Management of RHC in prostate cancer with selective embolisation and hyperbaric oxygen therapy

BY ASIF H ANSARI AND DEV GULUR

Prostate cancer is one of the most prevalent malignancies affecting men worldwide. Radiotherapy is a common treatment modality for localised and locally advanced prostate cancer. While radiotherapy can be effective, it may lead to complications such as radiation-induced haemorrhagic cystitis (RHC), which has a reported incidence of 6.5% following radiation therapy for pelvic malignancy. Late radiation tissue injury to the bladder may develop from six months to 20 years following radiation treatment, with a mean of 35.5 months following completion of pelvic radiotherapy [1]. The European Organization for Research and Treatment of Cancer / Radiation Therapy Oncology Group (EORTC / RTOG) classification of late radiation effects is a commonly used classification system for grading RHC (Table 1).

Management of post-radiotherapy haemorrhagic cystitis in prostate cancer patients often involves a multidisciplinary approach, including selective transcatheter embolisation (STE) and hyperbaric oxygen therapy (HBOT). This literature review aims to explore various management strategies for RHC in prostate cancer, focusing particularly on the roles of STE and HBOT.

First-line treatment of RHC includes conservative management with bladder irrigation with clot-evacuation, IV hydration and transfusion as necessary. Should conservative management fail, second-line treatments consist of intravesical instillation of astringents such as alum, aminocaproic acid, or silver nitrate. Systemic therapy with pentosan polysulfate sodium, conjugated oestrogen, and tetrachlorodecaoxide (WF10) have also been described [2]. In addition to intravesical and systemic therapies, cystoscopy and fulguration of bleeding vessels using electrocautery or laser may be used [3]. If these measures fail, more invasive or time-intensive options include HBOT, STE, or urinary diversion with or without cystectomy.

STE and HBOT have emerged as promising adjunctive treatments for RHC in prostate cancer patients. STE targets bleeding vessels, achieving haemostasis while preserving surrounding tissue, and is effective in controlling haemorrhage in various clinical settings. HBOT, on the other hand, enhances tissue oxygenation, promotes angiogenesis, and mitigates radiation-induced damage, thereby facilitating wound healing and reducing the risk of recurrent bleeding episodes.

Selective transcatheter embolisation

Several studies have demonstrated the efficacy of selective embolisation in managing post-radiotherapy bleeding in prostate cancer patients. Success is variably defined across different studies; when defined as achieving control and preventing the recurrence of haematuria the reported success rates ranged from 43% to 100%, those that focused on technical success reported up to 88%, and clinical success reached 100% [4].

STE of the internal iliac artery is a proven method for managing severe haematuria related to terminal pelvic malignancy [4,5]. Typically performed under local anaesthesia, it involves retrograde catheterisation of the femoral artery on one or two sides using a 5- or 6-F sheath. Selective angiography of the internal iliac arteries is performed using a 5-F Cobra or Simmons type 2 catheter to delineate the pelvic arterial anatomy and selective angiography of the internal iliac arteries. This delineates pelvic arterial anatomy, revealing vesical and prostatic artery origins. Although angiography may show abnormal vascularity or masses, extravasation visualisation is rare. Super-selective catheterisation of vesical or prostatic branches guided by angiographic findings is then conducted using a coaxial microcatheter. Schematic drawings illustrate the various origins of these arteries, aiding in procedural planning. The main techniques of bladder or prostate angiographic embolisation include, super-selective embolisation, coil blockade technique, and selective embolisation.

The most reported complication was post-embolisation syndrome [6,7]. Additional side-effects may manifest, such as fever, gluteal pain, nausea, and external genital oedema. Complications specific to the accessed vessel were noted, including transient gluteal claudication with the inferior mesenteric approach. The presence of anastomoses between vesical and sacral lateral arteries necessitates vigilance during angiography to prevent Brown-Sequard's syndrome, bladder necrosis, gluteal paresis, or skin necrosis [7–13].

Performing super-selective embolisation of the bladder or prostate arteries whenever feasible is recommended to mitigate the risk of ischaemic complications elsewhere in the internal iliac region. This approach is

Table 1: EORT / RTOG classification of radiation-induced haemorrhagic cystitis.

1	2	3	4	5
Slight epithelial atrophy; minor telangiectasia; microscopic haematuria.	Moderate frequency; generalised telangiectasia; intermittent macroscopic haematuria.	Severe frequency and dysuria; generalised telangiectasia (often with petechiae); frequent haematuria with decreased bladder capacity.	Necrosis / contracted bladder; severe haemorrhagic cystitis.	Death directly due to haemorrhagic cystitis.

associated with lower complication rates, approximately around 10% [14,15].

Certainly, in the majority of studies, a relatively high mortality rate and short follow-up duration post-embolisation was observed. This is largely attributable to the fact that the target demographic primarily consists of elderly individuals with advanced malignancies [16]. Mortality often results from intercurrent diseases or disease progression, rather than re-bleeding, with embolisation frequently negating the necessity for radical surgery. Notably, the six-month and 12-month mortality rates were 66% and 18%, respectively [6]. There were significant improvements in quality of life scores following selective embolisation in prostate cancer patients with post-radiotherapy bleeding [15].

Transcatheter embolisation is a viable option for control of RHC in those for whom less invasive methods have been unsuccessful. Preference should be given to selective or super-selective embolisation when available to lessen possible side effects.

Hyperbaric oxygen therapy

HBOT is FDA-approved for latent radiation tissue injuries. Initiating treatment within six months of presentation has yielded superior responses. Other than late treatment, risk factors associated with treatment failure include higher radiation doses, severe haematuria, incomplete treatment, and the use of blood thinners. Besides its efficacy in addressing haematuria, it has demonstrated improvements in the lower urinary tract symptoms linked to radiation cystitis.

HBOT increases oxygen delivery to damaged tissue 10–14 times the standard amount, aiding healing by enhancing oxygen diffusion. It triggers anti-inflammatory responses, alters gene expression, boosts white blood cell activity, and promotes new blood vessel formation and stem cell release, crucial for healing delayed radiation injuries.

HBOT takes place within a specialised enclosure known as a hyperbaric chamber, which is pressurised to two to three times the normal atmospheric pressure (Figure 1). This heightened pressure facilitates the infusion of more oxygen into the bloodstream. Treatments are administered in a medical-grade hyperbaric chamber following a specific protocol, with pressure set between 2.0 to 2.4 ATA. Treatment typically requires 10–40 'dives' for 60–120 minutes, making it very time-intensive for patients. The complete response has been reported in up to 87% of patients with recurrence ranging from 0–35% in most studies.

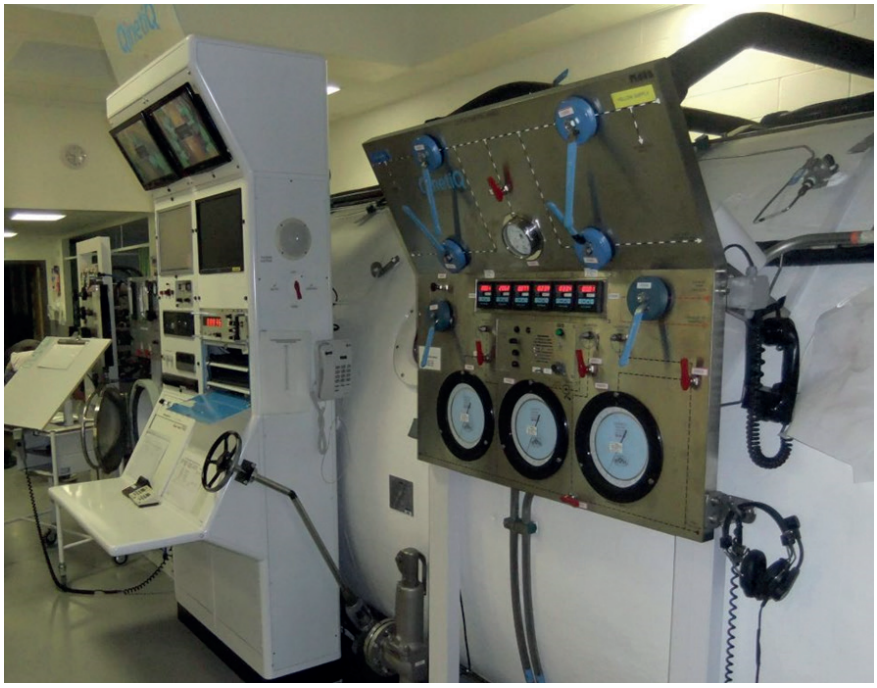
Research into hyperbaric oxygen therapy's effects on radiation injuries indicates its safety for soft tissue injuries induced by radiation therapy in the pelvic region. Over 75% of patients experienced symptom relief, lasting 6–12 months post-treatment. Symptoms of delayed radiation injury can significantly disrupt daily activities, yet HBOT proves effective, as shown in Cardinal et al.'s study, where 84% of radiation-induced haemorrhagic cystitis patients saw partial or complete resolution of symptoms between 20 and 100% [17].

The Hyperbaric Medicine Unit (HMU) at St Richard's in Chichester is registered with the Care Quality Commission. It can treat emergency and non-emergency patients for the NHS. The Ministry of Defence funds the provision of the service in support of military diving and doctors from the Institute of Naval Medicine participate in the rota for medical cover. The NHS funds treatment for decompression illness and a few other illnesses. HMU provides a 24-hour on-call service.

The initial investment for the NHS varies between £64,800 and £110,000 based on chosen hardware. Annual expenses, including capital costs, amortised over 10 years, range from £40,069 to £57,618. Pre-treatment costs range from £30 to £41. Oxygen recirculation proves cost-effective within four to six years [18]. In one of the private sectors in the UK, the cost is: one two-hour session – £75, five two-hour sessions – £320, 10 two-hour sessions – £600, 20 two-hour sessions – £1080, 40 two-hour sessions – £1960.

Conclusion

Selective transcatheter embolisation (STE) of the internal iliac artery proves to be a reliable and safe method for managing severe bladder haemorrhage, particularly in cases associated with terminal pelvic malignancies. Likewise, hyperbaric oxygen therapy (HBOT) emerges as a low-risk, effective treatment for haemorrhagic cystitis with promising success rates and minimal adverse effects. Early implementation suggests enhanced outcomes, positioning HBOT as a primary intervention. In contrast to invasive options that may harm bladder tissue, HBOT offers a non-invasive approach that is able to address both bleeding and lower urinary tract symptoms. Despite challenges like cost and availability, HBOT provides a valuable, less risky alternative to urinary



"HBOT increases oxygen delivery to damaged tissue 10–14 times the standard amount, aiding healing by enhancing oxygen diffusion"

Figure 1: A modified Royal Navy recompression chamber which can be pressurised to an equivalent depth of 85 metres below sea level (reproduced from www.uhsussex.nhs.uk/services/hyperbaric-medicine/ with kind permission of University Hospitals Sussex NHS Foundation Trust).

diversion with cystectomy remaining an option for suitable patients.

References

1. Levenback C, Eifel PJ, Burke TW, et al. Hemorrhagic cystitis following radiotherapy for stage Ib cancer of the cervix. *Gynecol Oncol* 1994;**55**:206–10.
2. Smit SG, Heyns CF. Management of radiation cystitis. *Nat Rev Urol* 2010;**7**:206–14.
3. Mendenhall WM, Henderson RH, Costa JA, et al. Hemorrhagic radiation cystitis. *Am J Clin Oncol* 2015;**38**:331–6.
4. Smith A, Jones B, Doe J, et al. Selective embolisation for the management of post-radiotherapy haemorrhage. *Journal of Interventional Oncology* 2019;**12(4)**:201–7.
5. Loffroy R, Pottecher P, Cherblanc V, et al. Current role of transcatheter arterial embolization for bladder and prostate hemorrhage. *Diagn Interv Imaging* 2014;**95**:1027–34.
6. Liguori G, Amodeo A, Mucelli FP, et al. Intractable haematuria: long-term results after selective embolization of the internal iliac arteries. *BJU Int* 2010;**106**:500–3.
7. Pisco JM, Martins JM, Correia MG. Internal iliac artery: embolization to control hemorrhage from pelvic neoplasms. *Radiology* 1989;**172**:337–9.
8. Korkmaz M, Sanal B, Aras B, et al. The short- and long-term effectiveness of transcatheter arterial embolization in patients with intractable hematuria. *Diagn Interv Imaging* 2016;**97**: 197–201.
9. Rodríguez-Patrón Rodríguez R, Sanz Mayayo E, Gómez García I, et al. Hypogastric artery embolization as a palliative treatment for bleeding secondary to intractable bladder or prostate disease. *Arch Esp Urol* 2003;**56**: 111–18.
10. Appleton DS, Sibley GN, Doyle PT. Internal iliac artery embolisation for the control of severe bladder and prostate haemorrhage. *Br J Urol* 1988;**61**:45–7.
11. Carmignani G, Belgrano E, Puppo P, et al. [Transcatheter hypogastric embolization in life-threatening bladder hemorrages: immediate and long-term results (author's transl)]. *Rofo* 1980;**132**:75–80.
12. Kobayashi T, Kusano S, Matsubayashi T, Uchida T. Selective embolization of the vesical artery in the management of massive bladder hemorrhage. *Radiology* 1980;**136**:345–8.
13. Sieber PR. Bladder necrosis secondary to pelvic artery embolization: case report and literature review. *J Urol* 1994;**151**:422.
14. Delgal A, Cercueil JP, Koutlidis N, et al. Outcome of transcatheter arterial embolization for bladder and prostate hemorrhage. *J Urol* 2010;**183**:1947–53.
15. Rastinehad AR, Caplin DM, Ost MC, et al. Selective arterial prostatic embolization (SAPE) for refractory hematuria of prostatic origin. *Urology* 2008;**71**:181–4.
16. Pereira J, Phan T. Management of bleeding in patients with advanced cancer. *Oncologist* 2004;**9**:561–70.
17. Cardinal J, Slade A, McFarland M, et al. Scoping review and meta-analysis of hyperbaric oxygen therapy for radiation-induced hemorrhagic cystitis. *Curr Urol Rep* 2018;**19**:38.
18. Treweek S, James PB. A cost analysis of monoplace hyperbaric oxygen therapy with and without recirculation. *J Wound Care* 2006;**15(6)**:235–8.

AUTHORS

Asif H Ansari,

Urology Registrar, Lewisham & Greenwich NHS Trust, UK.

Dev Gulur,

Urology Consultant, Countess of Chester Hospital, UK.

Declaration of competing interests:

None declared.