Rectal Sparing in Prostate Brachytherapy

- Numerous RCTs of dose escalation have shown improved tumour control outcomes
  - BUT, late toxicity increased

- Brachytherapy lowers proctitis risk,
  - BUT serious rectal complications can occur

- The acute form generally occurs within 6 weeks of implantation and occurs in approximately 30-35% of patients undergoing BT
Rectal Sparing in Prostate Brachytherapy

- Problem
- Patient selection
- Planning
- Technique
- Spacers
- Quality assurance
- New and Novel developments
Rectal Sparing in Prostate Brachytherapy

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Beware Brachytherapy toxicity!!!
Brachytherapy Rectal Toxicity - Problem
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**Brachytherapy Rectal Toxicity - Problem**

- Rare but major late rectal complication is the development of **rectal fistula**
  - Early series varied from <1%- 7%. Recent series, rates are 0%-1%

- Rectal bleeding prompts a colonoscopy and a reflex biopsy of the radiation-scarred anterior rectal wall

- Elliott et al. Medical malpractice of prostate brachytherapy. Brachytherapy 2004
  - 13 Brachytherapy-related medical malpractice cases, 11 because of a prostatic-rectal fistula - beware

- **Recommend avoidance of anterior rectal wall biopsy for the investigation of rectal bleeding after prostate brachytherapy**
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Rectal Toxicity - Patient selection

- Usual contraindications for radiotherapy
- Inflammatory bowel disease - but often referred, avoid active disease
- Short Urethro-rectal distance --- ??? distance
- Previous ano-rectal surgery
Rectal Toxicity - Patient selection
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Prostate Brachytherapy -Planning

- Snyder et al Proctitis Grade >2 at 5ys
  - V100 ≤1.3 cc 5%
  - V100 >1.3 cc 18%

Fig. 4. Rectal volume thresholds associated with ≤5% risk of Grade 2 proctitis at 5 years.
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Brachytherapy Rectal Toxicity - Technique

**Clinical Investigation**

**Perirectal Seeds as a Risk Factor for Prostate Brachytherapy-Related Rectal Bleeding**

Amy Mueller, M.D.,* Kent Wallner, M.D.,*† Gregory Merrick, M.D.,§ Eric Ford, Ph.D.,*† Steven Sutlief, Ph.D.,*† William Cavanagh, M.S.,* and Wayne Butler, Ph.D.§

![Graphs showing likelihood of bleeding with different volumes of RV100 and seeds near the rectum.](image)
Brachytherapy Rectal Toxicity - Technique

- Use Sagittal imaging particularly on the 1 and 1.5 rows
- Allow 3-5 mm from seed to rectal wall
- Ensure distal seed train not implanted into rectum
- Posterior row - Implant 5mm anteriorly - steer needle posteriorly if necessary
- Deflate rectal balloon
Brachytherapy Rectal Toxicity - Technique
Rectal toxicity and rectal dosimetry in low-dose-rate $^{125}$I permanent prostate implants: A long-term study in 1006 patients
Mira Keyes$^{1,*}$, Ingrid Spadinger$^1$, Mitchell Liu$^1$, Tom Pickles$^1$, Howard Pai$^2$, Amy Hayden$^1$,
Veronika Moravan$^1$, Ross Halperin$^3$, Michael McKenzie$^1$, Winkle Kwan$^4$,
Alexander Agranovic$^5$, Vince Lapointe$^1$, W. James Morris$^1$

Fig. 2. Kaplan–Meier curves for late rectal Radiation Therapy Oncology Group $\geq$2, illustrating the institutional learning curve.
### Late rectal toxicity

<table>
<thead>
<tr>
<th>Late rectal toxicity</th>
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</thead>
<tbody>
<tr>
<td>RTOG late ≥1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline IPSS</td>
<td>0.0379</td>
<td>1.02 (1.001–1.04)</td>
</tr>
<tr>
<td>Acute RTOG ≥1</td>
<td>0.0001</td>
<td>1.793 (1.386–2.319)</td>
</tr>
<tr>
<td>VR₁₀₀</td>
<td>0.0001</td>
<td>1.263 (1.146–1.391)</td>
</tr>
<tr>
<td>RTOG late ≥2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implant order (learning curve)</td>
<td>0.0273</td>
<td>0.999 (0.998–1.0)</td>
</tr>
<tr>
<td>Acute RTOG ≥1</td>
<td>0.0074</td>
<td>2.181 (1.217–3.562)</td>
</tr>
<tr>
<td>Acute RTOG ≥2</td>
<td>0.0288</td>
<td>2.181 (1.084–4.387)</td>
</tr>
<tr>
<td>VR₁₀₀</td>
<td>0.0304</td>
<td>1.223 (1.019–1.467)</td>
</tr>
</tbody>
</table>

RTOG = Radiation Therapy Oncology Group; VR = rectal volume in cc; IPSS = International Prostate Symptom Score; OR = odds ratio; HR = hazard ratio.
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Spacer Substances

- **Hyaluronic acid**
  - Wilder 8-18mm AP in prostate IMRT patients. Rectal V70 reduced from 25% to 4%.
  - Prada (n=57), randomised, 27 received HA injection into anterior perirectal fat. Mean separation 15mm achieved, rectal Dmax reduced from 7Gy to 5Gy. Spacer still present when patients scanned 9 months later.
  - Cheaper, biocompatible, but long residence times in body.

- **Collagen**
  - Noyes; difficult to procure, human collagen very expensive and difficult to obtain, immunological reactions with bovine collagen.

- **Polyethylene glycol**
  - Susil 20ml PEG hydrogel in cadavers; mean separation 12.5mm, rectal V70 decreased from 20% to <5%. **10mm of separation sufficient to achieve mean rectal V70 reduction of ~80%**
  - Pinkawa (n=18): 10ml hydrogel injected prior to prostate IMRT/3DCRT; mean separation 10mm, rectal V50, V60, V70, V76 decreased by 22%, 35%, 56%, 89%
  - >90% water by weight, Biocompatible, hydrolyses after 3-4 months, TGA approved.
Rectal Sparing in Prostate Brachytherapy - Spacers

First report of transperineal polyethylene glycol hydrogel spacer use to curtail rectal radiation dose after permanent iodine-125 prostate brachytherapy

Nadine Beydoun¹,*, Joseph A. Bucci¹, Yaw S. Chin¹, David Malouf², Ese Enari¹, Samuel D. Painter¹

¹Department of Radiation Oncology, St George Hospital, Kogarah, New South Wales, Australia
²Department of Urology, St George Hospital, Kogarah, New South Wales, Australia
Rectal Sparing in Brachytherapy - Spacers
Rectal DVH

Rectal Dose Volume Histograms With and Without Spacer

- Uncorrected no spacer
- Uncorrected with spacer
- Corrected rectal dose
# Rectal Sparing in Brachytherapy - Spacers

<table>
<thead>
<tr>
<th>Group</th>
<th>Rectal Toxicity</th>
<th>Early</th>
<th>Rectal Toxicity ≥ 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDR</td>
<td>G1-2</td>
<td>G≥3</td>
<td>G1-2</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1 rectal pain</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>/infection</td>
<td></td>
</tr>
<tr>
<td>Seed</td>
<td>G1-2</td>
<td>G≥3</td>
<td>G1-2</td>
</tr>
<tr>
<td></td>
<td>1 rectal pain</td>
<td>1 rectal ulcer</td>
<td>0</td>
</tr>
<tr>
<td>Post-seed</td>
<td>G1-2</td>
<td>G≥3</td>
<td>G1-2</td>
</tr>
<tr>
<td></td>
<td>1 rectal pain</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>EBRT</td>
<td>G1-2</td>
<td>G≥3</td>
<td>G1-2</td>
</tr>
<tr>
<td></td>
<td>2 diarrhoea, 2 rectal pain</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
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Dosimetric and Seed position Imaging

Medipix

Pixelated 300 μm thick Si detector chip (256 x 256 pixels, 55 μm pitch)

Detector bias voltage (~100V)

Read-out ASIC chip Medipix2
BrachyView™

- In-phantom test of BrachyView
  - Ultrasound (anatomy)
  - CT seed locations (blue)
  - BrachyView seed locations (red)

- BrachyView - a solution for a device which meets the criteria for real-time monitoring and intervention
• Simulated operation

Ir-192 HDR Source

Magic Plate embedded in couch
Rectal Sparing in Prostate Brachytherapy - New and Novel Developments

- The histone H2AX is phosphorylated to γH2AX at the sites of radiation-induced DNA double-strand breaks, localising with the DNA repair protein 53BP1.

DNA double-strand breaks were investigated by staining blood samples with immunofluorescence antibodies to γH2AX and 53BP1 proteins.

Assay could have clinical utility as a method for intervention to reduce rectal dose using perirectal hydrogel spacers for patients with high levels of circulating DSBs at early time points after seed implant.
Rectal Sparing in Prostate Brachytherapy - New and Novel Developments

- The histone H2AX is phosphorylated to γH2AX at the sites of radiation induced DNA double-strand breaks (dsb’s), where it co-localises with the DNA repair protein 53BP1.

- DNA dsb’s were investigated by staining lymphocytes with immunofluorescence antibodies to γH2AX and 53BP1 proteins.

- Assay could have clinical utility as method for intervention:
  - to reduce rectal dose using perirectal hydrogel spacers for patients with high levels of circulating DSBs at early time-points after seed implant.
Rectal Sparing in Brachytherapy - Conclusions

- Devastating complication careful planning and technique essential
- PEG hydrogel effectively increases prostate rectum separation and reduces rectal radiation exposure
- Safe in EBRT and post-seed implantation
  - Use in brachytherapy patients concurrently with their implant should be avoided
- Real time quality assurance should be a goal
- Predictive tools for individualisation on the horizon
THANK YOU