Medical Policy

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Title: Hydrogel Spacer use During Radiotherapy for Prostate Cancer

Professional / Institutional
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Populations	Interventions	Comparators	Outcomes
Individuals: • With prostate cancer who are undergoing radiation therapy	Interventions of interest are: • Perirectal hydrogel spacer	Comparators of interest are: • External beam radiotherapy	Relevant outcomes include: • Symptoms • Quality of life • Treatment-related morbidity

DESCRIPTION

For low- or intermediate-risk prostate cancer, radiation therapy is an option. Because the rectum lies in close proximity to the prostate, the risk of rectal toxicity is high. One approach is to push the rectum away from the prostate, increasing the space between the 2 and reducing the radiation dose to the rectum. A variety of biomaterials, including polyethylene glycol hydrogels (e.g., SpaceOAR™ System), hyaluronic acid hydrogels (Barrigel Injectable Gel), or absorbable balloon implants (BioProtect Balloon Implant™ System), have been evaluated as perirectal spacers.

OBJECTIVE

The objective of this evidence review is to determine whether the use of a perirectal hydrogel spacer in individuals with prostate cancer who are undergoing external beam radiation therapy improves the net health outcome.

BACKGROUND

Prostate Cancer

Prostate cancer is a complex, heterogeneous disease, ranging from microscopic tumors unlikely to be life-threatening to aggressive tumors that can metastasize, leading to morbidity or death. It is the second most common cancer in men, with approximately 1 in 8 men diagnosed with prostate cancer over their lifetime.[1,] Cancer is typically suspected due to increased levels of prostate-specific antigen upon screening. A digital rectal exam may detect nodules, induration, or asymmetry, which is then followed by an ultrasound-guided biopsy with an evaluation of the number and grade of positive biopsy cores.

Clinical staging is based on the digital rectal exam and biopsy results. T1 lesions are not palpable while T2 lesions are palpable but appear to be confined to the prostate. T3 lesions extend through the prostatic capsule, and T4 lesions are fixed to or invade adjacent structures. The most widely used grading scheme for a prostate biopsy is the Gleason system.[2,] It is an architectural grading system ranging from 1 (well-differentiated) to 5 (poorly differentiated); the score is the sum of the primary and secondary patterns. A Gleason score of 6 or less is low-grade prostate cancer that usually grows slowly; 7 is an intermediate grade; 8 to 10 is high-grade cancer that grows more quickly. A revised prostate cancer grading system has been adopted by the National Cancer Institute and the World Health Organization.[3,] A cross-walk of these grading systems are shown in Table 1.

Table 1. Prostate Cancer Grading Systems

Grade Group	Gleason Score (Primary and Secondary Pattern)	Cells
1	6 or less	Well-differentiated (low grade)
2	7 (3 + 4)	Moderately differentiated (moderate grade)
3	7 (4 + 3)	Poorly differentiated (high grade)
4	8	Undifferentiated (high grade)
5	9 to 10	Undifferentiated (high grade)

REGULATORY STATUS

In October 2014, SpaceOAR™ (Augmenix, a subsidiary of Boston Scientific) was cleared by the U.S. Food and Drug Administration (FDA) through the De Novo process (DEN140030). Barrigel Injectable Gel (Palette Life Sciences) was approved by the FDA via the premarket approval process in March 2022 (K220641; FDA product code: OVB), followed by BioProtect Balloon

Implant™ System (BioProtect, Ltd) in 2023 (K222972; FDA product code: OVB).The intended and approved use of SpaceOAR System, Barrigel, and BioProtect Balloon Implant is to temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer and in creating this space it is the intent of these hydrogel spacers to reduce the radiation dose delivered to the anterior rectum.

DuraSeal® Exact (Integra) was approved by the FDA through the premarket approval process as a spine and cranial sealant (dura mater) and has been used off-label as a perirectal spacer.

POLICY

A. Hydrogel spacer use during radiotherapy for prostate cancer is considered **medically necessary** in individuals undergoing external beam radiation therapy.

B. Use of a hydrogel spacer for any other indication is **experimental / investigational**.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This policy was created with searches of the PubMed database. The most recent literature update was performed through May 22, 2024.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

HYDROGEL PERIRECTAL SPACER

Clinical Context and Therapy Purpose

Early localized prostate cancer can usually be treated with surgery and radiotherapy, although active surveillance may be adopted in men whose cancer is unlikely to cause major health

problems during their lifespan or for whom the treatment might be dangerous. In individuals with inoperable or metastatic disease, treatment consists of hormonal therapy and possibly chemotherapy. Treatment decisions are based on the anatomic extent of the lesion, the histologic grade from biopsy, and serum prostate-specific antigen (PSA) level. Other factors in treatment decisions are expected outcomes, potential complications, other medical conditions, age, comorbidities, and personal preferences. For individuals with clinically localized low-risk cancer (no palpable tumor and PSA of 10 ng/mL or less), active surveillance is an option. Definitive therapy with radical prostatectomy or radiation therapy (RT) with external beam and/or brachytherapy is also an option for low- or intermediate-risk disease. Dose escalation of RT improves cancer outcomes but also increases the risk of urinary or rectal toxicity. Image-guided RT and intensity-modulated RT may be used to limit margins and reduce toxicity, but because the rectum lies in close proximity to the prostate, the risk of rectal toxicity remains high. Hypofractionation that reduces the number of treatments, dose-escalation, and salvage RT protocols can be particularly prone to rectal toxicity.

One approach to the problem of rectal toxicity is to push the rectum away from the prostate, increasing the space between the 2 organs and reducing the radiation dose to the anterior rectal wall. A variety of biomaterials, including collagen, polyethylene glycol (PEG) hydrogels, hyaluronic acid (HA) hydrogels, and absorbable balloons have been evaluated as a means to reduce rectal radiation exposure. The SpaceOAR System is the first PEG hydrogel that was cleared by the U.S. Food and Drug Administration (FDA) specifically for use during RT of the prostate. Subsequently, Barrigel Injectable Gel, an HA hydrogel, and BioProtect Balloon Implant, an absorbable balloon hydrogel spacer, were FDA-approved in 2022 and 2023, respectively.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with prostate cancer who are being treated with external beam radiotherapy (EBRT) or brachytherapy.

Interventions
The therapy being considered is a PEG hydrogel (SpaceOAR System), an HA hydrogel (Barrigel), and an absorbable balloon hydrogel (BioProtect Balloon Implant) that is injected or implanted between the prostate and rectum.

The chemical composition of the SpaceOAR is similar to a PEG-based hydrogel that is FDA-approved as a dural sealant. Hydrodissection is achieved with saline between the retroprostatic (Denonvilliers') fascia and the anterior rectal wall using a transperineal approach. Once the needle placement is confirmed, 2 solutions in a 2-channel syringe are injected into the perirectal space. The hydrogel then polymerizes to form a soft mass. The hydrogel maintains the space for approximately 3 months, the duration of radiotherapy, and is completely absorbed by 12 months. The PEG hydrogel may be injected at the same time as the placement of fiducial markers in the prostate. The gel increases the space between the rectum and the prostate to about 12 mm. It maintains space for approximately 3 months and then is gradually absorbed and cleared.

Barrigel is composed of non-animal HA in phosphate buffered saline and is implanted transperineally between the rectum and prostate. It does not require hydrodissection prior to

injection and maintains space (about 10 mm) for approximately 3 months before gradually being absorbed and cleared.

The BioProtect Balloon Implant System is composed of an inflatable, bioresorbable copolymer balloon implant, meant to be implanted transperineally between the rectum and prostate. The balloon implant is inflated with saline and can be deflated and repositioned, if needed, providing 10 to 18 mm space height. It maintains space for approximately 3 months and then is gradually absorbed and cleared.

Comparators

The following therapies are currently being used to make decisions about the treatment of prostate cancer: EBRT or brachytherapy without a spacer. Rectal toxicity of Grade 2 or greater was reported to be 1.5% at 3 to 15 months following moderate hypofractionated EBRT, indicating a number needed to treat (NNT) of 68 to avoid 1 case of clinically significant rectal toxicity.[4,]

Outcomes

The outcomes of interest are symptoms of rectal toxicity, adverse events, and QOL.

Rectal toxicity according to the Common Terminology Criteria for Adverse Events is classified as Grade 0: no symptoms or complications; Grade 1: mild symptoms are present but no intervention is required; Grade 2: a moderate event affecting daily activities, intervention is required; Grade 3: a severe event that requires hospitalization; Grade 4: a life-threatening event; and Grade 5: death. Clinically significant rectal toxicity requiring intervention is considered to be Grade 2 or higher.

Prostate cancer-specific QOL can be measured by the Expanded Prostate Cancer Index Composite (EPIC) health-related QOL questionnaire, with 5- and 10-point thresholds for minimum clinically important differences (MCID). Skolarus et al (2015)[5,]reported the bowel and vitality/hormonal domains had an MCID 4 to 6 point range, while the sexual domain had an MCID range of 10 to 12. Urinary incontinence had a greater MCID range (6 to 9) compared with the urinary irritation/obstruction domain (5 to 7).

Although considered a surrogate outcome, studies may also report estimated radiation doses to the rectum from radiation planning, with the rectal volume predicted to receive a radiation dose over the threshold (e.g., rectal volume receiving 70 Gray [Gy]). Guidelines recommend that the volume of rectum receiving 70 Gy should be less than 10 ml.[6,]

Beneficial outcomes would be reduced rectal toxicity and reduced impairment in QOL following radiotherapy.

Harmful outcomes would be the adverse effects of the spacer, spacer insertion, or spacer absorption.

Follow-up should be for at least 2 years since the median time for the occurrence of radiation toxicity is 18 months.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

EXTERNAL BEAM RADIOTHERAPY

Pivotal Randomized Controlled Trial

Results from the pivotal RCT for the SpaceOAR System were published by Mariados et al (2015), with a 3-year follow-up published by Hamstra et al (2017) (see Table 2).[7,8,] A total of 222 men were randomized 2:1 to the spacer or control group. All individuals were implanted with fiducial markers for image-guided intensity-modulated radiation therapy and received 79.2 Gy in 1.8-Gy fractions to the prostate. The primary outcome was the percent of the rectal volume receiving 70 Gy in dose planning studies, which was 3.3% with the peri-rectal spacer and 11.7% in the control group (p<.001, see Table 3). Blinded adjudication identified no spacer-related adverse events. Grade 1 or greater adverse events were similar between the groups at 6 and 15 months but were reduced at 3 years in the group with the SpaceOAR System (2% vs. 9%, p<.03) with an NNT of 14.3. Fewer patients reported a clinically significant decline in bowel or urinary-related QOL with an NNT of 6.3 and 6.7, respectively (see Table 3). Individuals were not blinded to treatment at the 3-year follow-up.

Results from the pivotal RCT for Barrigel were published by Mariados et al (2023) to evaluate whether an HA spacer could improve rectal dosimetry and affect acute grade 2 or higher gastrointestinal toxic effects for hypofractionated radiation therapy.[9,] A total of 201 men were randomized 2:1 to the spacer or control group. All individuals were implanted with fiducial markers for image-guided intensity-modulated radiation therapy and received 60 Gy in 20 fractions to the prostate. The primary outcome was the percent of patients who achieved at least a 25% reduction in rectal volume receiving 54 Gy (V54) after placement of the HA spacer compared with the baseline rectal V54 before spacer placement, which was based on primary effectiveness end points for the PEG hydrogel pivotal trial. The primary hypothesis tested if the percentage of patients achieving the primary effectiveness outcome was greater than a minimally acceptable success rate of 70%, with 1-sided significance defined as p<.03. Of the 133 evaluable patients in the HA spacer group, 131 (98.5%) patients experienced at least a 25% reduction in rectum V54, which was significantly higher than the minimally acceptable rate of 70% (p<.001) (Table 3). In terms of adverse effects, 4 of 136 patients (2.9%) in the spacer group and 9 of 65 (13.8%) in the control group experienced acute grade 2 or higher toxic effects (p=.01). Patients were blinded to treatment assignment throughout the trial.

Table 2. Summary of Key Randomized Controlled Trial Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Mariados et al (2015)[7], Hamstra et al (2017)[8],	U.S.	20	2012-2013	222 patients with clinical stage T1 or T2 prostate cancer with Gleason score of ≤7, PSA ≤20 ng/mL, Zubrod performance status 0 to 1, who were planning to undergo IG-IMRT	149 patients who received perirectal injection of a hydrogel between the prostate and rectum prior to IG-IMRT	73 patients who received only fiducial markers inserted in the prostate prior to IG-IMRT (79.2 Gy in 1.8-Gy fractions)
Mariados et al (2023)[9],	U.S., Australia, Spain	12	2020-2021	201 patients with clinical stage T1 or T2 prostate cancer with Gleason score of ≤7, PSA ≤20 ng/mL	136 patients who received HA spacer plus fiducial markers and HFRT	65 patients who received only fiducial markers followed by HFRT

HA: hyaluronic acid; HFRT: hypofractionated radiation therapy; Gy: gray; IG-IMRT: image-guided intensity-modulated radiation therapy; PSA: prostate-specific antigen.

Table 3. Summary of Key Randomized Controlled Trial Results

Study	Rectal Volume Receiving ≥70 Gy	Percent of Patients with ≥25% Reduction in Rectal Volume Receiving ≥70 Gy	Grade ≥1 Rectal or Procedure Adverse Events at 6 mo	Patients with Grade ≥1 Late Toxicity	10 Point Decline in Bowel QOL[a]	10 to 12 Point Decline in Urinary QOL
Mariados et al (2015)[7],					*15 mo*[b] n (%)	*15 mo*
N	219	219		219	219	219
Hydrogel spacer	3.3%	97.3%	34.2%	145 (98.0%)	11.6%	≈10%
Control	11.7%	NA	31.5%	66 (93.0%)	21.4%	≈12%
p-Value	<.001		.70	.044	.087	NS
Hamstra et al (2017)[8],					*3 yr*[c] *% (95% CI)*	*3 yr*
N				140	140	140
Hydrogel spacer				2% (1 to 6)	5%	8%
Control				9% (4 to 20)	21%	23%
p-Value				<.03	.02	.03

Study	Rectal Volume Receiving ≥70 Gy	Percent of Patients with ≥25% Reduction in Rectal Volume Receiving ≥70 Gy	Grade ≥1 Rectal or Procedure Adverse Events at 6 mo	Patients with Grade ≥1 Late Toxicity	10 Point Decline in Bowel QOL[a]	10 to 12 Point Decline in Urinary QOL
OR (95% CI)					0.28 (0.13 to 0.63)	0.31 (0.11 to 0.85)
NNT				14.3	6.3	6.7
Mariados et al (2023)[9,]	**% of Patients Achieving ≥25% Reduction in Rectal Volume Receiving 54 Gy**		**Patients with Grade ≥ 1 GI and GU Acute Adverse Events (within 3 months), n (%)**	**Patients with Grade ≥ 1 GI and GU Late Adverse Events (6 months)**	**10 Point Decline in Bowel QOL at 3 months[a]**	**10 to 12 Point Decline in Urinary QOL at 3 months**
N	133					
Hydrogel spacer	98.5% (95% CI, 94.7% to 99.8%)		GI: 21 (15.4%); GU: 79 (58%)	GI: 1 (0.8%); GU: 7 (5.1%)	35 (26.5%)	57 (43.8%)
Control	NA		GI: 29 (44.6%); GU: 37 (56.9%)	GI: 5 (8.1%); GU: 7 (11.3%)	23 (37.7%)	27 (43.5%)
p-value	<.001		NA	NA	.13	NA

CI: confidence interval; GI: gastrointestinal; GU: genitourinary; Gy: gray; NA: not applicable; NNT: number needed to treat; NS: not significant; OR: odds ratio; QOL: quality of life.
[a] Expanded Prostate Cancer Index Composite health-related QOL questionnaire
[b] Difference between groups due primarily to grade 1 toxicity. There was one case of grade 3 toxicity in the control group and no cases of grade 4 toxicity.
[c] There was no grade ≥ 2 rectal toxicity in the spacer arm compared with 6% (95% CI, 2% to 17%, p<.015) in the control arm.

Limitations in relevance and design and conduct are shown in Tables 4 and 5. The primary limitation of all trials in relevance was the population, which was restricted for this pivotal controlled trial. The primary limitations in design and conduct were the lack of investigator blinding and the loss to follow-up at 3 years for the SpaceOAR trial and 6 months for the HA spacer trial.

Table 4. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Mariados et al (2015)[7,]	4. Patients with prostate volumes >80 mL, extracapsular extension, or prior radiation or surgery were excluded				1, 2. 15-month follow-up; 3-year follow-up was reported by Hamstra et al 2017
Hamstra et al (2017)[8,]	4. Patients with prostate volumes >80 mL, extracapsular extension, or prior radiation or surgery were excluded				
Mariados et al (2023)[9,]	4. Patients with prostate volumes >90 mL or prior radiation or surgery were excluded				1, 2. Only 6 month follow-up obtained.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 5. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Mariados et al, (2015)[7,]		1, 3. Not blinded to treatment assignment				
Hamstra et al (2017)[8,]		1, 2, 3. Not blinded to treatment assignment		1. 3 yr data were available for only 63% of patients		
Mariados et al (2023)[9,]		1, 2, 3.Single (patient) blinded to treatment assignment				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p-values not reported; 4.Comparative treatment effects not calculated.

Fischer-Valuck et al (2017) reported secondary analysis of magnetic resonance imaging for the 149 patients enrolled in the pivotal trial who received the hydrogel spacer.[10,] The spacer was symmetrically placed at midline for 71 (47.7%) patients, with 78 (50.9%) having some asymmetry and 3 (2.0%) with greater than 2 cm lateral distribution. The greater the asymmetry the lower the decrease in rectal radiation, although all but 4 patients achieved a 25% or greater reduction in rectal volume receiving 70 Gy. Infiltration of the rectal wall occurred in 9 (6%) patients but was not associated with procedure-related adverse events or acute or late rectal toxicity.

Systematic Reviews

Forero et al (2018) conducted a systematic review for the Technology Assessment Unit of the McGill University Health Centre.[4,] They included the RCT reported by Mariados et al (2015) and Hamstra et al (2017) and 5 non-randomized comparative studies (3 from the same institution) that evaluated the effect of SpaceOAR on rectal radiation exposure, rectal toxicity, or QOL (See Table 6). Four studies found that placement of SpaceOAR resulted in lower rectal radiation exposure, but 3 studies that assessed rectal toxicity did not show important differences between the SpaceOAR and control groups. The RCT and 3 observational studies that evaluated QOL found no major differences between the SpaceOAR and control groups in the first year of follow-up. Longer-term results were inconsistent across studies. All of the studies had major limitations. The review concluded that while SpaceOAR does reduce rectal radiation exposure, it is unclear whether this impacts rectal toxicity and QOL.[4,]

Miller et al (2020) reported a manufacturer-sponsored meta-analysis that included the studies described in Table 6 plus 2 additional prospective cohort studies, and 2 retrospective comparative studies on SpaceOAR for brachytherapy.[11,] The percentage of rectal radiation over 70 Gy was 3.5% with SpaceOAR compared to 10.4% in controls (mean difference, −6.5%; 95% confidence interval [CI], -10.5% to -2.5%; p=.001). The spacer did not reduce the risk of early grade 2 or greater rectal toxicity, but was associated in this analysis with a reduced risk of late grade 2 or higher rectal toxicity (1.5% vs 5.7%; risk ratio, 0.23; 95% CI, 0.06 to 0.99; p=.05). These results were driven by the studies by Mariados et al (2015) and Pinkawa et al (2017) described in Table 6. There was imprecision in the other 2 studies included for this outcome (te Velde et al 2019 and Whalley et al, 2016) and did not show a significant reduction of rectal toxicity. Bowel-related QOL was reported in only 2 studies (Mariados et et 2015 and Pinkawa et al 2017), with higher QOL reported in patients treated with SpaceOAR. Interpretation of these results is limited by the small number of included studies, most of which were non-randomized, and limited follow-up duration for the detection of long-term outcomes of rectal irradiation.

Babar et al (2021) conducted a systematic review describing clinical outcomes of SpaceOAR in men undergoing EBRT for localized prostate cancer.[12,] Eight studies were included, including all those analyzed in the systematic review by Miller et al (2020), plus an additional retrospective review by Navaratnam et al (2019) and a pooled analysis on long-term outcomes by Seymour et al (2020) (summarized in the Longer-term Follow-up section below). Unlike the publication by Miller et al (2020), a meta-analysis of the data was not performed. However, following a review of the available evidence, the authors concluded that SpaceOAR may be beneficial for those patients who 1) do not meet the standard rectal dose-volume criteria 2) have higher risk factors for the development of rectal toxicities post-radiation, and 3) wish to decrease the length and costs of radiotherapy by increasing the dose of radiation per fraction.

Table 6. Characteristics of Included Studies

Study	Design	Control	N SpaceOAR/ controls	Treatment	Radiation Dose - Gy	Follow-up mo	Outcome Measures			
							Rectal Dose - Volume	Acute Rectal Toxicity	Late Toxicity	Quality of Life
Mariados et al (2015) Hamstra et al (2017) [7,8,]	RCT	Blinded through 15 mo	149/73	IMRT	79.2	15 and 36	x	x	x	x
Whalley et al (2016) [13,]	Prospective cohort	Historical controls	30/110	IMRT	80	28	x	x	x	
Te Velde et al (2017) [14,]	Retrospective	Concurrent controls	65/60	IMRT	81	4	x	x	x	
Pinkawa et al (2012) [15,]	Retrospective	Matched controls	28 vs 28 vs 28	IMRT	78 vs 76 vs 70	3	x			x
Pinkawa et al (2017) [16,]			101/66	IMRT	76-80	12				x

Study	Design	Control	N SpaceOAR/ controls	Treatment	Radiation Dose - Gy	Follow-up mo	Outcome Measures			
Pinkawa et al (2017) 5 yr[17,]			54/60	IMRT	76-78	72				x

Gy: gray; IMRT: intensity-modulated radiation therapy; RCT: randomized controlled trial.

Longer-term Follow-up

Te Velde et al (2019) published a 3-year follow-up of patients from their 2017 report (See Table 6).[18,] Patients were excluded from analysis if their follow-up evaluations were not completed. The cumulative incidence of Grade 1 diarrhea (6.2% vs. 21.4%, p=.016) and Grade 2 proctitis (0% vs. 7.1%, p=.043) were statistically lower in the SpaceOAR group, but these outcome measures were not significantly different when assessed at 3 years after radiotherapy. The clinical significance of a difference between groups of Grade 1 diarrhea at any time during follow-up, but not at final follow-up, suggests that mild rectal toxicity resolves by 3 years. Fecal incontinence and hemorrhoids were not significantly different at any time point. In addition to questions of clinical significance, this study is limited by the potential for selection bias and detection bias due to unblinded and non-randomized methodology. All patients had been offered the SpaceOAR, but only patients with private insurance underwent the procedure, raising the possibility of differences in health or other personal factors between patients who had received the SpaceOAR and those who had not.

Seymour et al (2020) published 5-yr QOL outcomes from a combined data set that included patients in the studies by Mariados et al (2015) and Pinkawa et al (2017) described in Table 6.[19,] Out of 125 patients from the RCT by Mariados and 165 non-randomized patients from Pinkawa (64% with the spacer and 36% without) there were 199 men who had prospective QOL data (EPIC) with at least 24-month follow-up (median 39.5 months, range 31 to 71.4). With a prespecified clinically important decline in EPIC of at least 5 points, controls had a decline of 5.1 points compared to an increase of 0.3 points in the spacer group (difference = 5.4, p <.001). A lower percentage of patients had a decline in bowel-related QOL of at least 5 points (14% vs 36%, p=.01) and 10 points (6% vs 19%, p=.008). Out of 13 questions, 4 were significantly impaired for bowel function (urgency, loose stools) and bother (urgency, frequency) at 36 months. Limitations of the long-term follow-up remain the same as in the original RCT (Tables 4 and 5), since the patients were no longer blinded to treatment and there was a high loss to follow-up (47%).

BRACHYTHERAPY WITH EXTERNAL BEAM RADIOTHERAPY

Non-Randomized Comparative Studies

Studies on the use of a hydrogel spacer with brachytherapy and EBRT for the treatment of prostate cancer are described in Tables 7 and 8.

Several retrospective comparative studies have been published that evaluated the effect of a hydrogel spacer on rectal toxicity and quality of life in men who are treated with brachytherapy and EBRT for prostate cancer.[20,21,22,] The studies are consistent in showing a decrease in rectal

dose with insertion of a hydrogel spacer, with no adverse effect on the dose to the prostate. No study has demonstrated a benefit of a hydrogel spacer on late rectal toxicity or quality of life in these patients. Investigators have noted that there may be some instances where the brachytherapy beads have migrated close to the rectum that might benefit from a spacer, but this will require further study.

Table 7. Characteristics of Non-Randomized Comparative Studies

Study	Design	Hydrogel	Participants	N Hydrogel/ controls	Brachytherapy Dose - Gy	EBRT Dose - Gy	Follow-up	Outcome Measures			
								Rectal Dose - Volume	Acute Rectal Toxicity	Late Rectal Toxicity	Quality of Life
Chao et al (2019)[20]	Retrospective analysis of consecutive patients	SpaceOAR	Patients with intermediate and high-risk prostate cancer between 2010-2017	32/54	HDR 16	54.1	3 mo	x	x	x	
Kahn et al (2020)[21]	Retrospective analysis of consecutive patients	DuraSeal	A first and second group of 40 consecutive patients between 2013-2014	40/40	LDR 145 if monotherapy LDR 110 when used as a boost to EBRT	:	2 yr	x	x	x	
Nehlsen et al (2020)[22]	Retrospective	SpaceOAR	Patients with intermediate and high-risk prostate cancer	22/146	100	EBRT: 45 SBRT: 25	5 yr	x			x
Butler et al (2021)[23]	Retrospective analysis of	SpaceOAR	Patients who received a low-dose-	174/174			NR	x			

Study	Design	Hydrogel	Participants	N Hydrogel/ controls	Brachytherapy Dose - Gy	EBRT Dose - Gy	Follow-up	Outcome Measures			
	consecutive patients		rate permanent seed brachytherapy implant between November 2016 and July 2020								

EBRT: external beam radiotherapy; Gy: gray; HDR: high dose rate; LDR: low dose rate; NR: not reported; SBRT: stereotactic body radiotherapy.

Table 8. Summary of Non-Randomized Comparative Study Results

Study	Rectal Dose-Volume	Early Gastrointestinal Toxicity		Late Gastrointestinal Toxicity	
		> Grade 1	Grade 2	> Grade 1	Grade 2
Chao et al (2019)[20],	Median V75 (cc)				
SpaceOAR	0 (0 to 0.22)	13.3%	0%	0%	0
Control	0.45 (0 to 1.46)	30.8%	1.5%	7.7%	0
p-value	<.001	.05	.48	.11	
Kahn et al (2020)[21],	V100 (cc)				
DuraSeal	0.0 (0.0)	12.5%	0%		0
Control	0.18 (0.25)	17.5%	2.5%		0
p-value	<.001	.35		NS	
Nehlsen et al (2020)[22],	V100 (cc)				
SpaceOAR	0.09				
Control	0.17				
p-value	.04				
Butler et al (2021)[23],	Average dose (% of the prescribed dose)				
SpaceOAR	22.8				

Study	Rectal Dose-Volume	Early Gastrointestinal Toxicity		Late Gastrointestinal Toxicity	
Control	34.1				
p-value	<.001				
	Maximum dose (% of the prescribed dose)				
SpaceOAR	32.6				
Control	51.5				
p-value	<.001				

NS: not significant.
V75 = volume of structure (X%) receiving 100% of the dose
V100 = volume of structure (X%) receiving 100% of the doseEvid

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Radiology

American College of Radiology appropriateness criteria, last reviewed in 2016,[24,] for dose-volume constraints for the rectum with external beam radiotherapy are described in Table 9.

Table 9. Dose Constraints for the Rectum With External Beam Radiotherapy

EBRT Dose-Volume	Dose	<15%	<25%	<35%	<50%
Conventional Fractionation	1.8 Gy X 44 fractions (79.2 Gy total)	V75	V70	V65	V60
Hypofractionation	2.5 Gy X 25 fractions (70 Gy total)	V74	V69	V64	V59

EBRT: External beam radiotherapy; Gy: gray.
V100 = volume of structure (X%) receiving 100% of the dose

American Society of Clinical Oncology, the American Urological Association, and the American Society for Radiation Oncology

In 2018, the American Society of Clinical Oncology, the American Urological Association, and the American Society for Radiation Oncology published a joint guideline on hypofractionated radiation therapy for localized prostate cancer.[25,] The guideline recommends that men be counseled about

the small increased risk of acute gastrointestinal (GI) toxicity with hypofractionation. "Moderately fractionated EBRT [external beam radiotherapy] has a similar risk of acute and late genitourinary and late GI toxicity compared with conventionally fractionated EBRT. However, physicians should discuss the limited follow-up beyond 5 years for most existing RCTs [randomized controlled trials] evaluating moderate hypofractionation." This was a strong recommendation based on high-quality evidence and 100% consensus. Additionally, the guideline mentions that prostate-rectal spacers can be used to allow rectal dose sparing.

National Comprehensive Cancer Network
The National Comprehensive Cancer Network guideline for prostate cancer (v4.2024) provides the following recommendation in principles of radiation therapy (PROS-F), "Overall, the panel believes that biocompatible and biodegradable perirectal spacer materials may be implanted between the prostate and rectum in patients undergoing external radiotherapy with organ-confined prostate cancer in order to displace the rectum from high radiation dose regions."[26,]

National Institute for Health and Care Excellence
In 2023, NICE updated their guidance on the biodegradable spacer.[27,] The NICE recommendations state that: "Evidence on the safety and efficacy of biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer is limited in quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 10.

Table 10. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04905069[a]	Effectiveness of the SpaceOAR Vue System in Subjects With Prostate Cancer Being Treated With Stereotactic Body Radiotherapy	500	Apr 2030
NCT05597852	Feasibility of Integrating Rectal Hydrogel Spacer for Salvage Treatment Using Stereotactic Ablative Body Radiotherapy for Locally Recurrent Prostate Cancer	10	Nov 2027
NCT05650021	Radiopaque Hydrogel Rectal Spacer for Prostate Cancer Radiation Image Guidance	30	Sep 2025
NCT05354440[a]	Long-Term Prospective Post Marketing Clinical Follow Up for Evaluation of the BioProtect Balloon Implant System	80	Jan 2026
Unpublished			
NCT05354427[a]	Evaluation of Commercially Available Implantable Spacers, in Prostate Cancer Patients Undergoing Radiotherapy	175	Jan 2022

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT00462124[a]	One-arm, Multi-center, Prospective Study to Assess the Safety and Efficacy of BioProtect Biodegradable Implantable Balloon in Prostate Cancer Subjects Undergoing Radiotherapy	7	May 2009

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
55874	Transperineal placement of biodegradable material, peri-prostatic, single or multiple injection(s), including image guidance, when performed

REVISIONS	
04-08-2020	Policy published April 8, 2020. Policy effective April 8, 2020.
06-01-2021	Updated Description section
	In the Policy section • In Item A-Replaced "experimental/investigational" with "medically necessary in individuals undergoing external beam radiation therapy."
	Updated Rationale section
	In the Coding section • Added ICD-10 codes C61, C79.82, D07.5, D29.1, D40.0, D49.59
	Updated References Section
09-17-2021	Updated Rationale Section
	Updated References Section
09-13-2022	Updated Description Section
	Updated Rationale Section
	Updated References Section
09-12-2023	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Removed ICD-10 Codes
	Updated References Section
08-27-2024	Updated Description Section
	Updated Rationale Section
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