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Case reports and case series

A biodegradable rectal balloon implant to protect the rectum during prostate cancer radiotherapy for a patient with active Crohn's disease

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ABSTRACT

Background: Radiotherapy in patients with active inflammatory bowel disease (IBD) is usually considered an absolute exclusion criterion for prostate cancer radiotherapy treatment.

There are no reports available on the use of a biodegradable rectal balloon implantation (RBI) in patients with active IBD for prostate cancer radiotherapy.

Case presentation: We report on a patient with high-risk prostate cancer with the comorbidity of an active IBD with pancolitis location. He was treated with neo-adjuvant hormonal therapy and high-dose external beam radiotherapy to the prostate and the seminal vesicles. Before radiotherapy treatment, a biodegradable RBI was implanted between the prostate and the anterior rectal wall to push the rectum outside of the high-dose area. This patient at high-risk for rectal toxicity was successfully irradiated to his prostate with only a grade I urinary toxicity, no acute rectal toxicity or toxicity flare of the IBD.

Conclusions: This case describes the use of a RBI implantation in patients with active IBD for prostate cancer radiotherapy. The use of a biodegradable RBI proved to be a promised solution for such patients, and have to be further investigated.

Introduction

Inflammatory bowel disease (IBD) is a chronic inflammation of the gastrointestinal (GI) tract in individuals with a genetic predisposition, who have been exposed to environmental risk factors, without an infectious cause [1]. IBD refers to a disease comprising two major disorders: ulcerative colitis and Crohn's disease. Active and medically controlled IBD are generally considered to be absolute or relative contraindications for using ionising radiation because of the severely increased risk of GI toxicity, with reported grade $\geq$3 late GI complications attributable to external beam radiation therapy (EBRT), up to as much as 73% using conventional EBRT techniques [2,3].

The current standard of care for locally advanced prostate cancer is high-dose EBRT and/or brachytherapy or radical prostatectomy [4,5]. EBRT for prostate cancer may lead to GI toxicity as a common side-effect, which has a negative impact on the quality of life even many years after the EBRT [6,7]. Several devices have been developed to spare anorectal structures [8]. Implantable rectum spacers (IRS) push the anterior rectal wall away from the prostate by injection of an absorbable hydrogel [9], a hyaluronic acid [10], a saline-filled balloon [11], or a collagen implant [12]. Several studies have confirmed that an IRS decreases the rectal dose leading to decreasing acute and late rectal toxicity, and consequently increasing cost-effectiveness [13–15].

In this report, we present a patient with a high-risk cT2N0 Gleason 4 + 5 prostate cancer treated with neo-adjuvant hormonal therapy and concurrent EBRT using volumetric-modulated arc therapy (VMAT). A biodegradable rectal balloon implant (RBI) was applied before the start of EBRT to protect and push the anterior rectal wall out of the irradiation field. This case report illustrates a possible workaround for the problem of active IBD for a patient in need of prostate cancer radiotherapy.

Case presentation

A 73-year-old man was diagnosed with a Gleason 4 + 5 = 9 adenocarcinoma of the prostate by a routine blood measurement

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(PSA 9.2 ng/ml). Transrectal ultrasound-guided biopsies of the prostate revealed a Gleason 4 + 5 prostate cancer, 6/6 in the right side in 30 to 80% of the biopsies. Left side was negative. The patient was in good condition, with a World Health Organization (WHO) performance status of 0, but with active IBD status (Crohn's). Crohn's-associated ulcerative lesions were reported over the whole colon-rectum, with approximately monthly exacerbations. The patient reported more than four stools a day, with loss of mucus, and urgency. He was on sustained medical treatment (golimumab 100 mg), adjusted with prednisone 15 mg for an exacerbation. Magnetic resonance imaging (MRI) revealed a tumour in the right side of the prostate with dubious extra-prostatic spread to the apex (Fig. 1). No suspected lymph nodes or seminal vesicles invasion were observed. A bone scan revealed no metastases. Clinical staging was a high-risk cT2-3a (dubious MRI) N0 prostate cancer.

The patient was discussed at a multi-disciplinary tumour board. In light of the patient's relatively young age and good life expectancy, a curative treatment was recommended. Brachytherapy as monotherapy was not considered because of the high Gleason score and the high-volume disease. Radical prostatectomy was not considered due to the high Gleason score, the dubious extra-prostatic spread to the apex, and the possible adhesions. The risk of a positive section margin was assumed to be very high, with consequentially the need for salvage EBRT with associated high rectal toxicity. Moreover, radical prostatectomy would preclude the implantation of an RBI to decrease GI toxicity. Therefore, primary neo-adjuvant hormonal therapy for six months was suggested to attempt a possible downstage of the prostate cancer and to diminish the activity of the Crohn's disease, followed with high-dose EBRT in combination with an RBI.

We started with neo-adjuvant hormonal therapy for six months to downstage [16]. After three months, the PSA had decreased to 0.4 ng/ml, with testosterone at castration level (<0.3 nmol/L). The IBD was relatively stable with one flare during these three months. After approximately six months the preparations for EBRT were started: First, fiducial markers were implanted intra-prostatically. Secondly, an RBI was implanted between the prostate and the anterior rectal wall. The RBI was implanted transperineally under bi-plane transrectal ultrasonography guidance. The injection technique has been described previously [17]. A bubble-free (sterile) saline solution was used to fill and inflate the RBI. The saline solution was mixed with approximately 1.5 cm^3 iodinated contrast medium to enhance the visualisation of the RBI on computed tomography (CT) scans and cone-beam CT scans. The volume of the prostate was adequately decreased with hormonal therapy (<35 cm^3), and therefore a 12 cm^3 of saline liquid was as enough to guarantee a prostate-rectum separation of at least 1 cm [17].

The implantation procedure was tolerated well, without complications. No pain or discomfort in the perineal region (according to Visual Analogue Scale (VAS)) was reported in the week after the implantation. The perineal region showed no signs of infection.

A CT scan and an MRI scan (Fig. 1) were performed 7 days after RBI implantation in supine position with a slice thickness of 3 mm for treatment planning and delineation purposes, respectively. A filled bladder was asked for the planning scans and every treatment fraction. The CT and MRI scans were co-registered on the fiducial markers.

Delineation of the prostate (: CTV = clinical target volume) was performed on the T2-weighted MRI scan, while the RBI, the base of the seminal vesicles (according to the prognostic Partin risk group) and the organs at risk were delineated on the CT scan [18]. The planning target volume (PTV1) was constructed according to the institutional protocol (CTV + 10 mm cranial - caudal, +7 mm anterior - posterior, +6 mm left - right).

This patient was treated using VMAT radiotherapy to a dose of 70 Gray (Gy) [19] (28 fractions of 2.5 Gy) with 10 MV photon beams (Eclipse Version ICD-10, Varian Medical Systems Inc., Palo Alto, USA) (Fig. 2). The overall treatment time was 7 weeks, at 4 fractions a week. The irradiation plan revealed a V65 (relative volume of rectum receiving 65 Gy or more) of 0.2%, a V54 of 8.4% and a maximum point dose on the rectum of 66.5 Gy.

The EBRT treatment was very well tolerated: the patient only had a slight difference in urinary excretion reported as a grade I according to the Common Terminology Criteria for Adverse Events (Version 4.0) [20]. The acute urinary side effects consisted only of slightly raised frequency with nocturia 2 to 3 times a night. No acute rectal toxicity, pain or urgency were reported by the patient. No additional medication was prescribed. Three weeks after EBRT, the patient reported no complaints at all. The IBD was unremarkable, and no exacerbation was observed during and after the EBRT. Ten months after EBRT, the PSA had dropped to an undetectable level and the patient reported no complaints.

Discussion

In the literature, an (active) IBD has long been considered to be a relative (or even absolute) contraindication for the use of ionising radiation therapy to sites including bowel structures, because of the extremely increased risk of GI toxicity (grade 3 up to 73% using

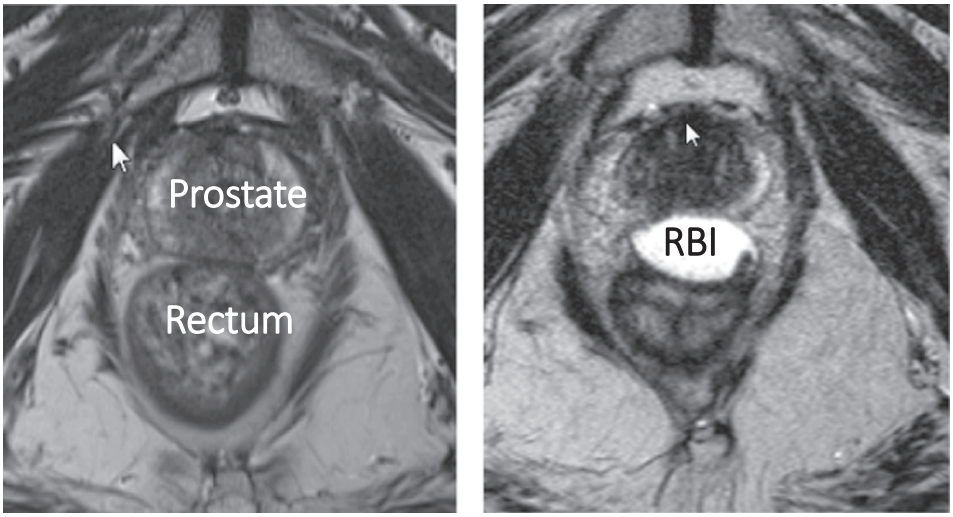

Fig. 1. Axial T2-weighted MRI of a patient with an RBI before (a) and after implantation (b). *Abbreviation*: MRI = Magnetic Resonance Image; RBI = Rectal Balloon Implant.

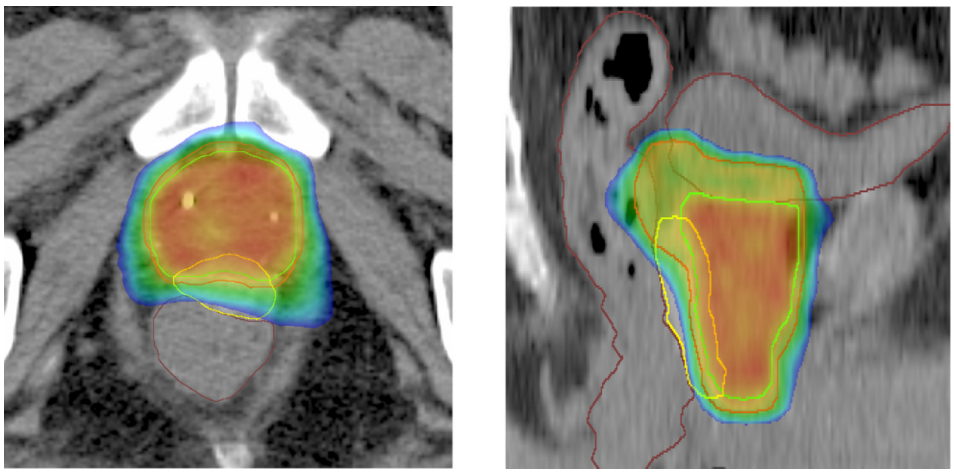

Fig. 2. Color-wash isodose distribution in an axial (a) and sagittal (b) CT plane after RBI (yellow) implantation, with prostate PTV1 (green), PTV2 (red). The prescribed dose to PTV1 and PTV2 was 65.8 and 70 Gy, in 28 fractions of 2.35 and 2.5 Gy, respectively. Image (a) shows the high-dose region >70% (blue) with nearly no overlap in the rectum (brown). The high-dose region >85% (green) reveals no overlap at all within the rectum. In image (b) at the more cranial part there is minimal overlap observed. *Abbreviation*: RBI = Rectal Balloon Implant; PTV = Planning Target Volume.

conventional EBRT techniques) [2,3]. A few papers have been published on the use of EBRT in IBD patients.

Willett et al. found a 46% incidence of serious acute, and 21% incidence of late side effects [2]. They observed a five-year late toxicity of 73% with conventional EBRT techniques, compared to 23% using specialised techniques ($p = .02$).

In a review, Tolia et al. reported that the grade ≥ 3 acute and late GI complications attributable to EBRT ranged between 20–21%, and 8–29%, respectively [3]. They observed that the location and the activity status of the IBD in combination with the EBRT bowel dose and volume are related to the severity of post-irradiation morbidity.

Recently, Murphy et al. analysed the acute GI toxicity exacerbation in patients on concomitant medical therapy for IBD during an EBRT treatment: 57% with medication versus 8% without (absolute difference of 49%; 95% CI 10 to 89%, $p = .03$) [21]. The five-year risk of late GI toxicity was relatively low with no significant differences. However, caution should be taken because of consequential late damage [22]. They concluded that EBRT should not be recommended for patients who are in an active flare of an IBD or had an acute flare in the year before treatment.

Furthermore, White et al. evaluated the association of the use of modern radiation techniques in patients with decreased acute toxicity: acute grade ≥ 2 toxicity occurred in 28% of patients treated with intensity-modulated radiotherapy (IMRT) versus 100% of patients treated with 3D-conventional RT ($p = .01$). They concluded that modern EBRT techniques diminish the risk of GI toxicity in IBD patients [23].

Song et al. reported an 21% incidence of acute grade ≥ 3 toxicity effects. All patients who had grade ≥ 3 had received concurrent chemotherapy ($p = .04$) [24].

The reported studies are difficult to interpret, because of the limited sample size with a very low number of events and the retrospective designs. Furthermore, wide confidence intervals are given, which indicates the need for careful selection to identify patients who are expected to face GI exacerbation from EBRT.

Given the fact that IBD comprises GI mucosal inflammation, the concern for using irradiation therapy is reasonable [23]. Caution should be taken when exposing a considerable volume of bowel structures to significant doses of radiation, either through EBRT or brachytherapy. High-dose ionising radiation (EBRT and/or brachytherapy) is therefore usually avoided for this patient population. As a result, the outcome and survival may be compromised for these patients. In case of IBD, the risk of radiation-related bowel toxicity constitutes an enormous problem. To our knowledge, no radioprotective agents are available to circumvent this serious side effect and, consequently, excluding the sensitive structures from the high-dose region seems to be the only reasonable solution. This is the first case describing a successful RBI implantation for dose-escalated EBRT in a patient with active IBD to decrease the radiation dose at the rectal wall.

Some limitations of the proposed workaround are important to take into consideration.

First, the follow-up period (ten months) is relatively short to evaluate a complete late toxicity report.

Secondly, an additional potential concern regarding the placement of an RBI in patients with Crohn's disease could be submucosal inflammation and scarring, complicating the placement of such a device. To avoid this problem, a hydrodissection using saline is performed to create tissue planes and facilitate correct placement of the RBI between the Denonvilliers' fascia and the anterior rectal wall. Susil et al. demonstrated on a histologic basis that Denonvilliers' fascia could be accurately injected: a prostate-rectum separation of 10 mm was demonstrated as sufficient to reduce the mean rectal volume receiving 70 Gy by 83.1% ($p < .05$) [25].

Next, perforation in the rectal wall is earlier reported by Fisher-Valuck and colleagues in 9 out of 149 cases (6%). However they observed no correlation between rectal wall infiltration and patient complications till now [26], the ramifications of rectum perforations are not yet described when a patient has active IBD. More clinical studies are needed to prove the safety of this procedure in this category of patients.

Finally, most research of the use of spacers is limited in patients with low-and intermediate-risk prostate cancer. The role of spacers in locally advanced and high-risk prostate cancers regarding potential rectal wall invasion is not yet clear. Villers and co-authors reported in their series of 243 prostatectomy specimens that prostate cancer invaded the Denonvilliers' fascia in 19% of cases [27]. They observed in no cases tumour invasion completely through the full thickness of this structure. The possible negative influence of a spacer in cases with a dorsal prostate capsule rupture (cT3a) is unclear, as tumour cells could be displaced out of the high-dose region by the spacer [28]. Future studies are therefore mandatory to evaluate the role of spacers in these patients.

Conclusion

An active IBD under active medical therapy for IBD, would generally be regarded as an absolute contraindication for EBRT, based on the data from the literature discussed above. This case report illustrates a possible workaround for the problem of active IBD for a patient in need of prostate cancer radiotherapy. In our opinion, this treatment strategy using EBRT in combination with an IRS should be considered in this specified high-feature patient population to obtain the best outcome and survival.

Conflicts of interest

There is no conflict of interest for this research.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tipsro.2018.01.004.

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