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FULL PAPER

SpaceOAR hydrogel distribution and early complications in patients undergoing radiation therapy for prostate cancer

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Objectives: Hydrogel spacers aim to separate the rectum from the prostate during radiation therapy for patients with prostate cancer to decrease the radiation dose and thus toxicity to the rectum. The aim of this study was to evaluate the distribution of the hydrogel spacer between the rectum and the prostate, to assess for hydrogel rectal wall infiltration and to assess for immediate complications

Methods: Retrospective study of 160 patients who had undergone hydrogel spacer placement. Distribution of the hydrogel was assessed on MRI. MRI images were reviewed for rectal wall injection or other malplacement of gel. Early post-procedure complications were recorded.

Results: 117 (73.1%) patients had a symmetrical distribution of the hydrogel spacer. The mean anteroposterior rectoprostatic separation was 10.2 ± 3.7 mm (range 0–27 mm). Seven (4.3%) patient had minimal rectal wall infiltration and one (0.6%) patient had moderate infiltration. One (0.6%) patient had an intraprostatic injection of hydrogel. Two (1.3%) patients required treatment in the emergency department: one for urinary retention and one for pain.

Conclusions: Transperineal hydrogel placement separates the prostate from the rectum with a symmetrical distribution in the majority of cases prior to radiation therapy with a low rate of rectal wall injection and immediate complications.

Advances in knowledge: SpaceOAR hydrogel can be safely injected into radiation naive patients with low- or intermediate-risk organ-confined prostate cancer. The spacer separates the prostate from the rectum with a symmetrical distribution in the majority of cases prior to radiation therapy.

INTRODUCTION

Treatments for prostate cancer include watchful waiting, active surveillance, radiotherapy and radical prostatectomy. The choice of treatment is dependent on patient preferences, pathological tumour characteristics, risk of progression,and comorbidities. In patients with localised prostate cancer, radiotherapy is associated with lower incidences of disease progression and metastases when compared with active surveillance.[1] Due to the close proximity of the rectum to the prostate, rectal toxicity is a recognised side effect.[2] Within two years of radiotherapy, it has been reported that 11% of patients (range 2–26%) experience at least one bowel complication requiring intervention.[3] Transperineal placement of a hydrogel spacer between the prostate and rectum allows for a reduction in the rectal dose by increasing the distance between the prostate and the rectum, thus reducing the amount of radiation to the rectum.[4] SpaceOAR and SpaceOAR Vue (Boston Scientific Corporation, Marlborough, MA, USA) are both hydrogel spacers composed of polyethylene glycol. Most radiation planning is performed using CT imaging. The original SpaceOAR product was of water density and was not reliably visible on CT. Thus, MRI was required for radiation planning. SpaceOAR Vue was introduced in 2021 and represented a modification of the original spacer incorporating iodine to improve visibility on CT. Hydrogel spacers are injected transperineally under ultrasound guidance in patients with prostate cancer before undergoing radiation

therapy. The material comes as two liquids injected through a Y connector. When the gel component comes in contact with the liquid accelerant, the liquids react to form a firm gel which lasts three months prior to being broken down and excreted renally.[5]

A recent systemic review examining hydrogel spacer injection prior to radiation therapy found that hydrogel effectively increased the distance between the prostate and the rectum, significantly reducing the rectal radiation dose.[4] Several studies have appraised the separation of the prostate from the rectum using a hydrogel spacer by measuring the anteroposterior distance between the two structures. There is less literature describing the distribution of hydrogel spacer along the axial and sagittal planes.[6,7] A prior study examining the distribution of the hydrogel spacer found that rectal dose increases when the hydrogel is more asymmetrical.[6] There is limited reporting of the overall rate of rectal wall injection of the hydrogel and immediate post hydrogel placement complications.

This study aims to evaluate the distribution of the spacer between the rectum and the prostate, assess for hydrogel rectal wall infiltration and assess for early complications associated with SpaceOAR and SpaceOAR Vue injection in patients being treated for the first time with low or intermediate risk organ-confined prostate cancer.

Spacer injection technique

Hydrogel spacer placement is indicated for dose-escalated radiotherapy for histologically confirmed low-to-intermediate risk prostate cancer.[8] Before the procedure, oral antibiotic prophylaxis is taken by the patients as per local guidelines (*e.g.,* 625 mg amoxicillin/clavulanic acid orally 1 h before). Hydrogel injection is completed in a procedure room with the patients placed in the lithotomy position under ultrasound guidance. The perineum is prepped and draped in a sterile manner. The skin and subcutaneous tissues, including puborectalis are anaesthetised with local anaesthetic using 20 ml Xylocaine 2% with Adrenaline. Under transrectal ultrasound guidance, an 18 G needle is advanced into the perirectal fat in the midline, about 1.5 cm anterior to the anus. The needle is advanced with the bevel angled down to minimise the risk of rectal wall injury. The inferior rectal wall thickens into the anal sphincter forming an anterior 'hump' below the apex of the prostate over which the needle must pass to enter the space between Denonvillier's fascia and the anterior rectal wall. The needle is carefully advanced anterior to the sphincter at a slight downward angle to lie just posterior to the prostatic fascia, in the potential space between the prostate and anterior rectal wall. Observing that the needle moves side-to-side independently of both the prostate and rectal wall on transverse imaging helps ascertain correct needle placement. Using hydrodissection with a small volume saline solution (approximately 10 ml), the potential space between the prostate and the rectum is identified in sagittal and axial planes. When the needle is in the correct space, injected puffs of saline will dilate the space and then dissipate. If saline only distends one-half of the space on axial images, the needle may be repositioned so that distribution is symmetric. The hydrogel is prepared according to the manufacturer's instructions into two solutions, which when mixed by injection through a Y connector into the correctly placed needle, solidify within seconds into a firm gel. Just prior to injection, aspiration is performed to ensure the needle tip is not intravascular. The hydrogel (10 ml) is then injected over 10 to 15 s distending the recto-prostatic space, thus physically separating the rectum from the prostate. The hydrogel spacer is stable for 3 months, after this time it is absorbed by the patient and is ultimately excreted renally.[5]

Table 1. Characteristics of the included 160 patients.

Age±stdev (years)	72.3 ± 6.7
Age range (years)	60–86
Time interval between hydrogel injection and planning MRI (days) ± stdev	19 days ± 10.8
Time interval between hydrogel injection and planning MRI (days) range	3–58 days
Prostate Volume±stdev (mL)	45.7 ± 23.2
Prostate Volume range (mL)	11.1–151.3

METHODS

Patients and design

This study was performed in a tertiary referral hospital for patients with prostate cancer. The study was approved by the Institutional Review Board and consent was waived. All patients who received hydrogel placement and follow-up MRI prostate prior to radiation therapy between February 2020, when the procedure was first completed in the institution, and September 2021 were included for analysis. Patient records were retrospectively reviewed and 160 patients radiation-naive patients who had undergone SpaceOAR placement were identified. The demographic and clinical characteristics of the cohort are summarised in Table 1. All patients had low-moderate risk organ-confined disease. Hydrogel injection was completed as described above. Each procedure was completed by one of two radiologists with a special interest in genitourinary radiology. Both radiologists were experienced with ultrasound interventional procedures, having between 10 and 20 years of experience with transperineal prostate procedures including transperineal biopsy.

Quantifying hydrogel placement

An MRI was acquired at a mean of 19 days (range 3–58 days) after hydrogel placement. This was performed on a 1.5 T scanner. Axial and sagittal T_2-weighted sequences of the pelvis were obtained. The hydrogel spacer is approximately 90% water which results in hyperintense T_2-weighted MRI signal. Two radiologists, with 3 and 25 years' experience, evaluated the post-implant T_2-weighted MRI for all 160 patients. Using the method previously described by Fischer-Valuck et al[6] Three axial slices were evaluated in each patient; the midgland axial slice, 1 cm superior to midgland, and 1 cm inferior to midgland. Each patient received a composite hydrogel symmetry score, examples of which are shown in Figure 1.

Symmetry Score 1 (SYM1) = all three slices with symmetric distribution;

Symmetry Score 2 (SYM2) = 1 of 3 slices with >1 cm but<2 cm asymmetry;

Figure 1. Axial T_2-weighted MRI of symmetrical hydrogel distribution (a), with >1 cm but <2 cm asymmetry (b) and >2 cm asymmetry (c).

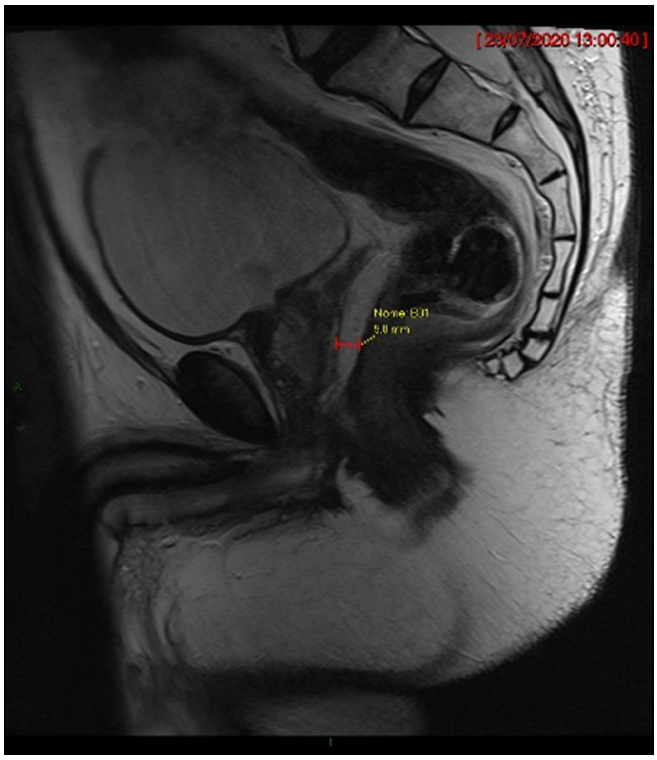
Symmetry Scores 3 (SYM 3) = 2 of 3 slices with >1 cm but <2 cm asymmetry;

Symmetry score 4 (SYM 4) = All 3 slices 1 cm lateral asymmetry or 1–2 slices > 2 cm lateral asymmetry;

Symmetry Score 5 (SYM 5) = All three slices with >2 cm lateral asymmetry.

To quantify the anteroposterior distance between the prostate and the rectum a measurement was taken at the level of the midland of the prostate between the posterior surface of the prostate and the anterior wall of the rectum as shown in Figure 2.

Figure 2. Sagittal T_2-Weighted MRI. Measurement of the anteroposterior distance between the prostate and the rectum at the level of the midland of the prostate.



The maximum length, width, and height of the prostate gland were measured on T_2-weighted MRI images. The prostate volume was calculated using the ellipsoid formula, (π/6) x L x W x H.

Rectal wall infiltration and gel misplacement

The post hydrogel MRI was also used to assess for rectal wall infiltration or other misplacement of gel. Each axial and sagittal slice was examined to look for abnormal high T2 signal within the rectal wall in keeping with rectal wall infiltration of the hydrogel spacer. Rectal wall infiltration was classified as no rectal wall infiltration; minimal infiltration (small discrete areas of <1 ml); moderate infiltration (<25% of rectum circumference); and severe infiltration (≥25% of rectum circumference). Examples of minimal rectal wall infiltration and moderate rectal wall infiltration are displayed in Figures 3 and 4, respectively. The MRI was also reviewed to assess for gel misplacement into the prostate or elsewhere within the pelvis.

Clinical Follow-Up

Clinical follow-up was completed by a nurse on day 2 post hydrogel injection. This consisted of a telephone call asking the patients if they had developed new symptoms or required medical treatment after the hydrogel injection. If the patient developed new symptoms the radiologist who completed the procedure spoke to the patient and determined if they should avail of further treatment at the hospital's emergency department. Patients were

Figure 3. Axial T_2-weighted MRI of an 80-year-old male with minimal infiltration of hydrogel spacer, involving a small discrete area of the anterior rectal wall just above the sphincter.

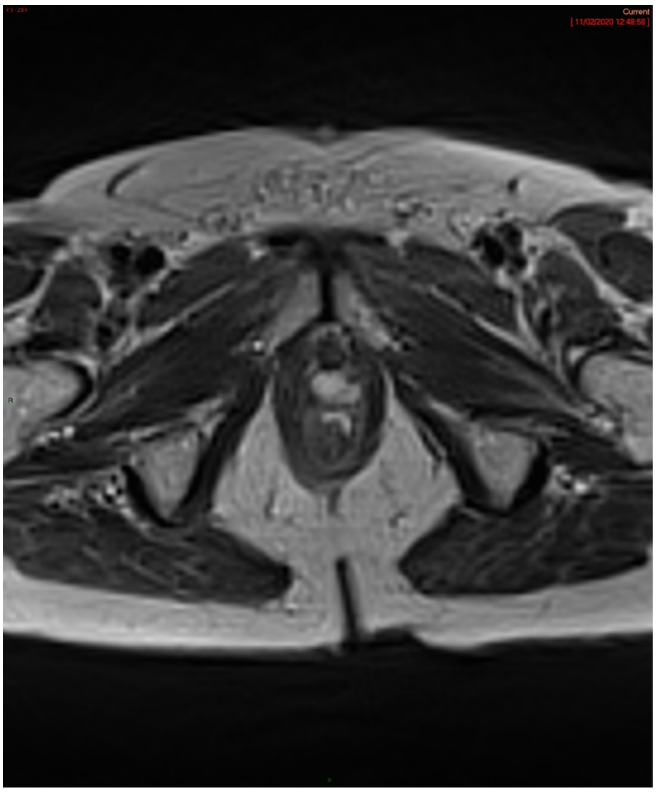


Figure 4. Axial T_2-weighted MRI of a 68-year-old male with moderate rectal wall injection involving <25% of the rectal circumference. Rectal wall thickening is also seen. The patient had increased frequency of bowel movements and passed a small volume of rectal blood. Radiation therapy was delayed by 3 months. The patient did not require further intervention.

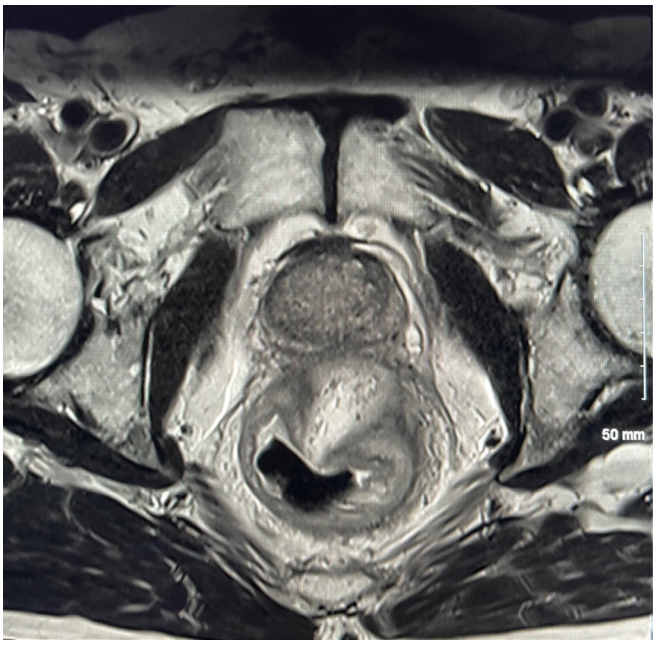


Table 2. Symmetry scores of the hydrogel post insertion

Characteristic	Number (%)	Prostate Volume (mL)
SYM 1	117 (73.1%)	45.9
SYM 2	26 (16.3%)	42.8
SYM 3	13 (8.1%)	48.8
SYM 4	3 (1.9%)	48.6
SYM 5	1 (0.6%)	45.0
Total	160 (100%)	45.7

further reviewed at clinic prior to radiation treatment, typically within 3 weeks of the procedure. Any new symptoms or medical treatment in the period after the procedure were documented in the patient's notes. These events were graded using Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.[9]

Statistical analysis

Continuous variables were summarised with means and standard deviations. These were shown to approximate a normal distribution with a Shapiro-Wilk normality test. Pearson correlation and multiple regression analysis were used to assess the relationships among continuous variables. Analysis was performed in Office Suite Excel 2019 (Microsoft Corporation, Redmond, WA) and SPSS v.23 (IBM, Armonk, NY).

RESULTS

Distribution of gel

Of the 160 patients included in the study, SpaceOAR was used in 103 (64.4%) of the cases and SpaceOAR Vue was injected in 57 (35.6%) cases. Anteroposterior distance between the prostate and the rectum at the level of the mid-gland of the prostate was measured on the MRI post hydrogel insertion. The mean anteroposterior distance was 10.2 ± 3.7 mm with a range of 0–27 mm. There was no statistical difference when SpaceOAR (10.0 ± 3.4 mm, range 0–19 mm) or SpaceOAR Vue (10.6 ± 4.1 mm, range 0–27 mm) was used ($p = 0.41$).

Symmetrical hydrogel placement on all three axial MRI slices (SYM1) was found in 117 cases (73.1%) as shown in Table 2. Twenty-six (16.3%) patients had mild asymmetry, with >1 cm but <2 cm asymmetry, on one of the three slices (SYM2) and 13 (8.1%) had mild asymmetry on two of the three slices (SYM3). Three (1.9%) patients scored SYM4 with mild asymmetry on all three slices or >2 cm lateral asymmetry on one or two slices. Two (1.3%) patients had >2 cm lateral asymmetry on all three slices (SYM5). There was no significant correlation between prostate volume and SpaceOAR distribution (Table 2).

Complications

Of the 160 patients, 8 (5.0%) patients had rectal wall infiltration on the MRI post hydrogel insertion and 152 (95.0%) had none (Table 3) Of the patients with rectal wall infiltration, seven (4.3%) patients had minimal rectal wall infiltration involving one small discrete area. All infiltrations were low in the rectal wall above the external anal sphincter. One

Table 3. Rectal wall infiltration of the hydrogel

Rectal Wall Infiltration	Number of Patients (%)
None	152 (95.0%)
Minimal (small discrete areas)	7 (4.3%)
Moderate (<25% of rectum circumference)	1 (0.6%)
Severe (≥25% of rectum circumference)	0 (0%)
Total	160 (100%)

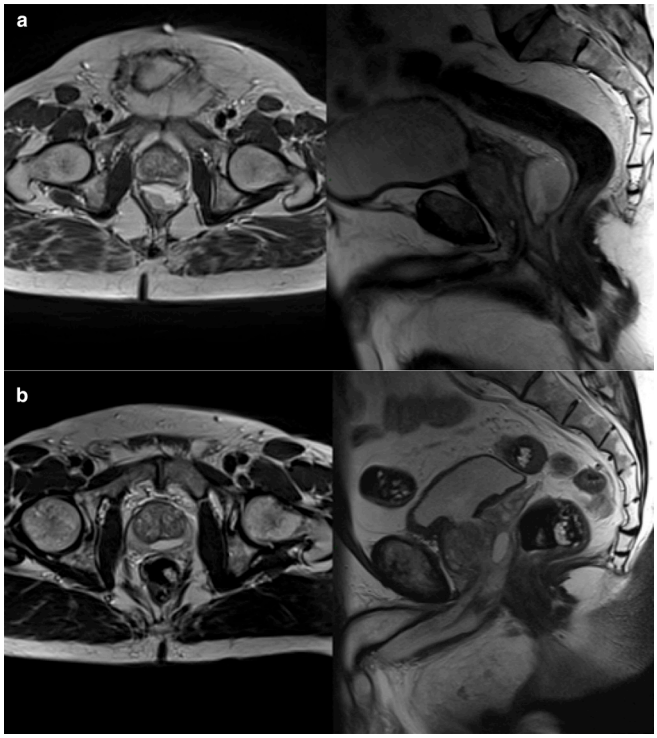
of these also had a small amount of gel (less than 1 ml) just below the skin at the perineum. These patients were all asymptomatic and required no further intervention. These events were categorised as Grade 1 mild adverse events using CTCAE v5.0 (Table 4). One (0.6%) patient had rectal wall infiltration involving <25% of the rectal circumference on MRI with associated rectal thickening (Figure 4). The patient developed an increased frequency of bowel movements and also reported passing a small volume of rectal blood. Colonoscopy showed a rectal wall ulcer. The patient did not require further intervention but radiation therapy was delayed by 3 months. This event was categorised as a Grade 3 severe or medically significant adverse event using CTCAE v5.0 (Table 4) due to the delay in radiation therapy. No patient had a rectal wall infiltration involving ≥25% of rectum circumference.

On the post-procedure MRI, one (0.6%) patient was found to have a larger than expected collection in the space between the rectum and the prostate with internal fluid-fluid layering, Figure 5a. This collection had a volume of 26 ml, much greater than the 10 ml of hydrogel injected. This patient had good separation of the prostate from the rectum with an anteroposterior distance of 27 mm between the structures. The patient was asymptomatic in the period immediately after the hydrogel placement and proceeded to radiation therapy. At the time of MRI, no blood-sensitive sequences were performed. The large size of the collection and fluid-fluid layering were felt to be due to periprocedural asymptomatic bleed. The was categorised as a Grade 1 mild adverse event as the patient was asymptomatic and did not require further intervention.

Table 4. Adverse events summarised using Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0

CTCAE Grade	Number of Patients (%)
None	148 (92.5%)
Grade 1 Mild; asymptomatic or mild symptoms	10 (6.3%)
Grade 2 Moderate; minimal, local or noninvasive intervention indicated	0 (0.0%)
Grade 3 Severe or medically significant but not immediately life-threatening	2 (1.3%)
Grade 4 Life-threatening consequences; urgent intervention indicated.	0 (0.0%)
Grade 5 Death related to adverse event.	0 (0.0%
Total	160 (100%)

Figure 5. a, Axial and sagittal T_2-weighted MRI of a 66-year-old male with a larger than expected collection in the space between the rectum and the prostate with internal fluid-fluid layering. This is thought to be due to asymptomatic bleeding at the time of spacer injection. b, Axial and sagittal T_2-weighted MRI of a 68-year-old male showing a pocked of increased T2-signal within the peripheral zone of the prostate in keeping with an intraprostatic injection of the hydrogel spaceOAR.



One patient (0.6%) had an intraprostatic injection of the hydrogel, Figure 5b. The abnormal distribution of gel was recognised during the injection after the administration of 6 ml of material. This patient had urgency and urinary discomfort symptoms following the procedure and was reviewed by urology and treated with tamsulosin. His symptoms settled after approximately one week. It was elected to defer radiation treatment until repeat hydrogel insertion could be repeated. The patient subsequently reported passing gel material per urethra 4 weeks after the procedure. Follow-up MRI at 3 months showed no remaining gel and the procedure was repeated successfully. The patient went on to complete radiation therapy. This was categorised as a Grade 3 severe or medically significant adverse event as the patient required a repeat procedure and delay the radiation therapy.

One (0.6%) patient reported severe perineal pain and pressure after hydrogel insertion and attended the emergency department. The pain resolved with analgesia within several hours. The patient did not require hospital admission and no further

treatment was required. There was no acute abnormality on the post-procedure MRI. One further patient (0.6%) developed urinary retention after the procedure. The patient attended the emergency department and the urinary retention resolved spontaneously without the requirement for catheterisation. There was no acute abnormality on the post-procedure MRI. Both of these patients were categorised as Grade 1 mild adverse events as intervention was not indicated.

DISCUSSION

The paper examines the distribution of SpaceOAR hydrogel and early complications prior to radiation therapy in radiation-naive patients with low to moderate risk organ-confined prostate cancer. The vast majority of patients had a satisfactory distribution of the hydrogel spacer with 156 (97.5%) of the 160 patients having satisfactory hydrogel distribution considered symmetrical (73.1%) or with only mild asymmetry on one of the axial slices (16.3%) or with only mild asymmetry on two of the axial slices (8.1%). Only 4 (2.5%) patients had a distribution that was considered less favourable with mild asymmetry on all three slices (1.9%) or more pronounced lateral asymmetry of the hydrogel spacer (0.6%). The spacer created good separation between the prostate and rectum in the vast majority of patients with a mean anteroposterior distance of 10.2 ± 3.7 mm ranging from 0 to 27 mm.

Very few patients developed significant complications in the period after hydrogel injection or during their radiation therapy. Ten (6.3%) patients had Grade 1 mild adverse events post hydrogel insertion which did not delay radiation therapy. Two (1.3%) patients had Grade 3 severe or medically significant adverse events delaying radiation therapy, in both cases by 3 months. One of these had rectal wall infiltration of the hydrogel spacer involving <25% of the rectal circumference on MRI with increased frequency of bowel movements and a small volume of rectal bleeding. The other had an intraprostatic injection of the hydrogel. In both cases, treatment was delayed by three months until symptoms resolved. In the case of the intraprostatic injection, gel was reinserted after three months with no complications. There were no cases of rectal wall infiltration involving ≥25% of rectum circumference.

Rectal wall injection without apparent consequence has been reported in 6% of cases in a randomised study.[10] Our review demonstrated rectal wall injection in 8/160 (5.0%) cases. Rectal wall infiltration in all cases was in the lower anterior rectal wall just superior to the sphincter or at the sphincter. We believe that this is due to the almost inevitable transgression of the outer fibres of the puborectalis muscle by the needle as it is being introduced. Rapid withdrawal of the needle immediately after injection of gel may lead to gel material being sucked back into the soft tissues along the needle track and result in beads of gel in the rectal wall if the needle has traversed the sphincter, or at the perineum as was observed in one case. We have now modified our technique in an effort to minimise this possibility. As well as ensuring a high (anterior) skin entry point for the needle to avoid the puborectalis 'rectal hump', we now leave the needle *in situ* for 30 s after injection of the gel. This ensures that any material remaining in the needle has completely solidified and escape back into the soft tissues during needle removal. The needle bevel (which is angled towards the rectum for insertion and gel delivery) is then turned away from the rectum and the needle is removed very slowly, to minimise any potential suction effect by the soft tissues as the needle is being withdrawn. No cases of rectal wall infiltration have been seen in 60 cases performed since this modification.

Our review found no case of severe rectal wall infiltration. There have been case reports of severe rectal injury related to intrarectal spacer injection leading to fistula and the utmost care must be taken to confirm and maintain correct needle placement prior to gel delivery.[11]

Two patients without rectal wall infiltration detected on the post-procedure MRI, reported new symptoms requiring medical treatment in the emergency department. One (0.6%) patient had severe perineal pain and one (0.6%) patient had urinary retention. Both cases were successfully managed in the emergency department and did not require further procedures or admission. One (0.6%) patient had a larger than expected collection in the space between the prostate and the rectum. This was most likely due to local bleeding at the time of spacer injection. The patient was asymptomatic and there was no delay in radiation therapy. An important step in the procedure is the aspiration of the needle prior to gel injection to ensure that the needle tip is not within a vessel. Intravascular injection has been reported as a very rare, but potentially very serious, complication by the manufacturer, resulting in embolisation of vital organs and pulmonary embolism (1/250,000 cases).[12] Even if no blood is aspirated prior to injection, it is possible that a periprostatic vein may have been traumatised during the process of needle placement and that bleeding could occur as a result. Bleeding was only seen in one of the 160 patients reviewed. There were no Grade 4 life-threatening adverse reactions.

There was a similar distribution of the hydrogel spacer in our patient cohort when compared to a prior study by Fischer-Valuck et al with 156 (97.5%) patients being categorised as SYM1, SYM two or SYM 3 and 5 (2.5%) patients with less favourable distribution and being categorised as SYM4 or SYM5.[6] There were however more patients categorised as SYM 1 (symmetrical on all slices) in our cohort when compared to earlier work which found a more equal distribution between categories.[6,7] The cause for this slight difference is unclear and may be due to a difference in procedure technique or a difference in interpretation of the MRI. The anteroposterior separation of the rectum and prostate created by the hydrogel spacer at 10.2 ± 3.7 mm concurs with prior research with a range of perirectal distance of 9.6 to 14.5 mm with a median of 10.8 mm.[4,7,13–15] There was a similarly low rate of rectal wall infiltration when compared to prior evidence.[6]

Overall, this study shows that hydrogel injection with SpaceOAR can be completed safely with a low rate of complication in patients with low-moderate risk organ-confined disease who had

not had prior treatment. It effectively separates the prostate from the rectum prior to radiation therapy which has previously been shown to reduce the radiation dose to the rectum.[4] Rectal wall injection is a rare event and when it does occur it is generally very small in size. A small number of rare major complications have been reported in the literature, none of which were identified in this study. While infrequent, these reported complications underscore the need for strict adherence to correct procedural technique.

This study has several limitations. As the study is retrospective there is an inherent risk of bias within the data collection and analysis. Although this is one of the largest studies to date examining hydrogel spacer distribution and immediate complications, the low rate of complications associated with this relatively new procedure necessitates further validation. At our institution, all patients had their procedures performed by one of two interventional radiologists with several years of experience in transperineal prostate procedures (brachytherapy guidance and biopsy), who had also undergone specific supervised training in SpaceOAR placement with certification. Both radiologists perform several procedures weekly. The low complication rate seen in this cohort may not be applicable to a more diverse group of operators with less experience performing occasional procedures. While this study chose to examine the outcomes in the period after injection and before radiation therapy, the lack of long-term follow-up is also a limitation. Complications can also occur several weeks to months after SpaceOAR injection and radiation therapy.[5]

CONCLUSION

SpaceOAR injection effectively separates the prostate from the rectum with a symmetrical distribution in the majority of cases prior to radiation therapy with a low rate of rectal wall injection and immediate complications amongst experienced operators.

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