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Authors
Hall, William A
Tree, Alison C
Dearnaley, David
et al.

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Considering benefit and risk before routinely recommending SpaceOAR

William A Hall, **Alison C Tree**, **David Dearnaley**, **Christopher C Parker**, **Vinay Prasad**, **Mack Roach III**, **Colleen A F Lawton**

Department of Radiation Oncology, Medical College of Wisconsin, WI 53226, USA (WAH, CAFL); The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, UK (ACT, DD, CCP); and Department of Epidemiology and Biostatistics (VP), and Department of Radiation Oncology and Urology (MR), University of California San Francisco, San Francisco, CA, USA

Localised prostate cancer is a common malignancy with multiple, large, prospective trials reporting a considerable number of patients who can be cured when treated with surgery or radiotherapy. Radiotherapy in this setting is associated with 5% or lower grade 3 toxicity rates, and grade 4 toxicity rates of less than 1%.[1,2] In April, 2015, a novel device, SpaceOAR, was given clearance by the US Food and Drug Administration (FDA) to attempt to further reduce toxicity in patients with prostate cancer treated with radiotherapy.[3] The device consists of placement of a hydrogel between the prostate and the rectum to physically separate these two structures, thereby reducing the dose of radiation delivered to the rectum. The biological plausibility of the device relies on the assumption that placement of a foreign body, and displacement of the rectum, does not inherently compromise the normal rectal parenchyma's tolerance to radiotherapy.

Approval of this device was based largely on the results of a single-blind, randomised phase 3 clinical trial.[4,5] In this study, 222 men receiving radiotherapy were randomly assigned (2:1) to either placement of a SpaceOAR device or not. The study did not meet its primary safety endpoint, which was grade 1 or greater rectal or procedural adverse events in the first 6 months (34·2% *vs* 31·5%, p=0.7). Secondary analyses claimed an improvement in grade 1 and grade 2 gastrointestinal toxicity, and grade 1 genitourinary toxicity, along with patient-reported bowel and urinary quality of life all favouring the use of the SpaceOAR device.[4] However, there was no difference in the radiotherapy dose given to the urinary structures to potentially explain a radiotherapy-related cause of genitourinary toxicity improvement, raising concerns that these results were spurious. With the publication of this trial, the use of the SpaceOAR device is rapidly increasing (appendix p 1).

There are several concerns with these data. First, the study did not meet the primary clinical safety endpoint. Second, there was an absence of any evaluation as to the reliability of patient masking in the study.[6,7] Third, the absence of physician masking is a concern. Providers who are not masked are at substantial risk of overestimating the effect of an

whall@mcw.edu .

intervention, which can affect subsequent management. Clearly, such masking would have been challenging given the physical device placement and visualisation to the doctor prescribing radiotherapy. However, there is a substantial risk that physician management of toxicity would be affected by knowledge of spacer presence. The potential for bias management by providers could have been alleviated by masking subsequent managing providers to the presence or absence of the device; however, this was not done.

Despite these limitations, trial data suggested the intervention with SpaceOAR was extremely safe, and largely this might be the case. However, there are published real world examples identifying adverse events associated with SpaceOAR placement. One small report examined cases of toxicity identified in the FDA Manufacturer and User Facility Device (MAUDE) database.[8] This publication collected a total of 22 reports citing a total of 25 patient cases. Complications reported included colostomy, pulmonary embolism, anaphylaxis, and prostatic abscess associated with SpaceOAR placement.[8] Some limitations to this report have been previously identified.[9] We sought to further understand these reported complications and expand the characterisation of these events.

To accomplish this, on May 15, 2020, the MAUDE database, which houses medical device reports submitted to the FDA by mandatory and voluntary reporters, was accessed via a publicly available online interface and events were searched for from May 1, 2015, to May 1, 2020, using the search term “SpaceOAR”. The description of each event was reviewed and scored by two independent radiation oncologists (WAH and CAFL). The results were then compared collectively, and a final adjudication of scored toxicity events was created. A total of 85 reported events in the MAUDE database were available for review. Among these, 80 (94%) had event descriptions that could be characterised using the Common Terminology Criteria for Adverse Events (version 5.0). Of the toxicity events, 59 (69%) were grade 3, 4, or 5. 20 (24%) were grade 4 events, including multiple independent descriptions of colostomy, anaphylactic events, rectal wall injection, or pulmonary emboli requiring hospital admission. One death was reported. The toxicity score distribution can be seen in the appendix (p 2).

Cautious management of prostate cancer is imperative. Many patients with prostate cancer will die of other competing medical comorbidities and interventions for prostate cancer must be carefully considered for the risks and benefits that they confer. Therefore, all prostate interventions should provide a substantial benefit before they are recommended as standard of care. Patients who are at high risk for toxicity associated with specific interventions must be studied.

We have presented a review of the toxicity events reported over a 5-year time period in the FDA MAUDE database. Given the substantial number of SpaceOAR procedures done per year, the incidence of documented MAUDE events is small. However, MAUDE is not intended to evaluate rates of adverse events. Reporting of adverse events by health-care providers is voluntary. It is possible that many events are missed. Moreover, reported events to the MAUDE database have limitations regarding accuracy, verifiability, and scope. Furthermore, the denominator in this setting is simply unknown. Despite these limitations, many of these independently described events follow a similar pattern and would be

considered as truly catastrophic in the spectrum of prostate cancer management. Given that it is unknown what percentage of actual events are reported to the MAUDE database, our findings might only represent a fraction of total adverse events that have occurred when using this device.

Considering the substantial uncertainty regarding the reported benefit, along with some doubt concerning cost-effectiveness of this device,[10] it remains perplexing why SpaceOAR is so rapidly gaining popularity. It also remains unknown if oncological outcomes are affected in some patients by placement of this device. Such conclusions would require much larger studies, with substantially long-term follow up.

In this context, urologists, radiation oncologists, and medical oncologists should pause to consider the routine use of SpaceOAR. Is such a device truly helpful? Is the potential for a relatively small (and questionably real) improvement in physician-reported and patient-reported toxicity events worth even the very small chance of a catastrophic toxicity? Do we really understand the implications of this device across all categories of prostate cancer risk and fractionation schedules? Reflection on the part of all genitourinary oncologists is needed to consider these events. Prostate cancer is highly curable with both surgery and radiotherapy and, even without SpaceOAR, is associated with an exceedingly low rate of adverse events requiring intervention. Critical reflection and careful consideration of the need, toxicity, and benefits of SpaceOAR are appropriate before the device is recommended for routine care.

In summary, genitourinary oncologists need to carefully review and consider the validity of the current data supporting the use of SpaceOAR before routinely using this device. Moreover, individuals who select patients for SpaceOAR implantation should be vigilant at reporting toxicity to MAUDE to ensure that the oncology community is aware of these events. Additional research into patients who might particularly benefit from SpaceOAR, or patients at high risk for toxicity from SpaceOAR, is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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