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Program in Evidence-based Care Advice Report: EDUCATION AND INFORMATION 2013

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Hyperbaric Oxygen Therapy for the Treatment and Prevention of Radionecrosis and Other Radiation-Induced Injuries in Cancer Patients

Program in Evidence-based Care Advice Report was reviewed in 2012 and put in the Education and Information section on March 26, 2013. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).

This resulting Evidence-based Series (EBS) consists of the following 3 sections

and is available on the CCO web site (http://www.cancercare.on.ca)
PEBC Collaborative Projects page at:

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1. Summary
2. Full report
3. Guideline Review Summary and Review Tool

Release Date: July 25, 2013

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program in evidence-based care
a cancer care ontario program

programme de soins fondé sur des preuves
un programme de action cancer ontario

Program in Evidence-based Care Advice Report: EDUCATION AND INFORMATION, 2013

Hyperbaric Oxygen Therapy for the Treatment and Prevention of Radionecrosis and Other Radiation-Induced Injuries in Cancer Patients

Guideline Report History.

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version January 2004	1996 to 2004	Full Report	Peer review publication Web publication	Not Applicable
Update July 2005	2005	Full Report	Web publication	Not Applicable
Reviewed version March 2013	2005 to 2012	New data found in Section 3: Guideline Review Summary and Review Tool	Updated Web publication	2005 guideline requirement: ARCHIVED

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Hyperbaric Oxygen Therapy for the Treatment and Prevention of Radionecrosis and Other Radiation-Induced Injuries in Cancer Patients

Program in Evidence-based Care Advice Report

Hyperbaric Oxygen Therapy Working Group

Report Date: August 28, 2005

The 2005 guideline recommendations are

ARCHIVED

This means that the recommendations will no longer be maintained but may still be useful for academic or other informational purposes.

SUMMARY

Question

Is hyperbaric oxygen therapy (HBOT) effective in treating or preventing radiation-induced injuries in cancer patients?

Target Population

This report applies to cancer patients whose cancer care involves radiation therapy.

Conclusions of the Hyperbaric Oxygen Therapy Working Group

It is the opinion of the Working Group that there is currently insufficient evidence from clinical studies to warrant further investment in HBOT for new indications in the treatment or prevention of radiation-induced injuries in cancer patients. However, the state of the evidence does not justify withdrawing this intervention where it is currently used as standard practice.

Better-controlled studies are needed to confirm the clinical utility of this intervention. Studies examining this intervention in the prevention of osteonecrosis in patients undergoing tooth extraction after radical radiotherapy for head and neck cancer are of particular interest, given that initial data show it to be most promising for this indication. In addition, future comparative studies should evaluate other alternative strategies for enhancing angiogenesis, which is hypothesized to be an important mechanism explaining the benefits of HBOT.

Methods

Entries to MEDLINE, EMBASE, CINAHL, HealthStar and the Cochrane Library (1996 until January 2004) were systematically searched for evidence relevant to this report. An update of the search was conducted in July 2005.

Evidence was selected and reviewed by members of the Program in Evidence-based Care Hyperbaric Oxygen Therapy Working Group, which is comprised of clinicians and methodologists. A review of a draft report by a sample of those involved in provincial Disease Site Groups and other Cancer Care Ontario guideline panels was undertaken, and the final document was submitted to Cancer Care Ontario's Clinical Council for endorsement.

Key Evidence

- The evidence available on the role of HBOT for radiation-induced injuries in cancer patients is limited in magnitude and quality.
- Eleven eligible studies were found, five of which were randomized controlled trials (RCTs). The number of participants in individual studies ranged from 12 to 160. The RCTs provide the strongest evidence available, but these had methodological limitations.
- Studies of HBOT for treatment of osteoradionecrosis or wound complications following radiotherapy for head and neck cancer were conflicting: one incomplete double-blind RCT reported encouraging results, and two retrospective studies failed to detect a statistically significant benefit for HBOT.
- Three non-blinded randomized trials found benefit in favour of HBOT for the prevention of complications from dental or reconstructive surgery after radiotherapy for head and neck cancer. This was supported by evidence from one retrospective comparative study but not by a prospective comparison of patients who received HBOT and a smaller number who did not.
- Two trials (one double-blind RCT and one comparative cohort study) suggested HBOT might improve quality of life for women suffering complications from radiotherapy for treatment of breast cancer.
- One retrospective study suggested a benefit of HBOT in the treatment of hemorrhagic cystitis compared to prostaglandin E2 (PGE2) in pediatric stem-cell transplant patients.

For further information about this report, please contact
Melissa Brouwers, Director, Program in Evidence-based Care (PEBC)

The PEBC is sponsored by Cancer Care Ontario &
the Ontario Ministry of Health and Long-term Care.

Visit http:// www.cancercare.on.ca/ for all additional PEBC reports.

PREAMBLE: About the Program in Evidence-Based Care

The Program in Evidence-based Care is a quality initiative of Cancer Care Ontario (CCO). The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of evidence-based reports by panels using the methodology of the Practice Guidelines Development Cycle.[1] This advice report includes a systematic review of clinical research and is intended as information for individuals and groups to use in making decisions and policies

Reference:

[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

For the most current versions of the guideline reports and information about the PEBC, please visit the CCO website at:
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FULL REPORT

I. QUESTION

Is hyperbaric oxygen therapy (HBOT) effective in treating or preventing radiation-induced injuries in cancer patients?

II. CHOICE OF TOPIC AND RATIONALE

Radionecrosis is a rare complication that results from the action of radiotherapy on small blood vessels. Radiation injury to these vessels can lead to a progressive obliterative endarteritis with tissue hypoxia and fibrosis. This damage can worsen over time so that ischemia can develop in the tissues weeks to years after the initial radiotherapy. The radiation injury produces a hypovascular area of tissue that cannot repair itself. This may be overt with tissue necrosis or may be subclinical and only revealed when there is tissue injury, and the tissue is unable to heal. Bone is the most commonly affected tissue. Skin is the most commonly affected soft tissue. Other radiosensitive soft tissues include the rectum, bladder, and central nervous system.

The most common form of radiation necrosis relates to the treatment of head and neck cancer where radiation may injure the bone of the jaw (mandible) and adjacent soft tissues. When bone is injured and dies, the condition is referred to as osteoradionecrosis, while muscle or skin injury is referred to as soft tissue radionecrosis. These outcomes can occur anytime after radiotherapy and may be trauma induced, in dental surgery, for instance, or may be spontaneous. Although these are rare complications in the management of head and neck cancer, they can lead to very significant morbidity. The necrotic bone and soft tissues usually become infected, and wound healing is extremely difficult to manage with antibiotics and/or reconstructive surgery. The resulting pain, orocutaneous fistula, exposed necrotic bone, pathologic fracture, and suppuration can make eating impossible.

HBOT is the medical use of 100% oxygen at between two and five times normal pressure (1). Oxygen is essential for normal cellular respiration and tissue function. Under normal conditions, 97.5% of oxygen is carried in the blood stream, bound to hemoglobin. The remaining 2.5% is dissolved in plasma. Above 200 mm Hg of pressure, the oxygen dissolved in plasma significantly increases. The total oxygen content of blood can be increased under hyperbaric oxygen conditions. At 3 atmospheres of pressure, while breathing 100% oxygen, the total dissolved oxygen content delivered is in excess of the body's metabolic requirements. Under these conditions, oxygen can be supplied to tissues even in the absence of hemoglobin.

Originally developed to treat victims of diving accidents, HBOT is used in a number of other clinical applications. Animal experiments provide the rationale for the use of HBOT in the treatment of soft tissue radionecrosis. Marx and Ehlar demonstrated that HBOT induced new blood vessel growth (neo-angiogenesis) in rabbits with the hyperbaric oxygen-treated group showing a 600 to 900% increase in angiogenesis compared to the control group ($p<0.001$) (2). Using a rat model, Greenwood and Gilchrist showed that HBOT reduced tissue necrosis by 60% in skin flaps made into previously irradiated areas (3).

The delivery of hyperbaric oxygen generally is undertaken in one of two different treatment chambers (1). Monoplace chambers house one individual placed in the supine position. The chamber has an acrylic shell, which allows the patient to observe the surroundings. Communication devices located within the chamber allow conversation between the patient and the hyperbaric medicine physician or technician. Multiplace chambers, which can accommodate two to 10 patients, require more space and have higher capital and operating costs than do monoplace chambers. They have the advantage, however, of accommodating a health care provider in the chamber to deal with complications such as pneumothorax or to conduct intensive care activities. In either case, the patient typically stays in the chamber for one hour and returns daily, five days a week, for six weeks.

Some patients cannot tolerate the close confinement of a hyperbaric oxygen chamber and do not complete the entire course of therapy. Claustrophobia can be a problem, particularly in monoplace units where the patient must lie in a very confined space. Potential serious adverse effects from HBOT include damage to the eardrums as a result of increased pressure and seizures or lung problems as a result of oxygen toxicity (1). Occasionally, patients experience a temporary disturbance of vision following the therapy session (4). With multiplace chambers, there is also the risk of decompression sickness amongst personnel working in such chambers.

In Ontario, three hospital-based hyperbaric oxygen facilities provide HBOT for cancer patients. These are located at the University Health Network (UHN) in Toronto, the Ottawa Hospital, and the Hamilton Health Sciences Corporation.

The purpose of this report is to document the evidence available from clinical studies and to determine if this evidence is sufficient to establish that hyperbaric oxygen therapy is or is not effective in managing radionecrosis and other radiation-induced injuries in cancer patients. The evidence was considered in the context of the need for effective therapy for a set of serious chronic adverse effects from cancer treatment that have a significant negative impact on patients' quality of life and for which other available therapies are of limited value.

III. METHODS

Development Process

Evidence was selected and reviewed by members of the Program in Evidence-based Care (PEBC) Hyperbaric Oxygen Treatment Working Group, which is comprised of clinicians and methodologists. Members of the Working Group were asked to disclose potential conflict of interest information, and no conflicts emerged. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

This report is presented as an advice report consisting of a systematic review, interpretative summary of the evidence, and a set of opinions based primarily on clinical expertise. In contrast to an evidence-based practice guideline, this report is based on a body of evidence that is limited in terms of quantity or methodological quality. This precludes the development of definitive recommendations and instead, conclusions of the Working Group are offered. The report, which provides an up-to-date summary of the best available evidence on the effectiveness of HBOT for radiation-induced injuries in cancer patients, is intended as information for individuals and groups to use in making decisions and policies about the role of HBOT in cancer care in Ontario.

External review was obtained from delegates from the Provincial Disease Site Groups and Guideline Development Groups of Cancer Care Ontario. The final document was presented to Cancer Care Ontario's Clinical Council for endorsement.

The PEBC has a formal standardized process to ensure the currency of each report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original report.

Literature Search Strategy

Searches were conducted in January 2004 in two stages. The first was a search for existing systematic reviews and the second a search for primary studies. Neither of the searches was restricted by language of publication. A second search was conducted in July 2005 to update the literature.

Search for systematic reviews

MEDLINE, EMBASE, HealthStar, CINAHL, the Cochrane Database of Systematic Reviews, and the Cochrane Database of Reviews of Effects were originally searched for systematic reviews indexed between 1996 and January 9, 2004. Search strategies were modified for each database, but all used text words and subject headings for hyperbaric oxygen, radiation effects

or injury, radionecrosis, osteoradionecrosis, radiotherapy, cancer, and neoplasm. Search terms added were review, systematic review, overview, meta-analysis, technology assessment, evidence-based medicine, and guideline, where appropriate. A set of articles assembled by Dr. Wayne Evans of the University Health Network (UHN) Hyperbaric Medical Unit, which included papers published in peer-reviewed journals and technology assessment reports, was also searched. The search was repeated in July 2005.

Search for primary studies

After appraising the systematic reviews found by the search described above and noting the primary studies included in the reviews, a search of MEDLINE, EMBASE, CINAHL, HealthStar and the Cochrane Central Register of Controlled Trials was searched for primary studies published after the completion of the search for the most recent published systematic reviews (i.e., between 2001 and December 2003). Search strategies were modified for each database, but all used text words and subject headings for hyperbaric oxygen, radiation effects or injury, radiation necrosis, radionecrosis, osteoradionecrosis, proctitis, cystitis, toxicity, radiotherapy, cancer, and neoplasm, along with terms for the following study designs of interest: clinical trial(s), randomized controlled trial, control groups, cross-over studies, double-blind method, matched-pair analysis, random allocation, single-blind method, cohort studies, and controlled study. Reference lists of primary study reports and review articles were scanned for additional studies. An update of this search was conducted in July 2005.

Inclusion criteria

Primary studies, identified from systematic reviews and technology reports by others or through literature searches, were eligible for inclusion in this systematic review if they met all the following criteria:

1. evaluated HBOT to treat or prevent radiation-induced injuries
2. compared patients who did and did not receive HBOT, defined as 100% oxygen delivered at >1.4 atmospheres absolute (1.0 atmosphere equals approximately the pressure of the atmosphere at sea level)
3. used either a concurrent or historical control group
4. reported data for clinical outcomes in both the treatment and control groups
5. enrolled patients who had received radiotherapy for cancer

In considering the evidence, most weight was placed on RCTs, but other types of comparative studies were also considered.

Exclusion criteria

Letters, editorials, and meeting abstracts were not included.

IV. RESULTS

Original Findings

Literature Search Results

The original literature search found 15 systematic reviews (5-19) and 11 primary studies (20-30). None of the systematic reviews included a quantitative synthesis of the evidence in the form of a meta-analysis. Some reviews were restricted to the English-language literature, but at least seven considered papers published in any language (8,10,12,14-17). Although the available systematic reviews were generally of good quality, no single review satisfied all of the eligibility criteria set out for our report. Some were not restricted to comparative studies (5-8,12-20), and others included only randomized trials (9,10). Many were comprehensive reviews on HBOT that included a range of conditions in addition to cancer (5-7,10-12,20), while others addressed a specific group of cancer patients (8,9,14-19). The authors of this report used these reports as background material and to identify comparative studies published prior to 2001 that

met our eligibility criteria. Rather than summarize the existing systematic reviews and technology assessments, we have relied on primary study reports as the basis for this report. In addition to six eligible studies included in previous reviews, five additional studies were found by our literature search, for a total of 11 studies.

There were eight controlled studies of HBOT for the treatment or prevention of radiation-induced injuries in head and neck cancer (20-27), two for symptoms in patients who had received breast irradiation (28,29) and one for hemorrhagic cystitis in pediatric stem-cell transplant patients (30). All eleven studies were relatively small, with the total number of patients evaluated ranging from 12 to 160, and it is unclear if any had sufficient power to detect clinically or statistically significant differences between treatment groups. Only five studies were randomized trials (20,23,25,26,28) and two of these were double-blind (20,28).

Systematic reviews also examined the literature on radiation-induced ear toxicity (12), proctitis (13,14) and sexual dysfunction (16), but no evidence was available from comparative studies for these indications.

Radionecrosis after Radiotherapy for Head and Neck Cancer

Eight studies of HBOT for the treatment or prevention of radiation-induced injuries in head and neck cancer are described in Tables 1 and 2 (20-27).

Treatment

Limited evidence is available on HBOT for the treatment of osteoradionecrosis following radiotherapy for head and neck cancer. Unfortunately, complete results from the only double-blind randomized trial were not available (20). In 1979, Tobey et al reported encouraging preliminary results from a trial of HBOT for patients with osteoradionecrosis of the mandible, but full results were never published. Because the study was conducted 25 years ago, we did not attempt to contact the investigators for further data. In a retrospective study, Maier et al examined data on 41 patients with severe osteoradionecrosis following surgery and postoperative radiotherapy for oral cancer (21). All were treated with debridement plus antibiotics or with partial mandibulectomy and microvascular transplantation. Twenty patients who received HBOT in addition to surgery for osteoradionecrosis were compared with 21 patients who received surgery alone. Follow-up was longer in the control group than in the intervention group (59 months versus [vs.] 18 months), raising a concern that the two groups might not be comparable. No difference was observed between the two groups in terms of the need for further surgery to deal with osteoradionecrosis (35% with HBOT vs. 33% without).

Neovius et al described 15 patients with major infected wounds or chronic fistulas after surgery and radiotherapy for head and neck cancer who were treated with HBOT (22). These patients were compared with 15 patients from an earlier study of reconstruction for oral and pharyngeal cancer who did not receive HBOT. The observed rate of healing was higher in the HBOT group than in the historical control group (80% vs. 47%).

Prevention

There is evidence from two studies that HBOT may prevent the development of osteoradionecrosis in patients who require oral surgery after radiotherapy for head and neck cancer (23,24). The strongest evidence comes from a randomized controlled trial by Marx et al, published in 1985, with 74 participants (23). Patients were randomly allocated to either HBOT or penicillin, administered before and after tooth extraction from a previously irradiated segment of the jaw. The trial was not placebo controlled, and there is no indication that outcome assessors were blind to the allocation group. Among 37 patients who underwent HBOT, two developed a total of four osteoradionecrotized sockets after tooth extraction, compared to 11 of 37 patients with 31 osteoradionecrotized sockets in the control group (p=0.005). In a non-randomized prospective study, Vudiniabola observed osteoradionecrosis among 3% of 29 patients who

received HBOT before and after surgery for tooth extraction, implant placement, resection, or plate removal, compared with 14% of seven patients who refused or were ineligible for HBOT (24). The investigators reported that they did not randomize patients to receive and not receive HBOT because they were of the opinion that the published evidence had established the benefits of HBOT.

In a text book on hyperbaric medicine published in 1994, Marx described two additional randomized trials but provided only limited information on study and treatment methods (25,26). In the first trial (25), observed rates of complications due to hemimandibular reconstruction were lower with HBOT (9% vs. 22% without HBOT), and surgical success rates were higher (Table 2). The second study assessed wound complications related to soft-tissue flaps (26). Compared to the control group, patients treated with HBOT experienced lower rates of wound infection (6% vs. 24%, p=0.005), wound dehiscence (11% vs. 48%, p=0.001), and delayed healing requiring extended hospital stay (11% vs. 55%, p=0.005).

Granstrom et al reviewed the charts of 52 patients who received osteointegrated implants for defects of the craniomaxillofacial region after surgery and radiotherapy for head and neck cancer (27). They detected a significant improvement in the success rate for implants in patients treated with HBOT compared to those who were not given HBOT as a preventive measure (p=0.001). Twenty patients who received a total of 99 implants in irradiated bone were treated with HBOT; of these, eight implants (8%) were lost among six patients. In contrast, 79 implants (54%) were lost among 32 patients who did not receive HBOT, and 28 patients lost at least one implant.

Table 1. Characteristics of primary studies of hyperbaric oxygen therapy for the treatment or prevention of radiation-induced injuries in head and neck cancer.

Study	Design	Patients	Treatment (hyperbaric oxygen)	Control
Treatment				
Tobey, 1979 (20)	RCT, double-blind	N=12 osteoradionecrosis of the mandible	2.0 ATA (2 hours, 40 sessions)	1.2 ATA (2 hours, 40 sessions)
Maier, 2000 (21)	retrospective, concurrent control group	N=41 severe osteoradionecrosis of the mandible after surgery and radiotherapy for oral carcinoma	2.5 ATA/hour (15-57 sessions) + surgery	surgery alone
Neovius, 1997 (22)	retrospective, historical control group	N=30 soft-tissue wounds with no signs of healing after radiation and surgery for head & neck cancer	2.5-2.8 ATA (75-90 minutes; 30-40 sessions)	no hyperbaric oxygen
Prevention				
Marx, 1985 (23)	RCT	N=74 needing teeth removed from a previously irradiated segment of mandible	2.4 ATA (90 minutes; 20 sessions before tooth removal and 10 after)	penicillin before and after tooth removal
Vudiniabola, 1999 (24)	prospective, concurrent control group	N=36 needing teeth removed, history of irradiation to the jaw	2.4 ATA (90 minutes; 20 sessions before tooth removal and 10 after)	patients who refused or were ineligible for hyperbaric oxygen treatment
Marx, 1994 (25)	RCT	N=104 undergoing hemimandibular jaw reconstruction in irradiated tissue	20 sessions before surgery and 10 after, no other details reported	no hyperbaric oxygen
Marx, 1994 (26)	RCT	N=160 requiring major soft-tissue surgery or flap in irradiated tissue	20 sessions before surgery and 10 after, no other details reported	no hyperbaric oxygen
Granstrom, 1999 (27)	retrospective, concurrent control group	N=52 receiving osseo-integrated implants after surgery and radiation for head & neck cancer	2.5 ATA (90 minutes; 20 sessions before implant and 10 after)	no hyperbaric oxygen

ATA, atmosphere absolute; RCT, randomized controlled trial

Table 2. Results of primary studies of hyperbaric oxygen therapy for the treatment or prevention of radiation-induced injuries in head and neck cancer.

Study	Outcome	Number of patients with outcome		p-value
		Hyperbaric oxygen	Control	
Treatment				
Tobey, 1979 (20)	healing progress, assessed by x-ray, signs and symptoms and soft tissue lesions	no data reported but paper stated that active treatment group experienced "significant improvement" compared to controls		not reported
Maier, 2000 (21)	no further surgical intervention required for osteoradionecrosis	13/20 (65%)	14/21 (67%)	>0.05*
Neovius, 1997 (22)	complete healing	12/15 (80%)	7/15 (47%)	>0.05*
Prevention				
Marx, 1985 (23)	socket wounds healed in 6 months	35/37 (95%)	26/37 (70%)	<0.01*
Vudiniabola, 1999 (24)	full healing following oral surgery	28/29 (97%)	6/7 (86%)	>0.05*
Marx, 1994 (25)	successful jaw reconstruction	48/52 (92%)	34/52 (65%)	<0.001*
Marx, 1994 (26)	wound healing after major soft tissue surgery or flap	71/80 (89%)	36/80 (45%)	0.005
Granstrom, 1999 (27)	successful osseo-integration of all implants	14/20 (70%)	4/32 (13%)	<0.001*

* reviewer's calculation

Chronic Adverse Effects of Radiotherapy for Breast Cancer

Two studies, including one randomized trial, evaluated HBOT for the treatment of complications from curative radiotherapy for early-stage breast cancer (28,29). These studies are described in Tables 3 and 4.

The strongest evidence in the breast cancer setting comes from a double-blind randomized trial with 34 patients by Pritchard et al (28). Women with moderate sensory and motor dysfunction related to radiation-induced brachial plexopathy were randomized to either HBOT or placebo that was equivalent to breathing 100% oxygen at surface pressure. The primary outcome for this study was the threshold for detecting warmth. Secondary outcomes included scores on the McGill Pain and Medical Outcomes Study Short Form Survey-36 (MOS SF-36) general health questionnaires. No significant differences were detected in sensory threshold, general health, mental health, social functioning, vitality, or pain; however, emotional role and physical functioning improved in the HBOT group and declined in the control group during treatment and for 12 months after randomization. These results should be interpreted with caution because they are based on multiple comparisons with unadjusted p-values.

In a non-randomized prospective study of women with symptomatic breast edema after lumpectomy and radiotherapy, Carl et al compared 32 patients treated with HBOT to 12 who refused hyperbaric oxygen (29). Control patients were followed for seven months and HBOT patients for 11 months. After treatment, overall symptom scores, assessed by a physician, were worse in the control group than the HBOT group. Patients treated with HBOT were observed to have less pain, edema, and erythema than controls.

Table 3. Characteristics of primary studies of hyperbaric oxygen therapy for the treatment of radiation-induced injuries in breast cancer.

Study	Design	Patients	Treatment (hyperbaric oxygen)	Control
Pritchard, 2001 (28)	Phase II RCT, double-blind	N=34 radiation-induced brachial plexopathy following radiotherapy for early breast cancer	2.4 ATA (90 minutes; 30 sessions)	1.0 ATA (90 minutes; 30 sessions)
Carl, 2001 (29)	prospective, concurrent control group	N=44 persisting, symptomatic breast edema after breast-conserving therapy	2.4 ATA (90 minutes; 7-60 sessions)	patients who refused hyperbaric oxygen therapy

ATA, atmosphere absolute; RCT, randomized controlled trial

Table 4. Results of primary studies of hyperbaric oxygen therapy for the treatment of radiation-induced injuries in breast cancer.

Study	Outcome	Hyperbaric oxygen	Control	p-value
Pritchard, 2001 (28)	Mean change from baseline in score on SF36 general health questionnaire at 12 months: - emotional role functioning - physical functioning	 (improvement) 1.9	 -10.4 (decline) -10.8	 0.02 0.006
Carl, 2001 (29)	Median pain score (out of 4) Median edema score (out of 3) Median erythema score (out of 3) Median total symptom score (out of 16) [higher scores = worse symptoms] # patients free of symptoms	0 1 0 2 7/32 (22%)	3 2 2 7 0/12	<0.001 <0.001 <0.001 <0.001

Radiation Cystitis after Bone Marrow Transplantation

Cesaro et al conducted a retrospective analysis of data on 44 children with hemorrhagic cystitis after hematopoietic stem cell transplantation (30). Eighty-four percent had been treated for hematological malignancies or solid tumours, and 57% had received a total-body-irradiation conditioning regimen. Fourteen patients received treatment for hemorrhagic cystitis with HBOT (2.5 ATA for 75 minutes) for at least one week. Hyperbaric oxygen sessions were discontinued when gross hematuria disappeared. Compared to 19 patients treated with prostaglandin E2 (PGE2), successful treatment of hemorrhagic cystitis was achieved more often among those who received hyperbaric oxygen therapy (78.5% vs. 37% with PGE2, p=0.002).

Adverse Effects of Hyperbaric Oxygen Therapy

In a recent systematic review of 57 studies (randomized trials, cohort studies, and case series) of HBOT for treating wounds, Wang et al noted that transient vision changes and barotraumatic otitis had been reported as adverse effects in a number of studies (5). Three of the studies in cancer patients summarized above reported data on adverse effects (22,24,29). Neovius et al noted “oxygen seizures” during treatment in one of 15 patients (22); Vudiniabola et al reported that one patient, among 29 receiving HBOT, experienced pulmonary oxygen toxicity (24); and Carl et al reported “no toxicities related to hyperbaric oxygen therapy” (29).

Updated Findings

The updated search yielded one systematic review of scientific literature that met our inclusion criteria (1u). A collaborative consensus meeting between the European Society for Therapeutic Radiotherapy and Oncology and the European Committee for Hyperbaric Medicine was held to address the HBOT indications for the treatment and prevention of late complications following radiotherapy. To facilitate their deliberations, Pasquier et al conducted a systematic search of the literature, published between 1960 and 2004 (1u), examining the role of HBOT in treating the late complications related to radiotherapy for cancers of the head and neck, pelvis, and nervous system. Although the parameters of the literature search were provided by the authors, the overall number of relevant studies found, the characteristics of these studies, their outcomes, and their quality were not explicitly reported. The investigators agreed with our observations that the quantity and quality of evidence was modest. However, based on the evidence available, the team concluded that there might be a role for HBOT in the treatment of mandibular osteoradionecrosis in combination with surgery, hemorrhagic cystitis resistant to conventional treatments, and the prevention of osteoradionecrosis after dental extraction.

V. ONGOING TRIALS

A search of the Web found two relevant ongoing trials:

Protocol ID(s) **Title and details of trial**

UPCC-17300 **Phase II Randomized Study of Hyperbaric Oxygen Treatments in Previously Treated Patients With Laryngeal or Adjacent Pharyngeal Malignancies Undergoing Laryngectomy** (31)

Objectives

1. Compare the post-surgical complication rate in patients with previously irradiated laryngeal or adjacent pharyngeal malignancies treated with hyperbaric oxygen before and after laryngectomy versus total laryngectomy only
2. Determine the effect of hyperbaric oxygen on mucosal and tumour oxygenation and hypoxia, as determined by EF5 and Eppendorf needle electrodes, in these patients.
3. Compare the recurrence-free and overall survival of patients treated with these regimens.
4. Compare the quality of life and functional status of patients treated with these regimens.

Outline

Patients are stratified according to type of prior radiotherapy (narrow vs. wide) and need for reconstructive flap (yes vs. no). Patients undergo laryngoscopy with biopsy and then are randomized to 1 of 2 treatment arms.

Arm I: Patients undergo pre-operative hyperbaric oxygen treatment for 2 hours daily for 20 days and post-operative hyperbaric oxbbygen treatment for 2 hours daily for 10 days.

Arm II: Patients undergo total laryngectomy only and receive standard care.

Projected Accrual

A total of 54 patients (27 per treatment arm) will be accrued for this study within 4.5 years.

Centres

Two centres in Philadelphia.

Sponsor

National Center for Complementary and Alternative Medicine (NCCAM), the National Institutes of Health (NIH)

HORTIS **Hyperbaric Oxygen Radiation Tissue Injury Study** (32)

Objectives

1. To determine the degree of benefit that hyperbaric oxygen therapy affords in the treatment of late radiation tissue injury.
2. To generate "benchmarking" data about complications associated with hyperbaric exposure, including incidence and degree of morbidity.

Outline

A randomized double-blind placebo-controlled clinical trial, with patient cross-over. The study has eight components: seven involve evaluation of established radionecrosis at varying anatomic sites. The eighth will investigate the potential of hyperbaric oxygen therapy to prevent late radiation tissue injury.

Patients will be randomized to receive oxygen at either 2.0 atmospheres absolute or air at 1.0 atmospheres absolute. The total number of exposures will depend on response and will vary from 20 to 40. Following a 30-day wash-out period, patients will be offered the opportunity to cross over to the alternate study arm.

Projected Accrual

Patient recruitment began in November 2000. HORTIS is expected to take five years to complete. Expected number of patients was not reported.

Centres

Nine centres in US, Australia, Mexico, Turkey, South Africa and Canada. None in Ontario.

Sponsor

The Baromedical Research Foundation (supported by two private philanthropic foundations).

VI. INTERPRETIVE SUMMARY

The evidence available on the role of HBOT for radiation-induced injuries in cancer patients is limited in magnitude and quality. Of 11 studies found originally, only five were randomized trials (20,23,25,26,28). The highest quality evidence comes from two published randomized trials (23,28). One trial was not blinded, which could introduce bias into assessment of the primary outcome, clinical diagnosis of osteoradionecrosis (23). The other published randomized trial was double blind but failed to adjust for multiple comparisons and may have been underpowered (28). Additional data are available from two non-blinded randomized trials that were not published in peer-reviewed journals. The incomplete randomized trial and six cohort studies do not provide definitive evidence for or against hyperbaric oxygen therapy but can point to areas for future investigation by randomized trials.

Three studies of HBOT as a treatment for established osteoradionecrosis or wound complications after radiotherapy for head and neck cancer failed to detect a statistically significant benefit for HBOT (20-22). Three non-blinded randomized trials and one retrospective cohort study indicated that the role of HBOT in preventing complications from reconstructive surgery after radiotherapy for head and neck cancer is promising and merits further investigation (23,25-27). The results from these studies showed a clinical and statistically significant benefit in favour of HBOT. A double-blind randomized trial and a prospective cohort study suggested that HBOT may improve the quality of life in women who have complications from radiotherapy for breast cancer and should be the subject of another randomized trial (28,29). A retrospective cohort study, which detected a significant improvement in the treatment of hemorrhagic cystitis with HBOT compared to PGE2 in stem-cell transplant patients (30), also pointed to an hypothesis that could be tested by a well-conducted randomized trial.

In the update of our literature search, one published systematic review was found, but no additional primary studies met our inclusion criteria. The systematic review published by Pasquier et al (1u) supports our observations that the quantity and quality of evidence regarding the role of HBOT is modest. However, based on the available evidence, Pasquier et al concluded that there might be a role for HBOT in the treatment of mandibular osteoradionecrosis in combination with surgery, hemorrhagic cystitis resistant to conventional treatments, and the prevention of osteoradionecrosis from dental extraction after radiotherapy. Given the lack of detail provided in the review regarding the totality of the literature they considered, it is difficult to generalize these conclusions to our own.

It is our belief that the currently available evidence does not clearly answer the question "Is hyperbaric oxygen therapy (HBOT) effective in treating or preventing radionecrosis and other radiation-induced injuries in cancer patients?" While the body of evidence would not be sufficient to support the introduction of HBOT if it was not already in use, neither does it support discontinuing its use in clinical practice. Further research, in the form of adequately powered randomized trials, is required to determine if HBOT should continue to be used in this setting. At least two such trials are currently open to recruitment. Both compare HBOT with control, in the form of placebo in one trial, indicating equipoise in the investigators' minds about the value of HBOT. Established HBOT facilities should strive to design multicentre collaborative studies to address these important clinical questions.

VII. CONCLUSIONS OF THE HYPERBARIC OXYGEN TREATMENT WORKING GROUP

It is the opinion of the Working Group that there is currently insufficient evidence from clinical studies to warrant further investment in HBOT for new indications in the treatment or prevention of radiation-induced injuries in cancer patients; however, the state of the evidence does not justify withdrawing this intervention where it is currently used as standard practice.

Better-controlled studies are needed to confirm the clinical utility of this intervention. Studies examining this intervention in the prevention of osteonecrosis in patients undergoing tooth extraction after radical radiotherapy for head and neck cancer are of particular interest given that initial data show it to be most promising for this indication. In addition, future comparative studies should evaluate other alternative strategies for enhancing angiogenesis, which is hypothesized to be an important mechanism explaining the benefits of HBOT.

VIII. EXTERNAL CONSULTATION

A draft of this advice report was circulated to selected members of the PEBC provincial disease site and guideline development groups including the Provincial Head and Neck Cancer Disease Site Group. No changes were recommended by these reviewers, and no additional studies were identified that were missed by the Working Group.

VIII. ACKNOWLEDGEMENTS

The Hyperbaric Oxygen Treatment Working Group members are Melissa Brouwers, George Browman, William Evans, and Mary Johnston.

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Update

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program in evidence-based care
a cancer care ontario program

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un programme de action cancer ontario

Program in Evidence-based Care Advice Report: ARCHIVED, 2013

Hyperbaric Oxygen Therapy for the Treatment and Prevention of Radionecrosis and Other Radiation-Induced Injuries in Cancer Patients

A.W. Evans, N.P. Varela and the Radiation Oncology Provincial Committee ROPAC.

Guideline Review Summary

Review Date: March 26, 2013

The 2005 guideline recommendations are
ARCHIVED
This means that the recommendations will no longer be maintained but may still be useful for academic or other informational purposes.

OVERVIEW

Evidence-based Series History

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2005. In August 2012, the PEBC guideline update strategy was applied. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert (SH) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be archived. PEBC and the Radiation Oncology Provincial Committee (ROPAC) archived the recommendations found in the summary (Practice Guideline).

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

Is hyperbaric oxygen therapy (HBOT) effective in treating or preventing radiation-induced injuries in cancer patients?

Literature Search and New Evidence

The new search (July 2005 to August 2012) yielded a systematic review with meta-analysis updated in March 2011 and thus only original studies from March 2011 up to August 16, 2012 were considered. Overall, a total of 3 new full text publications were identified that were published after March 2011: 2 meta-analyses and 1 systematic review. In addition, 4 ongoing and/or unpublished randomized trials were identified in a search of clinicaltrials.gov.

Brief results of these publications are shown in the Document Review Tool at the end of this report.

Impact on Guidelines and Its Recommendations

With approval from the Radiation Oncology Provincial Committee (ROPAC) and in accordance with the PEBC Document Assessment and Review Protocol, PEBC decided to ARCHIVE the 2005 recommendations on Hyperbaric Oxygen Therapy for the Treatment and Prevention of Radionecrosis and other Radiation-Induced Injuries in Cancer Patients. This indicates that the guideline and its recommendations will no longer be maintained by the PEBC but it may be useful for academic or other informational purposes. The ROPAC will decide if and when a new document will cover hyperbaric oxygen therapy for treatment and prevention of radiation-induced injuries in cancer patients will be produced.

cancer care ontario | action cancer ontario
program in evidence-based care | programme de soins fondé sur des preuves

Document Review Tool

Number and title of document under review	00-HBOT Hyperbaric Oxygen Therapy for the Treatment and Prevention of Radionecrosis and other Radiation-Induced Injuries in Cancer Patients
Current Report Date	August 28, 2005
Clinical Expert	Dr. Wayne Evans
Research Coordinator	Norma P. Varela
Date Assessed	September 2011
Approval Date and Review Outcome (once completed)	March 26, 2013

Original Question(s):

Is hyperbaric oxygen therapy (HBOT) effective in treating or preventing radiation-induced injuries in cancer patients?

Target Population:

This report applies to cancer patients whose cancer care involves radiation therapy.

Study Section Criteria:

Inclusion Criteria:

Articles were selected for inclusion in this systematic review of the evidence if they met all the following criteria:

1. Evaluated HBOT to treat or prevent radiation-induced injuries.
2. Compared patients who did and did not receive HBOT, defined as 100% oxygen delivered at >1.4 atmospheres absolute (1.0 atmosphere equals approximately the pressure of the atmosphere at sea level).
3. Used either a concurrent or historical control group.
4. Reported data for clinical outcomes in both the treatment and control groups.
5. Enrolled patients who had received radiotherapy for cancer.

In considering the evidence, most weight was placed on RCTs, but other types of comparative studies were also considered.

Exclusion Criteria:

Letters, editorials, and meeting abstracts were not included.

Search Details:

- July 2005 to August 2012 (Cochrane Library) - Intended to identify the most current systematic review/meta-analysis, if existing.
- March 2011 to August 2012 (MedLine, Embase, CINAHL, HealthStar, ASCO Annual Meeting) – Intended to update the literature of the systematic review/meta-analysis retrieved from the Cochrane Library.

Brief Summary/Discussion of New Evidence:

Of a 65 hits from Medline and Embase + 23 from The Cochrane Library + 7 from ASCO Conference abstracts + 3 from CINAHL (EBSCOHOST), a systematic review with meta-analysis assessing the benefits of hyperbaric oxygen therapy for treating or preventing late radiation tissue injury in cancer patients was found. This meta-analysis was updated in March 2011 and thus only studies from March 2011 up to August 16, 2012 were considered. One meta-analysis (Overgaard, 2011) was excluded because overlaps with Bennett et al., 2012b. Overall, a total of 3 new full text publications were identified that were published after March 2011: 2 meta-analyses and 1 systematic review. In addition, 4 ongoing and/or unpublished randomized trials were identified in a search of clinicaltrials.gov.

Meta-Analysis					
Interventions	**Study**	**Population (n)**	**Outcomes**	**Brief Results**	**References**
Hyperbaric Oxygen Therapy (HBOT) Vs No Treatment	11 RCTs	n = 669	Proctitis Tissue Damage or Necrosis LENT-SOMA Score Osteoradionecrosis Head and Neck Tissue Lymphoedema	There is some evidence that HBOT improves outcomes in Late Radiation Tissue Injury • HBOT significantly increased the chance of improvement or cure of radiation proctitis RR = 1.72 [95% CI = 1.03 to 2.86]. • HBOT significantly improved the probability of complete resolution of tissue damage or necrosis for patients requiring hemimandibulectomy RR = 1.41 [95% CI = 1.14 to 1.75]. • HBOT significantly improved the LENT-SOMA score at completion of therapy FES = 2.39 [95% CI = 0.89 to 3.89]. • HBOT significantly improved the probability of resolution (complete mucosal cover) of osteoradionecrosis RR = 1.30 [95% CI = 1.09 to 1.55]. • HBOT significantly improved the probability of attaining bony continuity with osteoradionecrosis RR= 1.41 [95% CI = 1.14 to 1.75]. • HBOT significantly improved the probability of healing of tooth sockets following extraction in irradiated field at 6 months RR = 1.35 [95% CI = 1.08 to 1.68]. • HBOT significantly increased the probability of avoiding wound dehiscence/breakdown in head and	Bennett et al., 2012a

			Quality of Life Neurological Tissue	neck following soft tissue flap or graft RR = 8.67 [95% CI = 2.73 to 27.49]. • Resolution of lymphoedema in arm at 6 and 12 months was higher in the HBOT group when compared to the control group but the difference in favour of HBOT was **not statistically significant** o At 6 months: 12% HBOT vs 0% Control p = 0.29 o At 12 months: 2.6% HBOT vs 0.3% Control p = 0.75 o > 8% reduction: 30% HBOT vs 19% Control p = 0.41 • HBOT does not have a significant clinical effect on: o Quality of life and functional outcomes o Neurological tissues, either peripheral or central	
Hyperbaric Oxygen Therapy (HBOT) Vs No Treatment	19 RCTs	n = 2286	Mortality Rate Local Tumour Control Local tumour Recurrence	• HBOT significantly reduced the mortality for head and neck cancer at one and five years after therapy RR = 0.83 [95% CI = 0.70 to 0.98] and RR = 0.82 [95% CI = 0.69 to 0.98], respectively. It was not the case at two years after therapy RR = 0.97 [95% CI = 0.83 to 1.12]. • HBOT significantly improved the probability local tumour control at three months after therapy RR = 0.58 [95% CI = 0.39 to 0.85]. • HBOT significantly decreased the probability of local tumour recurrence at one, two and five years o One years: RR = 0.66 [95% CI = 0.56 to 0.78] o Two years: RR = 0.60 [95% CI = 0.38 to 0.97] o Five years: RR = 0.77 [95% CI = 0.62 to 0.95].	Bennett et al., 2012b

Systematic Review

Interventions	Study	Population (n)	Outcomes	Brief Results	References
Hyperbaric Oxygen Therapy vs Prednisone	1 RCT	n = 79	Bell's palsy	HBOT significantly improved the probability of facial function recovery RR = 1.26 [95% CI = 1.04 to 1.53] but the study was excluded because the outcome assessor was not blinded to treatment allocation.	Holland et al., 2012

Ongoing Randomized Controlled Trials (RCTs)

Intervention	Official Title	Protocol ID / Status	Last Updated	Estimated Completion Date
HBOT vs No HBOT	Hyperbaric Oxygen – a New Treatment Modality in Patients With Radiation Damaged Salivary Gland Tissue	NCT01606644/ Recruiting	May 2012	April 2014
HBOT vs No HBOT	Radiation Induced Cystitis Treated With Hyperbaric Oxygen – A Randomized Controlled Trial	NCT01659723/ Recruiting	Aug. 2012	March 2015
HBOT + Surgery vs Surgery	Efficacy of Hyperbaric Oxygen Therapy in the Treatment of Osteoradionecrosis	NCT00989820 / Recruiting	July 2011	Oct. 2012

HBOT + Surgery vs Surgery	Hyperbaric Oxygen Treatment of Mandibular Osteoradionecrosis. A Randomized Clinical Study	NCT00760682 / Recruiting	May 2012	April 2015

RC (Randomized Controlled Trial); RR (Risk Ratio); FES (Fixed Effect Size); LENT-SOMA (Late Effects Normal Tissues – Subjective, Objective, Management, Analytic); DAHANCA (The Danish Head and Neck Cancer Group).

Clinical Expert Interest Declaration:

Instructions. Instructions. For each document, please respond YES or NO to all the questions below. Provide an explanation of each answer as necessary.

1. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?	Yes – key value of hyperbaric oxygen therapy in pelvic radiation necrosis is a significant omission and invalidates current guidance
2. On initial review, a. Does the newly identified evidence support the existing recommendations? b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?	Yes – in part. NO
3. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	Yes – if – the status of cited trail NCT00989820 should be updated in the event that publication is imminent.
4. Do the PEBC and the DSG/GDG	Unable to comment as resource base unknown

responsible for this document have the resources available to write a full update of this document within the next year?	to me.
Review Outcome	ARCHIVE
DSG/GDG Approval Date	March 26, 2013
DSG/GDG Commentary	

New References Identified

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3. Holland NJ, Bernstein JM, Hamilton JW. Hyperbaric oxygen therapy for Bell's palsy. Cochrane Database of Systematic reviews [Internet]. 2012; (2). Available from: http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD007288/frame.html.
4. Overgaard J. Hypoxic modification of radiotherapy in squamous cell carcinoma of the head and neck – A systematic revview and meta-analysis. Radiotherapy and Oncology. 2011;100(1):22-32.

Literature Search Strategy

Cochrane Library

Hyperbaric oxygen AND radiation

Medline

1. meta-Analysis as topic.mp.
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
5. (systematic adj (review$ or overview?)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or scisearch or bids or sigle or cancerlit).ab.

9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random$.tw.
23. (clinic$ adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or random alllocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. Animal/
38. Human/
39. 37 not 38
40. 36 not 39
41. (cancer? or carcinoma? or neoplasm? or tumo?r or carcinogen$).tw.
42. (radiation effect? or radiation injur$ or radiation necrosis or radionecrosis or osteoradionecrosis or proctitis or cystitis or toxicity or radiotherap$).tw.
43. 41 and 42
44. exp hyperbaric oxygen therapy/
45. 43 and 44
46. 40 and 45
47. (200507: or 2006: or 2007: or 2008: or 2009: or 2010: or 2011: or 2012:).ed.
48. 46 and 47

Embase

1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling ir mathematical pooling or statistical summar$ or matematical sumar$ or quantitative synthes?s or quantitative overview).tw.
4. (systematic adj (review$ or overview?)).tw.
5. exp review/ or review.pt.

6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8
10. (cochraine or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or science citation index or scisearch or bids or single or cancerlit).ab.
11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and random.tw.
18. (clinic$ and trial$1).tw.
19. ((singl$ or doubl$ or tre$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
20. placebo/
21. (placebo? or random allocation or random allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
26. practice guideline.pt.
27. or/24-26
28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
30. 28 not 29
31. limit 30 to english
32. Animal/
33. Human/
34. 32 not 33
35. 31 not 34
36. (cancer? or carcinoma? or neoplasm? or tumo?r or carcinogen$).tw.
37. (radiation effect? or radiation injur$ or radiation necrosis or radionecrosis or osteoradionecrosis or proctitis or cystitis or toxicity or radiotherap$).tw.
38. 36 and 37
39. exp hyperbaric oxygen therapy/
40. 38 and 39
41. 35 and 40
42. (200526$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$).ew.
43. 41 and 42

ASCO Annual Meeting - http://www.ascopubs.org/search

Hyperbaric Oxygen AND Radiation

Clinicaltrials.gov **-** http://www.clinicaltrials.gov/

Hyperbaric Oxygen AND Radiation

CINAHL Cumulative Index to Nursing and Allied Health Library (EBSCOHOST) -
http://web.ebscohost.com/ehost/search/advanced

Hyperbaric Oxygen AND Radiation