Advances in Radiation Oncology (2022) 7, 101043

advances in radiation oncology

www.advancesradonc.org

Teaching Case

Postprostatectomy Radiation Therapy in the Setting of a Rectal Vascular Malformation

Krishnan R. Patel, MD,[a,*] Wael Saad, MD,[b] Theo Heller, MD,[c] Baris Turkbey, MD,[d] and Deborah E. Citrin, MD[a]

[a]Radiation Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; [b]Radiology and Imaging Sciences Division, National Institutes of Health, Bethesda, Maryland; [c]Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland; [d]Molecular Imaging Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Received May 10, 2022; accepted July 25, 2022

Introduction

External beam radiation therapy (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 radiation therapy (RT). Historically, rectal bleeding has been considered a well-documented side effect of EBRT for prostate cancer, both in the intact[1] and postoperative[2] settings. For example, in the SWOG 8794 study, the rate of rectal bleeding in the adjuvant, postoperative group was 3.3% versus 0% in the observation group.[3] Risk factors, such as 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 RT, 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, 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 RT, 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 postprostatectomy RT 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 RT 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 postprostatectomy RT was indicated with a discussion of the resultant management considerations.

Case Report

A 70-year-old Caucasian man with a past medical history significant for internal hemorrhoids presented with unfavorable intermediate-risk prostatic adenocarcinoma (cT1c N0 M0, Gleason score 3 + 4 = 7 [9 of 12 systematic

Sources of support: Funding was provided by grant ZIA BC 011552, awarded by the National Institutes of Health Clinical Center for Research.

Disclosures: None.

Data sharing statement: Research data are stored in an institutional repository, and will be shared upon request to the corresponding author.

*Corresponding author: Krishnan R. Patel, MD; E-mail: Krishnan.Patel@nih.gov

https://doi.org/10.1016/j.adro.2022.101043

cores, 10 of 10 targeted cores], prostate-specific antigen [PSA] level = 9.4 ng/mL). Multiparametric magnetic resonance imaging (MRI) with an endorectal coil was performed during staging evaluation, and revealed 5 suspicious intraprostatic lesions and no abnormalities of the rectum. The patient underwent an uncomplicated robotic assisted radical prostatectomy with obturator lymph node dissection, revealing a single focus of pT2 N0 (R0) Gleason score 3 + 4 = 7 adenocarcinoma involving 40% of the gland bilaterally. The lymphadenectomy specimen revealed 0 of 10 lymph nodes involved with metastatic disease. His postoperative PSA level was undetectable (< 0.02 ng/mL) at the 3-month postoperative follow-up timepoint.

At the 8-month postoperative timepoint, the patient was noted to have a detectable PSA level (0.1 ng/mL) that was confirmed on a second measurement. A restaging evaluation included a multiparametric MRI of the prostate bed with a phased array surface coil, computed tomography (CT) imaging of the chest, abdomen, and pelvis with contrast, and gallium 68 prostate-specific membrane antigen R2 positron emission tomography/CT imaging to investigate for evidence of gross locoregional recurrence. Although 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 (Fig. 1A).

In retrospect, this abnormality had likely been compressed and obscured by the endorectal coil during the presurgical staging MRI procedure and not noted at the time of surgical resection. The CT scans corroborated these findings, and additionally detected a component of this vascular malformation that extended to the anterior rectal wall (Fig. 1B). There was no evidence of locoregional recurrence on the positron emission tomography/CT scan. A lower endoscopy was performed to further characterize the lesion, and the results demonstrated the previously described internal hemorrhoids. In addition, a submucosal vascular malformation, which was compressible with insufflation, was visualized and deemed consistent with an arteriovenous malformation (AVM) or a rectal varix (Fig. 1C).

Based on 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, but the venous portion was found to map to a branch of the inferior mesenteric vein (Fig. 2). The portal venous pressure was noted to be elevated at 16 mm Hg. 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, MRI (Fig. 1E), CT (Fig. 1F), and a postembolization endoscopy verified a thrombosed rectal vascular malformation without signs of mucosal ischemia (Fig. 1G).

The patient was evaluated for possible causes of portal hypertension, including pre-, post-, and intrahepatic pathology testing. Laboratory tests included hepatitis serologies, human immunodeficiency virus testing, alanine and aspartate aminotransferase, gamma glutamyl transferase, bilirubin, haptoglobin, ceruloplasmin, rheumatoid factor, antinuclear antibody, antimitochondrial antibodies, and a full hematology panel, all of which showed unremarkable results. There was no history 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.

After successful ablation of the vascular malformation, the patient underwent salvage RT to a dose of 70.2 Gy in 39 daily fractions. Treatment was delivered concurrently with a 6-month course of androgen deprivation therapy. 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 genitourinary adverse events that did not require management. The patient had 2 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 before EBRT.

RT concluded in September 2019, and androgen deprivation therapy concluded in January 2020 with testosterone recovery by June 2020. At 32 months after EBRT, the patient 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], calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia[21], or Ehlers−Danlos[22] syndrome), 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 diagnosis of an AVM or rectal varix, because the lesion shared characteristics of both of these entities.

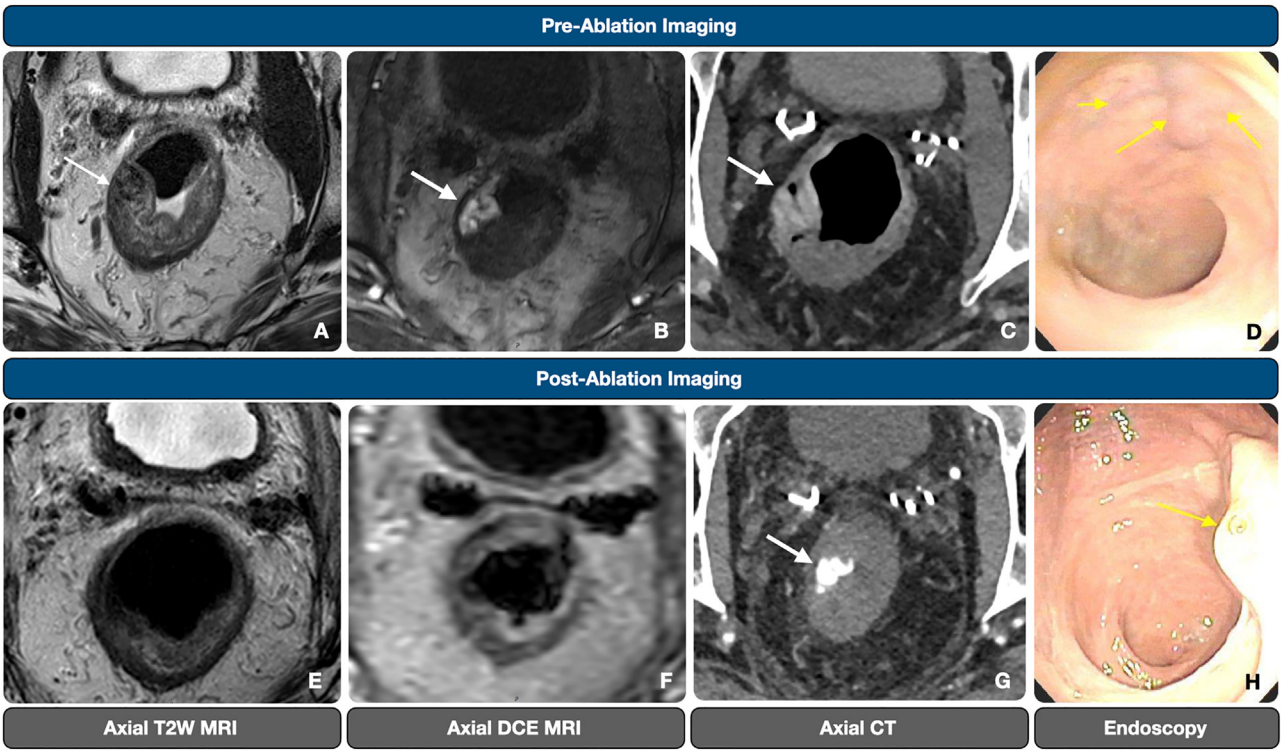

Fig. 1 Multimodal representations of preablation, A-D, and postablation, E-H, appearance of rectal vascular malformation, showing, A, preablation T2-weighted magnetic resonance imaging (MRI) with arrow indicating vascular malformation; B, preablation dynamic contrast-enhanced MRI with arrow indicating vascular malformation; C, preablation computed tomography with contrast with arrow indicating vascular malformation; D, preablation endoscopic view with arrows indicating mucosal distortion overlying vascular malformation; E, postablation T2-weighted MRI; F, postablation dynamic contrast-enhanced MRI; G, postablation computed tomography with contrast with arrow indicating iodinated embolization agent used to ablate vascular malformation; and H, postablation endoscopic view with no evidence of residual vascular malformation and arrow indicating ablation zone without evidence of residual malformation. *Abbreviations:* MRI = magnetic resonance imaging.

The arteriogram of the malformation demonstrated a large caliper arterial supply draining directly into a large caliper vein without routing through an intervening capillary plexus, which is consistent with an AVM. In contrast, moderately elevated portal venous pressures were observed on portal vein manometry, suggesting a diagnosis of a rectal varix. In this case, the arterial supply originated from the internal iliac artery, which typically

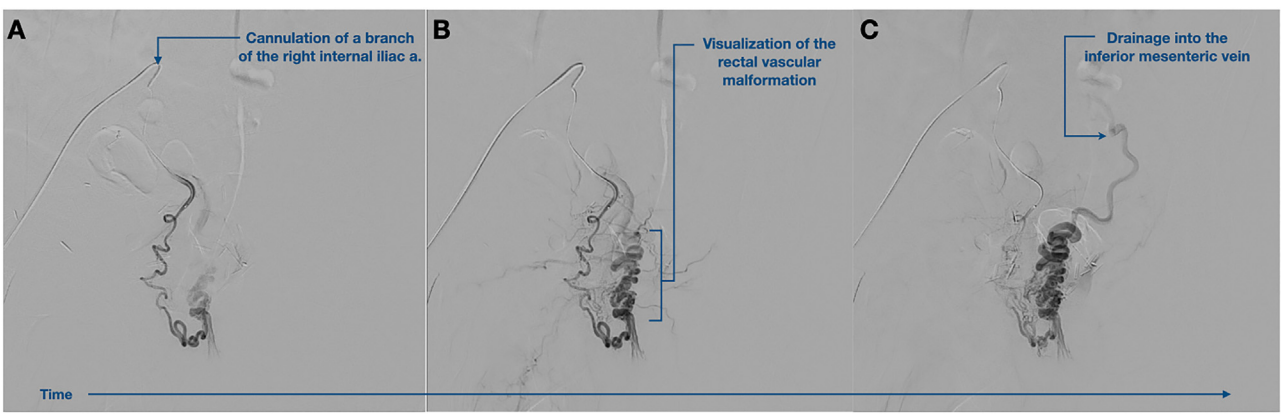

Fig. 2 Representative views of angiogram showing, A, cannulation of a branch of the right internal iliac artery; B, visualization of rectal vascular malformation; and C, drainage into inferior mesenteric vein.

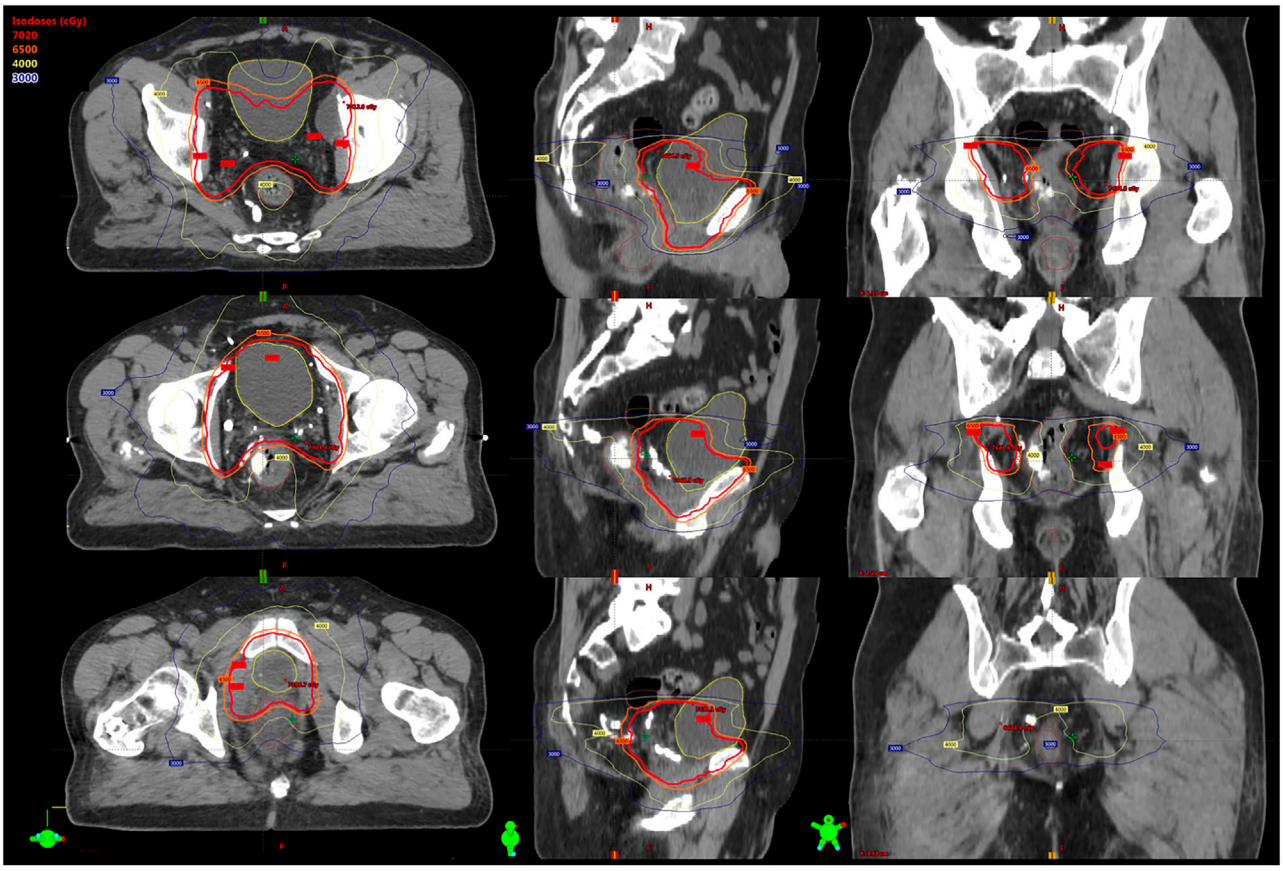

Fig. 3 Representative axial, sagittal, and coronal views of delivered plan with 70.2 Gy, 65 Gy, 45 Gy, and 30 Gy isodose lines overlaid.

supplies the middle and inferior rectal arteries. Classically, this territory often drains via systemic venous drainage (iliac veins to inferior vena cava), but in this case, the drainage was through the portal venous system via the inferior mesenteric artery.

Patients often only present for medical attention with bleeding; thus, the incidence of asymptomatic AVMs within the population remains unknown. In patients undergoing a colonoscopy to evaluate GI bleeding, 1.4% to 3% will be found to have an AVM.[29,30] Although most AVMs of the intestine are located in the cecum or ascending colon,[31] AVMs of the rectum are not uncommon (14%).[29] Asymptomatic AVMs are often observed, because the risk of subsequent bleeding is thought to be low, but 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, RT is not a standard management strategy for other GI vascular malformations.

Varices are another cause of symptomatic GI bleeding, however, most available literature describes the management of esophageal varices resulting 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 (3%-5%). Although 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 that are independently associated with GI bleeding.

In the present case, the vascular malformation had features of both an AVM and 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 RT. 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 androgen deprivation therapy with or without EBRT, no difference was observed between the 2 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 because 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 postprostatectomy EBRT, or procedural ablation preceding a standard course of EBRT. In this case, the concurrent treatment of the vascular malformation was preferred less because of the variceal features of the lesion.

Moreover, 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 RT treatment volume, because the lesion was located largely within the anatomic region at the 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 RT may limit the effectiveness of future procedural ablation of the malformation in the event of a catastrophic bleed. As such, pre-RT procedural ablation was chosen, which led to the desired clinical outcome producing durable oncologic control without serious or persistent rectal bleeding. However, because of the follow-up duration of this report, the risk of late rectal bleeding (>2.7 years) in this patient cannot be excluded.

Acknowledgments

This research was supported by the Intramural Research Program of the National Institutes of Health.

References

1. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med*. 2008;358:1250–1261.
2. Iyengar P, Levy LB, Choi S, Lee AK, Kuban DA. Toxicity associated with postoperative radiation therapy for prostate cancer. *Am J Clin Oncol*. 2011;34:611–618.
3. Thompson Jr IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: A randomized clinical trial. *JAMA*. 2006;296:2329–2335.
4. Willett CG, Ooi CJ, Zietman AL, et al. Acute and late toxicity of patients with inflammatory bowel disease undergoing irradiation for abdominal and pelvic neoplasms. *Int J Radiat Oncol Biol Phys*. 2000;46:995–998.
5. Valdagni R, Vavassori V, Rancati T, et al. Increasing the risk of late rectal bleeding after high-dose radiotherapy for prostate cancer: The case of previous abdominal surgery. Results from a prospective trial. *Radiother Oncol*. 2012;103:252–255.
6. Michalski JM, Moughan J, Purdy J, et al. Effect of standard vs dose-escalated radiation therapy for patients with intermediate-risk prostate cancer. *JAMA Oncol*. 2018;4: e180039.
7. Garin O, Suárez JF, Guedea F, et al. Comparative effectiveness research in localized prostate cancer: A 10-year follow-up cohort study. *Int J Radiat Oncol Biol Phys*. 2021;110:718–726.
8. Williams HRT, Vlavianos P, Blake P, Dearnaley DP, Tait D, Andreyev HJN. The significance of rectal bleeding after pelvic radiotherapy. *Aliment Pharmacol Ther*. 2005;21:1085–1090.
9. Johansen K, Bardin J, Orloff MJ. Massive bleeding from hemorrhoidal varices in portal hypertension. *JAMA*. 1980;244:2084–2085.
10. McCormack TT, Bailey HR, Simms JM, Johnson AG. Rectal varices are not piles. *Br J Surg*. 1984;71:163.
11. Wilson SE, Stone RT, Christie JP, Passaro Jr. E. Massive lower gastrointestinal bleeding from intestinal varices. *Arch Surg*. 1979;114: 1158–1161.
12. Amarapurkar D, Jadliwala M, Punamiya S, Jhawer P, Chitale A, Amarapurkar A. Cavernous hemangiomas of the rectum: Report of three cases. *Am J Gastroenterol*. 1998;93:1357–1359.
13. Yorozuya K, Watanabe M, Hasegawa H, et al. Diffuse cavernous hemangioma of the rectum: Report of a case. *Surg Today*. 2003;33: 309–311.
14. Brown CJ, Falck VG, Maclean A. Angiosarcoma of the colon and rectum: Report of a case and review of the literature. *Dis Colon Rectum*. 2004;47:2202–2207.
15. Lo YM, Gillett MB, Vina M, Collin J, Fleming KA. Hemangiosarcoma of the rectum after chronic anorectal ulceration. *J Clin Gastroenterol*. 1989;11:77–81.
16. Lorenz HP, Wilson W, Leigh B, Schecter WP. Kaposi's sarcoma of the rectum in patients with the acquired immunodeficiency syndrome. *Am J Surg*. 1990;160:681–683.
17. Kumar A, Nautsch D. Kaposi's sarcoma of the rectum in a homosexual male with HIV-AIDS. *ACG Case Rep J*. 2016;3:e192.
18. Abdalla SA, Letarte M. Hereditary haemorrhagic telangiectasia: Current views on genetics and mechanisms of disease. *J Med Genet*. 2005;43:97–110.
19. Jin XL, Wang ZH, Xiao XB, Huang LS, Zhao XY. Blue rubber bleb nevus syndrome: A case report and literature review. *World J Gastroenterol*. 2014;20:17254–17259.
20. Bean WB. Blue rubber bleb nevi of the skin and gastrointestinal tract. *Vasc Spiders Rel Lesions Skin*19581958:178–185.
21. Duchini A, Sessoms SL. Gastrointestinal hemorrhage in patients with systemic sclerosis and CREST syndrome. *Am J Gastroenterol*. 1998;93:1453–1456.
22. Paepe AD, Malfait F. Bleeding and bruising in patients with Ehlers—Danlos syndrome and other collagen vascular disorders. *Br J Haematol*. 2004;127:491–500.
23. Ishikawa S, Mukai S, Hirata Y, et al. Rectal arteriovenous malformation treated by transcatheter arterial embolization. *Case Rep Gastroenterol*. 2020;14:7–14.
24. Mahmood S, Bollipo S, Steele S, et al. It's all the RAVE: Time to give up on the "chronic radiation proctitis" misnomer. *Gastroenterology*. 2021;160:635–638.
25. Fuchizaki U, Kamata T, Miyamori H. Endoscopic management of life-threatening rectal Dieulafoy-like lesions. *Gastroint Endosc*. 2007;65:AB264.
26. Kalman DR, Banner BF, Barnard GF. Rectal Dieulafoy's or angiodysplasia? *Gastroint Endosc*. 1997;46:91–92.

27. Yeoh KG, Kang JY. Dieulafoy's lesion in the rectum. *Gastroint Endosc*. 1996;43:614–616.
28. Wiechowska-Kozłowska A, Białek A, Milkiewicz P. Prevalence of 'deep' rectal varices in patients with cirrhosis: An EUS-based study. *Liver Int*. 2009;29:1202–1205.
29. Höchter W, Weingart J, Kühner W, Frimberger E, Ottenjann R. Angiodysplasia in the colon and rectum. Endoscopic morphology, localisation and frequency. *Endoscopy*. 1985;17:182–185.
30. Richter JM, Hedberg SE, Athanasoulis CA, Angiodysplasia Schapiro RH. Clinical presentation and colonoscopic diagnosis. *Dig Dis Sci*. 1984;29:481–485.
31. Meyer CT, Troncale FJ, Galloway S, Sheahan DG. Arteriovenous malformations of the bowel: An analysis of 22 cases and a review of the literature. *Medicine (Baltimore)*. 1981;60:36–48.
32. Karlsson B, Lindqvist M, Blomgren H, et al. Long-term results after fractionated radiation therapy for large brain arteriovenous malformations. *Neurosurgery*. 2005;57:42–49.
33. Shimizu K, Sunagawa Y, Ouchi K, Mogami T, Harada J, Fukuda K. External beam radiotherapy for angiographically diagnosed arteriovenous malformation involving the entire pancreas. *Jpn J Radiol*. 2013;31:760–765.
34. Sato M, Kishi K, Shirai S, et al. Radiation therapy for a massive arteriovenous malformation of the pancreas. *Am J Roentgenol*. 2003;181:1627–1628.
35. Kishi K, Shirai S, Sato M, Sonomura T. Role of external beam radiotherapy for arteriovenous malformation of the pancreas. *Jpn J Radiol*. 2011;29:517–520.
36. Al Khalloufi K, Laiyemo AO. Management of rectal varices in portal hypertension. *World J Hepatol*. 2015;7:2992–2998.
37. Shudo R, Yazaki Y, Sakurai S, Uenishi H, Yamada H, Sugawara K. Clinical study comparing bleeding and nonbleeding rectal varices. *Endoscopy*. 2002;34:189–194.
38. Waxman JS, Tarkin N, Dave P, Waxman M. Fatal hemorrhage from rectal varices. Report of two cases *Dis Colon Rectum*. 1984;27:749–750.
39. Slagsvold JE, Viset T, Wibe A, Kaasa S, Widmark A, Lund JÅ. Radiation therapy did not induce long-term changes in rectal mucosa: Results from the randomized Scandinavian Prostate Cancer Group 7 trial. *Int J Radiat Oncol Biol Phys*. 2016;95:1268–1272.
40. Rowe LS, Harmon S, Horn A, et al. Pattern of failure in prostate cancer previously treated with radical prostatectomy and postoperative radiotherapy: A secondary analysis of two prospective studies using novel molecular imaging techniques. *Radiat Oncol*. 2021;16:32.
41. Harmon G, Chan D, Lee B, et al. Validating modern NRG Oncology Pelvic Nodal and Groupe Francophone de Radiothérapie Urologique prostate bed contouring guidelines for post-prostatectomy salvage radiation: A secondary analysis of the LOCATE trial. *Int J Radiat Oncol Biol Phys*. 2021;111:1195–1203.