Review Article

Effectiveness of rectal displacement devices during prostate external-beam radiation therapy: A review

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ABSTRACT

Dose-escalated prostate radiotherapy (RT) can improve treatment outcomes, but rectal toxicity is the main limiting factor for introducing dose-escalated RT. Pushing rectal wall away from the prostate reduces the volume of the rectum in high-dose region, which can decrease both short- and long-term rectal toxicities after RT. This review focuses on the literature using different rectal displacement devices such as endorectal balloons, tissue spacers, rectal retractor, and ProSpare during prostate External beam radiotherapy, with regard to dosimetric effects, clinical benefits, prostate motion, and postoperative RT setting.

KEY WORDS: Endorectal balloon, prostate cancer, rectal retractor, rectal toxicity, tissue spacer

INTRODUCTION

External-beam radiotherapy (EBRT) is an effective treatment approach for localized prostate cancer.[1] Dose-escalated prostate radiotherapy (RT) has been improved the biochemical control rates but increased rectal toxicities.[2,3] This risk of rectal toxicity is primary related to the anatomical proximity of the rectum and the prostate gland.[4] Early and late RT-induced rectal toxicities lead to moderate or severe effects on patient's quality of life (QOL). As the primary efforts, gold fiducial-based image-guided RT (IGRT), intensity-modulated RT (IMRT), and adaptive RT play a great role to reduce radiation-associated rectal complications.[5-7] The IGRT allows for reducing the planning target volume (PTV) margin, resulting in reducing rectal toxicity, and more rectal sparing can be achieved using IMRT.[7-9]

Recently, several studies have demonstrated that physical displacement of the rectum from the prostate is an effective method to reduce the rectal dose. According to this, rectal displacement devices (RDDs) such as endorectal balloons (ERBs), tissue spacers, rectal retractor (RR), and ProSpare are introduced to limit rectal exposure dose because these technologies push the rectal wall away from the prostate and reduce the volume of the rectum receiving high-radiation doses.[4,10-14]

The aim of this review is to critically synthesize the literature on the use of RDDs during prostate EBRT with regard to dosimetric effects, clinical benefits, inter-/intra-fraction prostate motion, and postoperative RT setting.

RECTAL DISPLACEMENT DEVICES

To spare rectum, several RDDs are introduced which are divided into ERBs, tissue spacers, RR, and ProSpare. ERBs have two main parts, including balloon and shaft; the balloon is made by latex or silicon. ERBs have been used during prostate RT as prostate stabilizer, have been used to reduce the prostate movement, and have also been used as rectal wall sparing technique. The deflated ERB

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is placed into the rectum and inflated with air or water. As a consequence, it pushes the lateral rectal wall and the posterior rectal wall (PRW) away from the high-dose areas.[15,16] A possible radiobiological reason for using an ERB can be associated with hypoxia in the rectal wall that is generated by stretching of the rectal wall, when an ERB is inflated and therefore leads to radioresistance of the rectal wall.[17]

To our knowledge, as displayed in Figure 1, there are four types of tissue spacers, including polyethylene glycol (PEG)-hydrogel, biodegradable balloon, hyaluronic acid (HA), and collagen, that these biomaterials implant or inject in the space between Denonvilliers fascia and the anterior rectal wall (ARW) and increase the distance from the prostate to the ARW.[11,18-21] The implantation or injection of these biomaterials is performed under local or general anesthesia. Patient is placed in the lithotomy position, and interstitial needle is inserted into the perirectal fat under transrectal ultrasound guidance; therefore, the procedure is invasive.[11,16]

An alternative method to ERB and tissue spacers for the rectum dose sparing is an RR that pushes the PRW away from the prostate. The RR consists of a rectal rod that inserts into the rectum in the supine or decubitus position. Then, it affixes to a vertical looking column to use to retract the rectum in the posterior direction. The vertical looking column fixes to a carbon-fiber base plate. The magnitude of retraction is determined by patient discomfort. In daily treatment, the position of RR reproduces like planning computed tomography (CT). The diameter of the rectal rod is 15 or 20 mm that is made of water-equivalent plastic such as Perspex.[4,14,22,23]

Recently, ProSpare has been introduced at the Institute of Cancer Research, London, UK. ProSpare is a novel rectal obturator that inserted into the rectum by the patient before planning CT and RT sessions and increases the distance between the ARW and the PRW. It is disposable and is made of Empera resin. Further, it provides guidance on the position of the ARW and the prostate localization due to series of radiopaque markers on the anterior and posterior (AP) wall of this device. There are three abstracts that address using a ProSpare.[12,24,25]

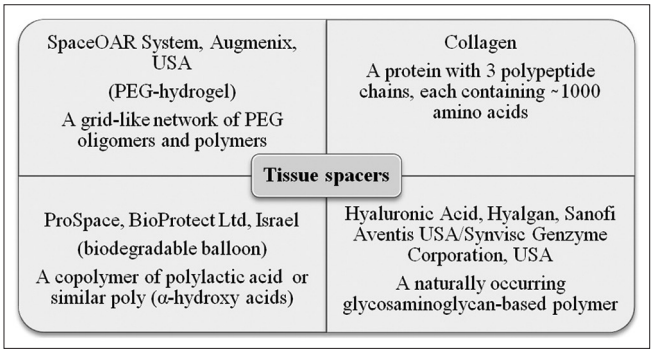

Figure 1: The tissue spacers mentioned in the literature

THE EFFECT OF RECTAL DISPLACEMENT DEVICES ON RECTAL DOSE REDUCTION AND RECTAL TOXICITY

Several groups of investigators investigated the effect of RDDs on the rectal wall dose. In prostate three-dimensional conformal RT (3DCRT), an ERB with intermediate volume (60 mL) significantly decreased the dose to the PRW.[26] The volume of ERB related to the volume of the clinical target volume (CTV). As demonstrated in several studies, it is necessary to select an ERB with intermediate volume (60 mL) when the CTV includes the seminal vesicles.[26] van Lin *et al*. compared three different types of ERBs (40, 80, and 100 mL) in both four-field 3DCRT and IMRT. In 3DCRT plan with different PTVs, using of each ERB led to significant reduction in the mean rectal wall dose, mean rectal wall volume receiving ≥50 Gy (V50 Gy) and ≥70 Gy (V70 Gy), and normal tissue complication probability (NTCP) of the rectal wall in comparison with non-ERB group. In IMRT plans, they observed no statistically significant reduction in the rectal wall mean dose and NTCP of rectal wall by three types of the ERBs.[15] Furthermore, the ERB could reduce the anal wall dose in prostate EBRT. Using an ERB resulted in an absolute reduction 12 and 7.5 Gy of anal wall mean dose in 3DCRT and IMRT, respectively.[27] On reducing rectal dose using tissue spacers during IMRT and 3DCRT, a prospective multicenter clinical trial by Song *et al*. involving 52 patients receiving IMRT for prostate cancer (39 Gy × 2 Gy) showed a reduction in the rectal V70 Gy ≥25% in 95.7% of patients after injection of PEG-hydrogel. After spacer implantation, for V70 Gy, a 60.7% relative reduction was found (13% vs. 5.1%).[28] The reduction in the rectal volume receiving high-radiation doses by tissue spacers directly is associated with a mean prostate–rectum separation of 10 mm after tissue spacer implantation. In prostate, IMRT with ProSpare also found a significant reduction in the minimum dose to the rectum and the anal V40–65 Gy ($P = 0.043$). In addition, the mean rectal surface doses were significantly reduced ($P = 0.001$).[24]

There are conflicting reports on the impact of an ERB on reducing dose to the rectum in prostate stereotactic body RT (SBRT). Although using an ERB significantly reduced the rectal and the ARW dose during prostate SBRT with CyberKnife,[16] these results did not reproduce during gantry-based RapidArc prostate SBRT.[29] These differences can be associated with dose delivery technique. In contrast to gantry-based RapidArc SBRT, using noncoplanar nonisocentric beams in CyberKnife-based SBRT can improve rectal sparing. However, further studies are required to elucidate the benefits of ERBs during prostate SBRT. A comparative study between the RR and PEG-hydrogel was performed by Wilton *et al*.[30] A significant reduction of rectal V30–80% could be detected with both devices in cases SBRT. Findings showed that RR could decrease further the volume of the rectum irradiated to low and intermediated doses than hydrogel spacer during SBRT.[30] In another comparative study, data showed that using PEG-hydrogel outperformed the ERB in any measured rectal dose metrics during prostate SBRT.[31]

Furthermore, few studies of RDDs have been published with prostate proton therapy with promising results.[23,32-34]

Although there are many studies on the effect of ERBs on the rectal dosimetry, clinical outcomes reported with using ERBs in a two-arm study are rare. A comparative study only indicated that late gastrointestinal (GI) toxicity reduced in prostate 3DCRT with ERB in comparison to without ERB. In study van Lin *et al*., two cohorts of 24 patients with and without an ERB treated with 3DCRT to a dose 67.5 Gy in 30 fractions. Endoscopic examinations of the patients were compared. The results showed that there were no significant differences in acute rectal toxicity between two groups. Late rectal toxicity (Grade ≥1) was significantly lower in the ERB group, and no patients had Grade ≥2 late rectal toxicity. Using an ERB reduced significantly high-grade telangiectasia.[17] In contrast with ERBs, several comparative studies evaluating the effect of tissue spacers in regard of toxicity have been performed until now. A pivotal prospective multicenter single-blind randomized controlled trial (149 with PEG-hydrogel and 73 without) has reported that acute rectal toxicity rates were similar between groups at 3 months after RT. After a median follow-up of 15 months, late rectal toxicity of Grade 1 significantly reduced (by 75%) in the spacer arm, and no Grade ≥2 late rectal toxicity was observed in spacer group. This study was first and only randomized trial of PEG-hydrogel spacer.[35] In addition, Folkert *et al*. have reported the first prospectively data of PEG-hydrogel spacer with high-dose SBRT. Forty-four patients underwent prostate SBRT with a total dose of 45 in 5 fractions, and at 12 months, no acute or late Grade ≥3 GI toxicity was reported.[36]

With regard to bowel QOL, studies have reported that there was an improvement in bowel QOL score for patients with tissue spacer.[37-39] The data of a prospective cohort study of 167 patients (101 with PEG-hydrogel and 66 without) with prostate cancer treated with IMRT or volumetric-modulated arc therapy (VMAT) using a spacer gel have shown that the frequency of treatment for bowel symptoms and endoscopic examinations were significantly less for the spacer arm.[39] At 17 months, the patients with at least a 10-point decline of bowel scores were significantly ($P < 0.01$) smaller for spacer group compared to nonspacer group. A bowel bother score change >10 points was reported in 5% of the patients with spacer versus 14% of the patients without spacer ($P = 0.2$) at 63 months.[38] Studies have shown that the rate of Grade ≥1 and Grade ≥2 late rectal toxicities was statistically significant reduced by hydrogel spacer.[35,37,40] Through 37 months, 2.0% and 9.2% of spacer and control arm, respectively, experienced Grade ≥1 late rectal toxicity ($P = 0.028$), and there was no Grade ≥2 late rectal toxicity in the spacer arm (0.0% vs. 5.7%, $P = 0.012$).[37] The rectum is a late responding tissue (low α/β ratio), and RT-induced rectal damage is a late effect therefore higher grade of late rectal toxicity occurs at longer follow-up duration (1.5–4.5 years). A summary of clinical studies that have reported the acute and late GI toxicities in patients with PEG-hydrogel injection is outlined in Table 1.

Although using an RR during proton boost (4 Gy × 5 Gy) has caused that the rectal doses reduced for the combined standard photon beam therapy (25 Gy × 2 Gy) and proton boost, these results did not translate into the reduction in the rectal toxicity.[43] A recent study has shown that the application of RR during dose-escalated prostate IGRT improved acute rectal toxicities, and no Grade ≥2 acute rectal toxicities during treatment were observed.[4] However, further randomized clinical trials (RCTs) are required to elucidate the clinical advantages of RR. Furthermore, there were several reports that showed the role of RDDs on postprostatectomy RT setting with promising results,[44-47] as outlined in Supplementary Table 1. This promising area can encourage investigators for future studies with different types of RDDs.

THE EFFECT OF RECTAL DISPLACEMENT DEVICES ON THE PROSTATE MOTION

Many reports evaluated the movement of the prostate gland in prostate EBRT using various imaging techniques.[48-50] The magnitude of prostate motion is large at AP direction, owing to vary filling of the rectum and bladder.[7] Understanding the impact of RDDs on the prostate motion clinically is important because this motion has a detrimental effect on the PTV margins. If these RDDs reduce the prostate motion, the need for imaging during treatment will be low, and also, a tight PTV margin can define that it can decrease RT-induced rectal toxicity in turn. With regard to ERBs, when an ERB is inflated, it pushes the prostate gland toward pubic symphysis and can reduce the prostate displacement during daily treatment. Several studies have been shown ERBs as a prostate immobilizer device that could reduce inter-/intra-fraction motion.[48,49] Published studies have demonstrated that ERBs significantly reduced the intra-fraction prostate motion,[48] but some studies reported that ERBs eliminate the inter-fractional prostate motion that can be associated with variations of daily ERB insertion and inappropriate rectal preparation.[49,51] 3D prostate shift >5 mm reduced from 3.1%–4.6% to 0.7% in the treatment time more than 6 min using an ERB, and a 5-mm internal margin could be enough for the intra-fraction prostate motion.[48] Compared with ERBs, tissue spacers did not have any effect on the prostate motion;[52] however, a study found that tissue spacers had a potential in the reduction of prostate displacement in the posterior direction.[53]

Using an RR increased the intra-fractional reproducibility of the rectal wall position, and it can prevent variations of the rectal volume. As a consequence, it can immobilize the prostate.[23] Several studies have quantified prostate motion during VMAT with RR.[54-56] Although it has indicated the average 3D prostate displacement >3 was rare compared to the patients without RR,[55] a study did not confirm the role of RR in reduction of intra-fraction prostate motion[56] that this controversy can

Table 1: Gastrointestinal toxicity reports with polyethylene glycol -hydrogel

Study/ years	Radiotherapy technique; PTV	Number of patients/study design	Median follow-up time (M)/scoring system	Results of GI toxicity
Uhl *et al*., 2014[41]	78 Gy in 39 F/IMRT; P+proximal 2/3 SV+4-10 mm (≤5 mm post)	48/prospective multicenter phase II trial	12/RTOG/EORTC	Acute GI Grade 1: 39.6% Grade 2: 6% Grade 3-4: 0% Late GI Grade 1: 4.3% Grade 2-4: 0%
Mariados *et al*., 2015[35]	79.2 Gy in 44 F/IG-IMRT; P±proximal SV+5-10 mm	149 with spacer versus 73 without spacer/prospective multicenter randomized controlled pivotal trial	15/NCI-CTCAE v4.0	Acute rectal toxicity Grade 1: 23.0% with spacer versus 27.8% nonspacer Grade >2: 4.1% with spacer versus 4.2% nonspacer *P*=0.525 for all toxicity endpoints Late rectal toxicity Grade 1: 2.0% with spacer versus 5.6% nonspacer Grade ≥2: 0.0% with spacer versus 1.4% nonspacer *P*=0.044 for all toxicity endpoints
Pieczonka *et al*., 2016[40]	79.2 Gy in 44 F/IG-IMRT; P±SV+5-10 mm (5 mm post)	149 with spacer versus 73 without spacer/multicenter, pivotal, randomized controlled trial	15/z v4.0	Acute rectal toxicity Grade ≥1 rectal toxicity was similar in both groups, *P*=0.6 Late rectal toxicity Grade ≥1 rectal toxicity reported in 3 of 148 patients with spacer (2.0%, all Grade 1) and 5 of 71 patients in control group (7.0%, up to Grade 3), *P*=0.044
Whalley *et al*., 2016[42]	80 Gy in 40 F/ IG-IMRT or VMAT; PSV + 7 mm (5 mm post)	30 with spacer versus 110 without spacer/ nonrandomized prospective trial	28/RTOG	Acute rectal toxicity Grade 1: 43.0% with spacer versus 50.6% nonspacer, *P*>0.05 Grade 2: 0% with spacer versus 4.5% nonspacer, *P*>0.05 Late rectal toxicity Grade 1: 16.6% with spacer versus 41.8% nonspacer, *P*=0.04 Grade 2: 3.3% with spacer versus 3.6% nonspacer, *P*>0.05
Hamstra *et al*., 2017[37]	79.2 Gy in 44 F/IG-IMRT; P±SV+5-10 mm	149 with spacer versus 79 without spacer/phase III randomized multicenter trial	37/CTCAE v4.0	Late rectal toxicity Grade ≥1: 2% with spacer versus 9.2% nonspacer, *P*=0.028 Grade ≥2: 0% with spacer versus 5.7% nonspacer, *P*=0.012
Folkert *et al*., 2017[36]	45 Gy in 5 F/ SBRT; P+3 mm	44/phase II nonrandomized multi-institution (two institutions)	12/CTCAE v4.0	No Grade ≥3 acute or late toxicity, no Grade ≥4 toxicity

PTV=Planning target volume, F=Fraction, IMRT=Intensity-modulated radiation therapy, P=Prostate, SV=Seminal vesicle, IG-IMRT=Image-guided intensity modulated radiation therapy, Post=Posterior, VMAT=Volumetric-modulated arc therapy, SBRT=Stereotactic body radiotherapy, M=Month, RTOG=Radiation therapy oncology group, EORTC=European Organization for Research and Treatment of Cancer, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; GI=Gastrointestinal. *P*≤0.05 was considered statistically significant

be associated with different preparation regimens before treatment. The impact of a ProSpare on the inter-fraction prostate and seminal vesicles motion has been studied. The analysis pretreatment cone-beam CT datasets showed that a ProSpare could reduce the inter-fraction prostate and seminal vesicles motion.[25] This can be associated with less variations of the rectal volume due to daily insertion of a ProSpare that increases the reproducibility of rectal position.

PATIENT'S TOLERANCE, WORKLOAD, AND CLINICAL PRACTICE

Several studies reported that ERBs were well tolerated by patients.[17] In a study with large sample size, more than 97% of the patients tolerated ERB throughout treatment days.[57] The insertion of ERB was facilitated by lubrication gel, and it sometimes is necessary to use a lidocaine jelly for avoidance of the rectal irritation.[15] For hygienic reasons, it is better to use disposable ERB; however, an ERB per patient covered by condom can use for the entire treatment.[15] There was no relationship between the age and ERB tolerance.[57] The application of an ERB should be cautioned in patients with painful and bleeding hemorrhoids. Placing an ERB into the rectum at the all treatment sessions by a person can prevent the incorrect ERB insertion.[15] The process of ERB and RR insertion into the rectum is time consuming and adds 3–4 min to daily treatment setup time.[4] It seems that the insertion of ProSpare also is time-consuming; however, studies have not mentioned it. Of note, rectal wall delineation is essential to clearly understand the impact of ERB, RR, and ProSpare on reducing rectal radiation doses.[58]

The stability of the space between the rectum and the prostate by tissue spacer during the RT course in achieving the expected results is an important factor that several reports have addressed this topic. The data have shown that tissue spacers were stable during the RT course by periodic imaging, and overall PEG-hydrogel, biodegradable balloon, and collagen completely absorbed at 6–12 months.[18,20,21,28]

Overall, complications directly associated with the placement of tissue spacers are rare, and implantation or injection of tissue spacers is well tolerated. Only PEG-based hydrogel (SpaceOAR™

Augmenix, Waltham, MA, USA) is approved by the US Food and Drug Administration and has a safe and feasible application technique.[11,21,37] However, a recent study by Dinh *et al*. reported a case of rectal ulcer (Grade 3 complication according to the CTCAE) after prostate IMRT with PEG-hydrogel in-place.[59] With regard to using biodegradable balloon, HA, and collagen, few studies have reported that hematuria, transit mild pain, urinary retention, penile bleeding, dysuria, nocturia, asthenia, and hematoma were found in some cases.[19,20] Furthermore, Schörghofer *et al*. have recently reported that overall complication rate following tissue spacer placement is below 2%. In that study, six cases experienced rectal perforation and uretheral damage following the implantation of biodegradeable balloon.[60] Daily application of the RR during the therapy can be stopped because this device is in direct contact with the rectal wall and daily insertion along with inflammation of the rectal mucus with irradiation leads to the anal and rectal irritation.[4] In addition, the same effect can observe with daily insertion of EBRs and ProSpare.

Among different tissue spacers, the implantation of PEG-hydrogel is time limited because it polymerizes at few seconds (approximately 8–10 s).[11] Biodegradable balloon can easily be visualized on the CT images in contrast to other types of the tissue spacers and can be helpful in delineating the ARW similar to ERBs. The application of biodegradable balloon is more invasive as compared to other tissue spacers and RDDs due to perineal incision, and also, *in situ* correction can only be performed on it in contrast to other tissue spacers.[18] The implantation of tissue spacers is not successful in all cases. To date, the rate of successful implantation of biodegradable balloon and PEG-hydrogel has been reported to be over 91%.[40] Furthermore, there are some potential caveats or disadvantages in RDDs application, as outlined in Supplementary Table 2.

COST-EFFECTIVENESS

At present, the utilization of IMRT or IGRT in the prostate cancer treatment has resulted in lower Grade 2–3 rectal toxicities.[42,61] Furthermore, studies have shown that desirable clinical outcomes using tissue spacers did not achieve for all cases (for approximately 20% of the patients, reducing toxicity risk was observed).[62] Furthermore, Jones *et al*. reported that the cost of ERB was $373.38 for six treatment sessions and the cost of one kit for the injectable spacer gel was $2850.00.[31] Therefore, using tissue spacers in the routine clinical setting may not be cost-effective. Because these procedures are invasive and expensive, it is necessary to consider a decision analysis model for spacer implantation.[63] Although the use of rectal spacer in conventional prostate RT is expensive, it is immediately cost-effective in high-dose extremely hypofractionated prostate RT.[64] Contrast with ERBs and tissue spacers, the RR is one-off department purchase, and also, the RR has a great potential in reducing the surgical risk and cost compared to tissue spacers; however, the effect of a RR on late rectal toxicities is unclear.[4] With respect to published studies, tissue spacers should be used for well -selected prostate patients, for example, low- or intermediate-risk prostate cancer in dose-escalated RT (76 Gy or more with standard RT regimen). The cost-effectiveness of tissue spacers in patients with diabetes, active bleeding disorders, and inflammatory bowel diseases is not clear. As demonstrated in a recent study and based on 2018 Physician Fee Schedule, the hydrogel spacer can be cost-effective in men with good sexual function, provided patients are willing to pay $100,000.[65]

CONCLUSION AND FUTURE PERSPECTIVE

There are several factors that should be considered when RDDs are used, including economic situation, equipment of department, clinical risk factors, workload of department, experience and training, patient willingness and collaboration, staff motivation, and complications related to procedure of RDDs. In localized prostate cancer EBRT, dose intensification, adequate PTV margin, and rectal tolerance dose (it also affects the two first factors) are the main issues. At the first glance, a proper RDD should be able to resolve above-mentioned factors.

Based on investigated end-points in the current review, the hydrogel spacer is superior in comparison with the other RDDs regarding rectal dose sparing and QOL outcomes. Furthermore, it has a minimal invasive procedure that is comparable with a gold fiducial markers' implantation. Furthermore, a reduction in the posterior displacement of prostate was reported by the hydrogel spacer. The majority of reports on tissue spacer technology showed that implantation or injection of tissue spacers is safe and effective, as well as well tolerated. However, cases of rectal ulceration/perforation have been reported. The implantation of a tissue spacer between the prostate and rectum results in statistically significant reduction in the volume of the rectal wall within high-dose radiation. The data from clinical trials have shown that the implantation of hydrogel spacer can improve QOL for prostate cancer patients after RT. Although the application of hydrogel spacer reduced acute rectal toxicities, a statistically significant difference was not observed between spacer and control groups. A possible reason for justifying this issue can be attributed to sigmoid colon or small bowel irradiation during RT that lead to acute toxicities. In the current prostate EBRT practices that involve IG-IMRT, the risk of moderate-to-severe long-term rectal morbidity is low. The hydrogel spacer significantly reduces the low risk of morbidity. The results from randomized controlled clinical trial demonstrated that the rate of Grade $\geq$2 late rectal toxicity was not observed in the spacer arm at 37 months' follow-up.

A promising approach to reduce the rectal wall doses and prostate inter-/intra-fraction movements in a cost-effective manner is RR, but RCTs will be required to clear its effect on QOL improvement. The primary aim of the use of ERBs is reducing intra-fraction motion of the prostate, and also,

the PRW dose is reduced by ERBs as a secondary aim. Daily application of ERBs and RR is time-consuming, and daily irradiation and repeated physical insertion of ERBs and RR may lead to anal and rectal irritation. Daily reproducibility of ERB position is low that should be accompanied by image guidance techniques. Studies on ProSpare are very few and its efficacy is not clear. Patients may not tolerate daily application of RR, ERB, and ProSpare during prostate EBRT with conventional regimen. Although the application of hydrogel spacers during prostate brachytherapy is outside the scope of this review, hydrogel spacers have a significant effect on reducing rectal doses and toxicities during prostate brachytherapy.[21] Overall, RDDs have a critical role in prostate EBRT because these technologies can improve therapeutic ratio.

Reports on RDDs in postprostatectomy RT setting are very rare. The application of ERBs resulted in reducing anorectal dose, but geometric and dosimetric reproducibility of the CTV is controversial by ERBs. The results of using hydrogel spacers are also promising. Further clinical studies are required to elucidate the role of RDDs in postprostatectomy RT.

There are many challenges for RT physicist and radiation oncologist in prostate RT, including geometric uncertainties, sparing of the rectum, and prescription dose. In addition, the field of prostate RT is moving toward hypofractionated regimens and high conformal techniques that considering prostate displacement, setup reproducibility and rectum sparing are important. Therefore, RDDs will play a critical role during prostate RT in the next few years, and also, clinical experience with RDDs will increase. RCTs will be required to well elucidate clinical benefits of these technologies in contrast to treatment without these devices. There is an important role and a great potential for using RDDs in prostate reirradiation that studies will increase in this area in the next years.

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Conflicts of interest
There are no conflicts of interest.

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SUPPLEMENTARY TABLE

Supplementary Table 1: The role of rectal displacement devices on postprostatectomy radiotherapy

Study	Number of patients	RT technique	Aim of study	Main results
			Studies with ERB	
Smeenk *et al*., 2011[1]	20	IMRT/35×2 Gy	Impact of an ERB on anorectal dose	Anal wall: All dosimetric parameters reduced by using ERB except V70Gy Rectal wall: Only there was a significant reduction in the rectal wall V30/40Gy and Dmax
Jameson *et al*., 2013[2]	10 with ERB versus 10 without ERB	IMRT/35×2 Gy	Improvement in dosimetric and geometric stability of rectum and CTV	Using an ERB improved the geometric reproducibility of target and rectum. This geometric stability did not translate into a significant dosimetric stability of target
Streller *et al*., 2017[3]	10	VMAT/30×2.2 Gy	Impact of an ERB on anorectal dose	The use of ERB increased mean rectal wall dose and the rectal V40/60/65 compared to plans without ERB. The dose-volume variability of anal wall was lower in plans with ERB
Ishiyama *et al*., 2013[4]	107	IMRT/32×1.9 Gy	Investigation of GI and GU toxicities after prostate IMRT with ERB	In a median follow up 37 months, Grade 2/3 late GI toxicity were 6/3% and Grade 2/3 late GU toxicity were 13/6%
de Leon *et al*., 2015[5]	7 with ERB versus 7 without ERB	IMRT/35×2 Gy	Improvement in geometric stability of rectum and CTV	Using an ERB increased the rectal and CTV stability. The ERB negates the impacts of bladder filling on CTV stability
Joo *et al*., 2016[6]	46	Not reported/30×2.2 Gy	Analysis of inter-fractional prostate bed motion	The inter-fractional prostate bed motion was small, with group systematic deviations of <0.3 mm in three direction. A margin of <5 mm was need to include 95% of the inter-fractional motions using an ERB and daily CBCT
Swisher-McClure *et al*., 2016[7]	10	PT/39×1.8 Gy	Optimization of PT by examining organ motion, and patient alignment during PT	Median PTV coverage (V98%) was increased from 93.3% to 97.1% by alignment of patients with ERB plus bony anatomy on kilovoltage films in post prostatectomy PT. In addition, this action decreased average displacement of the CTV
			Studies with hydrogel spacer	
Pinkawa *et al*., 2015[8]	1	IMRT/38×2 Gy	Impact of an hydrogel spacer on rectal wall doses	The relative reductions in the rectal wall V70/V60/V50Gy were 100/100/93.5%. This technique can be used in specially selected patients
Lehrich *et al*., 2018[9]	21	IMRT/40×1.8 Gy	5-year bRFS, late GI and GU toxicities after prostate IMRT with spacer hydrogel	The 5-year overall bRFS rate was 62.2%. Late Grade 0/1/2 rectal GI toxicities were 81%/14%/5%. Late Grade 0/1/2 rectal GU toxicities were 62%/24%14%. The patients well tolerated hydrogel spacer implant
			Studies with rectal retractor	
Ghaffari *et al*., 2019[10]	1	IMRT/26×2.7 Gy	Impact of an rectal retractor on rectal wall doses	The relative reduction of the rectal wall V40 Gy, V50 Gy, V60 Gy, and V70 Gy were 47.2%, 37.1.6%, 33.5%, and 76.2%. Using a rectal retractor also reduced the anterior rectal wall doses

ERB=Endorectal balloon, RT=Radiotherapy, IMRT=Intensity-modulated radiotherapy, VMAT=Volumetric-modulated arc therapy, PT=Proton therapy, CTV=Clinical target volume, GI=Gastrointestinal, GU=Genitourinary, VxGy=Percentage of rectal structure receiving ≥ xGy, Dmax=Maximum dose of the structure, CBCT=Cone-beam computed tomography, PTV=Planning target volume, bRFS=Biochemical-relapse free survival

Supplementary Table 2: The potential caveats in rectal displacement devices application

Type of RDD	Caveats or disadvantages
Endorectal balloons	One of the challenges using ERBs is variations of the depth of insertion that may deform the shape of the prostate and significantly influence the dosimetric outcomes. Study suggested that manual intervention on ERB position is necessary for the accuracy of delivery planned dose distribution to the target and preventing the prostate deformation. Image-guided techniques have shown that intervention was needed to increase the PTV coverage, and also reduce the prostate deformation in AP direction. Therefore, pretreatment verification of ERB position is necessary for increasing the daily reproducibility of ERB position.[10] A waiting period between the ERB insertion into the rectum and irradiation was suggested to reduce intra-fractional shift in the ERB.[11] Another drawback of using an ERB is increasing dose to the ARW due to pushing the ARW toward prostate when an ERB is inflated that was addressed by several reports.[12,13]
Tissue spacers	Regarding treatment planning after hydrogel injection, a period of 3-5 days after hydrogel insertion is necessary for the absorption of saline and air bubbles. A stable space between the prostate and the ARW is obtained after this period, and then planning CT is performed.[14] Rectal ulceration or perforation directly related to the implantation procedure is rare.[15,16]
Rectal retractor	The application of ERBs, RR, and ProSpare increase the rectal volume, but it should be noted that the volume of the rectal wall is constant with and without ERB or RR.[17] Patient may not tolerate the RR insertion throughout a radiotherapy course with conventional schedule.[18]
ProSpare	There were variations in the daily reproducibility of ProSpare in the SI direction. The analysis pretreatment CBCTs indicated SI displacement ≥6 mm,[19] that this may be associated with self-insertable device and lack of connection of the ProSpare shaft to the vertical locking column

RDD=Rectal Displacement device, ERB=Endorectal balloon, PTV=Planning target volume, AP=Anterior-posterior, ARW=Anterior rectal wall, CT=Computed tomography, RR=Rectal retractor, SI=Superior-inferior, CBCT=Cone-beam computed tomography

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