Hyperbaric oxygen therapy for late radiation tissue injury in gynecologic malignancies

P. Craighead MBChB,† M.A. Shea–Budgell MSc,† J. Nation MD,*† R. Esmail BSc MSc,‡ A.W. Evans MD,§ M. Parliament MD,†|| T.K. Oliver MD,#** and N.A. Hagen MD*†*

ABSTRACT

Background

Late radiation tissue injury is a serious complication of radiotherapy for patients with gynecologic malignancies. Strategies for managing pain and other clinical features have limited efficacy; however, hyperbaric oxygen therapy (HBO_2) may be an effective option for some patients.

Methods

In a systematic review of the literature, the Ovid MEDLINE, EMBASE, Cochrane Library, National Guidelines Clearinghouse, and Canadian Medical Association Infobase databases were searched to June 2009 for clinical practice guidelines, systematic reviews, randomized controlled trials, or other relevant evidence. Studies that did not evaluate soft tissue necrosis, cystitis, proctitis, bone necrosis, and other complications were excluded.

Results

Two randomized trials, eleven nonrandomized studies, and five supporting documents comprise the evidence base. In addition, information on the harms and safety of treatment with HBO_2 were reported in three additional sources. There is modest direct evidence and emerging indirect evidence that the use of HBO_2 is broadly effective for late radiation tissue injury of the pelvis in women treated for gynecologic malignancies.

Conclusions

Based on the evidence and expert consensus opinion,

- HBO_2 is likely effective for late radiation tissue injury of the pelvis, with demonstrated efficacy specifically for radiation damage to the anus and rectum;
- the main indication for HBO_2 therapy in gynecologic oncology is in the management of otherwise refractory chronic radiation injury;
- HBO_2 may provide symptomatic benefit in certain clinical settings (for example, cystitis, soft-tissue necrosis, and osteonecrosis); and
- HBO_2 may reduce the complications of gynecologic surgery in patients undergoing surgical removal of necrosis.

KEY WORDS

Hyperbaric oxygen therapy, HBO_2, late radiation tissue injury, LRTI, radiotherapy, gynecologic cancers, adverse effects, cancer pain, clinical practice guideline, systematic review

1. BACKGROUND

In gynecologic cancers treated with a combination of external-beam radiation and brachytherapy, especially cervical, vaginal, and vulvar cancers, the apex of the vagina or perineum receives a high dose of radiation. The tolerance of the lateral apical vagina can be as high as 140 Gy, but the tolerance of the perineum is lower: up to 80 Gy can be tolerated if given over more than 6 weeks. The tolerance is less for the rest of the vagina and elsewhere in the pelvis, and high-dose radiation to those areas can result in complications.

Radiation-related complications that develop months or years after treatment with radiation are known as late radiation tissue injuries (LRTIs) and are estimated to affect 5%–15% of all long-term survivors who have received radiation [1–4]. For patients with gynecologic malignancies, the estimated prevalence of LRTI is 2%–4% among those who have undergone pelvic radiotherapy [5]. The absolute risk of radionecrosis increases with radiation doses greater than 60 Gy. The risk is disproportionately higher in patients who

undergo treatment with fraction sizes of 250 cGy or more daily.

The mechanics of LRTI are only partially understood. One major theory suggests that radiation causes progressive endarteritis of the small blood vessels, resulting in cellular hypoxia and damage to fibroblasts. This damage inhibits the ability of the irradiated tissue to repair itself, resulting in nonhealing ulcers. In patients inherently prone to radiation damage, it is probable that cells within organ stroma are unable to repair DNA damage, resulting in a critically low volume of stem cells and lack of tissue healing. Within the pelvis, a radionecrotic wound can gradually progress to involve surrounding tissue, frequently resulting in vaginitis, proctitis, perineal ulcers, and vesicovaginal and rectovaginal fistulae.

Persisting symptoms often include pelvic pain, deep dyspareunia, frank hematuria, vaginal discharge, or frank ulceration and necrosis. Ulceration and necrosis can be particularly disabling, being characterized by pain and a malodorous serosanguineous discharge. Affected patients often become socially isolated and are at risk for depression, nutritional deficiency, or repeated hospitalizations [5].

Medical treatment typically involves topical wound care and surgical repair, but unfortunately, treatment failure is common. Surgical repair of fistulae related to radiation necrosis is not only technically difficult, but has met with only limited success because of a compromised blood supply in the skin and myocutaneous flaps used [5].

Hyperbaric oxygen therapy (HBO_2) has been used as a treatment modality to promote repair of radiation-induced vascular changes. Transcutaneous oxygen measurements 4 years after HBO_2 have revealed near-normal levels, implying that HBO_2-induced angiogenesis is essentially permanent. Thus, HBO_2 is the first available treatment for delayed radiation injuries that potentially modifies the underlying mechanism of tissue damage and that is associated with healing of otherwise treatment-refractory ulcerated tissue [6]. Preoperative HBO_2 can contribute to a higher rate of surgical success.

The mechanism by which HBO_2 is thought to treat radiation tissue injury is the induction of neovascularization that reverses tissue hypoxia. The stimulus for angiogenesis appears to be mediated through macrophages responding to the oxygen gradient between the damaged hypoxic cells and the surrounding normal tissue [7]. Other biochemical pathways involved include mobilization of stem cells from bone marrow [8] and vasculogenesis [9], resulting in elevated levels of vascular endothelial growth factor [10]. The subacute and chronic phases of radiation wounds are particularly suited to this form of therapy. The HBO_2 acts to stimulate collagen formation at the wound edges through elevation of local tissue oxygen tension. The growth of new microvasculature, which is dependent on a collagen matrix, is greatly enhanced in this setting and allows for re-epithelization to occur. The HBO_2 also stimulates fibroblast proliferation. A range of studies has characterized mechanism of action, treatment approaches, economic evaluation, and other aspects of HBO_2 [5,11–15].

2. OBJECTIVES

This evidence-based clinical practice guideline aims to provide recommendations for the use of HBO_2 therapy in LRTI with respect to soft-tissue necrosis, cystitis, proctitis, bone necrosis, and other complications in women treated with radiation for gynecologic cancers. Although the importance of preventing LRTI is recognized, this guideline does not address prevention, but rather treatment of LRTI.

2.1 Question

Is HBO_2 effective in treating LRTI with respect to soft-tissue necrosis, cystitis, proctitis, bone necrosis, and other complications in women who have undergone radiation therapy for gynecologic malignancies?

2.2 Target Population

This clinical practice guideline applies to women treated with radiation for gynecologic cancers who have developed LRTI (soft-tissue necrosis, cystitis, proctitis, bone necrosis, and other complications) and for whom the use of HBO_2 therapy is being considered.

2.3 Target Users

This clinical practice guideline is intended to inform health practitioners on the use of HBO_2 among women with LRTI consequent to radiation for gynecologic malignancies. It is also intended for use by health authorities and key administrative and policy decision-makers to inform policy decisions concerning the use of HBO_2 and by cancer survivors with gynecologic malignancies to assist in making informed decisions on treatment options for LRTI.

3. METHODOLOGY

3.1 Guideline Development

The review process for this guideline was developed based on

- the U.K. National Institute for Health and Clinical Excellence overview of clinical guideline development for stakeholders, the public, and the National Health Service [16];
- Cummings and Rivara's methodology for reviewing manuscripts [17]; and
- the AGREE collaboration [18].

With that methodologic foundation, the guideline recommendations were drafted by 2 radiation oncologists from the Tom Baker Cancer Centre, with support from the Guideline Utilization Resource Unit and the Alberta Gynecologic Oncology Provincial Tumour Team. Members of the Alberta Gynecologic Oncology Provincial Tumour Team include gynecologic oncologists, medical oncologists, radiation oncologists, nurses, pathologists, and pharmacists. The evidence base for the present guideline was informed by a systematic review of the literature, which was current to June 2009.

Before completion, the guideline was distributed to an external review panel consisting of 4 reviewers (a gynecologic oncologist, 2 radiation oncologists, and a clinical expert in hyperbaric medicine) for feedback concerning the collection and interpretation of the evidence and the development and content of the recommendations. Feedback from reviewers was summarized, reviewed, and addressed by the guideline developers in a teleconference. Finally, in an internal review of the guideline, members of the Alberta Gynecologic Oncology Provincial Tumour Team were invited to submit feedback on the draft guideline. After the feedback was incorporated, the guideline was circulated back to the group for consensus approval. Final consensus was reached through an informal voting process. The literature will be periodically reviewed, and the guideline will be updated as new or compelling evidence is identified.

3.2 Literature Search Strategy

The Ovid MEDLINE (1965 through June 25, 2009), EMBASE (1980 through June 25, 2009), Cochrane Library (2000 to June 25, 2009), National Guidelines Clearinghouse, and Canadian Medical Association InfoBase databases were searched to June 2009 for clinical practice guidelines, systematic reviews, randomized controlled trials, or other relevant evidence deemed eligible to inform the topic. Reference lists of related papers and recent review articles were also scanned for additional citations.

Literature search terms included "hyperbaric oxygen therapy" or "hyperbaric oxygenation"; "pelvic" or "pelvis" or "gynecol*" or "gynecology"; and "radiation injury" or "proctitis" or "cystitis" or "lesions." The search was limited to articles in the English language. The search identified 45 citations; of those, 13 were selected for full-text review.

From among the 13 full-text articles, two randomized controlled trials [19,20], eleven nonrandomized studies [21–31], and five additional supporting documents [12,32–35] representing indirect evidence, were considered eligible for inclusion. They comprise the evidence base for the systematic review of the literature. In addition, supporting documentation on the risks and safety of treatment with HBO_2 were reported in three additional sources [36–38].

3.3 Study Selection Criteria

3.3.1 Inclusion Criteria

Articles were selected for inclusion in the review of the evidence if they reported on patients with pelvic malignancies that were experiencing LRTI after receiving radiotherapy for treatment of their disease, and they investigated the use of HBO_2 in that treatment population. Preference was given to clinical practice guidelines, systematic reviews, or randomized controlled trials; however, given the anticipated paucity of data, nonrandomized studies addressing the topic and indirect evidence involving other oncology patient populations treated with HBO_2 were also deemed eligible if insufficient primary evidence were to be available.

3.3.2 Exclusion Criteria

Articles were excluded from the review of the evidence if they were qualitative or descriptive studies, opinion papers, letters, or editorials. Because of a lack of translation services, articles in languages other than English were excluded from the review of the evidence.

3.4 Synthesizing the Evidence

Because of differences in outcomes studied and a limited sample size, it was not appropriate to conduct a meta-analysis of the data.

4. RESULTS

Table I summarizes key studies, which include retrospective, prospective, and case studies and randomized controlled trials. Further details of the studies and other relevant publications [12,19–38] are available on the *Current Oncology* Web site.

There is evidence that HBO_2 has efficacy in LRTI of the pelvis, rectum, bladder, soft tissue, and bone. Among women experiencing LRTI from treatment for gynecologic malignancies, the response rate to HBO_2 is of the order of 70%. Studies have found positive effects and a range of specific response rates for various clinical features of LRTI (including cystitis, proctitis, and other gastrointestinal complications) and pain [23–27]. There is some evidence to suggest that outcomes are better when HBO_2 is initiated by 6 months from the start of symptoms rather than being delayed beyond that point [26].

Randomized controlled trials have demonstrated that HBO_2 significantly improves pelvic radiation symptoms. Sidik *et al.* [19] showed that, compared with control patients, women undergoing HBO_2 [100% oxygen at 2.0–3.0 atmospheres absolute (ATA) for at least 18 sessions] experienced significantly ($p = 0.008$) fewer side effects from pelvic radiation (median dose not reported) and significantly better quality of life ($p < 0.001$ after

TABLE I Efficacy of hyperbaric oxygen therapy for the treatment of late radiation tissue injury to the pelvis

Reference	*Study design*	*Patients* (n)	*Measures*	*Pressure (ATA) [time (min)]*	*Sessions* (n)	*Follow-up (months)*	*Overall improvement*
Fletcher *et al.,* 1977 [29]	Prospective randomized controlled trial	17	Clinical hematuria	3.0 (40)	14 (mean)	24	88.2% (complete resolution or marked improvement)
Williams *et al.,* 1992 [21]	Prospective case study	14	Clinical vaginal necrosis and fistula	2.0 (90–120)	15	36	92.9% (complete resolution)
Feldmeier *et al.,* 1996 [22]	Retrospective	41	Clinical	2.4 (90)	24 (mean)	NR	81.0% (healing of the injuries or closure of fistulas)
Del Pizzo *et al.,* 1998 [31]	Retrospective	11	Clinical hematuria	2.0 (90)	40	60 (median)	27.0% (complete resolution)
Corman *et al.,* 2003 [30]	Prospective case study	57	Clinical hematuria	2.4 (90)	33 (mean)	55 (median)	86.0% (complete resolution or marked improvement)
Bui *et al.,* 2004 [28]	Retrospective	7	RTOG criteria (principal symptom)	2.4 (100)	40 (median)	0 (post HBOT)	100.0% (median: 72 weeks' duration)
Chong *et al.,* 2005 [26]	Retrospective	60	Clinical hematuria	2.36 (90)	36 (median)	12	80.0% (complete or partial resolution)
Fink *et al.,* 2006 [23]	Retrospective	14	Physician assessment	2.4 (90)	32.8 (mean)	38 (median)	71% (>50% improvement or complete healing)
Jones *et al.,* 2006 [25]	Retrospective	10	LENT-SOMA	2.4 (90)	38.5 (median)	25 (median)	77.8% (rectal bleeding resolved or downgraded) 60.0% (rectal pain resolved) 80.0% (diarrhea resolved or downgraded)
Sidik *et al.,* 2007 [19]	Prospective randomized controlled trial	32	LENT-SOMA Karnofsky	2.0–3.0 (NR)	>18[b]	6	13.95%[c] LENT-SOMA 12.80%[c] Karnofsky
Clarke *et al.,* 2008 [20]	Prospective randomized controlled trial	64	SOMA-LENT Bowel function	2.0 (90)	NR	24	2.30 points SOMA-LENT 9.17 points bowel function
Safra *et al.,* 2008 [24]	Retrospective	13	NCI Common Toxicity Criteria	2.0 (90)	27 (median)	0 (post HBOT)	3.0 points[a] 83.3% (proctitis resolved) 85.7% (cystitis resolved) 100.0% (scar complications resolved)
Rud *et al.,* 2009 [27]	Prospective case study	16	Brief Pain Inventory, Depression Scale	2.4 (90)	21	6	50% (some or good effect, patient-reported) No change in Brief Pain Inventory or Depression Scale scores

[a] Significant ($p \leq 0.001$) compared with control group.
[b] Authors reported that most patients received at least 18 sessions.
[c] Significant ($p \leq 0.01$) compared with control group.

ATA = atmospheres absolute; NR = not reported; RTOG = Radiation Therapy Oncology Group; HBOT = hyperbaric oxygen therapy; LENT = Late Effects in Normal Tissues; SOMA = Subjective, Objective, Management and Analytic scales; NCI = U.S. National Cancer Institute.

Further details on these studies and other relevant publications are available at the Alberta Health Services Cancer Care Web site [40]. Search for "hyperbaric oxygen" at http://www.albertahealthservices.ca/services.asp?pid=stype&type=7.

intervention, $p = 0.007$ after 6 months). More recently, the ongoing Hyperbaric Oxygen Radiation Tissue Injury Study [20] demonstrated highly favourable results among patients (88.3% of whom were women) experiencing proctitis as a result of radiation therapy (median total dose: 78.4 Gy; range: 36.5–120.2 Gy) for cancer of the uterine cervix (83.2%) or other pelvic malignancy, 2 years after treatment with a course of HBO_2. Compared with placebo, treatment (100% oxygen at 2.0 ATA for 90 minutes, once daily, 5 times weekly) was associated with a near doubling of the improvement in symptoms (for example, pain, frequency, bleeding, and ulceration, among others; $p = 0.0019$). The full results for patients with gynecologic malignancies treated with HBO_2 are pending.

Evidence from earlier nonrandomized studies suggests that HBO_2 is particularly effective in the treatment of radiation-induced hemorrhagic cystitis, especially in patients who have failed to improve with the use of other treatment modalities [28]. Fletcher *et al.* [29] demonstrated complete resolution of hemorrhagic cystitis in 64% of patients treated with HBO_2 once daily for a mean of 14 sessions or until resolution. A response rate of 86% has also been reported [30]. Furthermore, the benefit of HBO_2 appears to be long-lasting (for example, after more than 5 years) in some patients [31].

Moderate success for HBO_2 as a treatment for soft-tissue necrosis has also been reported. Williams *et al.* [21] prospectively examined the therapeutic effects of HBO_2 on radiation-induced soft-tissue necrosis in 14 patients who had previously received treatment for a gynecologic malignancy. Fourteen patients whose necrotic wounds failed to heal after 3 months of conservative therapy underwent 15 courses of HBO_2. All patients with vaginal radiation necrosis or rectovaginal fistula experienced complete resolution of necrosis with HBO_2; only 1 treatment failure occurred. Other studies have found similarly positive effects and response rates for a range of clinical features of LRTI, including proctitis, cystitis, proctitis and other gastrointestinal complications, and pain [22–27].

A systematic review conducted by Bennett *et al.* [12] concluded that, for patients with LRTI affecting tissues of the head, neck, anus, and rectum, HBO_2 is associated with improved outcomes. Application of HBO_2 also appeared to reduce the risk of osteoradionecrosis after tooth extraction in an irradiated field. An earlier systematic review of 74 publications reporting on the use of HBO_2 in the treatment or prophylaxis of delayed radiation injury found that all but seven publications reported a positive result for HBO_2. The authors concluded that HBO_2 should be recommended for delayed radiation injuries in soft tissue and bone at most sites [39].

However, the evidence remains preliminary overall. A 2005 report from Cancer Care Ontario's Program in Evidence-Based Care concluded that the evidence from clinical studies is currently insufficient to warrant further investment in HBO_2 for new indications in the treatment or prevention of radiation-induced injuries. The report also indicated that the state of the evidence does not justify withdrawing this intervention where it is currently used as standard practice. The report declared that better-controlled studies are needed to confirm the clinical utility of HBO_2 [33].

By contrast, the BC Cancer Agency [34] lists referral for HBO_2 therapy as an option for selected patients with LRTI, and the Scottish Intercollegiate Guidelines Network [35], writing on the diagnosis and management of head-and-neck cancer, recommended that HBO_2 facilities should be available to selected patients with head-and-neck cancer. Likewise, at the European Concensus Conference on Hyperbaric Medicine, the European Society for Therapeutic Radiology and Oncology and the European Committee for Hyperbaric Medicine listed myelitis and plexopathy, proctitis and enteritis, cystitis, radionecrosis of the larynx, and osteoradionecrosis as indications for the use of HBO_2 [40].

There are risks and benefits associated with HBO_2. It is advisable to have all potential candidates evaluated by an experienced hyperbaric physician to determine "fitness to dive" (that is, to assess treatment-associated risks) [36]. Of particular concern are patients who present with middle or inner ear disorders, congenital heart disease, claustrophobia, chronic obstructive pulmonary disease, high fever, cataracts, pregnancy, or use of a pacemaker or an epidural pain pump, among others [36,37]. Absolute contraindications to the use of HBO_2 include untreated pneumothorax or untreated cancer (that is, concurrent use of bleomycin, cisplatin, disulfiram, doxorubicin, or mafenide acetate) [37]. However, the use of HBO_2 therapy is considered safe when the chamber is properly installed according to municipal and provincial regulations and when operators and attendants are properly trained. Operators should be able to manage any serious complications that could be encountered by patients and should be supervised by a physician trained in hyperbaric medicine [38].

Can HBO_2 increase the risk of cancer recurrence?

A retrospective analysis of 22 patients with recurrent head-and-neck cancer concluded that HBO_2 increases the risk of cancer re-recurrence: 5-year disease-free survival rates were lower in patients receiving HBO_2 (32.7% vs. 70.0%, $p = 0.048$) [41]. However, as Hermann and Carl and Feldmeier *et al.* noted, the high risk of stratification bias and small sample size are problematic, and larger controlled trials have shown no effect or an inhibitory effect of HBO_2 on recurrence [42,43]. Nevertheless, patients should be clinically cancer-free at the onset of tissue ulceration, and recurrent cancer should be ruled out before HBO_2 is initiated.

5. DISCUSSION

There is little strong evidence to definitively recommend HBO_2 for women with LRTI secondary to radiation for gynecologic malignancies; the area has not been well studied. But despite the limited evidence, several studies showed positive therapeutic effects with HBO_2 for LRTI of the pelvis, and several other studies suggest that HBO_2 may be beneficial for improving quality of life in patients with radiation toxicity after treatment for pelvic malignancy. Overall, the body of evidence, although modest, favors HBO_2 as a therapeutic option.

However, the mechanism of action of LRTI and the evidence supporting clinical benefit with HBO_2 are thought to be similar after radiation treatment administered for gynecologic malignancies and radiation treatment administered for other indications and to other parts of the body. A cogent argument can be made that positive outcomes in studies of HBO_2 treatment for LRTI together contribute to a broader field of evidence. This field of evidence suggests that HBO_2 for LRTI related to chronic vascular injury can be anticipated to be of benefit in many clinical scenarios.

If HBO_2 is being considered as a therapeutic option, the clinical condition to be treated (that is, pain from cystitis, proctitis, bone necrosis, soft-tissue necrosis, and so on) should be quantified, and clinical endpoints should be determined, case by case before the HBO_2 is initiated. Currently, no strong evidence or agreement has emerged to indicate the most appropriate dosing regimen; however, treatment typically consists of once-daily treatments at 2.0–2.5 ATA, usually for 90 minutes (range: 60–120 minutes), 5 days weekly, for up to 40 treatments, depending on the patient's condition [12]. In general, after 20–25 treatments with HBO_2, a clinical evaluation should reassess the patient's condition and determine whether significant improvements were achieved. In the absence of significant improvements, the case should be re-evaluated to determine whether HBO_2 is an appropriate treatment option.

Some organizational barriers may be associated with the use of HBO_2, including access to equipment and funding, whether for direct costs (per course of treatment) or indirect costs (such as accommodations for patients, staffing requirements, time requirements, treatment for side effects, and referring physician knowledge) [44].

To conclude, modest direct and emerging indirect evidence supports HBO_2 as being broadly effective for LRTI of the pelvis in women treated with radiation for gynecologic malignancies. Treatment with HBO_2 should be considered for women for whom conservative care has failed. Emerging interest in validated tools will support collaborative approaches to document outcomes across jurisdictions. Acumen in HBO_2 will benefit from more rigorous reporting of outcomes from its use in LRTI populations.

6. RECOMMENDATIONS

The recommendations that follow are based on

- a modest quality of evidence that supports the use of HBO_2 for LRTI,
- review by external content experts, and
- the expert consensus opinion of the Alberta Gynecologic Oncology Provincial Tumour Team.

The recommendations apply to women presenting with LRTI, including soft-tissue necrosis, cystitis, proctitis, bone necrosis, and other complications subsequent to radiation therapy for gynecologic malignancies.

- HBO_2 is effective for LRTI, particularly that of head, neck, anus, and rectum. That is, there is an emerging field of evidence, with contributions from specific and diverse areas of clinical study, of positive outcomes in patients with LRTI involving head, neck, anus, or rectum.
- Among women with LRTI secondary to radiation for gynecologic malignancies, the main indication for the use of HBO_2 therapy is the management of treatment-refractory chronic radiation injury.
- There is evidence for symptomatic benefit with the use of HBO_2 therapy in certain clinical settings (cystitis, soft-tissue necrosis, or osteonecrosis) after radiotherapy for cervical cancer. The small number of case series and the low patient numbers limit the construction of more specific recommendations; however, HBO_2 should be considered for women in whom conservative care fails. In patients being considered for surgical removal of necrosis, limited but consistent evidence supports the use of HBO_2 to reduce the complications of gynecologic oncology surgery, purported to occur through the stimulation of small-vessel angiogenesis.

7. ACKNOWLEDGMENTS

The authors acknowledge the contributions of Drs. Prafull Ghatage, Alexandra Schepansky, Harold Lau, and Simon Pavamani to the development of this clinical practice guideline.

8. CONFLICT OF INTEREST DISCLOSURES

There authors have no conflicts of interest to declare.

9. REFERENCES

1. Rubin P, Casarrett GW. *Clinical Radiation Pathology.* Vol. 1. Philadelphia, PA: Saunders; 1968: 58–61.
2. Stone HB, Coleman CN, Anscher MS, McBride WH. Effects of radiation on normal tissues: consequences and mechanisms. *Lancet Oncol* 2003;4:529–36.

3. Thompson IM, Middleton RG, Optenberg SA, *et al.* Have complication rates decreased after treatment for localized prostate cancer? *J Urol* 1999;162:107–12.
4. Waddell BE, Rodriguez–Bigas MA, Lee RJ, Weber TK, Petrelli NJ. Prevention of chronic radiation enteritis. *J Am Coll Surg* 1999;189:611–24.
5. Albany Medical Center (AMC). *A Physician's Guide to the Hyperbaric Oxygen Service.* Albany, NY: AMC; 2006. [Available online at: http://www.amc.edu/Patient/services/hyperbaric_oxygen/documents/hbo_physician_guide.pdf; cited April 14, 2009]
6. United States, Department of Health and Human Services, Food and Drug Administration (FDA), Center for Devices and Radiological Health. *Traditional 510(k) Pre-market Notification Summary (Per 21CFR807.92).* Bethesda, MD: FDA; 2005. [Available online at: http://www.accessdata.fda.gov/cdrh_docs/pdf5/K053498.pdf; cited April 17, 2009]
7. Knighton DR, Hunt TK, Scheuenstuhl H, Halliday BJ, Werb Z, Banda MJ. Oxygen tension regulates the expression of angiogenesis factor by macrophages. *Science* 1983;221:1283–5.
8. Thom SR, Bhopale VM, Velazquez OC, Goldstein LJ, Thom LH, Buerk DG. Stem cell mobilization by hyperbaric oxygen. *Am J Physiol Heart Circ Physiol* 2006;290:H1378–86.
9. Milovanova TN, Bhopale VM, Sorokina EM, *et al.* Hyperbaric oxygen stimulates vasculogenic stem cell growth and differentiation *in vivo*. *J Appl Physiol* 2009;106:711–28.
10. Fok TC, Jan A, Peel SA, Evans AW, Clokie CM, Sándor GK. Hyperbaric oxygen results in increased vascular endothelial growth factor (VEGF) protein expression in rabbit calvarial critical-sized defects. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008;105:417–22.
11. Marx RE, Johnson RP, Kline SN. Prevention of osteoradionecrosis: a randomized prospective clinical trial of hyperbaric oxygen versus penicillin. *J Am Dent Assoc* 1985;111:49–54.
12. Bennett MH, Feldmeier J, Hampson N, Smee R, Milross C. Hyperbaric oxygen therapy for late radiation tissue injury. *Cochrane Database Syst Rev* 2005;(3):CD005005.
13. Chuck AW, Hailey D, Jacobs P, Perry DC. Cost-effectiveness and budget impact of adjunctive hyperbaric oxygen therapy for diabetic foot ulcers. *Int J Technol Assess Health Care* 2008;24:178–83.
14. Dempsey J, Hynes N, Smith T, Sproat JE. Cost effectiveness analysis of hyperbaric therapy in osteoradionecrosis. *Can J Plastic Surg* 1997;5:221–9.
15. Australia, Department of Health and Ageing, Medicare Services Advisory Committee (MSAC). Home > Completed Assessments and Reports > Application 1018-1020: Hyperbaric Oxygen Therapy (HBOT) [Web page]. Canberra, Australia: MSAC; 2001. [Available at: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/app1018-1020-1; cited April 21, 2009]
16. National Institute for Health and Clinical Excellence (NICE). *How NICE Clinical Guidelines Are Developed: An Overview for Stakeholders, the Public and the NHS.* 4th ed. London, U.K.: NICE; 2009.
17. Cummings P, Rivara FP. Reviewing manuscripts for *Archives of Pediatrics and Adolescent Medicine. Arch Pediatr Adolesc Med* 2002;156:11–13.
18. AGREE Enterprise. *Appraisal of Guidelines for Research and Evaluation (AGREE) Instrument.* AGREE Enterprise; 2000. [Free download available at: http://www.agreetrust.org; cited November 15, 2009]
19. Sidik S, Hardjodisastro D, Setiabudy R, Gondowiardjo S. Does hyperbaric oxygen administration decrease side effect and improve quality of life after pelvic radiation? *Acta Med Indones* 2007;39:169–73.
20. Clarke RE, Tenorio LM, Hussey JR, *et al.* Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomized and controlled double-blind crossover trial with long-term follow-up. *Int J Radiat Oncol Biol Phys* 2008;72:134–43.
21. Williams JA Jr, Clarke D, Dennis WA, Dennis EJ 3rd, Smith ST. The treatment of pelvic soft tissue radiation necrosis with hyperbaric oxygen. *Am J Obstet Gynecol* 1992;167:412–15.
22. Feldmeier JJ, Heimbach RD, Davolt DA, Court WS, Stegmann BJ, Sheffield PJ. Hyperbaric oxygen an adjunctive treatment for delayed radiation injuries of the abdomen and pelvis. *Undersea Hyperb Med* 1996;23:205–13.
23. Fink D, Chetty N, Lehm JP, Marsden DE, Hacker NF. Hyperbaric oxygen therapy for delayed radiation injuries in gynecological cancers. *Int J Gynecol Cancer* 2006;16:638–42.
24. Safra T, Gutman G, Fishlev G, *et al.* Improved quality of life with hyperbaric oxygen therapy in patients with persistent pelvic radiation-induced toxicity. *Clin Oncol (R Coll Radiol)* 2008;20:284–7.
25. Jones K, Evans AW, Bristow RG, Levin W. Treatment of radiation proctitis with hyperbaric oxygen. *Radiother Oncol* 2006;78:91–4.
26. Chong KT, Hampson NB, Corman JM. Early hyperbaric oxygen therapy improves outcome for radiation-induced hemorrhagic cystitis. *Urology* 2005;65:649–53.
27. Rud AK, Bjørgo S, Kristensen GB, Kongsgaard UE. Hyperbaric oxygen therapy for late radiation tissue injury in gynaecological patients. *Support Care Cancer* 2009;17:1517–21.
28. Bui QC, Lieber M, Withers HR, Corson K, van Rijnsoever M, Elsaleh H. The efficacy of hyperbaric oxygen therapy in the treatment of radiation-induced late side effects. *Int J Radiat Oncol Biol Phys* 2004;60:871–8.
29. Fletcher GH, Lindberg RD, Caderao JB, Wharton JT. Hyperbaric oxygen as a radiotherapeutic adjuvant in advanced cancer of the uterine cervix: preliminary results of a randomized trial. *Cancer* 1977;39:617–23.
30. Corman JM, McClure D, Pritchett R, Kozlowski P, Hampson NB. Treatment of radiation induced hemorrhagic cystitis with hyperbaric oxygen. *J Urol* 2003;169:2200–2.
31. Del Pizzo JJ, Chew BH, Jacobs SC, Sklar GN. Treatment of radiation induced hemorrhagic cystitis with hyperbaric oxygen: long-term followup. *J Urol* 1998;160:731–3.
32. Hailey D. Hyperbaric oxygen therapy—recent findings on evidence for its effectiveness. Edmonton, AB: Alberta Heritage Foundation for Medical Research; 2003. [Available online at: http://www.ihe.ca/documents/hyperbaric_oxygen_therapy.pdf; cited August 30, 2011]
33. Cancer Care Ontario (CCO), Program in Evidence-Based Care, Hyperbaric Oxygen Therapy Working Group. *Hyperbaric Oxygen Therapy for the Treatment and Prevention of Radionecrosis and Other Radiation-Induced Injuries in Cancer Patients.* Toronto, ON: CCO; 2005.
34. BC Cancer Agency (BCCA). Home > Health Professionals Info > Cancer Management Guidelines > Head and Neck > 6.

Management > Radiation Reactions [Web page]. Vancouver, BC: BCCA; 2003. [Available online at: http://www.bccancer.bc.ca/HPI/CancerManagementGuidelines/HeadnNeck/Management/RadiationReactions.htm; cited April 13, 2009]
35. Scottish Intercollegiate Guidelines Network (SIGN). *Diagnosis and Management of Head and Neck Cancer: A National Clinical Guideline.* Edinburgh, U.K.: SIGN; 2006. [Available online at: http://www.sign.ac.uk/pdf/sign90.pdf; cited April 21, 2009]
36. College of Physicians and Surgeons of Alberta. *Medical Hyperbaric Oxygen Therapy—Private Facility: Standards and Guidelines.* Edmonton, AB; College of Physicians and Surgeons of Alberta; 2008. [Available online at: http://www.cpsa.ab.ca/Libraries/Pro_QofC_HyperbaricOxygen/Standards_Hyperbaric_Oxygen.sflb.ashx; cited September 12, 2010]
37. Kindwall EP, Whelan HT. *Hyperbaric Medicine Practice.* 2nd ed. Rev. Flagstaff, AZ: Best Publishing Company; 2002.
38. Health Canada. *Hyperbaric Oxygen Therapy.* It's Your Health series. Ottawa, ON: Health Canada; 2005. [Available online at: http://www.hc-sc.gc.ca/hl-vs/alt_formats/pacrb-dgapcr/pdf/iyh-vsv/med/hyper-eng.pdf; cited July 14, 2009]
39. Feldmeier JJ, Hampson NB. A systematic review of the literature reporting the application of hyperbaric oxygen prevention and treatment of delayed radiation injuries: an evidence based approach. *Undersea Hyperb Med* 2002;29:4–30.
40. European Society for Therapeutic Radiology and Oncology and European Committee for Hyperbaric Medicine. *Hyperbaric Oxygen Therapy in the Treatment of Radio-Induced Lesions in Normal Tissues.* Consensus Conference; Lisbon, Portugal; October 19–20, 2001. [Available online at: http://www.estro.org/estroactivities/Documents/LisboaconsensusHBOpdf.pdf; cited December 1, 2010]
41. Lin HY, Ku CH, Liu DW, Chao HL, Lin CS, Jen YM. Hyperbaric oxygen therapy for late radiation-associated tissue necroses: is it safe in patients with locoregionally recurrent and then successfully salvaged head-and-neck cancers. *Int J Radiat Oncol Biol Phys* 2009;74:1077–82.
42. Hermann RM, Carl UM. Hyperbaric oxygen therapy for late radiation-associated tissue necroses: is it safe in patients with locoregionally recurrent and then successfully salvaged head-and-neck cancers? *Int J Radiat Oncol Biol Phys* 2010;76:1600. [Comment on *Int J Radiat Oncol Biol Phys* 2009;74:1077–82; with author reply]
43. Feldmeier J, Carl U, Hartmann K, Sminia P. Hyperbaric oxygen: does it promote growth or recurrence of malignancy? *Undersea Hyperb Med* 2003;30:1–18.
44. Evans AW, Gill R, Valiulis AO, Lou W, Sosiak TS. Hyperbaric oxygen therapy and diabetic foot ulcers: knowledge and attitudes of Canadian primary care physicians. *Can Fam Physician* 2010;56:444–52.

Correspondence to: Peter Craighead, 1331–29 Street NW, Calgary, Alberta T2N 4N2.
E-mail: peter.craighead@albertahealthservices.ca

* Department of Oncology, University of Calgary, Calgary, AB.
† Alberta Health Services Cancer Care, Calgary, AB.
‡ Alberta Health Services Cancer Care, Guideline Utilization Resource Unit, Calgary, AB.
§ Hyperbaric Medicine Unit, Toronto General Hospital, and Department of Anesthesia, University of Toronto, Toronto, ON.
‖ Department of Oncology, and Alberta Health Services Cancer Care, Edmonton, AB.
Capacity Enhancement Program, Canadian Partnership Against Cancer, Hamilton, ON.
** Department of Oncology, McMaster University, Hamilton, ON.