is that these may never happen, for the ethical and possible legal consequences outlined above.

6. FACTORS RELEVANT TO NHS POLICY

There are no National Service Frameworks relating to the use of HBO and there is a lack of other national guidance.

It is important that HBO is seen as part of a therapeutic continuum and not an isolated treatment modality. At present, whilst the Marx Protocols for the delivery of HBO are followed, there appears to be little in the way of a protocol identifying patients who would most benefit from therapy. Access to therapy, therefore, depends upon clinician familiarity with the existing facilities. The development of clear referral criteria is essential.

Some patients access HBO at a facility where there is no physician present, e.g. in Sheffield. There may be issues of liability in terms of the adequacy of technical competence and personnel skills at the facility. In addition, there are issues relating to the appropriateness of patients receiving HBO where there is a lack of medical supervision.

7. OPTIONS FOR PURCHASERS/COMMISSIONERS

There are four conditions in oral and maxillofacial surgery where HBO can be considered following treatment for oral cancer. They are:

- the treatment of osteoradionecrosis;
- prophylactically before and after radiotherapy which involves the mandible to prevent osteoradionecrosis;
- the promotion of wound-healing;
- before and after the placement of implants.

A number of options are available to purchasers:

1. *Do not purchase HBO for any of the four conditions*

This option would, however, prevent further evidence being produced. Given that existing evidence supports the use of HBO in some situations, this does not appear to be an ethical way forward.

2. *Purchase HBO only within the context of clinical trials*

The number of patients is small and this would make the recruitment to clinical trials within the UK extremely difficult.

3. *Purchase HBO for selected conditions, on the basis of agreed criteria, as follows:*

- the treatment of established ORN which has failed to respond to conservative therapy within a defined time-period;
- do not purchase for the prevention of ORN, but purchase for the treatment of established ORN;
- purchase for complicated wound-healing.

Further work is required to determine the appropriateness of purchasing for implants. Current evidence suggests that only patients receiving high doses of radiation (say >65Gy) will benefit. In many health authorities limited funding for implants is currently restricting the number of patients offered implants.

The demand for HBO in association with the placement of implants is likely to increase, if further funding is made available. The use of implants offers the patient the best option for

quality reconstruction. The number of cases will increase with the improvement in surgical skills and reconstructive techniques. A possible way forward is to recruit patients to multi-centre studies.

In addition, there should be consideration at a regional and national level of the need to identify recognised centres for the delivery of HBO therapy.

8. DISCUSSION and CONCLUSIONS

The evidence for the use of HBO in the treatment of oral cancer is limited. Whilst there is some research evidence available, much is still unknown and there is a need for further research into its use in the treatment of patients with oral cancer. In relation to the treatment of ORN, the weight of evidence supports the effectiveness of HBO; but suggests that it might not be necessary for all patients. For the prevention of ORN, the evidence is unclear. Management protocols based on careful wound care and good surgical technique should be used to minimise the risk of ORN. The use of HBO should not be used as a substitute for the high quality management of patients. There is limited evidence to support the use of HBO prior to the placement of endosseous implants, but further evidence is required.

The number of patients who may benefit from therapy is small; however, the impact of oral cancer upon a person's physical and psychological well-being is great. There is potential to increase the number of potential patients by including people affected by head and neck cancer as well as those with oral cancer. In addition, there is a wider pool of patients who may benefit from the use of endosseous implants. Current funding of this reconstructive procedure is limited.

There is a need for better information systems pertaining to the diagnosis and management of people with head and neck cancer. There appears to be a lack of criteria for the use of HBO and work at a local and national level is required in order to produce clinical consensus on treatment. As this procedure is not without risk, patients need to have access to comprehensive information and this is difficult in the absence of agreed clinical guidance.

At present, the service provided does not allow equitable access across the Trent Region. In some units, a physician is not present when the treatment is given.

In summary, it is recommended that HBO in the treatment of oral cancer is used in the context of a clear statement of clinical practice, fully informed consent, comprehensive information and the collection of clinical data which allows the analysis of benefits and risks. Patients should only receive HBO from a unit which has the necessary quality controls, both with respect to the pressure used and patient observation.

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APPENDIX A RESULTS OF A SURVEY ON THE USE OF HYPERBARIC OXYGEN IN THE TREATMENT OF PATIENTS WITH ORAL CANCER IN THE TRENT REGION

31 questionnaires were sent to ENT and Oral and Maxillofacial surgeons in the Trent Region and 18 were returned. The contents were as follows:

1. Do you refer patients with oral cancer for hyperbaric oxygen therapy?
14 respondents indicated they did refer patients (oral and maxillofacial surgeons); 4 respondents (ENT surgeons) did not.
2. Do you refer patients for hyperbaric oxygen therapy:
 - a) in the treatment of osteoradionecrosis?
13 respondents indicated that they did.
 - b) pre and post radiation therapy in order to prevent osteoradionecrosis?
4 respondents indicated that they did.
 - c) pre and post surgery in order to promote wound healing?
6 respondents utilised HBO therapy in this way.
 - d) Prior to the placement of endosseous implants in order to improve implant survival?
9 respondents replied that they did.
3. Are there agreed referral criteria for patients?
7 respondents indicated that referral criteria were in place.
4. Is there an agreed protocol for hyperbaric oxygen therapy, e.g. exposure time: number of exposures?
10 respondents replied that protocols existed.
5. How many patients have you referred for therapy in the last 12 months?

No. Patients Referred	Consultants Referring
0	1
1	5
2	3
3	1
4	2
10	1
Unknown	1

6. Where do you refer patients for hyperbaric oxygen therapy?

The centres identified were:

- Plymouth
- Peterborough
- Hull Mobile Unit
- Sheffield Multiple Sclerosis Unit
- Ellesmere Port
- Lincoln.

7. Have you any comments to make in relation to this therapy?

- Efficacy is proven in the literature.
- I would be keen to learn of site, availability, costings and protocols.
- Information regarding questions relating to the use for wound healing and prior to implant placement.
- Our experience has been confined to very long-term complications of radiotherapy (the last case 15 years or so). Revascularisation with tissue transfer has been used instead on a few patients.
- It has proven effective in certain patients, but its use is controversial in other areas within the oral cavity. I am sure more patients would be sent if facilities were better and the costs lower.
- There is an increasing need.
- Unless there are other uses for hyperbaric oxygen therapy – other than oral cancer, it would seem sensible to use local facilities in Peterborough.
- I would like to see a physician staffed unit locally (we do not use it enough). There is some evidence that it may reduce recurrence in cancer patients used in combination with radiotherapy.
- The hyperbaric O₂ facilities at Lincoln are not appropriate, because the pressure cannot be raised to 2.2 – 2.4 atmospheres; we will have to refer elsewhere now.
- Other metabolic bone disease, e.g. osteopetrosis with osteomyelitis.
- A valuable addition to our armamentarium that is clinically effective.

APPENDIX B MARX PROTOCOL FOR THE TREATMENT OF ESTABLISHED OSTEORADIONECROSIS^{39,77}

Marx introduced a staging system, relative to the severity of the mandibular necrosis, permitting a plan of therapeutic intervention which is a logical outgrowth of the stage of necrosis. Stage I mandibular necrosis includes those patients who have had exposed bone for six months or more. Stage II patients represent those who do not resolve when treated as Stage I, Stage III patients are those with poor prognostic factors, including pathologic fracture, orocutaneous fistulae or evidence of osteolytic involvement extending to the inferior mandibular border.

Stage I

When patients fit the appropriate selection criteria, they enter the HBO treatment protocol as Stage I patients. In Marx's protocol, these patients begin with a course of 30 HBO treatments at 2.4 ata for 90 oxygen minutes. If progression is satisfactory, including coverage of exposed bone, another 10 treatments are administered. If the patient's progress has not been satisfactory at 30 treatments, he or she is advanced to Stage II.

Stage II

In Stage II, a local surgical debridement (typically a transpolar alveolar sequestectomy) is performed after 30 treatments. If healing progresses satisfactorily, this group typically completes another 10 HBO2 treatments post-debridement.

Stage III

For patients who do not progress appropriately in Stage II or for patients who present with advanced disease initially, treatment is delivered according to stage III guidelines. Patients received 30 HBO treatments as in Stage II, then undergo a transoral partial mandibulectomy. Ten additional post-operative HBO sessions are delivered. These patients then enter into a mandibular reconstructive phase. About 10 weeks following completion of all 40 HBO treatments, the patient undergoes a reconstruction with a transcutaneous approach to avoid oral flora contamination. This surgery is done utilising freeze-dried cadaveric bone as the carrier tray, into which the patient's own bone (harvested from the iliac crest with both cortical and cancellous components) is grafted. The patient then completes a course of 20 post-reconstruction HBO treatments.

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