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Research Article

Radiation-induced haemorrhagic cystitis after prostate cancer radiotherapy: factors associated to hospitalization and treatment strategies

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ABSTRACT

Background: Late onset of radiation-induced haemorrhagic cystitis (RHC) after radiation therapy (RT) for prostate cancer (PCa) may present or evolve severely, requiring hospitalization with invasive interventions. In the present study, we have analysed the prevalence and risk factors associated with the onset of RHC.

Methods: From January 2002 to May 2017, 1421 patients undertook RT for PCa as a primary, adjuvant, or salvage treatment option. RHC presented in 5.6% (n = 80) of the patients; the diagnosis was based on clinical and endoscopic characteristics. Variables in observation included patients, tumours, and RT-dosimetry characteristics. Patients with a previous history of bladder cancer were excluded. Univariate (Student *t*/Chi square) and uni-/multivariate Cox regression analysis were performed; the events and time-points were hospitalization and time-to-event, respectively.

Results: There were 80 patients with a mean age at RT of 70.1 years (SD 6.4), mean time lag to RHC of 43.9 months (SD 37.5). Median Emergency attendance was two and three times for patients without/with hospitalization, respectively. There were in total 64 admissions with invasive treatment required in 26/36 (72.2%) of the patients hospitalised, including transurethral fulguration in 22 and radical cystectomy in 5. Patients at higher risk of hospitalization were those undertaking antiplatelet/anticoagulant treatment (HR:3.30; CI 95%:1.53–3.30; $p = 0.002$) and those treated with salvage RT with higher bladder volume receiving >70 Gy (bladder V70) (HR:1.03; CI 95%:1.01–1.05; $p = 0.027$). At receiving operating characteristic analysis, the cutoff for bladder V70 was 29%.

Conclusion: Nearly half of patients presenting RHC may require invasive treatment including cystectomy. Risk factors associated with hospitalization are patients undertaking antiplatelet/coagulant treatment and bladder V70 > 29% in salvage RT patients.

1. Introduction

Radiotherapy (RT) is one of the treatment options available for patients affected by prostate cancer (PCa); it is indicated for primary treatment, in an adjuvant regime, or in the setting of salvage treatment after biochemical recurrence postradical prostatectomy [1,2]. However, adverse events may occur acutely or during follow-up due to toxic effects on the gastrointestinal (GI) and/or of the genitourinary (GU) systems.

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Radiation-induced cystitis (RC) includes bladder toxicities of Grade ≥2 according to the Radiation Therapy Oncology Group (RTOG) classification and refers to different degrees of low urinary tract symptoms (LUTS) and haematuria [3].

Incidences of RC reported in literature range between 2% and 59% of patients treated for pelvic cancers: this wide range may be due to the heterogeneity of definitions adopted in literature, which may include acute and/or late toxicities, or even all types of RC (including bladder loss capacity, LUTS, etc.) or just the subgroup of the radiation-induced haemorrhagic cystitis (RHC) [4,5].

The RHC is among the most threatening RT complications as it may account for a significant proportion of urological emergency (A&E) admissions and/or hospitalization [6]. Treatment options involve a variety of approaches depending on the severity of the haematuria, including conservative managements like hydration and/or bladder irrigation up to the endoscopic fulguration or even cystectomy.

RHC can develop from 6 months to as long as 20 years after RT, with a mean latent time of 35 months [7].

In the present study, we report the prevalence of RHC in a single-centre cohort of patients who received RT for PCa (either as primary or as adjuvant/salvage treatment), the types of management undertaken, and the risk factors associated with hospitalization.

2. Patients and methods

A cohort of 1421 patients that underwent RT for PCa in a single center was retrospectively analysed from January 2002—corresponding to the local establishment of the three-dimensional conformal external beam RT (EBRT) with high energy linear accelerator —to May 2017. We included patients that received RT as a primary treatment, in adjuvant regime or as a salvage option in case of biochemical recurrence after radical prostatectomy.

The diagnosis of RHC was based on the combination of visible haematuria requiring admission to A&E not related to urinary tract infection, and of cystoscopic findings; diagnostic criteria on this latter regard included the absence of bladder lesions and/or stones as well as the presence of pale mucosa, diffused telangiectasia and/or petechiae, or even ulcerations, as described and standardised by Fajardo in 1978 [8]. Moreover, urine cytology was always performed to further rule out bladder urothelial carcinoma *in situ* (CIS): in case of suspicious or positive findings, random bladder biopsies and CT scan were performed.

Patients with a history of bladder cancer (BCa) were excluded, as well as patients diagnosed of BCa within 6 months from the diagnosis of RHC (see Table 1 with inclusion/exclusion criteria). In patients with later diagnosis of BCa, the RHC follow-up was discontinued at the date of the latest control prior to the BCa diagnosis. For the remainder of the patients, follow-up was counted until the latest outpatient clinic visit or the date of death.

The primary endpoint consisted of the identification of factors associated with Grade ≥3 RTOG bladder toxicity requiring hospitalization; secondary endpoint included a descriptive narration of the treatments undertaken as well as their efficacy and morbidity. Events and time-points consisted of hospitalization (yes vs. no) and time-to-event, respectively. Patients not requiring hospitalization were labeled as Group 1, those who needed hospital admission were identified as Group 2.

Among the variables taken into account for analysis, there were patient's comorbidities, antiplatelet/coagulant therapy, age at the time of RT, indication of RT, fraction dose, percentage bladder volume receiving 70 Gy (bladder V70), mean bladder dose, acute bladder toxicity during RT, number of emergency room attendance, number of hospital admissions, and treatment for RHC. The bladder V70 parameter was chosen according to the findings of Schaake et al and measured on the outer layer of the bladder wall [9].

Table 1
Inclusion/exclusion criteria

Inclusion criteria
Patients with diagnosis of prostate cancer
Patients treated with radiotherapy for primary tumour, or in adjuvant/salvage regime after radical prostatectomy
Patients with visible/gross haematuria and endoscopic characteristics of radiation-induced haemorrhagic cystitis (RHC) according to predefined criteria [8]
Exclusion criteria
Patients with past medical history of bladder cancer
Diagnosis of bladder cancer within 6 months from the diagnosis of RHC
Suspicious or positive urine cytology
Patients with radiation therapy (RT) for other diseases
Patients presenting RHC with RT performed in other centres

For patients requiring hospitalization, continuous bladder irrigation, transurethral fulguration (TUF) of the bladder and cystectomy were the treatment modalities adopted according to the gravity and/or persistency of haematuria. TUF was performed with low-energy monopolar setting (≤50 Hz) in the bleeding spots and areas with telangiectasia [10]. Bladder instillations with hyaluronic acid (HA) and hyperbaric oxygen therapy (HBOT) were planned after haematuria remission (either with or without hospitalization) to prevent recurrence, in an ambulatory regime.

Statistical analysis included descriptive statistics of the variables in observation (standard deviation, median and interquartile range—IQR—25–75), univariate (Student *t* and Chi square), and uni-/multivariate Cox regression analysis performed to assess risk factors for hospitalization. Relevant cutoff values were calculated by means of the Receiving Operating Characteristic (ROC) curve analysis. Tests significance level was set at P values <0.05 (R Statistical Software).

3. Results

After screening for the inclusion/exclusion criteria, a total of 80 PCa patients treated with RT presented RHC in the period in observation, corresponding to the 5.6% of the overall cohort of RT patients, and were included in the analysis. Half of the patients undertook primary RT, and another half received salvage RT; no patient in the final cohort underwent adjuvant RT.

The median follow-up of the patients was 36 months (IQR: 18.75–49.25). Most of the patients harbored intermediate (40%) and high risk (33.75%) PCa according to the National Comprehensive Cancer Network risk stratification [2]. In 97.5% of the cases, a three-dimensional conformal RT was undertaken, with a median fractionation of 1.8 Gy. The demographics of patients are detailed in Table 2.

Out of 80 patients (55%; Group 1), 44 attended A&E at our institution because of intermittent haematuria that remitted either spontaneously with hydration or temporal catheterization with/without bladder wash-out; median times of A&E attendance was 2 (IQR 1–4).

Only one patient in this subgroup of patients received HA instillations, completing the induction course (1-weekly ×6) with no maintenance instillation performed.

Hospitalization was needed in the remainder 36 patients (45%; Group 2), due to persisting haematuria requiring continuous bladder irrigation and/or urgent endoscopic bladder clot washout in the theater; median A&E attendance prior to hospitalization was three times (IQR: 1–6) because of haematuria, dysuric symptoms

Table 2
Patients' demographics.

	Total sample N = 80	Group 1 (no hospital admission) N = 44	Group 2 (hospital admission) N = 36	*P*
Age at the RT (SD)	70.1 (6.4)	68.8 (6.5)	71.4 (6.1)	0.067
Diabetes mellitus (SD)	24 (30%)	11 (25%)	13 (36.1%)	0.646
Hypertension (SD)	53 (66.25%)	25 (56.8%)	28 (77.7%)	0.354
Anticoagulant or/and antiplatelet treatment	20 (25%)	5 (11.3%)	15 (41.6%)	0.012
NCCN prostate cancer risk group				
- Very low risk	4	0	4	0.011
- Low risk	4	0	4	
- Intermediate risk	32	20	12	
- High risk	27	15	12	
- Very high risk	10	8	2	
- N/A	3	1	2	
Indication for RT				
- Primary	40 (50%)	18 (40.9%)	22 (61.1%)	0.150
- Adjuvant	0	0	0	
- Salvage	40 (50%)	26 (59.1%)	14 (38.9%)	
Type of RT				
- Brachytherapy	1	0	1	0.45
- 3D CRT	1	43	35	
- IMRT/IGMT	1	1	0	
Fractionation-Gy (median)	1.8	1.8	1.8	0.972
RT of lymph nodes				
• Yes	68 (85.0%)	38 (86.3%)	30 (83.3%)	0.175
• No	12 (15.0%)	6 (13.7%)	6 (16.7%)	
GU acute toxicities (during RT)				
- Visible/gross haematuria	1 (1.25%)	1 (2.7%)	0 (0%)	0.980
- Acute urine retention	1 (1.25%)	1 (2.7%)	0 (0%)	0.980
- Urinary tract infection	1 (1.25%)	1 (2.7%)	0 (0%)	0.980
- Dysuria	77 (96.25%)	41 (93.2%)	36 (100.0%)	0.714
Hormonal treatment	38 (47/5%)	19 (43.18%)	19 (52.7%)	0.928
Mean bladder dose (Gy)	60.5 (9.7)	61.4 (9.3)	59.6 (10.1)	0.432
Mean bladder V70 (%)	35.0 (27.8)	32.4 (26.8)	37.8 (28.8)	0.395
Time from RT to cystitis, months	43.9 (37.5)	42.3 (35.1)	45.7 (40.3)	0.682

RT, radiotherapy; SD, standard deviation; NCCN, National Comprehensive Cancer Network; 3D CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; IGRT, imaging-guided radiotherapy; Gy, gray.

and/or catheter tamponade for clots. Nearly half of these patients (n = 15/36; 41.66%) were hospitalised for more than once (IQR: 2–3). There were in total 64 hospital admissions, with 26 patients (72.2% of Group 2) requiring invasive procedures in theatre and with a mean hospital stay of 7 days (IQR: 4–11.75).

The treatment modalities undertaken are summarised in Table 3. All patients were admitted with continuous bladder irrigations. TUF was commonly performed (n = 22, 61.1%) with six and two patients needing a second and a third TUF during the follow-up, respectively. Ambulatory consolidative treatment was performed in seven patients, six with HA instillations (median of 6 instillations), and one with HBOT. Only one of these patients progressed to refractory haematuria requiring cystectomy.

Blood transfusions were needed in 38.9% of Group 2 patients with a median of 2 units transfused per patient (IQR: 2–5.5), including all the admissions recorded.

Table 3
Treatments undertaken in patients hospitalised.

Treatment	N (%)
Bladder catheter + washout	36/36 (100%)
TUF (+ second or third repeated TUF)	22/36 (61.1%) (+6 + 2)
Cystectomy	6[a)]/36 (16.6)
Blood transfusion	14/36 (38.9)
Consolidation treatment:	
-HA bladder instillation	6/36 (16.6)
-HBOT	1/36 (2.7)

TUF, transurethral fulguration; HA, hyaluronic acid; HBOT, hyperbaric oxygen therapy.
[a)] Includes one patient undertaking radical cystectomy for bladder cancer.

Bladder urothelial cancer was detected in five patients during the follow-up, after >6 months from the diagnosis of RHC, with one patient requiring radical cystectomy in the follow-up.

Radical cystectomy was also performed in further five RHC patients as a result of severe haematuria not responding to conservative management (n = 3) and of remittent RHC in a low-volume bladder capacity associated to severe dysuria (n = 1). All these patients experienced a range of complication: two patients experienced Grade II (ileus requiring parenteral nutrition), two patients had a Grade IIIb (ileal anastomosis leakage at 8 days post-op, and ileal conduit fistula at 60 days post-op, both requiring surgical interventions), and one developed a Grade IV (sepsis requiring intensive care unit management) according to the modified Clavien–Dindo classification for postoperative complications [11]. One of these patients eventually died 6 months after surgery for the complications of pseudomembranous colitis that required total colectomy.

At univariate analysis, clinical variables associated to the admission to the hospital were time from RT to diagnosis of HRC (HR:0.91; CI 95%:0.88–0.98; $p = 0.041$) and anticoagulant treatment (HR:2.89; CI 95%:1.40–3.38; $p = 0.030$).

At multivariate Cox regression analysis (see Table 4), anticoagulant/antiplatelet treatment and bladder V70 in the setting of salvage RT patients were found to be the only variables significantly associated to the events (HR:3.30; CI 95%:1.53–3.30; $p = 0.002$, HR:1.03; CI 95%:1.01–1.05; $p = 0.027$, respectively). At ROC, the cutoff value for the bladder V70 was 29%.

A sensitive analysis was performed by removing from the Cox regression analysis patients with BCa detected in follow-up, and no difference of the outcomes was observed.

Table 4
Multivariate Cox model analysis.

	Adjusted model		*p*
	HR	CI 95%	
Time from RT to RHC	0.96	0.92–1.01	0.072
Antiplatelet/anticoagulant treatment	10.9	4.23–10-7	<0.001
Age at the onset of RHC	1.09	0.98–1.22	0.110
Bladder v70 in salvage RT patients	1.03	1.01–1.05	0.027
Type of RT (primary vs. salvage)	1.15	0.55–1.35	0.650

RT, radiotherapy; RHC, radiation-induced haemorrhagic cystitis.

4. Discussion

RHC has been shown to be a serious late adverse event of RT: although reported rates range from 5% to 10% of patients with prior pelvic RT, it may account for a significant proportion of A&E admission for urological causes. Recently, an Australian study reported a 7.2% of RT patients admitted from A&E for RT complications (90% after prostate RT), with RHC accounting for more than half of the cases; similarly, two-thirds of the RT complications required surgical intervention, with bladder TUF for RHC being the most common one [6]. Our study is in line with these latter figures, with a prevalence of 5.6% of prostate RT patients experiencing HRC, and a median of three attendances per patient to our A&E; nearly half of these patients required hospitalization, requiring a variety of low urinary tract manipulations.

Factors associated with the development of RHC have been investigated in few studies with modern series of EBRT patients; although Martinez-Ribas et al could find a relationship with the anticoagulant/antiplatelet therapy at univariate analysis, in both publications the authors failed to identify at multivariate analysis statistically significant variables associated to RHC [5].

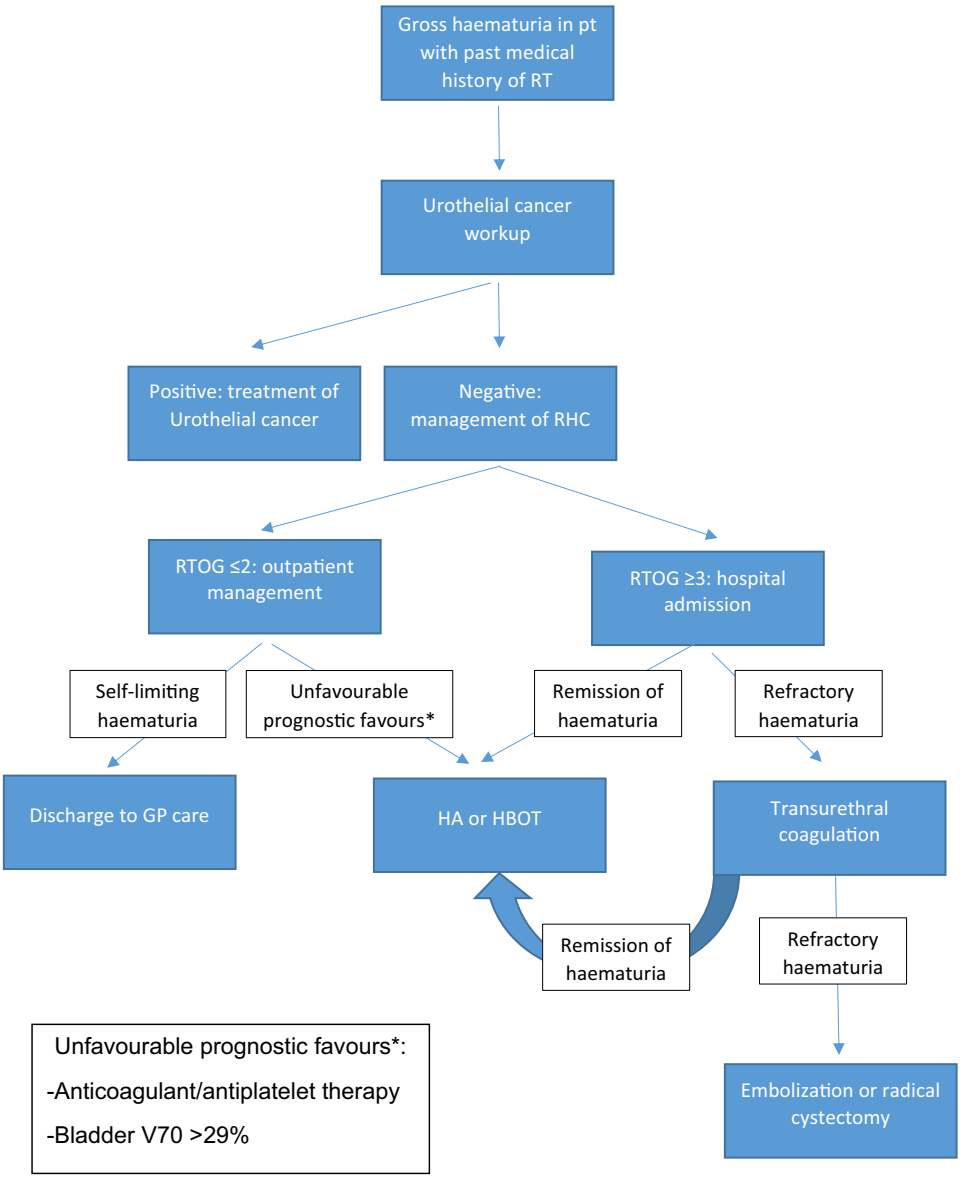

Figure 1. Diagnostic and therapeutic pathway for patients presenting gross haematuria with past medical history of prostate radiotherapy.

To identify patients at higher risk for hospital admission and invasive management, we looked at factors associated with hospital admission, finding at multivariate analysis the anticoagulant/antiplatelet therapy and bladder V70 in the subgroup of salvage RT patients as factors significantly associated to the events. This latter finding is consistent with a recent publication regarding a cohort of salvage RT patients after radical prostatectomy biochemical failure where the relevant dosimetric parameter was associated with a significantly higher risk to develop a Grade >2 late genitourinary toxicity (HR 1.05, CI 95%: 1.02–1.08. $p = 0.001$) [12]. The association of anticoagulant/antiplatelet therapy with a severe degree of RHC is very much intuitive as it is likely the result of the induced bleeding diathesis on an affected urothelium. On the other hand, the role of bladder V70 in patients receiving salvage RT after radical prostatectomy could be multifactorial: from one side, the treatment of the surgical field expose to a direct effect of the radiations to the bladder; moreover, it must be noted that some of these patients may suffer a certain degree of incontinence (for surgery or aging) which might prevent them in keeping a full bladder during the RT sessions being this latter described as a protector to GU and GI toxicity [13].

While bladder washout and TUF are established first-line treatments, HA and HBOT are treatment options usually adopted as consolidation therapy to prevent the recurrence of haematuria after the resolution of an acute episode [14] [15].

In our series, all patients were initially managed with bladder washout (either at A&E or as inpatients) and TUF was necessary for nearly two-thirds of patients requiring hospitalization, with six of them undertaking multiple TUF and four patients (plus further two patients with metachronous BCa) ending up with radical cystectomy.

Eight patients, one of the non-hospitalised group and seven of the hospitalised group, received a consolidation therapy, with only one nonresponding to the treatment and requiring finally a radical cystectomy. Most of these patients received HA (n = 7) as HBOT was logistically difficult to get access to. Although HBOT has been more extensively investigated, the intravesical instillation of HA (+/− chondroitin sulfate—CS-) in the setting of pelvic radiation cystitis is a more recent therapeutic option: Gacci et al found a significant improvement in patients who developed severe LUTS after prostate RT in a cohort of 80 patients undergoing intravesical instillation of HA + CS [16]. In a head-to-head comparison, 36 RHC patients were randomly assigned to receive either HBOT or HA, and no differences in efficacy were recorded at all the time-points, suggesting that both therapies are equally effective [17].

Cystoprostatectomy is the last resort for RHC refractory to all the conservatory treatment options as it is strongly associated with severe comorbidities and with a higher risk of intra-/post-operative mortality: in our cohort, three out of five patients (60%) undergoing cystectomy with final histology of actinic cystitis experienced severe complications (Clavien–Dindo Grade ≥3), and one patient died as a result of later complications of the surgery at 6-month post-op. These results are consistent with the outcomes published by Linder et al with 42% of severe complication rate and 16% of mortality rate, respectively, within 90 days from surgery [18].

Our findings may help practitioners in identifying those RHC patients at higher risk to eventually prompt prophylactic measures. An emerging option is the glycosaminoglycan replenishment therapy for patients experiencing acute bladder toxicity during pelvic RT: one pilot study showed a benefit of the instillation of chondroitin sulfate in a small cohort of 20 female symptomatic patients receiving pelvic RT; a further randomised controlled trial with prophylactic HA + CS instillation in PCa patients receiving RT is ongoing [19] [20].

AS a result of our outcomes, we have established a protocol to undertake appropriate actions in an attempt to reduce the risk of progression of RHC after the first presentation of haematuria; we strongly believe that its application can be generalised although further studies might be needed (see Fig. 1).

Our study has some limitations: it is a retrospective study, and relevant confounding factors (like selection bias) may be present. We have not weighted our findings against the rest of the RT cohort during the study period; however, the study design intentionally involved only the patients with diagnosis of RHC as the primary endpoint consisted in identifying factors associated with bladder toxicity requiring hospitalisation and invasive treatment.

Also, we were unable to measure how the patients' quality of life was affected, as no patients' reported outcomes tools were used due the retrospective nature of the study; however, it is reasonable to estimate that with several admissions to A&E, eventual hospitalization ± the relevant invasive manoeuvres, patients with RHC have a severely impaired quality of life.

Finally, we believe that on the basis of this study's outcomes future trials could be undertaken with better patients' selection and appropriate planning of treatment strategies.

5. Conclusion

RHC is a fearsome late complication of prostate RT even in the modern era of RT. Antiplatelet/anticoagulant therapy and bladder V70 > 29% are the factors associated with the need of patients' hospitalization. A variety of treatment options are available, although they are associated to an impairment of quality of life and severe risk of complications. Prophylactic measures in patients at higher risks of severe RHC may prevent the progression of the disease, but further investigations are needed.

Conflicts of interest

None.

Abbreviations

RT	radiotherapy
PCa	prostate cancer
GU	genitourinary
GI	gastrointestinal
RC	radiation-induced cystitis
RTOG	Radiation Therapy Oncology Group
RHC	radiation-induced haemorrhagic cystitis
A&E	accident and emergency department
EBRT	external beam radiotherapy
BCa	bladder cancer
Bladder V70	percentage of bladder volume irradiated with 70 Gray
TUF	transurethral fulguration
HA	hyaluronic acid
HBOT	hyperbaric oxygen therapy

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