



HORTIS-III: Radiation Cystitis – a multicenter, prospective, double-blind, randomized, sham-controlled trial to evaluate the effectiveness of hyperbaric oxygen therapy in patients with refractory late radiation cystitis

SG Smit¹, CF Heyns¹, FJ Cronje², CJ Roberts²

Department of Urology¹, Department of Community Health², Stellenbosch University and Tygerberg Hospital

Objective

HORTIS (Hyperbaric Oxygen Radiation Tissue Injury Study) is a multicenter study conducted by the Baromedical Research Foundation, South Carolina, USA. [1] consists of 8 components (soft tissues, mandible, bladder, rectum, colon, gynaecology, larynx, and prophylaxis). Stellenbosch University and Tygerberg Hospital is one of 6 centers recruiting patients for the radiation cystitis arm (HORTIS-III). The aim of this multicenter, prospective, double-blind, randomized, sham-controlled trial is to evaluate the effectiveness of hyperbaric oxygen therapy (HBOT) in patients with refractory late radiation cystitis.

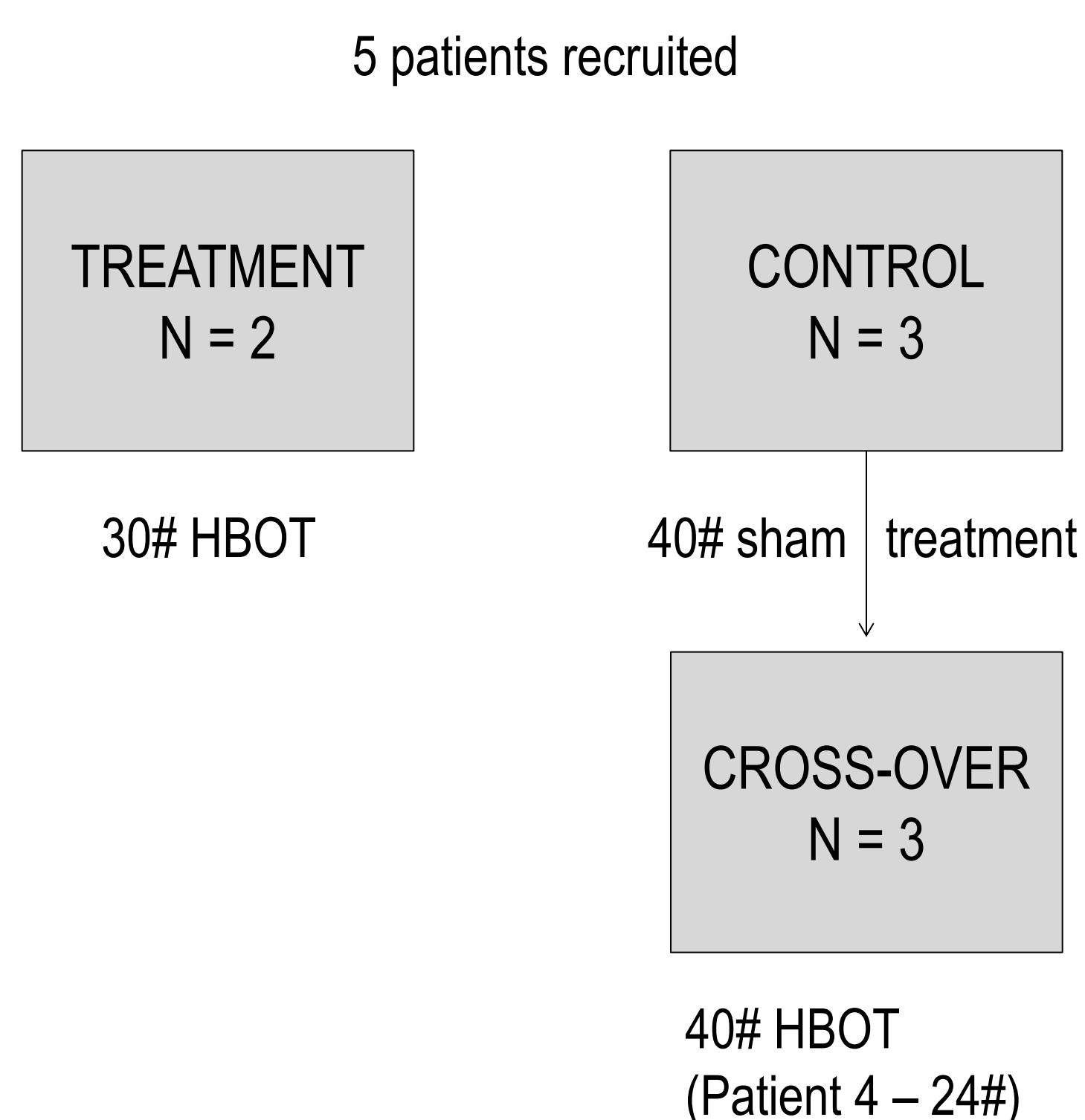
Methods

Patients whose cancer treatment included radiotherapy and who have developed late radiation tissue injury to the bladder (i.e. clinical diagnosis of radiation cystitis); the **diagnosis** of which should have existed for **at least 3 months** despite conventional management. Inclusion and exclusion criteria were applied to recruit patients. [1]

Recruited patients were then prospectively randomized into two groups. Group A (treatment) received HBOT (100% oxygen at 2.0 atmospheres). Group B (control) received sham treatment (21% oxygen at 1.0 atmosphere). Patients and referring physicians were blinded to the randomization process. Patients received 30-40 sessions of either HBOT or sham treatment. After unblinding, patients in the control group were offered crossover to the treatment group. Primary outcome measures included clinical evaluation, SOMALENT and EPIC scores.

Results

Recruitment of patients started on 1st April 2009. In total, 34 patients were screened, 5 met the inclusion and exclusion criteria and agreed to participate. Two patients were randomized to Group A. One patient received 30 sessions of HBOT. One patient absconded after 26 sessions of HBOT. Three patients were randomized to Group B and received 40 sessions of sham treatment. All 3 control patients elected to cross over: two patients completed 40 sessions of HBOT, one stopped at 24 sessions due to an unrelated medical condition (critical limb ischemia). No serious adverse events occurred. One patient developed ear pain, which was managed conservatively with equalization techniques and nasal decongestants. No grommets were necessary. No other adverse events were reported.



At 1 year follow-up after HBOT, 3 patients showed improvement in SOMALENT and EPIC scores (See Figures 1 and 2). One patient with a vesicovaginal fistula showed complete radiographic resolution at 14 months follow-up (See Figures 4 and 5).

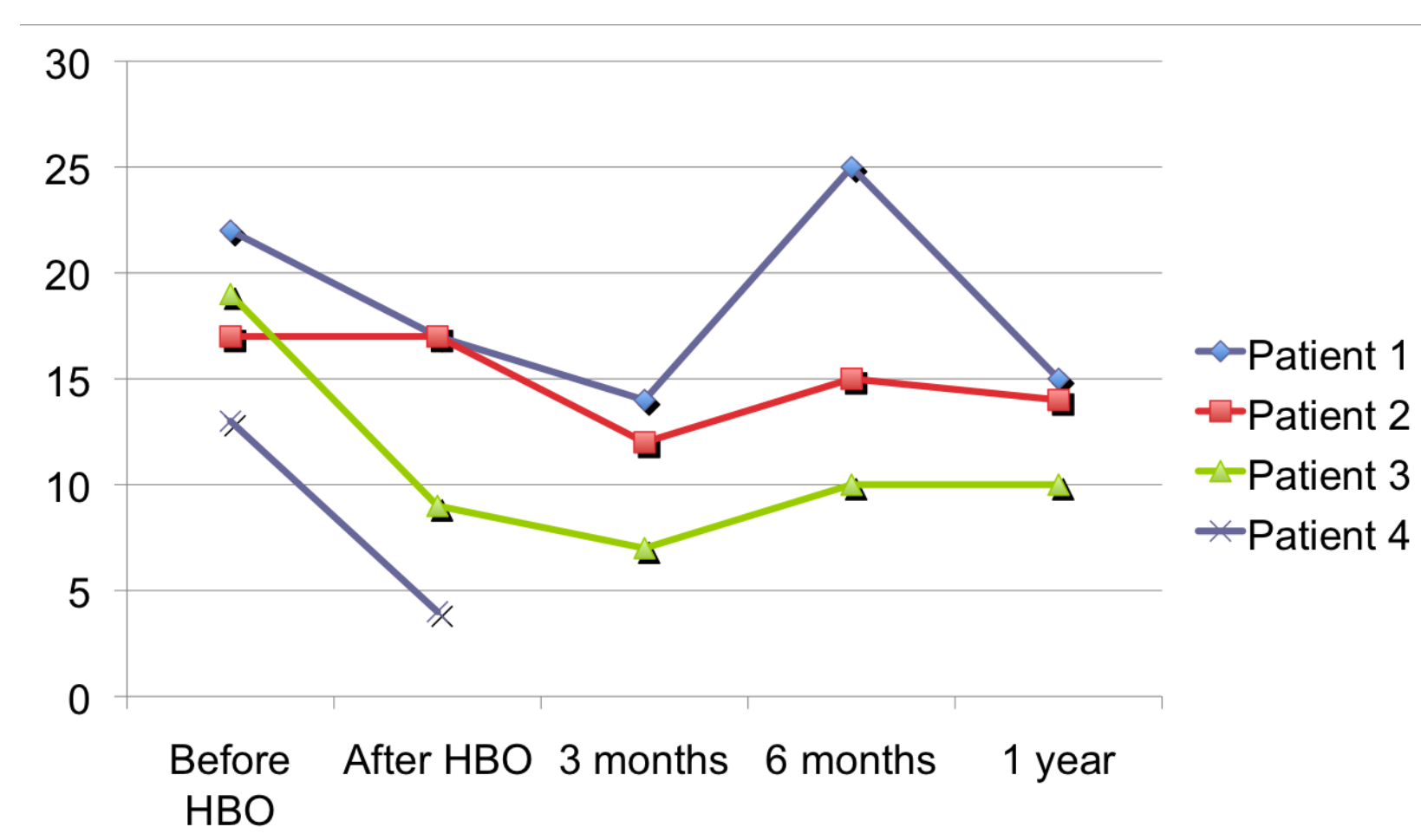


Fig 1: SOMALENT scores (y-axis) showing improvement from before HBOT to up to 1 year after HBOT

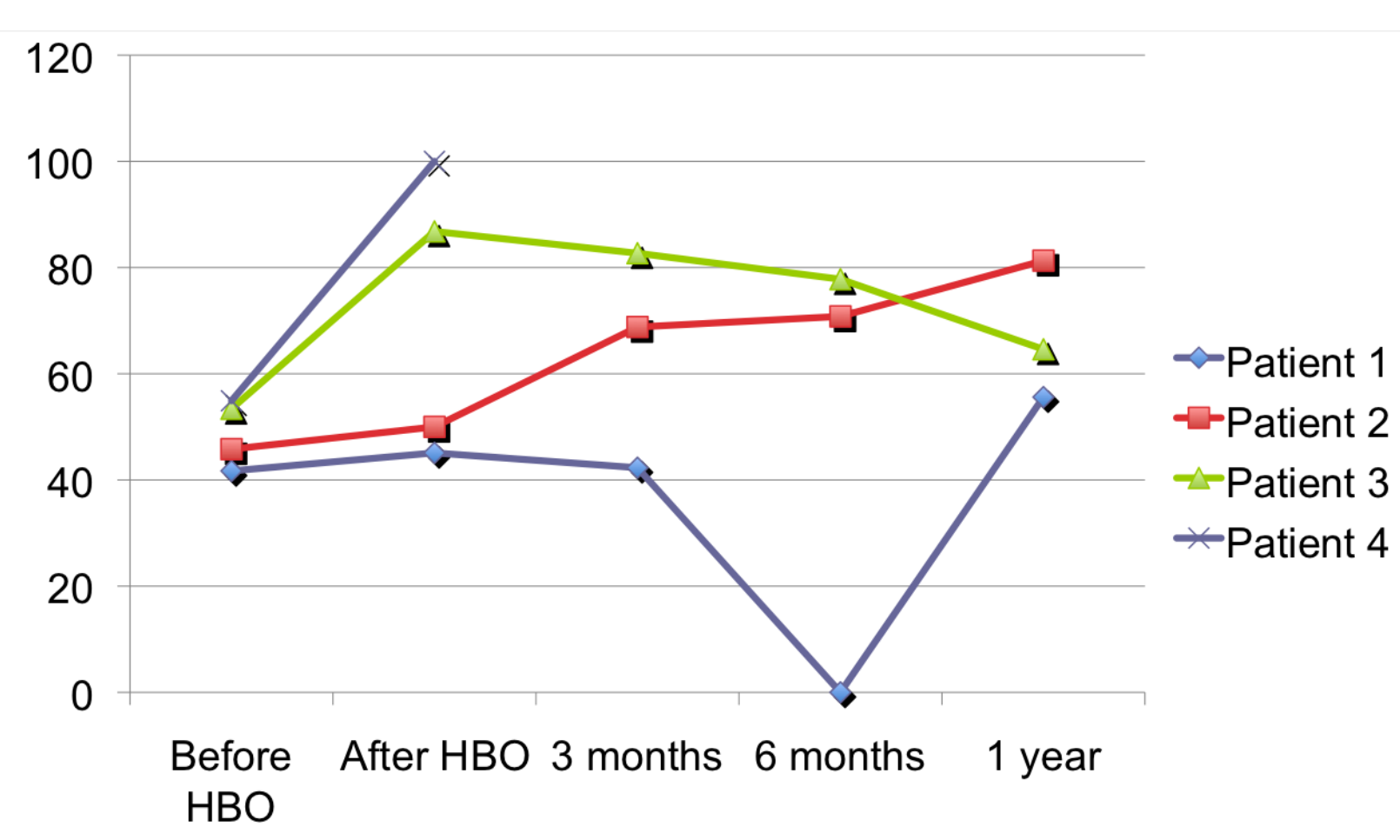


Fig 2: EPIC scores (y-axis) showing improvement from before HBOT to up to 1 year after HBOT

Discussion

Hyperbaric oxygen therapy (HBOT) involves the administration of 100% oxygen in a pressurized treatment chamber (Figure 3). The hyperbaric chamber provides conditions under which haemoglobin is fully saturated and oxygen is dissolved in the blood plasma at very high concentrations, which is then circulated to provide therapeutic benefits, such as increased angiogenesis and fibroblast activity, in damaged tissues. Thus, it can be considered as an alternative treatment for patients with an underlying ischemic process that is unresponsive to conventional therapy. The degree of hyperoxygenation in HBOT cannot be achieved by any other means.

HBOT has been proposed as a treatment option for patients with radiation cystitis that does not respond to conventional management, based on the rationale that it can correct ischemic injury secondary to radiation damage. A number of investigators have studied the use of HBOT in this setting. An advantage of HBOT in these patients is the absence of the adverse effects on bladder structure or function that may be seen with other therapies, such as formalin or silver nitrate instillations, while avoiding the need for surgery. HBOT is also very well tolerated with few adverse effects, the most common being pressure-related in the form of ear and sinus barotrauma. Serious complications, such as oxygen toxicity, are very rare.

The reported success rate of HBOT for radiation cystitis varies from 60% to 92%. [2,3] These results are highly in favour of HBOT as a treatment option for refractory radiation-induced hemorrhagic cystitis. The technique is variable, in that 100% oxygen is administered at pressures from 1.5 to 2.5 atmospheres (ATM) for 45 to 120 minutes. This includes allowing time for compression and decompression. Moreover, 5-minute "air-breaks" can be introduced each half hour to reduce the risk of oxygen toxicity. Each session occurs once daily and for a predetermined length of time, usually 20 to 30 sessions.

Our preliminary results show that HBOT remains an effective treatment option for refractory late radiation cystitis, with 3 patients showing clinical improvement and improvement in SOMALENT and EPIC scores at 1 year follow-up. Due to the low numbers of patients involved, no comparisons between the two groups can be made at this stage. The trial is still ongoing, with a 6th patient recently recruited. In total, 15 patients have been recruited internationally.

Clarke *et al.* [4] reported the results of HORTIS-IV, which evaluated the effectiveness of HBOT in 120 patients with refractory radiation proctitis. Patients were randomized to undergo either HBOT at 2 ATM (group 1) or air at 1.1 ATM (group 2). The mean SOMALENT score improved in both groups; however, the mean score was significantly lower ($P = 0.015$), and the amount of improvement nearly twice as great (5.00 versus 2.61, $P = 0.0019$), in group 1 compared to group 2. Group 1 also had a greater portion of responders per clinical assessment than did group 2 (88.9% versus 62.5%, $P = 0.00009$). Thus, HBOT significantly improved the healing responses in patients with refractory radiation proctitis: at 5 years' follow-up ($n = 14$), there remained a clear trend towards continued and enduring healing.

The estimated cost of HBOT is R500 per session. 160 sessions were given to 5 patients, with a total cost amounting to R80 000. This amount was covered by the HBO Unit at the University of Stellenbosch, Department of Community Health. Patients' travel expenses were refunded by funds donated by the SAUA Research Fund.



Fig 3: Patient in hyperbaric oxygen chamber (Patient 1)



Fig 4: Cystogram before HBOT showing VVF (Patient 2)

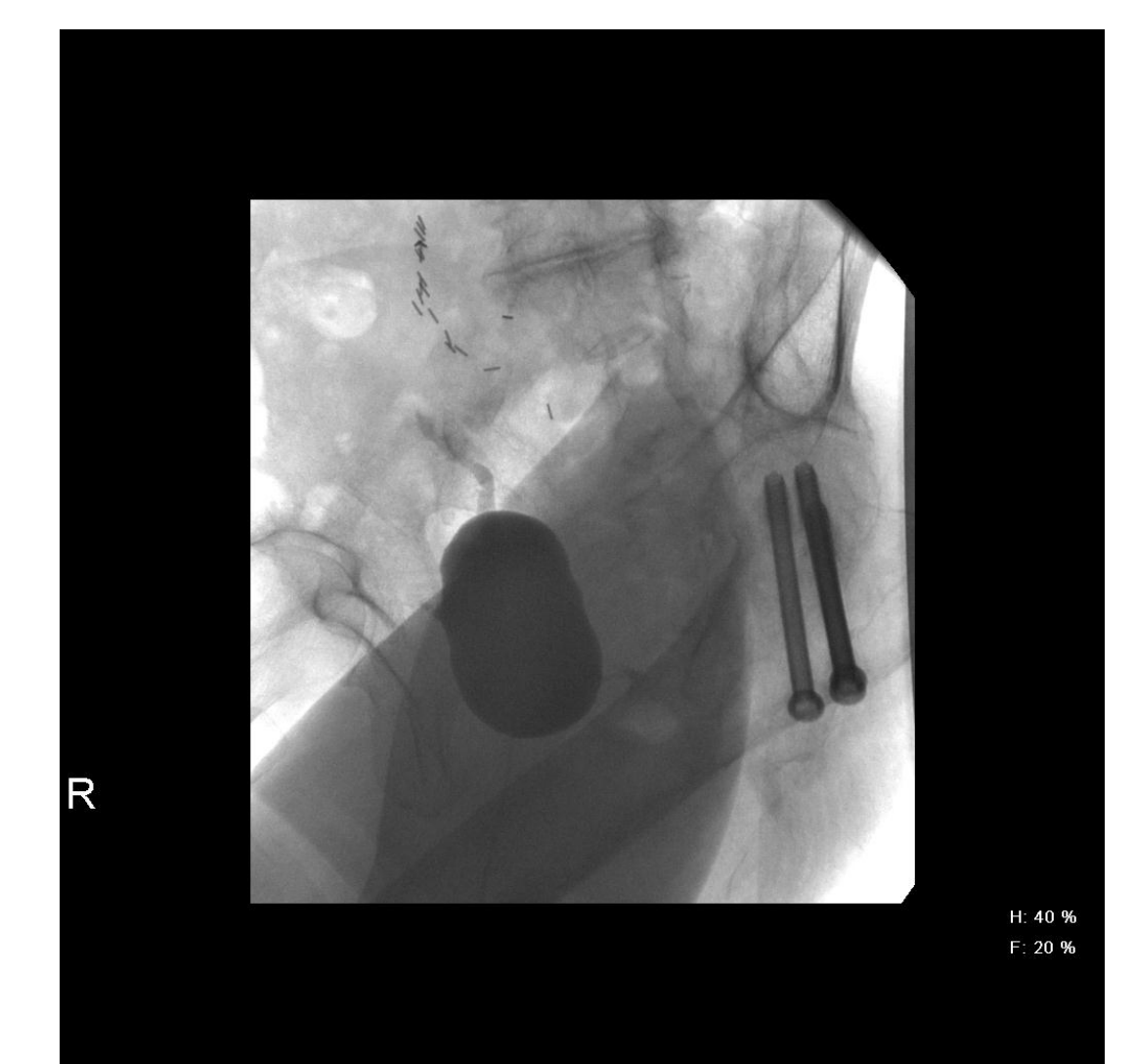


Fig 5: Cystogram 6 months after HBOT showing resolution of VVF (Patient 2)

Conclusion

- ✓ HBOT remains a treatment option for refractory late radiation cystitis.
- ✓ The evidence presented here is inconclusive due to the low number of patients.
- ✓ The ongoing multicenter trial is expected to provide conclusive evidence.

References

- 1) Smit SG, Heyns CF. Hyperbaric oxygen therapy in urology. SAUGR 6:30-35 (2009)
- 2) Smit SG, Heyns CF. Management of radiation cystitis. Nat Rev Urol. 7:206-214 (2010)
- 3) Clarke *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. 72:134-143 (2008).
- 4) www.baromedicalresearch.org/overview.asp