Current management of radiation cystitis: A review and practical guide to clinical management

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Abbreviation	Term
ATMs	atmospheres
BPH	Benign prostatic hypertrophy
CBI	Continuous bladder irrigation
CR	Complete response
GAG	glycosaminoglycan
HBO(T)	Hyperbaric oxygen (therapy)
IMRT	Image modulated radiation therapy
NKTCs	Natural killer cells
NR	Not recorded
PR	Partial response
QoL	Quality of Life
SPP	Sodium pentosan polysulphate
TCDO	tetrachlorodecaoxygen
TF	Treatment failure
YAG	Yttrium-aluminium-garnet

Abstract

Haemorrhage is a frequent complication of radiation cystitis leading to emergency presentations in patients with prior pelvic radiation therapy. Standard initial patient management strategies involve resuscitation, bladder washout with clot evacuation and continuous bladder irrigation. Beyond this, definitive surgical treatment is associated with significant morbidity and mortality. Alternative less invasive management options for non-emergent haemorrhagic cystitis include systemic medical therapies, hyperbaric oxygen, intra-vesical therapies and laser ablation. However, evidence to support and compare treatment for haemorrhagic radiation cystitis is limited. Herein, a literature search pertaining to the current management of haemorrhagic cystitis was conducted. With evaluation of existing literature, this narrative review also provides a stepwise clinical algorithm to aid the urologist in treating patients presenting with complications associated with radiation cystitis.

1.0 Introduction

Chronic haemorrhagic cystitis occurs up to 5% of patients following pelvic radiotherapy [1]. Although the advent of intensity modulated radiation therapy (IMRT) may decrease radiation induced bladder toxicity; robust data on long-term outcomes are limited [2]. The response of the urinary bladder to radiation treatment can be classified into acute or subacute reactions that typically occur within 3-6 months of radiation treatment and late reactions that occur after six months. Delayed radiation induced endothelial cell damage and perivascular fibrosis result in ischaemia and obliterative end arteritis leading to a range of symptoms including urinary frequency, urgency, pelvic pain and haematuria[3].

Complications associated with radiotherapy account for up to 7% of emergency urology admissions [4]. Initial management of radiation cystitis with haemorrhage frequently involves a sequential algorithm consisting of initial resuscitation and reversal of anticoagulation as clinically appropriate, copious bladder washouts with clot evacuation, followed by continuous bladder irrigation (CBI) and blood transfusions as required. Characteristic cystoscopy findings are telangiectasia with friable erythematous mucosa [5]. Intractable haemorrhagic cystitis severely impacts on a patient's quality of life (QoL) with

persistent bleeding resulting in life threatening hypovolaemic shock [6]. The management of complex patients on anticoagulation requires balanced clinical decisions regarding the risks and benefits of blood transfusions and cessation of anticoagulation by the treating physician, however often short periods without anticoagulation may be required to interrupt the pathological cycle. Urinary diversion and cystectomy for end-stage haemorrhagic cystitis is associated with a 44% mortality rate [7, 8]. Alternative less invasive management options for non-emergent haemorrhagic cystitis include systemic medical therapies, hyperbaric oxygen, intravesical therapies and laser ablation. These treatment strategies have several limitations including difficulty obtaining and administering some of the more historical treatments, such as formalin and alum, in the contemporary clinical setting. There is also a dearth of level one evidence for the efficacy of such treatments. A further limitation is the absence of a pre-determined management algorithm regarding best clinical practice for patients presenting with symptomatic radiation induced haemorrhagic cystitis. In this narrative review, we summarise available therapies for treating chronic radiation induced hemorrhagic cystitis and propose a practical management algorithm.

2.0 Methods

A literature search was undertaken using Medline, Embase, Pub Med and Google Scholar. The following terms were entered into the search algorithm to identify peer-reviewed articles that investigated management strategies for radiation induced hemorrhagic cystitis: “radiation or radiotherapy”, “cystitis”, “haemorrhage or hemorrhage”. A further search of commonly used treatments utilising the terms “hyperbaric oxygen*”, “formalin”, “aluminium”, “ablation or laser” and “oral therapy” was performed. Results were limited to publications in the English language, involving adult human patients and published after 1990. Reference lists were checked to identify relevant studies not captured in the initial search. Reviews and case reports were excluded and, where possible, studies including patients who had received either radiation or cyclophosphamide, as a precursor, were filtered to assess intervention effect on those who received radiation therapy only. Abstracts and complete manuscripts were reviewed individually by two authors and discrepancies reviewed by a third party.

Inclusion criteria were studies describing onset of haematuria ≥3 months post completion of radiation therapy and pelvic radiation for any cause. For comparative purposes, outcomes were classified as either complete response (CR) corresponding to resolution of haematuria, partial response (PR) corresponding to improvement but not resolution of haematuria or treatment failure (TF) corresponding to requirement of alternative intervention for persistent severe haematuria. Those denoted as "unknown" were patients that were lost to follow up or patients that discontinued a trial.

224 manuscripts were identified through database search and a further five were included after identification through other sources. After removal of duplicates and further screening by title and abstract to ensure adherence with inclusion and exclusion criteria 51 articles were further assessed for eligibility. Due to the heterogeneity of the clinical causes for haemorrhagic cystitis, articles were excluded due to absence of previous pelvic radiation as a underlying cause of the haemorrhagic cystitis. A total of 28 studies were included for qualitative synthesis. Within these studies, patient groups were small and not divided by underlying malignancy and as such all eligible studies including patients with haemorrhagic radiation cystitis were reviewed.

3.0 Treatment options

A variety of treatment options are described for radiation induced hemorrhagic cystitis. These management strategies can be subclassified into systemic medical therapies, hyperbaric oxygen, intravesical, ablative, interventional radiological and definitive surgical techniques. Their advantages, disadvantages and most recent comparative data on clinical efficacy are discussed in detail below.

3.1 Systemic therapies

Medical systemic therapies for haemorrhagic cystitis are appealing as they are non-invasive and circumvent inpatient hospital admission (Table 1). WF10 is an intravenous formulation, manufactured from the drug substance OXO K993, also referred to as Tetrachlorodecaoxygen (TCDO). Its proposed mechanism of action for treating haemorrhagic radiation cystitis relies on the model of a post irradiated bladder being in a state of chronic inflammation. WF10 induces natural immunity

and stimulates cellular defence mechanisms through its actions on natural killer cells (NKTCs), cytotoxic T-lymphocytes, and modification of the monocyte-macrophage system. It reduces inflammation promptly so that a host-derived healing can commence [9]. In one randomised controlled trial, Veerasan *et al.* demonstrated that patients treated with WF10 (n=37) had a significantly decreased rate of recurrent haematuria recurrence after 12 months (47% vs 77%, p=0.01) [9]. A potential limitation to this study is that the treatment failure group in both arms may be over-estimated as details of partial response were not described. Table 1 summarises patients' response rate with WF10 in detail.

Sodium pentosan polysulphate (SPP) is a synthetic sulphated polysaccharide that is used to decrease urothelial permeability by replacing defective GAGs. Sandhu *et al.* assessed SPP, oral administration of 100mg three times daily, for managing radiation induced haemorrhagic cystitis in 60 patients. In total, 51 patients were available for follow-up and the dose was gradually reduced to a maintenance dose of 100 mg in 21 patients due to PR. In 10 patients SPP was stopped due to CR. A limitation with medical therapies, as noted by the authors, is 'time to effect' [10]. The onset of action was 1-8 weeks. In this timeframe, 15 patients required inpatient admission for bladder irrigation; of which 5 required irrigation under general anaesthetic and 14 required blood transfusions [10].

Tranexamic acid has been used to treat urological haemorrhagic emergencies however evidence of efficacy in the haemorrhagic radiation cystitis patient is lacking. It can be administered in the initial resuscitation and conservative management phases of active haemorrhage in patients with prior radiotherapy. As tranexamic acid acts by inhibiting fibrinolysis, attention must be directed at preventing formation of large thrombi with resultant clot urinary retention. Tranexamic acid has been associated with increased risk of thromboembolic events however the evidence not clear. It may be considered in problematic acute surgical bleeding such as in haemorrhagic radiation cystitis however complications of clot retention limit its use. [11]

3.2 Hyperbaric oxygenation

The underlying pathophysiology of radiation cystitis involves a progressive end arteritis that leads to poor tissue oxygenation and eventual tissue ischemia. Necrosis and tissue sloughing ensues with fibroblast deposition on ischaemic tissue layers. Compensatory neovascularisation and telangiectasia leads a friable vascular network with resultant haematuria. Hyperbaric oxygen (HBO) therapy increases oxygen delivery to tissues by increasing the amount of dissolved oxygen in the plasma to induce and restore normal reparation of granulocytes and fibroblasts. Administration of HBO has been shown to induce neo-angiogenesis with restoration of ≤80% of capillary density [12-14]. Studies reporting on outcomes of HBO are mainly retrospective in patients who have failed conservative management for radiation-induced haemorrhagic cystitis. Their main findings are summarised in table 2 with complete resolution of haematuria occurring in 34-87.5% of patients. Commencement of HBO within 6 months of haematuria increases the potential of complete resolution to 96% [15]. With HBO, patients spend 90 minutes 5-7 days per week in a hyperbaric chamber inspiring 100% oxygen between 2-2.4 atmospheres (ATMs). A total of 40 HBO treatments extending over an 8-week period are typically administered [16]. The follow up of patients following HBO varied between 12-120 months, with the majority of patients being followed up for a mean of 24 months of less, as outlined in table 2. As such, the evidence for long-term efficacy of HBO in the treatment of haemorrhagic radiation cystitis is lacking.

3.3 Intravesical therapies

Contemporary evidence and outcomes for intravesical therapies are summarised in Table 3. Response rates with these agents typically range from 60-90%. Historical evidence-based intravesical therapies for the treatment of haemorrhagic radiation cystitis are instillations of formalin and alum [17]. Formalin functions by precipitating cellular proteins within the epithelial layer causing occlusion fixation of the telangiectatic and friable microvasculature. There is limited contemporary evidence on the use of formalin and devastating complications, such as patient mortality, have

been described with concentrations of 2-4%. Notably, lower concentrations demonstrate equivalent clinical efficacy with a lower complication rate [18, 19]. A contemporary study of 8 patients with haemorrhagic radiation cystitis, treated with formalin instillation, 7 of whom had failed other therapies, describes a response in 6, patients. However, 5 of the 8 patients required blood transfusions within 30 days of instillation, one patient developed acute kidney injury and respiratory failure requiring intensive care management. Urinary diversion was required in 2 patients that did not respond and in 1 patient that developed recurrent symptoms [20]. Therefore, formalin is only recommended in cases of intractable haemorrhagic cystitis that may require urinary diversion [21]. Aluminium salts (usually potassium or ammonium aluminium sulphate) act by precipitating proteins on the surface of cells. Intravesical instillation of alum is not as effective as formalin but is associated with an improved side-effect profile and may represent an early treatment option if initial more conservative measures are unsuccessful. [17]

More recently, novel intravesical therapies have aimed to replenish the glycosaminoglycan (GAG) protective layer to reduce exposure of underlying epithelial cells to host urine. Hyaluronic acid is a major mucopolysaccharide than can be instilled into the urinary bladder. It has immunomodulatory properties that enhance connective tissue healing [22]. Epsilon aminocaproic acid inhibits fibrinolysis to counteract urokinase on exposed telangiectatic vessels in the post-radiation bladder and can be instilled into the bladder. Singh *et al*. described intravesical instillation in 37 patients with intractable haemorrhage associated with radiation or chemotherapy induced cystitis and reported a partial or complete response rate in 34 patients (92%) [23]. Other intravesical therapies have been described in smaller case series'. Silver nitrate (0.01-0.4%) was ineffective for managing haemorrhage in 9 patients with radiation cystitis [24]. Several other agents, including prostaglandins, botulinum toxin, polydeoxyribonucleotides and early placental extract, have also been reported with limited response rates [22].

3.4 Ablative therapies

Ablation and coagulation of ruptured submucosal vasculature with laser (yttrium-aluminium-garnet [YAG] and Greenlight©) therapy or argon beam therapies is advantageous as both modalities can immediately control haemorrhage and are associated with complete response in 75-97.5% of cases (Table 4). Disadvantages with these modalities are requirement of general or spinal anaesthesia. Greenlight© laser can ablate blood vessels with selective absorption of green light by intravascular oxy-haemoglobin thereby sparing the surrounding tissue [25]. Conversely, the YAG laser is non-selective and has an increased risk of bladder or bowel perforation in conjunction with irritative post procedural urological symptoms due to sloughing of necrotic tissue [26]. Argon beam coagulation does not use laser technology. Instead, the bladder is filled with argon gas and an argon probe is directed approximately 3mm from the vessel and a monopolar current is aimed towards it. Uniquely, argon ablative therapy has a safety mechanism for preventing perforation as the current follows the path of least resistance and moves onto adjacent tissue after coagulation has been achieved. Also, the depth of ablation can be altered by adjusting power and gas flow settings [5].

3.5 Interventional radiological

There is limited evidence on arterial embolisation for managing haemorrhagic radiation cystitis. Small case series describe clinical scenarios of haemorrhagic radiation cystitis combined with additional causes of intractable haematuria originating from the urinary bladder or prostate gland. In these series, resolution of haematuria varies from 90-100% and is dependent on the underlying patient group requiring embolisation [27, 28]. Long-term resolution of haematuria ranges from 70-81% after a median follow-up of 16-18 months. Loffroy *et al* [29] found that embolisation can be selected to treat any cause of intractable haematuria (including radiation cystitis) as complete resolution occurs in 92.6-100% of patients. Notably, depending on the selectivity of embolization, ischaemic complications occur in 10-62.5% and may include skin or bladder necrosis, gluteal paresis, Brown-Sequard syndrome, and perineal or buttock pain.

3.6 Definitive surgical treatment

Urinary diversion with or without cystectomy can be performed if all other less invasive treatment modalities have failed. One series on 21 patients undergoing cystectomy and urinary diversion for intractable haemorrhagic cystitis demonstrated that 42% of patients developed a complication that was either Clavien-Dindo Grade III or Grade IV during the perioperative period. Furthermore, the 90 day mortality was 16% and overall survival at one year was 84% [8].

4.0 Management algorithm

There are no widely adopted definitive treatment algorithms for managing patients with radiation-induced haematuria. Therefore, definitive and effective treatment of this patient population is often challenging for the urologist. To optimise clinical outcomes in this difficult patient cohort; we propose the following stepwise, evidence-based approach to treatment of the acutely haemorrhagic patient (Fig. 1). A clinical guide to each step in the algorithm can be found in Table 5.

4.1 Haemorrhagic radiation cystitis with active bleeding

Acute active bleeding in the setting of previous pelvic radiotherapy can result in hypovolaemic shock. Therefore, we advocate inpatient admission for patients with acute haemorrhagic radiation cystitis. Initial management involves stabilisation with fluid resuscitation, insertion of a large 24-26Fr 3-way indwelling catheter (IDC), manual washout with extensive clot evacuation and commencement of continuous bladder irrigation (CBI). Tranexamic acid, administered orally, intravenously or intravesically, may be considered in the initial conservative management of urological haemorrhage.[30]

A thorough patient history and physical examination should be performed to exclude other causes of haematuria such as urinary tract infection, anti-thrombotic agents, pre-existing urological malignancy, benign prostatic hyperplasia (BPH), urinary stone disease and known underlying coagulopathies. Laboratory investigations including full blood count, blood urea, serum creatinine and coagulation profile should be performed. Urinalysis and urine culture should be performed to rule out infection.

Urine cytology can be performed if the patient is at risk of bladder cancer however this may be difficult to interpret. Computed Tomography (CT) with intravenous pyelography may be performed to rule out upper tract bleeding.

Rigid cystoscopy should initially be performed in all patients to further rule out bladder malignancy and confirm the diagnosis of radiation cystitis. At this stage further clot evacuation and fulguration with diathermy can be performed at this time if required. If conservative measures fail, ablative therapies should be performed which may lead to immediate control of the bladder haemorrhage. This process can be repeated if required. If ablative resources are not available, then intravesical aluminium may be administered.

When minimally invasive measures are unsuccessful we recommend consideration of bladder preserving urinary diversion with bilateral nephrostomies or an ileal conduit. Embolisation can also be considered at this time. If bleeding persists despite urinary diversion, intravesical formalin at a non-toxic concentration may be considered however definitive cystectomy may at this stage be required. Finally, we suggest consolidation with hyperbaric oxygen in patients undergoing bladder preservation treatment strategies once bleeding has been controlled and the patient is stable.

4.2 Haemorrhagic radiation cystitis with bothersome intermittent bleeding.

Bothersome intermittent bleeding can be defined as multiple episodes of frank haematuria for which patients seek medical attention or microscopic haematuria resulting in a haemoglobin drop that requires medical attention. As detailed above, these patients should undergo thorough clinical investigation to rule out other cause for bladder haemorrhage. Part of this diagnostic work up should initially include a rigid cystoscopy to further rule out other cause for bleeding including bladder malignancy and enable diagnosis of radiation cystitis. Bladder wash out and fulguration or ablation of bleeding or immanently bleeding vessels can be performed at this time.

Hyperbaric oxygen for management of haemorrhagic radiation cystitis has the most robust evidence for efficacy, however it is cumbersome for patients requiring long duration of treatment and a certain level of fitness that many patients with radiation cystitis will not achieve. Patients with intermittent self-limiting episodes of bleeding should be prescribed hyperbaric oxygenation, where possible, and considered for medical systemic or intravesical therapies. There are no direct comparative trials between oral and intravesical therapy for the management of haemorrhagic radiation cystitis. As such, we advocate a step-by-step management algorithm that can be tailored to the specific clinical situation of each patient with consideration of the side effect profile and acceptability of the intervention. These patients should also be offered regular follow-up appointments in the urology outpatients department.

Future perspectives and conclusions

The relationship between novel pelvic radiation techniques and haemorrhagic radiation cystitis will become apparent in future, as symptoms can develop ≥10 years once radiotherapy has been completed. In the interim, many treatment options are available for the management of chronic radiation cystitis, however level one evidence is lacking. Medical systemic therapies are appealing as they are non-invasive but are most efficient for chronic haemorrhagic radiation cystitis. Hyperbaric oxygen therapy is also non-invasive but requires commitment from patients and is not freely available as a healthcare resource. Intravesical therapy is associated with an acceptable short-term response rate, however limited evidence is available on durability. If laser ablative therapies are required, selection of the green light spectrum is preferable due to its more favourable safety-profile compared to YAG-laser. Most importantly, we advocate a stepwise management algorithm with multimodal treatment in patients presenting with severe acute haemorrhagic radiation cystitis.

6.0 References

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GROUP	DRUG	STUDY TYPE	N	MEAN RADIATION DOSE	MEAN NUMBER AND (DURATION OF TREATMENT)	FOLLOW-UP	ADVERSE EVENTS	OUTCOME
VEERASAN, 2004 [9]	WF10 (Immunokine)	Randomised, open arm, two-label	102 (51 in treatment arm)	Not described	10 (6 weeks)	7-52 weeks	Headache, fever	**Treatment** *CR=20 ^TF= 29 Unknown=2 **Control** *CR=8 ^TF=40 Unknown=2
SANDHU, 2004 [10]	Sodium Pentosan Polusulfate	Prospective	60	Not described	180 (21-1745 days)	450 (19–4526) days	nil	*CR=10 **PR= 21 TF=20 Unknown=9

Table 1: Summary of evidence for systemic medical therapies for the treatment of haemorrhagic radiation cystitis.

*complete resolution
**partial resolution
^treatment failure

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GROUP	STUDY TYPE	N	MEAN RADIATION DOSE	MEAN NUMBER OF TREATMENTS	MEAN FOLLOW-UP	OUTCOME
YOSHIDA, 2008 [31]	Retrospective	8	56.6 Gy	19 (10-42), 90min each	15.5 months (2-34)	*CR=7. (87.5%) ^TF=2 (2.5%)
CHONG, 2005 [15]	Retrospective	60	Not described	33 (9-63), 90min each	12 months	*CR= 21 (35%) **PR= 27 (45%) ^TF=10 (17%) Unknown=2 (3%)
DEGENER, 2015 [32]	Retrospective	13	65~Gy (60-74)	34 (6-128), 90min each	68 months (16-142)	*CR = 11 (84%) **PR = 1 (8%) ^TF=1 (8%)
CORMAN, 2003 [33]	Retrospective	57	Not described	33 (9-68), 90 min each	Av not stated (10-120 months)	*CR =21 (34%) **PR = 28 (45%) ^TF =8 (13%) Unknown =5 (8%)
NEHMAN, 2005 [34]	Prospective	7	64 ~Gy	30 (18-57)	24 months (3-53)	*CR = 7 (100%)
POLOM, 2012 [35]	Retrospective	10	72.6 ~Gy	43.4 (8-60)	24.5 months (7-48)	*CR=6 (60%) **PR= 3 (30%) ^TF=1 (10%)
OLIVEIRA, 2015 [16]	Retrospective	176	56.27 ~Gy	36.53 (7-179)	12 (months) (0-108)	*CR=118(67%) **PR= 40 (23%) ^TF=18 (10%)

Table 2: Summary of evidence for hyperbaric oxygen for the treatment of haemorrhagic radiation cystitis.

~Gray
*complete resolution
**partial resolution
^treatment failure

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GROUP	DRUG	STUDY TYPE	N	MEAN RADIATION DOSE	MEAN NUMBER AND DURATION OF TREATMENTS	MEAN FOLLOW-UP	ADVERSE EVENTS	OUTCOME
SCHWALENBER, 2015 [36]	IV chonrdoitin	Observational	16	^^NR	6 x weekly instillation 0.2% chondroitin 40ml	6 weeks	Nil	100% *CR of haematuria, 8 *CR/**PR other symptoms
SHAO, 2012 [37]	IV hyaluronic acid vs HBOT	RCT	36	45-70 ~Gy	Intervention (hyaluronic acid): 40mg weekly x 4, monthly x 2	18 months	nil	HA Group *CR: 50%; **PR: 75%
					Control (HBOT): 30 x daily 60min 2.5atm absolute			Control Group (HBOT) : *CR 45%; **PR 75%
VASSSILIS, 2014 [38]	IV hyaluronic acid	Prospective observational	20	72-74~Gy	4x weekly then 2monthly	6 months	nil	Downgrading of radiation cystitis from Grade III/II 70/ to II/I 55/45%
SINGH, 1992 [23]	Epsilon aminocaproic acid	Observational	37	^^NR	^^NR	^^NR	Nil	Response (combined *CR/**PR) 34 (92%)
WESTERMAN, 2016 [39]	Alum 1%	Retrospective Observational	40	^^NR	1% alum at 250-300cc/hr for variable duration	16.4 months	38%, bladder spasms, transient delirium, UTI	CR 60%, - durable response 54% of responders (1/3 of total)
GOSWAMI, 1993 [40]	Alum 1%	Observational	2/12	^^NR	^^NR	^^NR	Transient low-grade pyrexia	*CR 4, **PR 6
ZIEGELMANN, 2017 [20]	Formalin	Retrospective observational	8	^^NR	1% formalin single instillation in 5/8. 2nd instillation of 1-2% in 2/8 patients. 3rd instillation of 4% in 1/8	8 months	Acute kidney injury, respiratory distress, contracted bladder with urgency, incontinence, bladder neck contracture (in patient who received 3 instillations)	*CR 37.%%, **PR 37.5%, ^ in25%
VICENTE, 1990 [41]	Formalin	Observational	196	^^NR	Formalin 4% and 10%	^^NR	Rectovaginal fistula, hydroutero-nephrosis, extravasation	*CR/**PR: 88%
DEWAN, 1993 [18]	Formalin	Observational	35	Average 68 Gy	Formalin 1%, 2% and 4%	^^NR – up to 17 months	Fever, frequency, dysuria, pain, incontinence, hydronephrosis, VUR, ureteral stenosis, vesicovaginal fistula, death, decreased bladder capacity, death	*CR 89%, **PR 8% at 8 hou with recurrence in 7 patient (median 8 months)
LOJANAPIWAT, 2002 [19]	Formalin	Prospective	19	^^NR	Group 1: 4% formalin instillation 15 min	25 months	Group 1: Anuria, bilateral hydronephrosis, vesicovaginal fistula, septic death	Group 1:*CR 82%
					Group 2: 10% formalin pledgets at bleeding points 15min		Group 2: nil major	Group 2:*CR: 75%, 1 pati required 2nd treatment

Table 3: Summary of evidence for intra-vesical therapies for the treatment of haemorrhagic radiation cystitis.

~Gray
*complete resolution
**partial resolution
^treatment failure

^^not recorded

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STUDY	MODALITY	STUDY TYPE	N	MEAN RADIATION DOSE	MEAN NUMBER OF TREATMENTS	MEAN FOLLOW UP	OUTCOME
WINES, 2006 [5]	Argon beam coagulator	Prospective	7	Not described	1	15 months (6-36)	*CR =6. (86%) ^TF=1 (4%)
RAVI, 1994 [42]	YAG Laser	Prospective	42	68 ~Gy	1	14 months	*CR= 41 (97.5%) ^TF = 1 (2.5%)
TALAB, 2014 [25]	KTP photo selective green light laser	Retrospective	20	Not described	1.3 (1-3)	14 months (1.7-37.1)	*CR=15 (75%) ^TF= 3 (15%) Unknown=2 (10%)
MARTINEZ, 2015 [43]	KTP photo selective green light laser	Retrospective	4	Not described	1	12 months	CR*=3 (75%) **PR =1 (25%)

Table 4: Summary of evidence for ablative therapies for the treatment of haemorrhagic radiation cystitis.

~Gray
*complete resolution
**partial resolution
^treatment failure

[5] Wines MP, Lynch WD. A new minimally invasive technique for treating radiation cystitis: the argon-beam coagulator. BJU International. 2006 Sep: **98**:610-2
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Treatment	Equipment	Method
Acute bladder washout and irrigation	▪ Large (24-26Fr) 3-way IDC ▪ 2L bags of Normal saline (0.9%) for continuous irrigation ▪ Irrigation giving set ▪ Toomey syringe for clot evacuation	▪ Sterile technique with lubrication for standard catheter insertion with large 3-way catheter. ▪ Using large Toomey or catheter syringe, manually evacuate blood clots from bladder via large working channel of the catheter until no further clots and output begins to clear. ▪ Establish irrigation through smaller channel using pump or standard IV giving set raised at 1-2m from the ground (above the height of the patient's bladder) ▪ Continue irrigation as needed. ▪ Repeat manual evacuation as required.
Tranexamic Acid [11]	▪ Need to evacuate clots from bladder prior to administration	▪ Oral dose: 1–1.5 g (15–25 mg kg^{-1}) 2–3 times per day. ▪ I.V. dose: 0.5–1 g by slow injection three times per day, or following initial dose, an infusion of 25–50 mg kg^{-1}over 24 h. ▪ In renal failure, reduce IV dose to 5-10mg/kg
Laser Ablation [44]	▪ 30 degree 24Fr Rigid cystoscope ▪ 2x 5Fr ureteric catheters ▪ Energy source ▪ Laser fibre ▪ 22Fr 3-way indwelling catheter ▪ urine bag ▪ large bore cannula ▪ Normal Saline for irrigation	▪ Rigid cystoscopy ▪ Bilateral open ended 5Fr ureteric catheters ▪ laser set to 80 vaporisation, 30 coagulation (to be used around ureteric orifices), ▪ active bleeding sites targeted first in order to optimise vision. ▪ Systematic lasering of the four quadrants of the bladder ▪ Ureteric catheters remain in situ for 24 h. ▪ Continue bladder irrigation (CBI) until urine clear ▪ Foley catheter & ureteric catheters are removed within 24 hours to minimise new inflammation secondary to foreign body ▪ Repeat process if required
Aluminium [39]	▪ Alum salts (usually potassium alum) 50gm for 5 litres Sterile water irrigation fluid	▪ Dissolve 50gm of alum dissolved in 5 liters of sterile water ▪ Irrigate bladder at rate of 250-300cc/hr ▪ Duration at discretion of the surgeon

Formalin [20]	▪ 100-150ml of Formalin 1% ▪ >18fr 3-way Foley catheter ▪ 2x Fogarty catheter if vesicoureteral reflux ▪ petroleum jelly	▪ Intravesical administration under anaesthetic (spinal or general) following cystoscopic removal of clots and any necrotic tissue, fulguration of any actively bleeding areas and assessment of integrity of bladder wall. Bladder emptied ▪ If vesicoureteral reflux, place Fogarty catheters to occlude ureteric orifices. Protect external genitalia with petroleum jelly ▪ Instil 1% formalin through 18f catheter under gravity at <15cm pressure(3rd channel spigotted). Clamp catheter and apply traction to avoid leakage around the balloon into the urethra. Instil for 10-15 minutes. Empty bladder completely and resume copious normal saline irrigation.
WF10 [45]	▪ WF 10 dose: 0.5ml/kg, diluted in 250ml 5% dextrose	▪ IV administration over 2 hours ▪ Duration: daily for 5 consecutive days, every 3 weeks for 2-4 cycles
Sodium Pentosan Polysulphate (SPP) [46]	▪ SPP 100mg tablets	▪ Oral administration of SPP 100mg three times daily ▪ Treatment cessation with complete resolution of haematuria ▪ No monitoring required

Table 5: Clinical guide to administration of treatments for haemorrhagic radiation cystitis

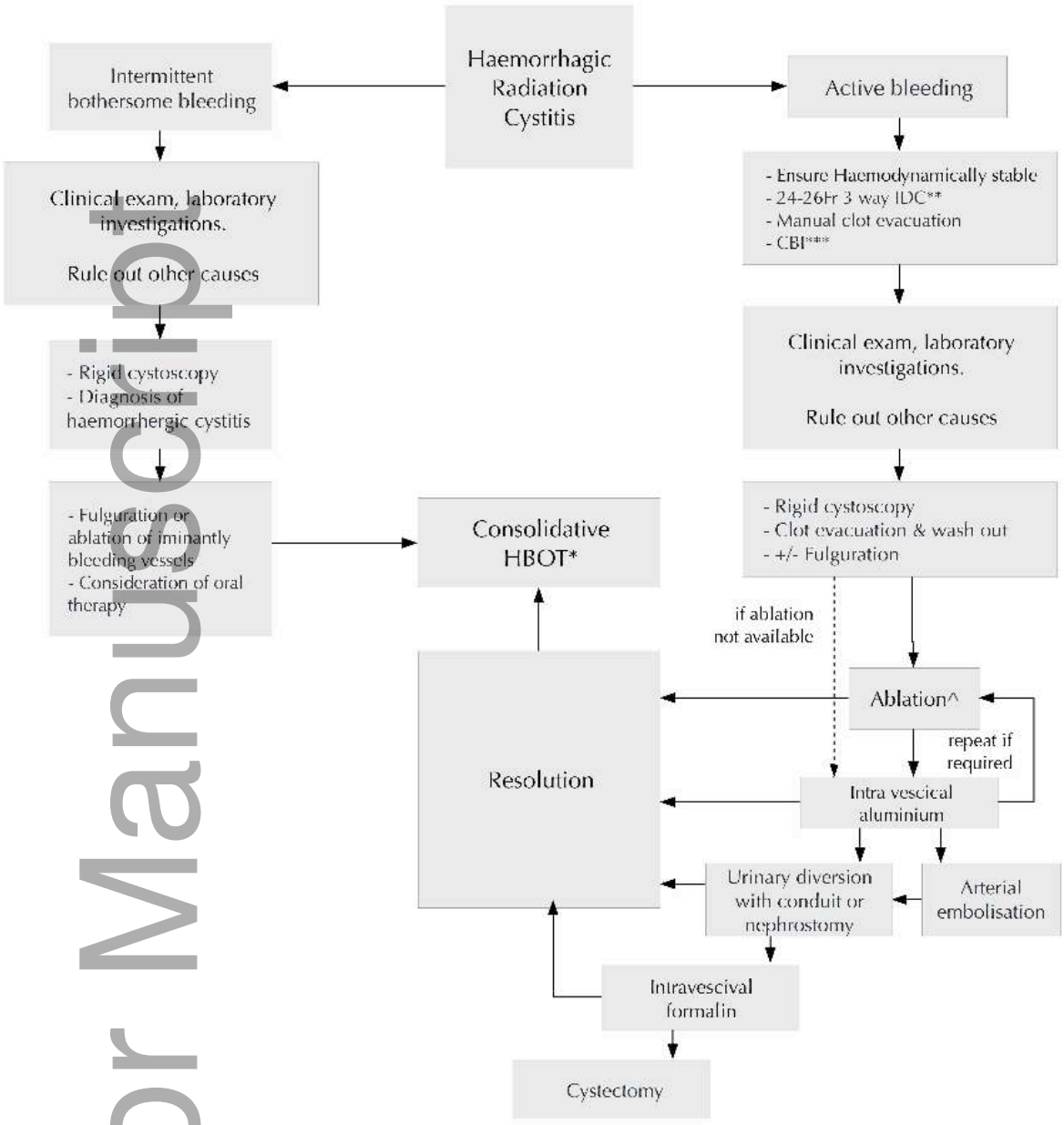

Figure 1: Practical management algorithm for radiation induced haemorrhagic cystitis

*Hyerbaric Oxygen Therapy
** Continuous Bladder Irrigation
^Bladder mucosal ablation therapy

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