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Emerging Indications for Novel Absorbable PEG Hydrogel Spacers

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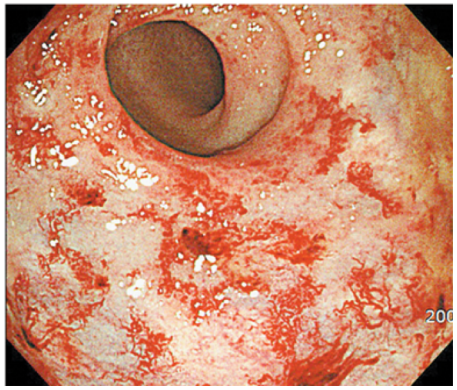
The Problem: OAR – Organ at Risk

- Rectum has been the dose-limiting factor
- Rectal Toxicity / Rectal complications
  - Bleeding, frequency, urgency, pain, fistulas
- Loss of QOL
  - Rectal injury can lead to bowel, urinary and sexual symptoms that can affect patient health and quality of life during RT and for years afterward



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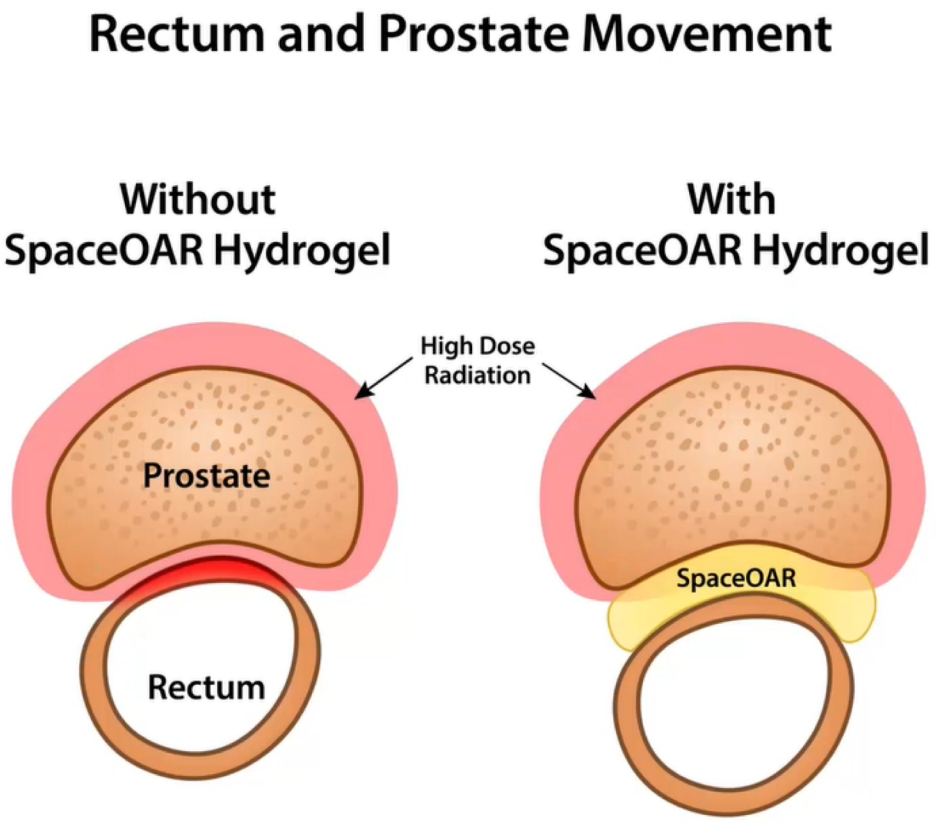
Radiation Dose to Rectum is Inevitable without Prevention

- Rectal radiation has been unavoidable due to close proximity to prostate
- Prostate movement between and during treatments



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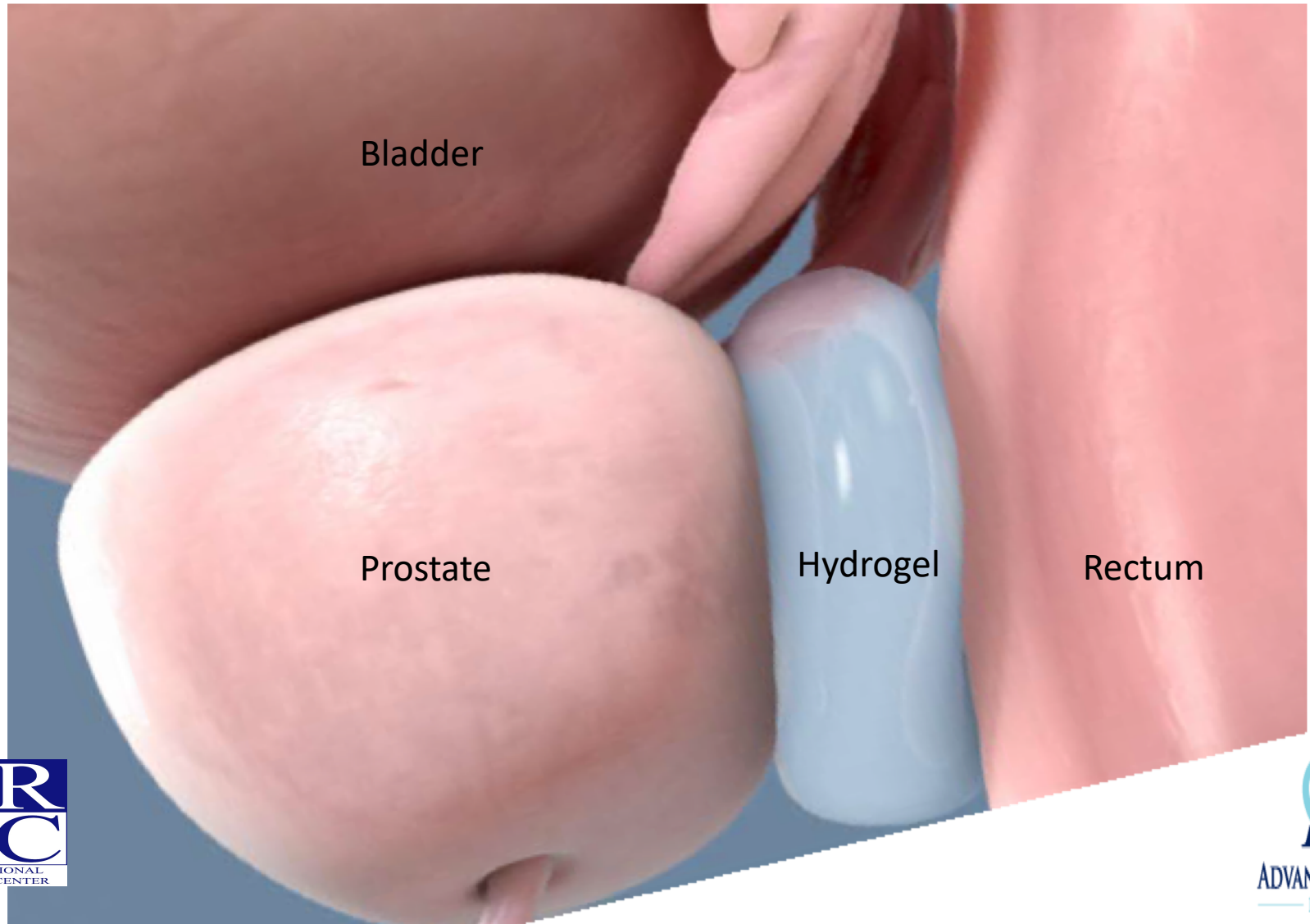
An Emerging Practical Solution: PEG Hydrogel Implant: ***What it is?***



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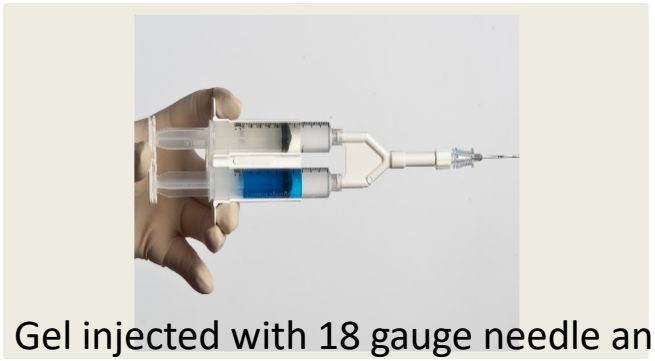
SpaceOAR is an FDA-Cleared PEG Hydrogel Implant that Protects the Rectum by Temporarily Moving it away from the Prostate During Radiation Therapy

SpaceOAR System

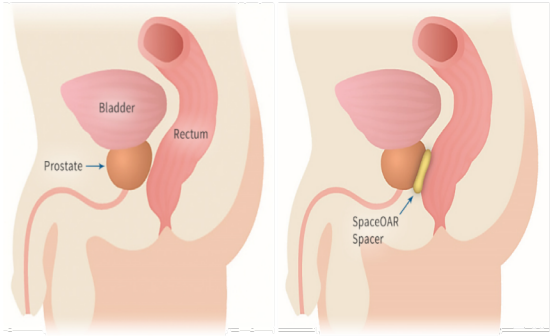
SpaceOAR®



Gel injected with 18 gauge needle and solidifies within **10 seconds**

SpaceOAR System	
Composition	PEG hydrogel
Absorption	Approximately 6 months
Formulation	In situ polymerizing
Visibility	MRI, Ultrasound
Indications	Prostate-rectum spacer
WW Adoption	27,000+ patients treated

How SpaceOAR System works

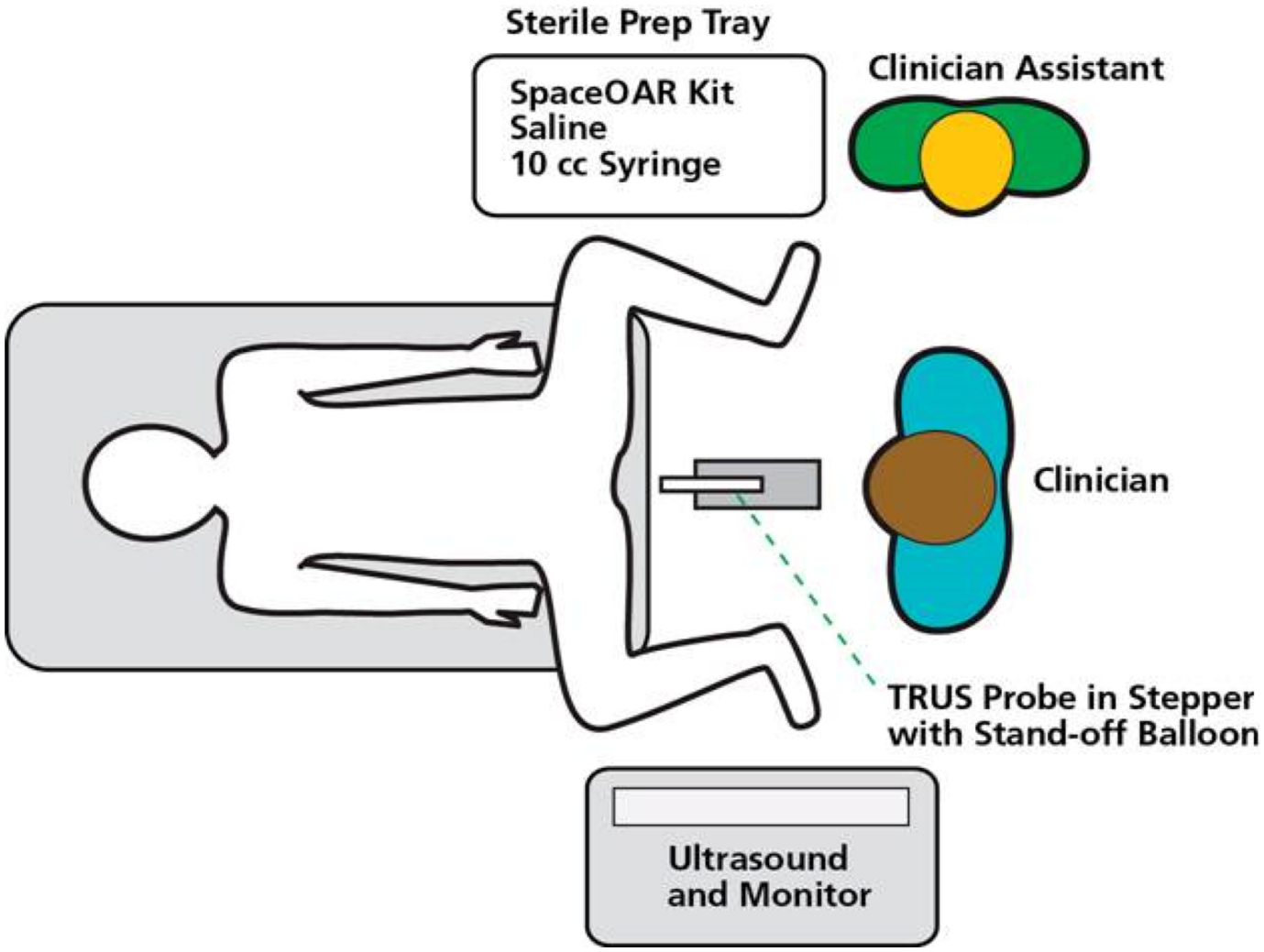


Creates a perirectal space to mitigate negative side effects of radiation therapy

Pre-implant space | **3 month persistence of SpaceOAR System** | **6 month absorption**

Remains in place for 3 months, absorbs and leaves body through urine

PEG Hydrogel Procedure is Relatively Simple and Quick in the Office



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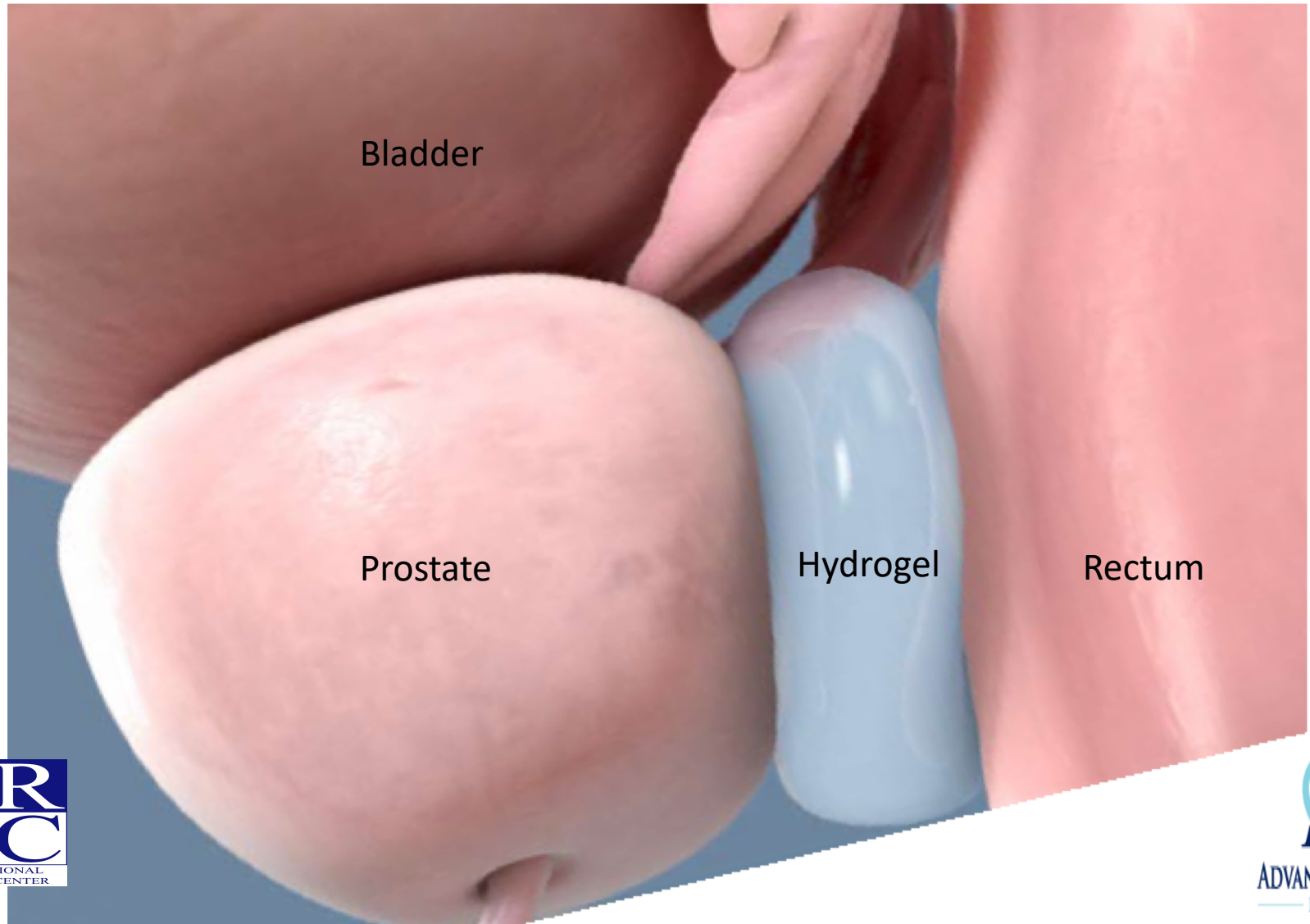
PEG Hydrogel Implant: ***Does it work?***



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Pivotal Definitive EBRT Study Demonstrated: Safety, Significant OAR Dose Reduction, and Long-Term Clinical Benefits

Study design[1]

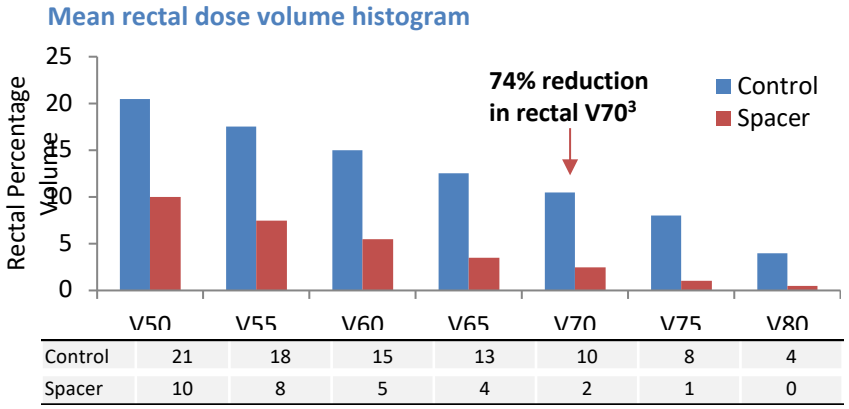
Study design

- Prospective
- Randomized: 222 patients
- Multi-center: 20 Centers
- Patient Blinded
- 6, 12, 15 and 37 month follow up
- MRI planning
- Plans were reviewed by Core Lab

Procedure results

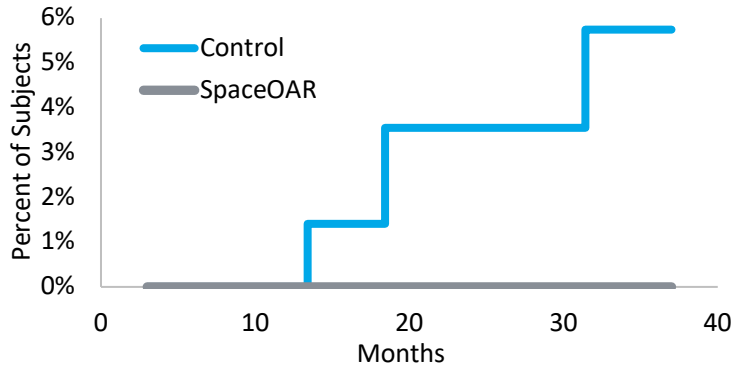
- 99% Technical success
- 99% "easy" or "very easy"
- No device related AE's
- No implant site infections
- 37% general, 32% local, 25% MAC
- 1.3 cm space created

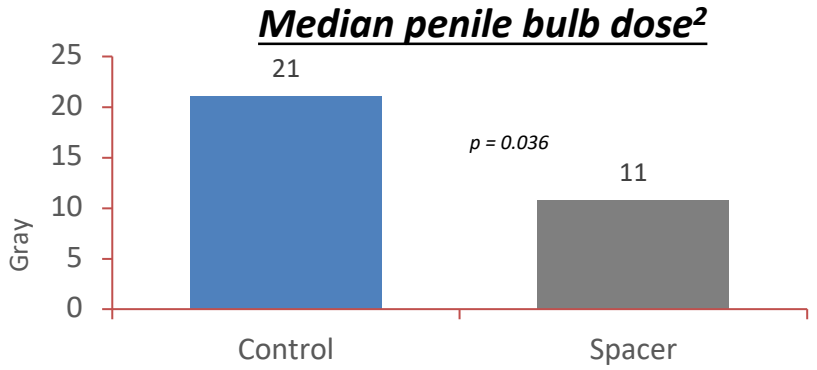
Dosimetry: protection of rectum and penile bulb



	V50	V55	V60	V65	V70	V75	V80
Control	21	18	15	13	10	8	4
Spacer	10	8	5	4	2	1	0

Late rectal toxicity, grade 2+[2]





No spacer patients developed G2+ late rectal toxicity out through 37 months

Source: [1]Mariodos et al, *Int'l J Radtion Biol Phys*, Vol 92, No 5, 2015; [2]Hamstra et al, *Int'l J Radiation Biol Phys,* "Continued, Benefit to Rectal Separation for Prostate Radiation Therapy: Final Results of a Phase III Trial", Vol 97, No 5; December 2016.
Note: [3]The rectal volume receiving ≥70 Gy

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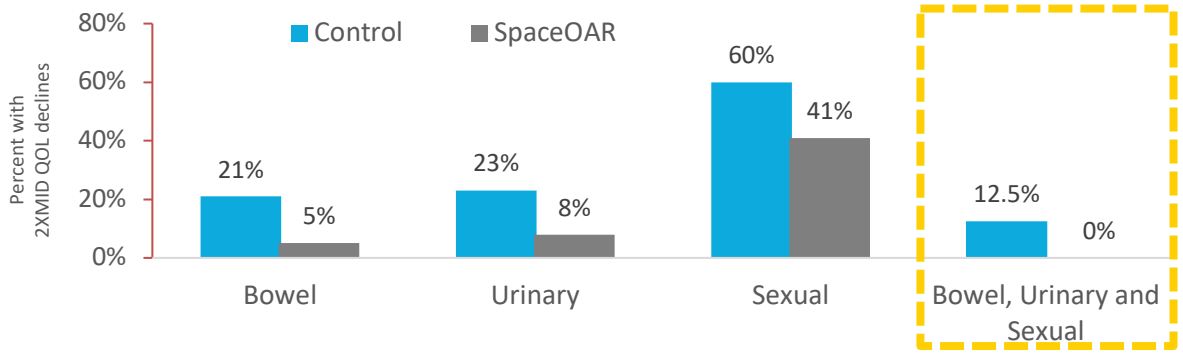
Pivotal Definitive EBRT Study Demonstrated: In Addition to Reduced Toxicity, Patients Experienced Long-term QOL Benefits

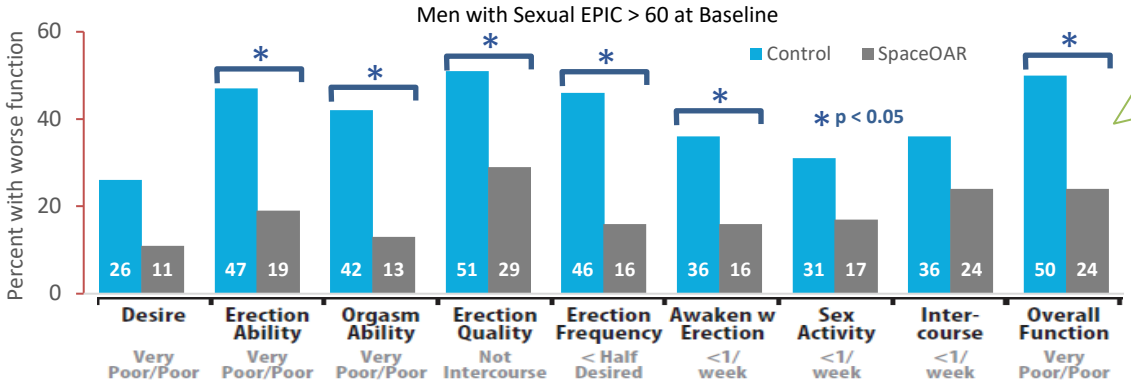
3-Year QOL findings in randomized clinical trial

Percent of men with clinically significant (2XMID) declines in quality of life, 3-years post RT[1]



1 in 8 control patients had significant declines in overall well-being in all three domains (bowel, urinary and sexual) compared to **0% of SpaceOAR patients**

Percent of men with worsening sexual function, 3-years post RT[2]



"No previous prospective randomized trials of other radiation treatment modalities (such as IMRT, image guidance, proton therapy, or stereotactic therapy) have identified **such an improvement in ED and sexual QOL**."[2]

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Source: [1] Hamstra et al, *Int'l J Radiation Biol Phys*, "Continued Benefit to Rectal Separation for Prostate Radiation Therapy: Final Results of a Phase III Trial," Vol 97, No 5; December 2016. [2] D. A. Hamstra et al., *Pract. Radiat. Oncol.*, "Sexual Quality of Life Following Prostate Intensity Modulated Radiotherapy (IMRT) with a Rectal/Prostate Spacer: Secondary Analysis of a Phase III Trial," Vol. 8, No 1, 2018.

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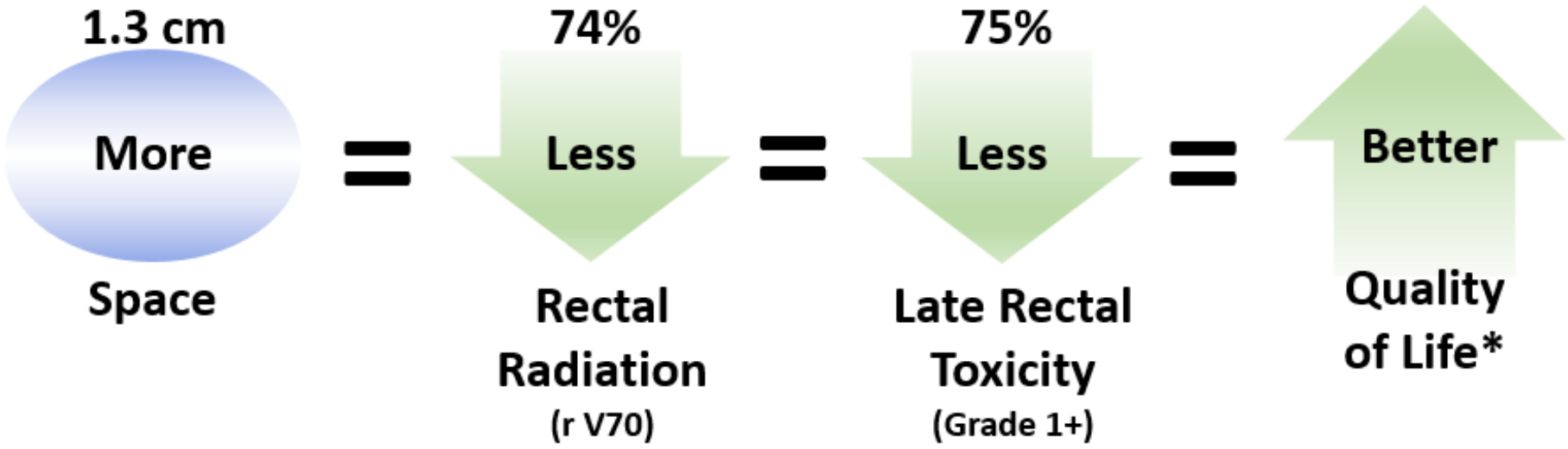
Summary:
Definitive EBRT Study Results



In the pivotal trial, SpaceOAR patients did not experience any Grade 2 or greater rectal toxicity (e.g. proctitis, rectal bleeding, or fecal incontinence).[1,2]

1) Hamstra D, et al. Continued Benefit to Rectal Separation for Prostate RT: Final Results of a Phase III Trial. Int J Radiation Oncol Biol Phys, Vol. 97, No. 5, pp. 976-985, 2017
2) Hamstra D, et al. Evaluation of sexual function on a randomized trial of a prostate rectal spacer. J Clin Oncol 35, 2017 (suppl 6S; abstract 69)

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PEG Hydrogel Implant Current Status

- 27000+ Procedures
- 500+ Centers
- Over 66 Peer Reviewed Publications
- Currently used in 19 out of the Top 20 US Cancer Centers
  (*U.S. News & World Report)*
- Emerging Use with All Forms of Prostate Radiation:
  - EBRT IMRT
  - Brachy (LDR/HDR)
  - Proton
  - SBRT
  - Combination therapies (EBRT + LDR/HDR/Proton boost)
- Standard-of-care use
  - NRG GU 005 Rodney Ellis hypofractionation
    - **SpaceOAR is allowed** in the same way rectal balloon
  - COMPPARE (Proton vs Photon Radiation)
    - **SpaceOAR is allowed** in the same way rectal balloon

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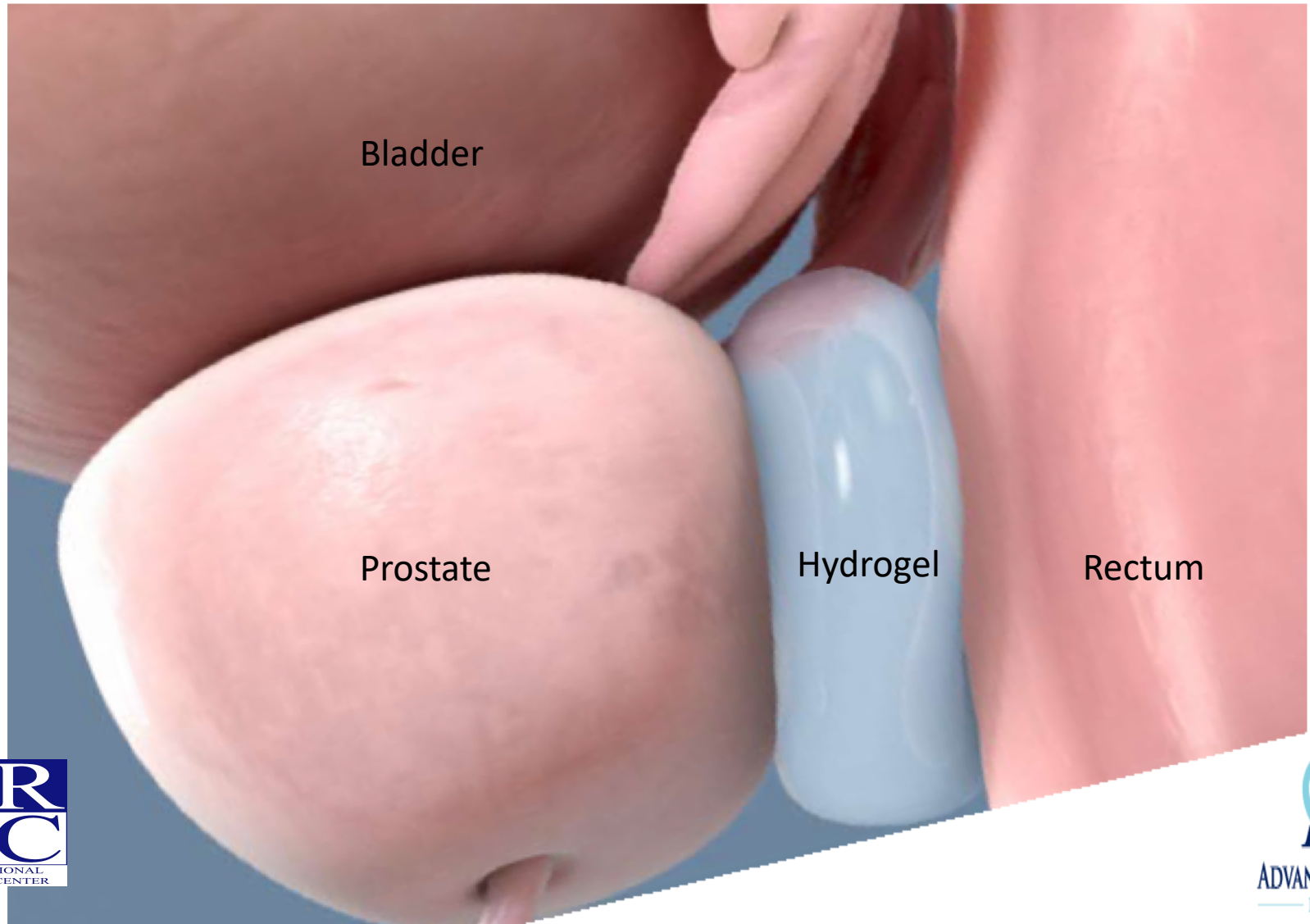
PEG Hydrogel Implant Emerging Status:
What it the future?



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SpaceOAR
Approved Definitive EBRT

- US pivotal trial inclusion criteria
  - T1 or T2 , Gleason Score ≤ 7, PSA ≤ 20ng/mL, ≤50% positive cores
  - MRI mandated

Indication for use:

SpaceOAR System is intended to temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer and in creating this space it is the intent of SpaceOAR System to reduce the radiation dose delivered to the anterior rectum. The SpaceOAR System is composed of biodegradable material and maintains space for the entire course of prostate radiotherapy treatment and is completely absorbed by the patient's body over time.

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Current use: All non-ECE radiation treatment setting

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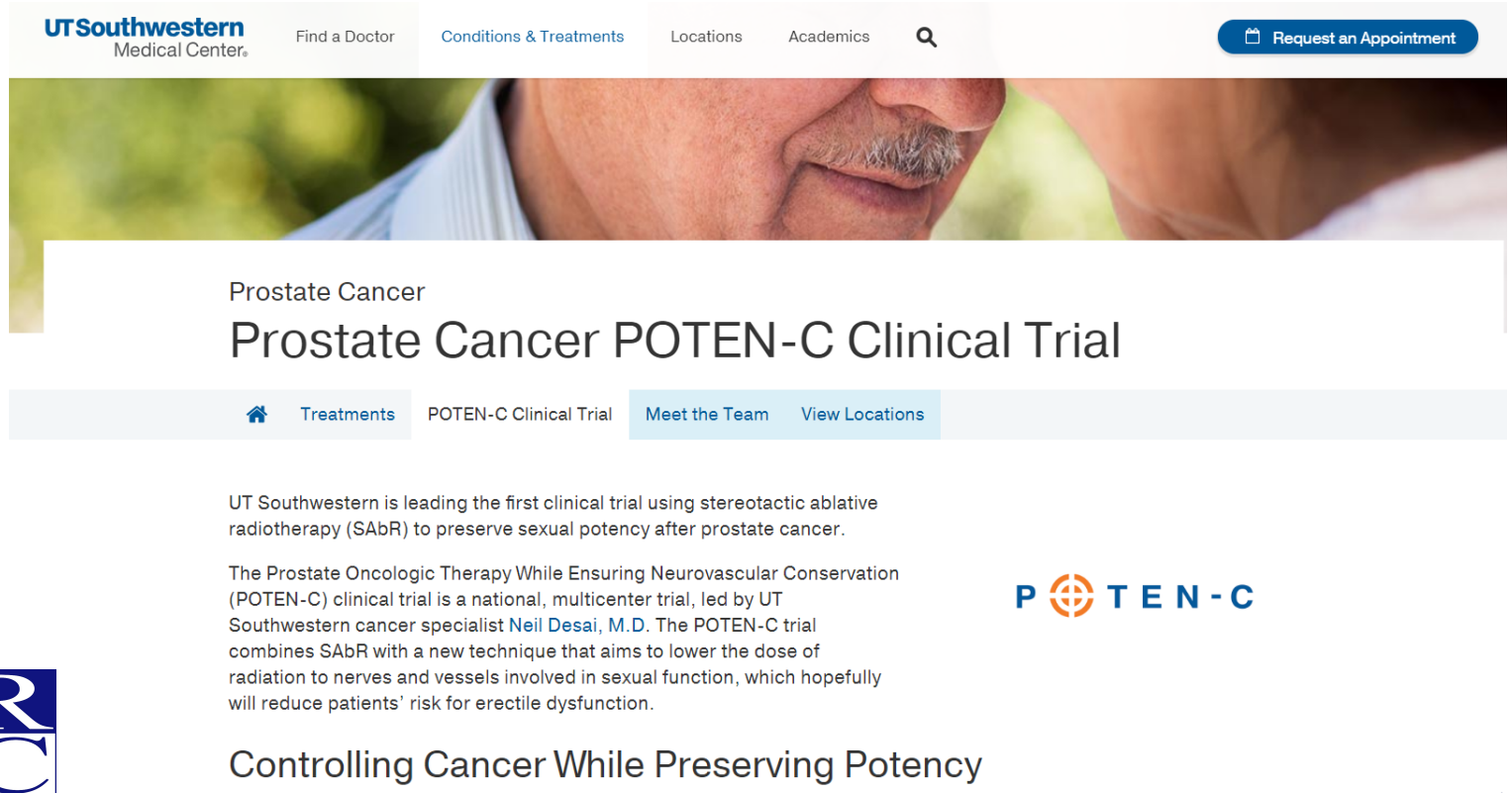
SpaceOAR
Ongoing Research: Definitive SBRT/SABR

POTEN-C study, UTSW: randomized, multi-institution investigator initiated study sexual function QOL study (**SAbR** with or without neurovascular-sparing dose plan)



https://www.clinicaltrials.gov/ct2/show/NCT03525262?term=Desai&cond=Prostate+Cancer&rank=2

SpaceOAR
Ongoing Research: Salvage Post-Prostatectomy

- Chao et al- Dosing study on 4 pts.
  - Mean of 12mm of space created with no complications
  - 51% reduction in V70
  - Only 1 pt. with Grade 1 toxicity at 3 months follow up

- Yeh et al- Salvage HDR in 69 pts.
  - No Grade 2+ Acute Toxicity
  - 1 pt with Grade 2 toxicity at 6 months that resolved

- Pinkawa et al- case report 20 years post-prostatectomy, urethrovesical anastomosis spacing
  - 1cm of space successfully created
  - Radiation therapy completed with no complications

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https://www.redjournal.org/article/S0360-3016(16)31658-3/pdf

https://www.ncbi.nlm.nih.gov/pubmed/25339311

SpaceOAR
Ongoing Research: Salvage Cryoablation

Salvage Cryoablation of prostate with transperineal Denonvillier's Fascia space expansion with SpaceOAR: a novel technique.
C. Shepherd, H. Clarke, Medical University of South Carolina

- Single center, 10 pt study, 3-6 month follow up

"Use of SpaceOAR with prostatic cryoablation provides a safe and effective modality for the protection against rectal injury while also allowing for increased depth of treatment penetration."

"Future studies evaluating the long term outcomes of this new technique are needed."

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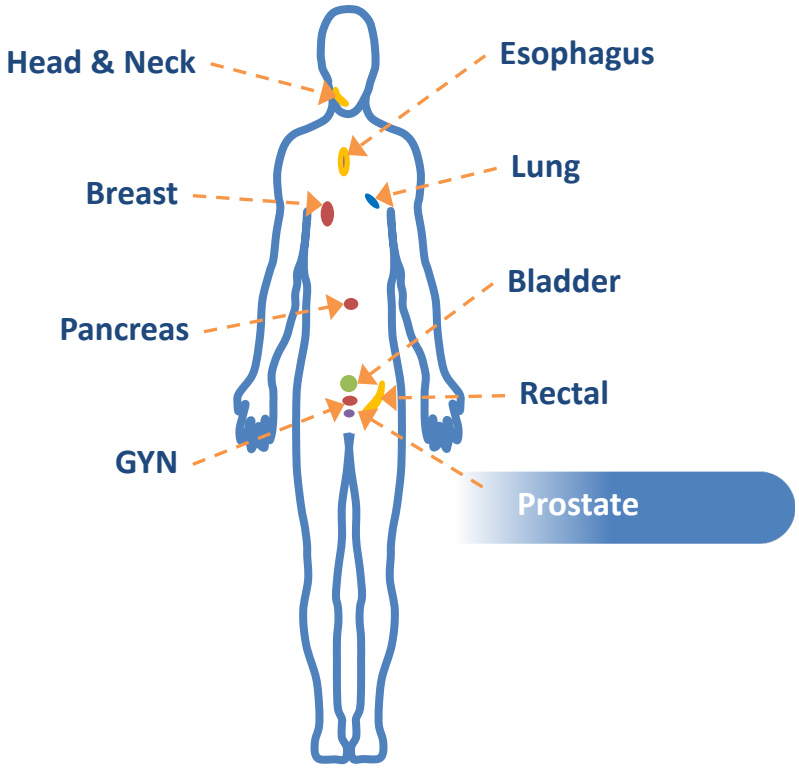
Future Directions:
Apply PEG Hydrogel Technology to Other Organs

In the future, **hydrogel technology may be applied to other organs throughout the body** that could benefit from space creation

Potential new indications



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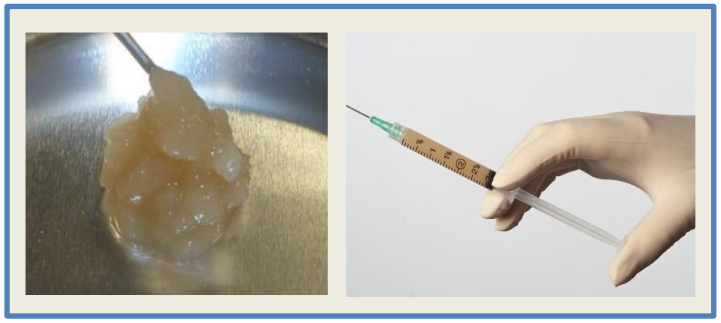
TraceIT hydrogel:
Soft tissue marker and platform for new spacing indications

Overview

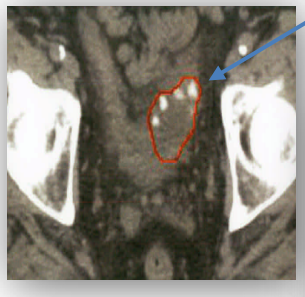


TraceIT	
Description	Similar hydrogel technology as SpaceOAR
Composition	PEG hydrogel with 1% bound iodine
Absorption	Approx. 7 months
Formulation	Particulated injection
Visibility	MRI, US, CT, CBCT, mammography
Indications	Soft tissue marker (US) Soft tissue marker and spacer (OUS)
Approvals	FDA, CE Mark, TGA

TraceIT tissue marker benefits

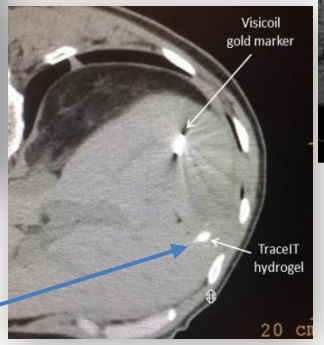
- **Benefits:**
  - CT and MR visible
  - Bioabsorbable
  - Less invasive (small needle diameter injections)
  - Does not migrate
  - No artifact
- **Target uses:**
  - Bladder, prostatectomy, head & neck, GYN, pancreas, liver, esophagus, tumor bed
- **Clinical experience:**
  - Bladder marking clinical studies (UW and Victoria, Australia)
  - Post-Prostatectomy urethral marking study (Australia)
  - GYN marking clinical study (Brigham & Women's Hospital)

Bladder



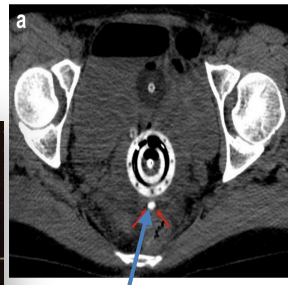
Stable in bladder wall

Liver



No artifact

GYN



CT and MR visible

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In Conclusion

- Hydrogel spacing is rapidly becoming standard of care for prostate cancer radiotherapy with growing adoption by the urology community
- Opportunities exist for clinical investigation of adjacent prostate indications (i.e. post prostatectomy, ablative therapies)
- Hydrogel technology may be applied to other organs throughout the body that could benefit from marking or space creation (i.e. Bladder, GYN, pancreas)

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