# Hydrogel spacer use during radiotherapy for prostate cancer

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Policy contains: Hydrogel spacer; polyethylene glycol; radiotherapy; prostate cancer; rectum

*This policy is a Sandhills Center Clinical Coverage Policy adopted from AmeriHealth Caritas of North Carolina. These clinical policies are used to assist with making coverage determinations. Sandhills Center's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Sandhills Center when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Sandhills Center clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Sandhills Center's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Sandhills Center will update its clinical policies as necessary. Sandhills Center clinical policies are not guarantees of payment.*

## Coverage policy

Hydrogel spacer is clinically proven and, therefore, medically necessary for reducing exposure of the rectum to radiotherapy in members with prostate cancer (Centers for Medicare & Medicaid Services, 2020; Morgan, 2018; National Comprehensive Cancer Network, 2020).

Polyethylene-glycol hydrogel is covered once in patients with clinically localized prostate cancer when any of the following are present:

- Low* or favorable intermediate prostate cancer risk group.
- Dose escalated (≥ 76 Gy) conventional fractionation (1.8 – 2 Gy fractions) or moderate hypofractionation (2.4 – 3.4 Gy fractions) image-guided, intensity-modulated radiation therapy planned.
- Eastern Cooperative Oncology Group performance status ≤ 1.
- Modern localization techniques would be insufficient to improve oncologic cure rates and/or reduce side effects due to at least one of the following:
    - Anatomic geometry precluding ideal rectal constraints (V70 < 10%, V65 < 20%, V40 < 40%):
- Conventional fractionation (V70 < 10%, V65 < 20%, V40 < 40%).
- Moderate HPX (dose constraints not yet standardized; employ those used in the supporting phase III trials).

- Medication usage (e.g., anticoagulants).
- Comorbid conditions (e.g., increased age, history of myocardial infarction or congestive heart failure).

None of the following exclusion criteria are present:

- Less than five-year life expectancy and asymptomatic.
- Prior prostate cancer treatment (surgery or radiation therapy).
- Active bleeding disorder or clinically significant coagulopathy.
- Active inflammatory or infectious disease in the perineum or injection area (e.g., prostatitis, anorectal inflammatory bowel disease).
- Prostate volume > 80 cc.

* Life expectancy ≥ 20 years (very low risk); ≥ 10 years (low risk)

Limitations

All other uses of hydrogel spacer are investigational/not clinically proven.

Alternative covered services

Endorectal balloon.

## Background

Prostate cancer is the most commonly diagnosed cancer among American males, with an estimated 191,930 cases in 2020. The estimated annual number of deaths from the disease in the United States is 33,330 (Howlader, 2020).

Prostate cancer patients can be treated with external beam radiotherapy (including intensity-modulated radiotherapy or stereotactic body radiation therapy), or with hypofractionated radiotherapy, proton beam therapy, and brachytherapy. The proximity of the rectum to the prostate gland raises the risk of rectal toxicity after radiation therapy for prostate cancer, prompting research on ways to minimize this adverse effect (Afkhami Ardekani, 2020; Forero, 2018).

Various materials, including collagen, polyethylene glycol hydrogel spacers, and absorbable balloons have been evaluated to reduce rectal radiation exposure. Radioprotective spacers, first reported 30 years ago for radiotherapy of tongue and abdominal cancers, have been developed for prostate cancer (Tang, 2018).

SpaceOAR™ (Augmenix) is a polyethylene-glycol hydrogel, injected through a trans-perineal approach into the Denonvilliers' space, under general or local anesthesia. The gel hardens to a soft hydrogel within 10 seconds, creating a separation of at least 10 mm between the prostate and rectum, in the attempt to limit rectal toxicity from relatively high doses of radiation; forms of toxicity include rectal urgency, diarrhea, bleeding, and pain (Forero, 2018). After three months (during radiotherapy) the gel undergoes hydrolysis, liquefaction, and absorption into the bloodstream, where it leaves the body through renal filtration (Karsh, 2018).

In April 2015, the U.S. Food and Drug Administration gave de novo clearance to Augmenix Inc. to use SpaceOAR in prostate cancer patients before they received radiation therapy. Previously, SpaceOAR was already approved for use in Europe and Australia (WGC FDA News, 2015). Augmenix was acquired by Boston Scientific Corporation (Marlborough, Massachusetts) in 2018. The Food and Drug Administration allowed legal marketing

of the device in July 2019 (U.S. Food and Drug Administration, 2019). The company claims that 50,000 procedures using SpaceOAR for prostate cancer have been performed worldwide (Spaceoar.com, 2021).

Another product used in hydrogel spacer procedures for prostate cancer is DuraSeal® (Covidien, Mansfield, Massachusetts). It has no Food and Drug Administration approval for this use, but is used off-label, having been approved in 2005 as an adjunct to sutured dural repair during spinal surgery (Afkhami Ardekani, 2020).

## Findings

The National Comprehensive Cancer Network guideline on prostate cancer includes a section on radiation therapy. The section states 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" (National Comprehensive Cancer Network, 2021).

The American Urological Association, American Society for Radiation Oncology, and American Society for Clinical Oncology collaborated on a guideline on hypofractionated radiation therapy for localized prostate cancer. The guideline supported use of one or more of the following: protocols to ensure that the bladder is comfortably full at time of treatment; prostate-rectal spacers to allow rectal dose sparing; and rectal balloon devices to assist in prostate immobilization (Morgan, 2018).

The National Institute for Health and Care Excellence issued a technology assessment supporting use of inserting biodegradable spacers in persons with prostate cancer prior to radiotherapy to reduce rectal toxicity, based on safety and efficacy evidence, and performed only by appropriately trained and experienced clinicians (National Institute for Health and Care Excellence, 2017).

The Centers for Medicare & Medicaid Services issued a Local Coverage Determination specifying criteria supporting medical necessity for use of hydrogel spacer prior to radiotherapy in males with prostate cancer, specified in the coverage section of this policy (Centers for Medicare & Medicaid Services, 2020).

An interdisciplinary consensus statement after a meeting of radiation oncologists and urologists experienced in hydrogel spacer injections concluded that the treatment's main indication was dose-escalated radiotherapy for histologically confirmed low- or intermediate-risk prostate cancer. The group did not recommend the treatment in cases of locally advanced prostate cancer (Muller, 2016).

A systematic review of eight studies of patients with localized prostate cancer undergoing external beam radiation therapy for localized prostate cancer found SpaceOAR reduced rectal radiation dose volume. Four studies analyzed toxicity; SpaceOAR decreased acute Grade 1 diarrhea in one study, and decreased late Grade 1 and Grade ≥2 rectal toxicities in two others. One study reported fewer large declines in bowel quality of life at three years among SpaceOAR patients, but another reported no benefit after five years (Babar, 2021).

A systematic review of 19 studies (n = 3,622) of outcomes in prostate cancer patients revealed SpaceOAR significantly reduced rectal radiation dose, regardless of type of radiation therapy. Use of the device also reduced gastrointestinal and genitourinary toxicities. Only one of the 19 studies was randomized (Armstrong, 2021).

A systematic review of nine studies (n = 1,208) of males with prostate cancer randomized 671 patients and 537

controls according to whether they received polyethylene glycol hydrogel spacer (DuraSeal or SpaceOAR) prior to brachytherapy. Insertion failure was 1%. The acute gastrointestinal complication rate was 33.7% for grade 1-2 toxicity, and 0.22% for grade 3-4 toxicity. (Vaggers, 2021).

A systematic review and meta-analysis of seven studies (one randomized, n = 1,011) of prostate cancer compared 486 subjects who received a hydrogel spacer prior to radiotherapy to 525 who did not. Mean follow-up was 26 months. The success rate of placement was 97.0%. Procedural complications were observed in < 10% of patients and were mild and transient. The treatment group received 66% less v70 rectal irradiation versus controls (3.5% and 10.4%, *P* = .001). The risk of grade 2 or higher rectal toxic effects was similar in early follow-up (4.5% and 4.1%, *P* = .38), but was 77% lower in the treatment group in late follow-up (1.5% vs 5.7%, *P* = .05). Changes in bowel-related quality of life were similar (*P* = .92) but greater in the hydrogel spacer group in late follow-up (*P* < .001) (Miller, 2020).

A systematic literature review of 21 studies addressing various rectal displacement devices during prostate external beam radiation therapy included four on hydrogel spacer effects. Compared with the endorectal balloon, the hydrogel spacer significantly reduces rectal dose and toxicity without influencing prostate immobilization (Afkhami Ardekani, 2020). Authors also found hydrogel spacers, compared with endorectal balloons, significantly reduced rectal dose and toxicity, with no effect on prostate immobilization (Afkhami Ardekani, 2021).

A review by the Canadian Agency for Drugs and Technology in Health was based on an October 4, 2017, literature search. Evidence was used from three systematic reviews, one randomized controlled trial, seven non-randomized studies, two economic evaluations, and three evidence-based guidelines. Authors found most studies were not of good quality. While acknowledging spacers led to reductions in rectal radiation dose, authors assert reduced rectal dose "did not translate into clinically important reductions in acute or long-term rectal toxicity, quality of life, and rectal bleeding within the first year of follow-up (Chao, 2019).

A Cochrane review of 92 studies on gastrointestinal effects of pelvic radioactivity for primary pelvic cancers included a statement that low-certainty evidence suggests balloon and hydrogel spacers for prostate cancer radiotherapy may make little or no difference to gastrointestinal outcomes (Lawrie, 2018).

## References

On August 11, 2021, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were "hydrogel spacer," "polyethylene glycol," "radiotherapy," "prostate cancer," and "rectum." We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

Afkhami Ardekani M, Ghaffari H. Optimization of prostate brachytherapy techniques with polyethylene glycol-based hydrogel spacers: A systematic review. *Brachytherapy*. 2020;19(1):13-23. Doi: 10.1016/j.brachy.2019.08.009.

Afkhami Ardenkani M, Ghaffari H, Navaser M, Moghaddam SHZ, Refahi S. Effectiveness of rectal displacement devices in managing prostate motion: A systematic review. *Strahlenther Onkol*. 2021;197(2):97-115. Doi: 10.1007/s00066-020-01633-9.

Armstrong N, Bahl A, Pinkawa M, et al. SpaceOAR hydrogel spacer for reducing radiation toxicity during radiotherapy for prostate cancer: A systematic review. *Urology*. 2021;S0090-4295(21)00421-0. Doi: 10.1016/j.urology.2021.05.013.

Babar M, Katz A, Ciatto M. Dosimetric and clinical outcomes of SpaceOAR in men undergoing external beam radiation therapy for localized prostate cancer: A systematic review. *J Med Imaging Radiat Oncol*. 2021;65(3):384-397. Doi: 10.1111/1754-9485.13179.

Centers for Medicare & Medicaid Services. Prostate Rectal Spacers. https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=37485&ver=14&Date=&DocID=L37485&bc=ggAAAAIAAAAA&. Local Coverage Determination DL37485. Effective August 1, 2020.

Chao Y-S, MacDougall D, de Nanassy A. Hydrogel spacers for patients with prostate cancer: A review of clinical effectiveness and cost-effectiveness. Canadian Agency for Drugs and Technologies in Health. https://www.ncbi.nlm.nih.gov/books/NBK544671/. Published February 22, 2019.

Forero DF, Almeida ND, Dendukuri N. Hydrogel spacer to reduce rectal toxicity in prostate cancer radiotherapy: a health technology assessment. Technology Assessment Unit of the McGill University Health Centre. Report number 82. https://muhc.ca/sites/default/files/micro/m-TAU/SpaceOAR.pdf. Published April 16, 2018.

Howlader N, Noone AM, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975-2017, National Cancer Institute. https://seer.cancer.gov/csr/1975_2017/. Published April 15, 2020.

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. Doi: 10.1016/j.urology.2017.11.016.

Lawrie TA, Green JT, Beresford M, et al. Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy for primary pelvic cancers. *Cochrane Database Syst Rev*. 2018;1(1):CD012529. Doi: 10.1002/14651858.CD012529.pub2.

Mariados N, Sylvester J, Shah D, et al. Hydrogel spacer prospective multicenter randomized controlled pivotal trial: Dosimetric and clinical effects of perirectal spacer applicxation in men undergoing prostate image guided intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys*. 2015;92(5):971-977. Doi: 10.1016/j.ijrobp.2015.04.030.

Miller LE, Efstathiou JA, Bhattacharyya SK, Payne HA, Woodward E, Pinkawa M. 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 Netw Open*. 2020;3(6):e208221. Doi: 10.1001/jamanetworkopen.2020.8221.

Morgan SC, Hoffman K, Loblaw DA, et al. Hypofractionated radiation therapy for localized prostate cancer: An ASTRO, ASCO, and AUA evidence-based guideline. *J Urol*. 2018;S0022-5347(18)43963-8. Doi: 10.1016/j.juro.2018.10.001.

Muller A-C, Mischinger J, Klotz T, et al. Interdisciplinary consensus statement on indication and application of a hydrogel spacer for prostate radiotherapy based on experience in more than 250 patients. *Radiol Oncol*. 2016;50(3):329-336. Doi: 10.1515/raon-2016-0036.

National Comprehensive Cancer Network. Prostate Cancer: NCCN Evidence Blocks. Version 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Published March 19, 2021.

National Institute for Health and Care Excellence. Biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer. Interventional procedures guidance number 590. https://www.nice.org.uk/guidance/ipg590/chapter/1-Recommendations. Published August 23, 2017.

SpaceOar.com. SpaceOARTM Hydrogel: Minimally Invasive Prostate Cancer Pre-Treatment Option. https://learn.spaceoar.com/patient-adwords-form/?keyword=spaceoar&gclid=EAIaIQobChMIxIzwqaa78gIVaGxvBB01IA6nEAAYAyAAEgLVMvD_BwE. Published 2021.

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.

U.S. Food and Drug Administration. Letter from Thalia T. Mills re. SpaceOAR Vue Hydrogel. https://www.accessdata.fda.gov/cdrh_docs/pdf18/K182971.pdf. Published July 19, 2019.

Vaggers S, Rai BP, Chedgy ECP, de la Taille A, Somani BK. Polyethylene glycol-based hydrogel rectal spacers for prostate brachytherapy: A systematic review with a focus on technique. *World J Urol*. 2021;39(6):1769-1780. Doi: 10.1007/s00345-020-03414-6.

WGC FDA News. Augmenix's SpaceOAR Prostate Treatment Receives FDA Clearance. https://www.fdanews.com/articles/170661-augmenixs-spaceoar-prostate-treatment-receives-fda-clearance. - Published April 6, 2015.

## Policy updates

11/2020: initial review date and clinical policy effective date: 12/2020

11/2021: Policy references updated.