Incidence and Morbidity of Radiation-Induced Hemorrhagic Cystitis in Prostate Cancer

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OBJECTIVE To determine if reported incidence rates of hemorrhagic cystitis after radiation therapy for prostate cancer are accurate, to investigate the effect of different radiation modalities on the development of hemorrhagic cystitis and to assess its morbidity and treatment.

MATERIALS AND METHODS A retrospective chart review was completed of 709 patients at 2 Detroit Medical Center hospitals who underwent radiation therapy for prostate cancer between January 2000 and September 2015. In patients who developed hemorrhagic cystitis, we analyzed the incidence, radiation modality, morbidity, treatment, and complications.

RESULTS The incidence rate of hemorrhagic cystitis after radiation for prostate cancer was 11.1%. There was no significant difference between external beam and intensity-modulated radiation therapy and the development of hemorrhagic cystitis (P = .18). Patients developed hemorrhagic cystitis an average of 79.1 months (4-230 months) after radiation. The average number of admissions was 2.5 (1-9) with an average length of stay of 7.6 days (1-42 days). Fifty-two percent of patients required blood transfusion with an average of 4.3 units transfused per patient (1-33U). The most common treatment was cystoscopy with fulguration/clot evacuation in 86% of patients. Complications included urinary tract infection, acute kidney injury, urosepsis, and even death.

CONCLUSION The incidence of hemorrhagic cystitis following radiation therapy for prostate cancer is under-reported in the literature. Hemorrhagic cystitis is associated with high morbidity and complications for patients, requiring multiple hospitalizations, blood transfusions, and procedures. Advances in radiation have not significantly reduced the risk of developing hemorrhagic cystitis. UROLOGY 131: 190–195, 2019. © 2019 Elsevier Inc.

Hemorrhagic cystitis (HC), or the presence of blood in the urine concomitant with irritative bladder pain, is a known side effect of pelvic radiation. It occurs secondary to obliterative endarteritis from hypoxia which causes atrophy and fibrosis of the mucosa. Ulceration of the mucosa leads to the development of fragile telangiectatic blood vessels that easily hemorrhage.[1] Cystoscopy shows white atrophic mucosa with telangiectasia.[2] Most studies in the literature quote the incidence of HC following pelvic radiation to be ~5%.[1-5] Mean delay in presentation is 2-3 years, but chronic radiation-induced cystitis can appear longer than 10 years after radiation.[2,3] These studies do not take into account that the incidence of HC increases with time, as symptomatic hematuria can develop more 5 years after treatment.[4,5]

Well-established treatment modalities for HC include bladder irrigation, cystoscopy with fulguration/clot evacuation, instillation of intravesical agents, hyperbaric oxygen therapy (HBO), and urinary diversion with or without cystectomy.[5] HC is a challenging problem for urologists, as patients often require multimodal treatment. Morbidity and complications of the disease have yet to be fully assessed in the literature. In this study we sought to investigate the difference in the incidence of HC by radiation modality as well as the incidence, treatment and associated morbidity of HC after radiation therapy for prostate cancer at our institution.

METHODS

We completed an institutional review board-approved, retrospective chart review of 736 patients who underwent radiation therapy for prostate or bladder cancer from January 1, 2000 to

Funding: None.
All the authors declare no conflict of interest.

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Submitted: December 17, 2018, accepted (with revisions): May 30, 2019

https://doi.org/10.1016/j.urology.2019.05.034
0090-4295

September 20, 2015. Data were obtained from the HDM coding and abstracting system. We first identified patients with prostate or bladder cancer who underwent radiation therapy using diagnosis codes 185, 188.0-188.9, 909.2, V15.3, V10.51, and V10.46, with procedure codes 92.20-92.2. Then we used the same system to subcategorize patients who also developed radiation/HC using cystitis codes 5950-5953, 595.9 and Hematuria codes 599.70 599.71 599.72. Inpatient and outpatient records from 2 Detroit Medical Center hospitals (Detroit Receiving and Harper Hutzel Hospital) were reviewed using the electronic medical record. Patients who did not have urologic documentation of HC or had radiation therapy for another primary malignancy that did not include prostate or bladder cancer, were removed. Patients were included those had radiation at outside institutions; however, admissions to outside hospitals were not included in the study. The primary outcome was the incidence of HC after radiation for prostate cancer. Among patients who developed HC, we analyzed patient demographics, prostate cancer stage and Gleason score, incidence, radiation modality, morbidity, treatment, and complications. Given the small population of patients who received radiation therapy for bladder cancer ($n = 27$) found in our review, these patients were not included in the analysis; therefore, our patient population included a total of 709 patients who underwent radiation therapy for prostate cancer. Each patient with HC was classified using the CTCAE version 4.0 grading system for hematuria. Data were analyzed with IBM SPSS Statistics v.19.0 (IBM Corp., Armonk, NY), using Pearson's chi-square and Fisher's Exact Test. All significance tests were 2-tailed, and a *P*value of ≤.05 was considered statistically significant. Statistical analysis was used to determine if there was a significant difference between the type of radiation modality and development of HC, as well as the time to HC development. We used a Kaplan-Meier curve to plot the HC-free survival after radiation for prostate cancer over time.

RESULTS

Incidence

From 2000 to 2015, 709 patients underwent radiation therapy for prostate cancer. Of these patients, 79 (11.1%) developed HC. In the patients who developed HC, 92.5% were African American (AA), 7.5% were Caucasian and the average age at radiation was 69 years old (48-89). According to the CTCAE version 4.0 grading system for hematuria, most patients with HC had grade 3 hematuria (60/79, 76%), followed by grade 2 (8/79, 10%), grade 4 (7/79, 9%), and grade 5 (4/79, 5%); no patients had grade I hematuria (Table 1). When looking at staging of prostate cancer at the time of radiation, the most common stage was T1c in 27% of patients (22/79). Only 1 patient had T4 disease and 1 had lymph node involvement (T3bN1). Unfortunately, 33% (26/79) of patients had an unknown stage of prostate cancer at the time of radiation (Table 2). The most common Gleason score was 3 + 4 in 24% of patients (19/79) followed by Gleason 3 + 3 (16%, 13/79 patients); however, 35% of patients (28/79) had an unknown Gleason score (Table 2).

Radiation

Of the 79 patients who developed HC, radiation treatment included 50% external-beam radiation therapy (EBRT), 13.9% intensity-modulated radiation therapy (IMRT), 8.5% mixed neutron/photon EBRT, 7.6% ERBT with brachytherapy, 7.6% unknown type, 4.9% mixed neutron/photon IMRT, 5% adjuvant radiation, and 2.5% salvage radiation. The highest incidence of HC was after mixed neutron/photon IMRT (19%), and the lowest was after brachytherapy (0%). Although a higher incidence rate of HC was seen with EBRT (16.7%) compared to IMRT (10.5%), there was no statistically significant difference ($P = .18$) (Table 3). Furthermore, there was no significant difference between the development of HC and EBRT vs mixed neutron/photon EBRT ($P = 1$) or IMRT vs mixed neutron/photon IMRT ($P = .28$). The only statistical significance found was between brachytherapy and all other types of radiation ($P = .001$) as no patient who underwent solely brachytherapy developed HC. The highest average dose of radiation was given in IMRT (78.1Gy; median 76.7Gy; STD 14.8) and EBRT (69.8Gy; median 75GY; STD 17.6); however, 59% (23/39) of patients who received EBRT and developed HC had an unknown dose of radiation. Forty percent (30/79) of all HC patients had an unknown dose of radiation (Table 3).

Treatment

Patients developed HC an average of 79.1 months (range 4-230; median 68; STD 55.2) after radiation. Using a Kaplan-Meier curve, we plotted HC-free survival over time in months. We found that overall by 230 months, HC-free survival was 72.5% with a mean time to HC of 110 months (95% CI 104.5-115.8) (Fig. 1). When comparing all different radiation therapies, HC-free survival was 71.3% at 197 months after EBRT ($n = 220$) (95% CI 263-304) and 82.7% at 88 months after IMRT ($n = 105$) (95% CI 179.2-209.6). No significant difference was found between the 2 treatments and HC-free survival ($P = .919$) (Fig. 1). A limitation of this data is that only 562/709 patients

Table 1. CTCAE version 4.0 grading system for hematuria. The number of study patients with hemorrhagic cystitis ($n = 79$) and their corresponding hematuria grades are shown

Grade	Definition	Number of HC Patients
Grade 1	Asymptomatic; clinical or diagnostic observation only; intervention not indicated	0
Grade 2	Symptomatic, urinary catheter or bladder irrigation indicated; limiting instrumental activities of daily living	8
Grade 3	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic, or operative intervention indicated; limiting self-care activities of daily living	60
Grade 4	Life-threatening consequences; urgent radiologic or operative intervention indicated	7
Grade 5	Death	4

HC, Hemorrhagic cystitis.

Table 2. Stage and Gleason Score of patients who developed hemorrhagic cystitis after radiation for prostate cancer

Prostate Cancer Characteristics	No. of Patients	% of HC Patients	
Stage	T1c	22	27
	T2a	16	20
	T2b	6	8
	T2c	2	3
	T3a	2	3
	T3b	3	4
	T4	1	1
	T3bN1	1	1
	Unknown	26	33
Gleason score	3 + 3	13	16
	3 + 4	19	24
	4 + 3	2	3
	4 + 4	9	11
	3 + 5	2	3
	4 + 5	6	8
	Unknown	28	35

HC, Hemorrhagic cystitis.

had known radiation dates which included 74/79 patients with documented HC.

The average number of hospital admissions was 2.5 (range 1-9; median 2; STD 2), with an average length of stay of 7.6 days (range 1-42; median 4; STD 12.9). Fifty-two percent (41/79) of patients required blood transfusion, with an average of 4.4U transfused per patient (range 1-33U; median 1; STD 7.1). For treatment of HC, the most common modality was cystoscopy with fulguration/clot evacuation (86%). Patients required an average of 2.2 cystoscopies (range 1-11; median 1.5; STD 2.2). Other treatments included intravesical aminocaproic acid (11.4%), HBO, 11.4%, formalin (10.1%), alum (6.3%), urinary diversion (6.3%), and silver nitrate (2.5%).

Complications

The most common complications included urinary tract infection (30%), acute kidney injury (24%), urethral stricture (15%), urosepsis (14%), hydronephrosis (5%), bladder neck contracture (5%), bladder rupture (3.8%), fistula (2.5%), and death (5%).

Four patients expired due to complications of HC. One patient was admitted with hematuria requiring 4 units of packed red blood cells (pRBCs). While admitted, he developed seizures requiring intubation and ICU admission. After a 7-day course, he went into asystole and could not be resuscitated. Another patient was admitted with hematuria and septic shock due to urinary tract infection. He was intubated, started on pressors, and admitted to the ICU. His condition did not improve and care was eventually withdrawn. One patient presented with symptomatic anemia due to hematuria. He required 4 units of pRBCs and cystoscopy with fulguration. This patient developed multiorgan failure, and care was eventually withdrawn. The final patient presented with persistent hematuria requiring 4 units of pRBCs and cystoscopy with fulguration. He could not be extubated after surgery and developed multiorgan failure while in intensive care. He was eventually transferred to hospice and expired.

DISCUSSION

Radiation-induced HC is a complication of pelvic radiation that can cause high morbidity for patients. The reported incidence in the literature varies; however, most series report an incidence of ~5%[1-4] but do not take into account that HC can develop even 10 years after radiation. A recent study by Afoso-Joao et al found that after 5 years of follow-up, the cumulative incidence of overall and severe radiation cystitis after radiation for prostate cancer was 9.1% and 1.6% in a cohort of 783 patients.[6] At our institution, we found an even higher incidence of 11.1% over a longer 15-year period. Ninety percent of patients who developed HC had moderate to severe hematuria (grade 3-5) with 52% requiring blood transfusion secondary to acute anemia, and an average of 4.4U transfused per patient. This data show how severe hematuria can be in patients with HC, with over half of our patients requiring multiple blood transfusions.

Patients developed HC an average of 79.1 months after radiation. Shilo et al reported a median interval between radiation and HC of 4 years, with a range of 1-26 years[7]; however, that series only included 32 patients. Our larger

Table 3. Incidence of hemorrhagic cystitis by radiation treatment modality as well as average dose of radiation given in patients who developed HC

Radiation Type	No HC	HC	Average Dose Radiation With HC (Gy)	No. Patients With HC and Unknown Dose Radiation	Total No. Patients	Incidence of HC	*P* Value (<.05 Considered Significant)
EBRT neutron + photon	47	9	48.6	2 (29%)	54	16.1%	*P* = 1*
EBRT	195	39	69.8	23 (59%)	234	16.7%	*P* = .18**
IMRT	94	11	78.1	0	105	10.5%	
IMRT neutron + photon	17	4	48.3	1 (25%)	21	19%	*P* = .28***
EBRT + brachytherapy	26	4	45	2 (33%)	32	13.3%	
Brachytherapy	44	0	n/a	n/a	44	0%	*P* = .001****
Adjuvant	22	4	89.5	2 (50%)	26	15.4%	
Salvage	11	2	71.1	0	13	15.4%	
Unknown	176	6	n/a	n/a	182	3.3%	

EBRT, external beam radiation therapy; HC, Hemorrhagic Cystitis; IMRT, intensity-modulated radiation therapy .
* *P* value development HC after EBRT vs mixed neutron/photon EBRT.
** *P* value development HC after EBRT vs IMRT.
*** *P* value development HC after IMRT vs mixed neutron/photon IMRT.
**** *P* value development HC after brachytherapy vs all other types of radiation.

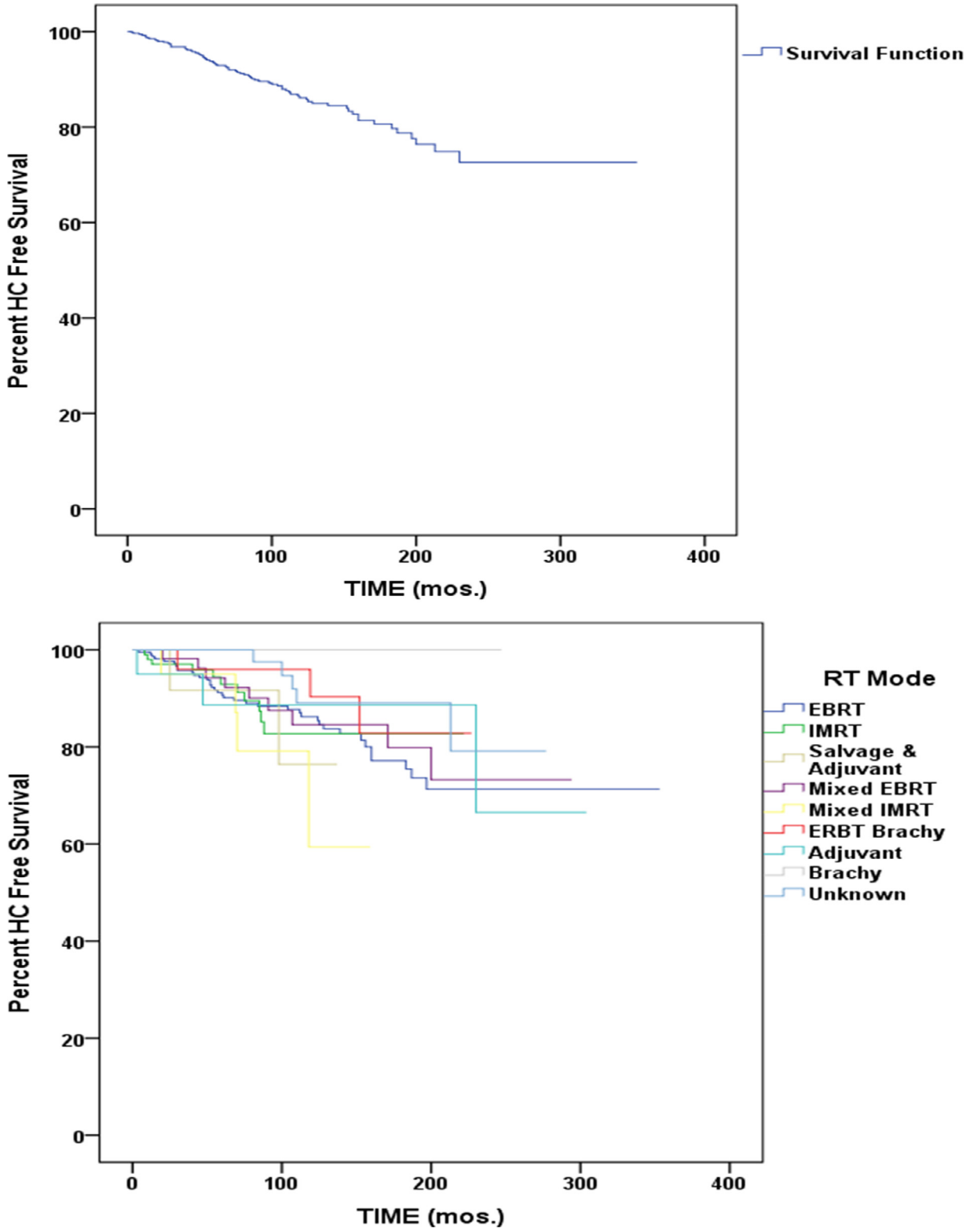

Figure 1. Kaplan-Meier curves showing percent of HC-free survival over time in months ($n = 562$). (**A**) At 230 months, 72.5% HC-free survival in patients treated with any radiation (mean HC time 110 months; 95% CI 104.5-115.8). (**B**) HC-free survival in different radiation modalities. HC-free survival was 71.3% at 197 months after EBRT ($n = 220$) (95% CI 263-304) and 82.7% at 88 months after IMRT ($n = 105$) (95% CI 179.2-209.6). No significant difference ($P = .919$). EBRT, External beam radiation therapy; HC, Hemorrhagic Cystitis; IMRT, Intensity-modulated radiation therapy. (Color version available online.)

sample size showed a median interval of 68 months. Using a Kaplan-Meier curve, we plotted HC-free survival over time. We found 72.5% HC-free survival at 230 months. We also found that there was no statistically significant difference between EBRT vs IMRT and HC-free survival over time ($P = .919$).

In our study, 92.5% of the patients who developed HC were AA. A limitation of our study is that our patient population is from Detroit, MI where the population is 79.1% AA according to the 2017 census.[8] This limits the racial diversity of our study; however, epidemiologic data published in the literature suggests that AA men have a disproportionately higher prostate cancer incidence and mortality compared to European Americans.[9] Despite these findings, the exact causes underlying these prevalent racial disparities are unknown. Socioeconomic factors likely account for some differences; however, many studies are trying to identify if there is a molecular basis behind this disproportion.[10] Since more AA are diagnosed with prostate cancer, there is a higher proportion of AA undergoing treatment and experiencing side effects from treatment. Both the higher incidence of prostate cancer in AA and the predominant AA population in Detroit are likely contributing factors for the high incidence of HC in AA seen in our study; whether there is a molecular basis behind this is unknown and needs future study.

EBRT was the most common form of radiation therapy found in our study. Evidence suggests that increasing radiation dose in the treatment of localized prostate cancer may improve local and biochemical control at the cost of increased toxicity. Analysis of 2 large Radiation Therapy Oncology Group trials (7506 and 7706) found that when looking at several factors that may impact urinary and intestinal sequela after radiation including previous laparotomy, stage of disease, hypertension, positive lymph nodes, previous transurethral resection, total dose, and energy of accelerator used, only total dose of radiation (>70Gy) had a significant impact on the incidence of urinary complications.[11] Since IMRT reduces the volume of normal tissue irradiated, it has been shown to limit toxicity compared to conformal radiation therapy. We found that although more patients developed HC after EBRT compared to IMRT, there was no significant difference. IMRT actually had a higher average dose of radiation (78.1Gy; median 76.7Gy; STD 14.8) compared to EBRT (69.8Gy; median 75GY; STD 17.6). Afoso-Joao et al also found no association between radiotherapy setting (primary vs adjuvant vs salvage) or radiation dose applied and the development of HC.[6] In another study of 60 patient undergoing IMRT for prostate cancer by Coote et al, a rate of 4% and 4.25% of Grade 2 bowel and bladder toxicity was found 2 years post-treatment.[12] The Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer (CHHiP) Trial also showed no clinically meaningful differences in acute toxicity between standard and hypofractionated radiotherapy schedules.[13] Similarly, Zelefsky et al found a decreased rate of acute and late rectal toxicity with IMRT but not genitourinary (GU) toxicity.[14] Sutani et al found the 3-year cumulative rates of late GU toxicity for EBRT, IMRT, PI alone, and PI + EBRT groups were 4.2%, 6.8%, 14.1%, and 17.0% (P = .003). Researchers found that the differences in the late GU/GI toxicity could not be explained by the treatment modalities themselves, but by the total radiation dose to the GU/GI tract.[15] The results of these studies and ours suggest that even with the advance of IMRT for radiation therapy for prostate cancer, GU toxicity, which includes HC, remains about the same.

The treatment of HC can cause severe morbidity for patients and require them to have multiple procedures. This was demonstrated in the present study as the most common treatment modality was cystoscopy with fulguration/clot evacuation (86%). Our findings suggest that the majority of patients who develop HC will likely require multiple cystoscopies throughout the course of their treatment. Indications for cystoscopy were done in the inpatient setting and included gross hematuria refractory to continuous bladder irrigation, recurrent catheter obstruction with clots, and decreasing hemoglobin with continued gross hematuria. Kaplan and Wolf studied 33 HC patients who required cystoscopy with fulguration/clot evacuation. Fifty-three percent of patients with radiation-induced HC had resolution of gross hematuria with a single cystoscopy while the remaining patients required multiple cystoscopies.[5]

Other treatments for HC in our study included intravesical aminocaproic acid (11%), HBO therapy (11%), formalin (10%), alum (6%), urinary diversion (6%), and silver nitrate (2.5%). Shilo et al found that HBO controlled bleeding in 84% of 32 patients, with freedom from significant hematuria in 96% of the patients.[7] Vilar et al found similar results in 38 patients with an 89% resolution rate.[16] Though HBO has high cure rates, its use is limited by availability, insurance coverage, and length of treatment. HBO usually requires acute episodes of hematuria with clot retention to resolve before being effective. The low rate of HBO treatment in our study is likely secondary to the fact that many of our patients are referred for HBO after inpatient hospitalization but are often unable to attend sessions before being readmitted for clot retention. Poor patient compliance in our population is another limitation to our study as it affects treatment modalities used including HBO therapy. Other intravesical treatments for HC described in the literature are in accordance with our findings. Aminocaproic acid was the most common intravesical agent used in our review, which is supported by other studies such as by Singh, where 34/37 patients responded well to treatment for intractable bladder hemorrhage.[17] Intravesical formalin has limited reported rates of resolution (70%-89%) and is associated with a complication rate of ~30%.[1,3] The morbidity of formalin makes it a less appealing treatment option and is why it is not often used at our institution. Alum use has been noted in the literature for severe refractory HC; however, no current studies support its use, as patients are at risk of alum toxicity. Out of 5 patients treated with alum found in our study, 1 acquired alum toxicity during treatment. We found silver nitrate to have the lowest percentage of use for treatment of HC. This is in accordance with a study by Montgomery involving 9 patients with HC who were treated with silver nitrate. They found silver nitrate to be ineffective for resolution of hematuria, with 100% of patients requiring another intervention.[18]

Not only does HC often require morbid treatments, it also incurs frequent complications. The complication rate associated with HC was 83% (66/79 patients). The 4 most common complications in our study included urinary tract infection (30%), acute kidney injury (24%), urethral stricture (15%), and urosepsis (14%). Death associated with HC complications did occur in 4 of the 79 patients (5%). Other complications included bladder neck contracture (5%), bladder rupture (3.8%) and fistula (2.5%).

Limitations

Our study was limited in that it was a retrospective chart review and because of this, not every variable could be found for every patient. About 25.4% of all patients and 7.6% of patients with HC had an unknown type of radiation, while 40% of patients who developed HC also had an unknown dose of radiation. Treatment interventions and incidence may also be under-reported, as patients could have received treatments for HC at outside institutions which were not included in this study. As mentioned previously, other variables affected by the retrospective nature of our study included prostate cancer stage and Gleason score as well as intricate details of radiation treatment for each patient. Our survival analysis was only able to include 562/709 patients because 147 patients had known radiation dates. Thirty-three percent of patients had an unknown stage which could affect radiation treatment planning, however, in previous studies stage and Gleason score were not associated with increased urinary complications after radiation therapy.[11] We realize that our study was also limited in racial diversity secondary to the large AA population in Detroit, MI. This review only illustrates our experience in Detroit, which may or may not be generalizable to populations in other cities receiving radiation therapy for prostate cancer.

CONCLUSION

Urologists must inform patients that radiation therapy for prostate and bladder cancer does not come without risk. Our series shows an 11.1% incidence rate of HC after radiation for prostate cancer. While most patients develop the condition within the first 5 years, a significant risk of developing HC still exists even 10 years after radiation. HC is associated with high morbidity for patients and often requires multiple hospitalizations, blood transfusions, trips to the operating room and various complications such as infection, AKI, hydronephrosis, urethral stricture, and occasionally death. Even with advances in radiation such as IMRT, there is no significant difference in the development of HC.

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