

# **HYPERBARIC OXYGEN THERAPY FOR LATE RADIATION TISSUE INJURY IN CERVICAL AND OTHER GYNECOLOGICAL MALIGNANCIES**

Date Developed: September, 2009

The recommendations contained in this guideline are a consensus of the Alberta Provincial Gynecologic Oncology Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

## BACKGROUND

Gynecological cancers treated with a combination of external beam radiation and brachytherapy, especially cervical and vaginal cancers, can result in the apex of the vagina receiving a high dose of radiation. The tolerance of the lateral apical vagina can be as high as 140 Gy. The tolerance is less for the rest of the vagina and can result in complications. These radiation-related complications, which develop months or years after treatment with radiation, are known as late radiation tissue injury (LRTI) and are estimated to affect 5 to 15% of all long-term survivors who have received radiation.<sup>1,2,3,4</sup> The estimated prevalence of LRTI is 2 to 4%<sup>5</sup> for those undergoing pelvic radiotherapy.

Radiation causes progressive endarteritis of the small blood vessels resulting in cellular hypoxia and damage to the fibroblasts. This inhibits the ability of the irradiated tissue to repair itself and can result in non healing ulcers. A radionecrotic wound gradually progresses to involve surrounding tissue and frequently results in vesicovaginal, colovaginal, and rectovaginal fistulae,<sup>5</sup> as well as a range of symptoms from vaginitis, deep dyspareunia, frank hematuria, and radiation proctitis to frank ulceration and necrosis. This is a particularly debilitating condition that is very painful, and associated with a malodorous and serosanguinous discharge. Most patients become socially isolated and are at risk for depression, nutritional deficiency, and require repeated hospitalizations.<sup>5</sup>

Medical treatment typically involves topical wound care, and unfortunately treatment failure is common. Surgical repairs of fistulae related to radiation necrosis are not only technically difficult, but even the use of skin and myocutaneous flaps have met with only limited success due to a compromised blood supply.<sup>5</sup>

However, hyperbaric oxygen therapy (HBOT) is a treatment modality which can repair the radiation induced vascular changes. Transcutaneous oxygen measurements four years after HBOT have revealed near-normal levels, implying that the angiogenesis is essentially permanent. In fact, HBOT is the first available treatment for delayed radiation injuries that is potentially disease modifying, and is associated with healing in ulcerated, necrotic tissues. In April 2005, the Undersea and Hyperbaric Medical Society approved HBOT as effective treatment for delayed radiation injury. That same year, the Food and Drug Administration (U.S.) also approved hyperbaric oxygen therapy for the treatment of delayed radiation injury (soft tissue and bony necrosis).<sup>6</sup>

The mechanism by which HBOT is thought to treat radiation tissue injury is via the induction of neovascularization, thereby reversing tissue hypoxia. The stimulus for angiogenesis appears to be mediated through macrophages responding to the oxygen gradient between the damaged hypoxic cells and the normal tissue surrounding them.<sup>7</sup> Other biochemical pathways involved include stem cell mobilization from bone marrow<sup>8</sup> and vasculogenesis,<sup>9</sup> resulting in elevated vascular endothelial growth factor levels.<sup>10</sup> The subacute and chronic phases of radiation wounds are particularly suited to this form of therapy. HBOT acts to stimulate collagen formation at the wound edges through elevation of local tissue oxygen tension. New microvasculature which is dependent on a collagen matrix is greatly enhanced in this setting and allows re-epithelization to occur. HBOT also stimulates fibroblast proliferation.

Typically, the treatment protocol for HBOT in patients with radiation-induced pelvic soft tissue injury and in whom the lesion is likely to remain chronic or deteriorate further, often consists of once-daily treatments at 2.5 atmospheres absolute pressure (ATA) on a five-days-per-week basis for up to 40 treatments, depending upon the patient's condition. Follow-up should be conducted at four weeks.<sup>5</sup> For the treatment and prevention of osteoradionecrosis, a protocol by Marx, et al. consists of 20 HBOT sessions prior to surgery in previously irradiated area and 10 sessions afterwards. Each session involves breathing pure

oxygen at 2.4 ATA for 90 minutes,<sup>11</sup> but can vary between 2.0 and 2.5 ATA and between 60 and 120 minutes, as well as the frequency per day.<sup>12</sup>

To date, no economical studies have been conducted that formally evaluate the cost effectiveness of HBOT for the treatment of gynecological late radiation tissue injury. However, a study out of the University of Alberta (Chuck, et al. 2008)<sup>13</sup> estimated the cost-effectiveness and budget impact of HBOT in the application of diabetic foot ulcers. A decision model comparing adjunctive HBOT with standard care alone, in a 65-year-old cohort, using a time horizon of 12 years (Ministry of Health perspective) revealed that the 12-year cost for patients receiving HBOT was CND\$40,695 compared with CND\$49,786 for standard care alone. Outcomes were 3.64 quality-adjusted life-years (QALYs) for those receiving HBOT and 3.01 QALYs for controls. Estimated cost to treat all prevalent DFU cases in Canada was CND\$14.4-19.7 million annually over 4 years. The authors concluded that adjunctive HBOT is cost-effective compared with standard care, for these patients. Another Canadian study analyzed the cost-effectiveness of HBOT for the management of osteoradionecrosis using a retrospective study design and showed that HBOT is cost saving compared to usual care in the management of osteoradionecrosis.<sup>14</sup> Finally, an Australian report estimated an incremental cost per case of osteoradionecrosis avoided to be Au\$28,480 for HBOT compared to penicillin.<sup>15</sup>

## GUIDELINE GOALS AND OBJECTIVES

To provide recommendations for the use of hyperbaric oxygen therapy in late radiation tissue injury with respect to soft tissue necrosis, cystitis, proctitis, bone necrosis, and other complications in women treated with radiation for gynecological cancer.

## GUIDELINE QUESTIONS

Is hyperbaric oxygen therapy (HBOT) effective in treating late radiation tissue injury with respect to soft tissue necrosis, cystitis, proctitis, bone necrosis, and other complications in women undergoing radiation for cervical cancer and other gynaecological malignancies? If so, when should HBOT be applied and what dosing regimen should be used? Should HBOT be used in combination with any other treatments?

While the authors recognize the importance of preventing late radiation tissue injury, this guideline does not address prevention, but rather the treatment, only, of late radiation tissue injury.

## DEVELOPMENT PANEL

This **guideline** was produced by two radiation oncologists from the Tom Baker Cancer Centre, with support from the Guideline Utilization Resource Unit and endorsed by the Alberta Provincial Gynecologic Oncology Tumour Team. Members of the Alberta Provincial Gynecologic Oncology Tumour Team include gynecologic oncologists, medical oncologists, radiation oncologists, nurses, pathologists, and pharmacists. **Evidence** was selected and reviewed by a working group comprised of members from the Alberta Provincial Gynecologic Oncology Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A review process for this guideline has been developed, based on the following three sources: (1) the National Institute for Health and Clinical Excellence (NICE) overview of clinical guideline development for stakeholders, the public, and the NHS,<sup>16</sup> (2) Cummings and Rivara's methodology on reviewing manuscripts for *Archives of Pediatrics & Adolescent Medicine* (2002),<sup>17</sup> and (3) the AGREE collaboration.<sup>18</sup>

## SEARCH STRATEGY

Entries to Medline, EMBASE, and Cochrane (1965 to June 25, 2009) and clinical practice guideline databases were searched for evidence relevant to this topic. 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 with a limit of English language. The search identified a total of 45 studies, four of which were clinical trials (Appendix).

## TARGET POPULATION

Women presenting with late radiation tissue injury, including soft tissue necrosis, cystitis, proctitis, bone necrosis, and other complications, due to radiation therapy for cervical cancer and other gynaecological malignancies.

## RECOMMENDATIONS

1. HBOT is effective for late radiation tissue injury, particularly head, neck, anus and rectum. Based on its mechanism of action, there is adequate basis to propose that HBOT is likely broadly effective for late radiation tissue injury (i.e. an emerging field of evidence contributed to by specific and diverse areas of clinical study such as outcomes of patients with late radiation injury involving head, neck, anus, or rectum).
2. The main indication for the use of HBOT therapy, among women with late radiation tissue injury after undergoing radiation for gynaecological malignancies is to treat refractory chronic radiation injury.
3. There is evidence<sup>22-24</sup> (level 4) for symptomatic benefit for certain clinical settings following RT for cervical cancer: cystitis, soft tissue necrosis, or osteonecrosis. The small number of case series and patient numbers make specific recommendations difficult; however, HBOT should be considered for women who fail conservative care.
4. In patients being considered for surgical removal of necrosis, there is evidence (level 4) supporting the use of HBOT to reduce complications of gynaecological oncologic surgery, purported to be through stimulating small vessel angiogenesis.

## DISCUSSION

There has been a systematic review in the Cochrane Gynaecological Cancer Group Cochrane Database of Systematic Reviews<sup>19</sup> that summarized randomized controlled trials (RCTs) comparing the effect of HBOT versus no HBOT on late radiation tissue injury prevention or healing. The review concluded that for patients with late radiation tissue injury affecting tissues of the head, neck, anus and rectum, HBOT is associated with improved outcome. HBOT also appears to reduce the chance of osteoradionecrosis following tooth extraction in an irradiated field. There was no such evidence either for or against any important clinical effect on neurological tissues. The application of HBOT to selected patients and tissues may be justified. Further research is required to establish the optimum patient selection and timing of any therapy. An economic evaluation should also be undertaken. There is no specific information from this review regarding the efficacy or effectiveness of HBOT for other tissues. Therefore, there is no level 1 evidence to recommend HBOT for women with late radiation tissue injury after undergoing radiation for cervical and vaginal cancer; this area has not been studied. However, since the mechanism of action of

late radiation tissue injury is thought to be similar following radiation treatment of cervical and vaginal cancer and radiation treatment elsewhere in the body, there is a cogent argument that positive outcome studies of HBOT treatment in specific clinical scenarios contribute to a broader field of evidence characterizing a mechanistic approach to the evidence supporting appropriate use of HBOT. There is currently no high level evidence or agreement as to the most appropriate dosing regimen; however lower level evidence on dosing is discussed below.

There is an ongoing study called HORTIS ([www.baromedicalresearch.org/pdf/HORTIS\\_Overview.pdf](http://www.baromedicalresearch.org/pdf/HORTIS_Overview.pdf)) that has been developed as an international, multi-center study, employing a randomized, double blind, placebo-controlled clinical trial design, with a patient cross-over option. The principle objective of this research is to more precisely determine the degree of benefit of hyperbaric oxygen therapy in the treatment of late radiation tissue injury at several specific body sites. The study has eight components. Seven involve evaluation of established radionecrosis at the mandible, larynx, skin, bladder, rectum, colon, and female pelvis. The eighth will investigate the potential of hyperbaric oxygen therapy to prevent late radiation tissue injury. This study will also generate more precise benchmarking data as to the complications associated with hyperbaric exposure, including incidence and degree of morbidity. Recent results for HORTIS IV<sup>20</sup> (radiation proctitis) have been published by Clarke, et al. (2008) and indicate highly favourable results two years after treatment with a course of HBOT. Patients with refractory radiation proctitis (121 of 150 were treated for uterine cervical tumours) were treated with either hyperbaric oxygen at 2.0 atmospheres absolute or air at 1.1 atmospheres absolute. Those treated with HBOT experienced a nearly two-fold improvement in symptoms (e.g. pain, frequency, bleeding, ulceration, etc.) using the SOMA-LENT score (mean score 5.00 vs. 2.61;  $p = 0.0019$ ). The response rate was also significantly higher for the HBOT (88.9% vs. 62.5%;  $p = 0.0009$ ). The results for the GYN arm of the trial are pending.

Sidik, et al. (2007) conducted a randomized, parallel, prospective study to evaluate the influence of HBOT on side effects and quality of life among 32 patients and 33 controls who underwent pelvic radiation. Using the LENT SOMA scale ratio and Karnofsky score, compared to controls, patients undergoing HBOT experienced significantly fewer side effects ( $p=0.008$ ) and significantly better quality of life ( $p<0.001$  after intervention;  $p=0.007$  after 6 months).<sup>21</sup>

Despite limited level 1 evidence, several studies have shown positive therapeutic effects of HBOT for late radiation tissue injury of the pelvis. Willams, et al (1992)<sup>22</sup> examined the therapeutic effects of HBOT on radiation-induced soft tissue necrosis in patients who previously received treatment for a gynaecologic malignancy. Fourteen patients whose necrotic wounds failed to heal after three months of conservative therapy underwent 15 courses of HBOT. All patients with vaginal radiation necrosis or rectovaginal fistula had complete resolution of necrosis with HBOT; only one treatment failure occurred. In 1996, Feldmeier, et al<sup>23</sup> described the use of HBOT in 44 patients (since 1979; 19 of whom had been treated for cervical cancer) with delayed radiation induced injuries of the pelvis and abdomen. Of the 41 assessable patients, 26 (63%) had healing of the injuries and six of eight patients with fistulas had closure with only three requiring surgical intervention, for an overall response rate of 81% in patients receiving at least 20 treatments. More recently, Fink, et al (2006)<sup>24</sup> conducted a retrospective analysis of 14 patients with gynaecological cancers with delayed radiation injuries, who were treated with HBOT from 1997-2003. At least 20 sessions of 100% oxygen inhalation at 2.4 Atmospheric Absolutes (ATA) for 90 min in a hyperbaric chamber were carried out. Over 70% (71.4%; 10) of patients healed or showed improvement of more than 50% with acceptable adverse events. The results suggest that HBOT should be considered for patients with delayed radiation injuries from pelvic radiation, not responding to other treatments.

Several studies strongly suggest that HBOT may be beneficial to improve quality of life in patients with radiation toxicity following treatment for pelvic malignancy. Safra, et al (2008)<sup>25</sup> also reported positive impacts of HBOT on persistent radiation-induced side effects: 13 women (median age 60.3 years) with radiation combined proctitis/cystitis (n=6), longstanding vaginal ulcers and fistulas (n=5) and longstanding skin injuries (n=2) underwent HBOT (100% oxygen, at 2 absolute atmospheres, for 90 min, once a day) in a multiplace chamber for a median of 27 sessions (range 16-40). Radiation-induced toxicity grading, using the National Cancer Institute's Common Toxicity Criteria (CTC) grading system, decreased from a mean score of  $3.3 \pm 0.75$  before HBOT to  $0.3 \pm 0.63$  after HBOT ( $P=0.001$ ). Rectal bleeding ceased in five of six patients; proctitis and dysuria resolved in six of seven cystitis patients; macroscopic haematuria stopped in seven of seven patients; scar complications resolved in two of two patients; and none reported HBOT-associated side-effects. Jones, et al. (2006) also reported that in patients with radiation proctitis refractory to standard therapy, HBOT resulted in complete resolution of rectal bleeding in four of nine symptomatic patients and improvement in three others; complete remittance of rectal pain in three of five symptomatic pts; and complete remittance of diarrhea in one of five patients and improvement in three others; only two patients did not respond to HBOT.<sup>26</sup> Finally, a recent study by Rud, et al. (2009) investigated the possible pain reducing effect of hyperbaric oxygen treatment (HBOT) in a study of 16 patients with late radiation tissue injury after radiation for gynaecological malignancy. The patients prospectively underwent HBOT for 21 consecutive days and were followed for a 6-month period after treatment using the Brief Pain Inventory, Montgomery and Aasberg Depression Rating Scale, as well as registration of global patient scores, analgesic consumption and magnetic resonance imaging (MRI) findings. Although HBOT was shown to have insignificant effect on pain, pain characteristics, daily function, the use of analgesics and MRI-related tissue injury, 50% of the patients still reported some or good effect of the treatment.<sup>27</sup>

In 2005, Chong, et al. demonstrated in a retrospective study that for patients with (pelvic) radiation-induced hemorrhagic cystitis HBO2 therapy at 2.36 atmospheres absolute pressure, with 90 minutes of 100% oxygen breathing per treatment (average of 33 sessions), resulted in resolution (total and/or partial) of hematuria in 80% of patients (48 of 60); however this effect was enhanced to 96% of patients when treatment was initiated within six months of onset ( $P=0.003$ ). Further, clot retention improved in 11 of 11 patients when initiated within six months of onset ( $P = 0.007$ ). The response rates were 81%, 83%, and 78% for patients who had undergone primary, adjuvant, or salvage external beam radiotherapy, respectively, to pelvis.<sup>28</sup> In another retrospective study, Bui, et al. (2004) patients with radiation-induced late side effects to the pelvis, the majority of whom had failed previous interventions, reported that symptom severity was improved after treatment with HBOT; 50% of patients reported improvement of soft tissue necrosis/mucous membrane side effects; relapse incidence among these patients was 22%.<sup>29</sup>

Following interest by the College of Physicians & Surgeons of Alberta, the Alberta Heritage Foundation (Hailey, 2003) prepared a paper providing evidence of the effectiveness of hyperbaric oxygen therapy (HBOT) for a range of clinical applications. Regarding soft tissue radionecrosis, there was insufficient evidence to support this application, given that no controlled studies have been identified. However, case series do suggest evidence of benefit.<sup>30</sup> Furthermore, a summary of an article from the US Agency for Healthcare Research and Quality (AHRQ) states that results suggest that HBOT may be beneficial as an adjunctive therapy for this condition. With respect to osteoradionecrosis, Hailey (2003) states that "health technology assessments seem generally supportive of this application, while noting the limited evidence of benefit that is available and the need for further studies."

Regarding the use of HBOT in other jurisdictions, Cancer Care Ontario's Program in Evidence-Based Care concluded 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. They also indicate the state of the evidence does not justify withdrawing this intervention where it is currently used as standard practice. The report also declared that better-controlled studies are needed to confirm the clinical utility of this intervention.<sup>31</sup> The British Columbia Cancer Agency (BCCA) lists referral for hyperbaric oxygen therapy as an option for some patients suffering from late radiation damage, due to its apparent ability to increase the blood supply to irradiated tissue and promote healing of necrotic areas.<sup>32</sup> In 2006, the Scottish Intercollegiate Guideline Network on diagnosis and management of head and neck cancer, recommended, based on high quality case control and cohort studies (level 2 evidence), that hyperbaric oxygen facilities should be available for selected patients with head and neck cancer.<sup>33</sup>

Emerging interest in validated tools will support collaborative approaches to document outcomes across jurisdictions. Acumen in HBOT will benefit from more rigorous outcome reporting from its use in late radiation injury populations.

Regarding potential risks and side effects associated with the use of HBOT, it is advisable to have all potential candidates evaluated by a CPSA guideline compliant<sup>34</sup> hyperbaric physician to determine “fitness to dive” (i.e. assess treatment associated risks). Of particular concern are those patients who present with any of the following: middle or inner ear disorders, congenital heart disease, claustrophobia, congenital spherocytosis, diabetes, seizures, lung problems, asthma, upper respiratory infections, chronic obstructive pulmonary disease, eustachian tube dysfunction, high fever, cataracts, pregnancy, or use of a pacemaker or epidural pain pump.<sup>35,36</sup> In addition, the following are absolute contraindications to the use of HBOT: untreated pneumothorax and concurrent use of bleomycin, cisplatin, disulfiram, doxorubicin, and sulfamylon.<sup>36</sup>

Health Canada must provide a license before any hyperbaric chamber is imported or sold in Canada. Under the Medical Devices Regulations, all medical devices imported or sold in Canada must be safe, effective, and of quality manufacture. In order to ensure safety, the device is reviewed prior to licensing and monitored for any adverse events, post-market. Health Canada has approved the use of hyperbaric chambers for the treatment of thirteen specific conditions, including delayed radiation injury. No device licenses have been issued for the use of hyperbaric chambers to treat other conditions.<sup>36</sup>

The use of hyperbaric oxygen therapy is considered safe when the chamber is properly installed according to municipal and provincial regulations and complies with CAN/CSA Z 275.1-93.<sup>34</sup> Operators and attendants should be properly trained in the technical function of the hyperbaric chamber but should also be able to manage any serious complications that could be encountered by patients, as uncommon as these may be, and be supervised by a hyperbaric physician.<sup>36</sup> Through application of these principles, serious risks are rare and more common side effects are mild and manageable.

Barriers to the use of HBOT may include access to HBOT equipment and funding for HBOT, including direct costs (per course of treatment) and indirect costs, such as accommodations for patients, staffing requirements, time requirements, and treatment for any side effects.

The clinical condition (i.e. pain from cystitis, proctitis, bone necrosis, soft tissue necrosis, etc.) for which HBOT is being considered as a therapeutic option should be quantified and clinical endpoints determined, on a case by case basis, prior to the initiation of HBOT. In general, after 20-25 treatments with HBOT, a clinical evaluation should be performed to reassess the condition and determine whether significant improvements were achieved. If no significant improvements were achieved, the case should be re-evaluated to determine whether HBOT is an appropriate treatment option.

## GLOSSARY OF ABBREVIATIONS

Acronym	Description
CTC	common toxicity criteria
HBOT	hyperbaric oxygen therapy
LRTI	late radiation tissue injury

## IMPLEMENTATION STRATEGY

- Present the guideline in the tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.

## EVALUATION STRATEGY

A formal review will be conducted in 2010, however if new evidence is brought forward before that time, the guideline will be changed accordingly.

## DECLARATION OF CONFLICT OF INTEREST

None of the authors of this guideline had any conflict of interest related to evidence or recommendations in this guideline.

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**APPENDIX: EVIDENCE TABLE**

Reference	Patients / Stage	Methods	Pts evaluated	Outcomes
<b>Clinical Trials</b>				
<i>Clarke, et al. 2008</i> <sup>20</sup>	Patients with refractory radiation proctitis (121/150 treated for uterine cervical tumours)	Randomized, controlled, double-blind crossover trial with long-term follow-up 1. hyperbaric oxygen at 2.0 atmospheres absolute (Group 1) 2. air at 1.1 atmospheres absolute (Group 2)	64 56	<b>Mean SOMA-LENT</b> Group 1 – lower mean (p = 0.0150); improvement was nearly double (5.00 vs. 2.61, p = 0.0019) <b>Response rate:</b> Group 1 – greater # of responders per clinical assessment (88.9% vs. 62.5%, p = 0.0009) <b>Quality of Life:</b> Group 1 – better result in the quality of life bowel bother subscale, but no diff after crossover
<i>Sidik, et al. 2007</i> <sup>21</sup>	Patients who underwent pelvic radiation	Open randomized, parallel, prospective study 1. HBOT 2. Control	32 33	<b>Lent SOMA ratio:</b> HBOT – -19.6 ± -69.4%; Control – -33.6 ± -57.6% (p=0.008) <b>Quality of Life:</b> After treatment: HBOT – 19.7 ± 9.6%; Control – 4.5 ± 10.7% (p<0.001) Six months after: HBOT – 15.2 ± 14.7%; Control – 2.5 ± 16.1% (p<0.007)

<i>Mathews, et al. 1999</i>	Patients with advanced cancers of the uterine cervix-- Stages IIB, IIA, IIIB, and IVA (70 year age limit)	Randomized clinical trial in patients receiving conventional fractionation 1. hyperbaric oxygen in a pressurized Vickers chamber at 3 atmosphere absolute 2. air in a pressurized Vickers chamber at 3 atmosphere absolute	233	<b>Absolute NED</b> (no evidence disease) survival: no diff for groups as a whole or by stage <b>Failures in the irradiated area:</b> no diff in numbers <b>Distant Mets:</b> no increase <b>Major complications:</b> no impact
<i>Fletcher, et al. 1977</i>	Patients (mean age 62 years) with hemorrhagic cystitis who did not benefit from standard treatment modalities	Cohort study: hyperbaric oxygen was administered on a once daily schedule (mean number of treatments 14) until hematuria resolved	17	<b>Hematuria:</b> resolved completely in 11/17 pts (64%); 2 had only residual microscopic hematuria; 2 improved but died of complications relating to cancer; 2 had recurrence of gross hematuria
<b>Lower Level Evidence</b>				
<i>Rud, et al. 2009<sup>27</sup></i>	Patients with LRTI after radiation for gynaecological malignancy	Patients treated with HBOT for 21 consecutive days and were followed for a 6-month period after treatment	16	<b>Pain</b> (pain characteristics, daily function, use of analgesics, and MRI-related tissue injury): insignificant effect <b>Patient perception:</b> 50% of patients still reported some or good effect of the treatment

<p><i>Safra, et al. 2008</i><sup>25</sup></p>	<p>Women with radiation combined proctitis/cystitis (n=6), longstanding vaginal ulcers and fistulas (n=5) and longstanding skin injuries (n=2)</p>	<p>HBOT delivered in a multiplace chamber for a median of 27 sessions (range 16-40); the treatment schedule was HBOT 100% oxygen, at 2 absolute atmospheres, for 90 min, once a day</p>	<p>13</p>	<p><b>Mean Common Toxicity Criteria (CTC):</b> 3.3 ± 0.75 before HBOT and 0.3 ± 0.63 after HBOT (P=0.001)  <b>Rectal bleeding</b> ceased in 5/6 pts with proctitis  <b>Dysuria:</b> resolved in 6/7 cystitis pts  <b>Macroscopic haematuria:</b> stopped in 7/7 pts  <b>Scar complications</b> resolved in 2/2 pts</p>
<p><i>Fink, et al. 2006</i><sup>24</sup></p>	<p>Patients with gynecological cancers suffering from delayed radiation injuries</p>	<p>At least 20 sessions of 100% oxygen inhalation at 2.4 Atmospheric Absolutes (ATA) for 90 min in a hyperbaric chamber were carried out</p>	<p>14</p>	<p><b>Response:</b> 10 pts have healed or showed ≥50% improvement (success rate of 71%)  <b>Mean follow-up:</b> 31.6 months (range 6-70 months)  <b>Adverse events:</b> acceptable</p>
<p><i>Jones, et al. 2006</i><sup>26</sup></p>	<p>Patients with radiation proctitis refractory to standard therapy (3 males and 7 females; mean age of 65)</p>	<p>Patients were treated with HBOT</p>	<p>10 (treatment completed by 9)</p>	<p><b>Median follow-up:</b> 25 months (6-43)  <b>Rectal bleeding:</b> completely stopped in 4/9 symptomatic pts; improved in 3 others  <b>Rectal pain:</b> completely remitted in 3/5 symptomatic pts  <b>Diarrhea:</b> remitted completely in 1/5 pts; improved in 3 others  <b>No response:</b> 2/10</p>

<p><i>Chong, et al. 2005</i><sup>28</sup></p>	<p>Patients with (pelvic) radiation-induced hemorrhagic cystitis (mean age 70 years)</p>	<p>Retrospective study: HBO2 therapy at 2.36 atm absolute pressure, with 90 minutes of 100% oxygen breathing per treatment. Outcome assessed at 12+ months of follow-up</p>	<p>60 55 ♂ 5 ♀</p>	<p><b>Average HBO2 sessions:</b> 33 (9-63) <b>Hematuria (total/partial) resolution:</b> 48/60 (80%); 96% (27/28) when treated ≤ 6 months of onset <b>Clot retention:</b> improvement in 11/11 if treated ≤ 6 months of onset <b>Response rates:</b> 81%, 83%, &amp; 78% (respective) for pts who had undergone primary, adjuvant, or salvage external beam RT to pelvis</p>
<p><i>Bui, et al. 2004</i><sup>29</sup></p>	<p>Patients with radiation-induced late side effects, the majority of whom had failed previous interventions</p>	<p>Retrospective Study: Patients answered a questionnaire documenting symptom severity before and after treatment (using Radiation Therapy Oncology Group criteria), duration of improvement, relapse incidence, and HBOT-related complications.</p>	<p>75</p>	<p><b>Participation:</b> 60% <b>Symptom improve:</b> 100% of pelvic (median duration response = 72 wks) <b>Soft tissue necrosis/mucous membrane side effects:</b> 50% of pts improved w/HBOT <b>Resistant tissues:</b> salivary (11% RR), neurologic (17%), laryngeal (17%), &amp; upper GI (22%) <b>Relapse incidence</b> low (22%) <b>HBOT-related complications:</b> minor; occurred in 31% of patients</p>

<p><i>Corman, et al. 2003</i></p>	<p>Patients with radiation induced hemorrhagic cystitis from prostate cancer (81%) and bladder cancer (10%); mean age 70 years (15-88)</p>	<p>Patients at a single institution were treated with hyperbaric oxygen; mean time to onset of hematuria post-radiation was 48 months (0-355); average 33 (9-68) hyperbaric oxygen treatments</p>	<p>57</p>	<p><b>Follow-up:</b> 10-120 months <b>Response:</b> 49/57 (86%) complete resolution or marked improve of hematuria post-HBOT; of 8 who didn't improve 4 had &lt;40 HBOT &amp; 7 prematurely terminated treat due to med co-morbidities (4), claustrophobia (2), and tem resolution of symptoms (1)</p>
<p><i>DelPizzo, et al. 1998</i></p>	<p>patients with radiation induced hemorrhagic cystitis due to radiation induced injury to the bladder</p>	<p>Patients treated with hyperbaric oxygen therapy; 100% oxygen in a hyperbaric chamber at 2.0 atmospheres for 90 min 5 days/week; mean number of treatments was 40 and median follow-up was 5.1 years</p>	<p>11</p>	<p><b>Response:</b> 3/11 (27%) complete and durable resolution; 3/11 had persistent symptoms and required urinary diversion; 5/11 initially responded but had recurrent symptoms needing urinary diversion</p>
<p><i>Williams, et al. 1992</i></p>	<p>Patients who previously received radiation for a gynecologic malignancy and suffer soft tissue necrosis</p>	<p>Prospective observational study: Patients conservatively for 3 months with no resolution; then enrolled to receive hyperbaric oxygen treatment (15 courses)</p>	<p>14</p>	<p><b>Response:</b> all with radiation necrosis of vagina alone or in with recto-vaginal fistula had complete resolution of necrosis; 1 failure</p>