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Publication Date

2024

DOI

10.1016/j.urology.2023.09.016

Real-World Complications of the SpaceOAR Hydrogel Spacer: A Review of the Manufacturer and User Facility Device Experience Database

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OBJECTIVE To characterize adverse events related to use of the perirectal spacing agent SpaceOAR, we examined the Manufacturer and User Facility Device Experience (MAUDE) database.

METHODS The MAUDE database was queried for "SpaceOAR" and "Augmenix" from June 2015 (when SpaceOAR was approved by the Food and Drug Administration) to October 2022. Reports were reviewed for adverse events (AEs), operative procedures performed because of the AE, and changes to the radiation plan. AEs were categorized using Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

RESULTS Six hundred fifty-four reports were reviewed. Eighty-four were excluded and 4 reports reviewed 2 separate cases of SpaceOAR administration. Five hundred seventy-four cases were ultimately included. Three deaths were reported (0.5% of all AEs). One point six percent of cases represented CTCAE grade 4 injuries (life-threatening consequences; urgent intervention indicated), 15.9% grade 3 (severe but not immediately life-threatening; hospitalization), 24.2% grade 2 (moderate; local/noninvasive intervention), and 57% of events were CTCAE grade 1 (mild; asymptomatic or mild symptoms). Bowel diversion occurred in 29 cases (9%).

CONCLUSION Both asymptomatic (n = 311) and debilitating (n = 12) complications of SpaceOAR hydrogel use were identified. Death, gel embolization, anaphylaxis, rectal ulcerations, and infections requiring bowel or urinary diversions were among the complications reviewed. Providers should consider these potential complications before perirectal spacer administration and during patient counseling. UROLOGY 183: 157–162, 2024. © 2023 Elsevier Inc. All rights reserved.

Prostate cancer is the most common cancer and the second leading cause of cancer-related death in men.[1] Management options for clinically localized prostate cancer include active surveillance, surgery, targeted therapy, and radiation therapy.[2] An analysis of the SEER database from 2004 to 2013 showed 38% of men with clinically localized prostate cancer underwent radiation therapy (including external beam radiation, brachytherapy, or combined approaches).[3] Both surgery and radiation therapy for prostate cancer can lead to significant side effects. Adverse events (AEs) related to radiation include lower urinary tract symptoms, erectile dysfunction, urethral stricture disease, rectourethral fistula, and gastrointestinal distress.[4,5]

Some outcomes related to bowel function and bother are worse in patients undergoing radiation compared to radical prostatectomy or observation, especially in the first 6 months after treatment.[4,6] Long-term complications related to rectourethral fistula are devastating, under-reported, and difficult to repair.[7] Rectal hydrogel spacers have been designed to increase the distance between the prostate and rectum in hopes of decreasing the rate of rectal radiation dose and toxicity. SpaceOAR (Boston Scientific, Marlborough, MA) and other hydrogel spacers are absorbable spacers placed between Denonvillier's fascia and the anterior rectal wall through an ultrasound guided transperineal approach. Systematic reviews and meta-analyses of SpaceOAR use have shown a decrease in rectal radiation dose with this device. These studies report a low rate of complications, such as an estimated 0%-10% risk of mild and transient periprocedural complications that mostly did not delay

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Submitted: July 18, 2023, accepted (with revisions): September 19, 2023

radiation treatment,[8,9] or a 3%-9% risk of misplacement of spacer gel.[9,10] The focus of these studies was primarily on rectal toxicity and subsequent AEs.[11,12] SpaceOAR Hydrogel has been implanted over 220,000 times as of 2022,[13] and the NCCN guideline acknowledges that peri-rectal spacers may be implanted prior to prostate irradiation.[14]

The Manufacturer and User Facility Device Experience database (MAUDE) is an anonymous reporting system managed by the Food and Drug Administration (FDA) to collect and categorize AEs related to medical devices. Reports are collected from voluntary reporters and mandatory reporters, such as manufacturers, importers, and device user facilities. This system allows for evaluation of "real life" experiences with devices beyond those within device approval studies. Prior analyses the MAUDE database have demonstrated a small number of significant complications after SpaceOAR placement,[15,16] though initial reports analyzed only the first 25-80 reported events. We hypothesize that updated MAUDE analysis will demonstrate significant complications related to SpaceOAR placement in a subset of patients.

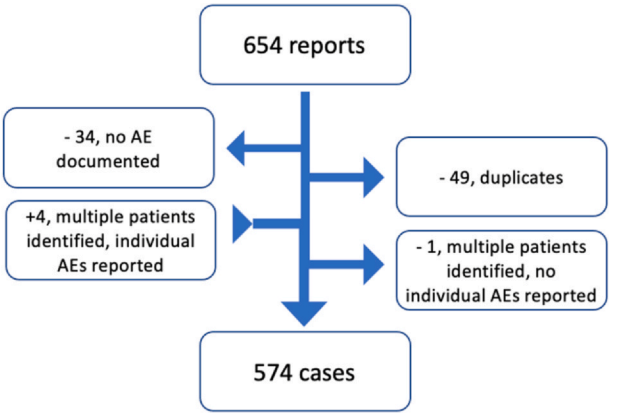

Figure 1. Schematic of report selection. Initial search of the MAUDE database revealed 654 reports of adverse events from SpaceOAR Hydrogel use. Duplicate reports and those not specifying a specific AE were excluded. Reports identifying multiple individuals were counted if the adverse events described could be attributed to a specific hydrogel placement event. This resulted in a total of 574 cases for analysis. AE, adverse events; MAUDE, Manufacturer and User Facility Device Experience.

Methods

The MAUDE database is an archive of anonymously reported adverse outcomes associated with medical devices maintained by the United States FDA (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm). The database was searched for reports of AEs related to the placement of SpaceOAR perirectal spacer. "SpaceOAR" and "Augmenix" were utilized as search terms. Reports spanned from June 2015, when SpaceOAR received approval status from the FDA, through October 2022. Reports were evaluated by 3 reviewers (C.J., A.F., U.G.) independently and each report was evaluated by at least 2 reviewers. Duplicate reports were excluded. Reports identifying multiple individuals were also excluded unless each adverse event could be attributed to a specific hydrogel placement event (Fig. 1). The AEs were noted from the clinical summary written. Some patients experienced multiple AEs after hydrogel placement, and all were counted. A "primary problem" was identified for each case as the adverse event that most affected patient wellbeing. Timing of the primary problem relative to initiation of radiation therapy, changes in management including alterations in the radiation plan, or additional procedures performed after SpaceOAR placement were noted when available. AEs were considered "symptomatic" if the MAUDE narrative described patient complaints of adverse symptoms. Severity of AEs were categorized using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.[17]

Results

The initial analysis yielded 654 reports from June 2015 through October 2022. After applying the exclusion criteria, 574 cases of hydrogel placement were included in our final analysis (Fig. 1). In 34 reports of the original 654 reports, no details of the AE experienced by the patient were provided, so the AE could not be characterized and these reports were excluded from analysis. When duplicate reports were identified, only one report was counted for analysis. Certain reports identified multiple individuals who suffered an AE after SpaceOAR implant. Reports were only included if the narrative indicated specific numbers of patients affected by each AE described.

All AEs recorded are summarized in Table 1. Fifty-seven percent of events were CTCAE grade 1 (mild; asymptomatic or mild symptoms without intervention), 24.2% grade 2 (moderate; local/noninvasive intervention), 15.9% grade 3 (severe but not immediately life-threatening; hospitalization, limiting self-care activities of daily livings), 1.6% grade 4 (life-threatening consequences; urgent intervention indicated), and 0.5% grade 5 (death related to AE) (Fig. 2). Three hundred eleven cases (54.1%) were symptomatic AEs. A total of 90 cases (15.7%) led to a delay or change in radiation plan. One hundred sixty-five cases (28.7%) had symptom onset prior to onset of radiation treatment.

The most cited AE was malpositioned gel (330 reports, 57% of total), which was symptomatic in 92 cases (28%). The malpositioned gel was most commonly injected into the rectal wall and was noted on post procedural imaging. This improperly placed gel caused delay in radiation or change to radiation plans in 55 cases. Infection after SpaceOAR placement was documented in 101 reports (17.6%) and a subsequent procedure was necessary in 43 of these cases, most commonly abscess drainage (28 cases). Rectal ulceration was noted in 60 cases (10.5%), with 16 of these events reported to have occurred before initiation of radiation. SpaceOAR placement was complicated by death in 3 cases (0.5%).

Table 1. Adverse events reported with SpaceOAR Hydrogel injection.

Adverse Event	Total Count	Primary Problem %	Symptomatic (%)	Delay or Change in Radiation Plan (%)	Symptom Initiation Before Radiation	CTCAE Gr1 (%)	CTCAE Gr2 (%)	CTCAE Gr3 (%)	CTCAE Gr4 (%)	CTCAE Gr5 (%)
Malpositioned gel	329	41.3	92 (28)	55 (16.7)	67 (20.4)	279 (84.8)	33 (10)	17 (5.2)	0 (0)	0 (0)
Infection/ inflammation/ abscess	99	14.9	98 (99)	16 (16.2)	30 (30.3)	2 (2)	61 (61.6)	33 (33.3)	2 (2)	1 (1)
Pain	70	7.2	67 (95.7)	12 (17.1)	40 (57.1)	20 (28.6)	33 (47.1)	16 (22.9)	1 (1.4)	0 (0)
Fistula	61	7.5	58 (95.1)	12 (19.7)	6 (9.8)	14 (23)	14 (23)	32 (52.5)	1 (1.6)	0 (0)
Rectal ulcer	54	9.6	50 (92.6)	11 (20.4)	16 (29.6)	18 (33.3)	23 (42.6)	13 (24.1)	0 (0)	0 (0)
Other	36	3.0	21 (58.3)	3 (8.3)	12 (33.3)	17 (47.2)	6 (16.7)	10 (27.8)	1 (2.8)	2 (5.6)
GI symptoms	34	3.3	34 (100)	5 (14.7)	25 (73.5)	13 (38.2)	18 (52.9)	3 (8.8)	0 (0)	0 (0)
Urinary retention	32	3.7	32 (100)	8 (25)	23 (71.9)	0 (0)	22 (68.8)	8 (25)	1 (3.1)	1 (3.1)
Other urinary symptoms	32	1.2	32 (100)	8 (25)	22 (68.8)	7 (21.9)	16 (50)	8 (25)	1 (3.1)	0 (0)
Bleeding	27	1.2	27 (100)	4 (14.8)	15 (55.6)	11 (40.7)	12 (44.4)	4 (14.8)	0 (0)	0 (0)
Embolism of gel	11	1.4	9 (81.8)	1 (9.1)	6 (54.5)	9 (81.8)	0 (0)	2 (18.2)	0 (0)	0 (0)
Allergic reaction	10	1.8	10 (100)	0 (0)	9 (90)	0 (0)	5 (50)	3 (30)	2 (20)	0 (0)
Syncope/LOC	7	0.5	7 (100)	0 (0)	7 (100)	0 (0)	2 (28.6)	1 (14.3)	2 (28.6)	2 (28.6)
Anaphylactic reaction	7	1.1	7 (100)	0 (0)	7 (100)	0 (0)	0 (0)	6 (85.7)	1 (14.3)	0 (0)
DVT/PE	6	0.9	5 (83.3)	1 (16.7)	5 (83.3)	0 (0)	0 (0)	6 (100)	0 (0)	0 (0)
ICU level care	6	0	6 (100)	0 (0)	6 (100)	0 (0)	0 (0)	1 (16.7)	4 (66.7)	1 (16.7)
Perforation	5	0.5	4 (80)	3 (60)	2 (40)	1 (20)	2 (40)	2 (40)	0 (0)	0 (0)
Death	3	0.5	3 (100)	3 (100)	2 (66.7)	0 (0)	0 (0)	0 (0)	0 (0)	3 (100)

CTCAE, Common Terminology Criteria for Adverse Events; DVT/PE, deep venous thrombosis/pulmonary embolism; GI, gastrointestinal; ICU, intensive care unit.

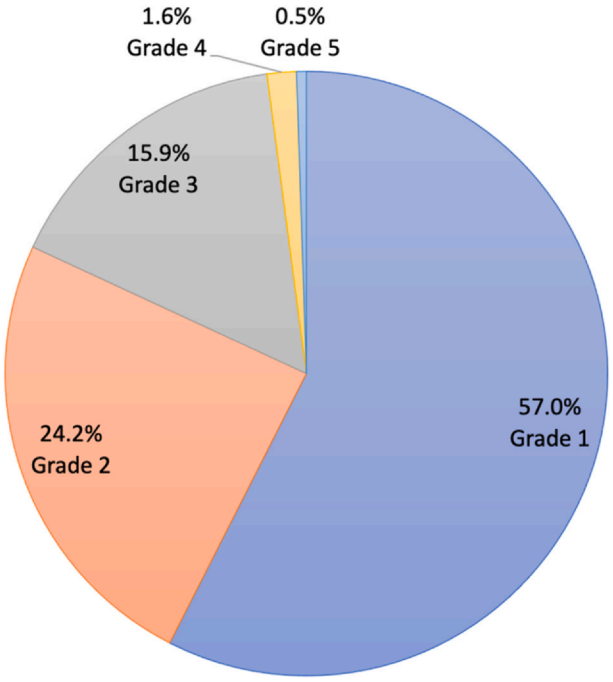

Figure 2. Common Terminology Criteria for Adverse Events Grading of adverse outcomes associated with SpaceOAR hydrogel injection. Grade 1: mild; asymptomatic or mild symptoms without intervention; Grade 2: moderate; local/noninvasive intervention; Grade 3: severe but not immediately life-threatening; hospitalization, limiting self-care ADLs; Grade 4: life-threatening consequences; urgent intervention indicated; Grade 5: death related to AE. ADL, activities of daily living. (Color version available online.)

Procedures performed after SpaceOAR placement are listed in Table 2. The most common procedure was gastrointestinal endoscopy. Colostomy or ileostomy creation was required in 29 cases, with 2 cases requiring ostomy before the initiation of radiation.

MAUDE report counts regarding SpaceOAR hydrogel are summarized by year of submission in Supplementary Figure 1.

Discussion

To our knowledge, the current work is the largest study of adverse events related to peri-prostatic hydrogel placement. We found that although most AEs are minor, placement of SpaceOAR hydrogel has resulted in several devastating outcomes that should be mentioned when discussing the risk and benefits of using the material. The true frequency of these complications cannot be characterized by the MAUDE database, as entries in the database are self-reported. Though they may be rare, the complications described here were not well described in the approval studies for the device. The pivotal, randomized-controlled trial led by Mariados et al showed a favorable safety profile for the SpaceOAR hydrogel. The study showed no significant difference in rectal or periprocedural AEs (grade 1 or greater) between 222 patients who were randomized to either SpaceOAR and fiducial marker placement or fiducial marker placement alone.[8] The primary study evaluating the effectiveness and safety of the SpaceOAR device showed a reduction in both bowel and urinary bothersome symptoms on secondary analysis at 3 years following the procedure.[18] In that study, no device-related adverse events were seen in the cohort undergoing SpaceOAR injection. The complications identified in the current review are novel.

Table 2. Procedures performed after injection of SpaceOAR.

Procedure	Count
GI endoscopy	61
Bowel diversion (ostomy)	29
Abscess drainage	28
Urinary catheterization	21
Fistula repair	5
Cystoscopy	5
Suprapubic tube placement	4
Unknown procedure	4
Urinary diversion (urostomy)	3
Cardiopulmonary resuscitation	3
Transurethral resection of prostate	2
Cystoprostatectomy	2
Airway intubation	2
Cardiac catheterization	1
Dialysis initiation	1
Transrectal ultrasound	1
Debridement	1
Arterial stenting	1
Artificial anus creation	1

GI, gastrointestinal.

Review of the MAUDE database for SpaceOAR revealed 3 cases of death. In one circumstance, outlined in MAUDE report 3008550999-2018-00003, death was questionably related to injection of the spacer. This describes a patient admitted for management of a prostatic abscess after SpaceOAR placement, whose demise may have been related to other comorbidities. However, the other 2 reports of patient death describe circumstances much more concretely related device implantation. MAUDE reports 3005099803-2022-01318 and 3008550999-2019-00004 describe events in which 2 patients experienced syncope and cardiac arrest immediately after injection of the SpaceOAR material and died during subsequent hospitalization.

In addition to 3 deaths, anaphylaxis was documented in 7 reports. Six cases of pulmonary embolism were described as occurring in the immediate aftermath of SpaceOAR injection. In another case (report 3005099803-2021-02973), a patient experienced inferior mesenteric artery occlusion and bowel ischemia requiring bowel resection immediately after gel placement. Additionally, 29 reports identified patients requiring surgical bowel diversion after perirectal spacer placement. Two of these reports

identified patients requiring ostomy creation prior to initiation of radiotherapy because of post-implantation perirectal infection.

The explanation for these outcomes is not well understood, particularly considering the benign safety profile documented in the approval studies for the SpaceOAR device. Perhaps the physicians in the initial studies were trained more effectively in safe use of the device, or perhaps the frequency of these complications was too low to be captured in the pre-approval studies. Yamaguchi et al demonstrated that the provider in their group who performed the most total number of hydrogel spacer implantations caused the fewest AEs, supporting the notion that safety of spacer placement may correspond positively with provider experience.[9]

Some asymptomatic events were also potentially hazardous. Two reports (3005099803-2022-04543 and 3005099803-2022-04132) identified hydrogel embolized to the internal iliac arteries after misplaced injection. In both cases, this was noted on routine follow-up imaging. Though not injurious to these patients, it is unclear if other sequalae will occur over time from the migration. Many reports identify a delay in radiation treatment due to asymptomatic gel misplacement. Though the oncologic effects of these delays are not well characterized, the deferral of care is generally unfavorable.

While previous studies on the AEs of SpaceOAR placement using the MAUDE database have been published, these studies performed analysis on small number of reports and did not provide a qualitative analysis of the complications.[15,16] The current analysis of the MAUDE database examines the nature of the adverse events as well as the procedures and delays or changes in radiation plans related to the AEs. This review of 574 reports sheds light on the breadth of AEs experienced by patients receiving SpaceOAR.

Studies based on the MAUDE database, including the present study, certainly have limitations. The number of complications may be under-reported as the database relies on submissions from voluntary and mandatory reporters. The rate of complications cannot be ascertained from MAUDE data, as the total number of procedures performed is not known. Our study aimed to qualitatively characterize the complications reported in hopes of improving the informed consent process for patients prior to undergoing SpaceOAR placement.

Though limited by the information available through the MAUDE database, this study characterizes the potential adverse events related to SpaceOAR placement. Many of these AEs did not require additional management (such as asymptomatic malposition of space gel), though a small number of patients had devastating outcomes. Regardless, this information should be considered when developing a therapeutic plan for prostate cancer treatment. Patients should be fully counseled about the small, but real, potential for these complications prior to SpaceOAR use.

Declaration of Competing Interest

Benjamin N. Breyer receives Fellowship funding from Boston Scientific Corporation. The other authors declare no conflict of interest.

Acknowledgment. None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.urology.2023.09.016.

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