Radiation-induced cystitis and hyperbaric oxygen therapy

Nicklas Oscarsson and colleagues' findings in the RICH-ART trial elevate efficacy evidence for hyperbaric oxygen treatment of less severe, yet common, forms of radiation cystitis.[1] Their 39% conversion ratio from 223 patients assessed to 87 enrolled patients that the suggests improved outcomes achieved with hyperbaric oxygen therapy are largely generalisable. Although not reported, the number needed to treat was an encouraging three for both the Expanded Prostate Index Composite score of 2·56 and the Late Radiation Morbidity Grading Scheme (LRMGS) score of 2·17. Shorter intervals between diagnosis and initiation of hyperbaric oxygenation were associated with improved responses, as was the case with reduced radiation to hyperbaric oxygen intervals. This interval-related improved response has been observed elsewhere[2] and further supports earlier applications of hyperbaric oxygen.

Patients with concurrent radiation proctitis also had an improvement in this condition, which suggests a unique benefit of systemically delivered hyperbaric oxygen in a setting of multiorgan involvement. More localised standard care is not expected to favourably affect other radiation-damaged anatomical sites. Improved bladder findings add to the contention that hyperbaric oxygen is uniquely disease modifying.[3-5] This effect serves to limit the frequency of remitting-relapsing consequences of care directed principally at relief of symptoms.

The absence of a sham component was unfortunate, given the subjective nature of the primary outcome measure. This decision eliminated the ability to blind patients, as it did LRMGS assessors. Adoption of sham controls and blinding would have further elevated this work within the evidence hierarchy. The authors' arguments against sham were unconvincing, and neither example suggesting that the study was negatively affected by inclusion of sham was correct. Sham control and double-blinding has been effectively incorporated into trial design of hyperbaric oxygen for the treatment of pelvic late radiation tissue injury.[5] Blinded sham controls might have served to minimise drop-outs after randomisation in those allocated to the control group, where such patients were now free to receive hyperbaric oxygen off protocol. It is encouraging that eventual reporting of histological data will have involved blinded assessors.

The trial did not include more advanced bladder injuries. The authors believed that withholding hyperbaric oxygen for such cases would have been unethical. This belief was somewhat difficult to reconcile as they note elsewhere that evidence supporting hyperbaric oxygen as a treatment for radiation cystitis "is weak".

The hyperbaric oxygen dosing protocol was appropriate for this condition. Related harms were minor and self-limiting, and supportive of the position that hyperbaric medicine is well tolerated, relatively safe, and an essentially mastered medical technology.

I declare no competing interests.

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1 Oscarsson N, Müller B, Rosén A, et al. Radiation-induced cystitis treated with hyperbaric oxygen therapy (RICH-ART): a randomised, controlled, phase 2–3 trial. *Lancet Oncol* 2019; published online Sept 16. http://dx.doi.org/10.1016/S1470-2045(19)30494-2.

2 Dellis A, Papatsoris A, Kalentzos V, et al. Hyperbaric oxygen as sole treatment for severe radiation-induced haemorrhagic cystitis. *Int Braz J Urol* 2017; **43:** 489–95.

3 Marx RE, Ehler WJ, Tayapongsak P, et al. Relationship of oxygen dose to angiogenesis induction in irradiated tissue. *America J Surg* 1990; **160:** 519–24.

4 Svalestad J, Hellem S, Thorsen E, et al. Effect of hyperbaric oxygen treatment on irradiated oral mucosa: microvessel density. *Int J Oral Maxillofac Surg* 2015; **44:** 301–07.

5 Clarke RE, Tenorio LMC, 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.