Interventional procedure overview of biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer

Description

Radiotherapy to treat prostate cancer can damage the rectum (the end part of the bowel). This can cause side effects such as bleeding, diarrhoea and faecal incontinence. The aim of this procedure is to reduce the amount of radiation reaching the rectum during radiotherapy, which may reduce the damage. It is usually done using general anaesthetic about 1 week before radiotherapy starts. The rectum is pushed slightly away from the prostate by inserting a balloon or injecting a gel (spacer) between them. This stays in place during radiotherapy. It is biodegradable, which means it breaks down and is absorbed by the body slowly over several months.

Contents

Abbreviations

Word or phrase	Abbreviation
Anterior posterior	AP
Brachytherapy	BT
Confidence Interval	CI
3-dimensional conformal radiation therapy	3D-CRT
External beam radiotherapy	EBRT
Expanded Prostate Cancer Index Composite	EPIC
Endorectal balloon	ERB
Fraction	fx
Gastrointestinal	GI
Genitourinary	GU
Grading of Recommendations, Assessment, Development and Evaluation	GRADE
Hazard Ratio	HR
High dose rate brachytherapy	HDR BT
Health technology assessment	HTA
Image-guided intensity modulated radiotherapy	IG-IMRT
Intensity modulated proton therapy	IMPT
Interventional procedure	IP
Low dose rate brachytherapy	LDR BT
Manufacturer and User Facility Device Experience	MAUDE
Mean difference	MD
Minimally Important Difference	MID
Non-randomised Control Trial	nRCT
National Cancer Institute Common Terminology Criteria for Adverse Events	NCI CTCAE
National Comprehensive Cancer Network	NCCN
Not significant	NS

Odds ratio	OR
Planning target volume	PTV
polyethylene glycol	PEG
Proton beam therapy	PBT
Preferred Reporting Items for Systematic reviews and Meta-Analyses	PRISMA
Prostate-specific antigen	PSA
Quality of life	QoL
Randomised Control Trial	RCT
Radiotherapy	RT
Radiation Therapy Oncology Group	RTOG
Risk difference	RD
Relative Risk	RR
Radiotherapy	RT
Reduction in rectal volume of dose of, for example 50Gy	rV
Stereotactic body radiation therapy	SBRT
Standard deviation	SD
Superior-inferior	SI
Volumetric modulated arc radiotherapy	VMAT
Vienna Rectoscopy scores	VRS

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in July 2021 and updated in September 2022.

Procedure name

- Biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer

Professional societies

- British Uro-Oncology Group (BUG; Predominantly formed by radiation/medical oncologists)
- British Association of Urological Surgeons (BAUS)
- Royal College of Radiologists (RCR)
- The Association of Coloproctology of Great Britain and Ireland.

Description of the procedure

Indications and current treatment

Prostate cancer is the most common cancer in men, and the second most common cancer in the UK. Most prostate cancers are either localised or locally advanced at diagnosis. Localised prostate cancer often does not cause any symptoms, but some people might have urinary problems or erectile dysfunction. Some people may not identify as men but may have a prostate.

Current treatment options for localised or locally advanced prostate cancer include 'watchful waiting', active surveillance, radiotherapy, radical prostatectomy, transurethral resection of the prostate, cryotherapy, high-intensity focused ultrasound, androgen deprivation therapy and chemotherapy (as recommended in NICE’s clinical guideline on prostate cancer: diagnosis and treatment).

Radiation therapy is an established curative treatment and can either be external-beam radiotherapy or brachytherapy (also called interstitial radiotherapy). Brachytherapy can be given at low- or high-dose rates. Low-dose-rate brachytherapy may be used alone or with external-beam radiotherapy.

What the procedure involves

Radiotherapy for prostate cancer can cause rectal damage because of the close proximity of the prostate and the rectum. Symptoms of rectal damage can include diarrhoea, incontinence, proctitis and ulceration of the rectal mucosa. Injecting a biodegradable substance (examples include polyethylene glycol hydrogel, hyaluronic acid, and human collagen), or inserting and inflating a biodegradable balloon spacer, in the space between the rectum and prostate is done to temporarily increase the distance between them. The aim is to reduce the amount of radiation delivered to the rectum and reduce the toxicity profile during prostate radiotherapy.

The procedure is usually done with the patient under general or local anaesthesia using transrectal ultrasound guidance, but it may also be done using spinal anaesthesia. The patient is placed in the dorsal lithotomy position. For gel injection, a needle is advanced percutaneously via a transperineal approach into the space between the prostate and the rectum. Hydrodissection with saline may be used to separate the prostate and the rectum for some gels but is always not necessary. After confirming the correct positioning of the needle, the gel is injected, filling the perirectal space; Some of the gels may polymerise to form a soft mass and some do not. The biodegradable hydrogel absorbs slowly over several months. Some gels are reversible and can be dissolved using enzymes. For balloon spacer insertion, a small perineal incision is typically used to insert a dilator and introducer sheath. The dilator is advanced towards the prostate base over the needle, which is then removed. A biodegradable balloon is introduced through the introducer sheath and is filled with saline and sealed with a biodegradable plug. The balloon spacer degrades over several months.

Efficacy summary

Placement success

In a prospective multicentre RCT of 222 patients with prostate cancer comparing hydrogel spacer injection (hydrogel, n=148) with no spacer injection as control (n=72) during IG-IMRT, spacer placement success in the spacer group (defined as hydrogel present in the perirectal space) was reported as 99%. Urologists and oncologists rated spacer application as ‘easy’ and ‘very easy’ 99% of the time (Mariados 2015, Karsh 2018).

In a systematic review and meta-analysis of 7 studies (1 RCT [Mariados 2015] and 6 cohort studies) comparing 486 patients who had a hydrogel spacer with 525 patients who did not have a spacer (controls) before radiotherapy (EBRT, BT with or without EBRT, or combination therapy) for prostate cancer, the hydrogel spacer was successfully placed in 97% (95% CI, 95% to 99%) of patients and procedure failure was reported in 3% of patients (data from 5 studies). The reasons for procedure failure include unsuccessful hydrodissection (in 5), inadvertent needle entry into the rectal lumen with no clinical sequelae (in 3), and an unspecified cause (in 1) (Miller 2020).

In a systematic review of 9 studies comparing 671 patients who had hydrogel spacers (of 2 different types) with 537 patients who did not have hydrogel spacers (controls) before brachytherapy for prostate cancer, most studies reported 100% success with hydrogel spacer placement. Procedure failure rate ranged between 4 to 27% (in 12 patients) across 3 studies and was most commonly because of failure of hydrodissection in 9 patients having salvage brachytherapy, unsuccessful hydrodissection of an unknown cause in 1 patient and because of operator inexperience and premature coagulation of the solution during injection in 1 patient. Both these procedures were aborted. There is some slight overlap of studies between the systematic reviews included (Vaggers 2021).

Perirectal separation distance

In the prospective multicentre RCT of 222 patients, perirectal space (defined as the distance between the posterior prostate capsule and anterior rectal wall on axial mid-gland T2 weighted MRIs) after hydrogel insertion was 12.6±3.9 mm in the spacer group (post application) and 1.6±2.0 mm in the control group, respectively (Mariados 2015).

In the systematic review and meta-analysis of 7 studies comparing 486 patients who had a hydrogel spacer with 525 patients who did not have a hydrogel spacer (controls), the pooled results from 5 studies showed that the weighted mean perirectal separation distance was 11.2 mm (95% CI, 10.1 to 12.3 mm) (Miller 2020).

In a HTA report by EUnetHTA on using biodegradable rectal spacers for patients with prostate cancer having curative radiotherapy, they summarise the findings from the RCT (Mariados 2015 with several related studies from the same trial) which reported that the mean perirectal distance (defined as the distance between the posterior prostate capsule and anterior rectal wall on axial mid-gland T2 weighted MRIs) in the hydrogel spacer plus radiotherapy group (n=149) increased by 1.1 cm (from baseline 0.16±0.22 cm to 1.26±0.39 cm after hydrogel insertion and 0.9±0.59 cm at 3 months). Perirectal space in the control group was 1.6±2.0 mm (NIPHNO 2021).

In the systematic review of 9 studies comparing 671 patients who had hydrogel spacers (of 2 different types) with 537 patients who did not have hydrogel spacers (controls) before brachytherapy for prostate cancer, the mean prostate-rectum space achieved varied between 7.7 mm to 16 mm in 6 studies that used a variety of techniques to measure the spacing distance (Vaggers 2021).

A systematic review of 11 studies on the use of different rectal spacers during different radiotherapy techniques for prostate cancer reported increased prostate-rectum space (ranging from 7 mm to 15 mm with hydrogel spacers in 4 studies, 19.2 mm with biodegradable balloon spacer in 1 study, 13 mm with collagen implant in 1 study, between 9.8 mm to 20 mm with hyaluronic acid in 5 studies) (Mok 2014).

Rectal dose volume

In the prospective multicentre RCT of 222 patients, there was a statistically significant reduction in mean rectal dose volume within the 70 Gy isodose in patients in the spacer group (from baseline, 12.4% to 3.3% after spacer injection, p<0.001) compared with patients in the control group (from baseline, 12.4% to 11.7%) (Mariados 2015).

In the systematic review and meta-analysis of 7 studies comparing 486 patients who had a hydrogel spacer with 525 patients who did not have a hydrogel spacer (controls), at a median follow up of 26 months (range, 3 months to 63 months), the pooled results from 6 studies showed that patients who had the hydrogel spacer before EBRT had 66% less v70 rectal irradiation compared with controls (3.5% versus 10.4%; MD, -6.5%; 95% CI, -10.5% to -2.5%; p=0.001) (Miller 2020).

In the HTA report by EUnetHTA on using biodegradable rectal spacers for patients with prostate cancer having curative radiotherapy, an RCT (n=220, with 5 companion studies from the same trial) reported that the proportion of patients in the hydrogel spacer plus radiotherapy group who had more than 25% reduction in rectal volume having an isodose of 70 Gy (rV70) was 97%. There was a statistically significant reduction in mean rectal dose volume within the 70 Gy isodose in patients in the spacer group (from 13% at baseline to 3% after spacer injection, p<0.001) compared with patients in the control group (from 13% at baseline to 12%). An nRCT included in the HTA also reported that hydrogel plus radiotherapy (n=29) and balloon spacer plus radiotherapy (n=30) may be effective in reducing the dose to the rectum when compared with radiotherapy alone (n=19), but the evidence is uncertain (p<0.001). Balloon spacer was superior in reducing rectum dose (-28%, p=0.034) but exhibited an average volume loss of more than 50% during the full course of treatment of 37 to 40 fractions, while the volume of gel spacers remained fairly constant (NIPHNO 2020).

A systematic review of 19 studies (1 RCT, 18 nRCTs; with 3,622 patients) comparing patients who had a perirectal hydrogel spacer with patients who did not have a spacer (controls) across all types of radiotherapy for prostate cancer reported that rectal dose decreased significantly across 13 nRCTs in the hydrogel spacer group regardless of the type of radiotherapy used (all 5 EBRT studies, 1 HDR BT alone, 7 BT plus EBRT studies) and for all dosimetry outcomes (for example, V40 average difference -6.1% in high dose-rate brachytherapy plus IG-IMRT [Chao 2019] to -9.1% in IG-IMRT [Whalley 2016]). The RCT (Mariados 2015) also showed that hydrogel spacer reduces rectal radiation dose (Armstrong 2021).

In the systematic review of 9 studies comparing 671 patients who had hydrogel spacers (of 2 different types) with 537 patients who did not have hydrogel spacers (controls) before brachytherapy for prostate cancer, the rectal D2 cc was reduced in the spacer group by between 22% and 53% and the median rectal V75% cc was reduced by between 92% to 100% (Vaggers 2021).

A systematic review of 11 studies on using different rectal spacers during different radiotherapy techniques for prostate cancer reported that the mean rectal dose reduced in spacer group when compared with no spacer regardless of dose (with hydrogel spacers, hyaluronic acid) and when comparing preimplantation plans with postimplantation plans (with collagen implants, biodegradable balloons) (Mok 2014).

Rectal and urinary tract toxicity

In the prospective multicentre RCT of 222 patients, acute rectal toxicity was similar between the spacer and control groups (p=0.525), as was urinary tract toxicity (p=0.488). There was statistically significantly less rectal toxicity at 3 to 15 months in patients with a spacer (2% of patients: grade 1 events rectal bleeding, rectal urgency and proctitis, each in 1 patient) compared with patients in the control group (7% of patients: grade 1 events rectal bleeding in 3, rectal urgency in 1 and grade 3 proctitis in 1; p=0.04). There was no late rectal toxicity greater than grade 1 in patients in the spacer group. The 3-year incidence of rectal toxicity greater than grade 1 (2.0% versus 9.0%; p=0.28) and greater than grade 2 (0% versus 5.7%; p=0.012) was lower in the spacer group than control group. Urinary toxicity greater than grade 1 was also lower in the spacer arm (4% versus 15%; p=0.046), with no difference in greater than grade 2 urinary toxicity (7% versus 7%; p=0.7) (Mariados 2015, Hamstra 2017).

In the systematic review and meta-analysis of 7 studies comparing 486 patients who had a hydrogel spacer with 525 patients who did not have a rectal spacer (controls), pooled results from 6 studies showed that the risk of early grade 2 or higher rectal toxic effects (at 3 months follow up) was comparable and not statistically significantly different between the hydrogel spacer and control groups (5% versus 4%; RR, 0.82; 95% CI, 0.52 to 1.28; p=0.38). However, in a pooled analysis of 4 studies, at late follow up (median, 38 months; range, 28 to 60 months) the risk of grade 2 or higher rectal toxic effects was lower in the hydrogel spacer group compared to controls (2% versus 6%; RR, 0.23; 95% CI, 0.06 to 0.99; p=0.05). Another pooled analysis showed that the risk of grade 1 or higher rectal toxic effects was lower in patients treated with the hydrogel spacer compared to controls at early follow up (21% versus 30%; RR, 0.72; 95% CI, 0.58 to 0.91; p=0.005; 7 studies); and at late follow up (median, 40 months; range, 28 to 60 months) (5% versus 16%; RR, 0.38; 95% CI, 0.22 to 0.65; p<0.001; 5 studies); (Miller 2020).

The HTA report by EUnetHTA on the use of biodegradable rectal spacers for patients with prostate cancer receiving curative radiotherapy included 2 prospective comparative studies (1 RCT [Mariados 2015] with 5 related studies, a registry record from the same trial and 1 nRCT) that assessed rectal and urinary or genitourinary toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE). In the RCT (220 patients) the risk of early grade 1 rectal toxicity (at 3 months follow up) was not statistically significantly different (RR 0.77, 95% CI 0.50 to 1.19) and the risk of grade 2 or greater rectal toxicity was also not statistically significantly different (RR 0.91, 95% CI 0.23 to 3.5) in the hydrogel spacer group compared with control group. No grade 3 or 4 toxicities were reported in the spacer group but 1 grade 3 toxicity was reported in the radiotherapy alone group. The risk of grade 1 urinary toxicity and the risk of developing grade ≥2 urinary toxicity were also not statistically significantly different (RR 1.03, 95% CI 0.87 to 1.21, p=0.74 and RR 0.97, 95% CI 0.81 to 1.18, p=0.79, respectively). No grades 3 or 4 were reported.

The risk of late grade 1 rectal toxicity (at 15 months follow up) was not statistically significantly different (RR 0.34, 95% CI 0.08 to 1.48). There was 1 grade 3 case in the radiotherapy alone group and no grades 2 or 4 were reported. At 15 months, the risk of late grade 1 urinary toxicity and the risk of late grade 2 or greater urinary toxicity were also not statistically significantly different (RR 0.65, 95% CI 0.15 to 2.85, p=0.57 and RR 1.57, 95% CI 0.44 to 5.53, p=0.47, respectively). No grade 3 or 4 urinary toxicities were reported.

The cumulative evidence (acute and late rectal toxicity, at a median follow up of 3 years, n=140), suggests that patients in the hydrogel spacer plus radiotherapy group were less likely to present grade 1 rectal toxicity than the radiotherapy alone group (HR 0.24, 95% CI 0.06 to 0.97, p<0.03). The HR was not presented for grades ≥2. There was 1 case of grade 3 toxicity in the radiotherapy alone group, and no cases of grade 4 reported. The difference between the groups for grade 1 urinary toxicity was HR 0.36, 95% CI 0.12 to 1.1, p=0.046 and for grade ≥2 urinary toxicity was HR 1.22, 95% CI 0.40 to 3.72, p=0.7.

In the nRCT at 3 months follow up, the risk of developing grade 1 rectal toxicity was not statistically significantly different in the radiotherapy alone group when compared with hydrogel spacer plus radiotherapy group (RR 1.58, 95% CI 0.34 to 7.60, p=0.55) or balloon plus radiotherapy group (RR 1.64, 95% CI 0.35 to 7.60, p=0.52). The risk of developing grade 2 GU toxicity was not statistically significantly different in the radiotherapy alone group (RR 1.39, 95% CI 0.57 to 3.38, p=0.46) or in the balloon plus radiotherapy group (RR 0.78, 95% CI 0.28 to 2.22, p=0.64). compared to hydrogel spacer plus radiotherapy group. No grades 3 or 4 were recorded (NIPHNO 2020).

The systematic review of 19 studies (1 RCT, 18 comparative nRCTs, with 3,622 patients) comparing patients who had a perirectal hydrogel spacer with patients who did not have a spacer (controls) across all types of radiotherapy for prostate cancer reported that GI and GU toxicities reduced but were not statistically significantly different in the hydrogel spacer plus radiotherapy group across 7 included nRCTs regardless of the type of radiotherapy used (5 EBRT studies, 1

HDR BT plus IG-IMRT study [Chao 2019], and 1 LDR BT alone or in combination with EBRT [Taggar 2018]). The RCT (Mariados 2015) included also showed that hydrogel spacer plus radiotherapy significantly reduced late GI and GU toxicities (Armstrong 2021).

In the systematic review of 9 studies comparing 671 patients who had hydrogel spacers (of 2 different types) with 537 patients who did not have hydrogel spacers (controls) before brachytherapy for prostate cancer, acute GI complications were mainly limited to grade 1 or 2 toxicity. One study (Chao 2019) on HDR BT with EBRT found a significantly lower rate of grade 1 acute GI complications in the spacer group compared with control group (13% versus 31%, p=0.05) but no statistically significant difference in grade 2 acute GI complications (0% versus 2%, p=0.48). Late grade 1 GI toxicity was less in the spacer group compared to control group (0% versus 8%, p=0.11). No late grade 2 or 3 GI toxicities were seen. In another case-control study (Taggar 2018), at a median follow up of 3 months, grade 1 or 2 rectal or GI toxicity was seen in 20% (n=15) patients in the spacer cohort and 24% (n=33) patients in the non-spacer cohort (p=0.95) (Vaggers 2021).

Quality of life

In the prospective multicentre RCT of 222 patients, at 15 months follow up, 12% of patients in the spacer group and 21% of patients in the control group reported a 10-point decline (p=0.087) in bowel QoL scores (assessed using the Expanded Prostate Cancer Index Composite self-assessment questionnaire). Bowel QoL consistently favoured the spacer group from 6 months (p=0.002), with the difference at 3 years (5.8 points; p<0.05) meeting the threshold for a minimally important difference (MID, 5 points). At 3 years, more patients in the control group than in the spacer group had experienced a MID decline in bowel QoL (5-point decline: 41% versus 14%; p=0.002; OR 0.28, 95% CI 0.13 to 0.63) and even large declines at twice the MID (10-point decline: 21% versus 5%, p=0.02, OR 0.30, 95% CI 0.11 to 0.83) (Mariados 2015, Hamstra 2017).

At 6 months follow up, 9% of patients in the spacer group and 22% of patients in the control group reported 10-point decline in urinary QoL scores (p=0.003). At 12 and 15 months follow up, the declines in urinary QoL scores were similar for both groups. At 3 years follow up, the control group had a 3.9-point greater decline in urinary QoL compared with the spacer group (p<0.05), but the difference did not meet the MID threshold (6 points). At 3 years, more patients in the control group than in the spacer group had experienced a MID decline in urinary QoL (6-point decline: 30% versus 17%; p=0.04; OR 0.41, 95% CI 0.18 to 0.95) and even large declines at twice the MID (12-point decline: 23% versus 8%; p=0.02; OR 0.31, 95% CI 0.11 to 0.85) (Mariados 2015, Hamstra 2017).

In the systematic review and meta-analysis of 7 studies comparing 486 patients who had a hydrogel spacer with 525 patients who did not have a spacer (controls), pooled analysis of 2 studies showed that changes in bowel-related QoL were similar between the 2 groups at 3 months follow up (MD, 0.2; 95% CI, -3.1 to 3.4; p=0.92). At late follow up (median, 48 months; range, 36 to 60 months), the changes showed an improvement in QoL in the hydrogel spacer group and exceeded the threshold for a minimal clinically importance difference (MD, 5.4; 95% CI, 2.8 to 8.0; p<0.001) (Miller 2020).

In the HTA report by EUnetHTA, an RCT (Mariados 2015) that assessed QoL according to the EPIC 50 item scale (in which higher values indicate better QoL) and summarised on 3 domains (bowel, urinary, and sexual QoL) reported that the proportions of patients experiencing minimally important differences (declines) in all 3 QoL summary domains at 36 months were 2.5% with hydrogel spacer plus radiotherapy group compared with 20% in radiotherapy group (p=0.002). Results also indicate that hydrogel spacer plus radiotherapy group may improve bowel QoL (p=0.002), may have little to no effect on urinary QoL (p=0.13) over the entire follow-up period (n=140), but the evidence is uncertain (NIPHNO 2021).

The systematic review of 19 studies (1 RCT, 18 comparative nRCTs, with 3,622 patients) comparing patients who had a perirectal hydrogel spacer with patients who did not have a spacer (controls) across all types of radiotherapy for prostate cancer reported that improvements were seen after perirectal spacer implantation in most EPIC QoL domains across 4 nRCTs but not statistically significant (in 3 EBRT studies with up to 60 months follow up). For example, in 1 study with EBRT plus LDR BT, bowel function score decreased at 3 and 6 months: average change of 0 versus -6.25 and -3.57, respectively. Another included study reported clinically meaningful differences in EPIC–bowel bother scores at 18 and 60 months (6 point and 5 points, respectively, p>0.05). The RCT also showed that hydrogel spacer significantly improves urinary, bowel and sexual QoL (MID declines in all 3 QoL domains, p=0.002) (Armstrong 2021).

Spacer absorption

In the prospective multicentre RCT of 222 patients, hydrogel absorption was confirmed at 12 months (on MRI scans) in all the patients in the spacer group, with 2% (3/148) of them having small water density remnant cysts in unremarkable perirectal tissues (Mariados 2015, Hamstra 2017).

The systematic review of 11 studies on using different rectal spacers during different radiotherapy techniques for prostate cancer reported that time to complete absorption is variable among the spacers (with PEG hydrogels and biodegradable balloons reporting complete absorption after 6 months, collagen implants and hyaluronic acid at 12 months) (Mok 2014).

Prostate motion or displacement

In a systematic review of 21 studies evaluating the role of the biodegradable rectal spacers on prostate motion, hydrogel spacer placement (in 4 studies) was not associated with statistically significant changes in prostate motion, compared with no spacer or endorectal balloons but significantly reduces rectal wall doses and GI toxicities. Endorectal balloon (ERB) placement (in 12 studies) significantly decreases intra-fractional prostate motion. This reduces PTV margins and additional rectal dose sparing. Even with an ERB, inter-fractional prostate displacements are seen (Ardekani 2021).

Safety summary

Procedure-related complications

In the systematic review and meta-analysis of 7 studies, authors state that procedural complications (defined as inability to inject the hydrogel spacer into the perirectal space or any complication, regardless of severity, occurring during the procedure) were infrequent and reported inconsistently (Miller 2020).

The RCT included within several reviews reported mild and transient procedural adverse events (perineal discomfort and others, grade 1 to 2) in 10% of patients in the hydrogel spacer group. Grade 2 events (treated with medication) included mild lower urinary tract symptoms and hypotension, and moderate perineal pain. Fewer patients with a spacer had rectal pain (3% compared with 11% in control group, p=0.02). Hydrogel rectal infiltration during the procedure was reported in 6% (n=9) patients. Inadvertent needle penetration of the rectal wall (needing termination of the procedure) and hydrogel injected beyond the prostate were reported in 1 patient each. There were no grade 3 to 4 related adverse events or deaths (Mariados 2015).

In the systematic review of 13 studies (n=671 patients with hydrogel spacer versus 537 patients without a spacer before prostate cancer brachytherapy), some procedure-related complications were reported in the hydrogel spacer groups (in 8 of the studies). These included:

- rectal ulcer 2 months after hydrogel injection (causing frequent rectal bleeding, mucus discharge and bowel movements that resolved without intervention by 3 months) in a case report of 1 patient (Teh 2014),
- perineal pain (that resolved without intervention within 1 week) in 3 patients,
- sensation of pressure or fullness in the rectum (that resolved by 3 months with medication) in 1 patient,

- sudden need for defecation (that resolved by 3 months with medication) in 1 patient,
- infection (bacterial prostatitis after biopsies in 2 patients and epididymitis in 1 patient, which resolved after adjusting antibiotic prophylaxis),
- rectal perineal abscess (in 1 patient after 1 month, needed incision, drainage and antibiotics),
- severe proctitis (in 1 patient), and fistulas needing diverting colostomy (in 2 patients),
- other complications such as rectal discomfort (n=7), bleeding (n=2), and diarrhoea were reported in 1 study of 74 patients with hydrogel (Taggar 2018) (Vaggers 2021).

A review of complications of hydrogel spacer injections in the Manufacturer and User Facility Device Experience (MAUDE) database reported 22 unique reports discussing 25 patient cases (from January 2015 to March 2019), with an increasing number of reports each year up to 2019. The reported complications included:

- venous injection in 3 (no sequelae),
- tenesmus with air in rectal wall in 1 (no sequelae),
- rectal wall erosion in 1 (no sequelae),
- purulent drainage from perineum in 1 (needing antibiotics),
- acute pulmonary embolism in 4 (needing anticoagulant),
- perineal abscess in 3 (needing drainage), proctitis in 1 (needing colostomy), rectal ulcer and haemorrhage in 1 (needing surgery),
- recto-urethral fistula in 4 (needing diverting colostomy),
- perirectal fistula in 1 (needing surgical intervention),
- urinary tract infection and prostatic abscess in 1 (needing drainage),
- perineal abscess and subsequent death from alcoholic cardiomyopathy in 1, severe urosepsis in 1 (needing ICU admission),
- severe anaphylaxis in 1, dizziness and nausea post-procedure leading to unresponsiveness and

- death in 1 (the cause of death was unclear) (Aminsharif 2019).

Another recent review of complications of hydrogel spacers in the MAUDE database reported 85 unique reports (from 2015 to 2020). Of these 69% (59/85) events were grade 3, 4, or 5. 24 per cent were grade 4 events, including colostomy (n=7) anaphylactic shock (n=2), rectal wall injection, pulmonary embolism requiring hospital admission (n=5), and recto-urethral fistula (n=8). One death was reported (Hall 2021).

Inadvertent injection of hydrogel into the rectal lumen resulting in focal rectal mucosal necrosis and bladder perforation was reported after the procedure in 1 patient in a case series of 52 patients. This resolved with no sequelae (Uhl 2014, Song 2013). The same study included in the meta-analysis reported 1 case of inadvertent injection into the rectal lumen without adverse sequelae (Miller 2020).

A case series of 27 patients with ERB (Gez 2013) included in the HTA report by EUnetHTA reported:

- Acute urinary retention (needed catheterisation, which resolved within a few hours) in 12% (3/26) of patients during balloon insertion and in 1 patient during radiotherapy.
- Dysuria and nocturia (grade 1 to 2) in 12% (3/26) of patients during balloon insertion and in 65% (15/23) of patients during radiotherapy.
- Penile bleeding in 1 patient during balloon insertion. Further details were not reported.
- Other events during radiotherapy in the same study, including diarrhoea in 17% (4/23) of patients, mild proctitis in 8% (2/23) of patients, and , blood in the faeces, constipation, erectile dysfunction, itching, fatigue and decreased urine flow in 1 patient each (NIPHNO 2021).

Haematoma developed behind the bladder in 1 patient with a moderate platelet count (within hours after injection) in a case series of 36 patients injected with a hyaluronic acid spacer. This was removed by laparotomy (Chapet 2015).

In the systematic review of 11 studies, a case series of 11 patients injected with collagen implant during IMRT reported that 3 patients had self-limiting light rectal pressure. One patient needed temporary catheterisation for acute urinary retention (presumed to be secondary to pudendal nerve blocking) (Mok 2014).

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened).

For this procedure, professional experts listed the following anecdotal adverse events: intraprostatic infiltration of gel, urinary retention, hydrogel not solidifying, loss of implant (user preparation error when the implant deployed while being prepared for insertion). They described that “there is a theoretical possibility that spacer insertion could cause displacement of extracapsular prostate cancer leading to reduced efficacy of radiotherapy*”.*

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer. The following databases were searched, covering the period from their start to 30.09.2022: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The inclusion criteria were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with prostate cancer.
Intervention/test	Insertion of biodegradable spacer for prostate rectum separation during radiotherapy.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the interventional procedures (IP) overview

This IP overview is based on 7,920 patients from 1 RCT, 2 meta-analysis, 1 HTA, 4 systematic reviews,1 review, 1 commentary and 1 case series. There is likely to be an overlap of primary studies between systematic reviews 2 to 7 and data between studies 9 and 10.

Other studies that were considered to be relevant to the procedure but were not included in the main summary of the key evidence are listed in the appendix.

Summary of key evidence on biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer

Study 1 Mariados N 2015, Hamstra DA 2017, 2018, Karsh 2018

Study details

Study type	**Randomised Controlled Trial**
Country	US (multicentre)
Recruitment period	2012 to 2013
Study population and number	n=**222 (149 with spacer versus 73 without spacer [control])** patients with clinical stage T1 or T2 prostate cancer (NCCN low or intermediate risk).
Age and sex	Mean age: spacer group 66.4 years; control group: 67.7% years; 100% male
Patient selection criteria	Men with stage T1 and T2 prostate cancer, a Gleason score of <7, PSA concentration of 20 nanograms/ml, and a Zubrod performance status of 0–1, planning to have image guided intensity modulated radiotherapy (IG-IMRT) were included. Patients with a prostate volume of >80 cm^3, extracapsular extension of disease or >50% positivity biopsy scores, metastatic disease, indicated for or had recent androgen deprivation therapy and prior prostate surgery or radiotherapy were excluded.
Technique	**Intervention: Injection of a prostate-rectum spacer (polyethylene glycol hydrogel-SpaceOAR system) during IG-IMRT** (total dose of 79.2Gy in 1.8 Gy fractions to the prostate with or without the seminal vesicles delivered 5 days weekly) A planning target volume of 5-10mm was used. **Control – IG-IMRT alone** (total dose of 79.2Gy in 1.8 Gy in 44 fractions to the prostate with or without the seminal vesicles delivered 5 days weekly) **with no injection.** Patients had CT and MRI scans for treatment planning, followed with fiducial marker placement using transperineal approach. Antibiotic prophylaxis was administered before procedure 95% of time. General anaesthesia in 36%, local in 31%, monitored anaesthesia in 26%, conscious sedation in 6%, other in 10%.
Follow-up	**Median 37 months (15 months, Mariados N, 2015; 3 years Hamstra DA 2017, 2018, Karsh 2018)**
Conflict of interest/source of funding	The study was supported by research funding from Augmenix. Two authors are shareholders and 1 author received speaking honoraria from the manufacturer. 2 authors have provided consulting services.

Analysis

Follow-up issues: short follow-up period. Patients evaluated at baseline, weekly during IG-IMRT, and at 3, 6, 12 and 15 months. Three patients were lost to follow up during the study period (15 months). Extended follow up at 3 years was voluntary, with each institute choosing whether to participate. 63% of both control and spacer patients were available at extended follow up and no differences were found in the median follow-up period between the 2 treatment groups (control median 37 months, spacer median 37.1 months, $p>0.05$).

Study design issues: prospective single-blind phase III trial in 20 centres evaluating safety and effectiveness of hydrogel spacer, Patients were randomised 2:1 (by opening envelopes) to have either spacer injection or no injection (control). Patients were blinded to randomisation, allocation concealed. The planning methodology from baseline and post procedural treatment plans was same. The primary effectiveness endpoint was the proportion of patients achieving >25% reduction in rectal volume having at least 70Gy (V70) because of spacer placement. The primary safety endpoint was the proportion of patients having grade 1 or greater rectal or procedural adverse events in the first 6 months. All IG-IMRT planning documentation and CT and MRI scans were assessed by a blinded independent laboratory. All adverse events were recorded and attributed by an independent clinical events committee blinded to treatment randomisation. Rectal and urinary adverse events attributed to radiation were included for toxicity analysis according to National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4 grading system. Quality of life (QoL) assessed using the Expanded Prostate Cancer Index Composite (EPIC) health related QoL questionnaire at different follow-up visits. Declines in QoL assessed using predetermined 5- and 10-point thresholds for minimal clinically detectable QoL changes.

Study population issues: There were no differences between the groups with regard to baseline tumour characteristics, demographics and medical morbidities.

Key efficacy findings

Number of patients analysed: 220 (148 with spacer versus 72 without spacer [control])

Spacer placement success in spacer group (defined as hydrogel present in perirectal space): 98.7% (146/148)

Ease of spacer application:

Urologists and oncologists rated spacer application as 'easy' and 'very easy' 98.7% of time.

Perirectal space (distance between the posterior prostate capsule and anterior rectal wall on axial mid-gland T2 weighted MRIs) (Mariados 2015).

	Spacer group	**Control group**
Baseline	1.6±2.2 mm	NR
Post spacer application	12.6±3.9 mm	1.6±2.0 mm
3 months	9.0±5.9 mm	NR

Rectal dose volume in spacer group (Mean±SD)[1]

Spacer group (n=148)					Control group (n=72)	p value
Parameter	rV50	rV60	rV70	rV80	rV70	
% before spacer	25.7±11.1	18.4±7.7	12.4±5.4	4.6±3.1	12.4	0.95
% after spacer	12.2±8.7	6.8±5.5	3.3±3.2	0.6±0.9	11.7	<0.0001
% of absolute reduction	13.442	11.56	9.078	3.933		
% of relative reduction	52.3	62.9	73.3	86.3		
p value	<0.0001	<0.0001	<0.0001	<0.0001		

Overall 97.3% of spacer patients had a 25% reduction in rV70. Additionally, 100% and 92% of all spacer and control patient plans met all rectal dose constraints respectively.

Spacer application did not increase the dose in neighbouring tissues (mean pre and post application bladder V70 being 11.3% and 11.0%). No differences were found in the values for bladder or bladder wall (p>0.001 for all).

The mean penile bulb dose was significantly reduced in spacer group than in the control group (18.0 Gy versus 22.8 Gy, p=0.036) and doses from V10 to V30.

Acute and late rectal and urinary tract toxicity

Acute toxicity (from procedure to 3-month visit)[Mariados 2015]						
Rectal toxicity scores (%)				Urinary tract toxicity scores (%)		
Grade	Spacer % (n=148)	Control % (n=72)	p value	Spacer % (n=148)	Control % (n=72)	p value
0	73 (108)	68 (49)	0.525	9.5 (14)	9.7 (7)	0.488
1	23 (34)	27.8 (20)		52.7 (78)	45.8 (33)	
>2	4.1 (6)*	4.2 (3)*		37.8 (56)*	44.4 (32)*	
Late toxicity (between 3 and 15 month visits)[Mariados 2015]						
Grade	Spacer % (n=148)	Control % (n=71)	p value	Spacer % (n=148)	Control % (n=71)	p value
0	98 (145)	93 966)	0.044	90.5 (134)	91.5 (65)	0.622
1	2 (3)+	5.6 (4)+		2.7 (4)	4.2 (3)	
>2	0	1.4 (1)+		6.8 (10)	4.2 (3)	
Late toxicity (between 15 months and 3 year visits)[Hamstra 2017]						
Rectal toxicity scores (%)				Urinary tract toxicity scores (%)		
Grade	Spacer % (n=94)	Control % (n=46)	p value	Spacer % (n=94)	Control % (n=46)	p value
>1	2.0 (95% CI 4-20%)	9.0 (95% CI 1-6%)	0.28	4 (95% CI 2-10%)	15 (95% CI 8-29%)	0.046

			HR 0.24 (95% CI 0.06-0.97)			HR 0.36 (95% CI 0.12 -1.1)
>2	0	5.7++ (95% CI 2-17%)	0.012	7	7	0.7

*No grade 3 or 4 toxicity reported within 3 months.

+ late rectal toxicity was seen in 2% of spacer patients (3 grade 1 events: 1 rectal bleeding, 1 rectal urgency, and 1 proctitis) and 7% of control patients (grade 1–3 rectal bleeding, 1 rectal urgency and 1 grade 3 proctitis). There was no rectal toxicity greater than grade 1 in spacer group[1]. ++ 1 case of grade 2 rectal toxicity in control arm (Hamstra 2017).

Bowel QoL (assessed using EPIC questionnaire)

At 15 months, 11.6% and 21.4% of spacer and control group patients had 10-point declines in bowel QoL (p=0.087)[1]. From 6 months onward, bowel QoL consistently favoured the spacer group (p=0.002), with the difference at 3 years (5.8 points; p<0.05) meeting the threshold for a MID (5-7 points). At 3 years, more patients in the control group than in the spacer group had experienced a MID decline in bowel QoL (5-point decline: 41% versus 14%; p=0.002; OR 0.28, 95% CI 0.13-0.63) and even large declines (twice the MID) (10 decline: 21% versus 5%, p=0.02, OR 0.30, 95% CI 0.11-0.83) (Hamstra 2017).

Urinary QoL (assessed using EPIC questionnaire)

At 6 months, 8.8% and 22.2% of spacer and control group patients had 10-point urinary declines (p=0.003). At 12 and 15 months the declines were similar for both groups (Mariados 2015).

The control group had a 3.9-point greater decline in urinary QoL compared with the spacer group at 3 years (p<.05), but the difference did not meet the MID threshold (5-7 points). At 3 years, more patients in the control group than in the spacer group had experienced a MID decline in urinary QoL (6-point decline: 30% vs 17%; p=0.04; OR 0.41, 95% CI 0.18-0.95) and even large declines (twice the MID) (12-point decline: 23% vs 8%; p=0.02; OR 0.31, 95% CI 0.11-0.85) (Hamstra 2017).

Sexual QoL: 41% (88/222) of patients with adequate baseline sexual QoL (EPIC mean, 77 ± 8.3) at 3 years had better sexual function (p=0.03) with a spacer with a smaller difference in sexual bother score (p=0.1), which resulted in a higher EPIC score on the spacer arm (58 ±24.1 versus control 45 ± 24.4) meeting threshold for MID without statistical significance (p=0.07). There were statistically nonsignificant differences favouring spacer for the proportion of patients with MID and 2× MID declines in sexual QoL (with 53% versus 75% having an 11-point decline, p=0.064 and 41% versus 60% with a 22-point decline, p=0.11). At 3 years, more patients potent at baseline and treated with spacer had “erections sufficient for intercourse" (control 37.5% versus spacer 66.7%, p=0.046) as well as statistically higher scores on 7 of 13 items in the sexual domain (all p<0.05) (Hamstra 2018, Karsh 2018).

Multi-domain changes (urinary, sexual and bowel): 46% of patients in the spacer group and 35% in the control group had no clinically detectable changes in any QoL domain at 3 years. 20% of patients in the control group had changes meeting the threshold for MID in all 3 domains compared with only 2.5% in the spacer group. Also, 12.5% of the control group had large changes (2xMID) in all 3 domains at 3 years compared with no patients in the spacer group (Hamstra 2017, 2018).

Spacer absorption (using MRI) at 12 months: confirmed in all, except 2% (3/148) patients exhibiting small water density remnant cysts in unremarkable perirectal tissues (Mariados 2015).

Safety

Primary safety endpoint

	Spacer group %	Control group %	p value
Rates of grade 1 or greater rectal or procedural adverse events at first 6 months	34.2	31.5	0.7
Acute rectal pain	2.7	11.1	0.022

No differences in acute rectal or urinary tract toxicities were seen in the first 3 months.

Overall adverse and serious adverse events

	Spacer group %	Control group %	p value
Adverse events	96.6	100	NS
Serious adverse events	13.4	15.1	NS

Spacer safety: there were no device related adverse events, rectal perorations, serious bleeding or infections in either group.

Study 2 Miller 2020

Study details

Study type	Systematic review and meta-analysis
Country	USA, UK, Switzerland and Germany
Study search details	Inception to September 2019; Databases searched: Cochrane Central Register of Controlled Trials, MEDLINE, and Embase; no language or date restrictions applied. Supplemental searches were done in the directory of open access journals, Google scholar, and reference lists of included articles and relevant meta-analyses searched. If outcomes were unclear in studies, authors were contacted.
Study population and number	n=7 studies with 1,011 patients (486 patients who had a perirectal hydrogel spacer injection versus 525 patients who did not receive a spacer [controls] before prostate cancer radiotherapy). (1 randomised clinical trial [RCT] and 6 cohort studies [1 prospective, 4 retrospective and 1 with prospective enrolment in spacer group and retrospective enrolment in no spacer group]) <u>Clinical stages:</u> localised or locally advanced prostate cancer (T1-T3) <u>prostate-specific antigen levels</u> ranged from 5.6 to 10.2 nanograms/ml
Age and sex	Mean age of 66 to 77 years.
Study selection criteria	<u>Inclusion criteria</u>: randomised clinical trials or cohort studies of patients who had the perirectal hydrogel spacer versus patients who had no spacer before radiotherapy for localised or locally advanced prostate cancer. Studies using external-beam RT that reported the percentage volume of the rectum receiving at least 70 Gy radiation (v70). <u>Exclusion criteria:</u> review articles, commentaries, letters, studies with no control or active control group, studies with fewer than 10 patients, pre-post dosimetric studies, studies that did not report a pre-specified outcome of this review, duplicate publications and unpublished or grey literature.
Technique	**Intervention:** Injection of a prostate-rectum spacer (absorbable polyethylene glycol hydrogel-SpaceOAR system) between the Denonvilliers fascia and anterior rectal wall before radiotherapy. <u>Radiotherapy protocols:</u> EBRT with a total therapeutic dose ranging from 76 to 81 Gy (5 studies), BT with or without EBRT (1 study), or combination therapy (1 study).
Follow up	Median 26 months (range, 3 to 63 months).
Conflict of interest/source of funding	The study was funded by Boston Scientific and they were involved in design and interpretation of data, review and approval of manuscript. Authors served as consultants, and either received personal fees, grants, honoraria, travel expenses, and non-financial support from Boston scientific and other companies.

Analysis

Follow-up issues: follow up varied across studies and data was analysed as reported by individual studies. Some attrition bias was reported at late follow up in included studies.

Study design issues: systematic review protocol was registered and was done according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines. Comprehensive literature search was done, studies were screened and data extracted into a predesigned form, any disagreements were resolved by discussion. Multiple studies with overlapping patients were carefully assessed and included. Small numbers of nRCTs were included and were associated with risks of bias. A random-effects meta-analysis model was used for analysis of outcomes (rectal irradiation, rectal toxic effects, and bowel-related QoL). Heterogeneity was noted among study designs, patient characteristics, and radiotherapy protocols.
Study population issues: patient characteristics and risk categories varied between studies.
Other issues: One included study compared outcomes with the hydrogel spacer, biodegradable balloon, and no spacer treatment, but results of the balloon group were excluded from the analysis by the authors. Authors state that no studies of hydrogel spacer placement in patients receiving SBRT were eligible for inclusion in this review.

Key efficacy findings

Number of patients analysed: 1,011 patients (486 patients who had a perirectal hydrogel spacer injection versus 525 patients who did not receive a spacer [controls])

Procedural outcomes

Spacer placement success in spacer group (5 studies): the hydrogel spacer was successfully placed in 97.0% (95% CI, 94.4%-98.8%) of cases and failure reported in 3% cases. Causes of delivery failure were unsuccessful hydrodissection (n=5), inadvertent needle entry into the rectal lumen with no clinical sequelae (n=3), and unspecified cause (n=1).

Perirectal separation distance (distance between the posterior prostate capsule and anterior rectal wall on axial mid-gland T2 weighted MRIs): the weighted mean perirectal separation distance after hydrogel spacer placement was 11.2 mm (95% CI, 10.1-12.3 mm [5 studies]).

Rectal irradiation with perirectal hydrogel spacer versus without spacer (control)

In a pooled analysis of 6 studies, patients who had the perirectal hydrogel spacer before EBRT had 66% less v70 rectal irradiation compared with controls- patients who did not receive perirectal hydrogel spacer (3,5% versus 10.4%; MD -6.5%; 95% CI -10.5% to 2.5%; I^2=97%; p=0.001).

Rectal toxicity

Grade 2 or higher rectal toxic effects with versus without rectal hydrogel spacer

Early grade ≥2: In a pooled analysis of 6 studies, the risk of early (≤3 months) grade 2 or higher rectal toxic effects was comparable and not statistically different between the hydrogel spacer group and control groups (4.5% versus 4.1%; RR, 0.82; 95% CI, 0.52-1.28; I^2=0%; p=0.38).

Late grade ≥2: In a pooled analysis of 4 studies, at late follow up (median, 38 months; range, 28-60 months), the risk of grade 2 or higher rectal toxic effects was 77% lower in the hydrogel spacer group compared to controls (1.5% versus 5.7%; RR, 0.23; 95% CI, 0.06-0.99; I^2=24%; p=0.05).

Grade ≥1 rectal toxicity with versus without perirectal hydrogel spacer

Early grade ≥1: In a pooled analysis of 7 studies, the risk of early (≤3 months) grade 1 or higher rectal toxicity in patients treated with the hydrogel spacer was significantly lower (20.5% versus 29.5%; RR, 0.72; 95% CI, 0.58-0.91; I^2= 0%; p=0.005).

Late grade ≥1: In a pooled analysis of 5 studies, late grade ≥1 rectal toxicity (median, 40 months; range, 28-60 months) was significantly lower in the hydrogel spacer group (4.8% versus 16.2%; RR, 0.38; 95% CI, 0.22-0.65; I^2= 0%; p < 0.001).

Bowel quality of life (QoL) with versus without perirectal hydrogel spacer

Changes in early bowel-related QoL: in a pooled analysis of 2 studies, change in early bowel quality of life (≤3 months) (on EPIC questionnaire reported on a 0 to 100 scale where higher values indicate better QoL) was not statistically different between the groups (MD, 0.2; 95% CI, –3.1 to 3.4; I^2=21%; p=0.92).

Change in late bowel-related QoL: in a pooled analysis of 2 studies, change in bowel-related QoL was greater in the hydrogel spacer group in late follow up (median, 48 months; range, 36-60 months) and exceeded the threshold for a minimal clinically importance difference (MD, 5.4; 95% CI, 2.8-8.0; I^2=0%; p< 0.001). A 4-point change from baseline was considered a minimal clinically important difference.

Key safety findings

Procedural complications (defined as inability to inject the hydrogel spacer into the perirectal space or any complication, regardless of severity, occurring during the procedure).

Mariados 2015	mild and transient complications (did not delay radiotherapy)	10%
Whalley 2016	Inadvertent injection into the rectal lumen (without adverse sequalae)	3% (1/30)
Pinkawa 2017, Taggar 2018	None	0

The frequency of procedural complications was uncommon but reported inconsistently; it was not reported in 3 studies (Chao 2019, te Velde 2019, Wolf 2015).

Study 3 Norwegian Institute of Public Health (NIPHNO) EUnetHTA 2020

Study details

Study type	HTA
Country	Europe
Study search details	2010 to 2019; Databases searched for existing evidence syntheses (systematic reviews, HTAs) and primary studies include MEDLINE, AMED, Embase, Epistemonikos, and Cochrane Central Register of Controlled Trials. Also searched trial registry records at ClinicalTrials.gov and WHO ICTRP, Devices@FDA, the American Society of Clinical Oncology conference abstracts, and the Radiation Therapy Oncology Group clinical trials protocols. Considered information from clinical practice guidelines, information from a general literature search and input from clinical experts, and manufacturers. No language, design, publication restrictions applied.
Study population and number	n=2 prospective comparative studies including 298 patients with T1 and T2 stage localised prostate cancer) (1 RCT [SpaceOAR plus radiotherapy versus radiotherapy alone]) including 3 companion studies from the same clinical trial (NCT01538628) and 1 non-randomised control trial (nRCT; hydrogel plus radiotherapy, balloon plus radiotherapy and radiotherapy alone)
Age	RCT: spacer group 66.4 years; control group: 67.7 years nRCT: not reported
Study selection criteria	Inclusion criteria: adults (>18yrs) who had prostate cancer (both localised and metastatic undergoing curative treatment); studies on biodegradable rectal spacers for prostate cancer radiotherapy compared with current pathway of care (radiotherapy); RCTs and prospective nRCTs or observational studies with a control group, prospective studies or registry studies, (for effectiveness), including prospective registry-based data (for safety); reporting effectiveness and safety outcomes, in all languages. Exclusion criteria: study designs other than those specified in inclusion criteria, studies with no outcome of interest, wrong population, no data on patients with spacers, or no full text.
Technique	**Intervention:** biodegradable rectal spacers for prostate cancer radiotherapy. 2 different spacers used: t**ransperineal hydrogel (SpaceOAR) or balloon (BioProtect) plus radiotherapy versus radiotherapy alone (EBRT)** Radiotherapy protocols: RCT (n=222) IG-IMRT dose of 79.2 Gy at 1.8 Gy fractions, delivered to ≥98% of the planning target volume (PTV) and 100% of the clinical target volume, with the clinical target volume maximum of ≤110% of the prescription dose. nRCT: IMRT total dose of 75.85 Gy in daily fractional doses of 1.85 Gy prescribed to the 95% isodose using multi-segmental 7-field and shoot IMRT.
Follow up	RCT: 3,6,12,15 (Mariados 2015) and 36 months (Hamstra 2017). nRCT: up to 6 months (Wolf 2015)

Conflict of interest/source of funding	All authors, and stakeholders involved in the production of this assessment have declared they have no conflicts of interest according to the EUnetHTA declaration of interest (DOI) form.

Analysis

Follow-up issues: follow up varied across both studies and data was analysed as reported by individual studies. High attrition (>20%) was reported during long term follow up in the RCT.

Study design issues: Comprehensive systematic literature search was done, 2 reviewers screened studies and data extracted into a predesigned form, any disagreements were resolved by discussion. Quality of studies was assessed using the Cochrane risk of bias tool for RCT and the ROBINS-I tool (risk of bias in nRCTs– of Interventions) for nRCTs. Studies included were considered to be at high risk of bias (in the RCT methods were not well described, patients unblinded, selective reporting, and high attrition and in the nRCT selection bias, confounding, short follow up were reported). Same radiotherapy protocol was used in both studies. GRADE approach was used to rate the evidence for each outcome through a structured process.
MID for the EPIC Short Form was used to identify MID standards for the outcomes and interpret the magnitude of effect sizes. Effect sizes were calculated for urinary and rectal toxicity (early and late) and QoL and for other outcomes, data was presented as reported in the individual studies. Multiple studies with overlapping patients were carefully assessed and included the study with final results. The 2 studies used the CTCAE grading system for grading adverse events.

Study population issues: patient characteristics were not well defined in both studies. RCT included patients at clinical stage T1 and T2, individuals in the control group had severe co-morbidities and compulsory anticoagulation.
Other issues: 15 trial registry records including biodegradable rectum spacers at different stages (completed, ongoing, recruiting) were identified by the authors but not were considered in this analysis. There were no comparative studies on hyaluronic acid.

Key efficacy findings

Number of patients analysed: 298 patients

Rectal and urinary toxicity (n=2 studies assessed according to the CTCAE)

Outcomes	**No of patients**		**Relative effect (95% CI)**	**Absolute effect (95% CI)**	**GRADE Certainty of evidence**	**Comments**
	Spacer+ radiotherapy	**Radiotherapy alone**				
RCT (**Mariados 2015, Hamstra 2017)**						
Rectal toxicity	**N=148 Spacer**	**N=71 no spacer**				
Acute (grade 1)-3 months	34	20	RR 0.77 (0.50 to 1.19), p=0.42	94 fewer per 1000 (from 204 fewer to 78 more)	Low [2-3]	

Acute (grade ≥2) – 3 months	6*	3**	RR 0.91 (0.23 to 3.5), p=0.89	6 fewer per 1000 (from 47 fewer to 152 more)		*no grade 3 or 4 toxicity reported **1 grade 3 case, no grade 4 reported
Late (grade 1) – 15 months	3	4	RR 0.34 (0.08 to 1.48), p=0.16	40 fewer per 1000 (from 56 fewer to 29 more)		
Late (grade≥2)[4] – 15 months	0	2*	RR 0.15 (0.01 to 3.71), p=0.25	13 fewer per 1000 (from 15 fewer to 41 more)		1 grade 3 case, no grade 4 reported
Cumulative (acute and late, grade 1) – median 3 years	2	4	HR 0.24, 95% CI 0.06 to 0.97, p<0.03	Not able to calculate	Very low [2,3,5]	Loss to follow up 37% (spacer+RT n=54 and RT alone n=25)
Cumulative (acute and late, grade ≥2) – median 3 years	0	3	HR not available	Not able to calculate		
nRCT (Wolf 2015)						
Acute rectal toxicity (grade 1) – 3 months	5	2	RR 1.58 (0.34 to 7.60), p=0.55	61 more per 1000 (from 69 fewer to 695 more)	Very low	hydrogel versus RT – no grade 2-3 toxicity
	5		RR 1.64 (0.35 to 7.60), p=0.52	67 more per 1000 (from 68 fewer to 695 more)	Very Low[3,6]	Balloon versus RT – no grade 2-3 toxicity

Outcomes	No of patients		Relative effect (95% CI)	Absolute effect (95% CI)	GRADE	Comments
	Spacer+ radiotherapy	Radiotherapy alone				
RCT (Mariados 2015, Hamstra 2017)						
Urinary toxicity	**N=148**	**N=71**				
Acute (grade 1)-3 months	78	33	RR 1.03 (0.87 to 1.21), p=0.74	25 more per 1000 (from 107 fewer to 173 more)	Low [2-3]	

Acute (grade ≥2) – 3 months	56	32	RR 0.97 (0.81 to 1.18), p=0.79	25 fewer per 1000 (from 156 fewer to 148 more)		*no grade 3 or 4 toxicity reported
Late (grade 1) – 15 months	4	3	RR 0.65 (0.15 to 2.85), p=0.57	15 fewer per 1000 (from 36 fewer to 75 more)		
Late (grade ≥2) – 15 months	10*	3*	RR 1.57 (0.44 to 5.53), p=0.47	25 more per 1000 (from 23 fewer to 196 more)		*no grade 3 or 4 toxicity reported
Cumulative (acute and late, grade 1) – median 3 years	4	7	HR 0.36 (0.12 to 1.1), p=0.046	Not able to calculate	Very low [2,3,5]	Loss to follow up 37% (spacer+RT n=54 and RT alone n=25)
Cumulative (acute and late, grade ≥2) – median 3 years	NR	NR	HR 1.22 (0.40 to 3.72), p=0.7	Not able to calculate		
Genitourinary toxicity (Wolf 2015)						
	n=30 hydrogel, n=29 balloon spacer)	**n=19 radiotherapy alone**				
Acute – grade 2	11	5	RR 1.39 (0.57 to 3.38), p=0.46	103 more per 1000 (from 113 fewer to 626 more)	Very Low [3,6]	hydrogel or Balloon versus RT – no grade 3 toxicity
		6	6 RR 0.78 (0.27 to 2.12), p=0.64	58 fewer per 1000 (from 192 to 295 more)		

QoL

Outcomes	No of patients		Relative effect (95% CI)	Absolute effect (95% CI)	GRADE	Comments
	Spacer+ radiotherapy	Radiotherapy				

RCT (Mariados 2015, Hamstra 2017)						
Bowel QoL assessed with EPIC 0-100 – greater values are better						
Summary Score: results suggest SpaceOAR +RT may improve bowel QoL (p=0.002) over the entire follow-up period (1 study, 220 participants; very low certainty of evidence) but the evidence is uncertain.						
Minimal Clinical Difference – 5-point decline						
Bowel QoL 3 months	49% (73/148)	46%(32/71)	RD 0.05, 95% CI -0.09 to 0.19	5 more people in intervention reported 5-point decline	Low [2,3]	
Bowel QoL 15 months	24%(36/148)	34% (24/71)	RD -0.09, 95% CI -0.22 to 0.04	9 less people in intervention reported 5-point decline		
Bowel QoL 36 months	14% (13/94)	41% (19/46)	OR 0.28, 95% CI 0.13 to 0.63*	27% less patients in the intervention experiencing 5-point decline	Very low [2, 3, 5]	
Minimal Clinical Difference X2 – 10 point decline						
Bowel QoL 3 months	34% (50/148)	32% (23/71)	RD 0.02, 95% CI -0.11 to 0.15	2 more people in the intervention reported 10-point decline	Low	
Bowel QoL 15 months	11%(17/148)	21% (15/71)	RD -0.09, 95% CI -0.20 to 0.01	10 fewer people in the intervention reported a 10-point decline	Low [2,3]	
Bowel QoL 36 months	5% (5/94)	16% (7/46)	OR 0.30, 95% CI 0.11 to 0.83	16% fewer patients in the intervention reported 10-point decline	Very low [2,3,5]	
Urinary QoL - assessed with EPIC 0-100 – greater values are better						
Summary Score: Results suggest SpaceOAR may have little to no effect on urinary QoL (p=.13) over the study follow-up period (1 study, 220 participants; very low certainty of evidence); the evidence is very uncertain.						
Minimal Clinical Difference – 6-point decline						
Urinary QoL 3 months	65%(97/148)	60% (42/71)	RD 0.07, 95% CI -0.07 to 0.21	7 more people in the intervention reported 6 point decline	Low [2,3]	

Urinary QoL 15 months	22% (32/148)	21% (15/71)	RD 0.01, 95% CI -0.11 to 0.12	There was no difference in the number of patients reporting 6 point decline		
Urinary QoL 36 months	30% (28/94)	17% (8/46)	OR 0.41, 95% CI 0.18 to 0.95	13% fewer participants in the intervention reported 6 point decline	Very low [2,3,5]	
Minimal Clinical Difference X2 – 10-point decline						
Urinary QoL 3 months	47% (70/148)	49% (34/71)	RD 0.00, 95% CI -0.14 to 0.14*	There was no difference in the number of patients reporting 12-point decline		
Urinary QoL 15 months	9% (14/148)	12% (9/71)	RD -0.03, 95% CI -0.12 to 0.06	3 fewer patients in the intervention reported 12-point decline		
Urinary QoL 36 months	23% (22/94)	8% (4/46)	OR 0.31, 95% CI 0.11 to 0.85*	15% fewer participants in the intervention reported 12-point decline		
Sexual QoL – assessed with EPIC 0-100 – greater values are better						
Summary Score: results suggest SpaceOAR may have little to no effect on sexual QoL (p=0.6) over the entire study period (1 study, 140 participants; very low certainty of evidence), but the evidence is very uncertain.						
36 months	94	46	Not estimable	Sexual composite over time p=0.59	Very low [2,3,5]	

Rectal dose

outcomes	No of patients		Relative effect (95% CI)	Absolute effect (95% CI)	GRADE	Comments
	Spacer+ radiotherapy	Radiotherapy				
RCT (Mariados 2015, Hamstra 2017)						
rV70 Mean ± SD	N=148	N=71	-	-	Low [2,3]	97%intervention patients reached ≧25%

						reduction in rV70
nRCT (Wolf 2015)						
Isodose	Hydrogel 30 Balloon 29	radiotherapy alone 19	95% isodose	38% and 63% less		g-gel, b-balloon c control
			10.9 cm^2-g 17.6 cm^2-c 6.6 cm^2-b	24% and 42% less 10% and 22% less	Very low [2,3,5]	
			85% isodose 18.3 cm^2-g 24.1 cm^2-c 13.2 cm^2-b 60% isodose 34.4 cm^2-g 38.3 cm^2-c 29.7 cm^2-b			
Distance between rectum and prostate – baseline, post-insertion, 3 months **RCT (Mariados 2015, Hamstra 2017)**						
Mean perirectal distance (mm)	149	-	Not estimable	Not estimable	Low [2,3]	1.6±2.2 mm, baseline 12.6±3.9 mm, after insertion 9±5.9 mm at 3 months
PSA relapse – baseline, 12 and 15 months						
Nanograms/ml – 12 months and 15 months	148	71	Not estimable	Not estimable	Low [2,3]	Values only presented as means (no SD available), no data for 36 months available.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

1 Assessed according to CTCAE v4

2 Downgraded one level due to limitations in design (high risk of bias) (e.g. blinding, selective reporting)

3 Downgraded one level due to imprecision (one or 2 small studies)

4 Grade 2 is presented in Mariados' publication as '>2' and in Hamstra's as '≥2'; we have assumed this is ≥2 and reported as such

5 Downgraded one level due to limitations in design (large loss to follow up without imputations) 6 Downgraded one level due to limitations in design (high risk of bias) (e.g. bias due to confounding, selection of participants, bias of measurement of outcome)

Key safety findings

Outcomes	**No of patients**		**Relative effect (95% CI)**	**Absolute effect (95% CI)**	**GRADE**	**Comments**
	Spacer+ radiotherapy	**Radiotherapy alone**				
1 RCT (Mariados 2015 and 5 companion studies) and 1 nRCT (Wolf 2015)						
Deaths related to adverse events, grade 5	207	91	There was no (device) death related to adverse events reported in these studies		1 RCT and 1 nRCT	
Adverse events, grades 3-4	207	91	There was no (device) grade 3-4 related to adverse events reported in these studies			
Adverse events grades 1-2 [1]	148	71	Procedural adverse events • no unanticipated SpaceOAR related adverse events. • 10% of the spacer patients had mild transient procedural adverse events (perineal discomfort and others) • n=10 events requiring no medication* • grade 2 events treated with medication included mild lower urinary tract symptoms and hypotension, and moderate perineal pain.		Low [2,3]	The information reported in the RCT and companions studies: Mariados 2015, Pieczonka 2015, Karsh and Fisher Valuck 2017

			• no implant infections, rectal wall ulcerations or other more serious complications. • SpaceOAR Hydrogel procedural rectal wall infiltration in 6% (n=9). • 2/149 spacer patients had no SpaceOAR Hydrogel present after application: hydrogel injected beyond the prostate in 1 patient, no hydrogel injected in the other due to inadvertent needle penetration of the rectal wall requiring study-mandated termination of the procedure.		

*Haematospermia, anorectal pressure, haematuria, tight pain, discomfort while sitting, perineal pain, rectal pain, rectal bleeding (attributed to preoperative enema), constipation and flatulence (1 each).

Safety from other previous papers found by authors

<u>Hydrogel spacer related adverse events:</u>
A review of procedure related adverse events in the MAUDE database from January 2015 to March 2019 suggests that there were 22 unique reports discussing 25 patient cases, with an increasing number of reports each year up to 2018. Authors mentioned reported complications include acute pulmonary embolism, severe anaphylaxis, prostatic abscess and sepsis, purulent perineal drainage, rectal wall erosion, and recto-urethral fistula (see study 5 for further details). Authors state that a recent letter in response to this study suggests that 'the increase in the number of medical device reports in MAUDE over time is normal and proportionate to device usage and the rate of reports has remained relatively constant over time, ranging from 0.3 to 0.6 per 1000 SpaceOAR cases performed' (Babayan 2020).

A rectal ulcer, 1 cm in diameter (causing frequent rectal bleeding, mucus discharge and bowel movements) was reported in a case report of 1 patient 2 months after hydrogel injection. This had resolved without further intervention by 3 months. Digital rectal examination at 6 months revealed a healed ulcer, with only a non-tender slit in the anterior rectal wall. At subsequent examinations over 3 years, there was no recurrence of bowel symptoms (Teh 2014).

Inadvertent rectal wall injection (with hydrogel) resulting in focal rectal mucosal necrosis and bladder perforation was reported after the procedure in 1 patient in a case series of 52 patients. This resolved with no sequelae (Uhl 2014).

Infections (bacterial peritonitis in 2 patients and bacterial epididymitis in 1 patient) were reported in 3% (3/100) of patients injected with a hydrogel spacer in a retrospective comparative case series of 200 patients. The bacterial peritonitis occurred after prostate biopsies. All 3 infections resolved with antibiotic therapy. No infections were reported in the 100 patients treated with high dose rate brachytherapy without hydrogel (Storm 2014).

<u>Balloon spacer related adverse events:</u> a case series of 27 patients (Gez 2013) reported the following adverse events during balloon insertion and radiotherapy: penile bleeding and acute urinary retention (needed

catheterisation, which resolved within a few hours) during balloon insertion, dysuria and nocturia (grade 1-2). Other events reported during radiotherapy in the same case series included diarrhoea, mild proctitis, and blood in the faeces, constipation, erectile dysfunction, itching, fatigue and decreased urine flow.

Study 4 Armstrong N 2021

Study details

Study type	Systematic review
Country	UK, USA and Germany
Study search details	Search period: inception to May 2020; databases searched: MEDLINE, Embase, PubMed, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), KSR Evidence, Econlit (EBSCO), and NHS EED (CRD). HTA agency websites, clinical trials registers, conference abstracts databases and reference lists of included articles were also searched. No restrictions on language or publication status were applied.
Study population and number	19 studies (3,622 patients who had a perirectal hydrogel spacer versus patients who did not receive a spacer [controls] before prostate cancer radiotherapy). 1 RCT (10 references), 18 comparative nRCTs.
Age	patients between 65 to 75 years
Study selection criteria	Inclusion criteria: RCTs and nRCTs with patients receiving radiotherapy (all types) for localised or locally advanced prostate cancer with or without rectal hydrogel spacer; reporting a number of outcomes including radiation dose, toxicity and QoL.
Technique	Intervention: Injection of a prostate-rectum spacer (absorbable polyethylene glycol hydrogel-SpaceOAR system) between the Denonvilliers fascia and anterior rectal wall before RT. Comparator (control): no spacer Radiotherapy protocols: different RT modalities used. 1. EBRT- IG-IMRT- 1 RCT 2. EBRT, BT and combinations thereof (in 18 comparative nRCTs): • non-hypofractionated IMRT-7 studies, • ultra-hypofractionation - SBRT-2 studies, • PBT 1 study, • HDR BT monotherapy (1 study), • BT plus EBRT combination-7 studies (HDR BT +EBRT 3 studies, LDR BT +EBRT 4 studies)
Follow up	Varied across studies
Conflict of interest/source of funding	4 authors worked for a company which received funding for the project from Boston Scientific, few authors are employed by Boston Scientific, some received honoraria for advisory boards, travel expenses to medical meetings and 1 served as a consultant for different companies.

Analysis

Follow-up issues: adequate follow up in most studies.

Study design issues: systematic review protocol was registered and was done according to the PRISMA reporting guidelines, the Cochrane Handbook and the Centre for Reviews and Dissemination. Comprehensive literature search was done, 2 reviewers selected studies, extracted data and quality assessed the studies using Cochrane Risk of Bias Tool for RCT and Joanna Briggs Institute Critical Appraisal Checklist for cohort studies. The included studies were mainly non-RCT of low quality and in many studies patients were recruited to either the intervention or comparator at the same time. Treatment in nRCTs is usually allocated based on clinician or patient preference but 3 studies used historical matched controls. Studies with a range of radiotherapy modalities used in clinical practice are included. Dosing is measured in different ways. Because of the heterogeneity of studies a narrative synthesis was done.

Study population issues: patient characteristics and risk categories varied between studies.

Other issues: authors did not find any hypofractionated radiotherapy studies.

Key efficacy findings

- Number of patients analysed: 19 studies (3,622 patients)

Rectal dosimetry

1 RCT Mariados 2015 (hydrogel spacer versus no spacer)

	Measures of dosimetry	With spacer	Without spacer	Absolute reduction	Relative reduction
Rectum	V50	9.6	20.8	11.2	53.9
	V60	5.3	15.4	10.1	65.6
	V70	2.3	10.5	8.2	78.0
	V80	0.1	4.0	3.9	97.3

Pre and post hydrogel spacer

	Measures of dosimetry	Baseline dose Gy (mean±SD)	Post spacer dose Gy (mean±SD)	% Change in dose from baseline, p value
Bladder	V70	11.3	11	NR
Rectum	V50	25.7±11.1	12.2±8.7	52.3, p=<0.0001
	V60	18.4±7.7	6.8±5.5	62.9, p<0.0001
	V70	12.4±5.4	3.3±3.2	73.3, p<0.0001
	V80	4.6±3.1	0.6±0.9	86.3, p<0.0001

(13 nRCTs hydrogel spacer versus no spacer)

EBRT

Study, n	Clinical stage, risk status	Measures of dosimetry	With spacer Mean/median	Without spacer Mean/median	P value
Pinkawa 2017 IMRT (n=167)	T1-T3 Low to high risk	V70 %	20	32	<0.01
		V90 %	4	13	<0.01
Te Velde 2019 IMRT (n=125)	T1-T3 Low to high risk	V40 %	25.9	33.3	<0.0001
		V75%	2.1	7.4	<0.0001
		V65%	5.2	12.6	<0.0001
Whalley 2016 IMRT (n=140)	T1-T3 Intermediate/ high risk	V40 %	22.9	32	<0.01
		V65%	5.3	13.5	<0.01
Navaratnam 2020 PBT (n=72)	T-1-T3	V70 %	NR	NR	-
		V75 %	NR	NR	-
Fried 2017 SBRT (n=94)	Low/intermediate risk	D10 Gy	26.66	30.44	0.000
		D50 Gy	10.9	11.4	0.47
BT					
Baghwala 2019 HDR BT (n=36)	Low/intermediate risk	V75 cc	0.02	0.7	<0.05
		V90 cc	>92	NR	<0.05
HDR BT in combination with EBRT					
Chao 2019 HDR BT+IG-IMRT (n=97)	T1-T3 Intermediate/ high risk	V40%	4.6	10.7	<0.001
		V75%	0	0.55	<0.001
		V80%	0	0.21	<0.001
Wu 2018 HDR BT +/- EBRT (n=54)	T-T3	V40 cc	8.11	9.38	0.16
		V75	<0.005	0.12	<0.0005
		V80	<0.005	0.01	0.007
		V90	NR	<0.005	0.1
Saigal 2019 HDR BT + EBRT (n=117)	NR	D1 Gy	35.3	54.6	<0.05
		D90	100.1	101.3	0.354
LDR BT in combination with EBRT					
Morita 2020 LDR BT+IMRT (n=300)	T1-T4 Very low to very high	V100 cc	0.026	0.318	<0.001
		V150	0.001	0.025	<0.001
Patel 2018 LDR BT + EBRT (n=57)	NR	V50	0.53	.21	<0.001
		V100	0.0001	0.25	<0.001

Taggar 2018 LDR BT+EBRT (n=210)	T1-T3	V100	0.01	0.07	0
Liu 2020 LDR BT +/- EBRT (n=81)	Low/intermediate risk	D2 Gy	-25.1	5	<0.0001
		D0.1	-65.7	-1	<0.0001

Toxicity outcomes

1 RCT Mariados 2015 (hydrogel spacer versus no spacer)

Type of adverse event	Follow up	With spacer	Without spacer	P value	OR (95% CI)
Rectal or procedure related adverse events	6 months	34.2%	31.5%	0.7	
Rectal toxicity late	3 to 15 months				
Grade 1+		2.03 (3/148)	6.94 (5/71)	0.044	0.28 (0.06,1.19)
Grade 2+		0	1.39 (1/71)		NE
1		2.03 (3/148)	5.63 (4/71)		0.35 90.08, 1.59)
2		0	0		NE
3		0	1.41 (1/71)		
4		0	0		
Grade>1	36 months	2.0%	9.2%	0.028	
Grade>2	36 months	0	5.7%	0.012	
Rectal toxicity acute	3 months				
Grade 1+		27.03 (40/148)	31.94 (23/72)	0.525	0.79 (0.43,1.46)
Grade 2+		4.05 (6/148)	4.17 (3/72)		0.97 (0.24,4)
1		22.97 (34/148)	27.78 (20/72)		0.78 (0.41,1.47)
2		4.05 (6/148)	2.78 (2/72)		1.48 (0.29, 7.52)
3		0	1.39 (1/72)		NE
4		0	0		

Urinary toxicity late	3 to 15 months				
Grade 1+		9.46 (14/148)	8.33 (6/71)	0.622	1.15 (0.42, 3.13)
Grade 2+		6.76 (10/148)	4.17 (3/71)		1.67 (0.44, 6.25)
1		2.70 94/148)	4.23 (3/71)		0.63 (0.14, 2.89)
2		6.76 (10/148)	4.23 (3/71)		1.64 90.44, 6.16)
3		0	0		NE
4		0	0		
Urinary toxicity acute	3 months				
Grade 1+		90.54 (134/148)	90.28 (65/72)	0.488	1.03 (0.4, 2.68)
Grade 2+		37.84 (56/148)	44.44 (32/72)		0.76 (0.43, 1.35)
1		52.70 (78/148)	45.83 (33/72)		1.32 (0.75, 2.32)
2		37.84 (56/148)	44.44 (32/72)		0.76 (0.43, 1.35)
3		0	0		NE
4		0	0		

nRCTs (hydrogel spacer versus no spacer, 7 studies)

Study	Adverse event (Grade)	Follow up (months)	With spacer % (n)	Without spacer % (n)	P value	OR (95% CI)
EBRT						
Te Velde 2019 IMRT (n=125)	Diarrhoea (grade 1)	During radiotherapy	13.8% (9/65)	31.7 (19/60)	0.02	0.34 (0.14,0.84)
		3 months	4.6%	5%	1	0.92 (0.18,4.72)
		36 months	1.7%	7.3%	0.192	0.22 (0.03,1.86)
	Proctitis (grade 1)	During radiotherapy	9.2	13.3	0.6	0.66 (0.22,2.03)
		3 months	1.5	5	0.3	0.29 (0.03,2.86)

		36 months	1.7	3.6	0.606	0.46 (0.04,4.88)
	Proctitis Grade (2)	During radiotherapy	4.6	1.7	0.6	2.79 (0.28,27.56)
		3 months	0	0	1	
		36 months	0	3.6	0.227	
	Faecal incontinence (grade 1)	During radiotherapy	3.1	3.3	1	0.94 (0.13,6.87)
		3 months	0	1.7	0.5	
		36 months	0	0		
	Haemorrhoids (grade 1)	During radiotherapy	23.1	20	0.8	1.2 (0.51,2.83)
		3 months	3.1	11.7	0.09	0.24 (0.05,1.21)
		36 months	5	7.3	0.708	0.67 (0.15,2.98)
	Haemorrhoids (grade 2)	During radiotherapy	4.6	3.3	1	
		3 months	0	0		
		36 months	1.7	1.8	1	0.94 (0.06,14.5)
Whalley 2016 IMRT (n=140)	Rectal toxicity late -grade 1	Median 26-28 months	16.6 (5/30)	41.8 (46/110)	0.04	0.28 (0.1,0.78)
	Grade 2		3.3 (1/30)	3.6 (4/110)	NR	0.91 (0.1,8.49)
	Rectal toxicity acute -grade 1		43 (13/30)	50.6 (56/110)		0.74 (0.33,1.66)
	Grade 2		0	4.5 (5/110)		
Wolf 2015 IMRT (n=78)	Rectal toxicity acute-grade 1	NR	16.6	9	NR	
	Genitourinary toxicity- grade 1		12.5	21		
	Grade 2		36.6	28.5		
	Any toxicity acute -grade 3		0	0		
Navaratnam 2020 PBT (n=72)	Rectal toxicity- any -grade 1	During radiotherapy	35.3 (18/51)	9.5 (2/21)	0.061	5.2 (1.09,24.89)
		Median 8.7 to 10.3 months	7.7 (3/39)	0 (0/14)	NR	

	Grade 2	During radiotherapy	2 (1/51)	0 (0/21)	NR	
		Median 8.7 to 10.3 months	0 (0/39)	7.1 (1/14)		
Zelefsky 2019 SBRT (n=551)	GI toxicity acute (grade 2+)	NR	1 (269)	2 (282)	0.09	0.33 (0.07,1.55)
	GI toxicity late (grade 2+)		1	6	0.01	0.16 (0.05,0.48)
	GU toxicity acute (grade 2+)		9	12	0.19	0.73 (0.42,1.26)
	GU toxicity late (grade 2+)		15	32	<0.001	0.38 (0.25,0.57)
HDR BT in combination with EBRT						
Chao 2019 BT+IG-IMRT (n=97)	GI toxicity acute (grade 2)	3 months	0 (0/32)	1.5 (1/65)	0.48	
	Grade1+		13.3	30.8	0.05	0.34 (0.11,1.11)
	GI toxicity late (grade 1)		0	7.7	0.11	
	GU toxicity acute (grade 2)		0	1.5	0.48	
	Grade 1+		83.3	92.3	0.22	0.42 (0.11,1.56)
	GU toxicity late (grade 3)		3.3	6.2	0.57	0.52 (0.06,4.82)
	Grade 1+		46.7	43.1	0.74	1.16 (0.49,2.71)
	Grade 2+		3.3	7.7	0.4	0.41 (0.05,3.66)
LDR BT alone or in combination with EBRT						
Taggar 2018 LDR BT/LDR BT+/- EBRT (n=210)	Any rectal GI toxicity	NR	20.3 (15/74)	24.3 (33/136)	0.95	0.79 (0.4,1.58)
Taggar 2018 LDR BT monotherapy	Diarrhoea		7.7 (2/26)	15.9 (7/44)	NR	0.44 (0.08,2.31)
	Proctitis		0 (/26)	0 (/44)	NR	
	Rectal bleeding		0 (/26)	6.8 (/44)	NR	
	Rectal discomfort		15.7 (/26)	0 (/44)	NR	

Taggar 2018 LDR BT monotherapy (salvage for recurrent PC)	Diarrhoea	NR	12.5 (1/11)	5.3 (1/19)	NR	2.55 (0.14,45.36)
	Proctitis		0	0	NR	
	Rectal bleeding		0	5.3	NR	
	Rectal discomfort		0	0	NR	
Taggar 2018 LDR BT+EBRT combination therapy	Diarrhoea	NR	12.5 (5/42)	4.1 (3/73)	NR	3.34 (0.76,14.76)
	Proctitis		0	5.5		
	Rectal bleeding		5	19.2		0.22 (0.05,1.03)
	Rectal discomfort		5	0		

Health related QoL outcomes

1 RCT Mariados 2015 (hydrogel spacer versus no spacer)

EPIC dimension	**Follow up (months)**	**With spacer**	**Without spacer**	**Mean difference** **P value**
Bowel domain	3	-7.5	-6.2	NR
	36	0.5	-5.3	5.8, p<0.05
Urinary domain	3	-11.5	-11.2	NR
	36	0.6	-3.3	3.9, p=0.04
Authors definition				**OR (95% CI), p value**
10-point decline in bowel QoL	15	11.6	21.6	0.49 (0.21, 1.11) P=0.087
	36	5	21	0.3 (0.11, 0.83) P=0.02
10-point decline in urinary QoL	6	8.8	22.2	0.27 (0.11, 0.64) P=0.003
12-point decline in urinary QoL	36	8	23	0.31 (0.11, 0.85) P<0.03
5-point decline in bowel QoL		14	41	0.28 90.13, 0.63) P=0.002
6-point decline in urinary QoL		17	30	0.41 (0.18, 0.95) P<0.05
Patients experiencing MID	36	2.5	20	NR

declines in all 3 QoL domains (bowel, urinary, sexual)				P=0.002
Decline of all 11 or more points in EPIC sexual score		53	75	NR, P=0.064
Potent patients at baseline retaining erections sufficient for intercourse		66.7	37.5	NR, =0.046

MID = minimally important differences in the EPIC summary scores were evaluated according to previously published thresholds: bowel (5 points), urinary (6 points), sexual (11 points), and vitality/hormonal (5 points).

nRCTs (hydrogel spacer versus no spacer, 4 studies)

Study	EPIC outcome	Follow up (months)	With spacer, Mean change from baseline	Without spacer, mean change from baseline	p value
Patel 2018 EBRT + LDR BT (n=57)	Bowel function score	3 months	Median: 0.00, IQR: -8.93 to 0.89	Median: -6.25, IQR: -12.95 to 0	0.312
		6 months	Median: 0.00, IQR: -8.92 to 0	Median: -3.57, IQR: -9.82 to 0	0.650
Pinkawa 2012 IMRT (n=72)	Urinary function	Last day radiotherapy	-10	-10	NR
		2-3 months	-1	-5	
	Urinary bother score	Last day radiotherapy	-17	-18	
		2-3 months	-4	-6	
	Bowel function	Last day radiotherapy	-15	-14	
		2-3 months	-3	-3	
	Bowel bother score	Last day radiotherapy	-16	-17	
		2-3 months	-2	-6	
	Sexual function	Last day radiotherapy	-15	-10	
		2-3 months	-5	-9	
	Sexual bother score	Last day radiotherapy	-20	-18	
		2-3 months	-11	-15	
	Hormonal function	Last day radiotherapy	-3	-6	

		2-3 months	-1	-2	
	Hormonal bother score	Last day radiotherapy	-3	-2	
		2-3 months	-2	-1	
Pinkawa 2016 IMRT (n=202)	Bowel bother score	Last day radiotherapy	-14	-18	NR
		2 months	-3	-6	
		17 months	0	-7	
	Sexual bother score	Last day radiotherapy	-6	-9	
		2 months	-12	-19	
		17 months	-12	-17	
	Urinary bother score	Last day radiotherapy	-18	-21	
		2 months	-14	-17	
		17 months	1	2	
Pinkawa 2017 IMRT (n=167)	Urinary function	End of radiotherapy	-10	-13	NR
		2 months	-2	-4	
		>12 months	1	-	
	Bowel function	End of radiotherapy	-11	-14	NR
		2 months	-4	-5	
		>12 months	0	-5	<0.01
	Sexual function	End of radiotherapy	-12	-10	NR
		2 months	-6	-8	
		>12 months	-6	-	
	Hormone function	End of radiotherapy	-5	-7	NR
		2 months	-3	-4	
		>12 months	2	-	
	Bowel bother score	18 months	-1	-7	0.13
		60 months	-1	-6	0.99
	Sexual bother score	18 months	-13	-18	0.28
		60 months	-21	-28	0.77
	Urinary bother score	18 months	2	3	0.49
		60 months	0	3	0.22

There were no studies reporting QoL in EBRT+ HDR BT, BT monotherapy or hypofractionated EBRT.

Study 5 Vaggers S 2021

Study details

Study type	Systematic review
Country	UK
Study search details	Search period: January 2013 to December 2019; databases searched: MEDLINE, Embase, PubMed, CINAHL, and Cochrane library Google scholar, and reference lists of included articles were also searched.
Study population and number	13 studies: (9 retrospective case series and 4 case reports of less than 10 patients) n=1208 patients (671 patients who had a perirectal hydrogel spacer injection versus 537 patients who did not receive a spacer [controls] before prostate cancer brachytherapy).
Age	Not reported
Study selection criteria	Inclusion criteria: English-language articles, randomised and non-randomised studies of patients with localised or locally advanced prostate cancer receiving brachytherapy with or without PEG hydrogel spacer (salvage and primary treatment); reporting a number of outcomes including radiation dose, prostate-rectum separation, toxicity and technique for hydrogel insertion. Studies of more than 10 patients evaluated for efficacy and less than 10 patients reviewed for only procedure related complications. Exclusion criteria: case reports, review articles and editorials, non-English-language studies, animal and laboratory studies.
Technique	Intervention: under ultrasound guidance a needle is inserted into perineum. Hydrodissection of the potential space is done first and then a prostate-rectum spacer (absorbable polyethylene glycol hydrogel) is injected posterior to the Denonvilliers fascia and anterior to the rectal wall at the level between mid-gland and apex of the prostate (4 studies used DuraSeal off label and 5 used SpaceOAR since 2017). Comparator (control): no hydrogel spacer (in 6 studies) Radiotherapy protocols: LDR or HDR BT alone or in combination with EBRT • LDR BT monotherapy (in 2 studies), • BT plus EBRT combination (in 7 studies: HDR BT +EBRT in 5, LDR BT +EBRT in 2) All LDR or HDR BT start with seed insertion followed by spacer insertion and subsequent IMRT.
Follow up	Varied across studies (range 6 to 60 months)
Conflict of interest/source of funding	Authors state that there is no potential conflict of interest.

Analysis

Follow-up issues: adequate follow up in some studies, 3 studies did not report follow up period.

Study design issues: systematic review protocol was registered and was done according to the PRISMA reporting guidelines and the Cochrane methodology. Comprehensive literature search was done, 2 reviewers selected studies, extracted data but quality assessment of studies was not done. The included studies were mainly retrospective nRCTs of low quality and only 4 studies compared with controls. Studies were heterogenous both in treatment method and type of spacer used therefore a narrative synthesis was done. Genitourinary complications were not analysed by authors. 2 papers included in this study reported on the same patient group (Chao 2019).

Study population issues: patient characteristics and risk categories varied between studies.

Key efficacy findings

- Number of patients analysed: 13 studies (9 case series and 4 case reports or case series of less than 10 patients)

Mean prostate-rectum separation, acute and late GI complications

Study details	Mean follow up/scoring system	Mean prostate-rectum separation (mm)	Rectal dosimetric reduction/percentage dose reduction^	Acute GI toxicity (spacer versus no spacer)	Late GI toxicity (spacer versus no spacer)	Failure rate
Mahal 2014 Salvage LDR BT; prior pelvic irradiation (n=11) DuraSeal spacer	15.7 months/ EPIC questionnaire	10.9 in patients with prior BT 7.7 in patients with prior EBRT	Median V75% (cc): 0.07	Grade 1: 0% Grade 2: 9% (n=1 fistula) Grade >3: 0	Grade 1 or 2: 36% (4/11) Grade 3 or 4: 9% (n=1 patient developed prostatorectal fistula requiring a diverting colostomy and an interposition rotational gracilis muscle flap) 16 months: 26% (3/11) bowel QoL change	27.2%
Heikkila 2014 LDR BT (n=10) DuraSeal spacer	-	10	Rectal D2 cc 64±13 Gy with gel versus 95±13 Gy without gel	1 patient reported a sensation of pressure in the rectum. 1 patient felt a sudden need for defecation.	-	0%

			(p=0.005)/ (32.6%)			
Wu 2017 HDR BT: HDR BT+EBRT Salvage HDR BT (n=18 with spacer and 36 without spacer) (SpaceOAR)	-	-	Median V75% (cc): <0.005 versus 0.12 (p≤0.0005)/ (100%)	1 patient developed a rectal abscess.	-	0%
Chao 2019 HDR BT+IMRT (n=32 with spacer and 65 without spacer) (SpaceOAR)	60 months NCICTCAE v4.0	10	Median V75% (cc) 0.0 versus 0.45 (p≤0.001)/ (100%)	Grade 1 12.5% versus 30.8% (p=0.05)	Grade 1: 0% versus 7.7% (p=0.11)	-
Chao 2019 HDR BT+IMRT or VMAT (n=30 with spacer and 65 without spacer) (SpaceOAR)	58 months NCICTCAE v4.0	-	Median V75% (cc) 0.0 versus 0.45 (p≤0.001)/ (100%)	Grade 1 13.3% versus 30.8% (p=0.05) Grade 2 0% versus 1.5% (p=0.48)	Grade 1: 0% versus 7.7% (p=0.11)	-

Storm 2014 HDR BT +IMRT (n=100 with spacer and 100 without spacer) (DuraSeal)	8.7 months	12	Rectal D2 cc 47±9% versus 60±8% (p<0.001)/ (21.6%)	-	-	0%
Yeh 2016 HDR BT +IMRT (n=326) (DuraSeal)	16 months NCICTCAE v4.0	16	maximum dose to rectum 78% versus 95% (SD=11.9%)/ (17.3%)	Grade 1: 37.4% Grade 2: 2.8% Most commonly diarrhoea	Grade 1:12.7% Grade 2: 1.4% Grade 3: 0.7% 1 case of severe proctitis 1 case of fistula and necrotising fasciitis requiring a diverting colostomy.	-
Taggar 2017 LDR BT. LDR BT+EBRT Salvage LDR BT (74 with spacer 136 without spacer) (SpaceOAR)	6 months RTOG	11.2	Rectal D2 cc 20.47% versus 43.16% (p=0.000)/ (52.6%)	**Grade 1 or 2** 20.3% (n=15) versus 24.3% (n=33) (p= 0.95) **Diarrhoea:** LDR BT alone 7.7% versus 15.9% LDR BT +EBRT 12.5% versus 4.1% Salvage 12.5% versus 5.3% **Proctitis:** LDR BT alone 0% versus 0%, LDR BT+EBRT 0% versus 5.5% Salvage 0% versus 0% **Rectal discomfort -**	-	6.8% (2 aborted due to unsuccessful hydro dissections)

				8% (n=7) versus 0 **Rectal bleeding** 5% (n=2) versus 21.3% (n=18). No grade 3 or 4 complications		
Morita 2019 LDR BT; LDR BT+EBRT (100 with spacer 200 without spacer) (SpaceOAR)	-	11.6	Median V100% 0.026±0.14 versus 0.318+/1 0.34 (p≤0.001)/ (91.8%)	**-**	-	4% (1 aborted due to operator inexperience and premature coagulation of the solution during injection)

^spacer versus non-spacer.

Key safety findings

Study	N	Complications	n
Procedure related complications			
Teh 2014	1 spaceOAR	Rectal ulcer (1 month after hydrogel spacer insertion, resolved without further intervention)	1
Beydoun 2013 (BT)	5 spaceOAR	Perineal pain or rectal discomfort (resolved without intervention within 1 week)	3
Heikkila 2014 (LDR BT)	10 DuraSeal	Sensation of pressure/fullness in the rectum (self-limiting symptoms, resolved by 3 months with medication)	1

Heikkila 2014 (LDR BT)	10 DuraSeal	Sudden need for defecation (self-limiting, symptoms resolved by 3 months with medication)	1
Storm 2014 (HDR BT with IMRT)	100 with DuraSeal versus 100 without	Infection (bacterial prostatitis and epididymitis), adjusted antibiotic prophylaxis before procedure	6% (n=3)
Wu 2018 (HDR BT boost to EBRT)	18 with spaceOAR versus 36 without spacer)	Rectal perineal abscess (1 month after SpaceOAR insertion. required incision, drainage and antibiotics)	1
Mahal 2014 (salvage LDR BT) Yeh 2016 (HDR BT +IMRT)	11 DuraSeal 326 (SpaceOAR)	Prostatorectal fistula requiring diverting colostomy and an interposition rotational gracilis muscle flap Fistula and necrotising fasciitis requiring a diverting colostomy.	1 1
Yeh 2016 (HDR BT +IMRT)	326 (SpaceOAR)	Severe proctitis	1
Other complications at follow up			
Taggar 2018 LDR BT LDR BT+EBRT Salvage LDR BT	(74 with spacer 136 without spacer) (SpaceOAR)	Diarrhoea	LDR BT alone 7.7% versus 15.9% LDR BT +EBRT 12.5% versus 4.1% Salvage 12.5% versus 5.3%
		Rectal discomfort	8% (n=7) versus 0
		Rectal bleeding	5% (n=2) versus 21.3 (n=18)

Study 6 Payne 2021

Study details

Study type	Systematic review and meta-analysis
Country	USA, UK, Switzerland and Germany
Study search details	Inception to August 2020; Databases searched: Cochrane Central Register of Controlled Trials, MEDLINE, and Embase; no language or date restrictions applied. Supplemental searches were done in the directory of open access journals, Google scholar, and reference lists of included articles and relevant meta-analyses searched. Unpublished or grey literature was also included.
Study population and number	n=11 studies (14 papers) with 780 people having SpaceOAR hydrogel spacer before SBRT for localised prostate cancer. (5 prospective and 6 retrospective studies) Clinical stages: localised or locally advanced prostate cancer (T1-T3), Risk category: varied but intermediate risk PSA levels median 8.2 (range 6.3 to 9.8 nanograms/ml)
Age and sex	Median age 70 years (range 69 to 73 years).
Study selection criteria	Inclusion criteria: randomised clinical trials or observational studies of people who had the perirectal hydrogel spacer versus patients who had no spacer before SBRT for localised or locally advanced prostate cancer. Exclusion criteria: review articles, commentaries, letters, studies with fewer than 5 patients, studies of other rectal spacers such as hyaluronic acid and rectal balloons, studies that did not report an outcome specified in this review and duplicate publications.
Technique	**Intervention:** Injection of a prostate-rectum spacer (absorbable polyethylene glycol hydrogel-SpaceOAR system) between the Denonvilliers fascia and anterior rectal wall before radiotherapy. Radiotherapy protocols: SBRT (≥5.0 Gy fractions) protocols varied and ranged from 7 Gy to 10 Gy per fraction with total dose ranging from 19 to 45 Gy. 561/780 had dose-escalated SBRT regimens (37.5 GY to 45Gy in 5 fractions).
Follow up	Median 20 months (range, 9 to 24 months).
Conflict of interest/source of funding	The study was funded by Boston Scientific and they were involved in design and interpretation of data, review and approval of manuscript. Authors served as consultants, and either received personal fees, grants, honoraria, travel expenses, and non-financial support from Boston scientific and other companies.

Analysis

- Follow-up issues: follow up varied across studies and was limited to only mid-term.
- Study design issues: systematic review protocol was registered prospectively and was done according to the PRISMA reporting guidelines. Comprehensive literature search was done, studies were screened and data extracted into a predesigned form by 2 reviewers, any disagreements were resolved by discussion. Multiple studies with overlapping patients were carefully assessed and included. Observational studies included were

associated with risks of bias. A random-effects meta-analysis was done for analysis of rectal irradiation only. Heterogeneity was noted among study designs, patient characteristics, and SBRT protocols.

- Study population issues: patient characteristics inconsistently reported and risk categories varied between studies. Androgen deprivation therapy usage also varied.
- Other issues: quality of life not reported in any studies. Toxicities in other organs not assessed in this review.

Key efficacy findings

- Number of patients analysed: 780 patients

Perirectal separation distance: the perirectal distance achieved with SpaceOAR implant ranged from 9.6mm to 14.5mm (median 10.8mm).

Rectal irradiation with perirectal hydrogel spacer versus without spacer (the percentage reduction with spacer versus without spacer in the percentage of rectum having 50% (A), 70% (B), and (C) 90% of the maximum prescribed radiation dosage)

In a pooled analysis of 5 studies, patients who had the perirectal hydrogel spacer before SBRT had 29% to 56% lower rectal irradiation compared with control patients who did not have perirectal hydrogel spacer.

Gastrointestinal [GI] toxicity (risk of a grade 2 or 3+ bowel complication in early [<3months] and late [>3months] follow up)

In early follow up, grade 2 GI complications were reported in 7%- 18% patients and no early grade 3 complications were reported. In late follow up, rates were 4% for grade 2 and 1% for grade 3 GI toxicity. Over a median follow up of 16 months (range 11 to 36 months), freedom from biochemical failure ranged from 96.4% to 100%.

Study	Early grade 2	Early grade 3	Late grade 2	Late grade 3	Freedom from biochemical failure
Alongi (2013) (n=8)	-	0	0	0	8/8 (100%)
Chen (2020) (n=250)	18/250 (7.2%)	0	10/250 (4%)	1/250 (0.4%)	241/250 (96%)
Cuccia (2020) (n=10)	0	0	-	-	-
Hwang (2019, 2018) (n=50)	2/50 (4%)	0	0	0	50/50 (100%)

Jones 2017 (Folkert 2017) (n=44)	1/44	0	-	0	44/44 (100%)
King 2018 (n=6)	0	0	-	-	-
Ogita 2019 (n=40)	7/40 (18%)	0	-	-	-
Pryor 2019 Wilton 2017 (n=80)	-	0/80	-	-	-
Ruggeri 2014 (n=11)	-	-	-	-	-
Saito 2020 (n=20)	-	-	-	-	-
Zelefsky 2019 (n=269)	-	-	-	3/269 (1.1%)	-

Study 7 Mok G 2014

Study details

Study type	Systematic review
Country	UK
Study search details	Search period: not reported; databases searched: MEDLINE
Study population and number	11 studies (reported within 12 articles), n=346 patients
Age	Not reported
Study selection criteria	Inclusion criteria: published articles and conference abstracts from preclinical and clinical studies; prostate cancer patients in whom PR spaces were implanted Exclusion criteria: not provided.
Technique	Intervention: Prostate-rectum spacers compared to each other: PEG spacers (4 studies), hyaluronic acid spacers (5 studies), biodegradable balloons (1 study), and collagen implants (1 study). An additional 3 preclinical studies were included (2 used PEG spacers and 1 used a biodegradable balloon spacer). Radiotherapy protocols: different treatment techniques used (IMRT, VMAT, IMPT, 3D-CRT, and HDR monotherapy) in the primary studies. EBRT (6 studies) and BT (5 studies).
Follow up	3 to 72 months
Conflict of interest/source of funding	None; Review funded by an institute for a health technology assessment report.

Analysis

Follow-up issues: varied across studies.

Study design issues: review compared different spacers; comprehensive literature search was done but the review did not describe the included primary studies in detail including study designs and also did not assess the risk of bias. Dosimetric effects and clinical benefits were assessed. A narrative synthesis was done but risk of bias not considered while interpreting results.

Study population issues: patient characteristics of the included studies not described in the overview.

Key efficacy findings

Number of patients analysed: 346

Mean prostate-rectum distance, dosimetric outcomes (EBRT 6 studies)

Study	Spacer type (ml injected)	Radiation technique	Mean prostate-rectum distance (mm)	Mean rectal Vxx Gy/% without spacer/ with spacer	Relative reduction of rectal Vxx Gy/%	Acute or late toxicity
Weber 2012 N=8	PEG hydrogel (10)	IMRT (78 Gy) VMAT (78 Gy) IMPT (78 Gy)	7-10 7-10 7-10	V70Gy: 9.8%/5.3% V70Gy: 10.1%/3.9% V70Gy: 9.7%/5.0%	V70Gy: 46% V70Gy: 61% V70Gy: 49%	-
Pinkawa 2011 N=18	PEG hydrogel (10)	IMRT (78 Gy) 3D-CRT (78 Gy)	10 10	V70Gy:17.2%/7.5% V70Gy:14.4%/6.1%	V70Gy: 56% V70Gy: 58%	-
Song 2013 N=48	PEG hydrogel (10)	IMRT (78 Gy)	9.7	V70Gy:13.0%/5.1%	V70Gy: 60%	Focal rectal mucosal necrosis and bladder perforation (n=3, self-limiting) (Uhl 2014) Acute GI toxicity grade 1 39.6% grade 2 toxicity 12.5%. No grade 3 or 4 toxicities. Acute GU toxicity grade 1 41.7% grade 2 35.4% grade 3 2.1%. No grade 4 toxicities Late grade 1 GI toxicity 4.3% (2) no grade 2 or worse toxicity. Late GU toxicity grade 1 in 17.0% grade 2 toxicity 2.1%. No grade 3 or worse GU toxicity.

Chapet 2013 n-16	Hyaluronic acid (10)	IMRT (62 Gy, 3.1 Gy/fx)	11.5	V90%: 7.7 cc/2.1 cc V70%: 13.3 cc/7.6 cc	V90%: 74% V70%: 43%	Rectal toxicity 0% versus 30% in historical controls
Chapet 2014 N=10	Hyaluronic acid (10)	SBRT (32.5 Gy, 6.5 Gy/fx) (42.5 Gy, 8.5 Gy/fx)	10.1	V90% 3.2 cc/0.3 cc V90% 3.5 cc/0.3 cc	V90%: 90% V90%: 91%	-
Noyes 2012 N=11	Collagen (20)	IMRT (75.6 Gy)	12.7	V40Gy: 7%-15% in collagen group 20 to 25% without collagen	V40Gy: 40%-65%	No GI toxicities
Melchert 2013 N=22	Balloon (16)	IMRT/3D-CRT (74 Gy)	19.2	V60Gy: 30% pre-implant /15% post implant	V60Gy: 50% (Gez 2013) V90%: 72%	Acute dysuria grade 1 or 2 (58%) Urinary retention needing catheter (n=1) Diarrhoea (grade 1 17%) Proctitis (grade 1 8%)

Spacer absorption: reported in 2 studies:

Melchert 2013 (n=22, balloon implantation): complete deflation and absorption at 6 months in all except 2.

Noyes 2011 (n=11, collagen): 50% at 6 months; 100% at 12 months.

BT (5 studies)

Study	Spacer type (ml injected)	Radiation technique	Mean prostate-rectum distance (mm)	Mean rectal Vxx Gy/% without spacer/ with spacer	Acute and late toxicity
Storm 2014 (n=100 hydrogel versus no hydrogel)	PEG hydrogel (15)	HDR BT monotherapy (13.5-14.0 Gy x 2 fx) IMRT (45 Gy) + HDR BT boost (9.5-11.5 Gy x 2 fx)	12	D2cc = 60%/47%	Bacterial peritonitis 2 (had prophylactic treatment).
Prada 2007 (n=27)	Hyaluronic acid (3-7)	3D-CRT (46 Gy) + HDR BT boost (11.5 Gy x 2 fx)	20	Dmax = 7.1Gy/5.1Gy	None related to HA implant

				Dmean = 6.1 Gy/4.4 Gy	
Prada 2009 (n=36)	Hyaluronic acid (6-8)	LDR BT ^{125}I 145 Gy	20	NA	Rectal mucosal damage 5%
Prada 2012 (n=40)	Hyaluronic acid (NA)	HDR BT ^{192}Ir 19 Gy x 1 fx	20	NA	None related to HA implant GI toxicity: asymptomatic anal mucositis (grade 1) 12.5% GU toxicity -urinary obstruction grade 1 requiring catheterisation in 1 (2.5%). At 6 months 27.5% had mild grade 1 urinary obstruction.
Wilder 2010 (n=10)	Hyaluronic acid (9)	IMRT (50.4 Gy) + HDR BT boost (5.4 Gy x 4 fx)	13	V70Gy = 4% in HA group 25% in controls	None related to HA implant Grade 1-3 diarrhoea 0% versus 29.7%

Key safety findings

Study	Complications	% (n)
Noyes 2012 n=11 Collagen	Acute urinary obstruction	5/11
	Self-limiting light rectal pressure	3/11
	Temporary catheterisation for acute urinary retention (presumed to be secondary to pudendal nerve blocking)	1/11
Gez 2013 n=2013 ERB	**During balloon insertion**	**n=26**
	Pain at the perineal skin/scar (ranging 1–7, VAS score)	27 (7/26)
	Acute pain in the anus (ranging 2–9, VAS score)	15 (4/26)
	Acute urinary retention (needed catheterisation, resolved within few hours)	12 (3/26)
	Dysuria and nocturia (grade 1–2)	12 (3/26)
	Penile bleeding	4 (1/26)
	Balloon failure after implantation (needing removal)	4 (1/26)
	Premature balloon deflation	3
	During radiotherapy	**n=23**
	Proctitis	8 (2/23)
	Diarrhoea (grade 1)	17 (4/23)
	Signs of blood in faeces (grade 1)	4 (1/23)
	Constipation (grade1)	4 (1/23)

	Erectile dysfunction	4 (1/23)
	Fatigue	4 (1/23)
	Decreased urine flow	4 (1/23)

Study 8 Ardekani 2021

Study details

Study type	Systematic review
Country	USA, Netherlands, UK, Germany,
Study search details	Search period: January 2000 to December 2019; databases searched: PubMed; Additionally, a further search was done from January 2010 to December 2019 for abstracts. Reference lists of articles were also reviewed for relevant articles.
Study population and number	21 studies of patients with prostate cancer who had a rectal spacer during radiation therapy (n=287).
Age and sex	Age not reported
Study selection criteria	Inclusion criteria: studies in English, in humans, full text articles specifically investigating the impact of rectal displacement devices on prostate motion. Exclusion criteria: review articles, case reports, animal studies, lack of relevant outcome data, non-English articles, editorials and commentaries.
Technique	Rectal spacers used during EBRT for prostate cancer. Different radiotherapy techniques (IMRT, 3DCRT, VMAT, PT) were used. 12 studies evaluated role of ERBs, 4 evaluated polyethylene glycol hydrogel spacers (SpaceOAR) 4 studies assessed rectal retractors (RR), and 1 study assessed ProSpare.
Follow up	Not reported
Conflict of interest/source of funding	None reported

Analysis

Study design issues: systematic review protocol was done according to the PRISMA reporting guidelines. There were no prospective randomised controlled trials. All studies included were either non-randomised two-arm studies or single-arm studies, relatively small (less than 20 patients in each arm) and were heterogenous in terms of population and outcomes reported. There are conflicting findings reported by different studies, which may be due to case mix or other contextual factors.

Other issues: only data on ERBs and hydrogel spacers is considered within this review. data on alternative rectal spacers (Prospare and RR) are out of the scope of this review as they are not biodegradable spacers.

Key efficacy findings

No of patients analysed: 287 (ERB in 180 and hydrogel in 107)

Effect of ERB on prostate motion (8 studies, n=180 patients)

Study	No of patients	Radiotherapy technique	Results

Wacher 2002	10 with 40ml air filled ERB and 10 without	3DCRT	AP displacement: >5mm in 20% of ERB patients. >5mm in 80% of non-ERB patients. ERB significantly reduces maximum AP displacement of prostate (p=0.008).
Hung 2011	14 with 120ml water filled balloon and 15 without	IMRT	AP displacement: mean 5.4±3.4 mm in ERB. mean 7.3± 4.8 mm in non-ERB ERB reduces inter-fractional prostate motion but not statistically significant (p=0.22–0.38)
Van lin 2005	22 with an 80ml air filled ERB and 30 without	IMRT	AP displacement: mean 0.4±4.7mm ERB. 0.6±4.3mm in non-ERB ERB does not decrease the inter-fractional prostate motion (p=NR)
Smeenk 2012	15 with an 100ml air filled ERB and 15 without	IMRT	AP displacement: 3.9 mm ERB, 3.8 mm non-ERB ERB does not significantly reduce the inter-fractional variation (p=0.06–0.92).
Takayama 2011	7 with a double ERB and 7 without	3DCRT or IMRT	AP displacement: 1.3 ± 0.9mm ERB; 2.8 ± 1.8mm non-ERB. ERB only reduces inter-fractional prostate motion in the AP direction (p=0.014)
Teh 2002	10 with an 100ml air filled ERB	Combined radioactive seed implant and IMRT	AP displacement: 1mm ERB can reduce inter-fractional prostate motion.
Mc Gary 2002	10 with an 100ml air filled ERB	IMRT	AP displacement: 0.42 ± 0.35mm Most improvements observe in AP displacement.
El-Bassiouni 2006	15 with a 60ml air filled ERB	3DCRT	AP displacement: 3.8±4.0mm; ERB does not eliminate prostate motion in anterior rectal wall.

5 studies (3 two-arm and 2 single-arm studies; 113 patients) reported that using an ERB reduces intra-fractional prostate motion

5 two-arm studies (115 patients) have reported that using an ERB does not result in a significant reduction of inter-fractional prostate motion.

3 single-arm studies (35 patients) have reported that use of an ERB may reduce inter-fractional prostate motion.

Effect of SpaceOAR hydrogel spacer on prostate motion (4 studies, n=107 patients)

Study	No of patients	Radiotherapy technique	Results
Juneja 2015	12 with hydrogel spacer versus 14 without spacer	VMAT	Mean prostate motion was 1.5 ± 0.8mm with spacer and 1.1 ± 0.9mm without spacer (p< 0.05). No significant difference in the average time of motion >3mm between group with and without hydrogel, which were 7.7 ± 1.1% and 4.5 ± 0.9% (p> 0.05), respectively. Therefore, hydrogel spacer has no effect on intra-fractional prostate motion.
Hedrick 2017	10 with ERB versus 16 with hydrogel spacer	IGRT-PBT	The mean vector shift was 0.9mm with hydrogel and 0.6mm with ERB (p< 0.001). These results were not clinically significant because the minimum robust evaluation tolerance was 3mm. Prostate vector shifts were similar between ERB and hydrogel for shifts >3mm (p=0.13) and >5mm (p=0.36). Prostate displacements were clinically comparable for both ERB and hydrogel spacer groups.
Picardi 2016	10 with hydrogel spacer and 10 without	IGRT-VMAT	Overall mean inter-fraction prostate displacements >5mm in AP and SI direction were similar between with and without spacer (AP direction p=0.78; SI direction p=0.47). Prostate displacements 45mm in the AP and SI directions were similar for both groups. Systematic and random setup errors were similar for both groups.
Pinkawa 2013	15 with hydrogel spacer and 30 without	IMRT	Prostate position displacement >5mm were similar for both groups (no statistically significant difference p>0.05), but posterior prostate displacement could be decreased in group with hydrogel spacer (p=0.03).

4 two-arm studies (117 patients) reported that prostate displacements were clinically comparable with or without hydrogel spacer. One of those studies compared hydrogel spacer against ERB and found no significant differences in prostate motion.

Toxicity results

ERB (5 studies, 3 prospective and 2 retrospective; follow up to 62 months)

Study	No of patients	Radiotherapy technique	Toxicity results
Van lin 2017 Prospective randomised study	24 with an 80ml air filled ERB versus 24 non-ERB	3D-CRT	Acute rectal toxicity ERB versus non-ERB Grade 1: 46% versus 50%, NS Grade 2: 29.2% versus 29.2%, NS Late rectal toxicity ERB versus non-ERB Grade ≥1: 21% versus 58.3%, p=0.003 No grade 2–3 in ERB
Goldner 2007 Prospective study	166 with a 40ml air filled ERB	3D-CRT	Late rectal toxicity Grade 0: 57%; Grade 1: 11% Grade 2: 28%; Grade 3: 3% VRS Grade 0: 32%; Grade 1: 22% Grade 2: 32%; Grade 3: 14%
Deville 2012 Retrospective study	100 with a 100ml water filled ERB	IMRT	Acute GI toxicity Grade 0: 69% 1: 23% Grade 2: 8% Grade 3–4: 0%
Wortel 2017 Prospective phase III trial	85 with an 80–100ml air filled ERB versus 242 without ERB	IMRT	Acute mucous loss: 28.4% in non-ERB versus 16.8% in ERB, p< 0.001. Acute rectal discomfort: 59.9% in non-ERB versus 41.0% in ERB, p=0.003. Late rectal complaints in the ERB group were statistically significantly lower than in the non-ERB group.
Teh 2018 Retrospective study	596 with a 100ml air filled ERB	IMRT	Late GI toxicity Grade ≥2: 8.5% Grade ≥3: 1.2%

Hydrogel SpaceOAR (7 studies, 3 prospective [including 1 RCT], 4 retrospective; follow up to 36 months)

Study	No of patients	Radiotherapy technique	Toxicity results
Uhl 2013 Prospective study	52	IMRT	Presented under study 3, 6
Mariados 2015, Hamstra 2017	149 with hydrogel spacer	IMRT	Presented under study 1, 2, 3,4

Prospective RCT	versus 79 without		
Pinkawa 2017 Retrospective study	101 with spacer versus 66 without	IMRT/VMAT	Presented under study 2, 4
Te Velde 2017 Retrospective study	65 with spacer versus 56 without	IMRT	Presented under study 2, 4
Hwang 2019 Retrospective study	50	SBRT	GI toxicity 1 month after RT Grade 1: 8% Grade 2: 4% No acute or late rectal toxicity was reported.
Dinha 2020 Retrospective study	92 with a 90ml water filled ERB versus 75 with hydrogel spacer	PBT	At 2 years actuarial rate of grade ≥2 late rectal bleeding was 19% in ERB arm and 3% in spacer arm; p=0.003. EPIC-bowel QoL composite scores were less diminished in spacer arm (absolute mean difference 5.5; p=0.030).

Study 9 Aminsharif A 2019

Study details

Study type	Review
Country	USA
Study search details	Search period: January 2015 to March 2019, in the MAUDE database.
Study population and number	N=25 patients
Age	Not reported
Study selection criteria	Not reported
Technique	Injection of a prostate-rectum spacer (absorbable polyethylene glycol hydrogel SpaceOAR) posterior to the Denonvilliers fascia and anterior to the rectal wall at the level between mid-gland and apex of the prostate before radiotherapy.
Follow up	Varied across studies (range 6 to 60 months)
Conflict of interest/source of funding	Authors state that there is no potential conflict of interest and no funding was received.

Analysis

Study design issues: authors reviewed the manufacturer website for the safety profile and complications associated with the SpaceOAR hydrogel and compared with voluntary reports submitted to the Manufacturer and User Facility Device Experience (MAUDE) database. The reports were examined for potential device malfunction, post-malfunction manufacturer assessment, and potential changes to patient management. All included reports and adverse events were classified and stratified according to the previously established MAUDE complication classification system.

Study population issues: limited data about the patient and disease characteristics, physician experience, case volume reported on the database.

Other issues: authors state that the cause of these complications is unclear and may be potentially related to the disease process or patient co-morbidities, injection or radiotherapy rather than the hydrogel spacer.

Key safety findings

- Number of patients analysed: 22 reports of 25 cases.

Complications reported on MAUDE database

Study	Year of report	Reported adverse event	N=25
Level I*	2015, 2017	Venous injection—No sequelae	2
	2017	Tenesmus with air in rectal wall—No sequelae	1
	2018	Venous injection—No sequelae	1
	2018	Rectal wall erosion—No sequelae	1
Level II*	2018	Purulent drainage from perineum requiring antibiotics	1
	2018	Pulmonary embolism requiring anticoagulant	4
Level III*	2016,2018, 2019	Perineal abscess requiring drainage^	3
	2016	Proctitis requiring colostomy^	1
	2017, 2018, 2019	Recto-urethral fistula requiring diverting colostomy^	4
	2018	Rectal ulcer and haemorrhage requiring surgery^	1
	2018	Perirectal fistula requiring surgical intervention^	1
	2019	Urinary tract infection and prostatic abscess requiring drainage^	1
Level IV*	2018	Perineal abscess^—subsequent death from alcoholic cardiomyopathy	1
	2018	Severe urosepsis—ICU admission	1
	2018	Severe anaphylactic reaction	1
	2019	Dizziness/nausea post-procedure leading to unresponsiveness and death (cause of death unclear)	1

*Classified according to MAUDE classification system: Level I (none/mild)—no harm, Level II (moderate)—minimal harm requiring minor intervention, Level III (severe)—significant harm requiring major/procedural intervention(s), Level IV (life threatening)—ICU admission/death.

Surgical intervention was needed in 11 patients with infectious complications (proctitis and abscesses, perirectal fistulae and significant bleeding from the procedure).

Study 10 Hall WA 2021

Study details

Study type	Commentary
Country	USA, UK
Study search period	Search period: May 1, 2015, to May 1, 2020, MAUDE database.
Study population and number	N=85 patients
Age	Not reported
Study selection criteria	Not reported
Technique	Commentary including data from MAUDE database, not primary data.
Follow up	
Conflict of interest/source of funding	The project was supported by the National Center for Advancing Translational Sciences, National Institutes of Health (NIH), the National Institute for Health Research (NIHR) Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, UK. Authors received some research and travel funding from companies, outside of this work. One author reports personal fees from The Institute of Cancer Research, during the conduct of the study and a patent for a prostate location and stabilisation device.

Analysis

Study design issues: data was accessed online. The description of each event was reviewed and scored by 2 independent radiation oncologists. Event descriptions were characterised using the Common Terminology Criteria for Adverse Events (version 5). The results were then compared collectively, and a final adjudication of scored toxicity events was created. Reporting of adverse events on the database is voluntary and is not comprehensive so it is difficult to calculate actual rates of adverse events. They are also limited in terms of accuracy, verifiability, and scope.

Key safety findings

- Number of patients analysed: 85 events related to hydrogel SpaceOAR

69% (59/85) events were grade 3, 4, or 5.

24% (20/85) were grade 4 events, including multiple independent descriptions of colostomy (n=7) anaphylactic shock (n=2), rectal wall injection, pulmonary embolism requiring hospital admission (n=5), recto-urethral fistula (n=8)

One death was reported.

Study 11 Chapet PJ [2015]

Study details

Study type	**Case series**
Country	France
Recruitment period	2010–12
Study population and number	n=**36** patients with low-risk to intermediate-risk localised prostate cancer Mean prostate volume: 45.9 cc Tumour classification: 1c (n=18), 2a (n=10), 2b (n=8). Gleason score: 6 (n=22), 7 (n=14) PSA: mean 9.46 nanograms/ml
Age and sex	Mean age: 71 years; 100% male
Patient selection criteria	patients aged between 18-80 years, adenocarcinoma of the prostate histologically proven, low- to intermediate-risk cancer according to the D'Amico classification (T1c to T2b, Gleason score <7, and PSA <20 nanograms/ml) and Karnofsky performance score >60 were included. Patients with metastases, regional lymph nodes1.5 cm on CT scan or MRI, inflammatory disease of the digestive tract, previous pelvic irradiation, and previous malignant disease other than basal cell carcinoma were excluded.
Technique	**Injection of 10 ml hyaluronic acid during hypofractionated intensity modulated radiation therapy (IMRT)** (with 20 fractions of 3.1 Gy, up to 62 Gy total dose over 4 weeks) Injection was done under local anaesthesia (10 ml lidocaine 1%). All patients had daily prostate repositioning on the 3 gold markers implanted. Antibiotics were given before and after injection.
Follow up	**3 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: 1 patient who developed an adverse event (grade 3 toxicity) was excluded from the analysis because no radiotherapy was administered.

Study design issues: prospective study in 2 centres designed to assess acute toxicity and tolerance of the injection. Acute toxicity was defined as occurring during radiotherapy or within 3 months after radiotherapy and graded according to the CTCAE version 4.0. Tolerance of hyaluronic acid (pain) was assessed on a 10-point visual analogue scale during the injection, 30 minutes after injection and then by the use of CTC at each visit. Patients who had at least 1 week of radiotherapy were included in the tolerance analysis

Key efficacy findings

Number of patients analysed: **36**

Acute toxicity during and at 3-month follow up (n=35)

Overall toxicity	**% (n)**
Grade 0 (no toxicity)	6 (2/35)
Grade 1	40 (14/35)
Grade 2	54 (19/35)
Grade 3 or 4 toxicity	0
During radiotherapy	
Acute GU toxicity^ (at least 1)	94.3 (33/35)
Grade 2 toxicity (at least 1): urinary obstruction, frequency*	54.2 (19/35)
Acute GI toxicity^^	57.1 (20/35)
Grade 1 (at least 1)	54.2 (19/35)
Grade 2	2.8 (1/35): proctitis
3-month follow up (n=34)	
GU toxicity	41.2 (14/34) 4 patients had grade 2 obstruction or frequency
GI toxicity: grade 1	2.9 (1/34)

*The toxicity was present at baseline in 7 patients.

^GU toxicities included obstruction, frequency, incontinence, haematuria, infection, spasms or stenosis.

^^ GU toxicities included diarrhoea, haemorrhoids, proctitis and rectal mucositis.

Key safety findings

Haematoma developed behind the bladder in 1 patient (within hours after injection) with a moderate platelet count. This was removed by laparotomy.

Tolerance of injection (measured on a VAS) (n=28)

At the time of injection the mean pain score was 4.6±2.3. Thirty minutes after the injection 2 patients reported pain scores as 2 and 3/10. 3 patients had other symptoms such as lower abdominal pain, haematuria and asthenia

Validity and generalisability of the studies

- Evidence assessments on different biodegradable perirectal spacers (including synthetic hydrogel, and biodegradable balloons) used during different radiotherapy techniques (EBRT or BT alone or in combination) for patients with low to intermediate prostate cancer were included within this overview.
- Systematic reviews included different types of studies but were predominantly based on 1 RCT done in the USA (Mariados 2015 and related publications) and non-randomised studies (nRCTs). There is overlap of primary studies between included systematic reviews.
- Hydrogel spacers were compared to no spacers in 3 systematic reviews (Miller 2020, Armstrong 2021, Vaggers 2021), and the RCT which was limited to T1 and T2 tumours (Mariados 2015). Hydrogel spacers were compared to balloons in a HTA (NIPHNO, EUnetHTA 2020) and 1 systematic review (Ardekani 2021). Biodegradable rectal spacers, including hydrogel spacers, balloons, and hyaluronic acid spacers, were compared to each other in one systematic review (Mok 2014).
- Outcomes assessed were mainly reduction in toxicity, reduction in radiation doses, increase in the distance between the prostate and rectum, quality of life and prostate motion or displacement. Outcomes such as survival, patient satisfaction were not reported in studies.
- Variations were noted in patient characteristics (tumour stages), radiotherapy techniques and protocols used (either on its own or in combination with other techniques), and follow-up periods across primary studies included within the systematic reviews. These variations might have influenced the performance of spacers and clinical outcomes.

- Follow-up varied across studies and ranged from 6 to 60 months.
- Most of the related case series with small sample sizes that assessed biodegradable rectal spacers have been included in the appendix. 3 of these small case series used a substance (DuraSeal) ‘off-label’ for this procedure.

Existing assessments of this procedure

The Institut national d'excellence en santé et en services sociaux (INESSS, in 2021) evaluated the use of a biodegradable spacer (SpaceOAR™ Hydrogel System) in patients with localized or locally advanced prostate cancer treated with external beam radiotherapy or brachytherapy combined or not with external beam radiotherapy. [Avis - Utilisation de l’hydrogel SpaceOARMD comme espaceur rectal lors de la radiothérapie de la prostate (inesss.qc.ca)]

Summary of deliberations

Authors concluded that based on best available data and given the significant uncertainty regarding the product’s therapeutic value that public coverage for the use of a biodegradable spacer is not supported. Additional evidence is necessary to support the adoption of this technology. Reasons for the unanimous position include:

- The limitations in the evidence, including the absence of data for groups considered to be at higher risk for rectal toxicity;
- The risk-benefit ratio, which does not appear to support the use of this technology;
- The possibility of major complications for patients;
- The possibility of an increased risk of complications for patients at increased risk for rectal toxicity;
- The observed dosimetric benefit (sometimes significant) in the evidence presented, which appears to offer only a small clinical benefit;
- The contradiction between the positions taken by other organizations;
- The potential difficulty of access to MRI.

Recommendation

The authors concluded that more evidence on safety and efficacy is needed to recommend this technology and that it should be available only within further research.

Cancer Care Ontario guideline (Chung 2019) provides clinical practice recommendations for the use of biodegradable spacers for prostate cancer treatment.

Recommendation 1 states that *‘biodegradable spacer insertion is a technology that may be used to decrease toxicity and maintain quality of life (QOL) in appropriately selected prostate cancer patients receiving radiotherapy (RT)’*.

- *Spacer insertion should be performed by individuals trained in the use of transperineal interventional procedures and where there is institutional support.*
- *Selection of appropriate patients remains to be fully defined but may include those in whom standard rectal dose-volume criteria are not met; those treated with ultrahypofractionated RT; and those at higher baseline risk of rectal toxicity.*

Interpretation of evidence for recommendation 1

- Key evidence for this recommendation was from a multicentre RCT, (Mariados 2015), a follow-up report for this RCT (Hamstra 2017), and 3 non-randomised studies (Pinkawa 2017, Prada 2009, Te Velde 2017).
- The authors state that *‘evidence is adequate to support the use of biodegradable rectal spacers for RT in patients with localized prostate cancer. However, given the low rates of toxicity observed overall in both arms of the RCT, there may be limited benefit to routine application of this technology. Further evidence to direct the appropriate selection of patients and to evaluate the efficacy of this technology beyond conventionally fractionated RT is warranted’*.

A CADTH rapid response report of clinical and cost effectiveness on hydrogel spacers for patients with prostate cancer in 2019 included 3 systematic reviews, 1 RCT (described within 2 eligible reports), 7 cohort studies, 2 economic evaluations, and 3 guidelines. Authors concluded that *'hydrogel spacers were effective in increasing the distance between the prostate and the rectum, and in reducing the radiation dose to the rectum while delivering radiation to the prostate in patients with localized prostate cancer’. However, 2 systematic reviews reported that the clinical benefits were not significant and were therefore uncertain. One systematic review developed for a HTA did not recommend the routine use of hydrogel spacers for prostate cancer, in consideration of the high costs for their patients. In contrast, 3 year follow-up results of an RCT indicated that hydrogel spacers were associated with improvements in bowel, urinary and sexual quality of life outcomes…… ‘The guidelines by Cancer Care Ontario, the National Comprehensive Cancer Network, and the National Institute for Health* *and Care Excellence recommended the use of hydrogel spacers to reduce rectal toxicity and improve quality of life'*.

The National Comprehensive Cancer Network (2018), in the USA states that "*endorectal balloons may be used to improve prostate immobilization. Perirectal spacer materials may be employed when the previously mentioned techniques are insufficient to improve oncologic cure rates and/or reduce side effects due to anatomic geometry or other patient related factors, such as medication usage and/or comorbid conditions".* It recommends that *"patients with obvious rectal invasion or visible T3 and posterior extensions should not undergo perirectal spacer implantation for prostate cancer"*.

A product brief from an ECRI Institute Health Technology Assessment information service (in 2017) on use of biodegradable spacers concluded that these devices are "*well tolerated and work as intended to reduce rectal irradiation, long-term (but not acute) rectal toxicity, and improve bowel quality of life (QOL), based on 1 RCT and 3 non-RCTs".* The brief also reported that:

- A comparative study included in the brief found that none of the used spacers resulted in a reduction in acute rectal toxicity (<3 months).
- Clinicians may need to perform at least 32 procedures before achieving optimal insertion of the spacer and patient outcomes, based on evidence from a retrospective, single-centre comparison study.
- Placement and hydrogel material appear to be well tolerated based on results from the RCT and case series.
- RCT evidence showed that no rectal perforation, haemorrhage, or infection were associated with use of the biodegradable spacer. Most events were mild, transient, and similar between groups. Case series (n=683) reported few adverse events: 4 rectal wall penetrations (with dose escalation), 1 Grade 3 telangiectasia, and 1 asymptomatic necrotic rectal lesion.
- Longer-term (>5 years) and comparative data are needed because late effects can occur many years after prostate irradiation. A single-arm post-marketing study is collecting 5-year data on 250 patients.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer. NICE interventional procedure guidance IPG590 (2017) (current guidance on same procedure under review).
- Irreversible electroporation for treating prostate cancer. NICE interventional procedure guidance IPG572 (2016) Available from http://www.nice.org.uk/guidance/IPG572
- Focal therapy using cryoablation for localised prostate cancer. NICE interventional procedure guidance IPG423 (2012) Available from http://www.nice.org.uk/guidance/IPG423
- Laparoscopic radical prostatectomy. NICE Interventional Procedures Guidance 193 (2006). Available from http://www.nice.org.uk/guidance/IPG193
- High dose rate brachytherapy in combination with external-beam radiotherapy for localised prostate cancer. NICE Interventional Procedures Guidance 174 (2006). Available from http://www.nice.org.uk/guidance/IPG174
- Cryotherapy as a primary treatment for prostate cancer. NICE Interventional Procedures Guidance 145 (2005). Available from http://www.nice.org.uk/guidance/IPG145
- Low dose rate brachytherapy for localised prostate cancer. NICE Interventional Procedures Guidance 132 (2005). Available from http://www.nice.org.uk/guidance/IPG132
- Cryotherapy for recurrent prostate cancer. NICE Interventional Procedures Guidance 119 (2005). Available from http://www.nice.org.uk/guidance/IPG119
- High-intensity focused ultrasound for prostate cancer. NICE Interventional Procedures Guidance 118 (2005). Available from http://www.nice.org.uk/guidance/IPG118

NICE guidelines

- Prostate cancer: diagnosis and treatment. NICE guideline 131 (2019) Available from http://www.nice.org.uk/guidance/NG131

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate.

9 professional expert questionnaires for biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer were submitted and can be found on the NICE website.

Patient organisation opinions

One patient organisation submission for biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer was received and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme sent questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). NICE received 22 completed questionnaires.

The patient commentators' views on the procedure were consistent with the published evidence and the opinions of the professional experts. See the patient commentary summary for more information.

Company engagement

A structured information request was sent to 3 companies who manufacture a potentially relevant device for use in this procedure. NICE received 2 completed submissions. These were considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

Ongoing studies:

- **NCT02353832** Stereotactic ablative radiotherapy (SABR) for low risk prostate cancer with injectable rectal spacer (phase 2 study); interventional single group; n=44; device: SpaceOAR, Duraseal or equivalent; primary outcome: percentage of participants with reduction in acute per-prostatic rectal ulcer events from 90%+ to <70%, effectiveness of space creation of >= 7.5 mm in protecting rectum from toxicity; location: USA; study completion date: January 2021; status: active.
- **NCT02361515** Moderate hypofractionated radiotherapy (62 Gy in 20 fractions of 3.1 Gy) versus stereotactic radiotherapy (37.5 Gy in 5 fractions of 7.5 Gy) with hyaluronic acid injection between the prostate and the rectum for prostate cancer of low- to intermediate risk; RPAH2. RCT, n=96, primary outcome - number of patients with late urinary toxicities of grade ≥ 2; location France; study completion date: September 2019.
- **NCT02165020**: Hypofractionated radiotherapy for prostate cancer (62 Gy in 20 fractions of 3.1 Gy) with hyaluronic acid injection; non-randomised single group study, n=36, primary outcome: number of patients with late rectal toxicities (> 3 months) of grade ≥ 2; location France; study completion May 2017; status active.
- **NCT03386045**: Optimal prostate fractionation study; RCT, n=214, moderate hypofractionation or standard radiotherapy plus SBRT (BOOSTER) with hydrogel versus moderate hypofractionation or SBRT; primary outcome: local control; location Australia; study completion date: March 2026, status recruiting.
- **NCT03400150:** clinical protocol for the investigation of the ProSpace™ balloon system pivotal study BP-007; RCT, n=222, ProSpace balloon in prostate cancer during IMRT versus only IMRT; primary outcomes: adverse

event rate, reduction in rectal radiation exposure at 6 months; international study; study completion date: April 2022; status active.

- **NCT03525262** A phase II randomized controlled trial of stereotactic ablative body radiotherapy (SABR) with or without neurovascular sparing for erectile function preservation in localized prostate cancer, hydrogel used in the intervention group. RCT, n=120, primary outcome: reduction in EPIC sexual function domain composite score; location USA, study completion date: June 2024; status recruiting.
- **ACTRN12612000524897:** A trial of polyethylene glycol (PEG) hydrogel to reduce rectal radiation dose during radiotherapy for prostate cancer. Nonrandomised single group study, n=40; primary outcomes: radiation dose, prostate-rectum separation, toxicity; location Australia, completion date and status unknown.

References

1. Mariados N, Sylvester J et al (2015). Hydrogel Spacer Prospective Multicenter Randomized Controlled Pivotal Trial: Dosimetric and Clinical Effects of Perirectal Spacer Application in Men Undergoing Prostate Image Guided Intensity Modulated Radiation Therapy. International Journal of Radiation Oncology Biology Physics.92 (5) 971-977.

   Hamstra da, Mariados N, Sylvester J et al (2017). Continued Benefit to Rectal Separation for Prostate Radiation Therapy: Final Results of a Phase III Trial. Radiation Oncology International Journal of biology physics. 9 (5) 67-985.

   Hamstra DA, Mariados N, Sylvester J, et al.(2018) Sexual quality of life following prostate intensity modulated radiation therapy (IMRT) with a rectal/prostate spacer: secondary analysis of a phase 3 trial. Pract Radiat Oncol. 8(1):e7-e15.

   Karsh LI, Gross ET, Pieczonka CM, et al. (2018) Absorbable hydrogel spacer use in prostate radiotherapy: a comprehensive review of phase 3 clinical trial published data. Urology.115:39-44.

2. Miller LE, Efstathiou JA, Bhattacharyya SK et al. (2020) Association of the Placement of a Perirectal Hydrogel Spacer with the Clinical Outcomes of Men Receiving Radiotherapy for Prostate Cancer: A Systematic Review and Meta-analysis. JAMA Network Open. 3(6):e208221-e

3. Norwegian Institute of Public Health (NIPHNO), National School of Public Health, Management and Professional Development (NSPHMPDB); et al. Biodegradable rectum spacers to reduce toxicity for prostate cancer. Collaborative Assessment. Oslo, Norway: EUnetHTA; 2020. Report No.: OTCA23.

4. Armstrong N, Bahl A, Pinkawa M, et al. (2021) SpaceOAR Hydrogel spacer for reducing radiation toxicity during radiotherapy for prostate cancer. A systematic review, Urology, doi: https://doi.org/10.1016/j.urology.2021.05.013

5. Vaggers S, Rai BP, Chedgy ECP et al. (2021) Polyethylene glycol-based hydrogel rectal spacers for prostate brachytherapy: a systematic review with a focus on technique. World Journal of Urology 39:1769–1780.

6. Payne HA, Pinkawa M, Peedell C et al. (2021) SpaceOAR hydrogel spacer injection prior to stereotactic body radiation therapy for men with localized prostate cancer: A systematic review. Medicine. 100 (49); e28111.

7. Mok G, Benz E, Vallee JP et al. (2014) Optimization of radiation therapy techniques for prostate cancer with prostate-rectum spacers: a systematic review. Int J Radiat Oncol Biol Phys. 90(2):278-288.

8. Ardekani MA, Ghaffari H, Navaser M et al. (2021) Effectiveness of rectal displacement devices in managing prostate motion: a systematic review. Strahlenther Onkol,197:97–115

9. Aminsharifi A, Kotamarti S, Silver D et al. (2019) Major complications and adverse events related to the injection of the SpaceOAR hydrogel system before radiotherapy for prostate cancer: Review of the manufacturer and user facility device experience database. J Endourol. 33(10):868-871.

10. Hall WA, Tree AC, Dearnaley D et al. (2021). Considering benefit and risk before routinely recommending SpaceOAR. The lancet oncology. 22 (1), 11-13.

11. Chapet O, Decullier E et al (2015). Prostate hypofractionated radiation therapy with injection of hyaluronic acid: Acute toxicities in a phase 2 study. International Journal of Radiation Oncology Biology Physics.91 (4) 730-736.

12. Institut national d’excellence en santé et en services sociaux (INESSS). Utilisation de l’hydrogel SpaceOARMD comme espace rectal lors de la radiothérapie de la prostate. Avis rédigé par Cathy Gosselin, Andréa Senay, Amélie Rousseau et Vanessa Dufour. Québec, Qc : INESSS; 2021. 200 p

13. Chao YS, MacDougall D, de Nanassy A. (2019) Hydrogel spacers for patients with prostate cancer: a review of clinical effectiveness and cost-effectiveness. Ottawa: CADTH; Feb. (CADTH rapid response report: summary with critical appraisal).

14. Chung P, Brown J, D‘Souza D, Koll W, Morgan S, SPACER RRG. Cancer Care Ontario: biodegradable rectal spacers for prostate cancer radiotherapy. (Program in Evidence-based Care recommendation report no.: 21-5). Toronto (ON): Cancer Care Ontario; 2019 Jan 16: https://www.cancercareontario.ca/sites/ccocancercare/files/guidelines/full/pebc21-5f.pdf . Accessed 2021 September 29.

15. National Comprehensive Cancer Network. NCCN Guidelines: prostate cancer v. 4.2018. Plymouth Meeting (PA): National Comprehensive Cancer Network; 2018. Accessed 2021 September 29.

16. SpaceOAR System (Augmenix, Inc.) Hydrogel Spacer for Reducing Exposure during Prostate Cancer Radiation Therapy. Product brief. ECRI Institute Health Technology Assessment Information Service, May 2017. Accessed 2021 September 29.

17. Babayan RK, Steinberg ML, Miller LE. Re: Aminsharifi et al. (2020) Major complications and adverse events related to the injection of the SpaceOAR hydrogel system before radiotherapy for prostate cancer: review of the manufacturer and user facility device experience database. J Endourol; 34: 240–41.

Literature search strategy

Databases	Date searched	Version/files
MEDLINE (Ovid)	14/09/2022	1946 to September 13, 2022
MEDLINE In-Process (Ovid)	14/09/2022	1946 to September 13, 2022
MEDLINE Epubs ahead of print (Ovid)	14/09/2022	September 13, 2022
EMBASE (Ovid)	14/09/2022	1974 to 2022 September 13
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	14/09/2022	Issue 8 of 12, August 2022
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	14/09/2022	Issue 8 of 12, August 2022
International HTA database (INAHTA)	14/09/2022	n/a

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

MEDLINE search strategy

Number	Search term
1	exp Prostatic Neoplasms/
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or chrondosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcinogenes* or leiomyosarcoma* or lump*)).tw.
3	1 or 2
4	Hydrogels/
5	Hydrogel, Polyethylene Glycol Dimethacrylate/
6	(hydrogel* or hydrodissect*).tw.
7	(spacer* or spacing).tw.
8	((perirect* or rect* or prostate-rectum or denonvillier* or transperineal*) adj4 space*).tw.
9	or/4-8
10	3 and 9
11	spaceOAR*.tw.
12	Augmenix*.tw.
13	11 or 12

14	10 or 13
15	animals/ not humans/
16	14 not 15
17	limit 16 to ed=20200622--20220930
18	limit 17 to english language

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the summary of the key evidence. It is by no means an exhaustive list of potentially relevant studies.

Additional papers identified

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Inert liquid-to-solid gels for prostate-rectum separation during prostate radiation therapy November (2010, 2013). Horizon scanning technology prioritising summary and Technology brief update: Prepared by Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S). Accessed 2021 September 29.	Horizon scanning summary report for Australia and New Zealand	A Horizon Scanning prioritising summary report concluded that *'some form of injected liquid-to-solid inert substance (mostly recently cross-linked hyaluronan gel) for prostate-rectum separation appears to be safe. It also appears to have the potential to lower rates of rectal toxicity and improve QOL for men having radiotherapy for prostate cancer. However, the technology is very early in its lifecycle and is not yet in clinical use'*. A 2013 technology update '*provides continued support for the safety and effectiveness of this modality. Although the evidence base remains small, injection of hyaluronic acid or the SpaceOAR™ System gel appears to successfully increase the distance between the posterior prostatic capsule and the anterior rectal wall which resulted in reduced gastrointestinal toxicity. Based on this, and the claim that inert liquid-to-solid gels have the potential to reduce the incidence of severe proctitis, necrosis, fistula or rectal bleeding by 50%, this technology will be monitored for a further 24 months*'	More recent assessments included.
Afkhami Ardekani M, Ghaffari H. Optimization of prostate brachytherapy techniques with	Systematic review 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	More comprehensive and recent reviews added.

polyethylene glycol-based hydrogel spacers: a systematic review. Brachytherapy. 2019:S1538-4721(19)30574-4.		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	
Aditama, E (2015). Evaluation of Hydrogel Spacer (SpaceOAR) to reduce rectal toxicity in dose-escalated intensity modulated radiotherapy (IMRT) 82Gy for prostate cancer. Journal of Medical Radiation Sciences (62) 89.	Case report A 54-year-old man was diagnosed with T1c prostate adenocarcinoma and treated with dose-escalated IMRT 82 Gy with injection of hydrogel spacer. Follow-up: 6 months	The injection of spacer results in reduction of rectal dose with V70 = 0% for post injection of spacer plan compared with V70Gy = 15% for pre injection of spacer plan. The distance created due to spacer is 7-10 mm.	Larger studies are included.
Alongi F, Cozzi L, Arcangeli S, Iftode C, Comito T, Villa E, et al. Linac based SBRT for prostate cancer in 5 fractions with VMAT and flattening filter free beams: Preliminary report of a phase II study. Radiation Oncology. 2013;8 (1) (no pagination)(171)	Case series N=40 patients prostate adenocarcinoma (T1-T2). hypo-fractionated SBRT programme with Volumetric Modulated Arc Therapy (VMAT) and Flattening Filter Free (FFF) beams. SpaceOAR™ gel was optionally implanted (in 8 patients). Median follow-up was 11 months (range: 5-16)	No acute G3 or greater toxicity was found. Median treatment time was 126 sec (120-136). Early findings suggest that SBRT with RapidArc and FFF beams for prostate cancer in 5 fractions is feasible and tolerated in acute setting.	Larger studies are included.

Alongi F, Riog M, Figlia V et al. (2020) Rectal spacer hydrogel in 1.5T MR-guided and daily adapted SBRT for prostate cancer: dosimetric analysis and preliminary patient-reported outcomes. Br J Radiol; 94: 20200848.	Case series N=20 patients with prostate cancer (cT1-T2 stage) treated using 1.5T MR-guided adaptive stereotactic body radiotherapy [SBRT - 35 Gy schedule delivered in 5 fractions] (10 patients in spacer group and 10 patients in no-spacer group).	Statistically significant dosimetric advantages were observed in favour of the spacer insertion, improving the planning target volume coverage in terms of V33.2Gy >95% and planning target volume 37.5 Gy <2% mainly during daily-adapted SBRT. Also, rectum V32, V28 and V18Gy and bladder V35Gy <1 ccs were significantly reduced in the spacer cohort. PROMS, showed no difference between the pre- and post-SBRT evaluation in both arms, excepting the physical functioning item of EORTC QLQ-C30 questionnaire that was declined in the no-spacer group.	Larger studies are included.
Ahmad Khalil D, Jazmati D, Geismar,D et al. (2022) Dosimetric feasibility of moderately hypofractionated/dose escalated radiation therapy for localised prostate cancer with intensity-modulated proton beam therapy using simultaneous integrated boost (SIB-IMPT) and impact of hydrogel prostate-rectum spacer. Radiation oncology. 17 (1); 64	N=23 patients with intermediate- and high-risk prostate cancer treated using IMPT -SIB technique prescribing 60 GyRBE and 72GyRBE in 30 fractions to PTV1 (prostate and seminal vesicle) and PTV2 boost (prostate and proximal seminal vesicle), respectively (15 had spacer, 8 were non spacer).	Hypofractionated/dose escalated radiotherapy with SIB-IMPT is dosimetrically feasible. Further reduction of the rectal volumes receiving high and medium dose levels (73-50 Gy) and rectal NTCP could be achieved through injection of spacers between rectum and prostate.	Dosimetry study. Larger studies with longer follow-up included.
Alshak MN, Eidelberg A, Diaz SM et al. (2022) Natural history of lower urinary tract symptoms among men undergoing stereotactic body radiation therapy for prostate cancer with and without a Rectal Hydrogel Spacer. World journal of urology. 40,1143–1150	Retrospective analysis n= 87 men (50 had SBRT+ SpaceOAR and 37 had SBRT with no SpaceOAR). Follow-up 6 months	Post-SBRT urinary frequency was more common in the non-SpaceOAR group versus the SpaceOAR group (68% versus 38%, *p* = 0.006), as was nocturia (35% vs. 8%, *p* = 0.002). Acute gastrointestinal symptoms did not differ. 58.8% of men were on α-inhibitors at 6-months of follow-up post-SBRT, an increase from 27.6% baseline usage (*p* < 0.001). Importantly, there was a difference of α-inhibitor use between non-SpaceOAR and SpaceOAR groups at the end of SBRT and at 1.5-, 3-, and 6-months follow up (86% vs. 53% [*p* = 0.002], 83% vs. 53%	Larger studies with longer follow-up included.

		[$p = 0.005$], 72% vs. 49% [$p = 0.038$], respectively).	
Babar M, Katz A, Ciatto M et al. (2021) Dosimetric and clinical outcomes of SpaceOAR in men undergoing external beam radiation therapy for localized prostate cancer: A systematic review. Journal of Medical Imaging and Radiation Oncology 65 (2021) 384–397	systematic review on controlled studies on the dosimetric and clinical outcomes of SpaceOAR in men undergoing external beam radiation therapy for localized prostate cancer. 8 studies were included.	All of the studies showed SpaceOAR to reduce the radiation dose volume to the rectum over numerous dosimetry levels. Of the four studies that assessed toxicity, one reported SpaceOAR to significantly decrease acute Grade 1 diarrhoea and two reported SpaceOAR to significantly decrease late Grade 1 and Grade ≥2 rectal toxicities. Two studies assessed cumulative incidence of toxicity at 3 years in which one reported SpaceOAR to significantly decrease urinary incontinence and Grade ≥1 and Grade ≥2 rectal toxicities, and the other reported SpaceOAR to significantly decrease Grade 1 diarrhoea and Grade 2 proctitis. Moreover, one study reported that fewer SpaceOAR patients experienced 10-point declines in bowel quality of life at 3 years, but another study reported no significant difference in 10-point declines in bowel quality of life between the SpaceOAR and control groups at 5 years. With the current research available, SpaceOAR may be beneficial to those who did not meet the standard rectal dose-volume criteria, have higher risk factors of developing rectal toxicities post-radiation, or wish to decrease the length and costs of radiotherapy by increasing the dose of radiation per fraction.	Similar comprehensive review on hydrogel spacers included.
Bahl A, Challapalli A, Jain S et al. (2021) Rectal spacers in patients with prostate cancer undergoing radiotherapy: A survey of UK uro-oncologists. Int J Clin Pract. 2021;75:e14338	Survey online questionnaire was completed by members of the British Uro-oncology Group (BUG).	63 specialists completed the survey (50% of BUG members at that point in time). Only 37% had used rectal spacers, mostly for private patients or those with pre-existing bowel conditions. However, many (68%) would like to use these devices in future. More than 70% of the uro-oncologists felt that bowel toxicity was under-reported, but 60% believed that the use of radiotherapy without bowel toxicity was	Survey

		achievable with the use of rectal spacers. The current use of rectal spacers by UK uro-oncologists for patients with localised or locally advanced prostate cancer receiving radiotherapy is low and largely restricted by resourcing issues.	
Beydoun N, Bucci JA et al (2013). First report of transperineal polyethylene glycol hydrogel spacer use to curtail rectal radiation dose after permanent iodine-125 prostate brachytherapy. Brachytherapy 12 (4) 368-374.	Case series n=5 prostate cancer patients with suboptimal rectal dosimetry after iodine 125 seed brachytherapy implant (low dose rate) and had hydrogel PEG spacer Follow-up: 6 weeks	All patients had a clinically significant reduction in the volume of rectum having greater than or equal to the prescription dose (RV100) on the post spacer postimplant dosimetry, compared with the pre-spacer postimplant dosimetry. Mean prostate-rectum separation that was achieved with the insertion of the spacer was 15.1 mm (+/-3.4). The mean difference in separation from before to after spacer insertion was 12.5 mm (+/-4.5). This was associated with a reduction in mean RV100 from 3.04 (+/-1.2) to 0.06 (+/-0.1) cc. Toxicities were limited to grade 1 perineal pain and rectal discomfort (3/5 patients). There were no grade 2 or greater toxicities reported after insertion of the spacer.	Larger and longer follow-up studies included.
Berlin A, Tomasso AD, Ballantyne H et al. (2017) Use of hydrogel spacer for improved rectal dose-sparing in patients undergoing radical radiotherapy for localized prostate cancer: First Canadian experience. : Can Urol Assoc J;11(12):373-5. http://dx.doi.org/10.5489/cuaj.4681	Case series N=5 patients with localised prostate cancer planned to undergo radical hypofractionated, image-guided, intensity-modulated radiotherapy (IG-IMRT using a hydrogel spacer SpaceOAR)	Authors discuss the impact of SpaceOAR in the context of hypofractionated IG-IMRT, and the particular considerations for its applications in the Canadian setting.	Larger studies included.
Boissier R, Udrescu C, Rebillard X et al (2017). Technique of Injection of Hyaluronic Acid as a Prostatic Spacer and Fiducials Before Hypofractionated External Beam Radiotherapy for Prostate Cancer. Urology (99) 265-269.	Case series n=30 patients with prostate cancer at low or intermediate risk. Implantation of fiducials and a prostatic spacer (hyaluronic acid [HA]) during image-guided external beam radiotherapy (EBRT) of 62 GY in 20 fractions of	The quality score increased from patients 1-10, 11-20, to 21-30 with respective median scores: 7 [2-10], 5 [4-7], and 8 [3-10]. The average thicknesses of HA between the base, middle part, and apex of the prostate and the rectum were the following: 15.1mm [6.4-29], 9.8mm [5-21.2], and 9.9mm [3.2-21.5]. The injection of the HA induced a median pain score of 4 [1-8]	Larger studies included.

	3.1 GY with intensity-modulated radiotherapy.	and no residual pain at mid-long term.	
Brooks E, Hu J, Yu J, et al. Cost effectiveness of the insertion of hydrogel spacer in men treated with radiation therapy for prostate cancer. Managed Care 2020;	Cost effectiveness		Costs not in remit.
Butler WM, Kurko BS, Scholl WJ et al. (2021) Effect of the timing of hydrogel spacer placement on prostate and rectal dosimetry of low-dose-rate brachytherapy implants. J Contemp Brachytherapy; 13, 2: 145–151	Retrospective study N=174 intermediate- and high-risk patients with hydrogel compared with 174 patients without hydrogel for prostate brachytherapy. Of the SpaceOAR™ patients, 91 had hydrogel upon completion of after brachytherapy implant, while 83 had hydrogel prior to EBRT, followed 2-10 weeks later by brachytherapy.	There was a significant rectal dose sparing in the cohort with hydrogel spacer compared to a reference group without spacer injection. The rectal dose sparing effect was similar in the sub-group of patients injected with hydrogel prior to EBRT and the sub-group injected with hydrogel at the conclusion of brachytherapy.	Larger studies included in table 2.
Chao M, Ho H, Chan Y et al. (2018) Prospective analysis of hydrogel spacer for patients with prostate cancer undergoing radiotherapy. BJU international, 122, 427-433.	Case series N=76 patients with prostate cancer Clinical stage T1-T3a Fiducial marker insertion plus injection of the hydrogel spacer into the perirectal space before intensity-modulated RT (IMRT) or volumetric-modulated arc RT (VMAT) 78 Gy in 2 Gy Follow-up Median 14 (IQR 12-29) months	16 patients (21%) developed acute Grade 1 GI toxicity, with all symptoms resolved within 3 months after completion of treatment. 1 patient (1%) developed a late Grade 1 rectal haemorrhage at 9 months after treatment; however, this was due to rectal haemorrhoids. 1 patient (1%) developed late Grade 1 proctitis at 8 months after treatment. No patients developed late GI toxicity of Grade ≥2.	Larger studies with controls included.
Chao, M. 2018. The use of hydrogel spacers in prostate radiation therapy. *BJU International,* 122**,** 10.	Case series N=31 patients with stage T1-T3a prostate cancer IMRT 78 Gy in 2 Gy fractions Follow-up median 12 (range 6-18) months		Larger studies included.
Chao M, Lim Joon D, Khoo V et al. (2019) The use of hydrogel spacer in men undergoing high-dose prostate cancer radiotherapy: results of a prospective phase 2 clinical trial. World J	Case series N=31 patients with cT1-3aN0M0 prostate adenocarcinoma receiving radical radiotherapy to 78 G and hydrogel spacer (SpaceOAR) implantation.	All patients had successful insertion of spacer with no peri-operative toxicity. The mean prostate-rectal separation achieved was 10.5 mm. 29 (93.5%) patients achieved a reduction in rV70 of at least 25%. Acute grade 1 GI toxicity was reported in 3 patients. All symptoms had	Larger studies with controls included.

Urol. 2019;37(6):1111-6.	Follow-up 12 months.	resolved by 3 months post RT. Late grade 1 GI toxicity was reported in one patient (3.2%) with bowel frequency occurring at 6 months and resolving by 12 months post RT.	
Chao M, Ow D, Ho H, et al. (2019) Improving rectal dosimetry for patients with intermediate and high-risk prostate cancer undergoing combined high-dose-rate brachytherapy and external beam radiotherapy with hydrogel space. Journal of Contemporary Brachytherapy. 11(1):8-13	Comparative study (retrospective) N=97 patients with prostate cancer 32 patients (33%) who had hydrogel spacer insertion compared with 65 patients (67%) without hydrogel spacer receiving combined HDR and EBRT. Median follow-up 60 months (12-125 months).	The median prostate-rectal separation achieved with hydrogel spacer (HS) was 10 mm (range, 5-14 mm). There were no post-operative complications following HS insertion. Patients with HS had significantly lower radiation dose to the rectum across all rectal dose volumes from rV30 to rV80, (p < 0.001). There was also significantly less acute > grade 1 GI toxicity (12.5% vs. 30.8%, p = 0.05) and a trend towards less late grade 1 GI toxicity (0% vs. 7.7%; p = 0.11) in the HS group compared to the non-HS group.	Larger studies included. Included in systematic review added.
Chao M, Bolton D, Joon DL et al. (2019) High dose rate brachytherapy boost for prostate cancer: Biochemical control and the impact of transurethral resection of the prostate and hydrogel spacer insertion on toxicity outcomes. Journal of Medical Imaging and Radiation Oncology 63, 415–421.	Retrospective case series N=95 patients with intermediate and high risk prostate cancer treated with high dose rate brachytherapy boost (HDR-BT, 50.4 Gy) combined with external beam radiotherapy (EBRT) Hydrogel spacers (HS) were used in 30 patients. Median follow-up was 58 months.	The 5-year biochemical progression free survival, local recurrence free survival (LRFS), metastatic free survival (MFS) and overall survival were 92%, 100%, 92% and 88%. Late > grade 2 genitourinary (GU) toxicity was 6.3%. The use of HS or prior TURP had no impact on late GU toxicity. Late Grade 1 gastrointestinal (GI) toxicity was 5.3%.	Larger studies included.
Chapet O, Udrescu C, Devonec M, et al (2013). Prostate hypofractionated radiation therapy: Injection of hyaluronic acid to better preserve the rectal wall. Int J Radiat Oncol Biol Phys; 86:72-76.	Case series n=16 patients with prostate cancer. Hyaluronic acid injection combined with hypofractionated radiotherapy (62Gy in 20 fractions) delivered via IMRT.	The mean rectal V90% 955.8Gy) for pre-implantation plans was 7.65cc compared with 2,1cc on plans generated in scans of patients who have implants. The mean rectal V90%, V705 AND v50% were reduced by 73.8% (p<0.001), 43% (p=0.007) and 25% (p=0.036) respectively.	Larger and longer follow-up studies.
Chapet O, Udrescu C, Tanguy R, et al (2014). Dosimetric implications of an injection of hyaluronic acid for preserving the rectal wall in prostate stereotactic body radiation therapy. Int J	Case series n=10 patients with prostate cancer Hyaluronic acid injection combined with hypofractionated radiotherapy (62Gy in 20 fractions) delivered via IMRT.	The mean rectal V90% and V80% were reduced by at least 90% (p=0.002) and 77% (p=0.002) respectively, regardless of the prescription dose.	Larger and longer follow-up studies.

Radiat Oncol Biol Phys; 88:425-432.			
Chapet O, Decullier E et al (2015). Prostate hypofractionated radiation therapy with injection of hyaluronic acid: Acute toxicities in a phase 2 study. International Journal of Radiation Oncology Biology Physics.91 (4) 730-736	Case series N=36 patients with low-risk to intermediate-risk localised prostate cancer. Injection of 10 ml hyaluronic acid (HA) during hypofractionated intensity modulated radiation therapy (IMRT) (with 20 fractions of 3.1 Gy, up to 62 Gy total dose over 4 weeks) Follow-up 3 months	The HA injection induced a mean pain score of 4.6/10 ± 2.3. 33 patients had at least 1 acute genitourinary toxicity and 20 patients at least 1 acute gastrointestinal toxicity. Grade 2 toxicities were reported for 19 patients with urinary obstruction, frequency, or both and for 1 patient with proctitis. No grade 3 or 4 toxicities were reported. At the 3-month visit, 4 patients described grade 2 obstruction or frequency, and no patients had any grade 2 gastrointestinal toxicities.	Larger studies included.
Chung H, Polf J, Badiyan S, Biagioli M, Fernandez D, Latifi K, et al. Rectal dose to prostate cancer patients treated with proton therapy with or without rectal spacer. J Appl Clin Med Phys. 2017;18(1):32-9.	Comparative study N=20 patients with prostate cancer treated with in silico with pencil beam scanning (PBS) photon therapy (12 with rectal spacer (DuraSealTM gel and 8 without).	Rectal spacers can significantly decrease rectal dose and predicted ≥grade 2 rectal toxicity in prostate cancer patients treated in silico with PBS. A minimum of 9 mm separation between the prostate and anterior rectal wall yields the largest benefit.	Larger studies included.
Cousins MM, Heckman P, Short E et al. (2022) Rectal sparing in prostate radiotherapy with combination-brachytherapy and hydrogel spacer. Brachytherapy.	Retrospective review N=60 patients (30 who had brachytherapy followed by EBRT with hydrogel spacer compared with 30 patients without spacer).	Through effective use of CBT and HS, extreme rectal dose restriction is possible. The goal for HS placement should be thickness >=1 cm from base to apex.	Dosimetry outcomes. Larger studies with longer follow-up included.
Cuccia F, Mazzola R, Nicosia L et al. (2020) Impact of hydrogel peri-rectal spacer insertion on prostate gland intra-fraction motion during 1.5 T MR-guided stereotactic body radiotherapy. Radiation Oncology 15:178.	Case series N= 20 patients who underwent MRI-guided prostate SBRT for low-to-intermediate risk prostate cancer with or without spacer.	A significant difference between spacer and no-spacer patients in terms of rotational shifts in the antero-posterior direction ($p = 0.033$) was observed; also for translational shifts a positive trend was detected in antero-posterior direction ($p = 0.07$), although with no statistical significance. We observed statistically significant differences in the pre-treatment planning phase in favor of the spacer cohort for several rectum dose constraints: rectum V32Gy < 5% ($p = 0.001$), V28 Gy < 10% ($p = 0.001$) and V18Gy < 35% ($p = 0.039$). Also for bladder V35 Gy < 1 cc, the use of spacer provided a dosimetric	Rectal spacer impact on intrafraction prostate motion was assessed.

		advantage compared to the no-spacer subpopulation (p = 0.04). Furthermore, PTV V33.2Gy > 95% was higher in the spacer cohort compared to the no-spacer one (p = 0.036).	
Dihn TK T, Lee HJ, Macomber MW et al. (2020) Rectal hydrogel spacer improves late gastrointestinal toxicity compared to rectal balloon immobilization after proton beam radiation therapy for localized prostate cancer: A retrospective observational study. Int J Radiation Oncol Biol Phys,108 (3), 635-643.	Retrospective review N=267 patients with localized, clinical stage T1-4 prostate adenocarcinoma treated with PBT (with rectal balloon, n=192 versus a hydrogel rectal spacer, n=75). Median follow-up 19-22 months	The 2- year actuarial rate of grade 2+ late rectal bleeding was 19% and 3% in the rectal balloon and hydrogel spacer groups, respectively (P =0.003). In univariable analysis, the probability of grade 2+ rectal bleeding was significantly correlated with increasing rectal dose. In multivariable analysis, only receipt of spacer hydrogel and anticoagulation use were significantly associated with grade 2+ bleeding. At 2-year follow-up, patient-reported EPIC bowel quality of life composite scores were less diminished in the hydrogel spacer group.	Larger studies included.
Drabble J, Drury-Smith H. What is the quality of hydrogel spacer insertions and which patients will benefit. A literature review. J Radiother Pract. 2019;Epub ahead of print doi: http://dx.doi.org/10.1017/S1460396919000979	Systematic review N=26 studies	HS showed a clinically significant relative reduction in rectal planning dose volumes for both high- and low-risk prostate cancer patients in a range of radiotherapy treatment modalities including volumetric modulated arc therapy, intensity-modulated radiotherapy, intensity-modulated proton therapy, stereotactic ablative body radiotherapy and brachytherapy. Spacer placements were successfully inserted in 99% of patients. However, rectal wall infiltration occurrence was 6% and ≥2 cm unsymmetrical placements in 2%. A spacer scoring system based on the HS symmetry has provided evidence of the quality of the position inserted, which was visually aided by T2-wieghted MRIs. Despite optimal HS placements ranging from 62 to 72%, HS had a clinically significant reduction of ≥25% in planned rectal V70 dose in 97% of patients	More comprehensive reviews on hydrogel spacers included.
Eckert F, Alloussi S et al (2013). Prospective evaluation of a	Case series	In 1 patient hydrodissection of the Denonvillier space was not possible. Radiation treatment	Larger and longer follow-up

hydrogel spacer for rectal separation in dose-escalated intensity-modulated radiotherapy for clinically localized prostate cancer. BMC Cancer.13 (no pagination).	n=11 patients with T1-2 N0 M0 localised prostate cancer having dose-escalated IMRT after injection of a hydrogel spacer. 78 Gy in 2 Gy fractions. Follow-up; 12 weeks	planning showed low rectal doses despite dose-escalation to the target. Acute rectal toxicity was mild without grade 2 events and there was complete resolution within 4 to 12 weeks.	studies included.
Forero D, Dendukuri N, Almeida N. Hydrogel spacer to reduce rectal toxicity in prostate cancer radiotherapy: a health technology assessment. (Report No. 82). Montreal (QC): Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC); 2018: https://muhc.ca/sites/default/files/users/user192/SpaceOAR%20Final%20May%2010%202018%20updated%20Dec13.pdf . Accessed 2021 September 21.	Systematic review informing an HTA N=10 studies (852 patients treated with EBRT) Included 1 RCT and 5 non-randomised studies, 1 HTA and 3 economic evaluations. Space OAR versus no spacer prostate cancer treatment: EBRT Follow-up: 3 to 72 months	Spacer OAR, a type of hydrogel spacer, was reported to be significantly associated with lower rectal radiation exposure; nonetheless, authors concluded that it may not contribute to an important reduction in rectal toxicity based on the review of one RCT and three observational studies. Quality of life within the first year of follow-up was not found to be significantly different between Spacer OAR and no spacer and the results of the four primary studies reporting on long-term quality of life were not consistent. Due to the high costs and limited benefits in long-term quality of life, routine use of Spacer OAR at the MUHC for patients with prostate cancer receiving radiotherapy was not recommended by the authors of the systematic review.	More comprehensive and recent reviews added.
Fagundes M, Rodrigues MA, Olszewski S et al. (2021) Expanding the Utilization of Rectal Spacer Hydrogel for Larger Prostate Glands (>80 cc): Feasibility and Dosimetric Outcomes. Advances in Radiation Oncology, 6, 100651	N=33 patients with localised prostate cancer with larger glands (>80 cm3) treated with intensity modulated radiation therapy (in 15) and proton therapy (PT in 18 patients). Conventional fractionation (CF) to 78 Gy in 39 fractions was used in 16 and moderate hypofractionation EBRT (HF) to 70 Gy in 28 fractions in 17 patients. Rectal hydrogel spacers inserted in all. Median follow-up was 10 months (range, 3-26)	In the CF group, mean rectum (r) V75, 70, 60, 50 was 0.87%, 2.25%, 5.61%, and 10.5%, respectively. For glands >80 to 100 cm3 and >100 cm3 , rV70 was 2.55% and 2%, respectively. In HF patients, mean rV65, 63, 60, and 50 was 1.67%, 2.3%, 3.4%, and 8.6%. For glands >80 to 100 cm3 and >100 cm3 , rV63 was 2% and 2.56%, respectively. Overall, the mean mid gland rectoprostatic hydrogel separation was 9.3 mm (range, 4.7-19.4 mm). All patients tolerated treatment well; no acute grade 2 or higher adverse gastrointestinal events were observed	Larger and more relevant studies included.
Farjam R Mahase, SS, Chen SL et al. (2021) Quantifying the impact of SpaceOAR hydrogel	Comparative case series N=20 prostate cancer patients (10 with and 10 without rectal spacer)	Inter-fractional changes in rectal and bladder dose were quantified in patients who underwent SBRT with/without	Dosimetry study. Larger and longer follow-up

on inter-fractional rectal and bladder dose during 0.35 T MR-guided prostate adaptive radiotherapy. Journal of applied clinical medical physics. 22 (9); 49-58	who had SBRT. Compared SBRT plans.	rectal SpaceOAR hydrogel. Rectal spacer does not eliminate the need for adaptive planning but reduces its necessity.	studies included in table 2.
Fischer-Valuck BW, Chundury A et al (2016). Hydrogel spacer distribution within the perirectal space in patients undergoing radiotherapy for prostate cancer: Impact of spacer symmetry on rectal dose reduction and the clinical consequences of hydrogel infiltration into the rectal wall. Practical Radiation Oncology no pagination.	Secondary analysis of a randomised controlled trial. 149 patients in a prospective randomised trial who had transperineal hydrogel spacer (SpaceOAR system) injection were assessed for hydrogel spacer symmetry with rectal dose reduction and rectal wall infiltration using a semi-qualitative scoring system. All patients had control treatment plans created before spacer injection.	Hydrogel spacer was symmetrically placed at midline for 71 (47.7%) patients at the prostate mid-gland as well as 1 cm superior and inferior to mid-gland. The remaining 78 (50.9%) patients had some level of asymmetry, with only 2 (1.3%) having far lateral distribution (i.e., >2 cm) of hydrogel spacer. All but the most asymmetrical 1.3% had significant rectal dose reduction ($P < .05$). Rectal wall hydrogel spacer infiltration was seen in 9 (6.0%) patients. RWI does not correlate with patient complications.	Spacer distribution and impact of spacer symmetry assessed. Included in HTA, systematic review added.
Folkert MR, Zelefsky MJ, Hannan R et al. (2021) A multi-institutional phase 2 trial of high-dose SAbR for prostate cancer using rectal spacer. Int J Radiation Oncol Biol Phys, Vol. 000, No. 00, pp. 1−9.	Prospective study N=44 men with stage ≤T2c localized grade group 1 to 3 prostate cancer underwent perirectal hydrogel spacer placement, followed by SABR of 45 Gy in 5 fractions. Median follow up 48 months.	Temporary hydrogel spacer placement before high-dose SABR treatment for localized prostate cancer and use of strict dose constraints are associated with a significant reduction in the incidence of rectal ulcer events compared with prior phase 1/2 trial results.	Larger studies included.
Fukumitsu N, Mima M, Demizu Y et al. (2022) Separation Effect and Development of Implantation Technique of Hydrogel Spacer for Prostate Cancers. Practical Radiation Oncology. 12 (3), 226-235.	N=160 patients with prostate cancer No spacer (group 1; n = 30), spacer placed using conventional technique-at the middle of the prostate gland (group 2; n = 100), and spacer placed using new technique-cranial:caudal ratio of 6:4 and close to the prostate gland (group 3; n = 30)	The separation, spacer thickness, and rectal exclusion from the middle to the apex of the prostate and the laterality of the hydrogel spacer affected the reduction in the rectal dose. The rectal dose can be further reduced by implanting a spacer on the caudal and prostate side.	Implantation technique and separation effect.
Gez E, Cytron S et al (2013). Application of an interstitial and biodegradable balloon system for prostate-rectum separation during prostate cancer radiotherapy: a prospective multi-	Case series N=27 patients with localised prostate cancer treated with biodegradable balloon implantation during external beam radiotherapy (EBRT). Follow-up 6 months.	The distance between the prostate and rectum increased 10-fold, from a mean 0.22 ± 0.2 cm to 2.47 ± 0.47 cm. Adverse events included mild pain at the perineal skin and in the anus and acute urinary retention. The implantation of the biodegradable balloon was	Larger studies included.

center study. Radiation Oncology 2013, 8:96.		safe and achieved a significant and constant gap between the prostate and rectum. This separation resulted in an important reduction in the rectal radiation dose.	
Gross A, Yuan J, Spratt D et al (2021) Case Report: Role of an Iodinated Rectal Hydrogel Spacer, SpaceOAR Vu eTM, in the Context of Low-Dose-Rate Prostate Brachytherapy, for Enhanced Post-Operative Contouring to Aid in Accurate Implant Evaluation and Dosimetry Frontiers in Oncology; 11; 810955.	Case series. N=13 patients with prostate cancer (low/ intermediate/high risk) treated with LDR brachytherapy/boost and iodinated hydrogel spacer (SpaceOAR VueTM). Follow-up 3 months.	The mean separation between the prostate and the rectum was 12.2 ± 2.1 mm. A favourable dose coverage was achieved in all. At 1-month follow-up, 54% of the patients experienced grade 2 urinary toxicity, and 46% had grade 0–1 urinary toxicity (urgency and frequency). There was a mean increase of 4.3 points on the International Prostate Symptom Score (IPSS) from baseline. At 3 months, 38.5% maintained grade 2 urinary toxicity, and reported a mean decrease of 4 points in IPSS compared to baseline. At 1-month follow-up, 92% reported no rectal toxicities, with only one patient experiencing grade 1 mild diarrhoea. No rectal toxicities were reported at 3 months.	Larger and longer follow-up studies included.
Giuliani J Fiorica, F (2021) Cost-effectiveness of SpaceOAR system during prostate cancer radiation therapy: Really helpful or excess of expectations?. Brachytherapy. 20 (6); 1341-1342.			Costs not in remit.
Jones S White N, Holt, T et al. (2021) Cost-effectiveness analysis of hydrogel spacer for rectal toxicity reduction in prostate external beam radiotherapy. Journal of medical imaging and radiation oncology. 65 (7); 931-939		The influence of parameter uncertainty currently limits the cost-effectiveness of this intervention in the Australian public health setting. However, a cost variation solution has been demonstrated to improve cost-effectiveness estimates for selected patients and should be examined further.	Costs not in remit.
Guimas V, Quivrin M, Bertaut A et al (2016). Focal or whole-gland salvage prostate brachytherapy with iodine seeds with or without a rectal spacer for postradiotherapy local failure: How best	Retrospective non-randomised comparative study n=18 Intervention: salvage prostate permanent implant (sPPI) with (125) I seed for local failure	The median cumulative dose after EBRT + sPPI was higher in patients treated with whole-gland sPPI than in patients treated with focal sPPI (313.5 Gy2 vs. 174.4 Gy2; p = 0.06 and 258.1 Gy3 vs. 172.6 Gy3; p < 0.01, respectively). The median D0.1cc was	Larger studies included.

to spare the rectum? Brachytherapy 15 (4) 406-411.	after external beam radiation therapy. (10 patients had whole-prostate sPPI, and 8 patients had focal sPPI). In 8 patients, hyaluronic acid (HA) gel was injected into the prostate-rectum space.	significantly lower in patients who had HA gel: 63.3 Gy (29.0-78.3) vs. 83.9 Gy (34.9-180.0) (p = 0.04).Cumulative prostate and rectum biological effective doses were lower with focal sPPI.	
Hamstra DA, Mariados N, Sylvester J, Shah D, Karsh L, Hudes R, et al. Continued benefit to rectal separation for prostate radiation therapy: final results of a phase III trial. Int J Radiat Oncol Biol Phys. 2017;97(5):976-85.	Randomised controlled trial N=222 men with low-risk or intermediate-risk prostate cancer Randomised 2:1 to spacer hydrogel (n=149) or control (n=73). Radiation treatment received: G-IMRT 79.2 Gy in 1.8-Gy fractions Follow-up 3 years	The 3-year incidence of grade >1 (9.2% vs 2.0%; P=.028) and grade >2 (5.7% vs 0%; P=.012) rectal toxicity favoured the spacer arm. Grade >1 urinary incontinence was also lower in the spacer arm (15% vs 4%; P=.046), with no difference in grade >2 urinary toxicity (7% vs 7%; P=0.7). From 6 months onward, bowel QOL consistently favoured the spacer group (P=.002), with the difference at 3 years (5.8 points; P<0.05) meeting the threshold for a MID. The control group had a 3.9-point greater decline in urinary QOL compared with the spacer group at 3 years (P<0.05) but the difference did not meet the MID threshold. At 3 years, more men in the control group than in the spacer group had experienced a MID decline in bowel QOL (41% vs 14%; P=.002) and urinary QOL (30% vs 17%; P=.04). Furthermore, the control group were also more likely to have experienced large declines (twice the MID) in bowel QOL (21% vs 5%; P=.02) and urinary QOL (23% vs 8%; P=.02).	Included in HTAs, systematic reviews added.
Hamstra DA, Mariados N, Sylvester J, et al. Sexual quality of life following prostate intensity modulated radiation therapy (IMRT) with a rectal/prostate spacer: secondary analysis of a phase 3 trial. Pract Radiat Oncol. 2018;8(1):e7-e15.	Randomised controlled trial N=222 men with low-risk or intermediate-risk prostate cancer Randomised 2:1 to spacer hydrogel (n=149) or control (n=73). Radiation treatment received: G-IMRT 79.2 Gy in 1.8-Gy fractions Sexual quality of life measured by the	Hydrogel reduced penile bulb mean dose, maximum dose, and percentage of penile bulb receiving 10 to 30 Gy (all P < .05) with mean dose indirectly correlated with erections sufficient for intercourse at 15 months (= 0.03). Statistically nonsignificant differences favouring spacer for the proportion of men with MID and 2× MID declines in sexual QoL with 53% vs 75% having an 11-point decline (p=0.064) and 41% vs 60% with a 22-point decline (p=0.11). At 3	Included in HTAs, systematic reviews added.

	Expanded Prostate Cancer Index Composite (EPIC). Median follow-up of 37 months.	years, more men potent at baseline and treated with spacer had "erections sufficient for intercourse" (control 37.5% vs spacer 66.7%, p=0.046) as well as statistically higher scores on 7 of 13 items in the sexual domain (all p<0.05). The use of a hydrogel spacer decreased dose to the penile bulb, which was associated with improved erectile function compared with the control group based on patient-reported sexual QoL.	
Hatiboglu G, Pinkawa M et al (2012). Application technique: Placement of a prostate-rectum spacer in men undergoing prostate radiation therapy. BJU International 110:E647-E652.	Case series n=29 patients with prostate cancer Hydrogel injected during radiotherapy	Hydrogel injection resulted in mean (SD) additional prostate – rectum space relative to baseline of 9.87 (5.92) mm. The mean (SD) procedure time was 6.3 (3.2) min. The relative reduction in rectal V70 Gy was 60.6%. There were no unanticipated adverse events.	Larger and longer follow-up studies included.
Hayes, Inc. Absorbable perirectal spacer (SpaceOAR System; Augmenix Inc.) during radiation therapy for prostate cancer. Heath Technology Assessment. HAYES, Inc. 2018.	Heath Technology Assessment		More recent HTAs added.
Fagundes MA, Robison B, Price SG et al. (2015) High-dose rectal sparing with transperineal injection of hydrogel spacer in intensity modulated proton therapy for localized prostate cancer. International Journal of Radiation Oncology Biology Physics.1: E230.	N=10 patients with localized prostate cancer treated with intensity modulated proton therapy and transperineal rectal hydrogel spacer. pre- and post-spacer scans were assessed.	The use of a rectal spacer significantly reduced the amount of rectal volume exposed to high doses of radiation in patients planned with intensity modulated proton therapy. The rectal dose-sparing benefit was achieved without compromising target coverage or bladder dose sparing.	Larger and longer follow-up studies included. Dosimetry study.
Harvey M, Ong WL, Chao M et al. (2022) Comprehensive review of the use of **hydrogel spacer**s prior to radiation therapy for prostate cancer. BJU International.	Review	Hydrogel spacers provide a low-morbidity method to potential reduce rectal toxicity after radiation therapy in men with prostate cancer. Data outlining sexual function and oncological outcomes are limited to date. Future studies, currently being conducted, may provide further clarification of the role of	Review

		hydrogel spacers in prostate cancer management.	
Hedrick SG, Fagundes M, Case S et al. (2017) Validation of rectal sparing throughout the course of proton therapy treatment in prostate cancer patients treated with SpaceOAR((R)). J Appl Clin Med Phys, 18, 82-89.	Case series N=41 patients with low/intermediate prostate cancer Image-guided proton therapy Conventional fractionation (n=27) Hypofractionation (n=14) Follow-up 5 weeks	By extrapolating patient anatomy from 3-4 QACT scans, we have shown that the use of hydrogel in conjunction with our patient diet program and use of stool softeners is effective in achieving consistent rectal sparing in patients undergoing proton therapy. Toxicity not reported.	Larger studies included.
Hedrick SG, Fagundes M, Robison B, et al. A comparison between hydrogel spacer and endorectal balloon: an analysis of intrafraction prostate motion during proton therapy. J Appl Clin Med Phys. 2017;18(2):106-112.	Prospective cohort study N=26 patients with prostate cancer treated with proton therapy and an endorectal balloon (n=10) or a hydrogel spacer (n=16) using orthogonal x-rays acquired before and after each treatment field. Patients from 2 different trials included. Follow-up time not reported.	There was a statistically significant difference in the mean vector shift between ERB (0.06 cm) and GEL (0.09 cm), (p<0.001). There was no statistical difference between ERB and GEL for shifts greater than 0.3 cm (p=0.13) or greater than 0.5 cm (p=0.36). Prostate motion is clinically comparable between an ERB and a hydrogel spacer, and the time dependencies are similar.	Included in HTA report.
Hojjat F, Fritsche-Polanz S et al (2016). Goldmarker and spacer balloon implantation for prostate radiation therapy (RT). European Urology, Supplements (15) 11 e1353-e1355.	Case series n=40 patients with localized prostate cancer. Gold marker and bio-protect-balloon-implanted transperineally during image-guided volumetric arc therapy (VMAT).	Median distance of 1.6 cm between the prostate and the anterior wall of the rectum was obtained. Localisation of the balloon was achieved in 33/40 patients. Implantation well tolerated, no intestinal bleeding, no mucosal injury and no postoperative infection have been observed. Mild perineal foreign body sensation was present, only 2/40 patients reported on moderate symptoms. Acute GI and GU toxicity were very favourable and assessed using the RTOG scale system. In 66% of patients no GI-side effect was seen, while 28% and 6% had grade 1 and 2 toxicity, respectively. GU-symptoms grade 1 were about 66% and 3% grade 2, whereas 31% had no adverse effect. For both, GI and GU, grade 3-5 toxicity was not observed.	Larger studies included.
Hoe V, Yao HH, Huang JG et al. Abscess formation following hydrogel spacer for prostate cancer	Case report Patient with hydrogel spacer during prostate cancer radiotherapy.	Periprostatic abscess is a rare complication of hydrogel spacers in radiotherapy for prostate cancer. We present the case of a 61-year-old man	Adverse event already reported in included studies.

radiotherapy: a rare complication. BMJ Case Rep. 2019 Oct 5;12(10). pii: e229143. doi: 10.1136/bcr-2018-229143		who developed this condition. Abdominopelvis CT scan revealed a 54×35×75 mm collection in the location of the SpaceOAR, for which ultrasound-guided transperineal percutaneous drainage of the periprostatic abscess was performed. The patient remains well with serial CT scans showing near resolution of the collection.	
Hong A, Ischia J, Chao M. (2022) Case Report: Reversal of Hyaluronic Acid Rectal Wall Infiltration with Hyaluronidase. Frontiers in Oncology; 12; 870388	Case report patient with prostate cancer undergoing radiation therapy and rectal spacer insertion (hyaluronic acid gel injected).	The patient was asymptomatic, and a sigmoidoscopy confirmed healthy bowel mucosa. The misinjected hyaluronic acid was successfully treated with targeted injection of hyaluronidase into the rectal wall portion. Follow-up imaging demonstrated rapid dissolution of the hyaluronic acid. no side effects noted.	Larger studies with longer follow-up included.
Hwang ME, Black PJ, Elliston CD, Wolthuis BA, Smith DR, Wu CC, et al. A novel model to correlate hydrogel spacer placement, perirectal space creation, and rectum dosimetry in prostate stereotactic body radiotherapy. Radiation Oncology. 2018;13 (1) (no pagination)(192).	Case series (retrospective) N=20 men with low- and intermediate-risk prostate cancer treated with stereotactic body radiotherapy to 36.25 Gy in 5 fractions underwent hydrogel (SpaceOAR) placement. Median follow up of 14 months	no rectal toxicity >grade 2 was observed. Low grade rectal toxicity was observed in a third of men and resolved. Optimal hydrogel placement occurs at prostate midgland, midline. The novel parameter θ*hydrogel volume describes a large proportion of rectum dosimetric benefit derived from hydrogel placement and can be used to assess the learning curve phenomenon for hydrogel placement.	Larger studies included. analysed the symmetry of hydrogel placement, developed new metric to correlate the effect of hydrogel placement on rectum dosimetry.
Hwang ME, Mayeda M, Liz M, Goode-Marshall B, Gonzalez L, Elliston CD, et al. Stereotactic body radiotherapy with periprostatic hydrogel spacer for localized prostate cancer: Toxicity profile and early oncologic outcomes. Radiation Oncology. 2019;14 (1) (no pagination)(136).	Case series N=50 men with low- or intermediate-risk prostate cancer treated with SBRT (3625 cGy in 5 fractions) with or without androgen deprivation therapy (ADT) also had periprostatic hydrogel spacer (SpaceOAR). Median follow up 20 (range 4–44) months.	Mean prostate-rectum separation achieved with SpaceOAR was 9.6±4 mm at the prostate midgland. No grade ≥ 3 GU or GI toxicity was recorded. During treatment, 30% of men developed new grade 2 GU toxicity (urgency or dysuria). GI toxicity was limited to grade 1 symptoms (16%), 4% of men developed grade 2 symptoms during the first 4 weeks after SBRT. No acute or late rectal toxicity was reported > 1 month after treatment. Periprostatic hydrogel placement followed by prostate SBRT resulted in minimal GI toxicity, and	Larger studies included.

		favourable early oncologic outcomes.	
Hwang ME, Mayeda M, Shaish H, et al. (2021) Dosimetric feasibility of neurovascular bundle-sparing stereotactic body radiotherapy with periprostatic hydrogel spacer for localized prostate cancer to preserve erectile function. Br J Radiol; 94: 20200433.	Case series N= 35 men with low- and intermediate risk prostate cancer underwent rectal hydrogel spacer placement and treated with prostate SBRT (36.25 Gy in 5 fractions).	Neurovascular bundle (NVB) sparing SBRT with rectal hydrogel spacer significantly reduces the volume of NVB treated with high-dose radiation. Rectal spacer contributes to this effect through a dosimetrically meaningful displacement of the NVB.	Nerve sparing treatment planning.
Hutchinson RC, Sundaram V, Folkert M, and Lotan Y (2016). Decision analysis model evaluating the cost of a temporary hydrogel rectal spacer before prostate radiation therapy to reduce the incidence of rectal complications. Urologic Oncology 34 (7) 291-26.	Decision analysis to evaluate the cost effectiveness of a rectal spacer gel (SpaceOAR) for the reduction of rectal toxicity of prostate radiation therapy (RT).	The overall standard management cost for RT was \$3,428 vs. \$3,946 with rectal spacer for an incremental cost of \$518 over 10 years. A 1-way sensitivity analyses showed the breakeven cost of spacer at \$2,332 or a breakeven overall risk reduction of 86% at a cost of \$2,850. For high-dose SBRT, spacer was immediately cost effective with a savings of \$2,640 and breakeven risk reduction at 36%. The use of a rectal spacer for conformal RT results in a marginal cost increase with a significant reduction in rectal toxicity assuming recently published 15 month rectal toxicity reduction is maintained over 10 years. For high-dose SBRT it was cost effective.	Costs not in remit of interventional procedures programme.
Jones RT, Hassan Rezaeian N, Desai NB, et al. (2017) Dosimetric comparison of rectal-sparing capabilities of rectal balloon vs injectable spacer gel in stereotactic body radiation therapy for prostate cancer: lessons learned from prospective trials. Med Dosim. 42(4):341-347.	Prospective cohort study N=72 patients with low- to intermediate risk prostate cancer treated with stereotactic body radiation therapy in combination with rectal balloons (n=36) or absorbable injectable spacer gel (n=36). Patients from 2 different trials included. Follow-up time not reported.	injectable spacer gel was superior based on the maximum dose to the rectum (42.3 vs 46.2 Gy, p<0.001), dose delivered to 33% of the rectal circumference (28 vs 35.1 Gy, p<0.001), and absolute volume of rectum receiving 45 Gy (V45Gy), V40Gy, and V30Gy (0.3 vs 1.7 cc, 1 vs 5.4 cc, and 4.1 vs 9.6 cc, respectively; p<0.001 in all cases). There was no difference between the 2 groups with respect to the V50Gy of the rectum or the dose to 50% of the rectal circumference (p=0.29 and 0.06, respectively). The V18.3Gy of the bladder was significantly larger with the rectal balloon (19.9 vs 14.5 cc,	Included in HTA report added. Dosimetric and volumetric outcomes, comparative costs of balloons and gel out of remit.

		p=0.003). Injectable spacer gel outperformed the rectal balloon in the majority of the examined and relevant dosimetric rectal-sparing parameters.	
Karsh LI, Gross ET, Pieczonka CM, et al. Absorbable hydrogel spacer use in prostate radiotherapy: a comprehensive review of phase 3 clinical trial published data. Urology. 2018;115:39-44.	Randomised controlled trial N=222 men with low-risk or intermediate-risk prostate cancer Randomised 2:1 to spacer hydrogel (n=149) or control (n=73). Radiation treatment received: G-IMRT 79.2 Gy in 1.8-Gy fractions Rectal and urinary adverse events and quality of life measured with the EPIC questionnaire. Median follow-up of 37 months	Spacer application was well tolerated with a 99% technical success rate. The mean additional space created between the prostate and the rectum was just over 1 cm, which allowed significant rectum and penile bulb radiation dose reduction, resulting in less acute pain, lower rates of late rectal toxicity, and improved bowel and urinary QoL scores from 6 months onward. Improvements in sexual QoL were also observed at 37 months in baseline-potent men, with 37.5% of control and 66.7% of spacer men capable of “erections sufficient for intercourse.”	Study included in HTAs added.
Kamran SC; McClatchy DM, Pursley J et al. (2022) Characterization of an Iodinated Rectal Spacer for Prostate Photon and Proton Radiation Therapy. Practical radiation oncology; 12 (2); 135-144	Retrospective study N=100 patients with intact prostate cancer treated with photon and proton radiation therapy (n = 50 with iodine spacers and 50 with conventional spacers)	Iodine spacers provide a manifest CT contrast, allowing for delineation on planning CT alone with no MRI necessary. Iodine spacers radiopacity, size, and relative position remained stable over courses of treatment from 28 to 44 fractions. No changes in plan quality or robustness were seen comparing iodine spacers and conventional spacers.	Description of spacers, no clinical outcomes reported.
Khan J, Dahman B, McLaughlin C et al. (2020) Rectal spacing, prostate coverage, and periprocedural outcomes after hydrogel spacer injection during low-dose-rate brachytherapy implantation. Brachytherapy 19 228e233	Case series N= 80 patients with prostate cancer treated with low-dose-rate (LDR) prostate brachytherapy. 40 had bioabsorbable hydrogel rectal spacer injected. Follow-up 1 month.	There were no acute genitourinary or rectal toxicities attributed to the hydrogel spacer. Comparing patients with and without hydrogel, the mean separation between the prostate and rectum was 13.9±5.2 mm vs. 6.5±5.0 mm ($p<0.0001$), respectively. The adjusted mean dose to 1 cc, 2 cc, and 5 cc of the rectum relative to prescription dose was decreased by 32% ($p<0.01$), 26% ($p<0.01$), and 17% ($p< 0.01$), respectively. There were no statistically significant differences in prostate coverage: mean V100 (92% vs. 91%), V150 (45% vs.	Larger studies included.

		48%), and D90 (106% vs. 106%), respectively. At 1 month follow-up, grade 1 rectal toxicity was 12.5% vs. 17.5% (p 5 0.35). No patients developed Grade 2 rectal toxicity with hydrogel, although one did without.	
King RB, Osman SO, Fairmichael C, Irvine DM, Lyons CA, Ravi A, et al. Efficacy of a rectal spacer with prostate SABR-first UK experience. Br J Radiol. 2018;91(1083):20170672	Case series N=6 patients with prostate cancer treated with SABR -VMAT and rectal hydrogel spacer (SpaceOAR)	Substantial improvements in rectal dose metrics were observed in post-spacer plans, e.g. rectal volume receiving 36 Gy reduced by ≥42% for all patients. Median NTCP for Grade 2 + rectal bleeding significantly decreased from 4.9 to 0.8% with the use of a rectal spacer (p=0.031). The spacer resulted in clinically and statistically significant reduction in rectal doses for all patients.	Larger studies included.
Kouloulias V, Kalogeropoulos T et al (2013). Feasibility and radiation induced toxicity regarding the first application of transperineal implementation of biocompatible balloon for high dose radiotherapy in patients with prostate carcinoma. Radiation Oncology.8 (1) (no pagination).	Case series n=15 patients with prostate carcinoma treated with high dose external 3DCRT (76-78 Gy in 38-39 daily fractions) combined with injection of biodegradable balloon (ProSpace) Follow-up: 3 months	The acute toxicities were as follows: grade 1 GI toxicity in 2 patients and GU toxicity -3 patients with grade 1 nocturia, 4 patients with grade 1 frequency, 2 patients with grade 1 and 2 patients with grade 2 dysuria. The mean score of rectal toxicity according to S-RS score was 1.8 ±0.6. The mean VAS score related to ProSpace was 1.4±0.5. Erectile dysfunction was unchanged. The ProSpace was found stable in sequential CT scans during irradiation.	Larger and longer follow-up studies included.
Kobayashi H, Eriguchi T, Tanaka T et al. (2021) Distribution analysis of hydrogel spacer and evaluation of rectal dose reduction in Japanese prostate cancer patients undergoing stereotactic body radiation therapy. International Journal of Clinical Oncology. 26:736–743.	Retrospective analysis 70 patients with low and intermediate-risk prostate cancer treated with SBRT. Hydrogel spacers were inserted in 53 patients. Follow-up 6 months.	Hydrogel spacers could contribute to rectal dose reduction, especially in high dose regions, by creating a prostate–rectum distance. There was no grade≥3 toxicity observed, but grade 2 toxicity of GU and GI occurred in 17.1% and 1.4% of the patients, respectively.	Larger studies included.
Kundu P, Lin EY, Yoon SM (2022) Rectal Radiation Dose and Clinical Outcomes in Prostate Cancer Patients Treated With Stereotactic Body	Retrospective case series 92 patients with prostate cancer treated with SBRT (51 hydrogel and 41 without hydrogel)	Hydrogel reduces rectal radiation dose in patients receiving prostate SBRT and is associated with a decreased rate of acute GI toxicity. hydrogel group experienced significantly less acute overall	Larger studies with longer follow-up included.

Radiation Therapy With and Without Hydrogel. Frontiers in Oncology. 12; 853246	Median follow-up of 14.8 months.	GI toxicity (16% hydrogel vs. 28% non-hydrogel, p=0.006), while the difference in late GI toxicity trended lower with hydrogel but was not statistically significant (4% hydrogel vs. 10% non-hydrogel, p=0.219).	
Juneja P, Kneebone A (2015). Prostate motion during radiotherapy of prostate cancer patients with and without application of a hydrogel spacer: a comparative study. Radiation Oncology 10: 215.	Prospective cohort study (data from 2 clinical trials) n=26 patients with prostate cancer treated with radiotherapy (12 with hydrogel and 14 without hydrogel). Type of radiotherapy not specified. Follow-up time not reported.	The average of the mean motion during the treatment for patients with and without hydrogel was 1.5 (+/-0.8 mm) and 1.1 (+/-0.9 mm) respectively (p<0.05). The average time of motion >3 mm for patients with and without hydrogel was 7.7 % (+/-1.1 %) and 4.5 % (+/-0.9 %) respectively (p>0.05). The hydrogel age, fraction number and treatment time were found to have no effect (R (2) <0.05) on the prostate motion. This result confirms that the addition of a spacer does not negate the need for intrafraction motion management if clinically indicated.	Study evaluating prostate position. Included in HTA added.
Lawrie TA, Green JT, Beresford M, Wedlake L, Burden S, Davidson SE, Lal S, Henson CC, Andreyev HJN. Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy for primary pelvic cancers. Cochrane Database of Systematic Reviews 2018, Issue 1. Art. No.: CD012529. DOI: 10.1002/14651858.CD012529.pub2.	Cochrane review N=92 studies (RCTs) included. (0nly 2 studies were related to this overview). n= 229 and 69 men undergoing RT for prostate cancer. transperitoneal hydrogel spacer/injection versus no spacer Prostate cancer treatment: all types of pelvic radiation therapy eligible; IG-IMRT (79.2 Gy in 1.8-Gy fractions) in Mariados 2015 and brachytherapy in Prada 2009. Follow-up: up to 15 months in Mariados 2015 and a median of 26 months in Prada 2009.	“IMRT may be better than 3DCRT in terms of GI toxicity, but the evidence to support this is uncertain”. “Low-certainty evidence on balloon and hydrogel spacers suggests that these interventions for prostate cancer RT may make little or no difference to GI outcomes”.	Only 2 of these studies were eligible for analysis within this review. More comprehensive reviews added.
Haute Autorite de Sante. SpaceOAR, espaceur synthétique résorbable en hydrogel.: HAS; 2020.			French article
Kong VC, Dang J, Li W et al. (2022) Dosimetric	Retrospective comparative study N=25	Despite the presence of large interfraction organ volumes	Dosimetric study.

comparison of MR-guided adaptive IMRT versus 3DOF-VMAT for prostate stereotactic radiotherapy. Technical Innovations and Patient Support in Radiation Oncology; 21; 64-70.	patients with prostate cancer treated with High Dose Rate (HDR) brachytherapy followed by SBRT (15 with hydrogel spacer).	changes, clinically acceptable dose was delivered to the prostate by both systems. A-IMRT facilitated a greater rectal sparing from the high dose region than 3DOF-VMAT. Further reduction in rectal dose could be achieved by hydrogel spacer to displace the rectum, or by adaptation delivered by VMAT.	
Lehrich BM, Moyses HM, Ravera J et al. (2019) Five-year results of post-prostatectomy patients administered a hydrogel rectal spacer implant in conjunction with dose escalated external beam radiation therapy. Journal of Radiation Oncology (2019) 8:31–38.	Case series N= 21 patients who underwent radical prostatectomy and received high dose (> 72 Gy) radiation therapy with an absorbable polyethylene glycol (PEG) rectal spacer implant. Mean follow-up time was 59 months (SD 12, range 40–97).	Gastrointestinal [GI] toxicities for acute, 3 months, and after 6 months are as follows: grade 0 (57%, 86%, 86%), grade 1 (43%, 14%, 14%), and grade 2 (0%, 0%, 5%). Our genitourinary [GU] toxicities for acute, 3 months, and after 6 months are as follows: grade 0 (43%, 48%, 62%), grade 1 (48%, 43%, 24%), and grade 2 (10%, 5%, 14%). There were no late grade 3 GI/GU toxicities. The 5-year overall biochemical-relapse free survival rate was 62.2% (95% CI 42.6–90.9%, SE 12.0%).	Large studies included.
Lin YH, Loon W, Tacey M et al. (2021) Impact of hydrogel and hyaluronic acid rectal spacer on rectal dosimetry and toxicity in low-dose-rate prostate brachytherapy: a multi-institutional analysis of patients' outcomes. Journal of Contemporary Brachytherapy. 13 (6); 605-614	Retrospective comparative case series N=70 men with prostate cancer treated with iodine-125 LDR brachytherapy (28 with or 42 without hydrogel spacer or hyaluronic acid spacer). Median follow-up was 23.5 months.	The median prostate-rectal separation with spacer at mid prostate was 10 mm (IQR, 8-11.5 mm). There were no post-operative complications. There was significantly reduced rectal dosimetry in spacer-group versus non-spacer group; the median RV100 was 0.0 cc (IQR, 0.0-0.0 cc) vs. 0.4 cc (IQR, 0.1-1.1 cc) (p < 0.001), respectively. There were significantly less grade 1 acute and late GI toxicities in spacer-group when compared to non-spacer group (0% vs. 24%, p=0.004 for acute GI toxicity; 4% vs. 33%, p=0.003 for late GI toxicity). There were no reported acute or late grade 2 or above GI toxicities.	Similar studies included.
Latorzeff I, Bruguiere E, Bogart E et al. (2021) Use of a Biodegradable, Contrast-Filled Rectal Spacer Balloon in Intensity-Modulated Radiotherapy for Intermediate-Risk Prostate Cancer Patients: Dosimetric	Prospective case series n=24 patients with intermediate-risk prostate cancer had mage-guided, IMRT(in 20) or VMAT (in 3) with a biodegradable rectal spacer balloon. Follow-up 24 months.	86% of the implantation procedures were easy. Dosimetric gains associated with spacer implantation were highly significant (p<0.001). For the rectum, the median relative gain was 15.4% for D20cc to 91.4% for V70 Gy (%). 15 patients (62%) experienced an acute grade 1 adverse event (AE), 8 (33%)	Similar studies on balloon spacers included.

Gains in the BioPro-RCMI-1505 Study Frontiers in Oncology; 11; 701998		experienced a late grade 1 AE, 1 (4.2%) experienced an acute grade 2 AE, and 3 experienced a late grade 2 AE. No grade 3 AEs were reported. Quality of life was good at baseline) and did not worsen during RT and up to 24 months.	
Levy Y, Paz A et al (2009). Biodegradable inflatable balloon for reducing radiation adverse effects in prostate cancer. J Biomed Mater Res B Appl Biomater 91: 855-867.		The proper functionality of the insertion-mounting device as well as the balloon capability to retain its inflated form during patients' radiation session was demonstrated both in vitro and in vivo.	Preclinical study with in-vitro and in-vivo data.
Levy JF, Khairnar R, Louie AV et al. (2019) Evaluating the Cost-Effectiveness of Hydrogel Rectal Spacer in Prostate Cancer Radiation Therapy. Practical Radiation Oncology (2019) 9, e172-e179	Cost effectiveness analysis patients with prostate cancer undergoing external beam RT (EBRT alone versus EBRT + hydrogel rectal spacer [HRS]).	The per-patient 5-year incremental cost for spacers administered in a hospital outpatient setting was $3578, and the incremental effectiveness was 0.0371 QALYs. The incremental cost-effectiveness ratio was $96,440/QALY for patients undergoing HRS insertion in a hospital and $39,286/QALY for patients undergoing HRS insertion in an ambulatory facility. Based on the current Medicare Physician Fee Schedule, HRS is cost-effective at a willingness to pay threshold of $100,000. These results contain uncertainty, suggesting more evidence is needed.	Costs not in remit of interventional procedures programme.
Liu H, Borden L, Wiant D, Sintay B, Hayes L, Manning M. Proposed hydrogel-implant quality score and a matched-pair study for prostate radiation therapy. Pract Radiat Oncol. 2020;10(3):202-208. doi: http://dx.doi.org/10.1016/j.prro.2020.02.006	Matched paired study (retrospective) LDR BT +/- EBRT N= 81 patients with prostate cancer had SpaceOAR implantation 21 had EBRT only, 7 had combined EBRT and Iodine-125 LDR, and 53 had Iodine-125 LDR only.	The average HIQS was 77 ± 10.8 (range, 49-97). Rectal anatomic distortions were seen in 17 cases. Significant rectal dose reductions between intraoperative and postoperative plans were found for SpaceOAR patients compared with non-SpaceOAR patients (25.1 Gy vs -5.0 Gy for D2cc and 65.7 Gy vs 13.0 for D0.1cc). Additional rectal dose reductions (8.4 Gy for D2cc and 12.7 Gy for D0.1cc) were found for patients without rectal distortion when SpaceOAR was used.	Included in systematic review.

Mahal BA, Ziehr DR, Hyatt AS et al. (2014) Use of a rectal spacer with low-dose-rate brachytherapy for treatment of prostate cancer in previously irradiated patients: Initial experience and short-term results. Brachytherapy, 13, 442-9.	Case series N=11 patients with prostate cancer and prior radiotherapy received (125)I brachytherapy after placement of 10cc of a diluted hydrogel spacer between the prostate and rectum. Follow-up median 15.7 months	Spacing was achieved in 8 of the 11 (73%) patients but was not possible in 3 owing to fibrosis and adhesions. The median space between the prostate and rectum was 10.9mm (prior EBRT) vs. 7.7mm (prior brachytherapy), p=0.048. One patient developed a prostato-rectal fistula requiring a diverting colostomy. The 16-month estimate of late Grade 3 or 4 gastrointestinal or genitourinary toxicity was 26%. One patient developed lymph node-positive recurrence. The 16-month prostate-specific antigen failure-free survival rate was 89%.	Included in systematic review added.
Mazzola R, Sicignano G, Cuccia F et al. (2021) Impact of hydrogel peri-rectal spacer insertion on seminal vesicles intrafraction motion during 1.5 T-MRI-guided adaptive stereotactic body radiotherapy for localized prostate cancer. The British journal of radiology; 94 (1126); 20210521	Comparative case series n=10 patients with prostate cancer had MRI guided SBRT (5 had hydrogel spacer and 5 did not).	A favourable impact of the hydrogel-spacer on seminal vesicles motion was observed only in cranio-caudal translational shifts, although not clinically significant. Further studies are required to fully investigate the potential contribution of this device on vesicles motion.	Intrafraction motion assessed.
Mark EH, Paul JB, Carl DE et al. (2018) A novel model to correlate hydrogel spacer placement, perirectal space creation, and rectum dosimetry in prostate stereotactic body radiotherapy. Radiation oncology (London, England), 13, 192.	Case series N= 20 men with low- and intermediate-risk prostate cancer underwent hydrogel placement. Median follow up of 14 months	no rectal toxicity >grade 2 was observed. Low grade rectal toxicity was observed in a third of men and resolved within 1 month of SBRT. Men who had these symptoms had higher rD_{max} 1 cc and smaller θ*hydrogel volume measurements	Larger studies included.
Mariados N, Sylvester J, Shah D, Karsh L, Hudes R, Beyer D, et al. Hydrogel spacer prospective multicenter randomized controlled pivotal trial: dosimetric and clinical effects of perirectal spacer application in men undergoing prostate image guided intensity	Randomised controlled trial N=222 men with low-risk or intermediate-risk prostate cancer Randomised 2:1 to spacer hydrogel (n=149) or control (n=73).	Spacer application was rated as “easy” or “very easy” 98.7% of the time, with a 99% hydrogel placement success rate. Perirectal spaces were 12.6 ± 3.9 mm and 1.6 ± 2.0 mm in the spacer and control groups, respectively. There were no device-related adverse events, rectal perforations, serious bleeding, or infections within either	Included in HTAs and systematic reviews added.

modulated radiation therapy. Int J Radiat Oncol Biol Phys. 2015;92(5):971-7.	Radiation treatment received: G-IMRT 79.2 Gy in 1.8-Gy fractions Follow-up 15 months.	group. Pre-to postspacer plans had a significant reduction in mean rectal V70 (12.4% to 3.3%, p<0.001). Overall acute rectal adverse event rates were similar between groups, with fewer spacer patients experiencing rectal pain (PZ.02). A significant reduction in late (3-15 months) rectal toxicity severity in the spacer group was observed (PZ.04), with a 2.0% and 7.0% late rectal toxicity incidence in the spacer and control groups, respectively. There was no late rectal toxicity greater than grade 1 in the spacer group. At 15 months 11.6% and 21.4% of spacer and control patients, respectively, experienced 10-point declines in bowel quality of life. MRI scans at 12 months verified spacer absorption.	
Manabe Y, Hashimoto S, Mukouyama H et al. (2021) Stereotactic body radiotherapy using a hydrogel spacer for localized prostate cancer: A dosimetric comparison between tomotherapy with the newly-developed tumor-tracking system and cyberknife. Journal of applied clinical medical physics. 22 (10); 66-72	Comparative case series N=20 patients with localised prostate cancer using a hydrogel spacer and had SBRT. 10 tomotherapy and 10 cyberknife SBRT plans were compared.	The tomotherapy plans were superior to the cyberknife plans for the rectum (V80% = 0.4 vs. 1.0 ml, p<0.001; D1ml = 26.4 vs. 29.0 Gy, p=0.013). Results suggested that tomotherapy with the tumour-tracking system has reasonable potential for SBRT for localized prostate cancer using a hydrogel spacer.	Dosimetry study. Larger and longer follow-up studies included in table 2.
Mathur M, Asch D & Israel G (2022). Polyethylene glycol-based gels for treatment of prostate cancer: pictorial review of normal placement and complications. *Abdom Radiol*.	Review	Polyethylene Glycol-based gels are the commonly used rectal spacers. Given their widespread use and the relative paucity of radiology literature, radiologist should recognize both the normal and abnormal placement of these polyethylene glycol-based rectal spacers, particularly they may be associated with suboptimal therapy and/or complications.	Review
Morita M, Fukagai T, Hirayama K, Yamatoya J, Noguchi T, Igarashi A, et al. (2019) Placement of SpaceOAR hydrogel spacer for prostate cancer patients treated	Case series N=100 patients with prostate cancer undergoing iodine-125 low-dose-rate brachytherapy and,	No complications were found during either the intraoperative or perioperative periods. The mean displacement distance of 11.64 mm was created, the mean value before spacer placement was 0.28 mm (P < 0.0001). The change of the	Included in systematic review added.

with iodine-125 low-dose-rate brachytherapy. International Journal of Urology. 27, 1, 60-66.	SpaceOAR hydrogel spacer was placed. Post-plan dosimetric data were compared with 200 patients treated without a spacer. Follow-up not reported.	prostate diameters showed a positive increase in all directions, with no significant negative change in any one direction. Regarding the change in distance between pubic symphysis and the prostate, no significant shortening trend was observed between the two groups (p=0.14). Whereas the dosimetric parameters showed means of 0.001 and 0.026 cc for RV150 and RV100 in the spacer group, they were 0.025 and 0.318 cc, respectively, in the non-spacer group, showing a significant decrease in both parameters (p<0.001).	
Melchert C, Gez E et al (2013). Interstitial biodegradable balloon for reduced rectal dose during prostate radiotherapy: results of a virtual planning investigation based on the pre and post-implant imaging data of an international multicenter study. Radiother Oncolo 106:210-214.	Case series n=26 patients with localized prostate cancer Interstitial inflatable and biodegradable balloon with radiotherapy (3D conformal external beam radiation treatment or IMRT). Follow-up; post implant CT imaging.	The dorsal prostate–ventral rectal wall separation resulted in an average reduction of the rectal V70% by 55.3% (±16.8%), V80% by 64.0% (±17.7%), V90% by 72.0% (±17.1%), and V100% by 82.3% (±24.1%). In parallel, rectal D2 ml and D0.1 ml were reduced by 15.8% (±11.4%) and 3.9% (±6.4%) respectively.	Study by same group reporting clinical and dosimetric outcomes included I systematic review added.
Muller AC, Mischinger J et al (2016). Interdisciplinary consensus statement on indication and application of a hydrogel spacer for prostate radiotherapy based on experience in more than 250 patients. Radiology and Oncology (50) 3 329-336.	Interdisciplinary meeting to develop consensus statement on hydrogel injections (SpaceOAR) in prostate cancer patients before dose-escalated radiotherapy.	A consensus was reached on the application of a hydrogel spacer. Current experience demonstrated feasibility, which could promote initiation of this method in more centres to reduce radiation-related gastrointestinal toxicity of dose-escalated IGRT. However, a very low rate of a potential serious adverse event could not be excluded. Therefore, the application should carefully be discussed with the patient and be balanced against potential benefits.	Interdisciplinary meeting to develop consensus statement.
Navaratnam A, Cumsky J, Abdul-Muhsin H et al. Assessment of polyethylene glycol hydrogel spacer and its effect on rectal radiation dose in prostate cancer patients receiving proton beam radiation	Retrospective cohort study N= 72 patients with prostate cancer (T1, T2, T3) EBRT-PBT-total dose 79.2 1.8 Gy per fraction	There was a 42.2% reduction in rectal dosing (mL3 rectum) in hydrogel patients (p<0.001). Increasing midline sagittal lift resulted in a greater mitigation of total rectal dose (p=0.031). The degree of prostate surface area coverage on coronal plane did not correlate with further reductions in rectal	Included in systematic review added.

therapy. Adv Radiat Oncol 2019; 5: 92–100.	51 with hydrogel spacers versus 21 without spacer Dose volume V70, , V75 Follow-up 9.5 months.	radiation dose (p=0.673). Patients who had PEG hydrogels placed reported more rectal side effects during treatment compared with those patients who did not (35.3% vs 9.5%, p =0.061). At median 9.5-month follow-up, there was no difference in reporting of grade >2 rectal toxicity between the 2 groups (7.7% vs 7.1%, p=0.145).	
Nehlsen AD, Sindhu KK, Moshier E et al. (2021). The impact of a rectal hydrogel spacer on dosimetric and toxicity outcomes among patients undergoing combination therapy with external beam radiotherapy and low-dose-rate. brachytherapy. Brachytherapy 20, 296-301.	Retrospective analysis N=168 patients with intermediate or high risk prostate cancer with a hydrogel spacer (n=22) or without a hydrogel spacer (n=146) prior external beam radiotherapy and low-dose-rate brachytherapy. Spacer group follow-up 9 months.	LDR brachytherapy appears feasible after the placement of a rectal hydrogel spacer. While there was a significantly reduced $V100_{rectum}$ among patients who had received a hydrogel spacer, there was no statistically significant difference in patients achieving a $D90_{prostate}$ of >100 Gy. Although there was no difference appreciated in QOL scores, the length of follow-up was limited in the rectal-spacer group.	Larger studies included.
Newman NB, Rajkumar, A, Cleary RK et al. (2021) Patient Reported Quality of Life Outcomes After Definitive Radiation Therapy With Absorbable Spacer Hydrogel for Prostate Cancer. Advances in Radiation Oncology; 6 (6); 100755	Prospective case series N=59 patients with low risk or favourable-intermediate risk localized prostate cancer had SBRT/ LDR brachytherapy, conventionally fractionated RT, or moderately hypofractionated RT with hydrogel spacer. Median follow-up 366 days.	There were no grade 3 toxicities. There were no significant changes in the American urology association symptom index (AUA-SI) score (p=0.69) compared with baseline, nor was there any change in Expanded Prostate Cancer Index Composite (EPIC-26) domain scores (p=0.19). There were no significant associations between AUA scores and EPIC-26 scores and the dose to the rectum, bladder, or urethra with the exception being dose to the 2 mL rectum correlated with decline in EPIC-26 rectal score (beta, -0.002; p=0.006). Patient-reported declines in bowel domains were less than previously reported data.	Larger and longer follow-up studies included.
SpaceOAR® perirectal spacing system for prostate cancer radiation. (December 2014) Technology Alert. National Institute for Health Research (NIHR) Horizon Scanning Centre.	Technology alert	This technology is predicted to have an impact on the following domains of the NHS Outcomes Framework: enhancing quality of life for people with long-term conditions; ensuring that people have a positive experience of care, treating and caring for people in a safe	More comprehensive and recent assessments added.

		environment; and protecting them from avoidable harm. If clinical and cost-effectiveness can be demonstrated, the SpaceOAR® system may offer an additional option for patients requiring prostate cancer radiation therapy.	
Nguyen PL, Devlin PM et al (2013). High-dose-rate brachytherapy for prostate cancer in a previously radiated patient with polyethylene glycol hydrogel spacing to reduce rectal dose: Case report and review of the literature. Brachytherapy.12 (1) 77-83.	Case report n=1 high risk prostate cancer patient previously irradiated. Hydrogel spacer during high dose rate brachytherapy.	The spacer allowed the rectal dose constraint goals to be easily met. Injecting an absorbable polyethylene glycol hydrogel to separate the prostate and rectum appears to be associated with decreased maximum and mean rectal doses and may have particular utility in previously irradiated patients.	Larger and longer follow-up studies included.
Noyes WR, Hosford CC et al (2012). Human collagen injections to reduce rectal dose during radiotherapy. International Journal of Radiation Oncology Biology Physics. 82: 1918-1922.	Case series N=11 patients with localised prostate cancer Injection of human collagen during IMRT (dose of 75.6 Gy in 42 fractions) Follow-up 12 months	The injection of human collagen in the outpatient setting was well tolerated. The mean separation between the prostate and anterior rectum was 12.7 mm. The mean reduction in dose to the anterior rectal wall was 50%. All men denied any rectal symptoms during the study.	Included in systematic review added.
Ogita M, Yamashita H, Nozawa Y et al. (2021) Phase II study of stereotactic body radiotherapy with hydrogel spacer for prostate cancer: acute toxicity and propensity score-matched comparison. Radiat Oncol.16:107, pp 1-11 Trial registration: UMIN-CTR, UMIN000026213	Case series N=40 patients with prostate cancer treated with SBRT (36.25 Gy in 5 fractions with volumetric modulated arc therapy) in combination with a hydrogel spacer.	Grade 2 acute GI and GU toxicity occurred in 7 (18%) and 17 (44%) patients. The EPIC bowel and urinary summary score declined from the baseline to the first month (p<0.01, p=0.04). For propensity score-matched analyses, no significant differences in acute GI and GU toxicity were observed between the two groups. The EPIC bowel summary score was significantly better in the spacer group at 1 month (82.2 in the spacer group and 68.5 in the control group). SBRT with a hydrogel spacer had the dosimetric benefits of reducing the rectal doses, did not reduce physician-assessed acute toxicity, but it improved patient-reported acute bowel toxicity.	Larger studies included.
Ogita M, Yamashita H, Sawayanagi S et al. (2020) Efficacy of a hydrogel spacer in	Case series N=39 patients who received stereotactic	Among 39 patients, 35 (90%), 19 (49%) and 13 (33%) and 38 (97%), 38 (97%) and 34 (87%) patients before and after the	Larger studies included.

three-dimensional conformal radiation therapy for prostate cancer. Japanese Journal of Clinical Oncology, 50(3)303–309.	body radiotherapy for prostate cancer inserted with a hydrogel spacer and underwent computed tomography scans before and after spacer insertion. 3D-CRT plans according to NCCN classification, low-, intermediate- and high-risk, were made. Dose constraints for rectum and bladder were V70 Gy ≤ 15%, V65 Gy ≤ 30% and V40 Gy ≤ 60%.	spacer insertion fulfilled rectum dose constraints for low-, intermediate- and high-risk plans, respectively. A hydrogel spacer significantly reduced rectum dose and improved the rectum dose constraints fulfilment rate in intermediate (p<0.01) and high (p<0.01), but no difference was found in low-risk 3D-CRT plan (P = 0.25). Although IMRT is the standard treatment, 3D-CRT using a hydrogel spacer may be a treatment option.	
Osman SOS; Fairmichael C, Whitten G et al. (2022) Simultaneous integrated boost (SIB) to dominant intra-prostatic lesions during extreme hypofractionation for prostate cancer: the impact of rectal spacers. Radiation oncology. 17 (1); 38	Case series N=12 patients with unfavourable intermediate or high risk prostate cancer treated with 5-fraction stereotactic ablative radiotherapy (SABR) volumetric modulated arc therapy (VMAT) 40 Gy or boosting up to 50 Gy in dominant intraprostatic lesions. Pre and post insertion plans assessed.	Compared to plans before spacer insertion, higher dose were achieved with spacer in situ for 25% of the patients. Moreover, significant reduction in rectal dose and better target coverage were also achieved for all patients with spacers in situ.	Dosimetry study. Larger studies with longer follow up included.
Padmanabhan R, Pinkawa M, Song DY. Hydrogel spacers in prostate radiotherapy: a promising approach to decrease rectal toxicity. Future Oncol. (2017) 13(29), 2697–2708	Review	Strategies for reducing dose to rectum include endorectal balloons as well as injection of rectal spacers like hydrogels. Early clinical studies with hydrogels have shown favourable outcomes. A low incidence of major procedural adverse effects with hydrogel use has been reported and it is well tolerated by patients. Hydrogel holds promise in establishing itself as an adjunct to standard of care in prostate radiation.	Review
Payne HA, Jain S. Peedell C et al. (2022) Delphi study to identify consensus on patient selection for hydrogel rectal spacer use during radiation therapy for prostate cancer in the UK. BMJ Open; 12 (7); e060506	Delphi study 6 clinical oncologists and 1 urologist from across the UK participated.	There is agreement that patients with prostate cancer undergoing radical radiation therapy have the potential to benefit from **hydrogel spacer**s. Currently, patients who could potentially benefit can access **hydrogel spacer**s. Implementation of the consensus recommendations would help prioritise access to rectal spacers for patients in the UK.	Consensus on patient prioritisation for hydrogel spacer use during radiotherapy.

Pepe P, Tamburo M, Pennisi M et al. (2021) Clinical Outcomes of Hydrogel Spacer Injection Space OAR in Men Submitted to Hypofractionated Radiotherapy for Prostate Cancer. In vivo (Athens, Greece); 35 (6); 3385-3389.	Case series N=32 patients with localized prostate cancer underwent hydrogel spacer (SpaceOAR) before hypofractionated radiotherapy. Median follow up 15 months	PSA levels was 0.52 nanograms/ml; 28.1% vs. 78.1% patients had GI vs. GU Grade 0 acute toxicity and 93.7% vs. 0% had GI vs. GU Grade 0 late toxicity. Furthermore, 88.1% of patients kept pretreatment sexual potency. The use of the hydrogel Spacer OAR before HRT is useful for reducing acute and late GU and GI toxicities.	Larger studies with longer follow-up included.
Patel AK, Houser C, Benoit R et al. (2020) Acute patient-reported bowel quality of life and rectal bleeding with the combination of prostate external beam radiation, low-dose-rate brachytherapy boost, and SpaceOAR. Brachytherapy 19, 477-483.	Retrospective review N=69 patients with prostate cancer treated with EBRT (45 Gy), cesium-131 LDR-BT (85 Gy), and SpaceOAR 3 months follow-up	With combination EBRT, LDR-BT, and SpaceOAR, bowel QOL returned to the baseline 3 months after LDR-BT. Clinically significant rectal bleeding was !5%. Further follow-up will confirm if low acute rectal toxicity translates to reduced late toxicity	Larger studies included.
Paetkau O, Gagne IM, Pai HH et al. (2019) Maximizing rectal dose sparing with hydrogel: A retrospective planning study. J Appl Clin Med Phys; 20:4: 91–98.	Retrospective study N= 13 prostate cancer patients implanted with 10 cc of SpaceOAR hydrogel.	Overall, treatment plans using the RW optimization structure offered the lowest rectal dose while VMAT treatment technique offered the lowest bladder and penile bulb dose.	Treatment planning study.
Pietro P, Maria T, Paolo P et al. (2022) Erectile dysfunction following hydrogel injection and hypofractionated radiotherapy for prostate cancer: Our experience in 56 cases. Archivio Italiano di Urologia e Andrologia 2022; 94, 2	N=56 patients with cT1c PCa were treated by HRT directed to the prostate and seminal vesicle. Follow-up 18 months	The use of hydrogel injection and intraprostatic fiducials followed by HRT allowed pre-treatment sexual potency in 62.5% of the cases.	Larger studies with longer follow-up included.
Pinkawa M, Bornemann C et al (2013). Treatment planning after hydrogel injection during radiotherapy of prostate cancer. Strahlentherapie und Onkologie.189 (9) 796-800.	Case study n=3 injection of 10 ml hydrogel in prostate cancer patients during IMRT.	Treatment planning based on imaging shortly after hydrogel injection overestimates the actual hydrogel volume during the treatment as a result of not-yet-absorbed saline solution and air bubbles.	Imaging for treatment planning study.
Pinkawa M, Piroth MD et al (2013). Spacer stability and prostate	Comparative case series n=15 prostate cancer patients with 10ml	Mean volume of the hydrogel increased slightly (17%; p< 0.01), in 4 of 15 patients >2	Study evaluating prostate position variability and

position variability during radiotherapy for prostate cancer applying a hydrogel to protect the rectal wall. Radiotherapy and Oncology.106 (2) 220-224.	hydrogen spacer injection (SpaceOAR) (G1) versus 30 patients without a spacer (g2) during radiotherapy Follow-up: 12 weeks	cm. The average displacement of the hydrogel centre of mass was 0.6 mm (87% < 2.2 mm), -0.6 mm (100% < 2.2 mm) and 1.4 mm (87% < 4.3 mm) in the x-, y- and z-axes (not significant). The average distance between prostate and anterior rectal wall before/at the end of radiotherapy was 1.6 cm/1.5 cm, 1.2 cm/1.3 cm and 1.0 cm/1.1 cm at the level of the base, middle and apex (G1). Prostate position variations were similar with or without hydrogel but significant systematic posterior displacements were only found in those without hydrogel.	spacer stability. Larger and longer follow-up studies.
Pinkawa, M (2015). Current role of spacers for prostate cancer radiotherapy. World Journal of Clinical Oncology 6 (6) 189-193.	General review.	Several studies have shown well tolerated injection procedures and treatments. Apart from considerable reduction of rectal irradiation, a prospective randomised trial demonstrated a reduction of rectal toxicity after hydrogel injection in men having prostate image-guided intensity-modulated radiation therapy.	General review.
Pinkawa M, Piroth MD et al (2012). Quality of life after intensity-modulated radiotherapy for prostate cancer with a hydrogel spacer Matched-pair analysis. Strahlentherapie und Onkologie.188 (10) 917-925.	Case –control study (matched pair analysis) n= 28 prostate cancer patients in each sub-group. Dose in spacer subgroup was 78 Gy in 2 Gy fractions compared with 2 matched-pair subgroups (treated without spacer): 3D conformal 70.2 Gy in 1.8 Gy fractions (3DCRT) and intensity-modulated radiotherapy (IMRT) 76 Gy in 2 Gy fractions.	Bowel bother scores were only significantly different in comparison to baseline levels in the spacer subgroup. The percentage of patients reporting moderate/big bother with specific symptoms did not increase for any item (urgency, frequency, diarrhoea, incontinence, bloody stools, pain). Moderate bowel quality-of-life changes can be expected during radiotherapy irrespective of spacer application or total dose.	Study evaluating quality of life. Larger and longer follow-up studies included.
Pinkawa M, Escobar Corral N et al (2011). Application of a spacer gel to optimize three-dimensional conformal and intensity modulated radiotherapy for prostate cancer. Radiotherapy and Oncology.100 (3) 436-441.	Case series n=18 patients with prostate cancer. Injection of a spacer gel (10 ml SpaceOAR™) done and 3D CRT and IMRT treatment plans used (78 Gy in 39 fractions). Follow-up: after injection	The injection of a spacer gel between the prostate and anterior rectal wall is associated with considerably lower doses to the rectum and consequentially lower NTCP values irrespective of the radiotherapy technique. Mean rectal V70 Gy of 14.4% on preimplantation scans compared with 6.1% on post implantation scans reported. A similar rectal V70Gy reduction	Dosimetric study. Larger and longer follow-up studies included.

		was reported in IMRT plans (pre-implantation 17.2%, post implant 7.2%). The spacer had no impact on the doses delivered to the PTV, bladder and femoral heads. 94% of IMRT plans met planning constraints compared with only 67% of 3D-CRT plans despite presence of spacers.	
Pinkawa M, Schubert C et al (2015). Application of a hydrogel spacer for postoperative salvage radiotherapy of prostate cancer. Strahlentherapie und Onkologie 191 (4) 375-379.	Case report n=1 prostate cancer patient presented 20 years after radical prostatectomy with a digitally palpable local recurrence at the urethrovesical anastomosis. hydrogel spacer application during salvage radiotherapy (IMRT total dose 76Gy in 2 Gy fractions)	Local recurrence was displaced more than 1 cm from the rectal wall. Patient reported rectal urgency during radiotherapy, resolved after treatment. PSA levels dropped after treatment. A hydrogel spacer was successfully applied for dose-escalated radiotherapy in a patient with macroscopic local prostate cancer recurrence at the urethrovesical anastomosis to decrease the dose at the rectal wall.	Larger and longer follow-up studies included.
Pinkawa M, Klotz J, Djukic V et al (2013). Learning curve in the application of a hydrogel spacer to protect the rectal wall during radiotherapy of localized prostate cancer. Urology; 82: 963-968	Case series n=64 patients with prostate cancer. PEG hydrogel with IMRT (78Gy in 38 fractions) Follow-up – until last day of radiotherapy.	A smaller mean perirectal separation of 1.1cm in the first 32 patients compared with 1.5 in the second 32 patients reported. Rectal V70 Gy in the first group was 6% compared with 2% in the second cohort. A greater relative reduction of 80% was reported in the second cohort compared with 62.5% in the first cohort. An increasingly symmetrical hydrogel distribution and significantly larger prostate-rectum distances with the same hydrogel volume was seen. An improved dosimetric rectum protection and smaller acute bowel quality-of-life changes resulted.	Learning curve, RT dosimetric study.
Pinkawa, M, Berneking, VK et al (2017). Hydrogel injection reduces rectal toxicity after radiotherapy for localized prostate cancer. Hydrogelinjektion vermindert die rektale Toxizitat nach Radiotherapie bei lokalisiertem Prostatakarzinom. (193) 1 22-28.	Prospective comparative study n=167 consecutive patients who received prostate RT with 2-Gy fractions up to 76 Gy (without hydrogel, n = 66) or 76-80 Gy (with hydrogel, n = 101) Follow-up: 17 months after RT.	Baseline patient characteristics were well balanced. Treatment for bowel symptoms (0 vs 11%; p<0.01) and endoscopic examinations (3 vs 19%; p<0.01) were performed less frequently with a spacer. Mean bowel function scores did not change for patients with a spacer in contrast to patients without a spacer (mean decrease of 5 points) >1 year after RT in comparison to baseline, with 0 vs. 12% reporting a new	Multiple publication of Pinkawa 2016 included in systematic review added.

		moderate/big problem with passing stools (p<0.01). Statistically significant differences were found for the items "loose stools", "bloody stools", "painful bowel movements" and "frequency of bowel movements".	
Pinkawa M, Berneking V, Schlenter M et al. (2017) Quality of Life After Radiation Therapy for Prostate Cancer with a Hydrogel Spacer: 5-Year Results. International Journal of Radiation Oncology Biology Physics. 99(2):374-7.	Case series N=114 prostate cancer patients (low/intermediate/high-risk) received external beam radiation therapy 76 -78Gy fractions (54 had hydrogel spacer and 60 had no spacer). QoL was measured by the EPIC-50 items scale. Follow-up 5 years	Mean bowel function and bother score changes of >5 points in comparison to baseline levels before treatment were found only at the end of RT (10-15 points; p < .01) for patients treated with a hydrogel spacer. No spacer patient reported moderate or big problems with his bowel habits overall. Mean bother score changes of 21 points at the end of RT, 8 points at 2 months, 7 points at 17 months, and 6 points at 63 months after RT were found for patients treated without a spacer. A bowel bother score change >10 points was found in 6% versus 32% (P<0.01) at 17 months and in 5% versus 14% (P=0.2) at 63 months with versus without a spacer.	Included in systematic review added.
Pinkawa M (2016). Rectal spacers to minimise morbidity in radiotherapy for prostate cancer. Radiotherapy and Oncology (119) S8.	Review	Biodegradable spacers, including hydrogel, hyaluronic acid, collagen or an implantable balloon can be injected or inserted in a short procedure under transrectal ultrasound guidance via a transperineal approach. A distance of about 1.0-1.5cm is usually achieved between the prostate and rectum, excluding the rectal wall from the high isodoses. Several studies have shown well tolerated injection procedures and treatments. Apart from considerable reduction of rectal dose compared to radiotherapy without a spacer, clinical toxicity results are favourable.	Review
Pinkawa M, Schubert C, Escobar-Corral N et al. (2018) Optimization of prostate cancer radiotherapy using of a spacer gel, volumetric modulated arc therapy and a single biological	Case series N=27 patients with localised prostate cancer: stage T1-T2c IMRT, VMAT 78 Gy in 2 Gy fractions VMAT versus IMRT plans	In addition to decreased rectal dose following spacer injection, VMAT with single biological organ at risk optimization resulted in further dose reduction to the organs at risk and improved dose homogeneity and conformity in	Larger studies included. Toxicity not reported.

organ at risk objective. International Journal of Radiation Research, 16, 169-176.	and plans before versus after spacer injection were compared.	comparison to the step-and-shoot IMRT technique with conventional objectives.	
Pinkawa M, Hermani H, Bischoff P et al. (2022) Focal injection of a radiopaque viscous spacer before focal brachytherapy as re-irradiation for locally recurrent prostate cancer Brachytherapy.	Case report N=2 patients with prostate cancer who had radiopaque viscous hydrogel spacer before brachytherapy. Follow-up 18 months.	The viscous hydrogel spacer can be injected focally at a specific prostate lobe or seminal vesicles. The spacer remains stable within fatty tissue in any areas that are accessible by an ultrasound guided needle injection to create a distance between the high brachytherapy dose within the target and the organ at risk.	Injection technique.
Pieczonka CM, veados N et al (2016). Hydrogel Spacer Application Technique, Patient Tolerance, and Impact on Prostate IMRT: Results from a Prospective Multicenter Pivotal Randomized Controlled Trial. Urology Practice 3 (2), 141–146.	RCT n=222 (149 spacer group versus 73 control group) men with stage T1 or T2 prostate cancer treated to 79.2 Gy with image guided intensity modulated radiation therapy in 44 fractions. Fiducial markers and perirectal spacer injection (spacer group) or fiducial markers alone (control group). Follow-up: 15 months Follow-up:15 months	Procedures were rated easy or very easy in 98.7% of cases with a 99.3% success rate. Mild transient rectal events were noted in 10% of patients in the spacer group (for example, pain, discomfort). Mean perirectal space was 12.6 mm after implant and 10.9 mm at 12.4 weeks with absorption at 12 months. A 25% or greater reduction in rectal V70 dose was produced in 97.3% of patients in the spacer group. The spacer group had a significant reduction in late rectal toxicity severity (p=0.044) as well as lower rates of decrease in bowel quality of life at 6, 12 and 15 months compared with the control group. There were no unanticipated adverse spacer effects or spacer related adverse events.	Multiple publication (of Mariados et al 2015) included in systematic review added.
Picardi C, Rouzaud M, Kountouri M et al. (2016) Impact of hydrogel spacer injections on interfraction prostate motion during prostate cancer radiotherapy. ACTA ONCOLOGICA, VOL. 55, NO. 7, 834–838	Prospective cohort study N=20 patients with prostate cancer had radiotherapy-IGRT (10 with or 10 without hydrogel spacers). Follow up time not reported.	In patients with or without HS, the overall mean interfraction prostate displacements were 0.4 versus -0.4 mm (p=0.0001), 0.6 versus 0.6 mm (p =0.85), and -0.6 mm versus -0.3 mm (p=0.48) for the left right, anterior-posterior (AP), superior-inferior (SI) axes, respectively. Prostate displacements 45 mm in the AP and SI directions were similar for both groups. No differences in setup errors were observed in the three axes between HS + or HS- patients. HS implantation does not significantly influence the	Included in HTA added.

		interfraction prostate motion in patients treated with RT for prostate cancer. The major expected benefit of HS is a reduction of the high-dose levels to the rectal wall without influence in prostate immobilization.	
Polamraju P, Bagley AF, Williamson T et al. (2019) Hydrogel Spacer Reduces Rectal Dose during Proton Therapy for Prostate Cancer: A Dosimetric Analysis. Int J Particle Therapy, 23-31	N=9 patients hydrogel spacer on rectal dose on plans for treating prostate cancer with intensity-modulated proton therapy (IMPT) or passive scattering proton therapy (PSPT)	Significant reductions in rectal dose occurred in both PSPT and IMPT plans, with the greatest reduction for IMPT-with-spacer relative to PSPT alone. Prospective studies are ongoing to assess the clinical impact of reducing rectal dose with hydrogel spacers.	Dosimetric analysis.
Porkhun K, Hagen G. “Hydrogel rectal spacer SpaceOAR™ in prostate cancer radiation therapy - Health economic evaluation” 2021. Oslo: Norwegian Institute of Public Health, 2021.	Health technology assessment.	Absolute shortfall for patients suffering from radiation-induced adverse events is 1.85 QALYs. • The cost-utility analysis indicated that SpaceOAR™ in combination with radiation therapy was more costly (incremental costs: 15,330 NOK) and slightly more effective (incremental effects: 0.008 QALYs) than radiation therapy alone. • The health benefit of the intervention is very uncertain. Our analysis indicates that the intervention only has a 59% likelihood of generating a net health benefit as measured in QALYs. • The incremental cost-effectiveness ratio (ICER) is NOK 2,006,985 per QALY. • The results of sensitivity analysis indicated that the price of the spacer, the quality of life weights and the efficacy of the treatment have the greatest impact on the results. • The budget impact analysis indicated that costs of the intervention would be approximately 15 million NOK per year. This report has assessed to what degree the technology meets the Norwegian priority setting criteria (health benefits, resource use and disease severity). The absolute shortfall is 1.85 QALY, placing	Economic evaluation. Not in remit.

		the disease in the lowest priority setting group following the approach suggested by the Magnussen group (https://www.regjeringen.no/no/dokumenter/pa-ramme-alvor/id2460080/). The health benefit of the intervention is small (0.008 QALYs) and very uncertain.	
Prada PJ, Fernandez J et al (2007). Transperineal Injection of Hyaluronic Acid in Anterior Perirectal Fat to Decrease Rectal Toxicity from Radiation Delivered with Intensity Modulated Brachytherapy or EBRT for Prostate Cancer Patients. International Journal of Radiation Oncology Biology Physics.69 (1) 95-102.	Case series n=27 intermediate and high risk prostate cancer patients Injecting hyaluronic acid (HA) during external beam radiation therapy (EBRT TO 43 Gy in 23 fractions) with HDR brachytherapy (23 Gy in 2 HDR BT boosts) over 5 week period. HA was injected before the second HDR fraction. Follow-up: median 13 months.	No toxicity was produced from the HA or the injection. In follow-up CT and MRI the HA injection did not migrate or change in mass/shape for close to 1 year. The mean distance between rectum and prostate was 2.0 cm along the entire length of the prostate. The median measured rectal dose, when normalized to the median urethral dose, demonstrated a decrease in dose from 47.1% to 39.2% ($p < 0.001$) with or without injection. For an HDR boost dose of 1150 cGy, the rectum mean Dmax reduction was from 708 cGy to 507 cGy, $p < 0.001$, and the rectum mean Dmean drop was from 608 to 442 cGy, $p < 0.001$ post-HA injection.	Included in systematic review added.
Prada PJ, Gonzalez H, Menéndez C et al (2009) Transperineal injection of hyaluronic acid in the anterior perirectal fat to decrease rectal toxicity from radiation delivered with low-dose-rate brachytherapy for prostate cancer patients. Brachytherapy; 8(2):210-7.	Pseudo-RCT N=69 patients with low- and intermediate-risk prostate cancer had BT with I-125 seeds; dose of 145 Gy Transperineal injection of hyaluronic acid (n=36) versus no transperineal hyaluronic acid injection (n=33) Follow up median 26 months	No toxicity in fat or in rectal function. Mucosal damage post therapy 5% (2/36) versus. 36% (12/33), p=0.002. Macroscopic rectal bleeding 0 versus 12% (4/23), p=0.047. No side effects related to injection or hyaluronic acid.	Included in systematic review added.
Prada PJ, Jimenez I, Gonzalez-Suarez H et al. (2012) High-dose rate interstitial brachytherapy as monotherapy in one fraction and transperineal hyaluronic acid injection into the perirectal fat for the treatment of favorable stage prostate cancer:	Case series N=40 patients with prostate cancer treated with high-dose-rate (HDR) brachytherapy (20.5 Gy) plus transperineal hyaluronic acid injection into the perirectal fat to displace the rectal wall from radiation.	All patients tolerated the implantation procedure very well with minimal discomfort. No intraoperative or perioperative complications occurred. Acute toxicity Grade 2 or more was not observed in any patients. No chronic toxicity has been observed after treatment. Logistic regression showed that the late Grade 1 GU toxicity was associated with D(90)	Included in systematic review added.

Treatment description and preliminary results. Brachytherapy.11(2):105-10.	Median follow-up 19 months (range 8-32 months).	(p=0.050). The 32-month actuarial biochemical control was 100% and 88%, respectively (p=0.06) for low- and intermediate-risk groups.	
Prada PJ, Ferri M, Cardenal J et al. (2018) High-dose-rate interstitial brachytherapy as monotherapy in one fraction of 20.5 Gy for the treatment of localized prostate cancer: Toxicity and 6-year biochemical results. Brachytherapy. 17(6):845-51.	Case series N=60 patients with low- and intermediate-risk prostate cancer were treated with high-dose-rate monotherapy in one fraction (20.5 Gy) and transperineal hyaluronic acid injection into the perirectal space. Median follow-up was 51 months (range 30–79)	HDR brachytherapy is well-tolerated. No intraoperative or perioperative complications occurred. Grade 1 acute genitourinary toxicity occurred in 36% of patients, Grade 2 or more was not observed, only 1 patient requiring the use of a catheter for 7 days in the immediate postoperative period. No gastrointestinal toxicity or chronic toxicity has been observed after treatment. The actuarial biochemical control was better, 82% (±3%) at 6 years.	Large studies included.
Quinn TJ, Daignault-Newton S, Bosch W et al. (2020) Who Benefits from a Prostate Rectal Spacer? Secondary Analysis of a Phase III Trial. Practical Radiation Oncology 10, 186-194	RCT SpaceOAR phase III trial Clinical and dosimetric data for the 222 patients enrolled on the original trial were analysed in the present study 218 were assessed for bowel quality of life (QOL) at 15 months, and 140 with a minimum of 3 years of follow-up were assessed for more long-term changes in bowel QOL.	There was little heterogeneity in the likelihood of spacer reducing the risk of declines in bowel QOL across clinical and dosimetric variables. Even for the >95% of plans meeting QUANTEC rectal criteria, hydrogel spacer provided potentially meaningful Therefore, we were not able to identify a subgroup within this population that did not potentially benefit from spacer placement.	Data from the RCT included.
Rossi PJ, Marcus DM, Adrian Hall W et al. (2021) Hydrogel spacers and prostate brachytherapy. Brachytherapy. 21 (1); 75-78.	Review	It is clear that spacing utilized in the setting of brachytherapy, may reduce early or late gastrointestinal side effects, and does not degrade the quality of the treatment. Although toxicities associated with spacers appear to be rare, clinicians should be aware of potential complications and should be trained on appropriate spacer placement. Further study with prospective evaluation is essential.	Review
Repka MC, Creswell M, Lischalk JW (2022). Rationale for Utilization of Hydrogel Rectal Spacers in Dose Escalated SBRT for the Treatment of	Review	Outlines a framework and rationale for the utilization of rectal spacers when treating unfavourable risk prostate cancer with dose escalated	Review

Unfavorable Risk Prostate Cancer. Frontiers in Oncology; 12; 860848		Stereotactic Body Radiation Therapy (SBRT).	
Ruggieri R, Naccarato S, Stavrev P et al. (2015) Volumetric-modulated arc stereotactic body radiotherapy for prostate cancer: dosimetric impact of an increased near-maximum target dose and of a rectal spacer. *The British journal of radiology,* 88**,** 20140736.	Prospective cohort study N=11 patients with low/intermediate risk prostate adenocarcinoma, had VMAT-SBRT 35 Gy in 5 fractions- IMRT (10 ml of hydrogel spacer versus no spacer) Patients selected from 2 different trials. Follow-up not reported.	The increased D2% was associated with improvements in target coverage, whereas spacer insertion was associated with improvements in both target coverage and rectal Vr X . By linear correlation analysis, spacer insertion was related to the reductions in rectal Vr X for X ≥ 28GyA slightly increased $D_{2\%}$ or the use of spacer insertion was each able to improve VPTV 33:2 . Their combined use assured VPTV 33:2 $ 98% to all our patients. Spacer insertion was further causative for improvements in rectal sparing.	Larger studies included.
Rucinski A, Brons S, Richter D, et al. (2015) Ion therapy of prostate cancer: daily rectal dose reduction by application of spacer gel. Radiat;10:56.	Retrospective cohort study N=19 patients with prostate cancer treated with photons and ions (10 with Hydrogel spacer versus 9 without spacer). Patients selected from 2 different trials.	The application of spacer gel did substantially diminish rectum dose. Dmax-1 ml on the treatment planning CT was on average reduced from 100.0 ± 1.0% to 90.2 ± 4.8%, when spacer gel was applied. Spacer gel results in a decrease of the daily V90Rectum index, which calculated over all patient cases and CT studies was 10.2 ± 10.4 [ml] and 1.1 ± 2.1 [ml] for patients without and with spacer gel, respectively.	Larger studies included.
Seymour ZA, Daignault S, Bosch W, Gay HA, Michalski JM, Hamstra DA, et al. Long-term follow-up after radiotherapy for prostate cancer with and without rectal hydrogel spacer: A pooled prospective evaluation of quality of life.. BJU Int 2020; 126: 367–372 doi:10.1111/bju.15097	Case series N=380 men treated with radiotherapy (RT) for prostate cancer (64% with rectal hydrogel spacer and 36% without) Pooled analysis of two series (a prospective Phase III multi-centred randomised trial and a prospective non-randomised single-institution analysis) Follow-up (median 39 months) QOL was examined using the Expanded Prostate Cancer Index Composite (EPIC) and mean changes from	Treatment with spacer was associated with less decline in average long-term bowel QOL (89.4 for control and 94.7 for spacer) with differences at >24 months meeting the threshold of a MID difference between cohorts (bowel score difference from baseline: control = -5.1, spacer = 0.3, difference = -5.4; P < 0.001). When evaluated over time men without spacer were more likely to have MIDx1 (5 points) declines in bowel QOL (P = 0.01). At long-term follow-up MIDx1 was 36% without spacer vs 14% with spacer (P In this pooled analysis of QOL after prostate RT with up to 5 years of follow-up, use of a rectal spacer was associated	Similar study included in HTA added.

	baseline in EPIC domains were evaluated.	with preservation of bowel QOL. This QOL benefit was preserved with long-term follow-up.	
Stavrev P, Ruggieri R, Stavreva N et al (2016). Applying radiobiological plan ranking methodology to VMAT prostate SBRT. Phys Med 32 (4) 636-641.	Case series n=11 patients (35Gy-in-five-fractions VMAT prostate SBRT) 4 plans were generated before and after spacer insertion.	The plans without rectal spacer were ranked worse compared to those with rectal spacer except for one set of Hom plans. The use of rectal spacer leads in general to lower risk of rectal complications, as expected, and even to better tumour control. Plans with increased near maximum target dose (D2%40.2Gy) are expected to perform much better in terms of tumour control than those with D2%37.5Gy.	Treatment planning study.
Strom TJ, Wilder RB et al (2014). A dosimetric study of polyethylene glycol hydrogel in 200 prostate cancer patients treated with high-dose rate brachytherapy+/- intensity modulated radiation therapy. Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology.111 (1) 126-131.	Retrospective comparative case series n=200 (100 gel versus 100 no gel) patients with clinically localised prostate cancer who had high dose rate (HDR) brachytherapy with or without intensity modulated radiation therapy (IMRT) and injection of a polyethylene glycol hydrogel spacer (10 ml Duraseal). Follow-up median 8.7 months.	There was a success rate of 100% (100/100) with PEG hydrogel implantation. PEG hydrogel significantly increased the prostate-rectal separation (mean±SD, 12±4mm with gel vs. 4±2mm without gel, p<0.001) and significantly decreased the mean rectal D2 ml (47±9% with gel vs. 60±8% without gel, p<0.001). Gel decreased rectal doses regardless of body mass index (BMI).	Study included in systematic review added.
Song DY, Herfarth KK et al (2013). A multi-institutional clinical trial of rectal dose reduction via injected polyethylene-glycol hydrogel during intensity modulated radiation therapy for prostate cancer: Analysis of dosimetric outcomes. International Journal of Radiation Oncology Biology Physics.87 (1) 81-87.	Case series N=52 patients with localised prostate cancer (T1-T2). Injection of a prostate-rectum spacer (polyethylene glycol hydrogel [SpaceOAR] during IMRT- 78 Gy in 2 Gy fractions Follow-up not reported	Injection of hydrogel into the prostate-rectal interface resulted in dose reductions to rectum for >90% of patients treated. Rectal sparing was statistically significant across a range of 10 to 75 Gy and was demonstrated within the presence of significant interinstitutional variability in plan conformity, target definitions, and injection results.	Included in systematic review added.
Sidhom M, Arumugam S et al (2016). Early results of Australian multicentre phase 2 trial of stereotactic "virtual HDR" radiation therapy for intermediate	Multicentre case series n=43 patients with intermediate and high risk prostate cancer who completed	Treatment was well tolerated. Genitourinary (GU) and gastrointestinal (GI) CTCAEv4 toxicities were minimal with no acute or late grade 3 GU or GI toxicity. At the end of treatment, any grade 1 GU	Injectable hydrogel spacer inserted in 10 patients only. Larger studies with longer

and high risk prostate cancer. Journal of Medical Imaging and Radiation Oncology (60) 48.	stereotactic body radiotherapy (SBRT) as a "virtual HDR" with stepwise dose escalation of 19 Gy in 2 fractions 1 week apart (in 28), followed by 46 Gy in 23 fractions (in 15). Median follow-up: 12 months	toxicity occurred in 54%, and grade 2 in 31%. Acute grade 1 GI toxicity occurred in 26%, while no patients experienced acute grade 2 GI toxicity. For the 31 patients with 6-month follow-up, at last follow-up the rate of late grade 2 GU toxicity was 10%, while no patients developed late grade 2 GI toxicity. Rectal displacement during SBRT was achieved with an injectable hydrogel spacer (SpaceOAR) in 10 patients, and an external rectal retraction system (Rectafix) in 33 patients. No SpaceOAR patients reported discomfort from rectal displacement, while 39% of Rectafix patients reported moderate discomfort and 11% severe discomfort during SBRT.	follow-up included.
Sato H, Kato T, Motoyanagi T et al. (2021) Preliminary analysis of prostate positional displacement using hydrogel spacer during the course of proton therapy for prostate cancer. Journal of Radiation Research. 62, 2, 294–299.	Case series N=22 patients with intermediate-risk prostate cancer (11 with hydrogel spacer [HS] insertion and 11 without HS insertion).	No significant difference was observed across the groups in the LR and SI directions. Conversely, a significant difference was observed in the AP direction ($P < 0.05$). The proportion of the 3D vector length ≤5 mm was 95% in the inserted group, but 55% in the non-inserted group. Therefore, HS is not only effective in reducing rectal dose, but may also contribute to the positional reproducibility of the prostate.	Effect of HS insertion on the inter-fraction prostate motion.
Saito M, Suziki T, Suguama Y et al. (2020) Comparison of rectal dose reduction by a hydrogel spacer among 3D conformal radiotherapy, volumetric-modulated arc therapy, helical tomotherapy, CyberKnife and proton therapy. Journal of Radiation Research, 61, 3, pp. 487–493.	Case series (retrospective) N=20 patients with hydrogel spacer for prostate radiotherapy (3D conformal radiotherapy (3DCRT), volumetric modulated arc therapy (VMAT), helical tomotherapy (HT), CyberKnife (CK) and proton therapy).	Significant rectal dose reduction ($P < 0.001$) between the treatment plans on pre- and post-CT images were achieved for all modalities for D50%, D20% and D2%. The dose reduction of high-dose (D2%) ranges were −40.61 ± 11.19, −32.44 ± 5.51, −25.90 ± 9.89, −13.63 ± 8.27 and −8.06 ± 4.19%, for proton therapy, CK, HT, VMAT and 3DCRT, respectively. The area under the rectum dose–volume histogram curves were 34.15 ± 3.67 and 34.36 ± 5.24% ($P = 0.7841$) for 3DCRT with hydrogel spacer and VMAT without hydrogel spacer, respectively. Results indicate that 3DCRT with hydrogel spacer would reduce the cost	Dosimetric outcomes.

		by replacing the conventional VMAT without spacer for prostate cancer treatment, from the point of view of the rectal dose. For the high-dose gradient region, proton therapy and SBRT with CK showed larger rectal dose reduction than other techniques.	
Schorghofer A, Drerup M, Kunit T et al. (2019) Rectum-spacer related acute toxicity – endoscopy results of 403 prostate cancer patients after implantation of gel or balloon spacers. Radiat Oncol J; 14 (47): 1–7.	Cohort study N=403 patients 139 with hydrogel spacer (SpaceOAR) versus 264 with endorectal balloon (prospace) using endoscopy. IMRT 276 patients were treated with normo-fractionated regimen (78 at 2Gy fraction), 125 treated with moderate hypofractionation (63 at 2 Gy fraction). 116 high risk patients additionally received 50 Gy in pelvic nodes. 12 months follow-up.	Overall rectal toxicity was very low with average VRS scores of 0.06 at the day after implantation, 0.10 at the end of RT, 0.31 at 6 months and 0.42 at 12 months follow up. Acute Grade 3 toxicity (rectum perforation and urethral damage) directly related to the implantation procedure occurred in 1.49% (n = 6) and was seen exclusively in patients who had received the spacer balloon. Analysis of post implant MR imaging did not identify abnormal or mal-rotated positions of this spacer to be a predictive factors for the occurrence of spacer related G3 toxicities.	Included in systematic review added.
Saito M, Suzuki T, Suzuki H et al. (2022) Minimum required interval between hydrogel spacer injection and treatment planning for stereotactic body radiation therapy for prostate cancer. Practical Radiation Oncology.	Retrospective study N=15 patients treated with SBRT + hydrogel spacer for prostate cancer. Pre and post MRI (within 3 days) with spacer were evaluated.	A single day is an acceptable interval between hydrogel spacer injection and treatment planning for SBRT for prostate cancer	Volume of spacer on MRI assessed.
Sturt P, Suh YE, Khoo V et al. (2022) The dosimetric advantages of perirectal hydrogel spacer in men with localized prostate cancer undergoing stereotactic ablative radiotherapy (SABR). Medical Dosimetry.	N=22 patients with hydrogel spacer (SpaceOAR) undergoing stereotactic ablative radiotherapy (SABR) for localized prostate cancer	The use of hydrogel spacer was able to significantly reduce planned dose to the rectum, bladder and penile bulb with SABR techniques associated with the CyberKnife VSI system.	Dosimetry outcome. Larger studies with longer follow-up included.
Sawayanagi S, Yamashita H, Ogita M et al. (2022) Injection of hydrogel spacer increased maximal intrafractional prostate motion in anterior and superior	Retrospective study. N= 38 patients who had definitive volumetric modulated arc therapy (VMAT)-stereotactic body radiation therapy (SBRT) for prostate cancer (8	Our findings suggest that maximum intrafractional prostate motion monitoring during VMAT-SBRT was larger in patients with hydrogel spacer injection in the superior and anterior directions. Since this difference seemed not to	Prostate motion outcome. Studies with similar outcomes reported in the overview.

directions during volumetric modulated arc therapy-stereotactic body radiation therapy for prostate cancer. Radiation oncology. 17 (1); 41	with spacer and 30 without spacer).	disturb the dosimetric advantage of the hydrogel spacer, we do not recommend routine avoidance of the hydrogel spacer use.	
See AW; Bowden P, Geoffrey W et al. (2022) Dose-escalated radiotherapy to 82 Gy for prostate cancer following insertion of a peri-rectal hydrogel spacer: 3-year outcomes from a phase II trial. Radiation oncology; 2022; vol. 17 (no. 1); 131	Prospective study N= 70 men with localised prostate cancer who had a IMRT 82 Gy in 2 Gy fractions after insertion of SpaceOAR. Median 37.4 months.	Dose-escalation to 82 Gy, and use of a hydrogel spacer, is safe and feasible, with minimal toxicity when compared to rates of rectal toxicity in previous dose-escalation trials up to 80 Gy.	Dosimetry outcomes. Larger studies with longer follow-up included.
Suziki T, Saito M, Onishi H et al. (2020) Effect of a hydrogel spacer on the intrafractional prostate motion during CyberKnife treatment for prostate cancer. J Appl Clin Med Phys; 21:10:63–68	Case series (retrospective) N=21 patients with prostate cancer (12 with and 12 without a hydrogel spacer during CyberKnife treatment) evaluated the effect of a hydrogel spacer on intrafractional prostate motion during CyberKnife treatment.	The offset values (mean ± SD) for the X-, Y-, and Z-axes were −0.04 ± 0.92 mm, −0.03 ± 0.97 mm (P = 0.66), 0.02 ± 0.51, −0.02 ± 0.49 mm (P = 0.50), and 0.56 ± 0.97 mm, 0.34 ± 1.07 mm (P = 0.14), in patients inserted without or with the hydrogel spacer, respectively. There was no effect of a hydrogel spacer on the intrafractional prostate motion in the three axes during CyberKnife treatment for prostate cancer.	Larger studies included.
Su Z, Henderson R, Nichols R et al. (2021) A comparative study of prostate PTV margins for patients using hydrogel spacer or rectal balloon in proton therapy. Physica Medica 81, 47–51.	Retrospective analysis N=190 prostate patients treated with proton therapy (96 had hydrogel spacer injection and 94 patients had only rectal balloons insertion).	Statistically significant differences were observed in the patient setup and prostate intrafraction motion errors of the two patient groups. However, under the current protocol of bladder preparation and daily marker-based x-ray image-guidance, population PTV margins were comparable between the two patient groups.	Retrospective planning study.
Taggar AS, Charas T, Cohen GN et al. (2018) Placement of an Absorbable Rectal Hydrogel Spacer in Patients Undergoing Low-dose-rate Brachytherapy with Palladium-103. Brachytherapy. 17(2): 251–258	Retrospective cohort study N=74 patients with prostate cancer had rectal hydrogel spacer inserted following LDR brachytherapy with Pd-103 seed-implant procedure. Brachytherapy was delivered a monotherapy to 26 (35%) patients; as part of planned	(SD 3.81), and112.4% (SD 12.0), respectively. Urethral D20, D5cc and D1cc were 122.0% (SD 17.27), 133.8% (SD 22.8), and 144.0% (SD 25.4), respectively. After completing all treatments, at the time of first the follow up, seven patients reported acute rectal toxicity –six experiencing grade 1 rectal discomfort and one (with pre-existing haemorrhoids)	Included in systematic review added.

	combination therapy with EBRT to 40 (54%) patients; or as a salvage monotherapy to 8 (11%) patients. Compared with 136 patients treated with seed implantation (from another cohort). Follow-up not reported.	experiencing grade 1 bleeding. (SD 3.81), and112.4% (SD 12.0), respectively. Urethral D20, D5cc and D1cc were 122.0% (SD 17.27), 133.8% (SD 22.8), and 144.0% (SD 25.4), respectively. After completing all treatments, at the time of first the follow up, seven patients reported acute rectal toxicity –six experiencing grade 1 rectal discomfort and one (with pre-existing haemorrhoids) experiencing grade 1 bleeding.	
Tang Q, Zhao F, Yu X, Wu L, Lu Z, Yan S. The role of radioprotective spacers in clinical practice: a review. Quant Imaging Med Surg. 2018;8(5):514-524. doi:10.21037/qims.2018.06.06	Review on different types of spacers and their application in various tumour sites.	Placement-related complications and the cost-effectiveness of the spacers are also discussed. With the increasing use of high-precision radiotherapy in clinical practice, especially the paradigm-changing stereotactic body radiotherapy (SBRT), more robust studies are warranted to further establish the role of radioprotective spacers through materials development and novel placement techniques.	Review
Taniguchi T, Iinuma K, Nakano M et al. (2022) Chronological changes of lower urinary tract symptoms after low-dose-rate brachytherapy for prostate cancer using SpaceOAR system. Prostate International; 2022	Retrospective study n=483 patients with prostate cancer who underwent low-dose-rate brachytherapy (LDR-BT) and SpaceOAR system (n=30) and (n=453) who had LDR BT alone. Follow-up 12 months	SpaceOAR use may temporally increase PVR; however, IPSS, OABSS, IPSS-QOL, Qmax, and voided volume were not significantly associated with LUTS before and after LDR-BT. The combination of LDR-BT and SpaceOAR may be acceptable for treating patients with prostate cancer regarding the chronological changes in LUTS after brachytherapy.	Larger studies with longer follow-up included.
Teyateeti A, Grossman C, Kollmeier, MA et al. (2022) Influence of hydrogel spacer placement with prostate brachytherapy on rectal and urinary toxicity. BJU international. 129 (3); 337-344	Retrospective comparative study. N= 224 patients with LDR brachytherapy +/-EBRT and hydrogel spacer compared with 139 without spacer. Follow-up 3 years.	Rectal doses of the spacer cohort were significantly lower compared to the non-spacer cohort. The incidence rates of overall and grade > 2 rectal toxicity were lower in patients with spacer compared non-spacer group: 12% and 1.8% vs 31% and 5.8%, respectively. The 3-year cumulative incidence of overall rectal toxicity was significantly lower with spacer than without (15% vs 33%; P < 0.001), (HR 0.45, 95% CI 0.28-0.73; P = 0.001). None of the urethral	Studies with similar outcomes included.

		dosimetric variables or the presence or absence of spacer was associated with late urinary toxicity.	
Trifiletti DM, Garda AE and Showalter TN (2016). Implanted spacer approaches for pelvic radiation therapy. Expert Review of Medical Devices 13 (7) 633-640.	Review describes the commercially available rectal spacers in pelvic radiation therapy, including prostate cancer and gynaecologic malignancies, and the application, dosimetric effects, and reports clinical outcomes to date.	Several groups have reported significantly reduced rectal doses and decreased rectal toxicity with prostate-rectal spacers, and additional evidence continues to emerge to support this promising approach	Review
te Velde BL, Westhuyzen J et al (2017). Can a peri-rectal hydrogel spaceOAR programme for prostate cancer intensity-modulated radiotherapy be successfully implemented in a regional setting? Journal of Medical Imaging and Radiation Oncology, 61, 528–533.	Retrospective case series n=125 patients with localised prostate cancer were treated with 81 Gy prostate intensity-modulated radiotherapy (IMRT). 65 with SpaceOAR 60 without SpaceOAR. Patients treated with 81 Gy in 45Fx of IMRT over 9 weeks. Follow-up: 12 weeks	Rectal volume parameters were all significantly lower in the SpaceOAR group, with an associated reduction in acute diarrhoea (13.8% vs 31.7%). There were no significant differences in the very low rates of acute and late faecal incontinence or proctitis, however, there was a trend towards increased haemorrhoid rate in the SpaceOAR group (11.7% vs 3.1%, P = 0.09).	Included in systematic review added.
te Velde BL, Westhuyzen J, Awad N et al (2019). Late toxicities of prostate cancer radiotherapy with and without hydrogel SpaceOAR insertion. Journal of Medical Imaging and Radiation Oncology. 2019.	Case series N=121 patients with localised prostate cancer (intermediate and high risk patients) treated with 81 Gy in 45 fx of IMRT over 9 weeks were retrospectively compared: 65 patients with SpaceOAR and 56 patients without SpaceOAR. Follow-up 3 years	The cumulative incidence of low-grade diarrhoea (G1) was significantly higher in the non-SpaceOAR group (21.4% vs 6.2%; P = 0.016). The cumulative incidence of proctitis (grades G1 and G2) was also higher in the non-SpaceOAR group (26.7% vs 9.2%; P = 0.015); the cumulative incidence of G2 proctitis was higher in the latter group (P = 0.043). There were no differences between the treatment groups for cumulative incidences of faecal incontinence and/or haemorrhoids. Three years after IMRT, diarrhoea and proctitis were higher in the non-SpaceOAR group, without reaching statistical significance. This finding was unchanged after correcting for baseline symptoms.	Included in systematic review added.
Teh AYM, Ko H-T et al (2014). Rectal ulcer associated with SpaceOAR hydrogel insertion during	Case report N=1 patient with intermediate risk prostate cancer.	Rectal ulcer associated with SpaceOAR hydrogel insertion during prostate brachytherapy.	Included in systematic review added.

prostate brachytherapy. BMJ Case Reports.2014 (no pagination).	Injection of hydrogel (SpaceOAR) spacer during low dose rate (LDR) prostate brachytherapy Follow-up 3 years		
Uhl M, Herfarth K et al (2014). Absorbable hydrogel spacer use in men undergoing prostate cancer radiotherapy: 12 month toxicity and proctoscopy results of a prospective multicenter phase II trial. Radiation oncology 9:96.	Case series N=52 patients with localised prostate cancer (T1-T2). Injection of a prostate-rectum spacer (polyethylene glycol hydrogel [SpaceOAR] during IMRT- 78 Gy in 2 Gy fractions Follow-up 12 months	19 (39.6%) and 6 (12.5%) patients experienced acute Grade 1 and Grade 2 GI toxicity, respectively. There was no Grade 3 or Grade 4 acute GI toxicity experienced in the study. 45 (95.7%) patients experienced no late GI toxicity (95.7%), with 2 (4.3%) patients experiencing late Grade 1 GI toxicity. There was no late Grade 2 or greater GI toxicity experienced in the study. 20 (41.7%), 17 (35.4%) and 1 (2.1%) patients experienced acute Grade 1, Grade 2 and Grade 3 GU toxicity, respectively (Table 1). There was no Grade 4 acute GU toxicity experienced in the study. 8 (17.0%) and 1 (2.1%) patients experienced late Grade 1 and Grade 2 GU toxicity, respectively. There was no late Grade 3 or greater GU toxicity experienced in the study.	Larger studies with longer follow-up included. Included in systematic review added.
Uhl M, van Triest B et al (2013). Low rectal toxicity after dose escalated IMRT treatment of prostate cancer using an absorbable hydrogel for increasing and maintaining space between the rectum and prostate: results of a multi-institutional phase II trial. Radiother Ocol 106:215-219.	Case series n=48 prostate cancer patients with hydrogel spacer injection then had intensity modulated radiotherapy (IMRT).	Hydrogel application was straight forward with minimal patient discomfort. Six patients (12%) had acute GI grade 2 toxicity, with no patients having grade 3 or 4 toxicity. In addition, no patients had early late GI toxicity ⩾ grade 2 after 12 months. The gel was stable during the course of radiotherapy and was not detectable in MRI after 9–12 months because of absorption in 42/43 patients.4 failed implantations occurred before routine implantation under TRUS guidance. 3 reports of focal rectal mucosal necrosis and bladder perforation were reported but were self-limiting without further complications. After TRUS guidance implementation no instances	Initial clinical outcomes with acute toxicity results of first 48 patients and late toxicity of 27 patients. Included in systematic review added.

		of failed implantations, perforations were reported.	
Underwood TSA., Voog JC, Moteabbed M et al. (2017). Hydrogel rectum-prostate spacers mitigate the uncertainties in proton relative biological effectiveness associated with anterior-oblique beams. Acta oncologica (Stockholm, Sweden), 56, 575-581.	Case series N=10 patients with rectal spacers treated with AO proton beams, SB proton beams and IMRT 29.2 Gy in 1.8 Gy fractions 60 Gy in 3 Gy fractions 36.25 Gy in 7.25 Gy fractions	Rectal spacers enabled the generation of anterior beam proton plans that appeared robust to modelled variation in RBE. However, further analysis of day-to-day robustness would be required prior to a clinical implementation of AO proton beams. Such beams offer almost complete femoral head sparing, but their broader value relative to IMRT and SB protons remains unclear.	Larger and longer follow-up studies included. Toxicity profile not reported.
van Wijk Y, Vanneste BGL, Walsh S, et al. (2018) Development of a virtual spacer to support the decision for the placement of an implantable rectum spacer for prostate cancer SpaceOAR 30 April 16, Technology Assessment Unit, MUHC radiotherapy: Comparison of dose, toxicity and cost-effectiveness. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2017.	Cost effectiveness (using Markov model comparing gains in quality of life versus increases in cost). Prediction model to identify patients most likely to benefit from SpaceOAR. Model included real spacers implanted (8 patients with hydrogel spacer and 15 with rectal balloon implant), and a group with virtual spacers (8 hydrogel and 8 balloon spacers) created using computed tomography scans of patients with rectal balloon implants	For a defined threshold of €80,000, the hydrogel spacer resulted in a cost-effective intervention in 2 out of 8 patients. The authors conclude that these devices are not cost-effective for all patients, and that more individual-patient information is needed.	Economic evaluation. Not in remit.
van Gysen K, Kneebone A et al (2014). Feasibility of and rectal dosimetry improvement with the use of SpaceOAR hydrogel for dose-escalated prostate cancer radiotherapy. Journal of Medical Imaging and Radiation Oncology.58 (4) 511-516.	Case series n=10 patients had 10ml injection of hydrogel and radiotherapy. Follow-up: 3 months	In the first 24 h, 2 patients had increase in bowel movement frequency. The comparison plans had identical prescription doses. Rectal doses were significantly lower for all hydrogel patients for all dose endpoints ($P < 0.001$). Post-treatment MRI showed gel stability. grade 1 bowel toxicity was reported in 6 patients during radiotherapy and 2 patients at 3 months' follow-up. No grade 2 or grade 3 acute bowel toxicity was reported.	Larger and longer follow-up studies included.
Van Gysen K, Kneebone A, Alfieri F, et al. (2013) Feasibility and rectal dosimetry improvement with the use of spaceOAR hydrogel for dose	Case series n=10 patients had 10ml injection of hydrogel and radiotherapy. Follow-up: 3 months	In the first 24 h, 2 patients had increase in bowel movement frequency. The comparison plans had identical prescription doses. Rectal doses were significantly lower for all hydrogel patients for all dose	Larger and longer follow-up studies included.

escalated prostate cancer radiotherapy. J Med Imaging Radiat Oncol. 1:59.		endpoints (P < 0.001). Post-treatment MRI showed gel stability. grade 1 bowel toxicity was reported in 6 patients during radiotherapy and 2 patients at 3 months' follow-up. No grade 2 or grade 3 acute bowel toxicity was reported.	
Van Der Meer S, Vanneste BGL et al (2016). A novel decision support method to estimate the value of a rectum spacer: 'Virtual Rectum Spacer'. Radiotherapy and Oncology (119) S638-S639.	Case series n=16 prostate cancer patients with CT imaging prior and 3-5 days after a gel RS implantation (SpaceOARTM System, Augmenix Inc.) Decision support system to predict the CT images with a 'virtual rectal spacers (RS) through non-rigid deformations based on a CT scan without RS to be integrated into a decision support system.	We have developed a novel method to simulate a model based virtual RS that is a useful tool to identify patients with a potentially high benefit of a RS implantation. The volume of the virtual RS can be estimated through the use of different deformation fields. In future, a dose comparison study is necessary to extend into a full decision support system using the virtual RS approach.	Decision support method.
Vassilis K, George M, John G et al (2013). Transperineal implementation of biocompatible balloon in patients treated with radiotherapy for prostate carcinoma: Feasibility and quality assurance study in terms of anatomical stabilization using image registration techniques. Journal of Bioequivalence and Bioavailability.5 (3), 142-148.	Case series n=10 patients with localised low risk prostate cancer treated with external 3 dimensional radiation therapy (3DCRT with 76-78 Gy in 38-39 daily fractions) combined with biodegradable balloon (ProSpace) implantation Follow-up: 3 weeks after treatment.	By using registration techniques, the ProSpace device was found stable in sequential CTs with x,y,z-axis displacements up to 2.1 mm, 3 mm and 2.2 mm respectively. The mean VAS score related to ProSpace was 1.4(± 0.5) and the mean score of rectal toxicity according to S-RS score was 1.9(± 0.6). The implementation of PROSPACE is feasible. Implant's position is relative stable. The procedure is minimally invasive with no recorded side effects. The incidence of patient-reported acute Gastrointestinal (GI) and Genitourinary (GU) toxicity as well as findings from flexible rectosigmoidoscopy, following high dose of 3DCRT after the implantation, were low.	Larger and longer follow-up studies included.
Vanneste Ben GL, Hoffmann AL (2016). Who will benefit most from hydrogel rectum spacer implantation in prostate cancer radiotherapy? A model-based approach for patient selection. Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology	Case series n=26 patients with localized prostate cancer a hydrogel rectum spacer injected. Dose distributions with (IMRT+IRS) and without (IMRT-IRS) IRS were calculated.	IMRT+IRS revealed a significant reduction in V40Gy (p=0.0357) and V75Gy (p<0.0001) relative to IMRT-IRS. For G2-3 acute GI toxicity and G2-3 LRB, the predicted toxicity rates decreased in 17/26 (65%) and 20/26 (77%) patients, and decision rules were derived for 22/32 (69%) and 12/64 (19%) respectively. From the decision rules, it follows that diabetes status	Larger studies with longer follow-up included.

and Oncology (121) 1 118-123.		has no impact on G2-3 acute toxicity, and in absence of pre-RT abdominal surgery, the implantation of an IRS is predicted to show no clinically relevant benefit for G2-3 LRB.	
Vanneste BGL, Buettner F et al (2016). Localizing the benefit of a hydrogel rectum spacer for prostate IMRT within the ano-rectal wall. Radiotherapy and Oncology (119) S412.	Case series n=26 patients with localized prostate cancer a hydrogel rectum spacer injected. Study assessed spatio-dosimetric differences in Dose-surface maps (DSMs) obtained from planned ano-rectal wall (ARW) dose distributions in patients receiving IMRT with and without implanted rectum spacer (IRS) (IMRT+IRS; IMRT-IRS, respectively).	Significant spatio-dosimetric differences in ARW DSMs exist between prostate cancer patients undergoing IMRT with and without IRS. The IRS particularly reduces the lateral and longitudinal extent of high-dose areas (>50 Gy) in anterior and superior-inferior directions.	Larger studies with longer follow-up included.
Vanneste BG, Pijls-Johannesma M, Van De Voorde L, et al. (2015) Spacers in radiotherapy treatment of prostate cancer: is reduction of toxicity cost-effective? Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2015;114(2):276- 281	Cost-effectiveness study Patients with prostate cancer who had intensity-modulated radiation therapy and a spacer (IMRT+S) versus IMRT-only without a spacer (IMRT-O). decision-analytic Markov model constructed to examine late rectal toxicity, costs and quality of life.	IMRT+S revealed a lower toxicity than IMRT-O. Treatment follow-up and toxicity costs for IMRT-O and IMRT+S amounted to €1604 and €1444, respectively, thus saving €160 on the complication costs at an extra charge of €1700 for the spacer in IMRT+S. The QALYs yielded for IMRT-O and IMRT+S were 3.542 and 3.570, respectively. This results in an incremental cost-effectiveness ratio (ICER) of €55,880 per QALY gained. For a ceiling ratio of €80,000, IMRT+S had a 77% probability of being cost-effective.	Costs not in remit of Interventional procedures programme.
Vanneste BG, Buettner F, Pinkawa M et al. (2019) Ano-rectal wall dose-surface maps localize the dosimetric benefit of hydrogel rectum spacers in prostate cancer radiotherapy. Clinical and Translational Radiation Oncology, 14: 17-24.	Case series n=26 prostate cancer patients receiving intensity-modulated radiation therapy (IMRT) with and without implantable hydrogel rectum spacers (IRS-SpaceOAR). Spatial differences in dose distributions of the ano-rectal wall (ARW) evaluated using dose-surface maps (DSMs). Dose surface maps are generated for prostate radiotherapy using an IRS.	Local-dose effects are predicted to be significantly reduced by an IRS. The spatial NTCP model predicts a significant decrease in Gr 2 late rectal bleeding and subjective sphincter control. Dose constraints can be improved for current clinical treatment planning.	Comparative dosimetric study. Larger studies included.

Vanneste BGL, Van Limbergen EJ, van de Beek K et al. (2018) A biodegradable rectal balloon implant to protect the rectum during prostate cancer radiotherapy for a patient with active Crohn's disease. Technical Innovations and Patient Support in Radiation Oncology;6:1-4	Case report Patient with Crohn's disease was implanted with a biodegradable balloon to protect the rectum during prostate cancer radiotherapy	The patient was at high-risk for rectal toxicity and was successfully irradiated to his prostate with only a grade 1 urinary toxicity, no acute rectal toxicity or toxicity flare of the IBD.	Larger studies included.
Vanneste BGL, van Wijk Y, Lutgens LC, Van Limbergen EJ, van Lin EN, van de Beek K, et al. Dynamics of rectal balloon implant shrinkage in prostate VMAT: Influence on anorectal dose and late rectal complication risk. Strahlenther Onkol. 2018;194(1):31-40	Case series N=15 patients with localized prostate cancer had a rectal balloon implanted during moderately hypofractionated prostate radiotherapy.	Despite significant decrease in rectal balloon implant volume (average 70.4%), the high-dose rectal volume and the predicted late rectal bleeding risk were not significant due to a persistent spacing between the prostate and the anterior rectal wall.	Larger studies included.
Vanneste BGL, Van Limbergen EJ, Marcelissen T et al. (2021) Is prostate cancer radiotherapy using implantable rectum spacers safe and effective in inflammatory bowel disease patients? Clinical and Translational Radiation Oncology,, 27, 121125.	Case report N= 8 patients with all-risk prostate cancer with the comorbidity of an IBD. 5 patients were treated with external beam RT (70 Gray (Gy) in 28 fractions), and 3 patients were treated with 125I-implant (145 Gy) in combination with a biodegradable prostate-rectum spacer balloon implantation. Median follow-up was 13 months (range: 3–42 months).	Only one acute grade 2 gastrointestinal (GI) toxicity was observed: an increased diarrhoea (4–6 above baseline) during RT, which resolved completely 6 weeks after treatment. No late grade 3 or more GI toxicity was reported, and no acute and late grade 2 genitourinary toxicity events were observed.	Larger studies included.
Wilton L, Richardson M, Keats S et al. (2017) Rectal protection in prostate stereotactic radiotherapy: A retrospective exploratory analysis of two rectal displacement devices. J Med Radiat Sci 64, 266–273.	Prospective cohort study (retrospective analysis of data from PROMETHEUS trial ACTRN 126150002235380) N=45 patients with non-metastatic intermediate- or high-risk prostate cancer and treated with stereotactic body radiation therapy (total dose of 19 or 20 Gy in two fractions followed by 46 Gy in 23 fractions).	In comparison (1) Rectafix demonstrated lower mean doses at 9 out of 11 measured intervals (P = 0.0012). Comparison (2) demonstrated a moderate difference with centre 2 plans producing slightly lower rectal doses (P = 0.013). Comparison (3) further demonstrated that Rectafix returned lower mean doses than SpaceOAR (P < 0.001). Although all dose levels were in favour of Rectafix, in absolute terms differences were small (2.6–9.0%). In well-selected prostate SBRT	Included in HTA added to table 2. hydrogel spacers were compared to Rectafix, a plastic rod.

	Centre 1:16 Rectafix and 10 SpaceOAR patients. Centre 2: 19 Rectafix patients. dosimetric difference between two methods of rectal displacement compared: (1) centre 1 Rectafix versus centre 1 SpaceOAR; (2) centre 1 Rectafix versus centre 2 Rectafix and (3) centre 1+ centre 2 Rectafix versus centre 1 SpaceOAR follow up time not reported.	patients, Rectafix and SpaceOAR RDD's provide approximately equivalent rectal sparing.	
Whalley D, Hruby G, Alfieri F, Kneebone A, and Eade T (2016). SpaceOAR Hydrogel in Dose-escalated Prostate Cancer Radiotherapy: Rectal Dosimetry and Late Toxicity. Clin Oncol 28(10):e148-e54.	Case series n=30 patients with prostate cancer. Injection of a prostate-rectum spacer (polyethylene glycol hydrogel (SpaceOAR) during dose escalated intensity modulated radiotherapy (IMRT) median 28 months (range 24-38)	There were no perioperative complications. Rectal doses were significantly lower for the post-hydrogel plans, especially above 65 Gy (V82 = 0.2% versus 1.3%; V80 = 0.8% versus 5.3%; V75 = 2.2% versus 9.5%; V70 = 3.7% versus 12.3%; V65 = 5.4% versus 14.7%; V40 = 22.9% versus 32% and V30 = 42.7% versus 49.4%). There was no significant difference in acute grade 1 and 2 gastrointestinal toxicity, which was 43% versus 51% and 0% versus 4.5% in the hydrogel and control groups, respectively. Late grade 1 was significantly less frequent in the hydrogel group (16.6% versus 41.8%, P ¼ 0.04).	Included in systematic review added.
Weber DC, Zilli T, Vallee J et al (2012). Intensity modulated proton and photon therapy for early prostate cancer with or without transperineal injection of a polyethylene glycol spacer: A treatment planning comparison study. International Journal of Radiat Oncol Biol Phys. 84: e311-318	Comparative case series n=8 patients with localised prostate cancer PEG hydrogel + intensity modulated radiation therapy [IMRT] (78 Gy in 39 fractions), volumetric modulated arc therapy [VMAT] (78Gy) and intensity modulated proton therapy [IMPT] (78 Gy).	Spacer injection significantly decreased the rectal dose in the 60 - 70 Gy range. Mean V70 Gy and V60 Gy with IMRT, RA and IMPT planning were 5.3+/-3.3% / 13.9+/-10.0%, 3.9+/-3.2% / 9.7+/-5.7% and 5.0+/-3.5% / 9.5+/-4.7% after Spacer injection. Spacer injection usually improved the PTV coverage for IMRT. With this technique, mean V70.2 Gy and V74.1 Gy were 100+/-0% - 99.8+/-0.2% and 99.1+/-1.2% - 95.8+/-4.6% with (p = 0.07) and without (p Z0.03) Spacer respectively. As a result of Spacer injection, bladder doses were usually higher but not significantly so.	Comparative dosimetric study. Included in systematic review added.

Wilder RB, Barme GA et al (2010). Cross-linked hyaluronan gel reduces the acute rectal toxicity of radiotherapy for prostate cancer. International Journal of Radiat Oncol Biol Phys. 77(3): 824-830.	Comparative case series with historical controls n=10 patients with early stage prostate cancer. Hyaluronan gel injection combined with HDR brachytherapy (4 fractions of twice daily for a total dose of 22 Gy) followed by IMRT to 50.4 Gy in 28 daily fractions over 5.5 weeks. Dosimetric profiles of these patients were compared with 239 historical controls without gel. Follow-up: median 3 months	There was 0% incidence of rectal toxicity versus 30% in historical controls (p=0.04). In the HA spacer group, the mean rectal radiation dose V70 Gy was 4% (73Gy) compared with 25% (106 Gy) in the control group (p=0.005) without the spacer.	Included in systematic review added.
Wilder RB, Barme GA et al (2010). Cross-linked hyaluronan gel improves the quality of life of prostate cancer patients undergoing radiotherapy. Brachytherapy.	Case series with contemporary controls n=30 had cross-linked hyaluronan gel before brachytherapy and IMRT. controls n=5 without spacer Follow-up: median 5 months	Acute GI related quality of life: results showed that EPIC bowel bother scores did not change (0±3) pre versus post-treatment for the patients who had implanted pre-radiotherapy (n=30) but scores declined by 11±14 for those who did not have the intervention (p=0.03).	Larger studies with longer follow-up included.
Wei B, See A, El-Hage L et al (2016). Dosimetric and clinical effects of hydrogel insertion in patients receiving dose-escalated prostate radiotherapy: Interim analysis of a phase II trial. Journal of Medical Radiation Sciences (63) 37.	Case series N=42 men with histologically confirmed adenocarcinoma of the prostate. Insertion of a hydrogel into the retro prostatic space undergoing dose-escalated prostate radiotherapy.	Increased perirectal space in post hydrogel scans resulted in improvement in rectal dosimetry in all patients. Our early results demonstrated that dose escalation and rectal sparing can be achieved with the application of hydrogel.	Larger and longer follow-up studies included.
Wolf F, Gaisberger C et al (2015). Comparison of two different rectal spacers in prostate cancer external beam radiotherapy in terms of rectal sparing and volume consistency. Radiotherapy & Oncology 116 (2) 221-225.	Comparative case series N=78 (30 spacer gel group versus 29 balloon spacer group versus 19 control group) patients with prostate cancer. Total dose was 75.85 Gy in daily fractional doses of 1.85 Gy prescribed to the 95% isodose using multisegmental 7-field and shoot IMRT. Follow-up 6 months.	Both spacer systems significantly reduced the rectum surface encompassed by the 95% isodose (gel: -35%, p<0.01; balloon -63.4%, p<0.001) compared to a control group. The balloon spacer was superior in reducing rectum dose (-27.7%, p=0.034), but exhibited an average volume loss of >50% during the full course of treatment of 37-40 fractions, while the volume of gel	Study included in systematic review added.

		spacers remained fairly constant.	
Wu SY, Boreta L, Wu A et al. (2018) Improved rectal dosimetry with the use of SpaceOAR during high-dose-rate brachytherapy. Brachytherapy. 17(2):259-64.	Cohort study N=18 patients with prostate cancer had HDR brachytherapy and underwent transperineal ultrasound-guided placement of 10 cc of SpaceOAR hydrogel. Then compared with 36 patients treated with HDR brachytherapy without SpaceOAR. Follow-up 13.3 months.	Patients who received SpaceOAR hydrogel had significantly lower dose to the rectum as measured by percent of contoured organ at risk (median, V80 ! 0.005% vs. 0.010%, p 5 0.003; V75 ! 0.005% vs. 0.14%, p ! 0.0005; V70 0.09% vs. 0.88%, p!0.0005; V60 5 1.16% vs. 3.08%, p!0.0005); similar results were seen for rectal volume in cubic centimetres. One patient who received SpaceOAR developed a perineal abscess 1 month after treatment.	Included in systematic review added.
Yang Y, Ford EC et al (2013).An overlap-volume-histogram based method for rectal dose prediction and automated treatment planning in the external beam prostate radiotherapy following hydrogel injection. Medical Physics.40 (1) (no pagination)	Case series n=21 prostate cancer patients Treatment planning both pre and post hydrogel injection with 5 field IMRT.	Application of the predicted rectum and bladder doses to automated planning produced acceptable treatment plans, with rectal dose reduced for eight of ten plans. The OVH metric can predict the rectal dose in the external beam prostate radiotherapy for patients with hydrogel injection. The predicted doses can be applied to the objectives of optimization in automated treatment planning to produce acceptable treatment plans.	Treatment planning study. Overlap volume histogram for rectal dose prediction evaluated.
Yang DX, Verma V, An Y et al (2020) Radiation dose to the rectum with definitive radiation therapy and hydrogel spacer versus postprostatectomy radiation therapy. Advances in Radiation Oncology, 5, 1225-1231	Retrospective analysis N=51 patients with prostate cancer who underwent RT with a hydrogel spacer (n=16) versus postoperative RT (n=35) Follow-up not reported.	Rectal dosimetry is more favourable for definitive RT (79.2 Gy) with a hydrogel spacer compared with postoperative RT (70.2 or 66.6 Gy).	Larger studies included.
Yeh J, Tokia K et al (2015). Rectal Spacer Injection in Postprostatectomy Patients Undergoing High-Dose Salvage External Beam. Oncology April (P141)	Case series n=32 patients who have had a prostatectomy and had high-dose (>72 Gy) salvage IRMT with the rectal spacer – Follow-up: 6 months	At the end of treatment, 23 patients (72%) had no change in rectal symptoms. Nine patients (28%) developed grade 1 gastrointestinal (GI) toxicity. No patients developed grade ≥ 2 GI toxicity. At 6 months after treatment, 29 patients (91%) were back to their baseline GI function, with only 3 patients (9%) with residual grade 1 GI toxicity. No	Poster presentation. Safety events reported.

		patients developed grade ≥ 2 GI toxicity.	
Yeh J, Lehrich B et al (2016). Polyethylene glycol hydrogel rectal spacer implantation in patients with prostate cancer undergoing combination high-dose-rate brachytherapy and external beam radiotherapy. Brachytherapy 15(3):283-287.	Case series N=326 prostate carcinoma patients had high-dose-rate brachytherapy 16 Gy and external beam radiotherapy of 59.4 Gy plus injected with 10 ml of a PEG hydrogel. Follow-up median 16 months	The mean anterior-posterior separation achieved was 1.6 cm (SD = 0.4 cm). Rates of acute Grade 1 and 2 rectal toxicity were 37.4% and 2.8%, respectively. There were no acute Grade 3/4 toxicities. Rates of late Grade 1, 2, and 3 rectal toxicity were 12.7%, 1.4%, and 0.7%, respectively. There were no late Grade 4 toxicities. PEG rectal spacer implantation is safe and well tolerated. Acute and chronic rectal toxicities are low despite aggressive dose escalation.	Included in systematic review added.
Zelefsky MJ, Pinitpatcharalert A, Kollmeier M, et al. Early tolerance and tumor control outcomes with high-dose ultrahypofractionated radiation therapy for prostate cancer. European Urology Oncology. 2019; doi: https://dx.doi.org/10.1016/j.euo.2019.09.006	Case series (retrospective) N=551 patients with low- or intermediate-risk prostate cancer were treated with 37.5–40 Gy SBRT in 5 fractions. 85% (471/551) received 40 Gy in 8 fractions. Follow-up 17 months SBRT	Acute grade 2 gastrointestinal (GI) toxicities occurred in 1.8% of patients, and late grade 2 and 3 GI toxicities were observed in 3.4% and 0.4% of patients, respectively. Acute grade 2 genitourinary (GU) toxicities occurred in 10% of patients, and grade 3 acute GU toxicities were observed in 0.7% of patients. Late grade 2 and 3 GU toxicities were observed in 21.1% and 2.5% of patients, respectively. The use of a hydrogel rectal spacer was significantly associated with reduced late GI toxicity and lower odds of developing late GU toxicity. The median follow-up was 17 months, and 53% of those with at least 2 years of follow up (103/193) had a biopsy performed. The 5-yr cumulative incidence of PSA failure was 2.1%, and the incidence of a positive 2-yr treatment biopsy was 12%. Limitations to this report include its retrospective nature and short follow-up time.	Included in systematic review added.
Zhang H, Wang L, Riegel AC et al. (2022) Biological effective dose in analysis of rectal dose in prostate cancer patients who underwent a combination therapy of VMAT and LDR with hydrogel spacer insertion. Journal of applied clinical	Retrospective analysis Prostate cancer patients who underwent a combination of volumetric modulated arc therapy (VMAT) and low-dose-rate (LDR) brachytherapy (35 with **hydrogel spacer** and 30 with no spacer)	Our result suggested a significant reduction of rectal doses in those patients who underwent a combination of VMAT and LDR with hydrogel spacer placement.	Dosimetry impact analysis. Larger studies with longer follow-up included.

medical physics. e13584			