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Optimization of prostate brachytherapy techniques with polyethylene glycol–based hydrogel spacers: A systematic review

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ABSTRACT

PURPOSE: The objective of this overview was to critically evaluate the effect of polyethylene glycol (PEG)-based hydrogel spacers during prostate brachytherapy with regard to dosimetric and clinical benefits, as well as procedure-related toxicity.

METHODS AND MATERIALS: A systematic search in the PubMed database was performed.

RESULTS: A total of 12 studies, involving 615 patients with PEG hydrogel injection, were included. Overall, patients well tolerated the implantation of PEG hydrogel spacers with an excellent safety profile. However, although there were some procedure-related complications, rates of these complications were very rare. Toxicities related to the spacer were limited to Grade 1 rectal discomfort and pain (9/615 patients), Grade 2 rectal ulceration (1 in 615 patients), perineal abscess (1 in 615 patients), and bacterial prostatitis (2/615 patients) according to Common Terminology Criteria for Adverse Events v4.0 grading scheme. The application of PEG hydrogel spacers significantly reduced radiation doses to the rectum during prostate brachytherapy in the different setting. Although there was no prospective randomized clinical trial, retrospective studies showed that reducing rectal doses by the implantation of PEG hydrogel may result in an improvement in rectal toxicity.

CONCLUSIONS: The insertion of hydrogel spacers is safe, resulting in a significant decrease in rectal doses. This may lead to a reduction in rectal or gastrointestinal toxicity. Prospective randomized clinical trials are warranted to confirm the clinical impact of rectal dosimetric improvements.

Keywords: Polyethylene glycol; Hydrogel spacer; Prostate cancer; Brachytherapy

1. Introduction

As demonstrated in several large randomized trials, dose-escalated radiotherapy can improve biochemical control in localized prostate cancer. However, dose escalation increased the rate of rectal toxicity (1, 2). In the last decade, modern radiotherapy techniques such as intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy, as well as proton therapy, have been incorporated into the routine clinical practice. Modern radiotherapy allows for an aggressive radiation dose escalation to the prostate while simultaneously reducing treatment-related toxicity (3–6).

Another definitive treatment option for prostate cancer is brachytherapy (BT). BT is considered as monotherapy in low-risk or favorable intermediate-risk prostate cancer patients, and it can also be used in combination with external beam radiation therapy (EBRT) for unfavorable intermediate- and high-risk prostate cancer (7). Dose-escalated BT has also resulted in increasing rectal or gastrointestinal (GI) toxicity (8). Despite advances in radiation therapy techniques and target localization, the rectum remains the primary dose-limiting organ at risk owing to the close proximity of the rectum to the prostate gland. Thus, rectal toxicity is a primary concern in dose-escalated prostate radiation therapy and is dependent on rectal doses.

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One way to reduce rectal toxicity is to increase the separation between the prostate and rectum. The use of endorectal balloons, rectal spacers (such as polyethylene glycol [PEG] hydrogel, biodegradable balloon, collagen, and hyaluronic acid), and rectal retractor to separate prostate and rectum led to significant reduction of radiation doses to the rectum. As a consequence, the application of rectal displacement devices resulted in a decrease of acute and late rectal toxicity from EBRT (9–16). Randomized studies demonstrated the clinical benefit of PEG hydrogel spacer in terms of acute and late rectal toxicities during prostate EBRT (10). Recently, several studies have been investigated the role of PEG hydrogel spacers during prostate BT in the different setting. The objective of this study, therefore, was to critically evaluate the effect of PEG-based hydrogel spacers during prostate BT with regard to dosimetric and clinical benefits, as well as procedure-related toxicity.

2. Methods and materials

2.1. Search strategy and selection criteria

We searched PubMed database for relevant articles published before June 4, 2019. The entry terms for the search were (“*Hydrogel spacer*” *OR* “*Spacer*” *OR* “*DuraSeal*” *OR* “*SpaceOAR hydrogel*” *OR* “*Polyethylene glycol hydrogel*”) *AND* (“*Brachytherapy*” *OR* “*Prostate brachytherapy*”). Published articles and abstracts in English from studies on human were included on the basis of relevance to the scope of this review. Principal exclusion criteria were lack of relevant outcome data, review articles, and animal studies. Outcomes were expressed as they were originally reported. No meta-analysis and statistical analysis were performed owing to obvious heterogeneity between publications and variation in the outcomes reported.

3. Results

3.1. Study selection and study characteristics

Search of PubMed resulted in 63 records. Based on title and abstract screening and exclusion criteria, 51 publications were excluded. After full-text screening, 12 studies, involving 615 patients with PEG hydrogel injection, met the inclusion criteria and were included in this systematic review, as shown in Fig. 1 (17–28). Characteristics of the included studies for prostate BT with PEG hydrogel spacer in-place are outlined in Table 1. Three of twelve studies were case reports (21, 23, 26). All articles except five investigated the role of PEG hydrogel spacers during high-dose-rate (HDR) prostate BT in the different setting. Five of twelve studies reported the effect of PEG hydrogel on reducing late rectal or GI toxicity. As observable in Table 1, the implantation of hydrogel spacers before salvage prostate BT after previous pelvic irradiation was reported in the four studies. All studies except three used SpaceOAR (Augmenix, Waltham, MA) as hydrogel rectal spacer in prostate BT.

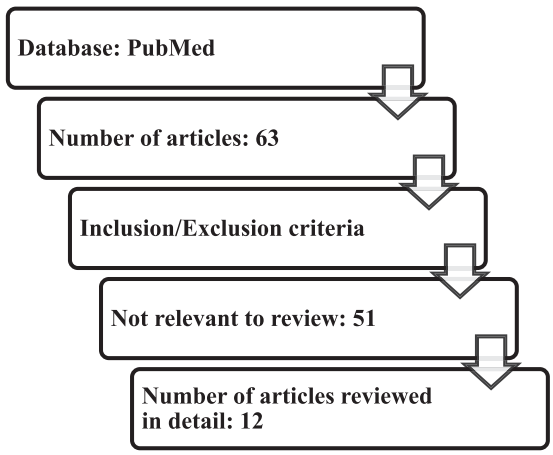

Fig. 1. Overview of the literature search.

3.2. Characteristics of PEG hydrogel

PEG hydrogel is a water-soluble polymer and nontoxic. As demonstrated in studies, PEG hydrogel has an excellent biocompatibility (29, 30). SpaceOAR and DuraSeal (Covidien, Mansfield, MA) are two types of commercially developed PEG-based hydrogel spacer that used as prostate-rectum spacer during prostate BT (18, 22, 24, 25). In 2005, DuraSeal received U.S. Food and Drug Administration (FDA) approval as an adjunct to sutured dural repair during spinal surgery (24). DuraSeal is used on an off-label basis and has no FDA approval for prostate injection (24, 25). On the contrary, SpaceOAR is the only product that has FDA de novo clearance for creating space between the prostate and rectum (25). In overall, PEG hydrogel is persistent up to 3 months before hydrolysis and elimination via renal filtration (24, 25, 31).

3.3. Application technique

Although there are several similar approaches to placing hydrogel spacers, transperineally injection of hydrogel using hydrodissection is considered as one of the most common techniques. Hydrodisscton results in creating space between Denonvilliers’ fascia and the rectal wall. As a consequence, it facilitates placement of hydrogel rectal spacer. After local, spinal, or general anesthesia, the patient is placed in the lithotomy position. Under real-time transrectal ultrasonography guidance, an 18-gauge needle is inserted between Denonvilliers’ fascia and the anterior rectal wall. Then, saline water is injected to create the potential space between the prostate and the anterior rectal wall before the hydrogel injection. When hydrodissection is

Table 1
Characteristics of included studies for prostate cancer brachytherapy with polyethylene glycol (PEG) hydrogel spacer in-place

Study/year	Treatment technique	Dose	No. of patients	Mean prostate−rectum separation (mm)/type of PEG hydrogel	Rectal dosimetry	Followup time (M)/scoring system	Acute GI toxicity	Late GI toxicity
Beydoun *et al.*, 2013 (17)	BT	—	5	15/SpaceOAR	V100% (cc): 3.04 without gel vs. 0.06 with gel	—	—	—
Nguyen *et al.*, 2013 (23)	Salvage HDR-BT; prior pelvic radiation	36 Gy in 6 fractions	1	15/SpaceOAR	V75% (cc): 0 Dose delivered to the hottest 2 cc of the rectum: ~3 Gy per fraction.	9/—	—	Mild rectal bleeding at 9 months treated with argon plasma coagulation at month 12
Mahal *et al.*, 2014 (22)	Salvage LDR-BT; prior pelvic irradiation	145 Gy	11	11 in patients with prior EBRT[a]; 8 in patients with prior BT[a]/DuraSeal	V75% (cc): 0.07	15.7/EPIC-CP questionnaire	Grade 1: — Grade 2: 1 patient Grade ≥3: 0	Grade 1 or 2: 4 patients; One patient developed a prostatorectal fistula requiring a diverting colostomy; 16-month estimate of late Grade 3 or 4 GI toxicity: 26% There were no significant changes throughout the study period in bowel QOL.
Storm *et al.*, 2014 (24)	HDR-BT ± IMRT	HDR-BT monotherapy: 27−28 Gy in two 13.5−14 Gy fractions separated by 2−3 weeks 45 Gy in 25 fractions IMRT + HDR-BT boost two 9.5−11.5 Gy fractions	100 with gel and 100 without gel	12/DuraSeal	$D_{2\ cc}$ (Gy): 60 without gel vs. 47 with gel ($p < 0.001$)	—	—	—
Heikkilä *et al.*, 2014 (20)	LDR-BT	145 Gy	10	10/DuraSeal	$D_{2\ cc}$ (Gy): 95 ± 13 Gy without gel vs. 64 ± 13 Gy with gel ($p = 0.005$)	—	—	—
Teh *et al.*, 2014 (26)	LDR-BT	145 Gy	1	Base:15; Apex: 7; Mid gland: 6/SpaceOAR	$D_{0.1\ cc}$ (Gy): 75.4 without gel vs. 69.3 with gel $D_{1\ cc}$ (Gy): 63.2 without gel vs. 54.8	—	—	—

(*Continued*)

Table 1 (*continued*)

Study/year	Treatment technique	Dose	No. of patients	Mean prostate–rectum separation (mm)/type of PEG hydrogel	Rectal dosimetry	Followup time (M)/scoring system	Acute GI toxicity	Late GI toxicity
					with gel $D_{2\ cc}$ (Gy): 55.2 without gel vs. 47.9 with gel			
Yeh *et al.*, 2016 (28)	HDR-BT + IMRT	16 Gy in 2 fractions BT and 59.4 Gy in 33 fractions IMRT	326	16/DuraSeal	When using a spacer, D_{mean} and D_{max} reduced by 7% and 17% of prescribed dose, respectively.	16/NCICTCAE v4.0	Grade 1: 37.4% Grade 2: 2.8%	Grade 1: 12.7% Grade 2: 1.4% Grade 3[b]: 0.7%
Taggar *et al.*, 2017 (25)	LDR-BT; LDR-BT + EBRT; Salvage LDR-BT	—	74 with gel[c] and 136 without gel/ retrospective	11.2/SpaceOAR	V100% (cc): 0.07 without gel vs. 0.01 with gel ($p < 0.001$) $D_{1\ cc}$ (Gy): 52.7 without gel vs. 25.3 with gel ($p < 0.001$) $D_{2\ cc}$ (Gy): 43.2 without gel vs. 20.5 with gel ($p < 0.001$)	6/RTOG	**Diarrhea (n) without gel vs. with gel** LDR-BT group: 7 vs. 2 LDR-BT + EBRT group: 3 vs. 5 Salvage LDR-BT group: 1 vs. 1 **Rectal discomfort (n) without gel vs. with gel** LDR-BT group: 0 vs. 4 LDR-BT + EBRT group: 0 vs. 2 Salvage LDR-BT group: 0 vs. 0 **Rectal bleeding (n) without gel vs. with gel** LDR-BT group: 3 vs. 0 LDR-BT + EBRT group: 14 vs. 2 Salvage LDR-BT group: 1 vs. 0 **Proctitis (n) without gel vs. with gel** LDR-BT group: 0 vs. 0 LDR-BT + EBRT group: 4 vs. 0 Salvage LDR-BT group: 0 vs. 0	—

(*Continued*)

Table 1 (*continued*)

Study/year	Treatment technique	Dose	No. of patients	Mean prostate−rectum separation (mm)/type of PEG hydrogel	Rectal dosimetry	Followup time (M)/scoring system	Acute GI toxicity	Late GI toxicity
Wu *et al.*, 2017 (27)	HDR-BT; HDR-BT + EBRT Salvage HDR-BT	HDR-BT monotherapy: 19−21 Gy per implant; EBRT + HDR-BT boost of 15 Gy; Salvage HDR-BT: 18 Gy in three fractions per implant for two implants	18 with gel and 36 without gel	—/SpaceOAR	**Median dose to the rectum without gel vs. with gel** V10 (cc): 47.5 vs. 58.5 ($p = 0.04$) V20−V40 (cc): similar between two groups V50−V80 (cc): Gel significantly reduce these parameters ($p \leq 0.008$)	—	—	—
Hepp *et al.*, 2018[d] (21)	HDR-BT	3 fractions of 11.5 Gy every second week	1	Base: 3.3; Apex: 7.4; Mid gland: 7.7/ SpaceOAR	$D_{2\ cc}$: <55% of prescribed dose in all implants	Every 3 months/ CTCAE v4.3	No GI toxicity	—
	Salvage HDR-BT; prior prostate HDR-BT with spacer in-place	3 fractions of 9 Gy every second week	1	Base: 2.9; Apex: 10.6; Mid gland: 5.3/ SpaceOAR	$D_{2\ cc}$: <59% of prescribed dose in all implants	12/CTCAE v4.3	No GI toxicity	—
Chao *et al.*, 2019 (18)	HDR-BT + IMRT or VMAT	16 Gy in 2 fractions BT and 50.4 Gy in 28 fractions IMRT or VMAT	30 with gel and 65 without gel	—/SpaceOAR	V75% (cc): 0.45 without gel vs. 0.0 with gel ($p < 0.001$)	Weekly during treatment, then at 2 weeks and at three monthly intervals in the first year/ NCICTCAE v4.0	Grade 1: 30.8% without gel vs. 13.3% with gel ($p = 0.05$) Grade 2: 1.5% without gel vs. 0.0% with gel ($p = 0.48$)	Grade 1: 7.7% without gel vs. 0.0% with gel ($p = 0.11$)
Chao *et al.*, 2019 (19)	HDR-BT + IMRT	18 Gy in 3 fractions BT + 50.4 Gy in 28 fractions IMRT 16 Gy in 2 fractions BT + 50.4 Gy in 28 fractions IMRT	32 with gel and 65 without gel	10[a]/SpaceOAR	V75% (cc): 0.45 without gel vs. 0.0 with gel Using gel results in relative reduction of 36.4/58.1/76.7/95.2/ 100/100/100 in V30/40/50/60/70/ 75/80 cc.	60/NCICTCAE v4.0	Grade 1: 30.8% without gel vs. 13.3% with gel ($p = 0.05$) Grade 2: 1.5% without gel vs. 0.0% with gel ($p = 0.48$)	Grade 1: 7.7% without gel vs. 0.0% with gel ($p = 0.11$)

BT = brachytherapy; HDR = high-dose-rate; LDR = low-dose-rate; IMRT = intensity modulated radiotherapy; EBRT = external beam radiotherapy; VMAT = volumetric modulated radiotherapy; EPIC-CP = Expanded Prostate Cancer Index Composite for Clinical Practice; NCICTCAE = National Cancer Institute's Common Terminology Criteria for Adverse Events; RTOG = Radiation Therapy Oncology Group; GI = gastrointestinal; QOL = quality of life.

[a] Median prostate−rectum separation was reported.

[b] Two of 326 patients experienced late Grade 3 rectal toxicities (fistula and severe proctitis).

[c] Seventy-nine patients underwent the hydrogel placement, but hydrogel was not successfully injected in 5 of 79 patients, and these patients excluded of study.

[d] Hydrogel rectal spacer was injected before salvage HDR-BT in a patient previously treated with HDR-BT.

accomplished, approximately 10 mL of the PEG hydrogel is injected into the created space (the perirectal fat), as shown in Fig. 2 (29). DuraSeal and SpaceOAR completely polymerize within 3 and 10 s after injection, respectively (17–28,31). Implantation time of hydrogel spacer relatively is short with a mean procedure time of 16 min (31). A wide description of application technique of hydrogel spacer was also presented by Hatiboglu *et al.* (32).

3.4. Prostate–rectum separation

The mean space achieved between the prostate and the anterior rectal wall was 10 mm (7–16 mm), as observable in Table 1 (17–28). The hydrogel spacer increases the separation between the prostate and rectum, regardless of patient's body mass index (24). DuraSeal clearance as a function of time has been reported by one study. The reduction of the gel volume is confirmed from CT images, without changing the separation between the prostate and the anterior rectal wall (20). The DuraSeal volume clearance half-life and the separation half-life were reported 47 and 110 days, respectively (20). The PEG-hydrogel is well visualized on T2-weighted MRI (20, 25, 28). SpaceOAR maintains stable separation up to 3 months, whereas DuraSeal is stable at 3 weeks and hydrolyzes over 4–8 weeks (17, 22, 24).

A number of reports have been reported that the implantation of hydrogel spacer was successful in all patients (17–21,23,24,26,27). Nonetheless, some studies have found that successful prostate–rectum spacing was not achieved in all patients (22, 25, 28). In the salvage BT setting in patients with a history of pelvic irradiation, Mahal *et al.* (22) have reported that only in 3 of 11 cases a suitable space was not achieved owing to fibrosis and scarring. In a single-arm retrospective study, Yeh *et al.* had also found a 94.5% (308/326 patients) clinical success rate with hydrogel spacer implantation. PEG hydrogel was injected into the rectal lumen in the remaining patients (18 patients) (28). In Taggar *et al.*'s (25) work, 5 of 79 placement attempts were not successful owing to unsuccessful prostate–rectum spacing at the time of hydrodissection. It has reported that a repeated hydrogel injection before salvage HDR-BT in a patient previously treated with HDR-BT was feasible (21).

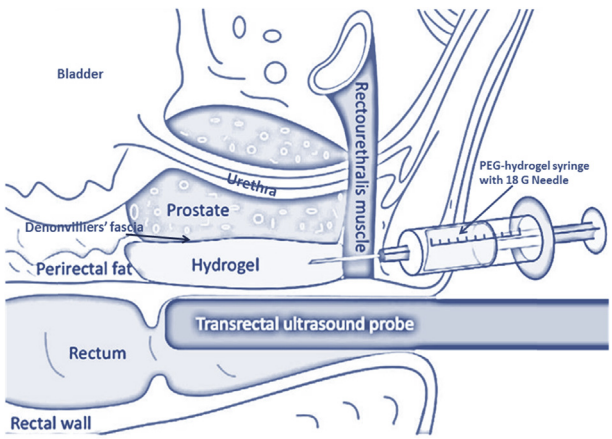

Fig. 2. Transperineal injection of PEG-based hydrogel under transrectal ultrasound probe.

3.5. Impact of hydrogel on rectal dosimetry and radiotherapy-induced rectal toxicity

The impact of PEG-based hydrogel spacers in prostate BT is summarized in Table 1. Several groups of researchers have been recently investigated the dosimetric impact of hydrogel spacers on prostate BT. Wu *et al.* compared the effect of PEG-based hydrogel spacer on rectal dosimetry between 18 patients with spacer and 36 patients without spacer during HDR-BT with different setting. Their results showed that although rectal $V_{2040\ cc}$–$V_{40\ cc}$ were similar between the two groups ($p > 0.05$), using PEG hydrogel spacer significantly reduced rectal $V_{10\ cc}$ ($p = 0.04$) and V_{50}–V_{80} cc ($p \leq 0.008$) (27). Heikkilä *et al.* (20) have found that mean ± SD rectal $D_{2\ cc}$ was 95 ± 13 Gy without spacer and 64 ± 13 Gy with spacer ($p = 0.005$). Furthermore, a small study involving five prostate cancer patients undergoing permanent iodin-125 BT was published by Beydoun *et al.* (17). Authors stated that clinically significant reduction in rectal V_{100} observed in all cases after hydrogel spacer injection, and mean rectal V_{100} for pre- and post-implantation plans were 3.04 cc and 0.06 cc, respectively (17). In a nonrandomized controlled trial, Strom *et al.* (24) treated 200 (100 with spacer implantation and 100 without spacer) localized prostate patients with HDR-BT ± IMRT. The HDR-BT doses as monotherapy were 27–28 Gy in two 13.5–14 Gy fractions separated by 2–3 weeks, and total dose of IMRT was 45 Gy in 25 fractions with an HDR-BT boost of two 9.5–11.5 Gy fractions. The results of that study indicated that prostate–rectum space achieved by hydrogel implantation reduced rectal $D_{2\ cc}$ from 60 Gy to 47 Gy ($p < 0.001$) for an average relative reduction of approximately 22% (24). Also, Strom *et al.* (24) noted that hydrogel spacer implantation does not influence the dose to the planning target volume and bladder volume. In a retrospective study, Taggar *et al.* have also reported similar results regarding rectal dosimetry, demonstrating the hydrogel spacers implantation significantly reduces the rectal V_{100}, $D_{1\ cc}$, and $D_{2\ cc}$ ($p < 0.001$). Rectal dose reduction resulted in improving diarrhea, rectal bleeding, and proctitis after BT alone or BT in combination with EBRT (25).

In a recent noncontrolled case series study, Yeh *et al.* have reported clinical efficacy of hydrogel spacer implantation at 16 months using the National Cancer Center Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0 grading scheme. Acute Grade 1 and 2 rectal toxicities were 37.4% and 2.8%, respectively. No acute Grade 3 or 4 rectal toxicity was observed. Late Grade 1,

2, and 3 rectal toxicities were 12.7%, 1.4%, and 0.7%, respectively. No late Grade 4 rectal toxicity was reported after 16 months followup (28).

Chao *et al.* published two retrospective case series reports of prostate cancer patients treated with HDR-BT + IMRT/volumetric modulated arc therapy, who had received hydrogel spacer injection. Although hydrogel spacer implantation reduced the rectal doses, statistically significant reduction in acute Grade 2 GI toxicities and late Grade 1 GI toxicities were not observed. However, hydrogel spacer implantation resulted in a minimal improvement in acute Grade 1 GI toxicity ($p = 0.05$), as shown in Table 1 (18, 19).

With regard to salvage BT after pervious pelvic radiation, two studies from Dana-Farber Cancer Institute have been indicated the feasibility of hydrogel spacer implantation in the patients underwent salvage BT for prostate cancer with prior pelvic irradiation (22, 23). Moreover, using hydrogel spacer resulted in reducing rectal V_{75} and urethra V_{125}, both parameters were less than 1 cc in all cases underwent salvage BT with spacer in-place (22, 23). Meanwhile, the 50% isodose line entirely excluded from the rectal wall when using hydrogel spacer in patient receiving BT (22). After a median followup of 15.7 months, late Grade 3 or 4 GI or GU toxicity was 26%. In the acute setting, only one patient experienced acute Grade 2 GI toxicity. Acute Grade 1 or 2 GU toxicities were 82% (9/11 patients). Only one patient (9.1%) developed a Grade 3 prostatorectal fistula requiring a diverting colostomy (22). In addition, the implantation of hydrogel spacer did not lead to statistically significant difference in Expanded Prostate Cancer Index Composite for Clinical Practice bowel scores compared with baseline after 3,6, and 12 months salvage prostate BT (22).

3.6. Procedure-related toxicity

Several studies have reported that the procedure of PEG hydrogel placement is safe and feasible with no postoperative complications and also is well tolerated by patients (18,19,21–23,28). However, there were some complications associated with hydrogel spacer insertion. A study from Finland has been recently indicated that although DuraSeal implantation causes no severe adverse events, 1 of 10 patients (10%) reported a sensation of pressure in the rectum, and another patient (1 in 10 patients [10%]) felt a sudden need for defecation. It should be noted that these adverse events did not warrant intervention and resolved without treatment 3 months after hydrogel placement (20). In another study, most patients reported a sense of fullness in the rectum without rectal pain or discomfort within few days after hydrogel implantation (25). At median followup of 1.3 months, 6 of 74 patients (8.1%) reported Grade 1 rectal–perirectal discomfort according to Radiation Therapy Oncology Group radiation toxicity grading system (25). A symptomatic rectal ulceration (CTCAE Grade 2) in the anterior rectal wall after SpaceOAR placement with low-dose-rate (LDR) prostate BT has also been reported in a case report (26). At St George Hospital Prostate Cancer Institute, 2 of 5 patients (40%) reported self-limiting, Grade 1 rectal discomfort according to CTCAE v4.0, and also one patient (20%) described Grade 1 perineal pain after hydrogel spacer insertion (17). These adverse events had resolved without treatment within 1 week of hydrogel spacer placement (17). No reports of complications associated with hydrogel spacer implantation have been reported 4–6 weeks after the implantation of hydrogel spacer (17). In another study, 2 (2/50 patients) cases of mild to moderate bacterial prostatitis (CTCAE Grade 2) were reported in patients who received prophylactic ciprofloxacin before PEG hydrogel implantation. But there was no infection in patients who received hydrogel spacer and underwent HDR-BT with ceftriaxone and gentamicin prophylaxis (24). Approximately 1 month after HDR boost BT after 5 weeks of EBRT, Grade 2 perineal abscess after successful SpaceOAR placement was reported by one patient of 18 patients (5.6%) treated. This infection required antibiotics as well as incision and drainage (27).

4. Discussion

The objective of this review was to critically synthesize the literature on PEG-based hydrogel spacers during BT for prostate cancer, focusing on the dosimetric and clinical benefits, as well as procedure-related toxicity. As shown in Table 1, the application of hydrogel spacer during prostate BT resulted in reducing radiation doses to the rectum, and a minimal improvement in rectal toxicities.

An average prostate–rectum separation of 10 mm is achieved by the hydrogel placement. Prostate-rectum separation achieved leads to improving dosimetric rectal profiles even with a minimal prostate–rectum separation rectal doses can significantly reduce because of the rapid dose fall off with BT. These results are consistent with other EBRT-specific reports (10, 13). Of the 615 patients, there were 26 patients that the placement of hydrogel spacer was not successful because of technically failures during implantation such as insufficient hydrodissection, and injection of hydrogel into the rectal lumen (25, 28). Besides, hydrogel spacer has been not inserted successfully in three cases undergoing salvage BT with prior history of pelvic irradiation due to fibrosis and adhesions (22). However, Hepp *et al.* (21) reported a successful hydrogel placement in a patient underwent salvage HDR-BT after initial BT. As stated earlier, increasing the separation between the prostate and the anterior rectal wall did not result in compromising planning target volume coverage and dose to bladder.

In general, the patients well tolerated the hydrogel implantation with a clinically acceptable safety profile. Complications associated with the procedure of the hydrogel

spacer placement have been well documented but are relatively rare. Cases of sensation of pressure in the rectum, sudden need for defecation, and Grade 1 proctitis and perineal pain have been reported. It should be noted that, however, these adverse events were self-limiting, without further complication (17, 20, 25). Recommending a low-residue diet (low-fiber diet) and/or laxatives can reduce pressure related to hydrogel spacer on the rectum during the course of the treatment. Patient may feel rectal discomfort and tenesmus, as relatively common complication after hydrogel spacer injection. Using ampyrone sulfonate analgesics (metamizole) for the day of the procedure and sometimes afterward can be an effective way to manage pain after hydrogel injection (33). One patient also experienced a perineal abscess requiring antibiotics as well as incision and drainage (27). Using antibiotic prophylaxis along with hydrogel insertion in a sterile environment can be an important way to prevent possible infections (33). Two cases of bacterial prostatitis have been also reported in patients who underwent HDR-BT with hydrogel spacer in-place. However, infectious complications were not reported by using prophylactic antibiotic regimens (24). Possible causes of prostatitis can be associated with the application of multiple kits/injections and/or their addition of contrast in the Storm *et al.* study (24). In addition, a rectal ulceration related to the SpaceOAR placement was reported during LDR prostate BT (26). Dinh *et al.* (34) have also reported a case of a severely symptomatic rectal ulcer (Grade 3 complication according to CTCAE) after prostate IMRT using SpaceOAR. Possible mechanisms of rectal injury associated with the hydrogel spacer implantation can be attributed to infection, mechanical injury, radiation injury, and ischemic injury (26). Ten microliter of hydrogel spacer is considered as optimum amount of gel that can prevent ischemia of the anterior rectal wall owing to the tension created by the hydrogel implantation (26, 32). During hydrogel spacer injection, the risk of mechanical injuries such as the needle and hydrogel penetrating the rectal wall, bladder, or prostate can be reduced by clear imaging under transrectal ultrasonography guidance following a rectal enema and well-trained physicians. Overall, the rate of rectal injury related to the implantation of hydrogel is very rare. Toxicities related to the spacer were limited to Grade 1 rectal discomfort and pain (9/615 patients), Grade 2 rectal ulceration (1 in 615 patients), perineal abscess (1 in 615 patients), and bacterial prostatitis (2/615 patients) during prostate BT.

Stability of separation achieved by hydrogel spacer should be in accordance with the biologic lifetime of the isotope to ensure a stable protection of the rectum throughout prostate BT, in particular in LDR-BT (17). It has demonstrated that PEG-based hydrogels are stable throughout the treatment, in particular SpaceOAR. It has also recommended that perform treatment planning few days after the insertion of hydrogel spacers to allow hydrogel spacer to stabilize and resorption of saline solution and air bubbles (21, 35).

As shown in Table 1, the application of hydrogel spacer significantly decreased the volume of the rectum in intermediate and high-dose regions. Furthermore, the percentage relative reduction in rectal V_{75} (cc) was approximately 100%. Rectal V_{75} constraint was easily achieved by the placement of hydrogel spacer in all patients, whereas this constraint did not accomplish for all patient without hydrogel spacer. Yeh *et al.* (28) have found that rectal D_{mean} and D_{max} reduced by 7% and 17% of prescribed dose using a spacer, respectively. In another study, Strom *et al.* (24) observed that in patients with hydrogel spacer, the mean rectal $D_{2\ cc}$ was 47 Gy compared with 60 Gy ($p < 0.001$) in the control group, as observable in Table 1. Using hydrogel spacers can also result in a minimal reduction of acute or late GI or rectal toxicities. HDR-BT in combination with EBRT compared with EBRT alone increases GI and GU toxicities (36). The risk of late Grade 3 GI toxicities were 3.9–7% in the two phase III randomized studies that compared HDR-BT combined with EBRT and EBRT alone (37, 38). A phase II Radiation Therapy Oncology Group 0321 study has also been reported a 2.6% late Grade 3 GI/GU toxicity (36). After a median followup of 5.3 years, Spratt *et al.* (39) have retrospectively reported that the rates of late Grade 2 and 3 GI toxicities were 4.1% and 1.4%, respectively. In prostate cancer patients treated with HDR-BT + IMRT or volumetric modulated arc therapy, Chao *et al.* (18, 19) reported that there was no statistically significant difference in late Grade 1 GI toxicity between spacer group (0%) and nonspacer group (7.7%). Yeh *et al.* treated 326 prostate cancer patients with aggressive dose-escalated HDR-BT (16 Gy in two fractions) + EBRT (59.4 Gy in 33 fractions). After median followup of 16 months, the rate of late rectal Grade 3 toxicity was 0.7%. On the other hand, two cases of late Grade 3 rectal toxicities were observed, including fistula and severe proctitis (28). As stated above, a reduction in the rates of late Grade 2 and 3 GI toxicities was observed using hydrogel spacer in patients treated with HDR-BT combined with EBRT in comparison with previous randomized studies (37, 38). As shown in Table 1, Taggar *et al.* reported low acute GI or rectal toxicity in comparison with historically reported rates of 15.8–36.5% rate of acute Grade 1–3 GI/rectal toxicity in patients underwent BT ± EBRT. They described that this reduction in the rate of acute toxicity can be associated with low rectal V_{100} (0.01 cc) in patients who received hydrogel spacer (25). No significant difference in the Expanded Prostate Cancer Index Composite for Clinical Practice bowel quality of life compared with baseline was found by the hydrogel placement in the salvage prostate BT after pelvic irradiation (22). A case of Grade 3 prostato-rectal fistula was reported after the salvage prostate BT after prior radiation. Possible cause of this fistula can be related to small rectal separation (3.7 mm) after hydrogel implantation (22). A recent trial has halted the use of hydrogel spacer during prostate proton or carbon ion therapy due to two rectal fistulas. The gradual

Table 2
Comparison of the DuraSeal and SpaceOAR devices for prostate injection

Characteristic	DuraSeal	SpaceOAR	References
FDA approval	No	Yes	(25)
Polymerization time	<4 s	10 s	(24, 27, 28)
Space stability	3–4 weeks	~3 months	(22, 27)
Core technology	PEG hydrogel	PEG hydrogel	(17–28)
Cost	Low	High	(20)
Implantation approach	Transperineal placement with hydrodissection	Transperineal placement with hydrodissection	(17–28)
Placement correction	Not possible	Not possible	(17–28,31)
Biocompatibility	Excellent	Excellent	(13, 29, 30)

FDA = Food and Drug Administration; PEG = polyethylene glycol.

accumulation of hydrogel within the confines of the anterior rectal wall led to rectal fistulas (40). Patient radiosensitivity can be another possible cause of rectal fistula. The toxicity results of studies investigating the role of hydrogel spacers in reducing rectal toxicities during prostate BT limited to the short-term followup. Longer followup will be required to clearly determine further possible effects of hydrogel spacers on late rectal toxicity.

Studies have suggested that hydrogel spacers should be only used in patients with localized prostate cancer without clinical or radiological rectal involvement (41). Nevertheless, Yeh *et al.* (28) did not exclude high-risk patients and expressed that even with advanced cases, Denonvilliers' fascia invasion is very rare. Further study is needed to investigate the feasibility of hydrogel spacers in high-risk patients and also evaluate cure rate of these patients with hydrogel spacer in-place.

Table 2 summarizes a comparison of the SpaceOAR and the DuraSeal. Both the SpaceOAR and the DuraSeal have a similar implantation procedure. But there are some differences in the handling of two PEG-based hydrogel spacers. SpaceOAR polymerizes *in situ* within 10 s (27, 28), whereas the polymerization time of DuraSeal is less than 4 s (24, 28). The polymerization time has a great role in the incidence of clogging and the need for repeated applications (27). Moreover, SpaceOAR will maintain integrity for 3 months, but DuraSeal degrades after almost 3–4 weeks. As a result, rectal dose sparing effect of DuraSeal can significantly change over a long course treatment (22, 27). Meanwhile, SpaceOAR is the only PEG-based hydrogel material that has U.S. FDA approval for prostate injection (25).

In prostate EBRT, in addition to hydrogel rectal spacers, rectal retractor is used to reduce rectal doses during prostate radiotherapy by retracting rectum posteriorly. As a consequence, rectal retractor increases the distance between the prostate and the rectal walls, thereby reducing radiation exposures to the entire rectum (14–16). Previous study by Mahdavi *et al.* has been demonstrated that using a rectal retractor during dose-escalated prostate, EBRT not only reduces the posterior rectal wall doses but also it can significantly decrease radiation doses to the anterior rectal wall (15). Furthermore, the rectal retractor can reduce inter- and intra-fraction prostate motions (42, 43). The use of endorectal balloon can also significantly reduce radiation doses to the posterior rectal wall (9). Using a hydrogel spacer in postprostatectomy radiotherapy setting can be resulted in reducing rectal doses and toxicities (44).

There are several limitations in studies reported in this review. First, the most studies were retrospective, which may have introduced a potential confounds and bias. Second, several studies had heterogeneous population and owing to small sample size and no control arm. Therefore, we cannot report definitive conclusions about the impact of hydrogel spacers on short- and long-term rectal toxicities. Third, unfortunately, there are no prospective randomized clinical trials currently evaluating the role of PEG-based hydrogel spacer during prostate BT.

5. Conclusion

This is the first systematic review assessing the use of PEG-based hydrogel spacers in prostate BT. Our conclusions are as follows: first, the implantation of hydrogel spacers was feasible with excellent safety profile, and also patients well tolerated the procedure. However, although the overall complication rate is very low, the advantages of PEG hydrogel spacers require to be weighed against the possible risks of complications such as rectal ulceration. Second, the rate of the clinical success with PEG hydrogels was very high; third, an average prostate–rectum separation of 10 mm was achieved by the hydrogel placement, which resulted in significant improvements in rectal dosimetry; and finally, reducing rectal doses may result in a decrease of acute and late rectal or GI toxicity from BT. Prospective randomized clinical trials will be required to clearly elucidate the effect of this rectal dose reduction on toxicity and quality of life.

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