Oncology

Major Complications and Adverse Events Related to Use of SpaceOAR Hydrogel for Prostate Cancer Radiotherapy

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OBJECTIVE To determine the prevalence and severity of SpaceOAR-related adverse events using the Manufacturer and User Facility Device Experience (MAUDE) database.

METHODS We analyzed SpaceOAR-related adverse event reports in the Manufacturer and User Facility Device Experience (MAUDE) database from January 2015 to May 2023. For each report, the event type, associated device and patient problems, event description, event timing, and event severity stratified by the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE) grading system were recorded.

RESULTS From 2015 to 2022, 206,619 SpaceOAR devices were sold. From January 2015 to May 2023, we identified 981 reports describing 990 SpaceOAR-related adverse events. Malfunctions were the most common event type (N = 626), followed by patient injuries (N = 350) with few reported deaths (N = 5). Device positioning problems were the most frequent device issue (N = 686). Pain was the most reported patient problem (N = 216). Abscesses and fistulas related to the device were each reported in 91 events. A noteworthy portion of relevant adverse events occurred before the initiation of radiation (N = 35, 22.4%), suggesting the device, rather than the radiation, was responsible. In total, 470 (50.2%) and 344 (36.7%) of the adverse events were CTCAE grade 1 and 2, respectively. There were 123 (13.1%) events that were CTCAE grade ≥3.

CONCLUSION We identified multiple reports of SpaceOAR-related adverse events, many of which are more serious than have been reported in clinical trials. While SpaceOAR use is common, suggesting these events are rare, these data highlight the need for continued postmarket surveillance. UROLOGY xx: xxx–xxx, xxxx.

An estimated 288,300 people will be diagnosed with prostate cancer in 2023, and approximately 30%-40% will undergo radiation therapy.[1-3] Rectal toxicity (hematochezia, proctitis, mucus discharge, tenesmus, and fecal incontinence) from prostate radiotherapy is dependent on treatment modality, but grade 2+ toxicity is estimated to occur in 5%-15% of patients, impacting patient quality of life.[4,5]

SpaceOAR (Boston Scientific, Malborough, MA) is an injectable polyethylene glycol hydrogel developed to increase the space between the prostate and rectum prior to radiation therapy with the goal of reducing rectal toxicity.[6] Approval of SpaceOAR by the FDA in 2015 came following a single-blind, randomized phase III clinical trial whose primary effectiveness endpoint was a >25% reduction in rectal volume receiving at least 70 Gy in patients receiving dose-escalated image-guided intensity-modulated radiation therapy.[6,7] In addition to this dose reduction, the trial found that SpaceOAR reduced late rectal toxicity and improved bowel quality of life in patients who underwent SpaceOAR. Subsequent studies have shown that SpaceOAR and SpaceOAR Vue (a modification that includes iodinated contrast approved in 2019[8]) reduce the measured radiation dose delivered to the rectum independent of radiation modality.[9,10]

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Several case reports and small reports have described device-related adverse events and major rare and life-threatening complications associated with SpaceOAR utilization.[11-18] The largest report, at the time of our analysis, published in The Lancet Oncology in 2021, included a total of 80 adverse events from the Manufacturer and User Facility Device Experience (MAUDE) database.[19] Here, we combine sales data from Boston Scientific with a review of the FDA's MAUDE database to provide the largest and most descriptive report available of postapproval SpaceOAR-related adverse events and major complications.

MATERIALS AND METHODS

MAUDE is a publicly accessible reporting system for postmarket surveillance of FDA-approved medical devices.[20] It contains reports of events that involve device malfunction or serious injury, including death. The FDA maintains the database and publishes voluntary reports, manufacturer reports, and facility reports. Manufacturers are required to report device-related events within 30 days of becoming aware. Facility reports are required to be submitted within 10 workdays.[20]

The MAUDE database was queried from January 2015 to May 2023 using the term "SpaceOAR." For each event, the database provides a report number, brand name (ie, SpaceOAR or SpaceOAR Vue), event type (ie, malfunction, injury, death), device problem, patient problem, and event text, which we captured. MAUDE does not provide reporting on tumor stage, risk group, radiation type and history, patient comorbidities for reported events, or characteristics about facilities and providers. Only small cohorts of event report descriptions will capture these factors. Subsequently, two reviewers (JM, ES) independently analyzed all the events. Each reviewer provided a one-sentence description of the event that included diagnosis/patient presentation and resulting treatment. Additionally, reviewers noted the temporality of the event as before radiation or during/after radiation therapy when absolutely certain. Events that did not reference radiation therapy in the event description were noted as having an "unknown" temporality.

The findings of each reviewer were compared, and discrepancies were resolved by a joint reanalysis of the event text with discussion as needed. Following review, the most prevalent events were identified, and all events were consolidated into one of 38 one-sentence descriptions categorized by Common Terminology Criteria for Adverse Events version 5.0 (CTCAE) grades. Events not described by one of the 38 listings were labeled as "other events." Lastly, our group reached out to Boston Scientific Corporation to obtain yearly sales volumes for SpaceOAR from 2015 to 2022, and an estimate of the percentage of the total cases performed in the US.

Table 1. Number of yearly SpaceOAR-related adverse events and cases per year.

Year	Reports	SpaceOAR Cases	Estimated (U.S. Cases)	Reports per 1000 SpaceOAR Cases
2015	1	1802	1442	0.694
2016	2	5544	4435	0.451
2017	3	9890	7912	0.379
2018	11	22,225	17,780	0.619
2019	85	31,675	25,340	3.354
2020	126	37,155	29,724	4.239
2021	272	48,110	38,488	7.067
2022	387	50,218	40,174	9.633

RESULTS

According to Boston Scientific Corporation, 206,619 SpaceOAR kits were sold from 2015 to 2022 (e-mail communication, July 31, 2023).[21] The number of MAUDE reports and SpaceOAR devices sold per year from 2015 to 2022 is shown in Table 1. In MAUDE, we identified 981 SpaceOAR-related adverse events reports describing 990 total events from January 2015 to May 2023. We observed a year-to-year increase in the complication rate per 1000 SpaceOAR sold from 0.62 in 2018 to 9.63 in 2022 (P = .0012 by linear regression) (Fig. 1).

Among MAUDE reports, SpaceOAR was used in 560 (57.1%) and SpaceOAR Vue in 421 (42.9%) of the reports. The most common broad event type classification was malfunction (N = 626), followed by patient injury (N = 350), with several deaths reported (N = 5). Each report had a single associated "device problem" describing the issue with the SpaceOAR device or its use during the procedure (Supplementary Table 1). In the category of device problem, a device positioning problem (inadequate or inability to place the SpaceOAR into the perirectal space between the prostate and rectum) was the most often reported (N = 686), followed by "adverse event without identified device or use problem" in 202 reports.

Patient complications from the SpaceOAR device, provided directly by MAUDE, are shown in Supplementary Table 2. These often overlapped, with the most frequent complication reported being pain from the device (N = 216) followed by discomfort (N = 135), device-related abscesses (N = 91), fistulas (N = 91), infections (N = 79), and ulcers (N = 71) were also reported. Hemorrhage was reported in 78 cases. Of note, 377 of the events listed "no clinical signs, symptoms, or conditions" for the patient complication.

All the events summarized and consolidated by the reviewers are organized by year and CTCAE grade in Table 2. There were 53 events with uncertain outcomes listed as "unknown" for the CTCAE grade. Nineteen events did not fit the consolidated events descriptions

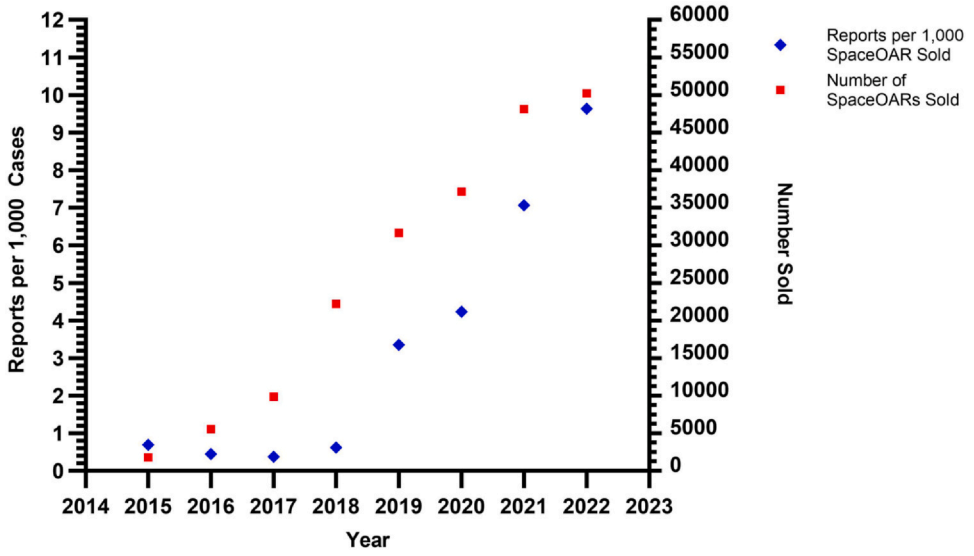

Figure 1. Number of reports submitted to MAUDE per 1000 SpaceOARs cases in the given year along with total number of SpaceOARs sold per year. (Color version available online.)

and were labeled "other events." Overall, 50.2% of adverse events reported were CTCAE grade 1 (N = 470), 36.7% grade 2 (N = 344), 10.6% grade 3 (N = 99), 2.0% grade 4 (N = 19), and 0.5% grade 5 (N = 5). Rectal wall infiltration was the most frequent, reported in 408 cases. No sequelae were reported in 280 of these events. However, there were 80 reports of rectal wall infiltration leading to delayed radiation therapy and 48 reports of rectal wall injury leading to symptoms requiring medical management. A list of all the surgical and life-threatening events (N = 123) is found in Supplementary Table 3. Of these events, 94 necessitated surgical intervention, including but not limited to abscess drainage, diverting colostomy, bilateral nephrostomy, and omental flap repair. In a total of 60 reports, we noted the occurrence of colostomy/bowel diversion and/or surgical repair. Common indications for surgery were perineal abscess (N = 27), rectourethral (N = 24), and perirectal fistula (N = 18). Five deaths were observed. One of the deaths was documented as the result of alcoholic cardiomyopathy, but it occurred during a hospitalization for sepsis; however, the sepsis was noted as resolved at the time of death and not likely from SpaceOAR. Three of the deaths were the result of cardiac arrest immediately postprocedure. The last death was also a cardiac arrest occurring immediately postprocedure, but it was attributed to hypertensive atherosclerotic heart disease.

Lastly, we performed an analysis based on the temporality of radiation therapy in relation to the placement of SpaceOAR (Table 3). Out of the 197 relevant adverse events recorded, the timing of radiation relative to the events was known in 156. Of these, 35 (22.4%) occurred before radiation therapy, and 121 (77.6%) occurred during or after radiation. Among the major surgical events, 5 perineal abscesses, 3 rectourethral fistulas, 1 perirectal fistula, 1 rectal ulcer, and 1 rectal perforation occurred before radiation. Of events that occurred during or after radiation therapy, 46 (38.0%) had positioning problem or device use problem listed as the device problem in the MAUDE report.

DISCUSSION

Despite the over 206,619 devices sold as of 2022, there has been a lack of robust reporting on the extent and range complications possible with SpaceOAR, which we address here. This report constitutes the largest description of adverse events and major complications related to SpaceOAR injection, including 981 MAUDE reports detailing 990 SpaceOAR-related adverse events.

In the pivotal phase III clinical trial, there were no reports of device-related adverse events or late rectal toxicity greater than grade 1.[6,7] After 3 years only three patients (2%) experienced grade 1 rectal toxicity (1 rectal bleeding, 1 rectal urgency, and 1 rectal proctitis).[6,7] A rectal wall infiltration rate of 6% (N = 9), was reported, which was also the most prevalent event noted in our investigation. Only one patient in the trial with rectal wall infiltration experienced late rectal toxicity (grade 1). In our analysis, we found that most reports of rectal wall infiltration did not lead to delayed radiation therapy. Interestingly, previous case reports identify rectal wall infiltration leading to mechanical or ischemic damage that precipitates the development of more severe rectal injury with radiation (ie, fistula and/or ulceration).[12,15,18]

A challenge of analyzing the MAUDE database is assessing the extent to which SpaceOAR contributed to a patient's condition. Many of the events reported in MAUDE can also be caused by radiation therapy alone, and the event descriptions tend to lack clinical detail to allow for precise evaluation.[22,23] However, prior case

Table 2. Device-related adverse events reported in the MAUDE database organized CTCAE grade.

CTCAE Grade	Description	Total Number of Events	Grade Total
Grade I	Suboptimal localization (rectal wall, prostate, venous/arterial, or urinary infiltration) – no sequelae	440	470 (47.5%)
	Kit failure (clogged, contaminated, bent needle, leakage, etc) – no sequelae	30	
Grade II	Rectal wall infiltration – delayed/altered RT	80	344
	Symptomatic rectal wall infiltration – medical management	48	(34.7%)
	Rectal symptoms and/or injury – nonsurgical management (hyperbaric O_2, medical management)	27	
	Rectal ulcer – nonsurgical treatment (medical management, hyperbaric O_2, cauterization)	24	
	Urinary symptoms – nonsurgical treatment (eg, medical management, catheterization)	21	
	Pain – medical management	18	
	Perineal abscess – medical management	13	
	Infiltration into urethra/bladder/penile bulb/seminal vesicle – nonsurgical treatment (medical management, catheterization, cystoscopy)	13	
	Injection/infiltration into the prostate – medical management and/or catheterization	12	
	Fluid collection around gel – nonsurgical management (medical management, catheterization)	12	
	Perirectal/perineal fistula – nonsurgical treatment (medical management, hyperbaric O_2)	10	
	Unspecified infection – medical management	10	
	"Other" events	9	
	Pulmonary embolism – medical management	9	
	Allergic reaction (nonanaphylaxis) – medical management	8	
	Abscess at implant site – medical management	7	
	Suboptimal localization – treatment required (medical management and catheterization)	6	
	Injection/infiltration into the prostate – delayed RT	5	
	Postprocedural event (vasovagal, seizure, vomiting) – on-site medical management	5	
	UTI – medical management	4	
	Venous/arterial injection – medical management	3	
Grade III	Perineal abscess – medical management and drainage	27	99 (10.0%)
	Rectourethral fistula – surgical management (surgical repair, diverting colostomy, suprapubic catheter/bilateral nephrostomy)	24	
	Perirectal/perineal fistula – surgical management (surgical repair, ileostomy, colostomy)	18	
	"Other" events	8	
	Rectal ulcer – surgical management (colostomy)	7	
	Abscess at implant site – medical management and drainage	7	
	Rectal injury – surgical management (colostomy)	4	
	Loss of consciousness – ER evaluation	4	
Grade IV	Anaphylactic shock/reaction	11	19 (1.9%)
	Septic event	5	
	Cardiac arrest	3	
Grade V	Patient death	5	5 (0.5%)
Unknown	Perirectal/perineal fistula – unknown treatment/outcome	19	53 (5.4%)
	"Other" events	2	
	Rectal ulcer – unknown treatment/outcome	17	
	Device anomaly (failure to dissolve, contrast not present, failure to polymerize)	8	
	Perineal abscess – unknown treatment/outcome	4	
	Rectourethral fistula – unknown treatment/outcome	3	
Total		990	

ER, emergency room; RT, radiation therapy; UTI, urinary tract infection.

Table 3. Analysis of event occurrence in relation to delivery of radiation therapy.

Event Description	Before Radiation	During/After Radiation	Unknown
Abscess at implant site – medical management	1	4	2
Abscess at implant site – medical management and drainage	2	4	
Fluid collection around gel – medical management	2	7	4
Perineal abscess – unknown treatment/outcome			4
Perineal abscess – medical management	3	7	3
Perineal abscess – medical management and drainage	5	16	6
Pelvic abscess – surgical management (colostomy)	1		
Perirectal/perineal fistula – nonsurgical treatment (medical management, hyperbaric O_2)	2	6	2
Perirectal/perineal fistula – surgical management (surgical repair, ileostomy, colostomy)	1	14	3
Perirectal/perineal fistula – unknown treatment/outcome	3	11	5
Rectal injury – surgical management (colostomy)	1	3	
Rectal ulcer – nonsurgical treatment (medical management, hyperbaric O_2, cauterization)	5	17	2
Rectal ulcer – surgical management (colostomy, surgical repair)	1	6	
Rectal ulcer – unknown treatment/outcome	4	6	7
Rectourethral fistula – surgical management (surgical repair, diverting colostomy, suprapubic catheter/bilateral nephrostomy)	3	19	2
Rectourethral fistula – unknown treatment/outcome	1	1	1
Total	35	121	41

reports identify SpaceOAR as the causative agent in the development of periprostatic abscess, rectal ulcer, and rectourethral fistula, which were noted in our dataset.[14-16,18,24] Commonly proposed mechanisms of SpaceOAR-induced injury include infection, inflammation, mechanical injury, and ischemia.[15,18] Event timing also helps inform the likely causality for these events. Major rectal complications following radiotherapy, such as fistulas and abscesses, although rare, develop > 3 months following therapy.[25,26] A previous report that used the MAUDE database found a total of 22 reports between 2015 and 2019 describing 25 events, ranging from venous injection to death.[11] Another analysis from May 2015 to May 2020 identified 80 events, among which 59 were CTCAE grade ≥3.[19] These previous reports using MAUDE did not address the timing of the adverse event in relation to initiation of radiation therapy. In our dataset, we noted a substantial number of adverse events that occurred prior to radiation, which eliminates radiation as a causative agent. Also, we note events that occurred during or after radiation that also denote a positioning problem. While a misplaced device may not be entirely responsible for the complication, reports of such are suggestive.

In total, our analysis found 123 events grade ≥3, including 94 patients requiring surgical intervention, which were not reported in the clinical trial and have not been reported to this extent until now. We observed year-to-year increases in the complication rate per 1000 SpaceOARs sold, among others, possible etiologies include increased instances of grouped retrospective reporting with absent concrete event dates as well as increasing use of SpaceOAR by nonexpert appliers. Our results provide support for continued postmarket monitoring and investigation into the SpaceOAR hydrogel system. It is imperative that patients are aware and informed of these rare but potentially debilitating outcomes.

We also want to note a recent report of SpaceOAR-related using MAUDE.[27] The authors described a similar distribution of complications with 57% and 18% out of 574 reports being CTCAE grade 1 and grade ≥3, respectively. Contrary to this study, we did not exclude "duplicate" MAUDE reports. According to Boston Scientific these "duplicates" usually result from bulk reporting following institutional retrospective analyses.[21] The MAUDE database requires each adverse event to be submitted as its own report. This allowed us to include 49 additional events on top of the 327 additional events we initially captured.

It is necessary to acknowledge the limitations of the MAUDE database and the data we report. Although the FDA mandates reporting of adverse events, confirming the absolute incidence of events is not possible. Underreporting is well-documented as a possible limitation of the MAUDE database.[21,25,26] Further, there is potential for duplicated event reporting by the patient, provider, or facility, which can introduce a degree of redundancy into our dataset. Another limitation is inherent to the quality of event reporting. The details recorded in the report are only as reliable as the individuals, who submit the report, and there is significant variability in detail provided within the reports used in our study. We also noticed reports with identical event descriptions, including 72 identical events of rectal wall infiltration reported on the same day (11-01-22). From our discussions with the Boston Scientific Corporation, who submitted the report, it was concluded that this represented a mass submission following a comprehensive retrospective analysis.

Despite these limitations, this study provides insight into adverse events resultant from SpaceOAR. It highlights the need for close postmarket surveillance, especially given our findings of rare but severe complications that did not occur in the initial phase III trial. Additionally, future focus should be placed on identifying factors, including a potential learning curve and provider volume, that contribute to the occurrence of severe adverse events. Lastly, continued research should focus on identifying patients that benefit most from SpaceOAR.[28]

CONCLUSION

Our analysis of the MAUDE database reveals a wide range of adverse events related to the SpaceOAR hydrogel system that were not noted in the pivotal phase III clinical trials. While SpaceOAR use is common, suggesting these events are rare, these data highlight the need for continued postmarket surveillance. This study should help inform physicians and patients about the risks of applying SpaceOAR.

Declaration of Competing Interest

Daniel E. Spratt receives research funding from the National Institutes of Health and the Prostate Cancer Foundation and personal fees from Astellas, AstraZeneca, Bayer, BlueEarth, Boston Scientific, Elekta, GT Medical Technologies Inc, Myovant, Pfizer, Janssen, Novartis, and Varian. Elisha T. Fredman serves as a consultant to Boston Scientific for the SpaceOAR product. The other authors have no conflict of interest to declare.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.urology.2023.12.034.

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