Rectal ulcer associated with lenvatinib 15 years after definitive radiotherapy for prostate cancer: A case report

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Abstract. Lenvatinib is a multi-kinase inhibitor that blocks vascular endothelial growth factor, fibroblast growth factor and platelet-derived growth factor receptors. The present study describes a case of rectal ulceration triggered by lenvatinib treatment for hepatocellular carcinoma 15 years after definitive radiotherapy for prostate cancer. A 58-year-old man underwent definitive external beam radiotherapy and high-dose-rate brachytherapy for prostate cancer. A total of 15 years after radiotherapy for prostate cancer, the patient was diagnosed with hepatocellular carcinoma with multiple metastases. Treatment with 12 mg/day lenvatinib was commenced. A total of 4 months after starting lenvatinib therapy, the patient experienced persistent anal pain with a deep ulceration of the anterior wall of the lower rectum. As the pain did not improve, the patient chose to undergo a colostomy, resulting in the resolution of the anorectal pain. To the best of our knowledge, the present case report is the first to report on lenvatinib-induced rectal ulcers after radiotherapy.

Introduction

Tyrosine kinase inhibitors (TKIs) have recently been used to treat many solid tumors. Multi-kinase inhibitors include sorafenib, sunitinib, and lenvatinib. Lenvatinib also has an angiogenesis-inhibiting effect by suppressing vascular endothelial growth factor (VEGF), fibroblast growth factor, and platelet-derived growth factor receptors. In Japan, it is used to treat thyroid, hepatocellular, thymic, endometrial, and renal cell cancers (1,2).

In treatments involving angiogenesis inhibitors, a history of radiotherapy is considered a risk factor for mucosal damage, such as perforation and fistula formation (3-5). Fatal colonic perforation due to sorafenib use and fatal bronchial perforation leading to a fistula due to sunitinib use have been reported in patients with a history of radiotherapy (6,7). To the best of our knowledge, there are no reports of prior radiation therapy being a risk factor for mucosal damage in the gastrointestinal tract or other organs during lenvatinib treatment. Herein, we report a case of rectal ulceration triggered by lenvatinib use 15 years after definitive radiotherapy for prostate cancer.

Case report

A 58-year-old man had a high prostate-specific antigen level (15.6 ng/ml) during a check-up. Subsequently, he underwent a transrectal prostate biopsy, and a diagnosis of prostate cancer was made on pathological analysis. He then underwent a thorough examination, which revealed a Gleason score of 7 (3+4), cT3bN0M0 cStage III, and a diagnosis of high-risk prostate cancer according to the National Comprehensive Cancer Network classification. A bilateral obturator lymph node biopsy was performed, and the pathological findings revealed no lymph node metastasis. The patient underwent external beam radiotherapy (EBRT) in 16 fractions of 2.3 Gy to a total dose of 36.8 Gy, and high-dose-rate brachytherapy (HDR-BT) in four fractions of 6.0 Gy within 30 h to a total dose of 24.0 Gy for the prostate cancer (Fig. 1). The EBRT included four-portal irradiation with 10 MV X-rays targeting the prostate and seminal vesicles, and HDR-BT was prescribed for the prostate and seminal vesicle periphery with 12 applicator needles (8). The biologically effective dose (BED) with the α/β set to 3 was 95.6 Gy for the rectum and 178.6 Gy for the urethra. Two weeks after the completion of radiotherapy, anal pain, odynuria, and dysuria appeared; these symptoms improved after the administration of prednisolone 20 mg/day for 3 days. Three weeks after prednisolone administration, a rectal endoscopic biopsy was performed, which revealed no fibroblast or fibrinoid degeneration of the small arteries typical of radiation colitis. There was no biochemical recurrence of the prostate cancer. Although grossly bloody stools were observed once a month, fecal occult blood tests were negative once every 6 months. Ten years after the completion of radiotherapy,

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Abbreviations: BED, biologically effective dose; EBRT, external beam radiotherapy; HDR-BT, high-dose-rate brachytherapy; TKIs, tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor

Key words: levantinib, multi-kinase inhibitor, radiotherapy, rectal ulcer, VEGF

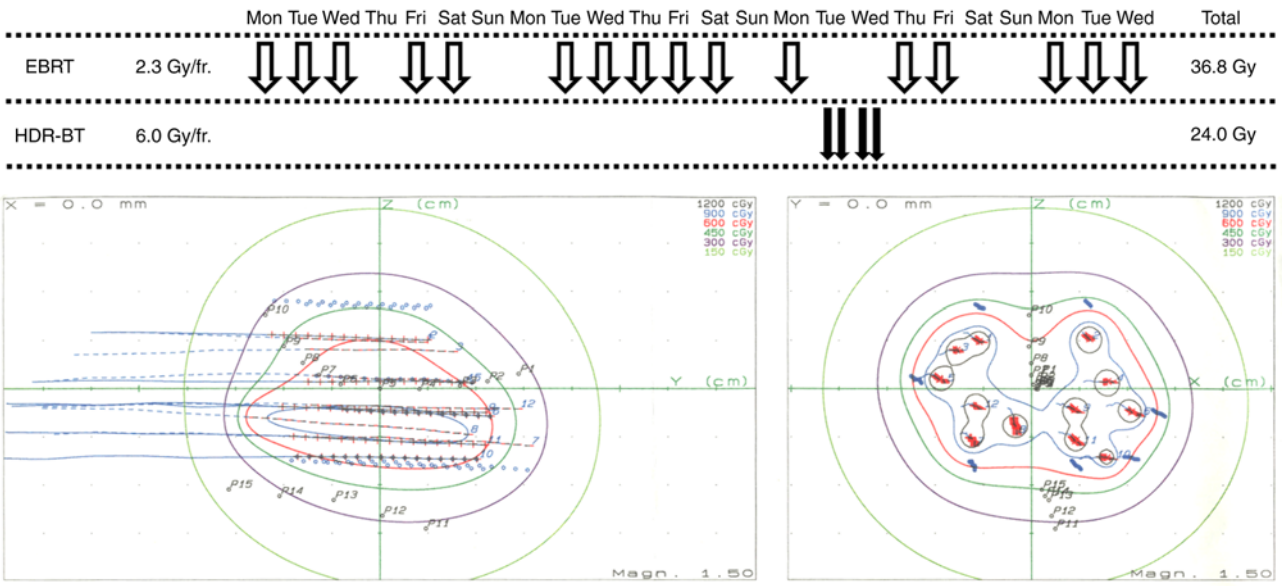

Figure 1. Radiotherapy schedule and dose distribution of high-dose-rate brachytherapy for prostate cancer. High-dose-rate brachytherapy was administered during the course of external beam radiotherapy. In the dose distribution diagram, 12 needle applicators were used and P1-P10 and P11-P15 indicate urethral and rectal reference points, respectively. EBRT, external beam radiotherapy; HDR-BT, high-dose-rate brachytherapy.

a lower gastrointestinal endoscopy was performed due to a positive stool occult blood test. Only vasodilatation consistent with an irradiated area in the rectoanal region was observed, with no active bleeding or ulcers (Fig. 2).

Fifteen years after radiotherapy for prostate cancer, the patient visited a hospital for fatigue, and a blood test revealed liver dysfunction. A computed tomography scan was performed, which led to the discovery of hepatocellular carcinoma with multiple lung metastases and bone metastasis to the fifth lumbar vertebra. The ECOG Performance Status at the start of lenvatinib administration was 1. The patient underwent treatment with 12 mg/day of lenvatinib. One month after commencing lenvatinib, the patient experienced pain due to the fifth lumbar vertebra metastasis; therefore, EBRT at 36 Gy in 10 fractions for 2 weeks (BED 79.2 Gy at $\alpha/\beta=3$) was concurrently administered with lenvatinib. Three months after starting lenvatinib, diarrhea, fatigue, and persistent anal pain developed, and a hydrocortisone ointment was administered to the perianal area. Four months after starting lenvatinib therapy, the patient underwent lower gastrointestinal endoscopy due to persistent anal pain. Circumferential vasodilatation was observed in the lower rectum, and a deep ulceration of the anterior wall of the lower rectum on the dorsal side of the prostate was observed with no inflammation in other areas of the colon (Fig. 2). Ten years after radiation therapy for prostate cancer, lower gastrointestinal endoscopy revealed blood vessel dilatation at that exact same location. Therefore, we assumed that this ulcer was related to the radiotherapy for the prostate cancer. An acute hemorrhagic rectal ulcer is considered an alternative diagnosis. However, patients presenting with acute hemorrhagic rectal ulcers are frequently elderly individuals with an ECOG Performance Status of 3-4. Since our case had an ECOG Performance Status of 1, it was unlikely that this patient had an acute hemorrhagic rectal ulcer. We believe that the EBRT for metastasis to the fifth lumbar vertebra did not affect the rectal ulcer due to the large distance between the irradiation field and the ulcer site. The computed tomography scan revealed rectal wall thickening, and poor contrast effect of the rectal wall only on the prostatic side, suggesting a deep ulcer and disruption of the rectal wall; however, there was no evidence of air outside the gastrointestinal tract, which would indicate perforation (Fig. 3). Therefore conservative treatment was administered. However, the symptoms did not improve. Therefore, the patient chose to undergo colostomy to improve inflammation and pain at the ulcer site by reducing the mechanical stimulation caused by defecation, and as a result, the anal pain resolved. Based on the Common Terminology Criteria for Adverse Events 5.0, the patient was diagnosed with a grade 3 rectal ulcer, which could be treated by standby surgery. Eight months after starting lenvatinib treatment, the patient died of liver failure associated with an enlargement of the hepatocellular carcinoma. Other than ulcers, no grade 2 or higher adverse events were noted with the use of lenvatinib.

Discussion

To the best of our knowledge, this is the first report of lenvatinib-induced rectal ulcers following radiotherapy. The safety of the concurrent or heterogeneous use of radiotherapy and molecular-targeted drugs is controversial. With respect to the VEGF inhibitor bevacizumab, a history of radiotherapy is known to be one of the risks for gastrointestinal perforation (5). The mechanisms of interaction between angiogenesis inhibitors and ionizing radiation are complex and may involve multiple interactions between the tumor stroma, vasculature, and tumor cells (9).

Multi-kinase inhibitors inhibit angiogenesis. With regard to the multi-kinase inhibitor sunitinib, although there are reports of good tolerability with concurrent radiotherapy, there are also reports of bronchobiliary fistulas and gastrointestinal perforations in patients previously treated with radiotherapy (10). Since lenvatinib inhibits angiogenesis, there is a potential risk of exacerbating adverse events with radiotherapy. A study of lenvatinib monotherapy in 261 patients with thyroid cancer showed grade 2 or less rectal bleeding in four patients (1.5%) and grade 3

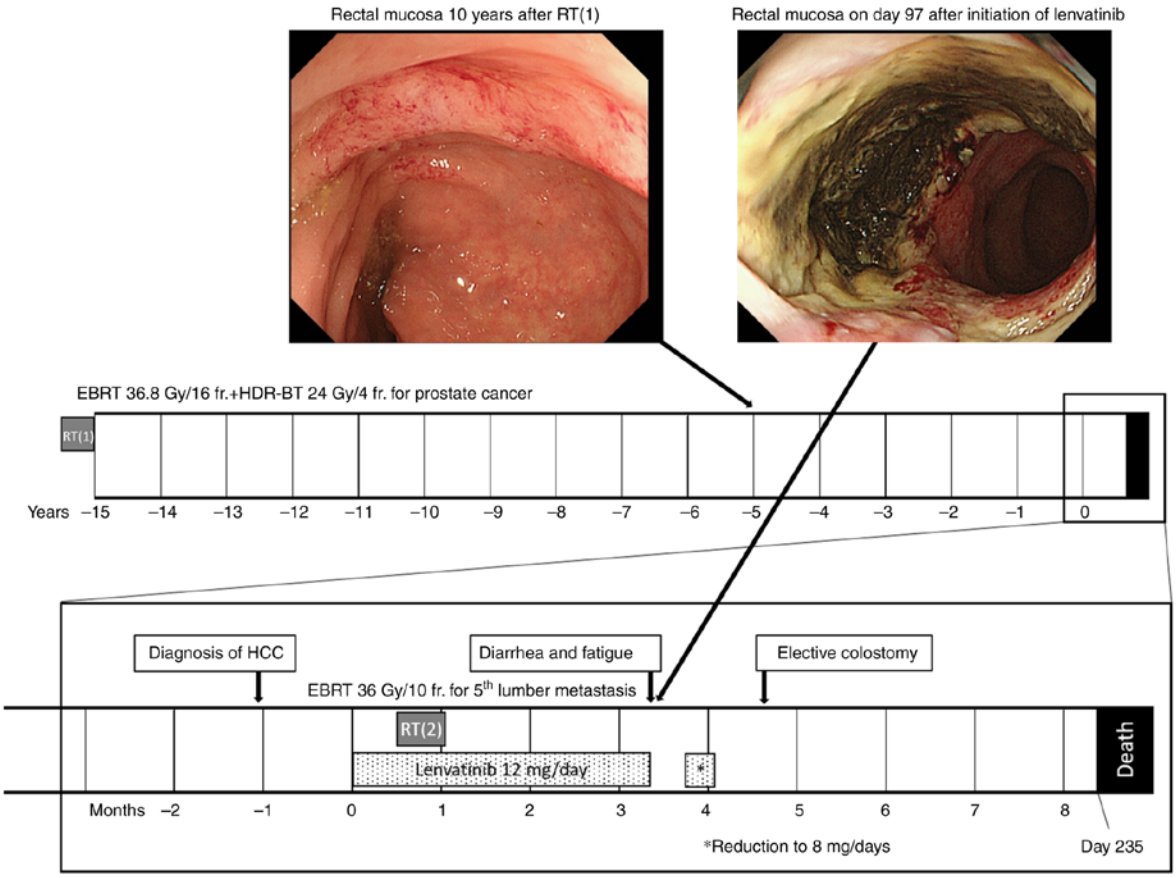

Figure 2. A schematic presentation of the clinical course. Ten years after the completion of radiotherapy for prostate cancer, only vasodilatation consistent with an irradiated area in the rectoanal region was observed. Fifteen years later, the patient was diagnosed with hepatocellular carcinoma and started on 12 mg/day lenvatinib. On day 97 after lenvatinib administration, a deep ulceration of the anterior wall of the lower rectum was observed. EBRT, external beam radiotherapy; HDR-BT, HCC, hepatocellular carcinoma; high-dose-rate brachytherapy.

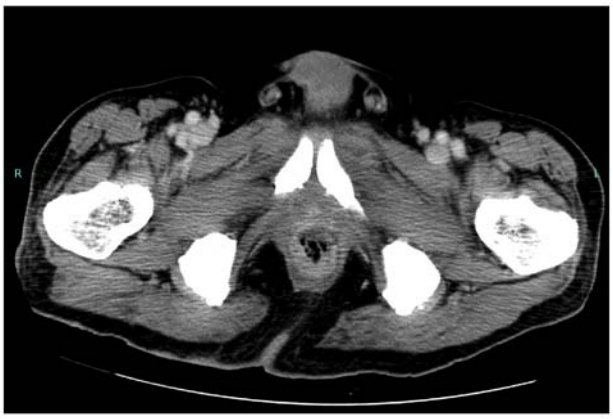

Figure 3. A computed tomography image of rectal ulcer. There were rectal wall thickening, and poor contrast effect of the rectal wall only on the prostatic side, suggesting a deep ulcer and disruption of the rectal wall; however, there was no evidence of air outside the gastrointestinal tract, which would indicate perforation.

gastrointestinal fistula in 2 patients (0.8%) in terms of adverse events (11). In a Japanese nationwide survey regarding HDR-BT for prostate cancer involving 3424 cases, there were three cases of grade 3 rectal ulcers (0.09%) and one case of grade 4 rectal fistula (0.03%) (12). The incidence of gastrointestinal ulcers was low when both treatments were administered alone.

In this case, the BED with the α/β set to 3 was 95.6 Gy for the rectum. Clark *et al* showed a low incidence of rectal adverse events when the rectal dose was less than 125 Gy for the BED (13), which was not a high-risk group for severe rectal ulceration in terms of rectal dose. In a long-term observational study of cervical cancer treated with a combination of EBRT and HDR-BT, the incidence rates of grade 3-5 rectosigmoid colon complications were 3.8, 4.4, and 5.3% at 5, 10, and 20 years, respectively (14). Moreover, rectosigmoid colon complications occurred most frequently during the first 2 years, after which the incidence decreased markedly (14). Therefore, it is unlikely that a serious radiation-related rectal adverse event occurred for the first time 15 years after HDR-BT.

In this case, only vasodilation of the rectum, consistent with the irradiated area, was observed 10 years after the completion of HDR-BT. Nevertheless, because the rectal ulcer appeared after lenvatinib administration, it is reasonable to assume that lenvatinib administration triggered a synergistic effect with the burden of the previous radiotherapy. Regarding late gastrointestinal complications after radiotherapy, Pollom *et al* reported complex wounds associated with fibrosis, vascular hypodensity, and thrombosis (15). VEGF inhibition not only inhibits the ulcer healing process but can also result in vascular hypodensity and thrombosis similar to those seen with radiation (15). Although the role of VEGF in repairing chronic or late radiation injury remains unclear, it has been reported that radiation-damaged

vessels are more sensitive to VEGF receptor inhibition in tumor model systems (16). The same mechanisms may have occurred in this case. In contrast, no enteritis was observed in the intestinal tract around the lumbar spine, where palliative irradiation was performed. Metcalfe *et al* reported that the labial chorionic villus structure was unchanged at doses of 2 Gy or less; however, it began to be compromised at higher doses of 6 Gy or more (17). If the dose in one fraction is low, the combination of both therapies may not cause impairment. Evaluation of the prevalence and potential risk factors of lenvatinib fistula and organ perforation in radioiodine-refractory thyroid cancer suggests that EBRT should not be considered an exclusion criterion for lenvatinib initiation (18). However, it should be noted that no details on the number of fractions are available because they are evaluated as greater than or less than 30 Gy. Moreover, the histologic type and degree of tumor invasion have been shown to be risks for fistula and organ perforation.

We believe that lenvatinib and anti-VEGF agents are important treatment options for hepatocellular and other carcinomas and may improve the prognosis; thus, their use should not be avoided even if there is a history of radiation therapy. However, it is important to keep in mind that, although rare, a history of high-dose radiotherapy of one fraction may lead to ulceration, as in this case. In conclusion, we present a case of rectal ulceration induced by lenvatinib treatment 15 years after the completion of definitive radiotherapy for prostate cancer. Further studies regarding this type of case are warranted.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YK collected the data. YK, KW and KK drafted the manuscript. YK, KW, RT, YM, AS and KK designed the study. YK and KW confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the wife of the patient with respect to the publication of this case report.

Competing interests

The authors declare that they have no competing interests.

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