



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 (HBO₂) 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 HBO₂ were reported in three additional sources. There is modest direct evidence and emerging indirect evidence that the use of HBO₂ 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,

- HBO₂ 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 HBO₂ therapy in gynecologic oncology is in the management of otherwise refractory chronic radiation injury;
- HBO₂ may provide symptomatic benefit in certain clinical settings (for example, cystitis, soft-tissue necrosis, and osteonecrosis); and
- HBO₂ may reduce the complications of gynecologic surgery in patients undergoing surgical removal of necrosis.

KEY WORDS

Hyperbaric oxygen therapy, HBO₂, 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 radiotherapy⁵. 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 hospitalizations⁵.

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 used⁵.

Hyperbaric oxygen therapy (HBO₂) has been used as a treatment modality to promote repair of radiation-induced vascular changes. Transcutaneous oxygen measurements 4 years after HBO₂ have revealed near-normal levels, implying that HBO₂-induced angiogenesis is essentially permanent. Thus, HBO₂ 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 tissue⁶. Preoperative HBO₂ can contribute to a higher rate of surgical success.

The mechanism by which HBO₂ 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 tissue⁷. Other biochemical pathways involved include mobilization of stem cells from bone marrow⁸ and vasculogenesis⁹, resulting in elevated levels of vascular endothelial growth factor¹⁰. The subacute and chronic phases of radiation wounds are particularly suited to this form of therapy. The HBO₂ 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 HBO₂ also stimulates fibroblast proliferation. A range of studies has characterized mechanism of action, treatment approaches, economic evaluation, and other aspects of HBO₂^{5,11–15}.

2. OBJECTIVES

This evidence-based clinical practice guideline aims to provide recommendations for the use of HBO₂ 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 HBO₂ 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 HBO₂ therapy is being considered.

2.3 Target Users

This clinical practice guideline is intended to inform health practitioners on the use of HBO₂ 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 HBO₂ 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 Service¹⁶;
- Cummings and Rivara's methodology for reviewing manuscripts¹⁷; and
- the AGREE collaboration¹⁸.

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 HBO₂ 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 HBO₂ 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 HBO₂ 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 1 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 HBO₂ 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 HBO₂ 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 HBO₂ is initiated by 6 months from the start of symptoms rather than being delayed beyond that point²⁶.

Randomized controlled trials have demonstrated that HBO₂ significantly improves pelvic radiation symptoms. Sidik *et al.*¹⁹ showed that, compared with control patients, women undergoing HBO₂ [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 1 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 <i>et al.</i> , 1977 ²⁹	Prospective randomized controlled trial	17	Clinical hematuria	3.0 (40)	14 (mean)	24	88.2% (complete resolution or marked improvement)
Williams <i>et al.</i> , 1992 ²¹	Prospective case study	14	Clinical vaginal necrosis and fistula	2.0 (90–120)	15	36	92.9% (complete resolution)
Feldmeier <i>et al.</i> , 1996 ²²	Retrospective	41	Clinical	2.4 (90)	24 (mean)	NR	81.0% (healing of the injuries or closure of fistulas)
Del Pizzo <i>et al.</i> , 1998 ³¹	Retrospective	11	Clinical hematuria	2.0 (90)	40	60 (median)	27.0% (complete resolution)
Corman <i>et al.</i> , 2003 ³⁰	Prospective case study	57	Clinical hematuria	2.4 (90)	33 (mean)	55 (median)	86.0% (complete resolution or marked improvement)
Bui <i>et al.</i> , 2004 ²⁸	Retrospective	7	RTOG criteria (principal symptom)	2.4 (100)	40 (median)	0 (post HBOT)	100.0% (median: 72 weeks' duration)
Chong <i>et al.</i> , 2005 ²⁶	Retrospective	60	Clinical hematuria	2.36 (90)	36 (median)	12	80.0% (complete or partial resolution)
Fink <i>et al.</i> , 2006 ²³	Retrospective	14	Physician assessment	2.4 (90)	32.8 (mean)	38 (median)	71% (>50% improvement or complete healing)
Jones <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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 site⁴⁰. 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 Study²⁰ 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 HBO₂. 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 HBO₂ are pending.

Evidence from earlier nonrandomized studies suggests that HBO₂ 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 modalities²⁸. Fletcher *et al.*²⁹ demonstrated complete resolution of hemorrhagic cystitis in 64% of patients treated with HBO₂ once daily for a mean of 14 sessions or until resolution. A response rate of 86% has also been reported³⁰. Furthermore, the benefit of HBO₂ appears to be long-lasting (for example, after more than 5 years) in some patients³¹.

Moderate success for HBO₂ as a treatment for soft-tissue necrosis has also been reported. Williams *et al.*²¹ prospectively examined the therapeutic effects of HBO₂ 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 HBO₂. All patients with vaginal radiation necrosis or rectovaginal fistula experienced complete resolution of necrosis with HBO₂; 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, HBO₂ is associated with improved outcomes. Application of HBO₂ 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 HBO₂ in the treatment or prophylaxis of delayed radiation injury found that all but seven publications reported a positive result for HBO₂. The authors concluded that HBO₂ should be recommended for delayed radiation injuries in soft tissue and bone at most sites³⁹.

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 HBO₂ 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 HBO₂³³.

By contrast, the BC Cancer Agency³⁴ lists referral for HBO₂ therapy as an option for selected patients with LRTI, and the Scottish Intercollegiate Guidelines Network³⁵, writing on the diagnosis and management of head-and-neck cancer, recommended that HBO₂ facilities should be available to selected patients with head-and-neck cancer. Likewise, at the European Consensus 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 HBO₂⁴⁰.

There are risks and benefits associated with HBO₂. 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 HBO₂ include untreated pneumothorax or untreated cancer (that is, concurrent use of bleomycin, cisplatin, disulfiram, doxorubicin, or mafenide acetate)³⁷. However, the use of HBO₂ 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 medicine³⁸.

Can HBO₂ increase the risk of cancer recurrence?

A retrospective analysis of 22 patients with recurrent head-and-neck cancer concluded that HBO₂ increases the risk of cancer re-recurrence: 5-year disease-free survival rates were lower in patients receiving HBO₂ (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 HBO₂ 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 HBO₂ is initiated.

5. DISCUSSION

There is little strong evidence to definitively recommend HBO₂ 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 HBO₂ for LRTI of the pelvis, and several other studies suggest that HBO₂ 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 HBO₂ as a therapeutic option.

However, the mechanism of action of LRTI and the evidence supporting clinical benefit with HBO₂ 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 HBO₂ treatment for LRTI together contribute to a broader field of evidence. This field of evidence suggests that HBO₂ for LRTI related to chronic vascular injury can be anticipated to be of benefit in many clinical scenarios.

If HBO₂ 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 HBO₂ 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 condition¹². In general, after 20–25 treatments with HBO₂, 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 HBO₂ is an appropriate treatment option.

Some organizational barriers may be associated with the use of HBO₂, 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 HBO₂ as being broadly effective for LRTI of the pelvis in women treated with radiation for gynecologic malignancies. Treatment with HBO₂ 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 HBO₂ 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 HBO₂ 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.

- HBO₂ 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 HBO₂ therapy is the management of treatment-refractory chronic radiation injury.
- There is evidence for symptomatic benefit with the use of HBO₂ 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, HBO₂ 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 HBO₂ to reduce the complications of gynecologic oncology surgery, purported to occur through the stimulation of small-vessel angiogenesis.

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8. CONFLICT OF INTEREST DISCLOSURES

There authors have no conflicts of interest to declare.

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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.