**Summary of Relevant Clinical Literature**

**SpaceOAR System Studies**

**Hamstra DA et al. *Continued Benefit to Rectal Separation for Prostate RT: Final Results of a phase III trial*** Int J Radiat Oncol Biol Phys. 2017 Apr 1;97(5):976-985. doi: 10.1016/j.ijrobp.2016.12.024. Epub 2016 Dec 23.

* Late (>90 days) CTCAE toxicity was evaluated for the subjects from the SpaceOAR pivotal study (Mariados et al). Mean changes from baseline in EPIC domains were also tested.
* The 3-year incidence of grade 1+ (9.2% vs 2.0%; p=0.28) and grade 2+ (5.7% vs 0%; p=.012) rectal toxicity favored the spacer arm.
* Grade 1+ urinary incontinence was also lower in the spacer arm (15% vs 4%; p=.046).
* From 6 months onward, bowel QOL consistently favored the spacer group (p=.002), with the difference at 3 years (5.8 points; p<.05) meeting the threshold for an MID.
* At 3 years, more men in the control group than in the spacer group had experienced a MID decline in bowel QOL (41% vs 14%; p=.002) and urinary QOL (30% vs 17%; p=.04). The control group was also more likely to have experienced large declines (twice the MID) in bowel QOL (21% vs 5%; p=.02) and urinary QOL (23% vs 8%; p=.02).

**Mariados et al. *Hydrogel Spacer Prospective Multicenter Randomized Controlled Pivotal Trial: Dosimetric and Clinical Effects of Perirectal Spacer Application in Men Undergoing Prostate IG-IMRT.*** [Int J Radiat Oncol Biol Phys. 2015 Aug 1;92(5):971-777. (222)]

T1-T2 patients at 20 US institutions, prospective, multicenter, randomized, single-blind controlled pivotal trial. Patients randomized 2:1 SpaceOAR: Control

* Patients underwent baseline scans, received fiducial markers and were randomized to Spacer or Control groups (patients blinded to treatment). During RT all AE’s were gathered, followed for 15 months for toxicity and quality of life.
* Perirectal space was 12.6+3.9mm and 1.6+2.0mm in the Spacer and Control groups, respectively.
* Spacer technical success rate was 99% (hydrogel present between prostate and the rectum)
* Pre to post-spacer plans had a 73.5% significant reduction in mean rectal V70 (12.4% to 3.3%, p<0.0001).
* Patients reporting acute rectal pain were 2.7% and 11.1% (p=0.02) in the Spacer and Control groups, respectively.
* No difference in Spacer or Control GU toxicity, acute or late.
* Late rectal toxicity was 2.0% (all Grade 1) and 7.0% (up to Grade3) in the Spacer and Control groups, respectively, with a statistically significant reduction in the severity of late rectal toxicity (p=0.04).
* At 15 months 11.6% and 21.4% of Spacer and Control patients experienced 10-point declines in bowel QOL, respectively.
* Safety: No spacer related adverse events, no delays to onset of IMRT, no spacer infections, no rectal wall ulcerations

**Song et al, *A multi-institutional clinical trial of rectal dose reduction via injected polyethylene-glycol hydrogel during intensity modulated radiation therapy for prostate cancer: analysis of dosimetric outcomes.*** [Int J Radia Oncol Biol Phys 2013 Sept 1; 87(1): 81-87. (52)]

Prospective, non-randomized, multi-center, single arm, open-label pilot clinical trial **-** 52 patients at 4 institutions, prospective, non-randomized, multi-center, single arm, open-label pilot clinical trial (48 patients received hydrogel).

* Patients underwent baseline scans and then were injected with perirectal spacing hydrogel and rescanned.
* IMRT plans were created on both scans for comparison.
* The objectives were to establish rates of creation of ≥ 7.5 mm of prostate-rectal separation, and decrease in rectal V70 of ≥ 25%.
* Hydrogel resulted in ≥7.5-mm prostate-rectal separation in 95.8% of patients; o95.7% had decreased rectal V70 of ≥ 25%, with a mean reduction of 8.0 Gy. P. 36 7
* Conclusion:
* Injection of hydrogel into the prostate-rectal interface resulted in clinically significant dose reductions to rectum for >90% of patients.
* Rectal sparing was statistically significant across a range of 10 to 75 Gy

**Pieczonka CM, et al. *Hydrogel spacer application technique, patient tolerance and impact on prostate intensity modulated radiation therapy: results from a prospective, multicenter, pivotal randomized controlled trial***/Urol Pract. 2015;3(2):141-146. doi:10.1016/j.urpr.2015.04.002/PMID N/A

* Application technique assessment of same patient cohort as Mariados et.al. study
* The spacer application success rate was 99.3% (applier assessment) and device ease of use was rated as very easy or easy in 69.4% and 29.3% of all cases, respectively.
* Hydrogel spacer application was straightforward and repeatable, resulting in consistent perirectal space creation and rectal dose reduction.
* Spacer application has the potential to improve prostate radiotherapy outcomes and enable advanced radiotherapy protocols.

**Fischer-Valuck B.W., et al. *Hydrogel spacer distribution within the perirectal space in patients undergoing radiotherapy for prostate cancer: Impact of spacer symmetry on rectal dose reduction and the clinical consequences of hydrogel infiltration into the rectal wall.*** [Practical Radiation Oncology, Volume 0, Issue 0]

Analysis of T2-weighted magnetic resonance imaging sets of Mariados et al. study cohort receiving SpaceOAR injection

* Patients receiving transperineal spacer injection were assessed for hydrogel spacer symmetry and rectal wall infiltration (RWI) using a semiqualitative scoring system.
* Hydrogel spacer was symmetrically placed at midline for 71 (47.7%) patients at the prostate midgland as well as 1cm superior and inferior to midgland. The remaining 78 (50.9%) had some level of asymmetry, with only 2 (1.3%) having far lateral distribution (i.e., >2cm) of hydrogel spacer.
* All but the most asymmetrical 1.3% had significant rectal dose reduction (p<0.05)
* Rectal wall hydrogel spacer infiltration was seen in 9 (6.0%) patients.
* There was no correlation between RWI and procedure-related adverse events or acute/late rectal toxicity.

**Uhl,** **et al. *Absorbable hydrogel spacer use in men undergoing prostate cancer radiotherapy: 12-month toxicity and proctoscopy results of a prospective multicenter phase II trial.*** *[*Radiat Oncol. 2014;9(1):96.]

Same cohort of patient as study outlined above (Song et al, 2013). Despite some differences in margins and dose delivered, the lower GI toxicity rates in this study are remarkable when compared to other studies[1],[2],[3].

* Of the patients treated 39.6% and 12.5% experienced acute Grade 1 and Grade 2 GI toxicity, respectively.
* There was no Grade 3 or Grade 4 acute GI toxicity experienced in the study.
* Only 4.3% showed late Grade 1 GI toxicity, and there was no late Grade 2 or greater GI toxicity experienced in the study.
* The SpaceOAR subjects had similar acute and late urinary toxicity as the rates reported in literature.
* This was expected as rectal spacers are not intended to impact GU toxicity.
* A total of 41.7%, 35.4% and 2.1% of the men experienced acute Grade 1, Grade 2 and Grade 3 GU toxicity, respectively. No Grade 4 GU toxicity experienced in the study.
* Late Grade 1 and Grade 2 GU toxicity was experienced in 17.0% and 2.1% of the patients, respectively. No late Grade 3 or greater GU toxicity experienced in the study.
* 71% of the patients had a Vienna Rectoscopy Scale (VRS) score of 0, and one patient (2%) had Grade 3 teleangiectasia.
* There was no evidence of ulceration, stricture or necrosis at 12 months.
* Conclusion: the use of PEG spacer hydrogel is a safe and effective method to spare the rectum from higher dose and toxicity.

**Pinkawa M, et al.** ***Hydrogel injection reduces rectal toxicity after radiotherapy for localized prostate cancer*** [Strahlenther Onkol (2016), doi:10.1007/s00066-016-1040-6]

A group of 167 consecutive patients who received prostate radiotherapy during the years 2010 to 2013.

* Patients were treated with 2-Gy fractions up to 76 Gy (without hydrogel, n=66) or 76-80 Gy (with hydrogel, n=101)
* The numbers of interventions resulting from bowel problems during the first 2 years after RT were compared.
* Patients were surveyed prospectively before RT, at the end of RT, and a median time of 2 months and 17 months after RT using the EPIC questionnaire.
* Treatment for bowel symptoms (0 vs. 11%; p<0.01) and endoscopic examinations (3 vs. 19%; p<0.01) were performed less frequently with a spacer.
* Despite the Spacer patients receiving higher prescription doses, at >1 year after RT: mean bowel function scores in comparison to baseline did not change for patients with a spacer (mean change of 0 points) in contrast to patients without a spacer (mean decrease of 5 points) with 0 vs. 12% reporting a new moderate/big problem with passing stools (p<0.01)
* Statistically significant differences were found for the items “loose stools,” “bloody stools,” “painful bowel movements” and “frequency of bowel movements”

**Te Velde B.L., et al. *Can a peri-rectal hydrogel SpaceOAR programme for prostate cancer intensity-modulated radiotherapy be successfully implemented in a regional setting?*** [J Med Imaging Radiat Oncol. doi:10.1111/1754-9485.12580]

Retrospective study, 125 patients with localized prostate cancer treated between April 2014 and June 2015 were compared: 65 treated with SpaceOAR and 60 treated over the same time period without SpaceOAR.

* Patients were treated with 81Gy in 45 fractions of IMRT over 9 weeks
* Acute toxicity was assessed weekly during radiotherapy and at 12 weeks
* Rectal volume parameters were all significantly lower in the SpaceOAR group, with an associated reduction in acute diarrhea (13.8% vs. 31.7%, p=0.02)
* Conclusion: a SpaceOAR programme in a regional setting with urologists performing low volumes of insertions (<1 per month on average) is of clinical benefit, and was associated with significantly lower radiation doses to the rectum and lower rates of acute diarrhea

**Whalley et al. *SpaceOAR Hydrogel in Dose-escalated Prostate Cancer Radiotherapy: Rectal Dosimetry and Late Toxicity, Clinical Oncology (2016).*** [<http://dx.doi.org/10.1016/j.clon.2016.05.005>]

30 patients with prostate cancer underwent an MRI before and after placement of SpaceOAR.

* First 10 patients had an additional MRI after the completion of radiation treatment. Primary endpoints were perioperative toxicity and comparison of rectal dosimetry.
* Secondary endpoints were acute and late radiation toxicity.
* Patients received 80Gy in 40 fractions. A control group of 110 prostate cancer patients treated with the same dose was identified for comparison.
* Rectal doses were significantly lower for the post-hydrogel plans, especially above 65Gy.
* Rates of acute Grade 1 and 2 GI toxicity were 43% vs. 51% and 0% vs. 4.5% in the Spacer and Control groups, respectively (p>0.05).
* Late Grade 1 was significantly less frequent in the Spacer group (16.6% vs. 41.8%, p=0.04).

**Supplemental Studies**

**Wood et al, Incidence, predictors, and cost implications of gastrointestinal complications following intensity-modulated radiation therapy for prostate cancer. 2015 Genitourinary Cancers Symposium; J Clin Oncol 33, 2015 (suppl 7; abstr 31).**

* Using Surveillance, Epidemiology, and End Results (SEER)-Medicare-linked data, 11,781 men diagnosed with non-metastatic prostate cancer from 2002 to 2006 who underwent definitive IMRT were identified.
* Patients had no pre-existing GI toxicity and had at least 36 months of follow-up after IMRT initiation.
* Over the 36-month follow-up period, the incidence of post-IMRT GI complications was 26.5% (n=3,118).
* The median Medicare annual incremental cost per patient associated with post-IMRT GI complications was $3,375 in 2014 dollars (95% CI $3,222-3,529, p<0.0001).

**Nam et al, *Incidence of complications other than urinary incontinence or erectile dysfunction after radical prostatectomy or radiotherapy for prostate cancer: a population-based cohort study.***

[The Lancet 2014;15:221-31.]

Population-based retrospective cohort study involving 32,465 patients.

* The 5-year cumulative incidences of five treatment-related complication endpoints were measured: hospital admissions; urological, rectal, or anal procedures; open surgical procedures; and secondary malignancies.
* The 5-year cumulative incidence of needing a urological procedure was 32·0% (95% CI 31·4–32·5) and that of a rectal or anal procedure was 13·7% (13·3–14·1.
* Patients who were given radiotherapy had higher incidence of complications for hospital admissions, rectal or anal procedures, open surgical procedures, and secondary malignancies at 5 years than did those who underwent surgery (adjusted hazard ratios 2·08–10·8, p<0·0001).
* The 5-year incidence rate of rectal/anal procedures in patients receiving radiation therapy was 18.4% with a 27% risk of treatment related readmission (n=16,595).