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Radiation-induced recto-urinary fistula: A dreaded complication with devastating consequences

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ABSTRACT

Purpose: This study was undertaken to evaluate our 16-year experience with fistulas between the rectum and urethra or urinary bladder, collectively called recto-urinary fistulas (RUFs), and their devastating consequences in patients treated with radiation for prostate cancer.
Methods: We downloaded the records of all patients with radiation-related RUFS from 2004 to 2020 at our institution using the electronic medical record system. Details concerning patient demographics, clinical presentation, diagnostic approaches and surgical management were obtained and assessed.
Results: We identified a total of seven patients with radiation-induced RUFS: all were male and had an average age of 66 at diagnosis. Each had a history of prostate cancer that was treated with external, internal (i.e. brachytherapy), or combination radiation therapy. No fistulas were noted in patients treated with radiation for another malignancy. Radiation proctitis with rectal ulcer formation occurred in 6 of 7 patients. Common symptoms included fecaluria, pneumaturia, urine leakage via rectum, rectal pain and urinary tract infection. CT scanning was the most useful diagnostic tool. Once confirmed, fistula management included both urinary and fecal diversion in all patients. Only one patient received definitive repair of the fistula. Five others either died before repair could be attempted or had prohibitive co-morbid diseases. One patient declined repair.
Conclusions: Although rare, the development of a recto-urinary fistula is a dreaded complication. Our results indicate that radiation proctitis with rectal ulcer formation precedes fistula formation in most patients and must be aggressively managed. While fecal and urinary diversion can manage fistula symptoms in the majority of patients, definitive fistula repair is only possible in selected individuals.

1. Introduction

A fistulous connection between the rectum and the urethra or urinary bladder can be a tragic problem that is often incredibly difficult to treat. First described in detail by Young and Stone [1] some one hundred years ago, these fistulas, collectively called recto-urinary fistulas (RUFs), can be either congenital or acquired. The acquired form is typically much more commonplace and can result from surgical complications, radiation treatment, trauma, chronic inflammation such as Crohn's disease, or malignancy [2]. A common subset of patients who can develop such a fistula are men diagnosed with prostate cancer who have received some form of radiation therapy for definitive treatment.

Our Veterans Affairs Hospital is a major treatment center for men with prostate cancer, many of whom receive radiation therapy. In this report, we discuss our experience with those unfortunate individuals who develop a recto-urinary fistula from such treatment over a 16-year period to highlight its clinical presentation, etiologic factors, and diagnostic modalities. Further, we evaluated the current management of RUFs, including surgical treatment options.

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2. Materials and methods

2.1. Patient study population

After obtaining approval from our Institutional Review Board (IRB #1572763) to conduct this study, we downloaded the records of all patients with RUFs from 2004 to 2020 at our institution using the electronic medical record system of the Department of Veterans Affairs, known as the Computerized Patient Record System (CPRS). Demographics, presenting symptoms, diagnostic approaches, management strategies, and follow-up information including postoperative problems and issues, were collected on all patients. Details concerning surgical management were also obtained. All patients were followed from the time of diagnosis until completion of the study or death.

Being a retrospective analysis, all patient information was de-identified. Thus, our IRB waived the need for patient consents.

2.2. Data analysis

No statistical analyses were performed in this study since it was an observational review and evaluation of a specific surgical problem induced from prior radiation treatment.

3. Results

We identified a total of seven patients with radiation-induced RUFs: all were male and had an average age of 66 at diagnosis (range 58 to 76). Each had a history of prostate cancer that was treated with external, internal (i.e. brachytherapy), or combination radiation therapy. We found no patient having had a RUF related to radiotherapy treatment for other types of cancer.

A total of 1006 patients received radiation treatment for a documented history of prostate cancer during the 16 years of this study. Of these, five patients (Patients 1,2,3,5 and 6) developed RUFs for a total incidence of this complication being 0.5%, indicating its rarity. The two additional patients reviewed (Patients 4 and 7) cannot be included in calculating the incidence as they received their radiation treatment at an outside hospital. Following such treatment these two patients received further management and care at our facility. Table 1 summarizes essential information about each patient's prostate cancer, onset of radiation proctitis, development of a recto-urinary fistula, and the radiation dosage each received.

Six of our seven patients were diagnosed with radiation proctitis, with the subsequent development of rectal ulcers, before a distinct fistula occurred. This diagnosis was confirmed endoscopically using sigmoidoscopy. Symptoms included rectal pain and hematochezia, resulting in treatments such as hyperbaric oxygen (HBO), argon (Ar) laser coagulation, and in some cases proctofoam, cholestyramine and steroids, or mesalamine enemas.

Table 2 details the timing of the presentation and symptoms of rectal proctitis for each patient after undergoing initial cancer treatment except for Patient Four who did not demonstrate a clinically verifiable proctitis. It was only after he was documented to have metastatic prostate cancer some two years following initial treatment that he presented with a urethral stricture for which he received an open suprapubic tube, and later developed fecaluria, following intermittent rectal bleeding. Table 2 also lists other relevant information that may be related to fistula formation.

Symptoms suggestive of a fistula began to emerge following the development of radiation proctitis. These expressed themselves in both the rectum and bladder with many "tipoffs" that a fistula was probably present coming from the bladder. The major symptoms and their frequency are highlighted in Table 3.

Diagnostic confirmation of a suspected fistula included CT scanning ($n = 5$), cystoscopy ($n = 1$), and voiding cystourethrogram (VCUG; $n = 1$) which confirmed the presence of a fistula in 6 of the 7 patients

Table 1
Patient profile for prostate cancer.

PATIENT	Age at Dx of Prostate cancer	Age at Dx of Radiation Proctitis	Age at Dx of Recto-urinary fistula	Cancer Stage	Histology of Cancer	PSA	Type of Treatment	Radiation Dose
One	65	72	76	Gleason 5	Moderately differentiated adenocarcinoma	6.0	Brachytherapy	I-125 145 Gy
Two	61	62	63	Gleason 6	Moderately differentiated adenocarcinoma	4.5	EBRT	70.2 Gy in 39 fractions
Three	63	64	65	Gleason 6	High grade intraepithelial cancer	4.5	Combination (EBRT+brachytherapy)	EBRT: 45 Gy in 25 fractions Brachytherapy: PD-103 90 Gy
Four	55	57*	58	Gleason 9	Poorly differentiated infiltrating adenocarcinoma	9.0	Combination (EBRT+brachytherapy)	Not available**
Five	58	60	60	Gleason 7	High grade adenocarcinoma	15.6	EBRT (IMRT)	72 Gy in 30 fractions
Six	62	63	65	Gleason 9	High grade aggressive adenocarcinoma	14.9	EBRT	72 Gy in 40 fractions
Seven	69	71	72	Gleason 6	Moderately differentiated adenocarcinoma	11.0	EBRT (IMRT)	79.2 Gy in 44 fractions

Dx: Diagnosis.
EBRT: external beam radiation treatment.
IMRT: intensity modulated radiation treatment.
PSA: Prostate Specific Antigen.
PD-103: Palladium-103.
I-125: Iodine-125.
Gy (Gray): unit of absorbed dose of radiation.
*Although the patient had symptoms suggestive of proctitis, this diagnosis could not be confirmed.
**Patient received radiation treatment at an outside hospital, documents of which have been destroyed per policy as the information was more than 10 years old.

Table 2
Patient profile for radiation proctitis.

PATIENT	Age at Dx of Radiation Proctitis	Time after Radiation Treatment	Symptoms Associated with Proctitis	Treatment Approaches for Proctitis	Other Relevant Information
One	72	7 years	Rectal pain, hematochezia	HBO, cholestyramine and steroids	Hx of rectal ulcer biopsy
Two	62	6 months	Fecal incontinence, hematochezia, rectal pain	Mesalamine, Ar laser	Hx of rectal ulcer biopsy
Three	64	1 year	Hematochezia, fecal and urinary incontinence, dysuria	Ar laser	N/A
Four	57*	2 years	Fecal incontinence, hematochezia	N/A	Hx of TURP; neurogenic bladder
Five	60	11 months	Hematochezia, rectal pain	Ar laser	Hx of rectal ulcer biopsy; Sjögren's syndrome
Six	63	11 months	Hematochezia, rectal pain, hematuria, dysuria	Proctofoam, HBO	Hx of bladder cancer
Seven	71	1 year 4 months	Dysuria, rectal pain, hematochezia	HBO	N/A

Dx: diagnosis.
HBO: hyperbaric oxygen therapy.
Ar: Argon laser.
Hx: history.
TURP: transurethral resection of prostate.
*Although the patient had symptoms suggestive of proctitis, this diagnosis could not be confirmed.

Table 3
Primary symptoms associated with recto-urinary fistulas.

PATIENT	Urinary Tract Infection	Leakage of urine via rectum	Dysuria	Fecaluria	Hematuria	Pneumaturia	Rectal pain
One		X		X	X		X
Two	X					X	X
Three	X	X	X				
Four	X		X	X			
Five	X	X	X				X
Six	X	X		X	X	X	X
Seven		X	X		X	X	X

(Patients 1,2,4,5,6 and 7). Patient 3 underwent CT scanning, but no definite fistula was identified. Of note, several months after this imaging, he started passing urine via his rectum, which in a short time was constant, with only negligible amounts coming from his bladder. These clinical observations were felt to confirm the diagnosis.

Once the diagnosis of a fistula was radiologically confirmed (6 patients) or strongly suspected on clinical grounds (Patient 3), management was directed toward diversion of both the urinary and fecal streams. Usually, this was accomplished with a surgically placed suprapubic (SP) tube and a diversionary colostomy. In two patients, the bladder was actually removed, and an ileal conduit was constructed. In one such patient (Patient 5), breakdown of tissue surrounding the fistula resulted in the formation of several pelvic abscesses, one directly invading the bladder. In addition to diverting the fecal stream, cystectomy, drainage of the abscesses, and isolating the urinary diversion away from the pelvic infection by means of an ileal conduit was considered to be the best approach to manage this complex situation. In the second patient (Patient 6), cystectomy and an ileal conduit were performed because an aggressive bladder cancer was discovered on workup of the fistula and this approach was felt to be the best means of treating this neoplasm and managing the fistula. While bladder cancer is known on rare occasion to cause a RUF [3], this patient's surgical findings and pathologic results were consistent with a radiation related etiology.

The clinical course of each patient following urinary and fecal diversion varied greatly and in some situations was quite harsh. Patient One underwent formal fistula repair transperineally using a gracilis muscle graft. The outcome was reasonably successful but intermittent urine output from the rectum occurred in subsequent years. He chose not to pursue any further surgical intervention. Patient Two experienced complete resolution of symptoms after fecal and urinary diversion which remained durable. He chose not to undergo formal fistula repair. Patient Three underwent permanent urinary diversion via cystectomy and the creation of an ileal loop some years after the original urinary and fecal diversions to more effectively manage his urinary drainage issues through the fistula. Regrettably, this procedure, along with his original colostomy, created considerable intra-abdominal adhesive disease that resulted in multiple episodes of intermittent small bowel obstruction over ensuing years. Patient Four died six weeks after urinary and fecal diversion of widespread bone metastases from his underlying prostate cancer. Patient Five continued to have lingering problems of an infectious nature in his pelvis following the cystectomy that included fluid collections (suspicious for recurrent abscesses but difficult to prove), persistent drainage from his rectal stump, osteomyelitis of the symphysis pubis (that responded to antibiotics), and intermittent small bowel obstruction (treated non-operatively), all of which required repeated re-hospitalizations for management. Ultimately, he succumbed to sepsis from underlying pelvic infection. Patient Six did reasonably well for the first year following his colostomy, cystectomy and ileal loop formation, but then started developing chronic abscess formation in his pelvis from the radiation damaged tissue. Over some six years, he required multiple re-operations to effectively drain the abscesses which in time necessitated anoperineal resection, proctectomy, and re-do of his end-colostomy because of abscess erosion resulting in a colonic-perineal-cutaneous fistula. Eventually this continuing pelvic infection eroded into portions of his small bowel necessitating small bowel resections. Such challenges severely impacted his nutritional state (requiring chronic parenteral feeding) and created a continued state of intermittent sepsis and metabolic stress, from which he eventually expired. Patient Seven was being evaluated for definitive fistula repair when he suffered necrotizing fasciitis of the thigh two months after urinary and fecal diversion, resulting in a septic death unrelated to the fistula itself.

4. Discussion

The present report details the devastating consequences that can occur in patients who develop RUFs. Several findings were noted that are clearly linked with the development of this complication in our cohort. First, all patients in our study developed prostate cancer and received radiation as the sole means of treatment. Second, radiation proctitis was clearly associated with the subsequent development of a fistula. Third, once fistula formation occurred, both fecal and urinary diversion were essential for initial management. Fourth, where possible, the ultimate goal in management should be definitive repair of the fistula. Each finding merits further discussion.

Although a variety of etiologies have been associated with recto-urinary fistulas, such fistulas in men occur primarily in those who are treated with some type of radiation therapy for prostate cancer. In a systematic review [2], it was noted that the profound increase in radiation usage since 1998 for the treatment of prostate cancer also resulted in a corresponding increase in the number of recto-urinary fistulas. Prior to 1997, the prevalence of RUFs related to radiation was less than 4%, but with the marked increase in radiation usage since 1998 it has mushroomed to some 50%. In our study, all seven patients identified with rectovesical or rectourethral fistulas had undergone external beam radiation therapy (EBRT), brachytherapy (placement of radioactive seeds), or a combination of the two.

One of the problems associated with radiation therapy is the development of radiation-induced proctitis. With the improvement in overall survival in patients with prostate cancer, there has been a rising number of patients receiving radiation who develop acute or chronic radiation proctitis. The acute form is usually self-limited, but the chronic form can be quite problematic. This has conditioned the need to test some supportive topical therapies during the radiotherapy course to prevent such issues. A recent study has provided evidence that hyaluronic acid enemas might be effective in reducing the severity of radiation proctitis [4] during radiotherapy for prostate cancer. While the results are quite interesting, additional validation of such treatment will require confirmation by other centers.

The true incidence of radiation proctitis is difficult to assess, but has been estimated to be prevalent in 5–11% of patients receiving some form of radiation therapy [5]. The pathophysiology behind this condition is the resultant microvascular injury due to local irradiation that causes acute mucosal damage and ischemia, and chronic progressive epithelial atrophy and fibrosis, which leads to the formation of rectal ulcers, strictures, perforations, and ultimately fistulas [6].

Over the last three decades, technological improvements in the delivery of EBRT has corresponded to an increase in the number of men receiving definitive radiation treatment for prostate cancer. Such improvements have enabled the delivery of higher doses of radiation (>74 Gy), which has consistently been shown to improve outcomes [7,8,9]. The transition from two-dimensional treatment planning to 3D-conformal radiotherapy (3DCRT) successfully reduced treatment related toxicity [10] due to improvements in target delineation, dose-calculation, and treatment planning. Further improvements in dose distribution conformality were made by the widely adopted use of intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT).

However, dose escalation and highly conformal radiation treatment plans require increased certainty regarding daily alignment prior to each treatment. More recently, the use of daily image guidance has allowed for more accurate delivery of radiation through daily target localization and assessment of nearby organs at risk. This is achieved with the use of orthogonal imaging of intra-prostatic fiducial markers or volumetric cone-beam CT (CBCT) prior to each treatment. The use of daily image guidance for prostate cancer is associated with improved biochemical control and toxicity [11,12,13].

Significant technological advances have been made in the delivery of radiation for localized prostate cancer, leading to improved outcomes and decreased toxicity, which has in turn led to a higher percentage of patients with newly diagnosed prostate cancer receiving definitive radiation. Although the rates of recto-urinary fistula after radiation are quite low, with most series reporting rates between 0 and 3% [14,15,16], it remains a serious complication which warrants better understanding.

Various strategies have been employed to manage radiation proctitis when it occurs. Ozone therapy, mesalamine, and metronidazole have been explored as potential treatments but evidence to support their efficacy long-term has been lacking [5,17]. Hyperbaric oxygen therapy and argon beam photocoagulation have been shown to be reasonably effective [5]. Six of our seven patients had suffered from radiation proctitis and subsequent rectal ulcer formation before presenting with symptoms pathognomonic for fistulas. They, too, had undergone treatments such as hyperbaric therapy, argon beam photocoagulation, mesalamine enemas, et cetera, with limited success. Our findings are consistent with those reported by Larson and colleagues [18], where ten of their fourteen patients developing rectal complications post-radiation therapy presented with signs of recto-urinary fistulas. The traditional treatment for radiation proctitis at some centers has been formalin with a high degree of reported success [5,19]. This agent when administered topically to the ulcerated mucosa induces cauterization of the ulcer bed with subsequent healing and cessation of bleeding. Since 2018, the American College of Colon and Rectal Surgeons has endorsed formalin therapy as first line therapy for bleeding radiation proctitis with a success rate approaching 90–95% [20]. Why such treatment was not given to any of our patients is unknown. One wonders whether some of our fistulas could have been prevented had formalin therapy been used. Taken together, these observations strongly suggest that radiation proctitis is the precursor for fistula development and, as such, must be managed aggressively.

In addition to these previous considerations, several other factors, noted in Table 2, may have played a role in the pathogenesis of RUFs in some of our patients. They include biopsy of rectal ulcers on the anterior rectal wall, transurethral resection of the prostate (TURP), and an autoimmune disorder such as Sjogren's disease. To what extent any or all of these factors were related to fistula formation is unknown, but several reports have suggested this possibility [21,22,23]. Of particular concern is biopsy of rectal ulcers that should virtually never be undertaken as it appears to be linked to fistula formation [21,22]. Patients One, Two and Five underwent such biopsy and this could have certainly accelerated fistula formation. The same is possible with Patient Four who received a TURP for his neurogenic bladder subsequent to receiving radiation treatment of his prostate cancer. The possibility that bladder cancer may be related to fistula formation in Patient Six was excluded by the surgical findings and the pathologic results as noted in the Results Section.

Our study has shown that once a fistula has developed, the initial diagnosis is heavily clinical. Some of the more characteristic symptoms that indicate the presence of a fistula include fecaluria, pneumaturia, and drainage of urine through the rectum as also noted by others [24]. Nonspecific symptoms are urinary tract infections (UTIs), rectal pain, and dysuria. As these symptoms can significantly lower the quality of life, it is prudent to evaluate them for the possible presence of fistula formation without delay.

Once the diagnosis of a fistula is suspected, some type of imaging procedure is required to establish its presence and help delineate its anatomy and concomitant pathology [25]. Such documentation was best noted in our series with CT imaging and proved very helpful in five of our seven patients. Only one patient was diagnosed solely with clinical history, with the presence of the fistula confirmed during the operation. Another patient was diagnosed with voiding cystourethrography (VCUG). As CT imaging continues to advance in its quality and precision, this technique will undoubtably continue to play a significant role in diagnosis and operative assessment of these fistulas.

The approach to fistula treatment, once diagnosed, involves two

levels of management. The first is focused on alleviation of symptoms, decreasing inflammation around the fistula and surrounding tissues, and providing an opportunity for the fistula to heal, if possible [26]. To accomplish these goals, both urinary and fecal diversion are carried out, as was done in all seven of our patients. It is important to note that such diversion is intended to be a *temporizing* technique. In the majority of patients, the fistula does not close with diversion, especially if it resulted from radiation therapy. Thus, the second level of management, namely definitive repair of the fistula, can be planned and patients optimized during this diversionary period for the forthcoming surgery [27]. Further, those patients with serious co-morbid diseases can also be identified at this time and excluded from any further surgery. It is generally agreed that if the fistula does not heal within a few months of diversion, definitive repair should proceed in suitable patients [26,27].

In our study, only one patient saw the resolution of his symptoms after fecal and urinary diversion and thus declined surgical repair. Whether the fistula actually closed was never confirmed with imaging studies, but he continued symptom-free thereafter. For the remainder of patients, however, diversion alone did not lead to any evidence of fistula closure, thus requiring some type of further care. Excluding the two patients who died before a fistula repair was even possible, one underwent surgical repair of the fistula while two others received permanent urinary diversion such as cystectomy with ileal loop formation. The final patient was not even given the option of fistula repair as he was such a poor surgical candidate due to his multiple comorbidities.

The transperineal method was used in the one patient in our series who underwent fistula repair. With this approach, the plane between the rectum and the urethra or bladder is dissected from the perineum up into the pelvis, the fistula divided and repaired, and a viable tissue flap brought up to interpose itself between the two sides, keeping them separated to promote optimal blood supply and healing. For this repair, the gracilis muscle is an ideal tissue flap, as it provides a flap with an excellent blood supply, length and reach, and easy availability [28]. In a multi-institutional study by Harris and colleagues, 79% of 210 patients with recto-urinary fistulas secondary to prostate cancer treatment with radiation received a transperineal repair, with a 92.8% success rate, indicating the effectiveness of this method [29].

In summary, as we reflect on the outcomes of each of our patients, it becomes clear that the best means of managing a recto-urinary fistula is its prevention. As already noted, advances in radiation therapy over the past decade or more have greatly lessened rectal toxicity and continue to give evidence that such toxicity will be reduced even more in the coming years. In the meantime, those patients who develop radiation proctitis should be vigorously treated and carefully followed, using agents such as topical formalin that have a high degree of success.

Conclusion

Development of a recto-urinary fistula following radiation treatment for prostate cancer is a dreaded complication. Radiation proctitis with rectal ulcer formation precedes fistula formation in most patients and must be aggressively managed. While fecal and urinary diversion can effectively manage symptoms in most patients, definitive fistula repair should be the ultimate goal if possible.

CRediT authorship contribution statement

Yu: design of paper, data collection, formating paper and final approval
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Smith-Harrison: design of paper, data collection
Hazell: formating paper and final approval
Timmerman: formating paper and final approval
Rivers: design of paper, formating paper and final approval
Miller: design of paper, formating paper and final approval

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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