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**Post-prostatectomy Radiotherapy in the Setting of a Rectal Vascular Malformation**

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**ABSTRACT**

**Purpose:** Rectal vascular malformations are rare and can present a unique challenge to the clinical management of prostate cancer with radiation therapy. The optimal management in patients with regional vascular malformations who require curative radiotherapy is unknown.

**Methods and Materials:** A 70-year-old male who was initially treated with a radical prostatectomy for unfavorable intermediate risk prostate cancer experienced biochemical recurrence. Restaging imaging demonstrated a previously undiscovered rectal vascular malformation. Endovascular and endoscopic evaluation identified this vascular malformation to have features of both an arteriovenous malformation and rectal varix.

**Results:** The patient underwent ablation of the vascular malformation followed by a standard course of salvage post-operative radiotherapy. At 2.7 years post-treatment, he has not experienced any significant rectal bleeding or other toxicity from bleeding and continues to have an undetectable PSA.

**Conclusion:** Vascular malformations within the rectum are rare and when present may present unique challenges to the treatment of prostate cancer. Procedural embolization and sclerosis can provide durable control to allow for safe delivery of regional radiotherapy.

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## INTRODUCTION

External beam radiotherapy (EBRT) is a potentially curative management option for patients with prostate cancer that recurs after prostatectomy. Although generally well-tolerated, the risk of moderate to severe rectal bleeding is an important consideration in defining the therapeutic index for a potential course of pelvic radiotherapy (RT). Historically, rectal bleeding has been considered a well-documented side effect of EBRT for prostate cancer both in the intact [1] and post-operative setting [2]. For example, in SWOG 8794, the rate of rectal bleeding in the adjuvant, post-operative group was 3.3% versus 0% in the observation group [3]. Risk factors such as a prior history of irritable bowel disease [4], prior abdominopelvic surgery [5], and higher radiation dose [6] have been associated with higher risks of rectal toxicity, including bleeding.

Contemporary techniques of EBRT including intensity modulated radiotherapy (IMRT) appear to mitigate a significant portion of the cumulative burden of rectal toxicity observed in prior eras [2, 7]. Although radiation is known to cause rectal injury, it may be true that only a subset of symptoms typically attributed to radiation toxicity are in fact a result of endoscopically diagnosed radiation proctitis. In one prospective study, of 141 patients who were observed to have rectal bleeding after radiotherapy, approximately half were found to have other findings in addition to radiation proctitis which may have been causally implicated in rectal bleeding [8].

Whether pre-existing colorectal vascular abnormalities increase the risk of moderate to severe rectal bleeding after a definitive course of post-prostatectomy radiotherapy is uncertain. Vascular malformations and anorectal varices are uncommon entities that present an independent risk of spontaneous bleeding, which can present as recurrent bleeding events or sudden onset, life-threatening bleeding. The rate of spontaneous bleeding in rectal varices is estimated to be between 0.45% and 3.6% [9-11]. Thus, the safety of pelvic radiotherapy in the setting of anorectal vascular malformation or anorectal varices is uncertain. We present a case of biochemically recurrent prostate cancer in a patient with a rectal vascular

malformation in whom post-prostatectomy radiotherapy was indicated with a discussion of the resultant management considerations.

## CASE REPORT

A 70-year-old Caucasian male with past medical history significant for internal hemorrhoids presented with unfavorable intermediate risk prostatic adenocarcinoma, cT1c N0 M0, Gleason 3+4=7 (9/12 systematic cores; 10/10 targeted cores), PSA 9.4 ng/mL. A multiparametric MRI with an endorectal coil was performed during staging evaluation and revealed 5 suspicious intraprostatic lesions and no abnormalities of the rectum. He underwent an uncomplicated robotic assisted radical prostatectomy with obturator lymph node dissection revealing a single focus of pT2 N0 (R0) Gleason 3+4 = 7 adenocarcinoma involving 40% of the gland bilaterally. The lymphadenectomy specimen revealed 0 of 10 lymph nodes involved with metastatic disease. His post-operative PSA was undetectable (< 0.02 ng/mL) at the 3-month post-operative follow-up timepoint.

At the 8-month post-operative timepoint, the patient was noted to have a detectable PSA (0.1 ng/mL) that was confirmed on a second measurement. Restaging evaluation included a multiparametric MRI of the prostate bed with a phased array surface coil, computed tomography (CT) of the chest, abdomen, and pelvis with contrast, and <sup>68</sup>Ga-PSMA-R2 PET/CT to investigate for evidence of gross locoregional recurrence. While the MRI did not reveal evidence of residual or recurrent disease, a vascular malformation was visualized in the right rectal wall, 4 cm from the anal verge (**Figure 1A**). In retrospect, this abnormality had likely been compressed and obscured by the endorectal coil during the presurgical staging MRI procedure and had not been noted at the time of surgical resection. The CT corroborated these findings and additionally detected a component of this vascular malformation that extended to the anterior rectal wall (**Figure 1B**). There was no evidence of locoregional recurrence on PET/CT. Lower endoscopy was performed to further characterize the lesion and demonstrated the previously described internal hemorrhoids. In addition, a submucosal vascular malformation, which was compressible with insufflation, was visualized and felt to be consistent with an arteriovenous malformation (AVM) or rectal varix (**Figure 1C**).

Based upon the concern for the possibility of future spontaneous, catastrophic bleeding or radiation-induced bleeding resultant from clinical or subclinical proctitis, an ablative procedure was performed. A fluoroscopy-guided arteriogram and venogram were conducted to map the vascular malformation, revealing that the arterial portion was fed by a branch of the right internal iliac artery whereas the venous portion was found to map to a branch of the inferior mesenteric vein (IMV) (**Figure 2**). The portal venous pressure was noted to be elevated at 16 mmHg. Vascular ablation was completed during the same procedure with a combination of sodium tetradecyl (Sotradecol®) sclerosis followed by embolization with an ethylene vinyl alcohol copolymer dissolved in dimethyl sulfoxide (Onyx®). Subsequently an MRI (**Figure 1E**), CT (**Figure 1F**), and post-embolization endoscopy verified a thrombosed rectal vascular malformation without signs of mucosal ischemia (**Figure 1G**).

The patient was evaluated for possible causes of portal hypertension including pre-hepatic, post-hepatic, and intra-hepatic pathology. Laboratory testing included hepatitis serologies, HIV testing, AST, ALT, GGT, bilirubin, haptoglobin, ceruloplasmin, rheumatoid factor, antinuclear antibody, anti-mitochondrial antibodies and a full hematology panel, all of which were unremarkable. There was no of significant ethanol ingestion. Imaging did not show any evidence of splenomegaly or vascular occlusion. An esophagogastroduodenoscopy did not show esophageal varices or other vascular abnormalities in the upper gastrointestinal (GI) tract. In summary, there was no identifiable cause for this vascular abnormality.

Following successful ablation of the vascular malformation, the patient underwent salvage RT to a dose of 70.2Gy in 39 daily fractions. Treatment was delivered concurrently with a 6-month course of ADT. Representative images of the plan from within the region of the vascular malformation are included in **Figure 3**. The patient did not require any treatment breaks and tolerated treatment as expected experiencing a maximum of grade 1 GI and GU adverse events which did not require management. He had two episodes of small volume (estimated < 2 mL) rectal bleeding between fractions 4 and 6 which resolved without management and were consistent with episodes he had experienced prior to EBRT.

Radiotherapy concluded in September 2019; ADT concluded in January 2020 with testosterone recovery by June 2020. At 32 months post-EBRT, he remains in biochemical remission and free of rectal bleeding.

## DISCUSSION

The differential diagnosis for vascular malformations of the rectum includes vascular tumors (hemangioma [12, 13], angiosarcoma [14, 15], or Kaposi's sarcoma [16, 17]), vascular malformations (with possible relation to Osler-Weber-Rendu [18], Bean's [19, 20], CREST [21], or Ehlers-Danlos [22] syndromes), or sporadic vascular abnormalities (angiodysplasia or AVM [23], radiation-induced vascular ectasias [24], Dieulafoy lesions [25-27], or rectal varices [28]). In this case, due the clinical features and historical findings, the differential diagnosis was refined to the most likely diagnoses of an AVM or a rectal varix as the lesion shared characteristics of both of these entities. The arteriogram of the malformation demonstrated a large caliber arterial supply draining directly into a large caliber vein without routing through an intervening capillary plexus, consistent with an AVM. In contrast, moderately elevated portal venous pressures were observed on portal vein manometry, suggesting the diagnosis of a rectal varix. In this case, the arterial supply originated from the internal iliac artery, which typically supplies the middle and inferior rectal arteries. Classically, this territory often drains via systemic venous drainage (iliac veins to inferior vena cava) whereas in this case the drainage was through the portal venous system via the inferior mesenteric artery.

As patients often only present to medical attention upon bleeding, the incidence of asymptomatic AVMs within the population remains unknown. In patients undergoing a colonoscopy for evaluation of GI bleeding, 1.4%-3% will be found to have an AVM [29, 30]. While most of the AVMs of the intestine are located in the cecum or ascending colon [31], AVMs of the rectum are not uncommon (14% of AVMs) [29]. Asymptomatic AVMs are often observed, as the risk of subsequent bleeding is thought to be low, while symptomatic AVMs are often managed with resection or sclerotherapy. Fractionated RT has been

used for ablation of cerebral [32] and pancreatic AVMs [33-35], however radiotherapy is not a standard management strategy for other GI vascular malformations.

Varices are another cause of symptomatic GI bleeding, however most of the available literature describes the management of esophageal varices resultant from portal hypertension in patients with cirrhosis. Rectal varices are less commonly described as a source of catastrophic bleeding with an estimated incidence of 38% to 94% in patients with portal hypertension [36]. In one report of 425 patients with portal hypertension, 40 patients with rectal varices were identified, and 15 of these patients were noted to have associated bleeding [37]. Other series have suggested that the rates of bleeding from rectal varices is lower, on the order of 3-5%. While most events are low grade, rectal variceal bleeding can be treatment-refractory [10], high-volume, and subsequently fatal [38]. Thus, this diagnosis merits close attention by clinicians, especially for individuals undergoing other treatments or procedures which are independently associated with GI bleeding.

In the present case, the vascular malformation had features of both an AVM and a rectal varix. Based on the size and location of the lesion, there was significant concern for clinically significant bleeding if proctitis or subclinical mucosal disruption resulted from radiotherapy. The development of rectal mucosal disruption might expose a submucosal AVM to the lumen, resulting in bleeding from elevated pressures during periods of straining or trauma caused by stool passage. In one prospective study, SPCG-7, which randomized patients to ADT with or without EBRT, no difference was observed between the two groups in the histologic appearance of the rectal mucosa at long-term follow-up, leading to the possible conclusion that any radiation-induced, late rectal bleeding may be a result of changes to the submucosa [39]. Based on this possibility, late submucosal remodeling may also have led to an increased risk of delayed bleeding as the vascular malformation was located in the submucosal compartment.

The optimal management for biochemical recurrence after prostatectomy in the context of a rectal vascular malformation is unknown. Possible options include an expansion of the standard radiation volume to intentionally cover the vascular malformation with the intent of ablation, limitation of the

standard radiation volume to avoid delivering high doses to the rectal mucosa and underlying connective tissue adjacent to the vascular malformation, close observation of the lesion after a standard course of post-prostatectomy EBRT, or procedural ablation preceding a standard course of EBRT. In this case, the concurrent treatment of the vascular malformation was less preferred due to the variceal features of the lesion. Further, extrapolated from the treatment of cerebral AVMs, the expected time course of complete nidus involution with the concurrent photon-based ablation strategy was judged to be longer than the time course for radiation-induced regional mucosal disruption, which was thought to increase the risk of rectal bleeding. The location of the lesion in the anterior rectal wall prevented exclusion from the radiotherapy treatment volume as it lies largely within the anatomic region at highest risk of harboring occult, recurrent prostate cancer [40, 41]. Observation of the vascular lesion was also not favored due to the concern that regional radiotherapy may limit the effectiveness of future procedural ablation of the malformation in the event of a catastrophic bleed. As such, pre-radiotherapy procedural ablation was chosen. This led to the desired clinical outcome producing durable oncologic control without serious or persistent rectal bleeding, although due to the follow-up duration of this report the risk of late rectal bleeding (> 2.7 years) in this patient cannot be excluded.

**Abbreviations**

<b>EBRT</b>	External beam radiotherapy
<b>ADT</b>	Androgen deprivation therapy
<b>IMRT</b>	Intensity modulated radiotherapy
<b>IMV</b>	Inferior mesenteric vein
<b>GI</b>	Gastrointestinal
<b>GU</b>	Genitourinary
<b>AVM</b>	Arteriovenous malformation

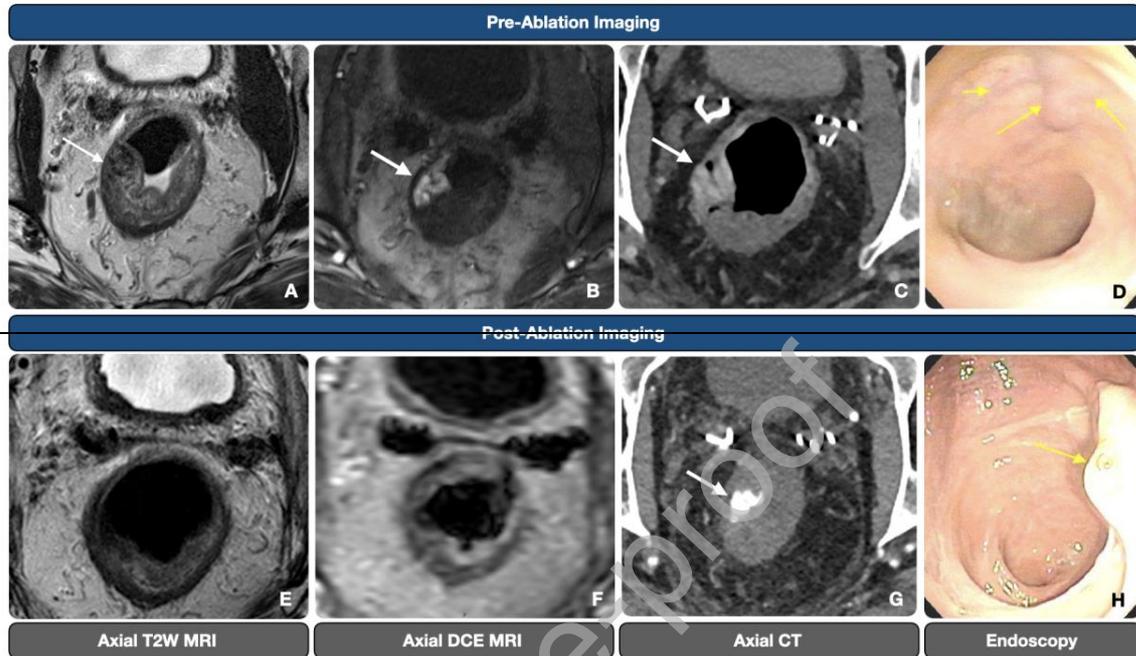
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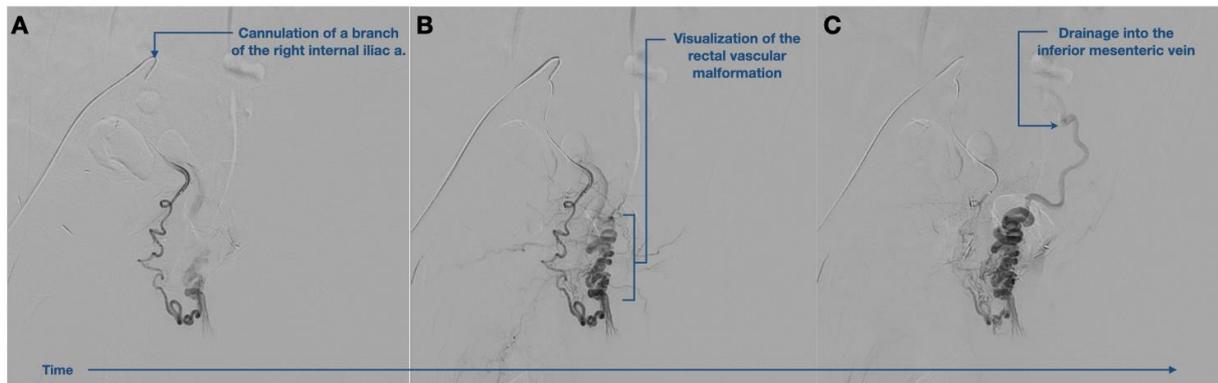
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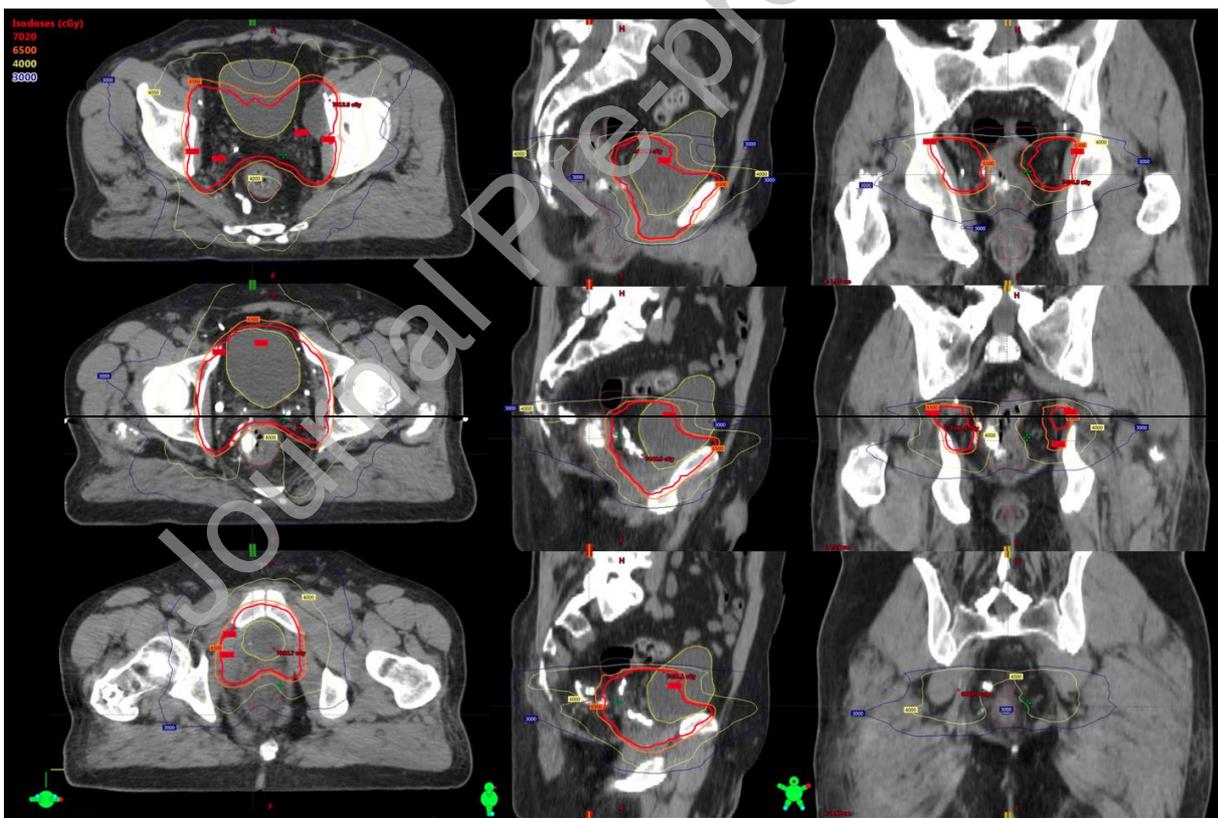
## Figure Captions



**Figure 1.** Multimodal representations of the pre-ablation (top; panels A-D) and post-ablation (bottom; panels E-H) appearance of the rectal vascular malformation are provided: pre-ablation T2-weighted MRI with arrow indicating the vascular malformation (A), pre-ablation dynamic contrast enhanced MRI with arrow indicating the vascular malformation (B), pre-ablation CT with contrast with arrow indicating the vascular malformation (C), pre-ablation endoscopic view with arrows indicating the mucosal distortion overlying the vascular malformation (D), post-ablation T2-weighted MRI (E), post-ablation dynamic contrast enhanced MRI (F), post-ablation CT with contrast with arrow indicating iodinated embolization agent used to ablate the vascular malformation (G), and post-ablation endoscopic view with no evidence of residual vascular malformation and arrow indicating the ablation zone without evidence of a residual malformation (H).



**Figure 2.** Representative views of the angiogram showing cannulation of a branch of the right internal iliac artery (A), visualization of the rectal vascular malformation (B), and drainage into the inferior mesenteric vein (C).



**Figure 3.** Representative axial, sagittal, and coronal views of the delivered plan with the 70.2Gy, 65Gy, 45Gy, and 30Gy iso-dose lines overlaid.