Hyperbaric oxygen therapy for the treatment of non-healing, refractory wounds in non-diabetic patients and refractory soft tissue radiation injuries

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Assessment report

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The Medical Services Advisory Committee is an independent committee which has been established to provide advice to the Australian Government Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform Government decisions about which medical services should attract funding under Medicare.

This report was prepared by the Medical Services Advisory Committee with the assistance of Dr Elmer Villanueva, Associate Professor Anthony Harris, Ms Emily Petherick, Dr Renea Johnston and Ms Alexandra Raulli, from the Centre for Clinical Effectiveness, Monash Institute of Health Services Research and Centre for Health Economics, Monash University and Edited by Dr Alana Mitchell, ScienceLink Pty Ltd. The report was endorsed by the Australian Government Minister for Health and Ageing on 31 August 2004.

Publication approval number: 3546

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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Hyperbaric oxygen therapy (HBOT) involves the intermittent inhalation of 100 per cent oxygen in chambers pressurised above one atmosphere absolute. Depending on the reason for HBOT, the duration of treatment session varies from 45 to 300 minutes, although times of 90 to 120 minutes are most common, for a variable number of sessions.

This report evaluates the safety, effectiveness, and cost-effectiveness of HBOT in the management of non-healing wounds in non-diabetic patients and in refractory soft tissue radiation injuries.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from the Institute of Health Services Research and the Health Economics Unit, Monash University, was engaged to conduct a systematic review of literature on hyperbaric oxygen therapy for treatment of refractory soft tissue radiation injuries and non-healing wounds in non-diabetic patients. A supporting committee with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of hyperbaric oxygen therapy for the treatment of non-healing wounds in non-diabetic patients and refractory soft tissue radiation injuries

Clinical need

Hyperbaric oxygen therapy is an established therapeutic modality in a number of indications. As stated in a previous report (MSAC 2001), there are no reliable Australian estimates for the prevalence of soft-tissue radiation injuries and non-healing wounds in non-diabetic patients.

Data presented at the 10th annual scientific meeting of the Hyperbaric Technicians and Nurses Association and the Australian and New Zealand Hyperbaric Medicine Group (Christchurch, 29-31 August, 2002) showed that 1,236 patients underwent 21,033 episodes of HBOT in Australia from 1 July 2001 to 30 June 2002. Of these, 120 patients

(9.7%) were treated for soft tissue radiation injuries and 166 patients (13.4%) were treated for hypoxic, non-diabetic wounds.

Safety

Estimates collected through national registries of the incidence of adverse events relating to HBOT suggested that most were self-limited and resolved after termination of therapy. As was presented in the previous report (MSAC 2001), the most common forms of adverse events were myopia, barotrauma, claustrophobia and oxygen toxicity. Serious, life-threatening events and fatalities were rare.

Effectiveness

Twenty one studies were included in the assessment of the effectiveness of HBOT, five examining non-healing wounds in non-diabetic patients and 16 dealing with refractory soft tissue radiation injuries. Although evidence in support of the effectiveness of HBOT in both indications includes higher level study designs such as randomised controlled trials (RCTs) and non-randomised controlled studies, it was of low methodological quality, failing to meet relevant validity criteria.

Furthermore, the majority of studies reported end-points of uncertain clinical significance or patient relevance. Relevant outcomes including healing of wounds were sometimes reported, however the validity of assessment of these outcomes was uncertain due to a lack of objective or blinded assessment, and failure to explicitly report measurement criteria.

Twelve case series (three reporting on non-healing, refractory wounds in non-diabetic patients and nine on refractory soft tissue radiation injuries) were identified that enrolled consecutive patients. The non-comparative nature of such studies limited the use of the information contained in the case series due to the considerable potential for bias inherent in such designs. Nevertheless, such studies were used to supplement the evidence available from comparative studies.

Non-healing wounds in non-diabetic patients

Two controlled studies met the entry criteria. One RCT showed a decrease in wound area and a comparative study using historical controls showed trends toward the prevention of wound breakdown and infection as well as reductions in length of hospitalisation.

Refractory soft tissue radiation injuries

Six controlled studies met the inclusion criteria. Four RCTs examined four different sub-indications related to radiation therapy. A small RCT examining the use of HBOT for cognitive impairment following brain irradiation showed non-significant improvement in neuropsychological function. Another RCT evaluating HBOT for radiation-induced brachial plexopathy showed no significant differences in sensory thresholds or quality of life between those receiving HBOT and controls. In a group of patients at high risk for the development of osteoradionecrosis, HBOT was found to increase the likelihood of healing tooth socket wounds following extraction compared to the administration of penicillin. The remaining RCT showed that HBOT reduced the likelihood of major

wound infection, major wound dehiscence and delayed wound healing in myocutaneous grafts in patients who had undergone radiation therapy.

Cost-effectiveness

The clinical evidence was inadequate to substantiate claims that HBOT was cost-effective in the treatment of refractory soft tissue radiation injuries or non-diabetic refractory wounds. There was not evidence of sufficient quality to substantiate claims that it will either lead to an overall saving in resource use, or that it would lead to substantial patient relevant gains in health-related quality of life compared to current medical treatments at an acceptable cost.

Recommendations

The clinical evidence was inadequate to substantiate claims that hyperbaric oxygen therapy (HBOT) was cost-effective in the treatment of refractory soft tissue radiation injuries or non-diabetic refractory wounds. However, MSAC recommended that, as there are no effective alternative therapies and in view of the progress of local data collections and an international trial, funding for HBOT continue for MBS listed indications at currently eligible sites, for a further three years.

- The Minister for Health and Ageing accepted this recommendation on 31 August 2004.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the therapeutic use of hyperbaric oxygen therapy (HBOT) for non-healing wounds in non-diabetic patients and refractory soft tissue radiation injuries. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for HBOT for the treatment of non-healing wounds in non-diabetic patients and refractory soft tissue radiation injuries.

Background

Hyperbaric oxygen therapy for the treatment of non-healing, refractory wounds in non-diabetic patients and refractory soft tissue radiation injuries

Previous evaluation

The Medical Services Advisory Committee has previously examined the effectiveness, safety, and cost-effectiveness of HBOT for a number of indications (MSAC 2001; Application 1018-1020). The previous report was endorsed by the Commonwealth Minister for Health and Aged Care on 9 February 2001.

The present report builds on the findings of this earlier publication. It is limited to the assessment of HBOT as last-line treatment of non-healing wounds in non-diabetic patients and refractory soft tissue radiation injuries. Some issues, such as descriptions of the procedure, general discussions of safety and primary studies previously identified as relating to the present indications remain unchanged. They are included here for completion.

The procedure

Hyperbaric oxygen therapy involves the intermittent inhalation of pure oxygen in chambers pressurised above one atmosphere absolute (ATA). One ATA is defined as atmospheric pressure at sea level which is equivalent to 101.3 kiloPascals (kPa) or 14.7 pounds per square inch (psi).

Exposure to hyperbaric oxygen (HBO) is measured jointly by the pressures used in single-treatment exposures and the duration and number of treatment sessions. Tolerance to therapy is dependent on these parameters. In general, HBOT is well tolerated if pressures do not exceed three ATA and the treatment session lasts less than two hours. Depending on the reason for HBOT, treatment duration can vary from 45 to 300 minutes, although most treatments last from 90 to 120 minutes, for a variable number of sessions.

Hyperbaric oxygen therapy is administered in two types of chambers – monoplace and multiplace. A monoplace chamber accommodates one patient and is the most common type used worldwide. It can be pressurised with either pure oxygen or air. In the latter case, oxygen is delivered to the patient via a mask, hood or endotracheal tube. The smaller size of the chamber provides relative portability and lower cost, but imposes limits on ready access to the patient. The risk of fire is increased in the event that pure oxygen is used to pressurise the chamber.

Multiplace chambers can accommodate several occupants, including observers and medical and support personnel. The multiplace chamber is pressurised with air instead of 100 per cent oxygen and subjects undergoing therapy breathe pure oxygen through masks, hoods, or endotracheal tubes. The chamber's larger size allows personnel to enter

and move about with relative ease in order to deal with acute problems. The risk of fire is also reduced by administration of pure oxygen through patient-specific devices.

The previous report on HBOT (MSAC 2001) noted that there were marked regional variations in the delivery systems used. Australian clinical practice and expertise is primarily with multiplace chambers which are generally used by the majority of established hyperbaric facilities. In contrast, many facilities in the United States, including those used for intensive care patients, are solely equipped with monoplace chambers (MSAC 2001).

According to expert clinical opinion, the therapeutic effect is the same regardless of the delivery system. As was the case for the previous report, no attempt has been made here to perform a comparative assessment of the two types of delivery systems. The higher pressures that multiplace chambers can deliver were considered irrelevant to the assessment as the majority of treatments are administered at less than three ATA (MSAC 2001).

Intended purpose

The focus of the present report is the use of HBOT as last-line therapy for non-healing, refractory wounds in non-diabetic patients and for refractory soft tissue radiation injuries.

Hyperbaric oxygen is thought to influence the restorative course through the major process of wound healing, generally defined as the physiologic repair of injured tissue to obtain restoration of integrity (Mustoe & Porras-Reyes 1993). Oxygen insufficiency is a major component of the pathophysiology of many diseases. The rationale behind HBOT is that improved delivery of oxygen to the affected tissues will facilitate recovery from disease (NHLBI 1991).

Hyperbaric oxygen increases the partial pressure of oxygen in all tissues of the body (Hammarlund 1994). In turn, increased partial pressure of oxygen contributes to the enhancement of leukocyte-killing activity (Mader et al 1980), a decrease in white cell adherence to capillary walls (Zamboni et al 1993), vasoconstriction in normal vessels, restoration of fibroblast growth and collagen production (Meltzer & Myers 1986), neovascularisation (Knighton et al 1981) and preservation of adenosine triphosphate in the cell membrane, with secondary reduction in tissue oedema, modulation of selected immune responses (Bonomo et al 2000), and increased cellular proliferation (Hammarlund 1994, Boykin 1996).

Regardless of the specific type of wound, the natural reparative process has the following general sequence: haemostasis, inflammation, angiogenesis, collagen synthesis, epithelisation, and contraction (Hom et al 1995). Non-healing wounds result from interruption or delay in one or more steps in this sequence.

In contrast, radiation induces acute adverse effects on soft tissue through a number of pathways, including modification of the normal cellular environment (Mustoe & Porras-Reyes 1993), direct killing of epithelial and parenchymal cells, fibrosis of the interstitial medium (Hom et al 1995), decreased vascularity, hypoxia, and impairment of the proliferative capacities of local tissues. This renders tissues less able to respond to the inflammatory stimulus through the normal repair process. These cellular effects manifest

as ulceration, oedema, and inflammation which are the epithelial and dermal changes characteristic of acute radiation injury (Mustoe & Porras-Reyes 1993).

Surgery in such tissues has an increased complication rate because the angiogenesis, fibroplasia and white cell activity required for wound healing are all compromised (Neovius et al 1997). Hyperbaric oxygen has been found to increase perfusion in irradiated tissues (Marx et al 1990) and induce fibroplasia and angiogenesis (Nemiroff et al 1985).

The physiologic action of HBOT on refractory soft tissue radiation injuries and non-healing wounds was established in experimental studies of wound healing. The benefit of HBOT in clinical settings is unclear and is the focus of the present report.

Burden of disease

As stated in the previous report of HBOT (MSAC 2001), there are no reliable Australian estimates for the prevalence of soft tissue radiation injuries and non-healing wounds in non-diabetic patients.

Data presented at the 10th annual scientific meeting of the Hyperbaric Technicians and Nurses Association and the Australian and New Zealand Hyperbaric Medicine Group (Christchurch, 2002 August 29-31) showed that 1,236 patients underwent 21,033 episodes of HBOT in Australia from 1 July 2001 to 30 June 2002. Of these, 120 patients (9.7%) were treated for soft tissue radiation injuries and 166 patients (13.4%) were treated for hypoxic, non-diabetic wounds (HTNA and ANZHMG 2002).

Existing procedures and comparators

In this review, the use of HBOT was compared to procedures that did not use HBOT, including standard or conventional therapy (variously defined), normobaric oxygen or placebo procedures. As discussed more fully under Approach to Assessment, we included all studies with HBOT as a primary therapy and employing a direct, head-to-head comparison, regardless of the nature of the comparator.

Marketing status of the device / technology

A large number of monoplace units are listed on the Australian Register of Therapeutic Goods. Multiplace chambers, if fixed installations, are exempt from listing.

Current reimbursement arrangement

Interim funding for hyperbaric oxygen therapy for the indications considered in this report is currently listed in the Medicare Benefits Schedule (MBS):

> **13015**: HYPERBARIC OXYGEN THERAPY for treatment of soft tissue radionecrosis or chronic non-diabetic wounds where hypoxia can be demonstrated performed in a comprehensive hyperbaric medicine facility, under the supervision of a medical practitioner qualified in hyperbaric

medicine for a period in the hyperbaric chamber between 1 hour 30 minutes and 3 hours including any associated attendance

In addition, HBOT is currently funded for a range of other indications (MBS Items 13020, 13025, 13030), which may be related to those presented in the current report.

Medicare item number 13020 is used to reimburse HBOT for treatment of decompression illness, gas gangrene, air or gas embolism; diabetic wounds including diabetic gangrene and diabetic foot ulcers; necrotising soft tissue infections including necrotising fasciitis, Fournier's gangrene and for the prevention and treatment of osteoradionecrosis.

All MBS entries are described in Table 1. No breakdown of these claims by indication was available from the Health Insurance Commission.

Table 1 Medicare Benefits Schedule item numbers and descriptions for hyperbaric oxygen therapy services

Item Number	Description
13015	HYPERBARIC OXYGEN THERAPY for treatment of soft tissue radionecrosis or chronic non-diabetic wounds where hypoxia can be demonstrated performed in a comprehensive hyperbaric medicine facility, under the supervision of a medical practitioner qualified in hyperbaric medicine for a period in the hyperbaric chamber between 1 hour 30 minutes and 3 hours including any associated attendance. Fee: $206.55
13020	HYPERBARIC OXYGEN THERAPY for treatment of decompression illness, gas gangrene, air or gas embolism; diabetic wounds including diabetic gangrene and diabetic foot ulcers; necrotising soft tissue infections including necrotising fasciitis, Fournier's gangrene or for the prevention and treatment of osteoradionecrosis, performed in a comprehensive hyperbaric medicine facility, under the supervision of a medical practitioner qualified in hyperbaric medicine, for a period in the hyperbaric chamber of between 1 hour 30 minutes and 3 hours, including any associated attendance. Fee: $209.80
13025	HYPERBARIC OXYGEN THERAPY for treatment of decompression illness, air or gas embolism, performed in a comprehensive hyperbaric medicine facility, under the supervision of a medical practitioner qualified in hyperbaric medicine, for a period in the chamber greater than 3 hours, including and associated attendance - per hour (or part of an hour). Fee: $93.85
13030	HYPERBARIC OXYGEN THERAPY performed in a comprehensive hyperbaric medicine facility where the medical practitioner is pressurised in the hyperbaric chamber for the purpose of providing continuous life saving emergency treatment, including any associated attendance - per hour (or part of an hour) Fee: $132.55

The number of services under each of the MBS entries is given by State and calendar year in Tables 2 to 5.

Table 2 Number of services claimed for MBS Item 13015, by state and calendar year

Calendar year	Number of services by State								Total number of services
	NSW	Vic	Qld	SA	WA	Tas	ACT	NT	
2001	61	69	124	0	0	8	0	0	262
2002	893	1,900	1,866	21	20	160	0	0	4,860
2001 and 2002 combined	954	1,969	1,990	21	20	168	0	0	5,122
2002 (services per 10,000 population[a])	(1.34)	(3.89)	(5.00)	(0.14)	(0.10)	(3.38)	(0.00)	(0.00)	(2.46)

Data available at www.hic.gov.au/providers/health_statistics/index.htm

[a] Rate per 10,000 population using the number of services in 2002 and State-specific population estimates from the Australian Bureau of Statistics

Table 3 Number of services claimed for MBS Item 13020, by State and calendar year

Calendar year	Number of services by state								Total number of services
	NSW	Vic	Qld	SA	WA	Tas	ACT	NT	
1997	823	297	89	335	409	490	0	0	2,443
1998	1,567	977	311	232	280	396	20	19	3,802
1999	1,982	1,540	1,678	211	332	540	147	10	6,440
2000	2,257	3,398	2,196	322	360	634	45	106	9,318
2001	2,467	3,090	2,315	168	114	618	129	38	8,939
2002	1,356	2,960	1,174	274	40	321	73	92	6,290
1997-2002[a]	10,452	12,262	7,763	1,542	1,535	2,999	414	265	37,232
2002 (Services per 10,000 population)[b]	(2.04)	(6.06)	(3.15)	(1.80)	(0.21)	(6.78)	(2.27)	(4.65)	(3.19)

Data available at www.hic.gov.au/providers/health_statistics/index.htm

[a] Total number of services for 1997-2002

[b] Rate per 10,000 population using the number of services in 2002 and State-specific population estimates from the Australian Bureau of Statistics

Table 4 Number of services claimed for MBS Item 13025, by state and calendar year

Calendar year	Number of services by state								Total number of services
	NSW	Vic	Qld	SA	WA	Tas	ACT	NT	
1997	3	6	0	1	2	2	0	0	14
1998	5	3	2	4	0	2	0	0	16
1999	3	1	2	0	1	1	0	2	10
2000	4	12	1	0	3	1	0	0	21
2001	9	6	2	3	7	1	2	0	30
2002	14	6	9	0	2	1	0	0	32
1997-2002[a]	38	34	16	8	15	8	2	2	123
2002 (Services per 10,000 population)[b]	(0.02)	(0.01)	(0.02)	(0.00)	(0.01)	(0.02)	(0.00)	(0.00)	(0.02)

Data available at www.hic.gov.au/providers/health_statistics/index.htm

[a] Total number of services for 1997-2002

[b] Rate per 10,000 population using the number of services in 2002 and State-specific population estimates from the Australian Bureau of Statistics

Table 5 Number of services claimed for MBS Item 13030, by state and calendar year

Calendar year	Number of services by state								Total number of services
	NSW	Vic	Qld	SA	WA	Tas	ACT	NT	
1997	1	0	0	0	0	0	0	0	1
1998	0	0	0	0	0	0	0	0	0
1999	1	0	0	0	0	0	0	0	1
2000	0	0	0	0	0	0	0	0	0
2001	0	0	0	0	0	1	0	0	1
2002	0	0	0	0	0	0	0	0	0
1997-2002[a]	2	0	0	0	0	1	0	0	3

Data available at www.hic.gov.au/providers/health_statistics/index.htm

[a] Total number of services for 1997-2002

Approach to assessment

Review of literature

The medical literature was searched to identify relevant studies and reviews published between 1966 and 2002 using the Ovid databases and specific Internet-based sites and search engines (Table 6).

Table 6 Electronic databases used in this review

Database	Period/Issue covered
Cochrane Library including: The Cochrane Database of Systematic Reviews (CDSR) Database of Abstracts of Reviews of Effectiveness (DARE) The Cochrane Controlled Trials Register (CCTR)	Issue 4, 2002
CINAHL (OVID)	1982 to October Week 4 2002
Current Contents (OVID)	1993 Week 27 to 2002 Week 45
Medline (OVID)	1966 to October Week 4 2002
PreMedline (OVID)	30 October 2002
Biological Abstracts (OVID)	1980 to September 2002
ACP Journal Club (OVID)	1991 to September/October 2002
EMBASE (OVID)	1966 to 12 November 2002
CancerLit (www.cancer.gov/search/cancer_literature/)	1993 to 2 December 2002
National Guidelines Clearing House (www.guideline.gov/)	Searched on 13 January 2003
HBO Evidence (www.hboevidence.com)	Searched on 13 January 2003

The search terms used are shown in Table 7. The health technology assessment agency websites listed in Appendix E were also searched. Reference lists of publications were scanned and relevant citations retrieved. Publications recommended by the supporting committee and the applicant were also retrieved and assessed.

Table 7 Search terms

Intervention	Indication 1 Soft tissue radiation injuries	Indication 2 Non-healing wounds in non-diabetic patients	Safety filter	Cost-effectiveness filter[b]
Hyperbaric oxygenation[MeSH] hyperbar$[a] hbo$ multiplace chamber$ monoplace chamber$	radiation injuries[MeSH] radiotherapy[MeSH] radiation sickness radiotherap$ radionecrosis$ radio$ necr$ soft tissue injuries[MeSH] soft tissue$	wounds and injuries[MeSH] decubitus ulcer[MeSH] leg ulcer[MeSH] skin ulcer[MeSH] foot ulcer[MeSH] sore$ ulcer$ wound$	safety[MeSH] intraoperative complications[MeSH] postoperative complications[MeSH] mortality[MeSH] complicat$ adverse event$	economic$ cost$

[a] '$' represent a series of letters at the end of a word segment (ie surg$). MeSH terms are indicated by '[MeSH]' after the actual term (ie neoplasia[MeSH])

[b] Search phrase construction involved appending the Boolean operator 'OR' for terms within a column. Across columns, the Boolean operator 'AND' was used

Selection criteria

The following criteria were developed *a priori* to determine eligibility of relevant studies, based on those used in the prior MSAC evaluation of HBOT (MSAC 2001) and refined iteratively.

Subject characteristics

Inclusions: non-diabetic patients with non-healing, refractory wounds who have failed conventional therapies; patients with soft tissue radiation injuries.

Exclusions: patients not diagnosed with either of the above conditions.

Characteristics of the intervention

Inclusions: HBOT in a monoplace or multiplace chamber.

Characteristics of the comparison intervention

Inclusions: procedures not using HBO, including standard or conventional therapy (currently not defined), normobaric oxygen, or placebo procedures.

Characteristics of the outcome

Inclusions: all patient-relevant outcomes for both indications.

Characteristics of the study design

Inclusions: health technology assessments, systematic reviews, meta-analyses, and RCTs were sought initially. The search was extended to other controlled trials, cohort studies,

and comparative studies. Case series were included if patients were enrolled consecutively or if all patients presenting within a specified time frame were included.

Exclusions: case series in non-consecutively selected patients, case reports, narrative reviews, abstracts, opinions.

Characteristics of the publication

Inclusions: studies in the English language, in addition to systematic reviews and RCTs published in any language.

Exclusions: non-systematic reviews or non-RCTs published in foreign languages.

Search results

Non-healing wounds in non-diabetic patients

The search strategy identified 1,009 articles. Based on a consideration of abstracts, 189 articles were ordered for full text assessment. One hundred and seventy-three of these were obtained by 20 February 2003 and assessed in full text. In addition, one case series (Cianci 1988; Appendix F3) was considered on expert advice that all patients within a specified time frame were enrolled. Of these 174 articles, five met the inclusion criteria.

Of the 168 articles that did not meet the primary inclusion criteria, three were animal studies, 16 were case reports, one did not use HBO as therapy, 75 were narrative reviews, eight did not use HBOT, 26 were not specific to the indication, 20 were opinion pieces, four were for topical oxygen therapy, and 15 did not have an appropriate patient spectrum.

Refractory soft tissue radiation injuries

The search strategy identified 793 articles. After abstracts were reviewed, 94 articles were ordered for full text assessment. Ninety-two of these were obtained by 20 February 2003 and assessed in full text. Of these 92 articles, 16 met the inclusion criteria. In addition, two case series (Bevers et al 1995, Lee et al 1994; Appendix F4) were considered on expert advice.

Of the 76 studies that did not meet the inclusion criteria, 15 were case reports, four did not use HBO as therapy, 21 were narrative reviews, three did not contain effectiveness data, five did not refer to soft tissue radiation injuries, five were opinion pieces, and 23 did not have an appropriate patient spectrum.

Following application of the selection criteria, the list of articles potentially eligible for further assessment was forwarded for review to the Supporting Committee which made further recommendations for inclusion.

Data extraction

Data were extracted using standardised instruments created for the assessment. Two reviewers examined each article and any discrepancies in evaluation were discussed and resolved through consensus. Attempts were made to contact the corresponding authors to clarify specific issues relating to validity or results, such as the consecutive enrolment of patients in case series.

Assessment of validity

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 2000).

These dimensions (Table 8) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of their determination.

Table 8 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design[a]
Quality	The methods used by investigators to minimise bias within a study design
Statistical precision	The *p*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect
Size of effect	The distance of the study estimate from the "null" value and the inclusion of only clinically important effects in the confidence interval
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used

[a] See Table 9

Collectively, three sub-domains (level, quality and statistical precision) measure the strength of the evidence. The designations of the levels of evidence are shown in Table 9.

Table 9 Designations of levels of evidence[a]

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

[a] Modified from NHMRC (1999)

Critical appraisal refers to the process of evaluating the study design of included articles. The most rigorous study design for assessing the validity of therapeutic interventions is considered to be an RCT (Guyatt et al 1993, Sackett et al 2000).

Assessment of primary studies

The UK NHS Centre for Reviews and Dissemination assembled a list of criteria used for evaluating the validity of evidence from various study designs. The relevant validity criteria used in this review for assessing the quality of evidence are listed in Table 10.

Criteria to assess the validity of case series were based on those reported by the UK NHS Centre for Reviews and Dissemination, with some modifications in order to attain consensus among the reviewers on the final criteria.

Table 10 Validity criteria according to study design

Study design	Validity criteria[a]
RCT	Randomised method
	Allocation concealment
	Blinding of patients, investigators and outcome assessors
	Proportion lost to follow-up
	Intention to treat analysis
Cohort	Prospective/ retrospective
	Comparable groups at inception
	Identification and adjustment for confounding factors
	Blind outcome assessment
	Sufficient duration of follow-up
	Proportion lost to follow-up
Case-control	Explicit definition of cases
	Adequate details of selection of controls
	Comparable groups with respect to confounding factors
	Interventions and other exposures assessed in same way for cases and controls
	Appropriate statistical analysis
Case series	Indication comparable across patients
	Disease severity comparable across patients
	Explicit entry criteria
	Outcome assessed in all patients
	Follow-up time uniform
	Outcomes assessed objectively
	Outcomes assessed in a blinded manner
	Outcome measures quantified

[a] Modified from NHS Centre for Reviews and Dissemination

Assessment of secondary studies

The critical appraisal of systematic reviews was performed against the qualitative criteria (Chalmers & Altman 1995, Greenhalgh 1997, Sackett et al 2000) outlined in Table 11. These were designed to assess whether the systematic review was performed so as to minimise bias. The criteria assessed whether the systematic review contained explicit statements of the objectives and methods and whether the methods used were reproducible. Specific criteria assessed whether the review asked a focused question, if the eligibility criteria for included trials were explicit, what search strategy was used, how the validity of included trials was assessed and whether results of included trials were similar.

Table 11 Validity criteria for appraisal of systematic reviews

Is there a focused research question? ie PICO elements: patient, intervention, comparator, outcomes
Are inclusion and exclusion criteria for selected studies stated?
Is there an explicit and comprehensive search strategy? Did review incorporate a search strategy comprehensive enough that it was unlikely to have missed studies?
Are the included trials appraised for validity? Are validity criteria stated?
Are results consistent from study to study? Is homogeneity assessed?

Adapted from Evidence Based Medicine Toolkit, University of Alberta (www.med.ualberta.ca/ebm/ebm.htm)

Data analysis

Where statistical analysis was not provided in the original publication, the data were analysed for this assessment using Intercooled Stata 8.0 (College Station, Texas, USA).

Expert advice

A supporting committee with expertise in hyperbaric medicine, surgery, radiation oncology, general practice and consumer issues was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for supporting committees, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the supporting committee is provided in Appendix B.

Results of assessment

Is it safe?

Table 12 presents the summary of a review of side effects observed following 21,033 HBOT episodes conducted in Australia between 1 July 2001 and 30 June 2002 for a variety of indications including those that are the focus of this review. The review revealed similar findings to those discussed previously (MSAC 2001).

Table 12 Side effects associated with HBOT in Australia for financial year 2001-2002

Side effect	Incidence per number of treatments
Persistent ocular changes	1/112 (0.90%)
Significant ear barotrauma causing treatment interruption	1/170 (0.60%)
Claustrophobia	1/910 (0.10%)
CNS seizures (all treatment pressures)	1/1,548 (0.06%)
Sinus barotrauma	1/4,864 (0.02%)
Pulmonary oxygen toxicity	1/6,766 (0.01%)
Pulmonary barotrauma	0/15,475 (0.00%)
Deaths	0/21,033 (0.00%)

Source: (HTNA and ANZHMG 2002)

The most common adverse events associated with the procedure were middle ear barotrauma and reversible myopia (Tibbles & Edelsberg 1996, Leach et al 1998). Other reported adverse events were oxygen toxicity and claustrophobia (MSAC 2001).

The previous report (MSAC 2001) noted that progressive myopia was associated with prolonged, daily exposure to HBO and was more common at higher pressures. However, in Australian clinical practice it is uncommon for the number of sessions to exceed 60, with the length of these sessions generally lasting 90 minutes at 2.4 ATA.

Mild sedatives may assist in the continuation of therapy for patients who experience anxiety from claustrophobia in the treatment chamber (MSAC 2001).

Oxygen toxicity manifests as pulmonary or neurologic changes. Seizures have been estimated to occur at a rate of about 0.01 per cent but do not seem to produce residual effects (MSAC 2001).

A search of the literature was conducted for adverse events reported since the previous report (MSAC 2001). The only available data were from case series and case reports as summarised in Tables 13 and 14.

In the study by Weaver & Churchill (2001) three female patients with cardiac disease and reduced left ventricular ejection fractions (of 1,028 patients undergoing 13,658 procedures) developed pulmonary oedema associated with HBOT. Of these, two diabetic patients aged 52 and 75 years recovered and one 77 year-old patient with severe aortic stenosis died. No reasons were given for the administration of HBOT.

The authors speculated that HBOT may have contributed to pulmonary oedema by increasing left ventricular afterload, filling pressures and oxidative myocardial stress, and by decreasing left ventricular compliance.

Ohrui et al (2002) reviewed the 39-year experience (1960 to 1998) of using HBOT at the Japan Air Self-Defence Force (Table 14). Of more than 58,000 treatments, the overall incidence of adverse events was 6.3 per cent. Ear pain was the most common adverse event, occurring in 4.79 per cent of treatment episodes. Pain in the paranasal sinuses and abdomen resulted from about 0.86 per cent and 0.34 per cent of treatments, respectively.

Plafki et al (2000) reviewed treatment complications and side effects related to HBOT in 782 patients treated for various indications with a total of 11,376 sessions in a multiplace chamber (Table 13). Pain or discomfort during decompression occurred in 216 (27.6%) patients and 12 of the 782 (1.5%) required the placement of a tympanostomy tube.

Table 13 Adverse events associated with hyperbaric oxygen therapy: case series

First author, year	Study size	Type of adverse event	Number of events	Average rate per 100 sessions	Rate of all events per 100 sessions	Total number of events
Ohrui, 2002	Sessions: 58,454	Ear pain	NR	4.79	6.29	NR
		Paranasal sinus pain	NR	0.86		
		Abdominal pain	NR	0.34		
		Hypoxia	NR	0.08		
		Hyperventilation	NR	0.08		
		Joint pain	NR	0.05		
		Toothache	NR	0.03		
		Other[a]	NR	0.11		
Plafki, 2000	Patients: 782	Pain and/or discomfort during decompression	216	NR	NR	228
	Sessions: 11,376	Tympanostomy tube placement	12	NR		

Abbreviations: NR, not reported
[a] Not specified

HBO in cancer growth and progression

Numerous pre-clinical studies have examined the role of HBO in initiating or enhancing the neoplastic process Feldmeier (2001). Hyperbaric oxygen directly inhibits the growth of tumour cells in culture (Kalns et al 1998) and reduces their metastatic potential (Feldmeier et al 1997). Immune suppression has not been demonstrated consistently as a mechanism of neoplastic development (Xu et al 1997, Brenner et al 1999), nor has increased cell damage due to free radical generation with HBO been established (Zamboni et al 1989, Kaelin et al 1990, Monstrey et al 1997).

The oxygen tensions used were much higher in most of these pre-clinical studies than those used clinically. In addition, the intermittent exposure to HBO seen in clinical settings is thought to induce adaptive mechanisms that reduce the damaging effects of free radicals between HBOT sessions (Feldmeier 2001).

The use of HBO to enhance the effect of radiation therapy (ie as a radiosensitiser) was first described by Johnson & Lauchlan (1966). A systematic review of 15 clinical studies on the potential effect of HBO on cancer development conducted in 1994 (Feldmeier et al 1994) and updated in 2001 (Feldmeier 2001) showed that 12 of the 15 were actually designed to test the efficacy of HBO as a radiosensitiser rather than its effect on primary neoplastic growth, cancer recurrence or metastasis (Table 14).

Table 14 Clinical studies of exposure to HBO and cancer development[a]

First author, year	Number of patients	Location of cancer	Exposure to HBOT (Sessions x ATA)	Effect on cancer
Johnson, 1966	25	Cervix	30 x 3	Increased growth
Van Den Brenk,1967	85	Head and neck	2-6 x 3	Decreased growth
Cade, 1967	49	Lung and bladder	40 x 3	Mixed results, trending to increased growth
Johnson, 1974	64	Cervix	25-30 x 3	Mixed results, trending to decreased growth
Henk, 1977	276	Head and neck	10 x 3	Mixed results, trending to decreased growth
Henk, 1977	104	Head and neck	10 x 3	Decreased growth
Bennett, 1977	213	Cervix	10 x 3	None
Perrins, 1978	236	Bladder	6-40 x 3	None
Watson, 1978	320	Cervix	6-27 x 3	None
Dische, 1978	1,500	Head and neck, bladder, lung, cervix	6-12 x 3	None
Brady, 1981	65	Cervix	10 x 3	Decreased growth
Eltorai, 1987	3	Urothelium	10-20 x 2	Increased growth
Denham, 1987	201	Head and neck	NR	Decreased growth
Bradfield, 1996	4	Head and neck	NR	Increased growth
Marx, 1999	405	Head and neck	NR	Decreased growth

Abbreviations: NR, not reported

[a] Adapted from Feldmeier (2001). Bibliographic details of studies cited in this table appear in Appendix G

Studies showing increased growth or tumour progression were designed without control groups. Comparative studies generally showed a lack of effect or decreased growth. The weight of clinical evidence suggests that HBO does not increase the risk of primary cancer, metastatic growth or recurrence. Feldmeier (2001) suggested that treatment should not be withheld due to concerns regarding a higher likelihood of tumour recurrence in patients where HBOT is likely to be beneficial.

In summary, estimates of the incidence of adverse events relating to HBOT collected through national registries suggested that most adverse events were self-limited and resolved after termination of therapy. As was found in the previous report on HBOT (MSAC 2001), the most common adverse events were myopia, barotrauma, claustrophobia and oxygen toxicity. Serious, life-threatening events and fatalities were rare.

Is it effective?

Non-healing, refractory wounds in non-diabetic patients

Two comparative studies met the inclusion criteria, the RCT by Hammarlund & Sundberg (1994) which was previously reported under the indication of non-diabetic wounds (MSAC 2001) and a comparative study by Reedy et al (1994).

In addition, three case series met the inclusion criteria (Rosenthal & Schurman 1971, Sakakibara et al 1987, Lee et al 1989). All described the use of HBOT in the setting of wound management in the 1980s and included a number of types of non-healing wounds. The three used different interpretations of 'wound healing' as an end-point but did not describe how the outcomes were assessed, whether assessment was made using objective, valid, and consistent criteria, or whether blinding was performed. Moreover, the authors failed to report whether disease severity was comparable across patient groups. The three case series are described in detail in Appendix F1.

Results from the randomised controlled trial

Hammarlund & Sundberg (1994) conducted an RCT (Level II evidence) in Sweden. They recruited 16 patients (nine males) with a median age of 67 years and a range of 42 to 75 years. Patients were enrolled if: i) they had had leg ulcers for more than one year which did not appear on inspection to progress towards healing during the two months before the study, ii) ankle and first digit blood pressures were within normal ranges and iii) if they did not smoke or suffer from concomitant chronic disease conditions such as diabetes mellitus. The authors did not report the nature or duration of any therapies prior to the administration of HBOT.

Validity

The study failed to meet three of the five criteria used to gauge validity. The authors did not report the method of randomisation, allocation concealment or blinding. All randomised patients were included in the analyses of outcomes at six weeks of follow-up.

Summary of findings

Two balanced groups of eight subjects were exposed to oxygen in a multiplace chamber at 2.5 ATA for 90 minutes, five times a week for a total of 30 sessions. The intervention group was given 100 per cent oxygen while the comparison group received air. The total length of follow-up was six weeks. Wound area was assessed as the primary outcome by placing a transparent film over the affected area, tracing the outline of the wound, scanning the film into a computer and calculating the size using a program designed specifically for the study.

The study looked at the mean changes in wound area over the course of therapy (Table 15). At four and six weeks, there were statistically significant decreases in the wound areas of those receiving 100 per cent oxygen compared to those receiving air.

Table 15 Percentage decrease in wound area following six weeks of exposure to 100 per cent oxygen or air in a pressurised chamber

Weeks of therapy	Percentage decrease in wound area[a] Mean (SD)		p-value[b]
	100% Oxygen	Air	
2	6.6 (14)	2.8 (11)	0.5557
4	22.0 (13)	3.7 (11)	0.0088
6	35.7 (17)	2.7 (11)	0.0004

Source: Hammerland & Sundberg 1994. Abbreviations: SD, standard deviation
[a] Compared to baseline (Week 0)
[b] Inter-group comparison

The authors found that improvement continued after the completion of HBOT, although this occurred only for smaller wounds and was based on a much smaller sample size due to losses to follow up. At week 18, healing occurred in two patients who had been exposed to 100 per cent oxygen for six weeks and in no patients who received air (ITT analysis: risk difference=25%; 95% confidence interval: -5%, 55%; p=0.4667).

Results from the non-randomised comparative study

The observational study by Reedy et al (1994) enrolled women who had experienced wound breakdown following radical vulvectomy. The age of the study subjects ranged from 13 to 98 years. The study used historical controls (Level III-3 evidence). Eight patients who were administered HBOT following surgery for squamous or Bartholin gland carcinoma (with or without lymph node dissection, LND) in a hospital in Texas, USA were enrolled prospectively from October 1990 to March 1993. Controls (n=22) were women with or without wound breakdown selected from medical records who had undergone surgery for the same indications but were not given HBOT.

Of the eight women who underwent HBOT, relevant co-morbidities included coronary artery disease (n=2), peripheral vascular disease (n=1), congestive heart failure (n=1), malnutrition (n=1), obesity (n=1), and illegal drug use (n=1). Information on co-morbidities was not available for the comparison group.

Validity

Three outcomes were reported: length of hospitalisation, wound breakdown defined as separation of the wound along the incision, and infection. The authors failed to report whether outcomes were assessed objectively using specific criteria, whether assessment was performed in a blinded manner or whether follow-up was of a sufficient duration to observe relevant end-points. There were no losses to follow-up in the group receiving HBOT.

The use of historical controls in this study may have introduced specific biases relating to the selection of a comparable set of patients, since different entry criteria were used. Clearly, there is no expectation that the distribution of specific confounders would be similar between groups, but the rigour of the study would have been increased by an attempt to control for these confounding factors. As comparisons were made using historical controls any temporal improvements in wound care practices or related technologies may bias the results in favour of those receiving HBOT.

Summary of findings

The intervention group was initially given pre-operative antibiotic prophylaxis and pneumatic compression stockings. Closed suction drains were placed at the discretion of the surgeon. Prophylactic intravenous antibiotics were given in the first three post-operative days, after which oral antibiotics were prescribed until all drains were removed.

Patients began treatment with HBOT immediately following surgery. Pure oxygen was administered at two ATA for 90 minutes, twice a day for the first five days. If hospitalisation was required beyond five days, HBOT was continued at two ATA for 120 minutes once a day until the ninth post-operative day.

Length of hospitalisation was shorter for those patients receiving HBOT where wound breakdown did not take place (Table 16). One (16.7%) of the six patients in the intervention group who underwent LND experienced both wound breakdown and infection. Of the nine patients who underwent LND and did not receive HBOT, there were seven (77.8%) cases of wound breakdown and four (44.4%) cases of infection.

Table 16 Wound breakdown and length of hospitalisation in patients undergoing HBOT following radical vulvectomy with or without lymph node dissection

Surgery and intervention	Sample size (n)	Wound breakdown		Infection		Length of hospitalisation, mean (range)
		n (%)	p-value[a]	n (%)	p-value[a]	
Vulvectomy with LND:						
. Without HBOT	9	7 (77.7)	0.041	4 (44.4)	0.580	13.6 (7-18) with wound breakdown
. With HBOT	6	1 (16.7)		1 (16.7)		6.5 (5-8) without wound breakdown
						9.0 (6-15) with wound breakdown
Vulvectomy without LND:	13	3 (23.1)	1.000	1 (7.7)	1.000	12.7 (2-21) with wound breakdown
. Without HBOT	2	0 (00.0)		0 (0.0)		6.8 (3-12) without wound breakdown
. With HBOT						7.5 (6-9) with wound breakdown

Source: Reedy et al 1994. Abbreviations: LND, lymph node dissection

[a] Calculated from data provided in the published article

Refractory soft tissue radiation injuries

One systematic review (Feldmeier & Hampson 2002) and six comparative studies (Marx et al 1985, Marx 1994, Neovius et al 1997, Carl et al 2001, Pritchard et al 2001, Hulshof et al 2002) met the inclusion criteria.

Nine case series met the inclusion criteria. Seven dealt with soft tissue radionecrosis (Roden et al 1990, Feldmeier et al 1993, Feldmeier et al 1995, Feldmeier et al 1996, Feldmeier et al 2000, Filntisis et al 2000, Yu et al 2002) and two considered other radiation injuries (Woo et al 1997, Mayer et al 2001). All shared the same methodological shortcomings identified in the previous indication, including the absence of objective and patient-relevant outcomes and blinding. The nine case studies are described in Appendix F2.

Results from the systematic review

A systematic review by Feldmeier & Hampson (2002) examined the evidence supporting HBOT in the prevention or treatment of delayed radiation injury.

Validity

Overall the validity of the above systematic review is uncertain as the methodology of the review was inadequately described. For example the authors did not identify a discrete research question, no inclusion/exclusion criteria was specified and no search strategy was described. Therefore it is difficult to ascertain whether the primary studies included in the systematic review were a complete and comprehensive set of studies on which to base inferential statements.

The authors appraised the quality of the supporting evidence using a number of 'review schemes'. However, neither the application of these criteria nor the reliability of decisions reached by the authors during the course of the appraisal was described. The authors' description of the review as systematic was not supported by current criteria used to assess systematic reviews.

Summary of findings

When considering the supporting evidence across various indications the authors applied the same decisions regardless of the weight of that evidence (Table 17). For instance, it is debatable whether the decision made by the authors that HBOT for radiation cystitis was "acceptable and useful based on very good evidence" is accurate given the evidence underlying this statement is all Level IV (one case report and 16 case series).

Table 17 Assessment of the supporting evidence for the use of HBOT in the management of refractory soft tissue radiation injuries

Indication	Evidence	Decision reached by the authors[a]	
		AHA scheme	Clinical evidence scheme[b]
Soft tissue radio-necrosis of the head and neck	5 case series, 1 comparative study with historical controls, 1 comparative study	Acceptable and useful based on fair to good evidence	Likely to be beneficial
Radiation cystitis	1 case report, 16 case series	Acceptable and useful based on very good evidence	Likely to be beneficial
Radiation injuries to the chest wall and breast	1 case report, 3 case series	Acceptable and useful based on fair to good evidence	Likely to be beneficial
Radiation proctitis and enteritis	2 animal studies, 2 case reports, 10 case series	Acceptable and useful based on fair to good evidence	Likely to be beneficial
Miscellaneous abdominal wall and pelvic injuries	1 case report, 2 case series	Acceptable and useful based on fair to good evidence	Likely to be beneficial
Various neurologic injuries	1 animal study, 4 case reports, 7 case series, 1 RCT	From not acceptable to indeterminate to acceptable and useful based on fair to good evidence	From unlikely to be beneficial to unknown effectiveness to likely to be beneficial
Radiation injuries to the extremities	1 case report, 1 case series	Acceptable and useful based on fair to good evidence	Likely to be beneficial

Abbreviations: AHA, American Heart Association; RCT, randomised controlled trial

[a] Feldmeier & Hampson 2002

[b] Based on the Clinical Evidence (BMJ publication) scheme

In some instances, a vote-counting method was applied to derive the likelihood of benefit. In its simplest form, the vote-counting method details the number of studies showing a particular benefit compared with the number of studies showing harm. A decision is based on whether a greater number of studies show harm or benefit. The outcome of this technique does not indicate the magnitude of the effect. Moreover, a major flaw in the vote-counting process is that the quality of the studies is not considered.

In spite of these methodological problems, the references provided by Feldmeier & Hampson (2002) were evaluated for inclusion, and assessed for validity in accordance with the approach to assessment described above. No new primary studies were identified as a result of this evaluation.

Results from randomised controlled trials

Four RCTs (Marx et al 1985, Marx 1994, Pritchard et al 2001, Hulshof et al 2002) on the use of HBOT on a variety of indications were identified (Table 18). They examined the use of HBOT in cognitive disorders following irradiation of the brain (Hulshof et al 2002), radiation-induced plexopathy (Pritchard 2001), and healing of myocutaneous flaps following radiation (Mark 1994). The study by Marx et al (1985), previously considered by MSAC for the prevention of osteoradionecrosis (MSAC 2001) was also considered here because it reported wound healing results.

None of the studies reported dates of enrolment. Only Pritchard et al (2001) reported the age distribution of the study population (Table 18).

Table 18 Descriptive characteristics of randomised controlled trials of HBOT in refractory soft tissue radiation injuries

First author, year	Study location	Enrolment dates	Patient characteristics			Indication
			Number of patients	Number of males	Median age (years)	
Hulshof, 2002	The Netherlands	NR	7	NR	NR	Cognitive disorders following irradiation of the brain
Marx, 1994	USA	NR	160	NR	NR	Healing of soft tissue flaps following radiation
Marx, 1985	USA	NR	74 (291 teeth)	NR	NR	Wound healing after tooth removal in patients at high risk of developing osteoradionecrosis
Pritchard, 2001	UK	NR	34	0	55	Radiation-induced brachial plexopathy

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

Validity

The methodological domains related to validity in RCTs were poorly described for the four trials (Table 19). None described methods of randomisation or processes of concealment. Only the study by Pritchard et al (2001) reported blinding during outcome assessment. The same study reported two withdrawals in those receiving HBOT and near-complete follow-up at 12 months.

Table 19 Methodological quality of randomised controlled trials of HBOT in refractory soft tissue radiation injuries

First author, year	Method of randomisation	Concealment of allocation	Inclusion of randomised participants	Blinding	Losses to follow-up
Hulshof, 2002	NR	NR	Yes	NR	None
Marx, 1994	NR	NR	NR	NR	NR
Marx, 1985	NR	NR	NR	NR	None
Pritchard, 2001	NR	NR	2 withdrawals	Yes	1/72 missed assessment

Abbreviations: NR, not reported (ie unclear, not stated, or unknown)

Summary of findings

Cognitive disorders following irradiation of the brain

Hulshof et al (2002) described a small study examining the effect of HBOT on cognitive functioning in patients with cognitive disorders after irradiation of the brain. Patients were enrolled if they: i) suffered from short-term memory loss; ii) had concentration problems or diminished speed of processing; iii) were at least 18 months post-radiation; iv) had an initial radiation dose of at least 30 Grays in three weeks (or biological equivalent); v) had no signs of tumour recurrence on computed tomography or magnetic resonance imaging; vi) were aged between 18 and 60 years; and vii) had a Karnofsky performance score of at least 70. Patients were excluded if they had concurrent severe neurological or vascular disease, uncontrollable epileptic seizures, previous chemotherapy or a general impediment to HBOT.

Seven patients (one male) aged between 39 and 56 years were randomised to immediate treatment with HBOT or treatment with HBOT after a three-month delay. This allowed assessment of the effect of HBOT versus no therapy during the first three months while ensuring that all patients received HBOT. Pure oxygen was given over 30 HBOP sessions, administered five to six times per week, at a pressure of three ATA for 125 minutes. A battery of neuropsychological tests was administered to all patients (Table 20).

Table 20 Neuropsychological tests used in Hulshof et al (2002)

Test	Type of measurement
Symbol Digit Modalities Test of the WAIS	Speed of information processing
Similarities of the WAIS	Ability to reason abstractly
Block design of the WAIS	Visual-spatial insight and visuo-constructive skills
Boston Naming Test	Naming line drawings of objects and animals
Auditory Verbal Learning Test	Verbal memory
Letter Fluency of the Multilingual Aphasia Examination	General vocabulary memory
Category Fluency of the GIT	Vocabulary memory related to animals and occupation
Logical Memory of the Rivermead Behavioural Memory Test	Memory for structured verbal material
Calculation of the GIT	Numerical ability
Warrington Recognition Memory Test Faces	Aspects of non-verbal memory
Trailmaking Test	Executive functioning, motor speed, attention
Stroop Color-Word Test	Selective attention, perceptual interference, response inhibition
Nelson's Modified Wisconsin Card Sorting Test	Cognitive flexibility
FEPSY	Reaction time and choice reaction time
Grooved Pegboard	Visual-motor and speed coordination

Abbreviations: GIT, Groninger Intelligence Test; WAIS, Wechsler Adult Intelligence Scale

One patient was reported to have experienced a 'meaningful improvement' in neuropsychological functioning. After three months of follow-up, patients given HBOT reportedly experienced a 'small but not significant benefit' in neuropsychological function. Overall, six of seven patients experienced an improvement in one to nine of the 31 tests, although these did not reach statistical significance. The clinical significance of these results is unclear.

Healing of soft tissue flaps following radiation

The study by Marx (1994) was previously evaluated under the indication of skin graft survival (MSAC 2001). The author enrolled 160 patients requiring tissue flaps in tissues radiated to a dose greater than 6,400 centiGrays. Patients were randomly allocated to receive HBOT for 20 sessions before surgery, then 10 sessions in the post-operative period. Pressure, frequency, and duration of HBOT were not described. The therapies provided to the comparison group were not stated.

Three clinical outcomes were examined: wound infection, dehiscence and delayed wound healing (Table 21). For wound infection and dehiscence, minor and major states were differentiated but not quantified in an objective or reliable manner. Patients receiving HBOT were less likely to develop major wound infections or major wound dehiscence. Delayed wound healing was seen in 55 per cent of those who did not receive HBOT versus 11.25 per cent in those receiving HBOT.

Table 21 Proportion of wound infection, dehiscence and delayed wound healing in patients receiving HBOT versus other therapy

Outcome	Intervention group (n=80) n (%)	Comparison group (n=80) n (%)	p-value
Wound infection:			
. Minor	3 (3.75)	6 (7.50)	0.3033
. Major	2 (2.50)	13 (16.25)	0.0028
. Total	5 (6.25)	19 (23.75)	0.0019
Wound dehiscence:			
. Minor	6 (7.50)	12 (15.00)	0.1333
. Major	3 (3.75)	26 (32.50)	<0.0001
. Total	9 (11.25)	38 (47.50)	<0.0001
Delayed wound healing	9 (11.25)	44 (55.00)	<0.0001

Source: Marx 1994

Wound healing following tooth removal in patients at high risk of development of osteoradionecrosis

Marx et al (1985) enrolled 74 patients who had an indication for removal of one or more teeth in a segment of the mandible which had received a documented absorbed dose of 6,000 rads or greater, and who agreed to maintain follow-up visits for a minimum of six months. The authors excluded patients if they had: i) received irradiation for less than six months or more than 15 years before enrolment; ii) known contraindications to penicillin or exposure to 100 per cent oxygen at 2.4 ATA; iii) showed evidence of persistent tumour or new primary malignant disease; iv) received chemotherapy including steroid drugs within six months of enrolment; or v) concomitant systemic disease which could be expected to affect wound healing.

Patients were randomly assigned to one of two groups. The comparison group (n=37) received one million units of aqueous penicillin G intravenously before surgery and 500 mg of phenoxymethylpenicillin four times a day for 10 days after surgery. The intervention group was exposed to HBO at 2.4 ATA for 90 minutes once daily for five to six days per week. This group underwent 20 sessions before surgery, then 10 sessions after tooth removal. As reported previously (MSAC 2001), the primary outcome reported by this study was clinical diagnosis of osteoradionecrosis during follow-up. However, only the results for wound healing were considered in the present report.

Penicillin was administered to 37 patients with 137 socket wounds. Six months after completion of therapy, 11 patients (29.7%) who were given penicillin had 31 socket wounds (22.6%) that failed to heal. In the group receiving HBOT, two patients (5.4%) had four socket wounds (2.6%) that failed to heal (Table 22).

Table 22 Proportions of patients and tooth sockets failing to heal after six months following treatment with HBOT or penicillin

Variable/Outcome	Intervention group	Comparison group	p-value
Number of patients	37	37	na
Patients with unhealed tooth sockets, n (%)	2 (5.4)	11 (29.7)	0.012
Number of tooth sockets	156	137	na
Proportion of unhealed tooth sockets, n (%)	4 (2.6)	31 (22.6)	0.005

Source: Marx et al 1985. Abbreviations: na, not applicable

Radiation-induced brachial plexopathy

Pritchard et al (2001) enrolled 34 patients with confirmed radiation-induced brachial plexopathy following radiation therapy for early stage breast cancer who were free from cancer recurrence and who were physically and psychologically fit for HBOT. Patients were randomly allocated to HBOT at 2.4 ATA using either 100 per cent oxygen or air comparable to 100 per cent oxygen at surface pressure (59 per cent nitrogen and 41 per cent oxygen). All participants were treated for 100 minutes including two five-minute air breaks, five days per week for six weeks to give a total of 30 sessions.

The primary end-point was the warm sensory threshold which is a measure of the function of the small sensory fibres. The test was performed with the hand resting on a paddle heated to 30°C. Participants were asked to indicate the sensation of increased temperature as it was raised by 1°C per second. As secondary end-points, the authors assessed heat pain threshold, cool sensation threshold, sensory action potentials in the median and ulnar nerves, pain using the McGill Pain Questionnaire and quality of life using the SF-36.

Two patients receiving HBOT withdrew from the study after 15 and 18 sessions, respectively.

The authors reported that there were no statistically significant differences between those receiving HBOT or air in terms of the primary or secondary sensory outcomes (Table 23).

Table 23 Sensory outcomes following 30 sessions of HBOT versus air in patients with radiation-induced brachial plexopathy

Outcome, follow-up	Change in outcome Mean (SD)		p-value[a]
	HBOT	Air	
Warm sensory threshold, °C above 30°			
1 week post treatment	-0.12 (5.01)	1.00 (3.92)	0.4732
12 months post treatment	1.41 (5.54)	0.53 (3.43)	0.5900
24 months post treatment	1.44 (6.21)	2.96 (5.84)	0.5964
Cool sensory threshold, °C			
1 week post treatment	-0.24 (3.05)	1.14 (5.23)	0.3544
12 months post treatment	2.45 (5.45)	0.82 (5.09)	0.3822
24 months post treatment	3.45 (6.91)	1.05 (7.18)	0.4721
Heat pain sensory threshold, °C			
1 week post treatment	-1.76 (4.91)	1.28 (3.76)	0.0511
12 months post treatment	1.78 (13.30)	5.13 (12.20)	0.4574
24 months post treatment	1.66 (12.55)	-5.59 (15.28)	0.2719
Sensory action potentials, median nerve, μV			
1 week post treatment	0.02 (1.63)	0.11 (0.67)	0.8346
12 months post treatment	-0.67 (3.77)	-1.03 (2.35)	0.7461
Sensory action potentials, ulnar nerve, μV			
1 week post treatment	-0.78 (1.40)	-0.38 (1.17)	0.3728
12 months post treatment	-0.69 (2.46)	-1.20 (2.22)	0.5373

Source: Pritchard et al 2001. Abbreviations: SD, standard deviation
[a] Inter-group comparison

Although the authors reported that the results of the SF-36 showed between-group differences in emotional role function and physical function at 12 months (Table 24), they also noted that the differences were difficult to interpret and did not reflect obvious improvements in the condition. No results for the McGill Pain Questionnaire were presented.

Table 24 Outcomes from the SF-36 following 30 sessions of HBOT versus air in patients with radiation-induced brachial plexopathy

SF-36 Scale	1 Week post treatment Mean (SE)		12 Months post treatment Mean (SE)	
	Control	HBOT	Control	HBOT
General health	68.4 (5.3)	68.6 (4.9)	61.1 (6.2)	58.8 (5.8)
Mental health	82.0 (4.0)	73.9 (6.7)	77.8 (3.4)	76.5 (4.1)
Role-emotional	79.2 (10.0)	77.0 (9.4)	66.7 (11.0)	82.2 (7.7)
Social functioning	94.3 (6.1)	86.5 (7.2)	93.3 (7.1)	88.6 (6.7)
Vitality	53.6 (5.4)	47.6 (4.1)	43.8 (3.9)	38.7 (3.8)
Bodily pain	60.4 (5.8)	46.8 (5.8)	54.2 (5.7)	40.8 (4.6)
Role-physical	44.2 (10.4)	48.4 (10.5)	29.7 (9.5)	35.3 (10.9)
Physical functioning	62.1 (5.2)	55.4 (5.1)	57.5 (5.4)	53.5 (5.7)

Source: Pritchard et al 2001. Abbreviations: SE, standard error

Results from non-randomised comparative studies

Two non-randomised studies compared the effectiveness of HBOT versus no treatment with HBOT in patients who had received post-operative radiation for cancers of the pharyngeal and laryngeal areas (Neovius et al 1997) or the breast (Carl et al 2001). Table 25 summarises the descriptive characteristics of these studies.

Table 25 Descriptive characteristics of non-randomised comparative studies of HBOT in refractory soft tissue radiation injuries

First author, year	Study Location	Study design	Dates of enrolment	Patient Characteristics			Indication
				Sample size	Number of males	Mean age (years)	
Carl, 2001	Germany	Prospective comparative study with concurrent controls (Level III-2)	Jul 1996-Mar 1999	44	0	NR	Late radiation injuries following breast-conserving therapy
Neovius, 1997	Sweden	Retrospective, comparative study using historical controls (Level III-3)	Oct 1993-Aug 1995	30	NR	63	Non-healing wounds following radiotherapy and surgery for oral, pharyngeal, and laryngeal cancers

Abbreviation: NR, not reported (ie unclear, not stated or unknown)

Carl et al (2001) conducted a prospective comparative study with concurrent controls (Level III-2 evidence) that examined the effectiveness of HBOT in women with late radiation injuries following breast-conserving therapy (limited surgery and radiation therapy). Late radiation sequelae were assessed using modified LENT-SOMA criteria developed by Pavy et al (1995). Patients with symptomatic breast oedema and subjective pain greater than Grade III (persistent and intense) or with a total score of at least eight points according to the LENT-SOMA criteria were eligible for inclusion in the study.

Of 635 patients undergoing breast-conserving therapy from July 1996 to March 1999 at the Radiation Oncology Clinic of the University of Dusseldorf, 44 patients met the inclusion criteria. Of these, 32 were enrolled in the treatment group. Twelve patients refused HBOT and served as the control group. No demographic details were provided for either the treatment or control groups. The authors reported that pre-treatment scores were the same between the groups.

Neovius et al (1997) reviewed the records of 30 patients with oral, pharyngeal or laryngeal cancer classified as T2 to T4 and treated previously with radiotherapy to a dose of 52 to 62 Grays. All had major infected wounds or chronic fistulas with no sign of healing at a minimum of three weeks post surgery.

The group receiving HBOT (n=15) had been treated between October 1993 and August 1995 in a Swedish hospital. There were 10 males and the mean age of all patients receiving HBOT was 63 years. An historical comparison group (Level III-3 evidence) of a similar mean age was enrolled from an earlier period in which HBOT was not administered. As discussed previously the use of historical controls may bias the results in favour of HBOT in the event that improvements in wound care practices or related technologies arise from one assessment period to the next.

Validity

The major outcomes reported by Carl et al (2001) were pre- and post-treatment scores using modified LENT-SOMA criteria for subjective pain, oedema, fibrosis, telangiectasia, and erythema, as well as the sum of all scores. The validity and reliability of these criteria have been established in other studies (Hoeller et al 2003). The authors did not report blinding of outcome assessors to treatment group allocation, which may have resulted in results biased in favour of HBOT (Table 26). The authors acknowledge that there may be systematic differences in selection or symptom grading due to the lack of randomisation that may also have resulted in bias.

The major outcome reported by Neovius et al (1997) was the healing status of the wound, although criteria for evaluation of this end-point were not defined. It was unclear whether outcomes were assessed objectively using specific criteria, whether assessment was performed in a blinded manner or whether follow-up was of sufficient duration to observe relevant end-points (Table 26).

Similar to Reedy et al (1994), the use of historical controls by Neovius et al (1997) may have introduced specific biases relating to the selection of a comparable set of patients since entry criteria were not explicitly reported. Additionally, no attempt was made to adjust for known confounders. Temporal progress of improvements in wound care or technology, especially as it relates to comparisons between different time periods, may bias the results in favour of HBOT.

Table 26 Validity characteristics of non-randomised comparative studies of HBOT in refractory soft tissue radiation injuries

First author, year	Comparable groups at inception	Identification and adjustment for confounding factors	Blind outcome assessment	Sufficient duration of follow-up	Proportion lost to follow-up
Carl, 2001	NR	No	NR	NR	None
Neovius, 1997	NR	No	NR	NR	None

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

Summary of findings

Late-radiation sequelae following breast-conserving therapy

Patients undergoing HBOT received treatment at a pressure of 240 kPa (2.4 ATA) for a breathing time of 90 minutes and a median total number of 25 sessions (range 7 to 60) at a rate of five times per week (Carl et al 2001). Patients continued therapy until three consecutive treatments failed to show any further improvement in the outcome scores.

Results are presented in Table 27. Carl et al (2001) reported statistically significant improvements in post-treatment scores for pain, oedema, erythema and the total score in patients treated with HBOT compared to those not receiving HBOT. No statistically significant differences in scores were observed between the treatment groups for fibrosis and telangiectasia.

Table 27 Outcomes in patients receiving HBOT versus no HBOT (Carl et al 2001)

Outcome	HBOT[a] (n=32) Median (range)	No HBOT[b] (n=12) Median (range)	p-value
Pain Score Pre-treatment Post-treatment	 3 (1-4) 0 (0-2)	 3 (1-3) 3 (1-4)	<0.001
Oedema score Pre-treatment Post-treatment	 3 (1-3) 1 (0-2)	 2 (0-3) 2 (0-3)	<0.001
Fibrosis score Pre-treatment Post-treatment	 0 (0-3) 0 (0-3)	 0 (0-3) 0 (0-3)	NS
Telangiectasia Pre-treatment Post-treatment	 0 (0-3) 0 (0-3)	 0 (0-2) 0 (0-2)	NS
Erythema Pre-treatment Post-treatment	 2 (0-3) 0 (0-2)	 3 (0-3) 0 (0-2)	<0.001
Total score Pre-treatment Post-treatment	 9 (6-14) 2 (0-6)	 8 (3-12) 7 (3-12)	<0.001

Abbreviations: NS, not significant – the actual value was not reported

[a] Median follow-up was 11 months with a range of 1-32

[b] Median follow-up was 7 months with a range of 2-38

Carl et al (2001) concluded that patients experienced an improvement in clinical state during the course of hyperbaric oxygen therapy for pain, oedema and erythema.

Non-healing wounds following radiotherapy and surgery for oral, pharyngeal, and laryngeal cancers

Neovius et al (1997) reported that patients received antibiotics, minor surgery, and wound dressings as required. The HBOT group received 100 per cent oxygen at 2.5 to 2.8 ATA for between five and 40 treatments of 75 minutes' duration. Patients were initially scheduled to receive 30 treatments. If wounds had not healed when this stage was reached, another 10 treatments were given.

Results are presented in Table 28. There was a statistically significant increase in the probability of complete wound healing in those undergoing HBOT (p=0.045). Two

patients in the comparison group suffered from severe haemorrhage post-operatively and died. There were no fatalities in the group receiving HBOT.

Table 28 Outcomes in patients receiving HBOT versus no HBOT (Neovius et al 1997)

Outcome	HBOT Group (n=15)	Comparison Group (n=15)
Complete healing	12	7
Partial healing	2	1
Failure to heal	1	7

Discussion

Although evidence in support of the effectiveness of HBOT in the treatment of non-healing wounds in non-diabetic patients and of refractory soft tissue radiation injuries included higher level evidence study designs (RCTs and non-RCTs), this evidence was deemed to be of low methodological quality because it failed to meet relevant validity criteria. Furthermore, the majority of studies reported end-points that were of uncertain clinical significance or patient relevance. Where relevant outcomes were reported, their validity was uncertain due to a lack of objective or blinded assessment and the failure to report explicit measurement criteria.

Non-healing wounds in non-diabetic patients

Only two controlled studies of HBOT for non-healing wounds in non-diabetic patients met the entry criteria. One RCT showed decreased wound area with HBOT while a comparative study using historical controls showed trends toward the prevention of wound breakdown and infection, as well as reductions in length of hospitalisation.

Refractory soft tissue radiation injuries

Six controlled studies of HBOT for refractory soft tissue radiation injuries met the inclusion criteria. Four RCTs examined four different sub-indications related to radiation therapy. A small RCT examining the use of HBOT for cognitive impairment following brain irradiation showed no significant improvement in neuropsychological function. Another RCT that evaluated HBOT for radiation-induced brachial plexopathy showed no significant differences in sensory thresholds or quality of life between those receiving HBOT and controls. Another RCT showed that HBOT improved wound healing in patients at high risk of osteoradionecrosis. The fourth RCT showed that HBOT reduced the likelihood of major wound infection, major wound dehiscence, and delayed wound healing in myocutaneous grafts in patients who had previously undergone radiation therapy.

There is general acceptance among radiation biologists that the underlying pathogenesis of radiation injury is common to all tissues, although the latency of onset and mode of expression of radiation injury can vary widely (Denham et al 2001; Travis 2001). Clinical opinion suggests that there is no reason to postulate inherent differences between the necrosis of soft tissue and that of bone.

All studies failed to meet the criteria used to assess the quality in RCTs. For instance, it is known that effect sizes are overestimated in RCTs if particular methodological

parameters such as description of the randomisation process, allocation concealment procedures, or blinding, are not met (Schulz et al 1995). This failure limited the extent to which inferences and generalisations could be made.

Two on-going clinical trials were found (Appendix E). In the area of refractory soft tissue radiation injuries, the National Centre for Complementary and Alternative Medicine (NCCAM) of the US National Institutes of Health is presently sponsoring a trial on the efficacy of HBOT in patients who have undergone laryngectomies and radiation for cancer. A larger study sponsored by the Baromedical Research Foundation is also under way. Both trials are in the stages of recruitment. Dates of completion are not presently known.

Three case series reporting on non-healing, refractory wounds in non-diabetic patients and nine dealing with refractory soft tissue radiation injuries were identified which enrolled consecutive patients. While the considerable potential for bias inherent in their design limited the use of the information contained in these case series, it was included to supplement the evidence available from the more rigorous comparative studies.

Limitations of the review of safety and effectiveness

While items from the grey literature (eg conference proceedings, abstracts, etc) identified by expert opinion were included, the search strategy was not designed to capture publications from these sources. However, the likelihood of missing good quality RCTs was minimised by searching trial registries and other databases including those specific to HBOT for HBO evidence.

The inclusion of Level IV studies in the form of case series expanded the breadth of evidence over that of the previous report. Moreover, since the decision to include studies was made independently of the assessment of quality, there was little chance that relevant studies would have been missed.

A large proportion of the evidence has been published as case series. Non-comparative studies are useful as initial positions against which the potential effectiveness of technologies may be viewed. However, they are of limited value in determining the effectiveness of new technologies in the complex milieu of existing therapy.

Assessment of the quality of case series evidence is challenging. There is no validated instrument and inherent biases exist in the interpretation of the comparative effectiveness of interventions from such study designs. A modification of the NHS CRD criteria was applied to determine the quality of the Level IV evidence. The reviewers developed additional criteria that do not appear in the original CRD inventory. These criteria were chosen *a priori* based on items appearing in studies of more rigorous design, but some degree of subjectivity was necessary to attain consensus among the reviewers on the final criteria.

A sensitive search strategy identified a wide range of studies and indications which required clinical expertise for determination of their eligibility for inclusion under the entity 'soft tissue radiation injuries' (eg cognitive impairment, plexopathy, etc). The use of such a sensitive strategy reduced the possibility that relevant studies may be missed.

What are the economic considerations?

The earlier report (MSAC 2001) included calculation of the cost-effectiveness of HBOT for a number of indications for which some evidence suggested the treatment was effective. The likely average cost of monoplace HBOT treatment was calculated under a range of assumptions about capacity utilisation, capital cost, and staffing. The current report used those indicative costs and applied them to the evidence for the effectiveness of HBOT in refractory soft tissue radiation injuries and non-healing wounds in non-diabetic patients.

The estimated direct cost of HBOT (MSAC 2001) was not based on a prospective study of HBOT treatment in clinical practice in Australia and was therefore unable to assess fully the implications for overall disease management. Given these limitations on the cost data, the present report can only provide an indication of the potential cost-effectiveness of HBOT in Australian practice.

It was estimated that the average cost of a course of treatment (30 sessions in a monoplace unit) was $6,941 with a range of $2,466 to $9,255 depending on the number of chambers in operation (one to four) and the number of sessions (15 to 40) (MSAC 2001, Appendix E). The direct cost made allowance for a feasible number of patients in a day and included staffing, overhead, maintenance, and capital costs.

Non-healing, refractory wounds in non-diabetic patients

As reported (MSAC 2001), Hammarlund & Sundberg (1994) exposed two groups of eight subjects with leg ulcers of more than one year's duration to different concentrations of oxygen in a multiplace chamber, five times a week for a total of 30 sessions.

The study looked at the mean changes in wound area over the course of therapy (Table 15). At four and six weeks of therapy, there were statistically significant decreases in the wound areas of the HBOT group compared to the comparison group. The HBOT group had a 35.7 per cent decrease in wound area from baseline at six weeks compared to 2.7 per cent decrease in wound area for the comparison group. This suggested that HBOT treatment of chronic leg ulcers might result in an expected one-third reduction in wound area for a treatment cost of $6,941 per patient.

The clinical significance of this outcome or its significance to patient welfare in the longer term is not sufficiently clear to allow assessment of whether this figure is acceptable. The study also reported an increase in healing at week 18 of 25 per cent which suggests an apparent extra $27,764 per additional person cured of a chronic leg ulcer in the study. However, given the p-value of 0.4667 for the risk difference in the study, it is not possible to be confident that this is a reasonable estimate of the cost-effectiveness of HBOT for this indication.

The comparative study by Reedy et al (1994) of HBOT in women who had experienced wound breakdown following radical vulvectomy suggested that there might be reductions in hospital stay as well as wound breakdown and post procedure infections. The reduction in mean length of hospital stay (Table 16) was less than five days when all wounds were considered and HBOT was given for an average of nine days as ten 90-minute sessions and four two-hour sessions.

Using the cost calculations in the previous report (MSAC 2001), the direct cost of HBOT amounts to $3,430. While a reduction in length of stay would offset that direct cost, it may not lead to financial savings. No accurate data are available on the cost of an extra day in hospital for this indication in Australia. In any case, the study design and sample size in Reedy et al (1994) are such that it is not possible for reliable inferences about the use of resource and comparative health outcomes to be made.

Cianci et al (1988) examined the costs and outcomes of HBOT for patients with serious lesions of the lower extremity that had proven refractory to standard medical or surgical treatments. The patients were given one or two treatments of 1.5 to 2 hour's duration at two ATA in a monoplace chamber. The study did not explicitly report the results for the non-diabetic wounds of 20 of the 39 patients, however re-analysis of the data suggested an average cost of hospital treatment of US$25,281. There appeared to be one amputation in the non-diabetic group at a reported cost of US$26,000 to US$30,000 and a further cost of comprehensive rehabilitation in California in excess of US$40,000. On this basis, the study suggested that HBOT compared favourably with the cost of standard treatment for those with limb-threatening refractory lesions of the leg.

In this study the cost of treatment with HBOT was 36 per cent of the expected total cost of surgery and rehabilitation for a patient requiring amputation. The study claims that there would be financial savings if HBOT resulted in at least 36 per cent fewer amputations among patients with serious lesions of the lower extremity that had proven refractory to standard medical or surgical treatments. The study did not provide evidence about the likely outcomes and treatment costs for a group of patients without HBOT. It is, therefore, not possible to conclude that there would be either reduced amputations or consequent savings as a result of HBOT.

Refractory soft tissue radiation injuries

An evaluation by the Canadian agency Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS 2001) drew on the findings of Marroni et al (1996) to calculate the financial savings from reduced length of hospital stay arising from HBOT in five conditions including problem wounds.

AETMIS (2001) suggested substantial savings in hospital expenditure in excess of direct HBOT costs associated with a 58 to 75 percent reduction in mean length of stay. Even if a similar reduction in length of stay could be inferred from these data, the evidence in Marroni et al (1996) was not of sufficiently quality to substantiate such a claim. The average cost of a session of HBOT at €120 is higher than the cost in Australia, but the reduction in length of stay in Marroni et al (1996) was not demonstrated convincingly. As the AETMIS study stated, Marroni et al (1996) merely gave the length of stay without explaining the protocol used to compare the two situations (with and without HBOT). Neither the study by Marroni et al (1996) nor the AETMIS review (AETMIS 2001) have demonstrated that such results would be achieved in Australia for HBOT compared to standard treatment for problem wounds including leg ulcers or soft tissue radionecrosis.

Marx (1994), in what was described as a randomised prospective study of wound complications related to soft tissue flaps and wound healing, suggested that HBOT led to a relative reduction in wound dehiscence, reduced infection, and improved wound healing. Each of these outcomes has the potential to lead to reduced health care resource use in terms of antibiotic use, wound irrigations, debridement surgery and hospital stay.

Marx (1994) reported the use of HBOT following the application of myocutaneous grafts to subjects requiring major soft tissue surgery or flap after radiation therapy. However, since neither the intervention nor the comparison therapies were adequately described, and no details of the frequency and duration of HBOT exposure were given, it was difficult to estimate the economic consequences of therapy. As stated previously (MSAC 2001), 'exposure to HBOT may well demonstrate a beneficial effect on the survival of split skin grafts and myocutaneous flaps, but the study (Marx 1994) possesses serious flaws that strictly limit its generalisability'. As a result, it is not, possible to reach a conclusion about the cost-effectiveness of HBOT in soft tissue radiation injuries.

A case study reported by Boykin et al (1997) estimated that HBOT would lead to a 31 per cent reduction in the expected cost of treatment for a radionecrotic wound. However, since this estimate is based on a single case study with a simulated untreated case, it cannot be regarded as sufficient evidence of actual costs saved from adjunctive HBOT for radiation injuries.

Only Pritchard et al (2001) included a measure of quality of life following treatment with HBOT. They reported the results of the SF-36 health status measures following 30 sessions of HBOT versus air in patients with radiation-induced brachial plexopathy. Quality of life at one week and 52 weeks appeared to have deteriorated in both groups and any differences between the groups were not consistently in favour of HBOT.

Conclusions

Safety

Estimates of the incidence of adverse events relating to HBOT collected through national registries suggested that most adverse events were self-limited and resolved after termination of therapy. As reported previously (MSAC 2001), the most common forms of adverse events were myopia, barotrauma, claustrophobia and oxygen toxicity. Serious, life-threatening events and fatalities were rare.

Effectiveness

Non-healing wounds in non-diabetic patients

Two controlled studies of HBOT for non-healing wounds in non-diabetic patients met entry criteria. One RCT showed a decrease in wound area while a comparative study using historical controls showed trends toward the prevention of wound breakdown and infection, and reductions in length of hospitalisation.

Refractory soft tissue radiation injuries

Six controlled studies of HBOT for refractory soft tissue radiation injuries met inclusion criteria. Four RCTs examined four different sub-indications related to radiation therapy. One small RCT examining the use of HBOT for cognitive impairment following brain irradiation showed non-significant improvement in neuropsychological function. Another RCT evaluating HBOT for radiation-induced brachial plexopathy showed no significant differences in sensory thresholds or quality of life between those receiving HBOT and controls. In a group of patients at high risk for the development of osteoradionecrosis, HBOT was found to increase the healing of tooth socket wounds following extraction compared to the administration of penicillin. The fourth RCT showed that HBOT reduced the likelihood of major wound infection and major wound dehiscence and delayed wound healing in myocutaneous grafts in patients who had undergone radiation therapy.

Cost-effectiveness

Chronic refractory wounds have a high morbidity that can have severe consequences on the quality of life of patients and their families as well as resulting in high acute care and rehabilitation costs for the health care system. This is particularly the case if there is a risk of a major amputation. To the extent that a course of treatment of HBOT could reduce that morbidity at a cost of $6,941, it has the potential to be a very cost effective intervention.

The clinical evidence was inadequate to substantiate claims that HBOT was cost effective in the treatment of refractory soft tissue radiation injuries or non-diabetic refractory wounds. There was not evidence of sufficient quality to substantiate claims that it will

either lead to an overall saving in resource use, or that it would lead to substantial patient relevant gains in health related quality of life compared to current medical treatments at an acceptable cost.

Recommendations

The clinical evidence was inadequate to substantiate claims that hyperbaric oxygen therapy (HBOT) was cost-effective in the treatment of refractory soft tissue radiation injuries or non-diabetic refractory wounds. However, MSAC recommended that, as there are no effective alternative therapies and in view of the progress of local data collections and an international trial, funding for HBOT continue for MBS listed indications at currently eligible sites, for a further three years.

- The Minister for Health and Ageing accepted this recommendation on 31 August 2004.

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and existing medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new and existing medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of MSAC comprises a mix of expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumer issues, and health administration and planning:

Member	Expertise or Affiliation
Dr Stephen Blamey (Chair)	general surgery
Professor Bruce Barraclough	general surgery
Professor Syd Bell	pathology
Dr Paul Craft	clinical epidemiology and oncology
Associate Professor Jane Hall	health economics
Dr Terri Jackson	health economics
Ms Rebecca James	consumer health issues
Professor Brendon Kearney	health administration and planning
Associate Professor Richard King	internal medicine
Dr Ray Kirk	health research
Dr Michael Kitchener	nuclear medicine
Mr Lou McCallum	consumer health issues
Dr Ewa Piejko	general practice
Professor John Simes	clinical epidemiology and clinical trials
Mr Chris Sheedy	Assistant Secretary, Diagnostics and Technology Branch, Australian Government Department of Health and Ageing
Dr Robert Stable	Australian Health Ministers' Advisory Council representative
Professor Bryant Stokes	neurological surgery
Associate Professor Ken Thomson	radiology
Dr Douglas Travis	urology

Appendix B Supporting Committee

Supporting committee for MSAC application 1054
Hyperbaric oxygen therapy for non-healing, refractory wounds in non-diabetic patients and refractory soft tissue radiation injury

Professor Peter Phelan (Chair) BSc, MBBS, MD, FRACP, MRACMA Emeritus Professor of Paediatrics University of Melbourne	Member of MSAC
Dr Michael Bennet MBBS, DA(Eng), FANZCA, MM(ClinEpi), DipDHM Department of Diving and Hyperbaric Medicine Prince of Wales Hospital, NSW	Nominated by the Australian and New Zealand Hyperbaric Medicine Group
Dr Stephen Blamey MBBS, FACS, FRACS Head of Gastrointestinal Surgery, Monash Medical Centre Chair, Infection Control Advisory Committee Southern Health	Chair of MSAC
Dr Michael Leung MBBS, FRACS Head, Plastic and Reconstructive Surgery Unit The Alfred Hospital	Co-opted member
Professor Lester Peters MBBS(Hons), MD, FRANZCR, FACR, AM Professor of Radiation Oncology Peter MacCallum Cancer Institute	Co-opted member
Dr John M Quinn MBBS, FRACS, FACS Senior Visiting Vascular Surgeon, and Senior Visiting Transplant Surgeon Princess Alexandra Hospital Brisbane Senior Visiting Vascular Surgeon Mater Miseracordiae Hospital Brisbane Examiner in Vascular Surgery RACS (Senior Examiner Elect)	Co-opted member

Dr David Smart BMedSci(Tas), MBBS(Hons), FACEM, FACTM, I DipDHM Medical Co-Director, Department of Diving and H Medicine Royal Hobart Hospital. Director of Emergency Medicine Calvary Health Care Tasmania Senior Clinical Lecturer, Faculty of Health Science University of Tasmania Chair Scientific Committee Australasian College for Emergency Medicine	Co-opted member
Dr Ross Taylor MBBS, FRACP, DDU, Ct Aerospace Medicine, GrDTh General Practitioner, Senior Examiner RACGP	Nominated by the Royal Australian College of General Practitioners
Mrs Robin Toohey AM	Nominated by the Consumers' Health Forum of Australia
Dr David Wilkinson MBBS, DipRACOG, DA(UK), FANZCA Director, Hyperbaric Medicine Unit Royal Adelaide Hospital	Co-opted member
Dr Robert Wong BSc, MBBS, FFARACS, FANZCA, DipDHM Medical Director Department of Diving and Hyperbaric Medicine Fremantle Hospital	Nominated by the Australian and New Zealand College of Anaesthetists

Appendix C Studies included in the review

Included studies: Non-healing, refractory wounds in non-diabetic patients

Hammarlund, C. & Sundberg, T. 1994. 'Hyperbaric oxygen reduced size of chronic leg ulcers: A randomized double-blind study', *Plastic & Reconstructive Surgery*, 93 (4), 829-833; discussion 834.

Lee, H.C., Niu, K.C., Chen, S.H., Chang, L.P. & Lee, A.J. 1989. 'Hyperbaric oxygen therapy in clinical application. A report of a 12-year experience', *Chung Hua i Hsueh Tsa Chih - Chinese Medical Journal*, 43 (5), 307-316.

Reedy, M.B., Capen, C.V., Baker, D.P., Petersen, W.G. & Kuehl, T.J. 1994. 'Hyperbaric oxygen therapy following radical vulvectomy: An adjunctive therapy to improve wound healing', *Gynecologic Oncology*, 53 (1), 13-16.

Rosenthal, A.M. & Schurman, A. 1971. 'Hyperbaric treatment of pressure sores', *Archives of Physical Medicine & Rehabilitation*, 52 (9), 413-415 passim.

Sakakibara, K., Takahashi, H. & Kobayashi, M. 1987. In: Kindwall, E.P. (ed.), *Proceedings of the 8th international congress on Hyperbaric Medicine* Best Publishers, San Pedro, California, 223-228.

Included studies: Refractory soft tissue radiation injuries

Carl, U.M., Feldmeier, J.J., Schmitt, G. & Hartmann, K.A. 2001. 'Hyperbaric oxygen therapy for late sequelae in women receiving radiation after breast-conserving surgery', *International Journal of Radiation Oncology, Biology, Physics*, 49 (4), 1029-1031.

Feldmeier, J.J., Heimbach, R.D., Davolt, D.A. & Brakora, M.J. 1993. 'Hyperbaric oxygen as an adjunctive treatment for severe laryngeal necrosis: A report of nine consecutive cases', *Undersea & Hyperbaric Medicine*, 20 (4), 329-335.

Feldmeier, J.J., Heimbach, R.D., Davolt, D.A., Court, W.S., Stegmann, B.J. & Sheffield P.J. 1995. 'Hyperbaric oxygen as an adjunctive treatment for delayed radiation injury of the chest wall: A retrospective review of twenty-three cases', *Undersea & Hyperbaric Medicine*, 22 (4), 383-393.

Feldmeier, J.J., Heimbach, R.D., Davolt, D.A., Court, W.S., Stegmann, B.J. & Sheffield P.J. 1996. 'Hyperbaric oxygen an adjunctive treatment for delayed radiation injuries of the abdomen and pelvis', *Undersea & Hyperbaric Medicine*, 23 (4), 205-213.

Feldmeier, J.J., Heimbach, R..D., Davolt, D.A., McDonough, M.J., Stegmann, B.J. & Sheffield, P.J. 2000. 'Hyperbaric oxygen in the treatment of delayed radiation injuries of the extremities', *Undersea & Hyperbaric Medicine*, 27 (1), 15-19.

Feldmeier, J.J. & Hampson, N.B. 2002. 'A systematic review of the literature reporting the application of hyperbaric oxygen prevention and treatment of delayed radiation injuries: An evidence based approach', *Undersea & Hyperbaric Medicine*, 29 (1), 4-30.

Filntisis, G.A., Moon, R.E., Kraft, K.L., Farmer, J.C., Scher, R.L. & Piantadosi, C.A. 2000. 'Laryngeal radionecrosis and hyperbaric oxygen therapy: Report of 18 cases and review of the literature', *Annals of Otology, Rhinology & Laryngology*, 109 (6), 554-562.

Hulshof, M.C., Stark, N.M., van der Kleij, A., Sminia, P., Smeding, H.M. & Gonzalez, D. 2002. 'Hyperbaric oxygen therapy for cognitive disorders after irradiation of the brain', *Strahlentherapie und Onkologie*, 178 (4), 192-198.

Marx R. 1994 'Radiation injury to tissue', In: Kindwall, E.P. (ed.), *Hyperbaric medicine practice*, Best Publishing, USA, 462-468.

Marx, R.E., Johnson, R.P. & Kline, S.N. 1985. 'Prevention of osteoradionecrosis: a randomized prospective clinical trial of hyperbaric oxygen versus penicillin', *Journal of the American Dental Association*, 111 (1), 49-54.

Mayer, R., Klemen, H., Quehenberger, F. et al,. 2001. 'Hyperbaric oxygen – an effective tool to treat radiation morbidity in prostate cancer', *Radiotherapy & Oncology*, 61 (2), 151-156.

Neovius, E.B., Lind, M.G. & Lind, F.G. 1997. 'Hyperbaric oxygen therapy for wound complications after surgery in the irradiated head and neck - a review of the literature and a report of 15 consecutive patients', *Head & Neck Surgery*, 19 (4), 315-322.

Pritchard, J., Anand, P., Broome, J. et al,. 2001. 'Double-blind randomized phase II study of hyperbaric oxygen in patients with radiation-induced brachial plexopathy', *Radiotherapy & Oncology*, 58 (3), 279-286.

Roden, D., Bosley, T.M., Fowble, B. et al,. 2001. 'Delayed radiation injury to the retrobulbar optic nerves and chiasm', *Ophthalmology*, 97 (3), 346-351.

Woo, T.C., Joseph, D. & Oxer, H. 1997. 'Hyperbaric oxygen treatment for radiation proctitis', *International Journal of Radiation Oncology, Biology, Physics*, 38 (3), 619-622.

Yu, S.Y., Chen, S.T., Chan, S.E., Kuo, S.J. & Niu, K.C. 2002. 'Hyperbaric oxygen therapy for late sequelae of breast irradiation', *Formosan Journal of Surgery*, 35 (4), 209-214.

Appendix D Studies excluded from the review

Non-healing, refractory wounds in non-diabetic patients

Pre-clinical (animal) studies

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Refractory soft tissue radiation injuries

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Appendix E Clinical trial registries and HTA websites searched

Ongoing clinical trials

Efficacy of Hyperbaric Oxygen Therapy in Laryngectomy Patients

This study, sponsored by the National Centre for Complementary and Alternative Medicine (NCCAM), was designed to develop a predictive model for the development of wound complications in patients undergoing laryngectomy surgery for laryngeal/adjoining structure cancers, and to evaluate the clinical efficacy of hyperbaric oxygen for the prevention/management of wound complications in this previously irradiated population. Patients are enrolled if in need of laryngectomies for newly-diagnosed cancers and for failed chemoradiation.

Baromedical Research Foundation Project HORTIS (Hyperbaric Oxygen Radiation Tissue Injury Study)

Project HORTIS was conceived to increase the current level of evidence regarding HORT and better determine its effectiveness. HORTIS will involve a total of eight different trials – seven at separate anatomic sites and one prophylactic arm. The seven sites are the mandible, larynx, skin, bladder, rectum, colon and cervix.

HORTIS was designed as a multi-centre randomised and double-blinded controlled clinical trial with patient cross-over. Recruitment has been under way since 1999. The first institution to become a part of HORTIS is the Mexican National Cancer Institute (INCAN). Additional centres that have completed their institutional ethics review process are Vancouver General Hospital, British Columbia Canada; Palmetto Richland Memorial Hospital, Columbia, South Carolina, USA; The University of Istanbul Medical Centre, Turkey; Prince of Wales Hospital, Sydney, NSW, and the Royal Adelaide Hospital, Adelaide, SA. Institutions in Israel and Europe have expressed preliminary interest.

Clinical trial registries searched

Current Controlled Trials
www.controlled-trials.com/ (Accessed 10 January 2003)

UK National Research Register
www.update-software.com/National/ (Accessed 10 January 2003)

NHMRC Clinical Trials Centre
www.ctc.usyd.edu.au/ (Accessed 10 January 2003)

HTA websites searched

Agence d'Évaluation des Technologies et des Modes d'Intervention en Santé (AETMIS)
www.aetmis.gouv.qc.ca (Accessed 13 January 2003)

Agencia de Evaluación de Tecnologías Sanitarias (AETS)
www.isciii.es/aets/ (Accessed 13 January 2003)

Agencia Andaluza de Evaluación de Tecnologías Sanitarias (AETSA)
www.csalud.junta-andalucia.es/orgdep/AETSA/default.htm (Accessed 13 January 2003)

Alberta Heritage Foundation for Medical Research (AHFMR)
www.ahfmr.ab.ca/ (Accessed 13 January 2003)

Agency for Healthcare Research and Quality (AHRQ)
www.ahrq.gov/ (Accessed 13 January 2003)

Agence Nationale d'Accréditation et d'Évaluation en Santé (ANAES)
www.anaes.fr/ANAES/anaesparametrage.nsf/HomePage?ReadForm
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Agence Nationale pour le Dévéloppement de l'Évaluation Medicale (ANDEM)
www.upml.fr/andem/andem.htm (Accessed 13 January 2003)

Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S)
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German Institute for Medical Documentation and Information (DIMDI)
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Danish Centre for Evaluation and Health Technology Assessment
www.dihta.dk/ (Accessed 13 January 2003)

Finnish Office for Health Care Technology Assessment (FINOHTA)
www.stakes.fi/finohta/e/ (Accessed 13 January 2003)

Health Council of the Netherlands (GR)
www.gr.nl/ (Accessed 13 January 2003)

Minnesota Health Technology Advisory Committee
www.health.state.mn.us/htac/ (Accessed 13 January 2003)

Institute of Clinical Systems Improvement (ICSI)
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Institute of Technology Assessment of the Austrian Academy of Sciences
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International Network of Agencies of Health Technology Assessment (INAHTA)
www.inahta.org/ (Accessed 13 January 2003)

Medical Technology and Practice Patterns Institute (MTPPI)
www.mtppi.org/frameset.asp?Pg=/&MI=1 (Accessed 13 January 2003)

National Co-ordinating Centre for Health Technology Assessment (NCCHTA)
www.hta.nhsweb.nhs.uk/ (Accessed 13 January 2003)

National Horizon Scanning Centre
www.publichealth.bham.ac.uk/horizon/ (Accessed 13 January 2003)

National Institute for Clinical Excellence (NICE)
www.nice.org.uk/ (Accessed 13 January 2003)

New Zealand Health Technology Assessment (NZHTA)
nzhta.chmeds.ac.nz/ (Accessed 13 January 2003)

Swedish Council on Health Technology Assessment in Health Care (SBU)
www.sbu.se/admin/index.asp (Accessed 13 January 2003)

Swiss Centre for Technology Assessment (TA-SWISS)
www.ta-swiss.ch/ (Accessed 13 January 2003)

The Norwegian Centre for Health Technology Assessment
www.oslo.sintef.no/smm/news/FramesetNews.htm (Accessed 13 January 2003)

TNO Prevention in Health (TNO)
www.health.tno.nl/homepage_pg_en.html (Accessed 13 January 2003)

Veterans Affairs Health Services Research and Development
www.hsrd.research.va.gov/ (Accessed 13 January 2003)

World Health Organisation Health Technology and Pharmaceuticals
www.who.int/technology/ (Accessed 13 January 2003

Appendix F1 Non-healing, refractory wounds in non-diabetic wounds: case series meeting primary inclusion criteria

Table 29 Descriptive characteristics of case series evaluating HBOT in non-healing, refractory wounds in non-diabetic patients

First author, year	Study location	Dates of enrolment	Number of patients	Number of males	Mean age (years±SD)	Co-morbidities	Inclusion/Exclusion criteria
Lee, 1989	China	1976 to 1987	149/1,288 (chronic ulcer patients only)	99	41.2±36.8 Range: 6-78	NR	All patients treated between 1976 and 1987 at the Department of Diving and Hyperbaric Medicine, Naval General Hospital, Kaoshing
Rosenthal, 1971	USA	NR	18	14	Range: 15-67	Vascular disease: 2 Quadriplegia: 3 Paraplegia: 12 Fracture: 1	All patients presenting with pressure ulcers treated at the authors' facility at the time of publications
Sakakabira, 1987	Japan	1966 to 1983	149/161 (non-diabetics)	NR	NR	Burger's disease Obstructive arteriosclerosis	Although no inclusion/exclusion criteria was reported all patients had received surgical treatment for chronic peripheral vascular disease and other adjunctive treatments that did not provide relief

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

Table 30 HBOT regimens used in case series of non-healing, refractory wounds in non-diabetic patients

First author, year	Type and location of wound	Time from wound/lesion to HBOT	Therapies tried before HBOT	Duration of therapy tried before HBOT	HBOT regimen	Concomitant therapies
Lee, 1989	Chronic ulcers	NR	NR	NR	Oxygen pressure and treatment schedules not reported Mean number of treatments: 25.2±36.8; Range: 3-280	NR
Rosenthal, 1971	Pressure sores	NR	Standard ulcer treatment including mechanical cleansing, frequent dressing changes, mechanical debridement and Hubbard tank therapy	NR	3 ATA for 1.2 hours daily, 5 days per week Mean number of treatments: 37 Range: 14-60	Standard ulcer treatment including mechanical cleansing, frequent dressing changes, mechanical debridement and Hubbard tank therapy
Sakakabira, 1987	Chronic peripheral vascular disease (location of ulcers not reported)	NR	Arteriography or artography Sympathectomy or arterial reconstructive surgery	NR	2 ATA for 75 minutes once a day for a total of 30 to 50 sessions	Most patients received cytochrome C

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

Table 31 Validity characteristics of case series examining HBOT in non-healing, refractory wounds in non-diabetic patients

First author, year	Explicit inclusion/exclusion criteria	Outcomes assessed in all patients	Uniform follow up	Measurement of outcomes	Outcomes quantified	Outcomes measured objectively	Blinded assessment of outcome	Indication/Disease severity uniform across patients	Description given of failed treatment
Lee, 1989	No	Yes	NR	NR	No	No	NR	NR	NR
Rosenthal, 1971	No	Yes	NR	NR	No	No	NR	NR	Yes
Sakakabira, 1987	No	Yes	NR	NR	No	No	NR	NR	Yes

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

Table 32 Results of case series examining HBOT in non-healing, refractory wounds in non-diabetic patients

First author, year	Outcomes reported	Result	Length of follow-up
Lee, 1989	Cured	77/149 (51.7%)	NR
	Improved	57/149 (38.3%)	
	Invalid	15/149 (10%)	
Rosenthal[a], 1971	Improved	27/38 (71%)	NR
	Required Surgery for closure	11/38 (29%)	
	Healed	22/38 (58%)	
Sakakabira, 1987	Soreness: ASO TAO	 74/106 (70%) improved 30/43 (70%) improved	NR
	Ulcer: ASO TAO	 35/43 (81%) improved 84/106 (79%) improved	
	Amputation Required: Fingers or Toes: ASO TAO	 6/43 (14%) 16/106 (15%)	
	Extremities: ASO TAO	 4/43 (9.3%) 12/106 (11.3%)	

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

[a] The 18 patients in the study had a total of 38 wounds

Appendix F2 Refractory soft tissue radiation injuries: case series meeting primary inclusion criteria

Table 33 Descriptive characteristics of HBOT in refractory soft tissue radiation injuries

First author, year	Study location	Dates of enrolment	Number of patients	Number of males	Mean age (years±SD)	Co-morbidities	Inclusion/Exclusion criteria
Feldmeier, 1993	USA	1980 to 1985	9	9	64.8±8.3 Range: 56-82	NR	Inclusion: All patients referred for HBO and treated for laryngeal necrosis at the hyperbaric medicine facility at Southwest Methodist Hospital, San Antonio, Texas, between 1980 and 1985 who had not had a total laryngectomy before referral
Feldmeier, 1995	USA	From 1980 onwards	8 patients with 23 soft tissue injuries	1	55.25±14.37 Range: 21-87	NR	Inclusion: Review of all patients with chest wall radiation necrosis referred to the hyperbaric medicine departments of Southwest Texas Methodist and Nix Hospitals, San Antonio, Texas
Feldmeier, 1996	USA	From 1979 onwards	42 with 44 soft tissue injuries	8	62.52±12.71 Range: 33-84	NR	Inclusion: All patients treated at Southwest Texas Methodist and Nix Hospitals, San Antonio, Texas for non-healing necrotic wounds of the extremities within previously irradiated fields between the years of 1979 to 1997
Feldmeier, 2000	USA	1979 to 1997	17	8	62.68±18.5 Range: 31-87	NR	Inclusion: All patients treated at Southwest Texas Methodist and Nix Hospitals San Antonio, Texas for non-healing necrotic wounds of the extremities within previously irradiated fields between the years of 1979 to 1997
Flintisis, 2000	USA	1990 to 1996	18	11	59.61±10.03 Range: 41-77	Hyponatremia (1) Chronic renal failure (3) Hypertension (3) COPD (3) Lung carcinoma (1) Diabetes (3) Angina (1) Basal cell carcinoma of the skin (1) Rheumatoid arthritis (1) Alcohol abuse (1)	Inclusion: All patients referred for HBO therapy to the FG Hall Hyperbaric Center at Duke University Medical Center Durham, North Carolina with the diagnosis of radio-induced laryngeal damage between 1990 and 1996

Table 33 cont Descriptive characteristics of HBOT in refractory soft tissue radiation injuries

First author, year	Study location	Dates of enrolment	Number of patients	Number of males	Mean age (years± SD)	Co-morbidities	Inclusion/Exclusion criteria
Roden, 2001	USA	Jul 1979 to Sep 1987	13	7	63.3±8.6 Range: 46-75	Radiation damage to areas of the brain outside the afferent visual system	Inclusion: All patients with presumed radiation damage to the optic nerves or chiasm that were referred to the Neuro-Ophthalmology service at Wills Eye Hospital Philadelphia, Pennsylvania Exclusion: Patients were excluded from this report due to alternative explanations of visual loss including tumour mass contiguous with the intracranial optic nerves or chiasms, possible optic neuritis, possible malignant meningitis and occipital lobe radiation
Yu, 2002	Taiwan	Jun 1998 to May 1999	5 patients with 6 soft tissue injuries	0	54±7.35 Range: 49-67	NR	Inclusion: All patients with breast sequelae post irradiation between June 1998 and May 1999 referred to the hyperbaric oxygen centre of the Changhua Christian Hospital, Changhua

Abbreviations: NR, not reported (ie unclear, not stated or unknown); COPD, chronic obstructive pulmonary disease

Table 34 Descriptive characteristics of case series of HBOT in other radiation-induced complications

First author, year	Study location	Dates of enrolment	Number of patients	Number of males	Mean age (years)	Co-morbidities[a]	Inclusion/Exclusion criteria
Mayer, 2001	Austria	Jun 1995 to Mar 2000	18	18	71.2 Range: 64-77 years	. Diabetes (6) . IgG-Kappa-plasmocytoma (1) . Bladder cancer (1) . Myelodysplasia (1) . Amyloidosis (1)	Inclusion: All patients suffering from radiation induced proctitis and/or cystitis able to undergo HBO treatment at the Division of Thoracic and Hyperbaric surgery, Graz, Austria, between June 1995 and March 2000 Exclusion: Patients with severe emphysema and patients unable to achieve pressure adjustment in the middle ear
Woo, 1997	Australia	NR	18	17	72 both groups[b]	NR	Inclusion: All patients completing a course of HBO therapy at the Fremantle Hospital Medicine Unit, Western Australia for radiation proctitis as assessed by proctoscope, sigmoidoscope, or colonoscope, and none had any concomitant bleeding disorder such as haemophilia

Abbreviations: NR, not reported (ie unclear, not stated or unknown)
[a] Patients may have had more than one co-morbidity
[b] Insufficient data available to calculate other values

Table 35 Validity characteristics of case series of HBOT in refractory soft tissue radiation injuries

First author, year	Explicit inclusion/exclusion criteria[a]	Outcomes assessed in all patients	Uniform follow up	Measurement of outcomes	Outcomes quantified	Outcomes measured objectively	Blinded assessment of outcome	Indication/Disease severity uniform across patients
Feldmeier, 1993	Yes	No	No	NR	No	No	NR	Chandler grade IV (8) Chandler grade III (1)
Feldmeier, 1995	Yes	Yes	No	Wound healing	No	NR	NR	Grade 3 radiation injury (2) Grade 4 radiation injury (6) using the late radiation morbidity scoring system
Feldmeier, 1996	Yes	Yes	NR	Wounds were healed, inadequate or did not heal	No	NR	NR	All patients Grade 4 radiation injury using the late radiation morbidity scoring system
Feldmeier, 2000	Yes	Yes	No	Healed Improved Amputation required	No No Yes	No No Yes	NR	No scoring system used. Description given of the size but not severity of the wounds
Flintisis 2000	Yes	No	NR	Major improvement Preservation of voice Failed response to HBOT Total laryngectomy required	No No No No	No NR No Yes		Chandler Grades III and IV
Roden, 2001	Yes	No	Unclear	Vision Improvement Visual acuity	Yes Yes	Yes Yes	NR	Heterogenous patient group according to tests of visual status
Yu, 2002	Yes	Yes	Yes	Recovered Partially recovered Pre/Post test $TcPO_2$	No No Yes	No No Yes	NR	NR

Abbreviations: NR, not reported (ie unclear, not stated or unknown); $TcPO_2$, transcutaneous oxygen pressure

[a] Despite explicit inclusion criteria being given, the decision to refer to HBO therapy may have been biased, dependent upon the referring physician

Table 36 Validity characteristics of case series of HBOT in other radiation-induced complications

First author, year	Explicit inclusion/exclusion criteria[a]	Outcomes assessed in all patients	Uniform follow up	Measurement of outcomes	Outcomes quantified	Outcomes measured objectively	Blinded assessment of outcome	Indication/Disease severity uniform across patients
Mayer, 2001	Yes	Yes	No	Described as healed etc but not defined	No	NR	NR	NR
Woo, 1997	Yes	Yes	No	Symptoms described as having improved, partially improved or completely improved	No	No	NR	NR

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

Table 37 Treatment descriptions of case series of HBOT in refractory soft tissue radiation injuries

First author, year	Radiation dose (cGray)	Details of radiation therapy	Type/location of STRN	Time from radiation exposure to injury	Time from injury to HBOT	Therapies tried prior to HBOT	HBOT regimen	Concomitant therapies
Feldmeier, 2000	3,000-6,000	NR	Extremities	6 months to 17 years	Immediate to 3 years	NR	100% oxygen at 2.4 ATA for 90 minutes (3x 30 minutes with 10 min air breaks) Total number of sessions: 1-95	9/16 soft tissue-only patients underwent a surgical procedure All patients received daily wound care
Feldmeier, 1996	2,000-8,500	NR	Abdominal wall (15) Groin (13) Pelvic Bone (2) Perineum (7) Small bowel (1) Skin of buttocks (1) Vagina (5)	Immediate to 53 years	Immediate to 2 years	Reconstructive surgeries: 5 prior to HBOT 3 at time of HBOT NR NR NR NR	100% oxygen at 2.4 ATA for 90 minutes, 6 days per week Total number of sessions: 3-69	Patient-specific daily wound care
Feldmeier, 1995	3,900-6,000	NR	Chest Wall Late radiation morbidity scoring system: Grade 3 (2) Grade 4 (6)	Immediate to 7 years	Immediate to 23 years	NR	100% oxygen at 2.4 ATA for 90 minutes Total number of sessions: 7-33	Patient-specific daily wound care Split thickness skin grafts and/or myocutaneous flaps (4)
Feldmeier, 1993	4,500-7,000 (Unit not specified)	NR	Laryngeal: Chandler grade IV (8) Chandler grade III (1)	3 months to 2 years	NR	NR	100% oxygen at 2.4 ATA for 3x10 minutes exposure once daily, 6 days per week Total number of sessions : 8-to 45	NR
Flintisis 2000	5,000-7,545	NR	Laryngeal: Chandler Grade III (2) Chandler Grade IV (16)	3 months to 3 years	NR	Symptomatic therapy as needed with parenteral antibiotics, steroids, racemic epinephrine, bronchodilators, and humidity before and after HBO therapy	100% oxygen at 2 ATA for 2 hours twice daily, 6 days per week Total number of sessions: 6-80	Symptomatic therapy as needed with parenteral antibiotics, steroids, racemic epinephrine, bronchodilators and humidity before and after HBO therapy

Table 37 (cont) Treatment descriptions of case series of HBOT in refractory soft tissue radiation injuries

First author, year	Radiation dose (cGray)	Details of radiation therapy	Type/location of STRN	Time from radiation exposure to injury	Time from injury to HBOT	Therapies tried before HBOT	HBOT regimen	Concomitant therapies
Roden, 2001	4,500-7,200	NR	Optic nerves or chiasm resulting in visual symptoms	4 to 35 months	NR	NR	100 % oxygen, pressure not reported Total numbers of hours of HBOT: 18-160 (Data missing for one patient)	Corticosteroids (11/13)
Yu, 2002	5,040-6,600	NR	Breast. Patients had a range of symptoms including: . breast/chest wall painful oedema (4) . axillary painful oedema with movement limitation (5) . non-healing ulcer (1)	NR	NR	Standard treatment including surgical debridement and regular wound care	100% oxygen at 2.5 ATA for 100 minutes (with a 5 minute air break every 30 minutes) daily, 6 days per week Total number of sessions: 15-40	NR

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

Table 38 Treatment descriptions of case series of HBOT in other radiation-induced injuries

First author, year	Radiation dose (Gray)	Details of radiation therapy	Type/location of STRN	Time from radiation exposure to injury	Time from injury to HBOT	Therapies tried before HBOT	HBOT regimen	Concomitant therapies
Mayer, 2001	66/2 (2)[a] 70/2 (15)	Photon beams of 8 or 23 Megavolts (Dose not reported)	Proctitis: 7 Cystitis: 8 Cystitis and proctitis: 3	Occurrence of late GI complications: median 7.75 months Occurrence of late GU complications: median 15.84 months	NR	Bladder irrigation: 4 patients with cystitis 2 patients with both cystitis and proctitis Intravesical agents: 2 patients with cystitis 1 patient with both cystitis and proctitis Laser coagulation: 2 patients with proctitis Local medicaments: 5 patients with proctitis 2 patients with both cystitis and proctitis Systemic therapy: 1 patients with proctitis 2 patients with both cystitis and proctitis	100% oxygen at 2.2 to 2.4 ATA for 60 minutes daily, 7 days per week. Total number of sessions: 2-60 (Patients were to have received a minimum of 20 treatments)	NR
Woo, 1997	>60 (Exact dose not reported)	Mega-voltage X-rays (Dose not reported)	Proctitis	NR	Mean 20 months	Most had failed previous therapies including: Steroids (13) Local anaesthetic cream (3) Narcotics (1) Zinc oxide gel (1) NSAIDs (1) Massage and acupuncture for pain (1)	100% oxygen at 2 ATA for 105-minute sessions daily, 6 days per week Total number of sessions: 12-40	NR

Abbreviations: NR, not reported (ie unclear, not stated or unknown); GU, genitourinal

[a] Total dose. Radiotherapy was either limited to the prostate and seminal vesicles/prostate bed by using an anterior and two lateral fields or included the pelvic lymph nodes in four field box technique (504 Gray/1.8 Gray) followed by a boost in a three field technique

Table 39 Results of case series of HBOT in refractory soft tissue radiation injuries

First author, year	Outcomes reported	Result	Duration of follow-up
Feldmeier, 2000	Healed	11/17 (65.0%)	NR
	Significantly Improved	1/17 (5.7%	
	Required amputation	4/17 (23.6%	
	Discharged to hospice (lung metastases)	1/17 (5.7%)	
Feldmeier, 1996	Healed	25/42 (59.5%)	NR
	Inadequate	10/42 (23.8%)	
	Did not heal	6/42 (14.3%)	
	Lost to follow up	1/42 (2.4%)	
Feldmeier, 1995	Healed	6/8 (75.0%)	NR
	Discontinued HBOT due to recurrent cancer	2/8 (25.0%)	
Feldmeier, 1993	Laryngectomy required	None	2-10 years
	Voice quality:		
	Good	7/9 (77.7%)	
	Slight hoarseness	2/9 (22.3%)	
	Tracheostomies able to be decannulated	3/3 (100.0%)	
	Fistulae able to close without surgery	2/4 (50.0%)	
	Required surgery	2/4 (50.0%)	
	Deaths:		
	Lung cancer 4 years post-treatment	1/9 (11.1%)	
	Ethanol Abuse 4 years post-treatment	1/9 (11.1%)	
	Respiratory arrest 2 years post-treatment	1/9 (11.1%)	
	Colon cancer 2 years post-treatment	1/9 (11.1%)	
Flintisis, 2000	Major Improvement	13/18 (72.2%)	5 months-4 years
	Voice and deglutition in good or normal condition	18/18 (100.0%)	
	Laryngectomy required	0/18 (0.0%)	

Table 39 (cont) Results of case series of HBOT in refractory soft tissue radiation injuries

First author, year	Outcomes reported	Result	Length of follow-up
Roden, 2001	Vision improvement	0/13 patients (26 eyes total)	1-4 years
	Visual acuity:		
	Remained within two lines of pre-treatment level	18 eyes per 26 eyes total	
	Lost vision in one eye	1 eye per 26 eyes total	
	Lost visual acuity	5 eyes per 26 eyes total	
Yu, 2002	Recovered	4/5 (80%)	2 years
	Partially relieved	1/5 (20%)	
	Local tissue oxygenation status	Pre test (range): 13-16 Post test (range): 43-67	

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

Table 40 Results of case series of HBOT in other radiation-induced injuries

First author, year	Outcomes reported	Result			Length of follow-up
Mayer, 2001	Underwent adequate treatment	16/18			4.8-26.9 months
	Significant Improvement	GI, p=0.004; GU, p=0.004			
	Improvement to level of no symptoms	4/18			
	Bleeding ceased	5/5 proctitis, 6/8 cystitis			
	Ineffective treatment outcome	2/18			
	Went on to cystectomy	1/18			
Woo, 1997		NI	PI	CI	3-65 months
	Overall improvement in all symptoms	8	8	2	
	Bleeding:				
	. Mild, no transfusions	6	1	4	
	. Moderate	3	1	0	
	. Severe (>6 units in 3 months)	1	1	0	
	Pain	2	1	1	
	Incontinence	1	1	2	
	Diarrhoea	4	2	2	

Abbreviations: GI, gastrointestinal; GU, genitourinal; NI, no improvement; PI, partial improvement; CI, complete improvement

Appendix F3 Non-healing, refractory wounds in non-diabetic wounds: case series considered on expert advice

Table 41 Descriptive characteristics of case series of HBOT in non-healing, refractory wounds in non-diabetic patients

First author, year	Study location	Dates of enrolment	Number of patients	Number of males	Mean age (years)	Co-morbidities[a]	Inclusion/Exclusion criteria
Cianci, 1988[a]	USA	Jan 1983 to Jul 1987	39, including 19 with diabetes	NR	67	Not reported	Inclusion: Patients who had serious lesions of the lower extremities which had been refractory to standard medical or surgical treatment and who had previously undergone treatment with HBOT. Patients had to have a non-healing lesion after at least two months of standard therapy and were assessed for blood flow, rehabilitation potential and the ability to cooperate in an aggressive wound care program

[a] It was unclear whether the study enrolled consecutive patients. Results were not presented separately for diabetics and non-diabetics

Table 42 Schedules used in case series of HBOT in non-healing, refractory wounds in non-diabetic patients

First author, year	Type and location of wound	Time from wound/lesion to HBOT	Therapies tried before HBOT	Duration of therapy tried before HBOT	HBOT regimen	Concomitant therapies
Cianci, 1988	Lesions of the lower limb	NR	Standard therapy (not defined)	$\geq$ 2 months	100% oxygen at 2 ATA for 1.5 to 2 hours once or twice daily	Patients were treated by a multidisciplinary team of medical specialists in the setting of aggressive wound care consisting of wound perfusion assessments; early surgical revascularisation; daily or twice daily wound inspection, dressing changes, and debridement; avoidance of topical toxins; maintenance of nutritional and metabolic control; antibiotic administration based on culture results

Table 43 Validity characteristics of case series of HBOT in non-healing, refractory wounds in non-diabetic patients

First author, year	Explicit inclusion/exclusion criteria	Outcome measured n all enrolled patients	Uniform follow-up	Measurement of outcomes	Outcomes quantified	Outcomes measured objectively	Blinded assessment of outcome	Indication/disease severity uniform across patients	Description given of failed treatment
Cianci, 1988	Yes	Yes	NR	NR	Some	Some	NR	NR	NR

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

Table 44 Results of case series in HBOT in non-healing, refractory wounds in non-diabetic patients

First author, year	Outcomes reported	Result	Length of follow-up
Cianci, 1988[a]	Vascular surgery	20/39 (51%)	Not reported
	Length of stay	30 days	
	Mean number of HBOT treatments	31	
	Mean HBOT cost	US$10,368	
	Total hospital charges	US$29,709	
	Successful salvage	36/39 (92%)	

[a] Combined results for 19 diabetic patients and 20 non-diabetic patients, total 39

Appendix F4 Refractory soft tissue radiation injuries: case series considered on expert advice

Table 45 Descriptive characteristics of case series of HBOT in refractory soft tissue radiation injuries

First author, year	Study location	Dates of enrolment	Number of patients	Number of males	Mean age (years)	Co-morbidities[a]	Inclusion/Exclusion criteria
Bevers, 1995	The Netherlands	Jan 1986 to Jan 1984	40	27	71.4 Range: 56-86	NR	Inclusion: Patients with severe haemorrhagic cystitis due to radiotherapy not responding to other treatments Exclusion: Patients with evidence of tumour recurrence in the bladder at cystoscopy, the presence of concomitant bleeding disorders, and/or severe pulmonary disease with pulmonary bullae
Lee 1994	Taiwan	Nov 1989 to Jan 1996	40	3	63±9 (SD) Range: 42-82	NR	Inclusion: Patients with haemorrhagic radiation cystitis

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

Table 46 Validity of case series of HBOT in refractory soft tissue radiation injuries

First author, year	Explicit inclusion/exclusion criteria	Outcomes assessed in all patients	Uniform follow up	Measurement of outcomes	Outcomes quantified	Outcomes measured objectively	Blinded assessment of outcome	Indication/disease severity uniform across patients
Bevers, 1995	Yes	Yes	No	Recurrence of severe haematuria, cystectomy, or death	Yes	Yes	No	No
Lee, 1994	No	Yes	No	Recurrence of gross haematuria, cystoscopic findings	No	No	No	NR

Table 47 Treatment descriptions of case series of HBOT in refractory soft tissue radiation injuries

First author, year	Radiation dose (Grays)	Radiation regimen	Type/ location of injury	Time from radiation exposure to injury	Time from injury to HBOT	Therapies tried before HBOT	HBOT regimen	Concomitant therapies
Bevers, 1995	Mean: ≥52	NR	Bladder	Mean: 53.1 months Range: 4-253	NR	Clot evacuation and electrocoagulation: (40) Tranexamic acid: (12) Alum: (11) Corticosteroids: (3) Neomycin: (1) Etoglucide: (1) Propantheline: (1) Silver nitrate: (1) Unspecified: (17) Most required multiple blood transfusions, mean 8.2 units	100% oxygen inhaled at 3 bars for daily sessions of 90 minutes in a multiplace chamber, 5 to 6 times a week Total number of sessions: 20	NR
Lee, 1994	63±(11) Range: 50-90	NR	Bladder	Mean: 9.1 years±5.25 (SD) Range: 2-26	NR	NR	100% oxygen by mask at 2.5 ATA for 100 minutes in a multiplace chamber	NR

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

Table 48 Results of case series of HBOT in refractory soft tissue radiation injuries

First author, year	Outcomes reported	Result	Length of follow-up
Bevers, 1995	Overall recurrence rate	0.12 per year	Median: 13 months
	No haematuria for three months following treatment	30/40 (75%)	
	Occasional, slight haematuria	7/40 (17.5%)	
	No effect	3/40 (7.5%)	
Lee, 1994	Resolution of haematuria	33/40 (82.5%)	Mean: 21 months±12 (SD) Range: 3-49
	"Marked decrease" in haematuria	3/40 (7.5%)	

Appendix G Bibliographic details of studies considered by Feldmeier, 2001

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Abbreviations

AETMIS	Agence d'Évaluation des Technologies et des Modes d'Intervention en Santé (Health technology agency based in Quebec)
ATA	atmosphere absolute
CRD	Centre for Reviews and Dissemination
GIT	Groninger Intelligence Test
HBOT	hyperbaric oxygen therapy
HBO	hyperbaric oxygen
HTA	health technology assessment
ICD-10-AM	International Classification of Disease, 10th edition, Australian Modification.
LND	lymph node dissection
MBS	Medicare Benefits Schedule
MeSH	medical subject heading
MSAC	Medical Services Advisory Committee
NCCAM	National Centre for Complementary and Alternative Medicine (USA)
NHLBI	National Heart, Lung, and Blood Institute (USA)
NHMRC	National Health and Medical Research Council
NHS	National Health Service (UK)
Pa	pascal
SF-36	Short Form 36
RCT	randomised controlled trial
WAIS	Wechsler Adult Intelligence Scale

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