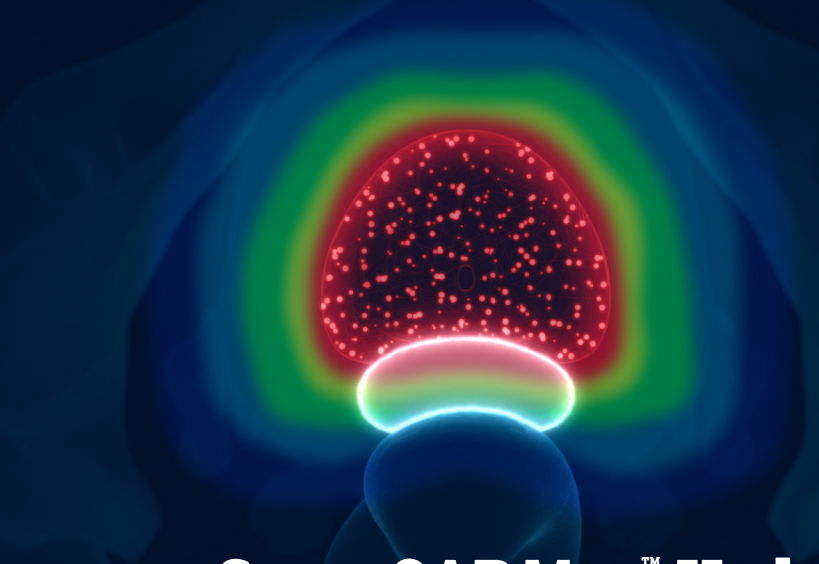

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SpaceOAR Vue™ Hydrogel

The Next-Generation Radiopaque Hydrogel Spacer

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Summary

- SpaceOAR Vue™ Hydrogel is the next-generation of SpaceOAR™ Hydrogel, a polyethylene glycol-based perirectal hydrogel spacer that is designed to position the anterior rectal wall away from the prostate during radiation
- SpaceOAR Vue Hydrogel is not contraindicated for use in patients with known iodine allergy, as the iodine is covalently bound and not in free form
- SpaceOAR Vue Hydrogel is designed to be well-visualized and contoured on CT simulation radiotherapy planning scans since the hydrogel contains covalently bound iodine, similar to intravenous contrast
- MRI may not be required for contouring because SpaceOAR Vue Hydrogel is designed for enhanced visibility on CT, expanding hydrogel spacer use to patients who cannot undergo MRI scans
- SpaceOAR Vue Hydrogel follows the same general placement protocol as SpaceOAR Hydrogel with the major difference that SpaceOAR Vue Hydrogel has increased viscosity and polymerizes more slowly
- SpaceOAR Vue Hydrogel may be easily distinguished from SpaceOAR Hydrogel due to its enhanced visibility on kV cone-beam CT used for daily image-guided radiation therapy

Introduction

Prostate cancer is the most common non-cutaneous cancer diagnosis and second leading cause of cancer death for men in the United States, with over 164,000 new cases and nearly 30,000 deaths estimated for 2020.[1] Radiotherapy is a non-invasive treatment alternative to surgery that has comparable clinical outcomes,[2,3] while avoiding surgical risks. Radiotherapy is a standard treatment option for patients with prostate cancer.

One drawback of radiotherapy is that healthy tissue surrounding the target area may inadvertently receive radiation, which can lead to side effects.[4] When healthy tissue receives radiation the organ at greatest risk for prostate cancer radiotherapy side effects is the rectum, due to the anatomic proximity of the anterior rectal wall within a few millimeters' posterior to the prostate.[5] Radiotherapy of the prostate is associated with dose-dependent side effects in the GI tract, which are further increased when pelvic lymph nodes are in the treatment field.[6-13] Both acute and late GI toxicities correlate with the volume of rectum that is included in the high-dose radiation field of the prostate.[4,14] Late rectal toxicity constitutes a spectrum of symptoms that can include increased stool frequency, cramping/tenesmus, fecal incontinence, rectal bleeding, and fistula formation that can significantly reduce a patient's quality of life following treatment.[15,16]

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Despite improvements in radiotherapy treatment techniques, GI toxicity can be a significant concern for patients undergoing prostate cancer treatment. Late GI toxicity is associated with factors commonly encountered in the prostate cancer patient population, namely advanced age and existing comorbidities.[17] Late GI toxicity is associated with the maximal rectal dose and volume of the anterior rectal wall irradiated, which can significantly decrease patient-reported quality of life.[4,15,16,18-21] Patient-reported outcomes are valuable metrics for assessing these side effects that often occur long after treatment ends.[22,23] Some approaches to increase patient convenience include using hypofractionated and ultra- hypofractionated (i.e., stereotactic body radiation therapy, SBRT) regimens, which are associated with comparable biochemical recurrence-free survival but may still be associated with increased late GI toxicity.[24-29] Fortunately, there are techniques that can limit the exposure of healthy GI tissue during radiation therapy for prostate cancer.

One pre-radiation approach to reduce radiation-associated rectal toxicity is to physically increase the distance between the rectum and prostate in a temporary manner.[30] The anterior rectal wall is typically within 2-3 mm of the posterior prostate border and is separated from the prostate and bladder by a single multi-layered fibromuscular fascia (i.e., Denonvilliers'). This tissue plane is a potential space that can be artificially expanded using exogenously introduced material such as rapidly polymerizing hydrogel.[5] In the authors' opinion, artificial expansion of the perirectal space prior to starting radiotherapy should:

- Be reproducible
- Be easily and safely performed in the outpatient setting with minimal time investment
- Cause minimal to no patient discomfort while in place
- Remain stable throughout the course of radiotherapy planning and treatment
- Have minimal to no adverse effect on daily setup and treatment
- Biodegrade within a reasonable timeframe following completion of therapy

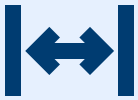
SpaceOAR™ Hydrogel (OAR = organs at risk) (Boston Scientific, Marlborough, MA) was designed to address these listed characteristics of an ideal spacer. Approved by the Food and Drug Administration (FDA) as well as CE marked, the SpaceOAR System is intended to temporarily displace the anterior rectal wall so as to reduce radiation exposure during prostate cancer radiotherapy treatment. Recently, a second-generation hydrogel spacer, SpaceOAR Vue™ Hydrogel, was developed by Boston Scientific that uses the characteristics of traditional SpaceOAR Hydrogel, while providing a contrast agent designed to be easily tracked by CT imaging. The purpose of this paper is to describe SpaceOAR Hydrogel and to highlight potential key benefits of SpaceOAR Vue Hydrogel for clinicians interested in using a hydrogel spacer for patients undergoing radiation therapy for prostate cancer.

SpaceOAR Hydrogel

SpaceOAR Hydrogel is a polyethylene glycol (PEG) hydrogel injected into the perirectal space prior to radiotherapy that reduces the amount of radiation to the anterior rectal wall through physical displacement of the rectum posteriorly away from the prostate.[5] A hydrogel is a material that forms from a chemical reaction of liquid components that crosslink monomeric subunits into polymers. These polymers absorb water and increase to several times the volume of the dissolved monomeric subunits.[31] For SpaceOAR Hydrogel, these polymers are comprised of PEG stabilized by crosslinking with trilysine to create a soft but non-deformable hydrogel that is designed to remain stable for approximately 3 months following placement.[32]

A key point of the SpaceOAR Hydrogel is that polymerization occurs rapidly upon mixing of the solubilized monomers and polymerizing agents. For perirectal spacing this is accomplished via rapidly mixing the liquid components and injecting them into the perirectal space between Denonvilliers' fascia and the anterior rectal wall through an aseptic transperineal approach under transrectal ultrasound guidance. Proper placement can be achieved following basic in-office training with a high success rate (> 98%).[5] The crosslinks that initially provide the hydrogel with firmness needed to displace the rectum away from the prostate are slowly hydrolyzed in the months after placement and are ultimately removed from the body by the kidneys. SpaceOAR Hydrogel is designed to exhibit complete resorption at 12 months post-placement as assessed by MRI.[32]

SpaceOAR Hydrogel is designed to successfully displace healthy tissue to decrease the amount of radiation delivered to the rectum. In a pivotal phase 3 trial of SpaceOAR Hydrogel, the distance between the posterior wall of the prostate and anterior rectal wall was increased by a mean of nearly 1.3 cm compared to 0.1 cm in patients with no spacer.[5] This distance was slightly less in patients with prostate glands > 80 to 100 cm^3 (9.9 mm) and > 100 cm^3 (8.8 mm).[33]



Increasing the distance between the prostate radiation target and anterior rectal wall corresponded with a significant reduction in the amount of radiation reaching the rectum.

Mariados et al. reported the mean volume of the rectum receiving 70 Gy (V70) had nearly a 10% decrease (12.4% vs. 3.3%, $P < 0.001$) in patients who had SpaceOAR Hydrogel.[5] Patients with larger prostates had a mean rV70 of 2.6% and 2.0% in patients with glands > 80 to 100 cm^3 and > 100 cm^3, respectively.[33] A meta-analysis including over 1000 patients across 7 hydrogel spacer trials demonstrated a mean perirectal separation of 1.1 cm and a 66% reduction in rectal V70.[34] Creating space between the prostate and rectum has been shown to significantly decrease the amount of radiation received by rectal tissue.[5]

Decreasing the amount of radiation received by healthy GI tissue has led to fewer bowel-related side effects. While the benefits of SpaceOAR Hydrogel correlate with a known dosimetric constraint (rectal V70) predictive for rectal toxicity, patients whose treatment plans met established Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) rectal constraints also reported improvement in their symptoms.[35] One study demonstrated that patients who had SpaceOAR Hydrogel during radiation therapy underwent significantly fewer endoscopic evaluations and treatment for bowel symptoms by 16% and 11%, respectively.[36] Patients who received SpaceOAR Hydrogel and dose-escalated radiotherapy continued to report lower rates of Grade ≥1 (9.2 vs. 2.0%, $P = 0.028$) and Grade ≥2 (5.7% vs. 0%, $P = 0.012$) rectal toxicity at 3 years post-treatment compared to patients without a spacer.[37] Another study showed a 77% reduction in ≥ Grade 2 long-term rectal side effects.[34] A pooled analysis of patient-reported outcomes for bowel-related quality of life showed a continued benefit of reduced bowel urgency, loose stools and frequency at up to 3 years post treatment.[36,38]

Using a hydrogel spacer can significantly improve bowel-related side effects in patients receiving radiotherapy treatment for prostate cancer.

Using a hydrogel spacer can also decrease radiation reaching other key areas of healthy tissue and improve late-occurring side effects in systems outside of the bowel. On a secondary analysis, SpaceOAR Hydrogel patients exhibited a decreased penile bulb radiation dose and reported improved erectile function, maintenance of potency (66.7% vs. 37.5%, $P = 0.046$), and higher scores on 7/13 patient-reported sexual health questions ($P < 0.05$) at 3 years post treatment compared to patients without spacer.[39] Since interventions for the late effects of radiotherapy for prostate cancer are not comprehensively studied, and it can be difficult to predict those patients who will experience side effects, use of a hydrogel like SpaceOAR can provide a treatment approach for patients who want to reduce their likelihood of experiencing late side effects.[40]

SpaceOAR Vue Hydrogel

SpaceOAR Vue Hydrogel received FDA approval in 2019, as well as CE marked in April 2020 and is a modification of standard SpaceOAR Hydrogel, containing approximately 1% iodine by volume covalently bound to the PEG hydrogel.

The addition of iodine to SpaceOAR Vue Hydrogel allows for enhanced viewing on CT planning (average HU of around 300) and daily cone-beam CT scans for image-guided radiation therapy,

while the high comparable water content of the hydrogel allows it to retain visibility on T2 MRI like SpaceOAR Hydrogel (Figure 1 - B and D). Despite its iodine content, SpaceOAR Vue Hydrogel is not contraindicated in patients with iodine allergy since the iodine is covalently bound to the PEG polymer. SpaceOAR Vue Hydrogel's design for CT visibility may give physicians another tool if T2 MRI imaging is not an option (Figure 1-C).

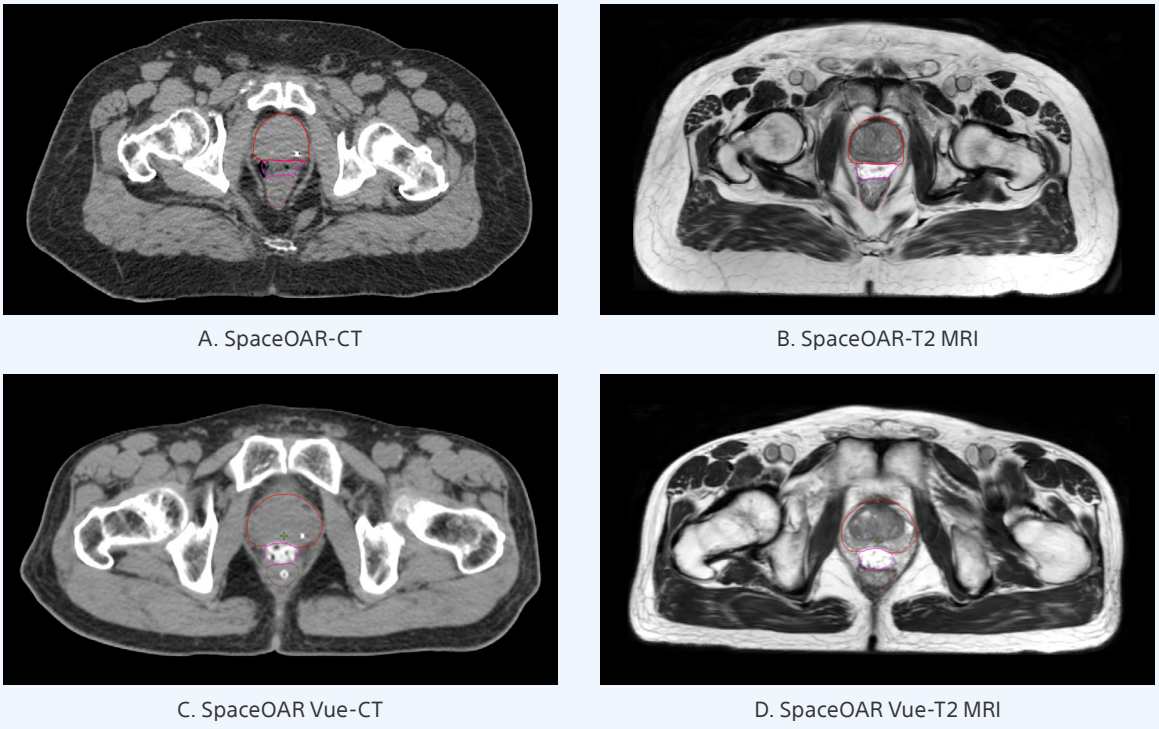
With standard SpaceOAR Hydrogel, injection into the perirectal space must be uniform and rapid (within 10 seconds) to reduce polymerization and occlusion of the injection needle. There is little time to correct for hydrogel asymmetry if hydrogel placement is started at an off-axis position. Asymmetric SpaceOAR Hydrogel placement has a small impact on dosimetry, with significant reduction in rectal radiation dose sparing occurring only with lateral hydrogel asymmetry > 2 cm from midline.[41] While such deviation has been observed to occur only in a small subset of patients,[41] technical considerations such as proper hydrodissection and precise needle placement are beneficial for successful midline placement of the hydrogel. In the authors' experience, unlike SpaceOAR Hydrogel with its 10-second polymerization rate, SpaceOAR Vue Hydrogel took 20-25 seconds to polymerize after starting the injection, making it more forgiving with regards to suboptimal placement in the perirectal space.

In the authors' experience, SpaceOAR Vue Hydrogel appears to provide perirectal spacing that is comparable to SpaceOAR Hydrogel. Unpublished data from the first 5 patients (average age = 72.6 ± 7.1 years) who received SpaceOAR Vue Hydrogel prior to external beam radiation (70 Gy/28 fractions) demonstrated an average anterior-posterior displacement of the rectum at mid-gland of 1.44 ± 0.24 cm. For placements 1 cm superior to mid-gland, the average anterior-posterior distance was 1.48 ± 0.40 cm, and for 1 cm inferior to mid-gland the average anterior-posterior distance was 1.37 ± 0.35 cm. The average hydrogel volume contoured on CT simulation scan following injection of 10 mL of SpaceOAR Vue Hydrogel into the perirectal space was 10.50 ± 1.19 cm^3. The average HU on CT simulation scans of these 5 patients was 150.92 ± 18.66 HU. Hydrogel placement was symmetric in 5/5 (100%) patients as assessed using a previously published symmetry scoring metric [41]. The average radiation dose to 90% of the rectal volume was 223.7 ± 163 cGy. Figure 2 displays the similarity in dose volume histograms (DVH) between SpaceOAR and SpaceOAR Vue Hydrogel. These data show perirectal spacing distance, hydrogel symmetry, and rectal DVH.

Workflow Advantages with SpaceOAR Vue Hydrogel vs. SpaceOAR Hydrogel

SpaceOAR Vue Hydrogel affords the opportunity for several changes to the workflow of hydrogel placement, simulation, and daily image-guided radiotherapy (IGRT) including:

- May increase hydrogel availability for practices that do not have access to MRI simulators by avoiding the added cost and inconvenience of MRI since SpaceOAR Vue Hydrogel is designed to be visible on CT
- The radiopacity of SpaceOAR Vue Hydrogel may provide a suitable option to MRI with implanted metallic devices, such as patients with pacemakers or defibrillators, both of which are contraindications to MRI[42]
- Opportunity to eliminate dependence on MRI simulation and fusion to CT planning scans in order to accurately contour hydrogel within the perirectal space
- May reduce daily treatment localization time by increasing the efficiency of patient repositioning with daily IGRT since SpaceOAR Vue Hydrogel is visible on kV cone-beam CT and may serve as an additional reference



A. SpaceOAR-CT

B. SpaceOAR-T2 MRI

C. SpaceOAR Vue-CT

D. SpaceOAR Vue-T2 MRI

Figure 1. SpaceOAR Hydrogel vs. SpaceOAR Vue Hydrogel on CT and 1.5T T2 MRI simulation scans. Representative axial CT and T2 MRI simulation scan images from two patients who received perirectal hydrogel spacer with SpaceOAR Hydrogel (A, B) or SpaceOAR Vue Hydrogel (C, D). For SpaceOAR Hydrogel (A, B) hydrogel was contoured on MRI and modified based on CT, whereas for SpaceOAR Vue Hydrogel (C, D) hydrogel was contoured directly on the CT simulation scan. Note that for SpaceOAR Hydrogel (A, B) the T2 MRI hyperintense region in B between the prostate and rectal contours is not easily seen on CT in A. For SpaceOAR Vue Hydrogel, the hyperintense region on the T2 MRI in D corresponds to the hyperdense region between the prostate and rectum on CT in C. Red- prostate contour, Magenta- hydrogel contour, Brown- rectal contour.

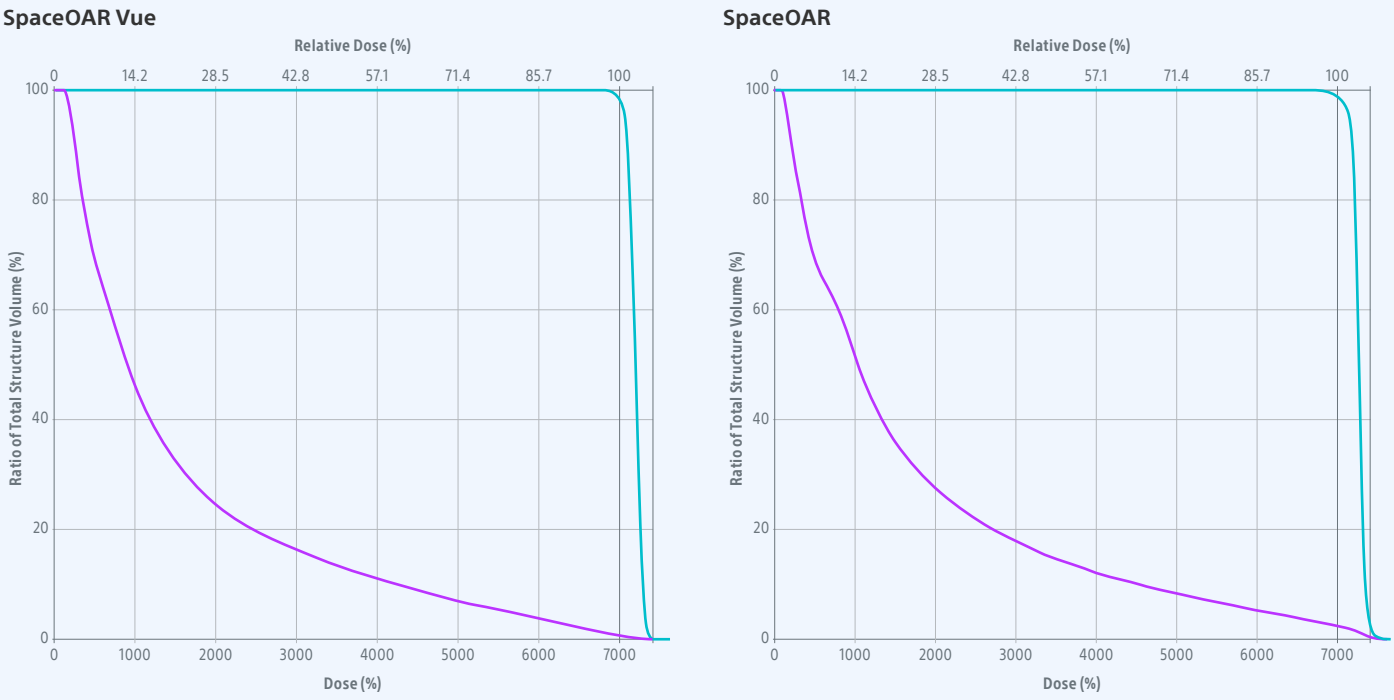
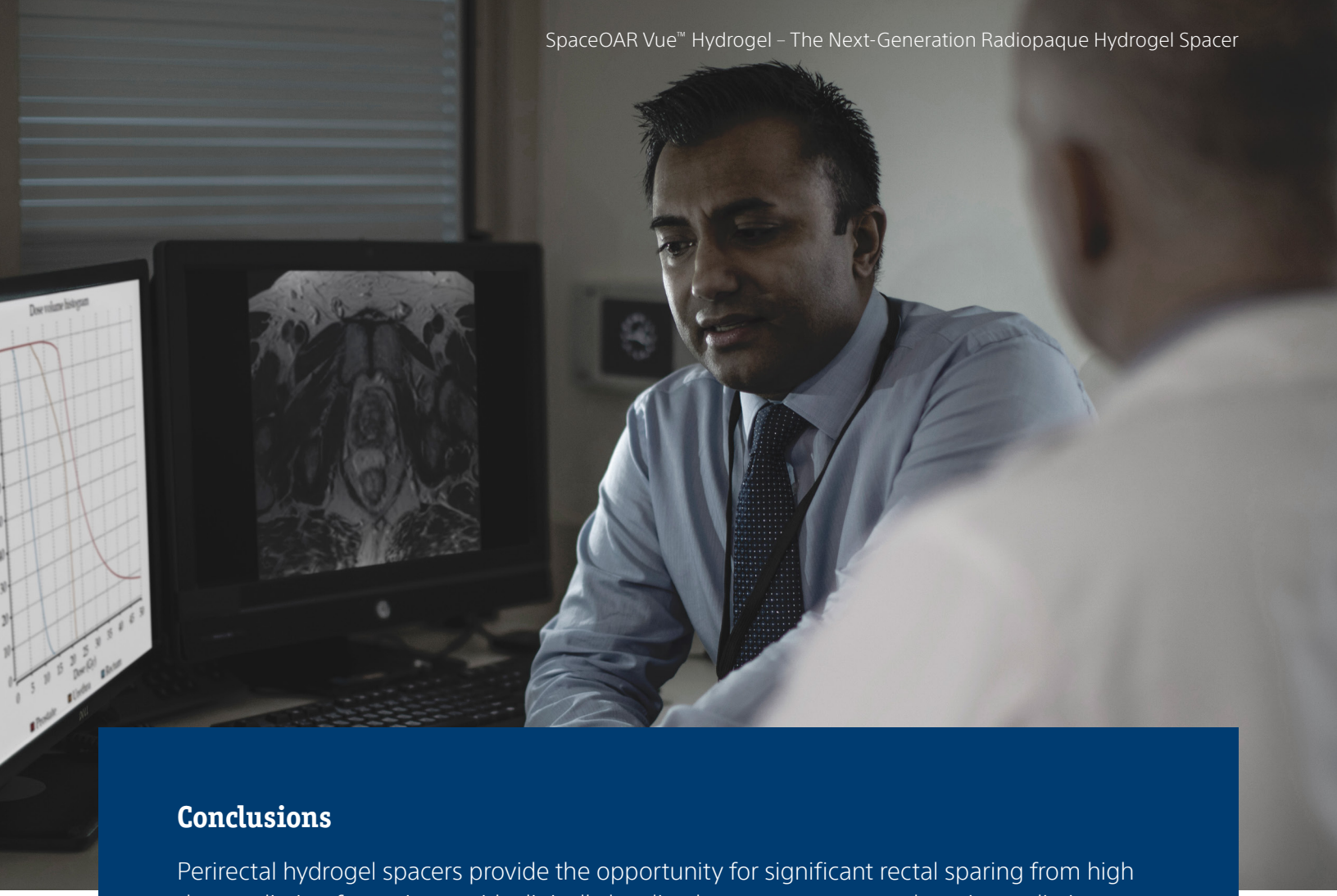


Figure 2. Dose Volume Histograms (DVH) for SpaceOAR Vue Hydrogel and SpaceOAR Hydrogel. Representative DVHs for SpaceOAR Vue Hydrogel (left) and SpaceOAR Hydrogel (right) for the two patients depicted in Figure 1. The DVH lines for rectum (purple) and PTV (prostate and proximal seminal vesicles - cyan) are shown for comparison.



Conclusions

Perirectal hydrogel spacers provide the opportunity for significant rectal sparing from high dose radiation for patients with clinically localized prostate cancer undergoing radiation therapy. SpaceOAR Vue Hydrogel is a new product that incorporates covalently bound iodine into the SpaceOAR PEG-based hydrogel, which has previously been shown to reduce rectal radiation dose and late GI toxicity when placed prior to radiotherapy. **Adding the potential for CT visibility to SpaceOAR Vue Hydrogel is anticipated to expand hydrogel accessibility for patients who cannot undergo MRI, eliminate dependence on MRI for hydrogel contouring, assist in daily IGRT, and further improve the convenience of hydrogel placement.**

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Case studies are not necessarily representative of clinical outcomes in all cases as individual results may vary.

SpaceOAR and SpaceOAR Vue Hydrogels are intended 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 SpaceOAR and SpaceOAR Vue Hydrogels to reduce the radiation dose delivered to the anterior rectum.

SpaceOAR and SpaceOAR Vue Hydrogels contain polyethylene glycol (PEG). SpaceOAR Vue Hydrogel contains iodine.

Prior to using these devices, please review the Instructions for Use for a complete listing of indications, contraindications, warnings, precautions and potential adverse events.

As with any medical treatment, there are some risks involved with the use of SpaceOAR and SpaceOAR Vue Hydrogels. Potential complications associated with SpaceOAR and SpaceOAR Vue Hydrogels include, but are not limited to: pain associated with SpaceOAR and SpaceOAR Vue Hydrogels injection, pain or discomfort associated with SpaceOAR and SpaceOAR Vue Hydrogels, local inflammatory reactions, infection (including abscess), urinary retention, urgency, constipation (acute, chronic, or secondary to outlet obstruction), rectal tenesmus/muscle spasm, mucosal damage, ulcers, fistula, perforation (including prostate, bladder, urethra, rectum), necrosis, allergic reaction (localized or more severe reaction, such as anaphylaxis), embolism (venous or arterial embolism is possible and may present outside of the pelvis, potentially impacting vital organs or extremities), syncope and bleeding. The occurrence of one or more of these complications may require treatment or surgical intervention.

Caution: U.S. Federal law restricts this device to sale by or on the order of a physician.

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