

Hyperbaric Oxygen Therapy for Soft Tissue Radionecrosis

A Summary of its Science and Evidence

HyperBaric Oxygen^{KC}
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Radiotherapy has long represented a major non-operative treatment for a number of different malignancies. Recent advances in its delivery have improved both efficacy and tolerance, yet adverse effects on non-target tissues continue to complicate its use.

Acute effects occur during or soon after completion of radiotherapy. They are usually mild and respond to supportive care. Late effects manifest after intervals of several months to many years. They tend to be more serious, are not infrequently refractory to a range of therapies and involve some mortality. Hyperbaric oxygen (HBO) therapy has gained increasing acceptance in the treatment of radiotherapy's late effects.^(1,2) HBO's value is unique in that it is disease modifying. Most other therapies provide supportive care or are directed at relief of symptoms. HBO therapy, on the other hand, directly overcomes the progressive obliterative endarteritis which characterizes late radiation injury's final common pathophysiologic insult.⁽³⁾ Across all anatomic sites, the reported incidence of late effects ranges from 1-22%. Its true incidence is probably unknown, secondary to limited reporting and unrecognized cases.

What follows is a summary of HBO's reported evidence of efficacy at the more commonly injured organs.

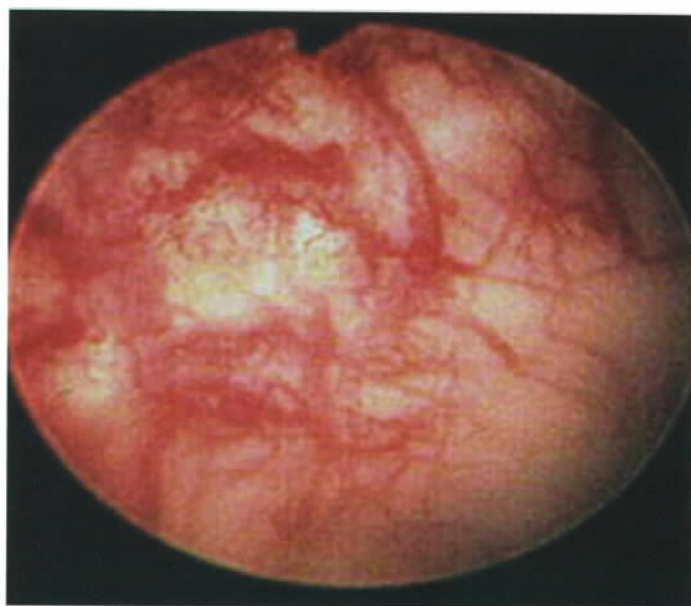
Rectum/Colon

Several published case reports that have been summarized by Feldmeier and Hampson suggest enhanced resolution rates.⁽¹⁾ These reports suffer from their retrospective nature and lack controls. Their corresponding level of evidence is, therefore, somewhat modest. In 2008, however, clear and unequivocal (Level 1) evidence of efficacy became available. A multi-institutional sham controlled and double-blind trial reported highly significant improvements in outcome in the HBO group vs. sham patients.⁽⁴⁾ Given the disease-modifying aspect of HBO, it was not surprising that the degree of improvement noted upon completion of active treatment became even greater over the ensuing years of follow-up. The relapsing nature of rectal radiation injury was essentially eliminated. A *quality of life* instrument was incorporated into this study, an important aspect of evidence-based medicine. Patients were asked to assess changes in *bowel bother* and *bowel function*. Both aspects were greatly enhanced and again continued to further improve with time. This Level 1 evidence of efficacy is unmatched in its ability

to resolve late radiation tissue injury, short of removal of the organ or structure in question, and its attendant quality of life implications.

Bladder

Radiation cystitis is not a frequently occurring problem but when present it is quite difficult to overcome. As is common elsewhere, most therapies are directed at relief of symptoms, which helps to some degree but also explains the remitting and relapsing nature of this condition. Feldmeier and Hampson have summarized 17 publications reporting the application of HBO therapy.⁽¹⁾ The paper by Bevers et al. was the largest in this series.⁽⁵⁾ It was prospective but uncontrolled and non-randomized. More recently Chong et al. from Virginia Mason Medical Center, in Seattle, take credit for the largest series of patients.⁽⁶⁾ Key findings in



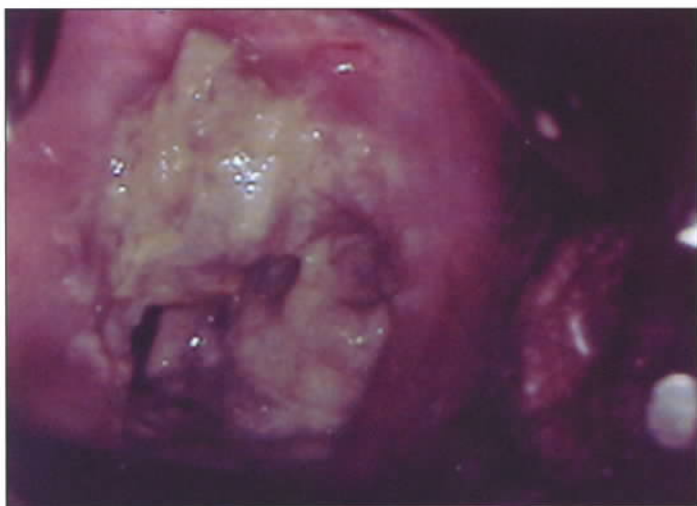
Bladder

the VMCC report are that improvement rates reach 90% with early (within six months of onset of hematuria), vs. 80% across all time frames. Consistent with the enduring nature of HBO therapy, one year follow-up remained very encouraging. Notably missing at one year was that typical group of patients who, when treated with other interventions, see an early response but experience relapse in a relatively short period. Early treatment of the pathophysiologic insult can be life-saving. The mortality rate in 378 patients treated symptomatically for bladder hemorrhage reached 3.7%. No other intervention meets or exceeds the present level of efficacy for HBO therapy short of cystectomy.

Gynecologic Sites

In 1992, a clinical series reviewed vaginal vault radionecrosis involving 14 patients who were analyzed retrospectively by Williams and Clarke.⁽⁷⁾ Thirteen had complete resolution (one only after a second course of HBO), the remaining patient succumbed to an overwhelming necrotizing infection. This group subsequently reported on additional 67 patients, who had been prospectively followed.⁽⁸⁾ Of this number, 21 did not receive HBO therapy. Reasons included patient refusal, unacceptable risk profile, cancer recurrence and insurmountable transportation problems. Of the 46 who underwent HBO therapy, 37 (80%) had significant improvement or complete healing. Of the remainder, one had tumor recurrence and eight were non-compliant to HBO.

Feldmeier et al. reported 44 patients treated with HBO for a variety of pelvic and abdominal radiation injuries.⁽⁹⁾ Thirty-one received at least 20 HBO treatments for perineum, groin, vagina and pelvic bone involvement. Twenty-six had complete resolution. Fink et al. reported the response of 14 patients who suffered pelvic injuries.⁽¹⁰⁾ Six involved the vagina, alone or in combination with other radiation-damaged sites. One had complete resolution, four had greater than 50% resolution. Combining all of the above reports, overall response rate was 87%.



Cervix

Head and Neck

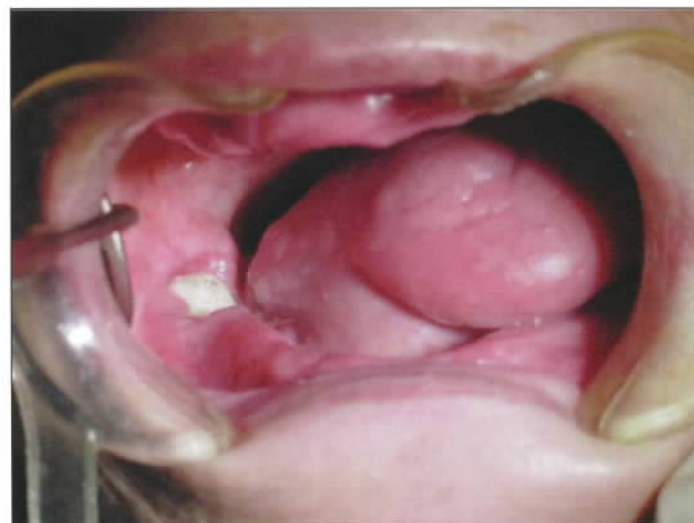
In modern medicine, involving well designed and appropriately fractionated radiotherapy, the incidence of laryngeal radionecrosis should be no more than 1%. This incidence occurs as either a direct consequence of radiation



Right side of neck

exposure or secondary to surgical wounding, as would occur for biopsy to rule out local recurrence. Four institutions have published case series, involving HBO therapy in the treatment of laryngeal radionecrosis.^(11,12,13,14) In the cumulative 43 patients only six were failures and required laryngectomy. As all of these hyperbaric treated cases were severe (Chandler Grade 3 or 4) this data, while non-controlled and retrospective, represents a very high salvage rate when compared to any other management. Most cases of Grade 3 or 4 have a high likelihood of laryngectomy.

Marx reported a controlled but non-randomized prospective study comparing HBO with standard care vs. standard care alone in the treatment of soft tissue radionecrosis to the neck.⁽¹⁵⁾ In 160 patients, those receiving HBO experienced less infections (6% vs. 24%) fewer instances of dehiscence (11% vs. 48%) and fewer instances of delayed healing (11% vs. 55%). All differences were statistically significant.



Right side of mandible



Exposed mandible; left inferior chin

Adjunctive HBO, 20 treatments administered preoperatively followed by 10 post-operatively, for radiated tissues reduced deformity, disability and length of hospital stay, resulting in an overall lowering of cost of care.⁽¹⁵⁾

Trunk and Chest Wall Sites



Lumbar spine

When patients are irradiated after mastectomy, the radiation dose to the skin is intentionally high. As a result of this technique most women will suffer acute reactions, some will suffer both acute and late effects. Late effects often culminate in superficial ulceration. Attempts to resolve ulcerations surgically will occasionally produce larger and deeper ulcerations due to the injurious effects of radiation throughout its portal. Early and more recent reports have demonstrated the benefit of HBO therapy in resolving these problems.^(16,17) In the most recent report a statistically significant reduction (improvement) in SOMA LENT score (a standardized radiation injury grading system) was observed in those who agreed to treatment with HBO vs. those who did not.⁽⁴⁾

Radiation tissue injury to the extremities is very rare, due largely to the infrequent occurrence of primary malignancies of the extremities. Published information on HBOs effects is, therefore, largely limited in a 2002 publication.⁽¹⁸⁾ Eleven of 17 (65%) patients treated with HBO therapy

had complete resolution of their soft tissue condition at completion of treatment. In 13 patients those for which long-term follow-up was available, 11 of 13 (85%) had fully resolved. Very limited evidence, however, but the results are consistent with other anatomic sites where evidence is more robust. As there is nothing to suggest that the injurious effects of radiotherapy on non-target tissues is anatomic-specific, it is not surprising to find that HBO therapy is broadly therapeutic.

In summary, the application of HBO therapy for soft tissue radionecrosis has produced very encouraging outcomes in an otherwise complex management problem. There is nothing to suggest that the damaging effects of radiotherapy are anatomic-specific, on the contrary. Consequently, HBO therapy is likely to be equally efficacious elsewhere, as clinical experience indicates.

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