The Role of Brachytherapy in Local Salvage Therapy for Prostate Cancer

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Recurrent/Relapsed Prostate Cancer

- “Biochemical progression” and other such terms are words physicians use to describe our failure to control prostate cancer.

- “Salvage” therapy is our attempt to help patients regain control of their cancer – while working to minimize additional side effects in the process.
I won’t go into too much depth here, but effective salvage therapies require an understanding of *where* the prostate cancer has recurred.

- After surgery, do we treat just the prostate bed? The pelvic nodes? Did it even fail at the site of the surgery?
- After radiation, do we treat the prostate? The whole prostate?
- Is local/directed therapy even appropriate?

Advances in diagnostic technology like the Axumin PET scans and multiparametric MRI have helped us “define the target” for salvage therapy - if you have had a PSA failure, we recommend a comprehensive workup (and biopsy!) before proceeding to any directed therapy.
Salvage Therapy for Intact Prostate Cancer

- There are many salvage treatments for prostate cancer that should be reviewed with you by your physician(s), and tailored to your situation.
  
  - Androgen Deprivation (Hormone Therapy)
  
  - Cryotherapy
  
  - HIFU
  
  - Repeat External Beam Radiation
  
  - Salvage Prostatectomy
  
  - Brachytherapy
  
  - Clinical Trials
Salvage Surgery for Prostate Cancer

- **Alliance Radical Prostatectomy Series (CALGB 9687)**

  - 41 men were enrolled between 1997 and 2006, who suffered biopsy-proven recurrent prostate cancer (CaP) after receiving ≥ 60 Gy radiation as primary treatment for cT1-2NXM0 disease (mostly intermediate risk).
    
    - At 5 years, 39% were salvaged.
    - 63% were incontinent at 2 years after surgery; 3 rectal and 1 obturator nerve injuries occurred.
    - Other series from other specialty hospitals have shown salvage rates from 30-80%, and incontinence rates from 30-70%; best if done at low PSA! (<<10)

1. Mohler JL et al, Prostate Cancer and Prostatic Disease (2018)
What is Brachytherapy?

- **Brachytherapy** is a means by which radiation sources are placed close to or within a target.

- In the setting of prostate brachytherapy, the radiation source is radionuclide-based, and can be a permanent implant (generally $^{125}$I, $^{103}$Pd, or $^{131}$Cs) or temporary, using $^{192}$Ir afterloading techniques.

- By taking advantage of the inverse-square law, large doses (even ablative doses) may be delivered to tumor or at-risk margins while sparing healthy tissues.

Early Brachytherapy: Technique

Fig. 3.—Author's Cystoscopic Radium Instrument 1 carrying a tube of radium in fenestrated platinum capsule in beak; closed with obturator.

Fig. 15.—Rectal radium carrier, applied under direction of index finger in rectum, and held in place by mechanical hand or clamp.

Fig. 17.—A case of cancer of the prostate and left seminal vesicle (right vesicle slightly involved). The radium treatments, each representing 100 milligram-hours, are shown, and the date of each is recorded.

Fig. 16.—Mechanical hand in use in treating cancer of seminal vesicles and prostate through rectum.

History: Brachytherapy Developments

- 1983: Introduction of image-guided (ultrasound-based) transperineal prostate brachytherapy by Holm et al., and later developments in biplanar imaging.
Current Techniques in Prostate Brachytherapy

- At present, prostate brachytherapy is performed in two primary ways;
  - Permanent interstitial low-dose-rate (LDR) implants (using $^{125}$I, $^{103}$Pd, or $^{131}$Cs)
  - or
  - Temporary high-dose-rate (HDR) implants (generally using $^{192}$Ir and a remote afterloader).
LDR Brachytherapy: Isotopes

- **Iodine-125 (I-125) (1965)**
  - Electron capture decay
  - $T_{1/2}$: 59.4 days
  - Energies: 27.4 – 35.5 keV (avg 27.4 keV)
  - Dose rate: 5-7 cGy/h

- **Palladium-103 (Pd-103) (1986)**
  - Electron capture decay
  - $T_{1/2}$: 17 days
  - Energies: 20.1 and 23 keV
  - Dose rate: 18-20 cGy/h

- **Cesium-131 (Cs-131) (2004)**
  - Electron capture decay
  - $T_{1/2}$: 9.7 days
  - Energies: 29.5 – 34.4 keV (avg 30.4 keV)
High-dose-rate (HDR) brachytherapy is the delivery of radiation at a dose rate of > 12 Gy/h (often higher)

- Requires afterloading of physically small high-activity sources from a remote system
  - Total doses range from 9-19 Gy in a single fraction, 24-27 Gy in two fractions, 26-38 Gy in four fractions

HDR Brachytherapy Advantages

- May offer additional benefits\(^1\) compared to LDR in terms of
  - **biological effectiveness of high-dose fractions** (*assuming low* \(\alpha/\beta\) *for prostate*)
  - decreased rates of **acute and late toxicity** relative to permanent seed implantation, and
  - **conformality of dose** to the target.

- No permanent radiation sources within patient
  - no concerns for dose delivered to patient family, friends

- **Potentially superior dose distribution to SBRT\(^2\):**

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A Note on Rectal Toxicity

- Radiation therapy to the prostate can lead to a range of side effects, generally divided into **urinary** (due to dose to urethra and bladder), **bowel** (due to dose to rectum and intestines), and **sexual** (due to dose to neurovascular elements and penile bulb).

- Repeat radiation therapy can intensify these effects; in the rectum, this can lead to **bleeding** and **ulcers**, and even **fistula** (a pathologic connection between tissues/organs).
To address this issue, we worked with Augmenix Inc. (now part of Boston Scientific, Inc.) to incorporate an FDA-approved therapy involving the injection of a temporary hydrogel in the plane between the prostate and rectum (SpaceOAR).¹
Rectal Spacers

- The hydrogel is injected transperineally using hydrodissection to facilitate placement; the potential perirectal space for hydrogel placement is between Denonvilliers fascia and the rectal wall.
Rectal Spacer Procedure - Injection

- After confirming the correct position of the needle with both sagittal and axial ultrasound views, and aspirating to ensure the needle tip was not in vessel, the saline syringe is removed.

- The syringe assembly is then attached, maintaining needle position, and 10 mL of hydrogel will be administered in one continuous motion in 8 – 10 s without moving the needle during injection.
Salvage Brachytherapy for Prostate Cancer

- Salvage brachytherapy has been a treatment option for many years, performed in small cohorts at specialty centers.

### Summary of Published Salvage Brachytherapy Series Reporting Prostate-specific Antigen Control

<table>
<thead>
<tr>
<th>Institution</th>
<th>Reference</th>
<th>Years treated</th>
<th>No. of patients</th>
<th>Image guidance</th>
<th>Median follow-up, mo</th>
<th>PSA failure definition</th>
<th>4-year PSA control, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo Clinic</td>
<td>Grado et al., 1999</td>
<td>1990-1996</td>
<td>49</td>
<td>Ultrasound</td>
<td>64</td>
<td>Two rises above nadir*</td>
<td>38</td>
</tr>
<tr>
<td>Uro-Radiology Prostate Institute</td>
<td>Koutrouvelis et al., 2003</td>
<td>1995-2002</td>
<td>31</td>
<td>CT-guided + STAD</td>
<td>30</td>
<td>ASTRO¹</td>
<td>83</td>
</tr>
<tr>
<td>Mount Sinai</td>
<td>Lo et al., 2005</td>
<td>NR</td>
<td>30</td>
<td>Ultrasound</td>
<td>59</td>
<td>Two rises above nadir*</td>
<td>83</td>
</tr>
<tr>
<td>DFCI/Brigham and Women's</td>
<td>Current study</td>
<td>2000-2005</td>
<td>25</td>
<td>MRI-guided</td>
<td>47</td>
<td>Phoenix⁵</td>
<td>57 (Crude)³</td>
</tr>
<tr>
<td>UCSF</td>
<td>Lee et al., 2005</td>
<td>1998-2005</td>
<td>21</td>
<td>Ultrasound HDR</td>
<td>19</td>
<td>ASTRO⁴</td>
<td>70</td>
</tr>
<tr>
<td>Arizona Oncology Services</td>
<td>Beyer, 1999</td>
<td>1989-1994</td>
<td>17</td>
<td>Ultrasound</td>
<td>62</td>
<td>ASTRO⁵</td>
<td>53 (5-yr)⁴</td>
</tr>
<tr>
<td>Dattoli Cancer Center</td>
<td>Dattoli et al., 1997</td>
<td>1991-1994</td>
<td>17</td>
<td>Ultrasound + STAD</td>
<td>38</td>
<td>PSA &gt; 1.0 ng/mL</td>
<td>65 (Crude)³</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>Wong et al., 2006</td>
<td>1999-2004</td>
<td>17</td>
<td>Ultrasound + STAD</td>
<td>44</td>
<td>ASTRO⁵</td>
<td>75</td>
</tr>
</tbody>
</table>

PSA indicates prostate-specific antigen; CT, computed tomography; STAD, 3 months of neoadjuvant, short-term androgen-deprivation therapy; NR, not reported; ASTRO, American Society for Therapeutic Radiology and Oncology; DFCI, Dana Farber Cancer Institute; MRI, magnetic resonance imaging; UCSF, University of California-San Francisco; HDR, high-dose rate.

* Failure was backdated to the date of the first rising PSA after nadir.

† According to the 1997 ASTRO consensus definition, failure required 3 consecutive PSA rises after a nadir. Failure was backdated to the midpoint between the nadir and the first rise (ASTRO, 1997²⁶).

‡ Crude failure was calculated as the number of patients who did not fail divided by the total number of patients and did not account for the time of failure. Both series with crude outcome were presented in abstract form.

§ According to the 2006 Radiation Therapy Oncology Group/ASTRO Phoenix Consensus Conference definition, failure was scored on the day the PSA rose above the nadir by at least 2 ng/mL.
Salvage Brachytherapy for Prostate Cancer

- **Prospective Phase 2, LDR**

  - Nguyen et al conducted a study using MRI-guided salvage brachytherapy in patients who had previously been treated with radiation therapy for mostly low and favorable intermediate risk prostate cancer.

  - They treated 25 men with I-125 seed implants:
    - At a median followup of 47 months, 30% of patients had a grade 3-4 toxicity, and 13% needed a surgical procedure (colostomy or urostomy) due to a fistula.
    - 70% of patients were salvaged.

Salvage Brachytherapy for Prostate Cancer

- **Prospective Phase 2, HDR**

  - Yamada et al conducted a study using high-dose rate salvage brachytherapy in patients who had previously been treated with radiation therapy for mostly intermediate and high risk prostate cancer.

  - They treated 42 men with 4 fractions via a single implant over 2 days.

    - At a median followup of 3 years, 3 patients (7%) developed strictures requiring dilation, with 1 patient developing Grade 3 incontinence.

    - 68.5% of patients were salvaged at 5 years.

Salvage Brachytherapy for Prostate Cancer

- HDR with rectal spacer

  - Nguyen et al reported on the use of HDR brachytherapy in a patient with recurrence after external beam radiation therapy; he received 6 fractions over 2 insertions, with a rectal spacer placed in the area between the prostate and rectum to protect the rectum from repeat radiation.

  - Patient did well, with some mild rectal bleeding treated with plasma coagulation a year later, and per communications with them he was salvaged.
Salvage LDR Brachytherapy for Prostate Cancer

- **Multi Institutional LDR Salvage**

  - Crook et al reported initial outcomes from NRG Oncology/RTOG-0526, in which 100 patients from 20 centers were registered from May 2007 to January 2014 with biopsy-proven local recurrence, and underwent a permanent seed brachytherapy implant (partial prostate implants were allowed).

    - At a median followup of 54 months, 14% rate of late Grade 3 GI/GU issues
      - Incontinence, Cystitis (bladder inflammation), Proctitis/Rectal Bleeding
      - 1 Urethral Stricture and 1 Fistula

    - **Salvage outcomes to be reported in a year or two…**
Salvage Focal Brachytherapy for Prostate Cancer

- Multi Institutional HDR Focal Salvage

  - Murgic et al treated 15 patients with locally recurrent prostate cancer with ultrasound-based HDR brachytherapy, 27 Gy in 2 implants separated by a week.
    - At a median followup of 3 years, 61% of patients were salvaged.
    - Only 1 grade 3 urinary toxicity (gross hematuria, spontaneously resolved)

Salvage Brachytherapy for Prostate Cancer

- At this year’s American Brachytherapy Society (ABS) Meeting, we will have two sessions developed to salvage and focal brachytherapy; many studies will be coming out to show progress in this area!
  
  • "High-Dose-Rate Brachytherapy as a Solution for Localized Recurrent Prostate Cancer after Primary Irradiation: A 10-Year Experience" (3 fraction regimen)
  
  • “MRI-Guided Focal Salvage HDR Brachytherapy for Locally Recurrent Prostate Cancer” (single fraction regimen)
  
  • “Feasibility and Early Toxicity Outcomes with Salvage Focal HDR Brachytherapy for Radio-Recurrent Prostate Cancer” (single fraction regimen)
HDR Interstitial Brachytherapy - Prostate

- There are many ways to plan and deliver HDR prostate interstitial brachytherapy, and many different dosing schemes.
  - I trained with CT and MR based planning, with lots of patient transfers, and this was a constant source of frustration, due to needle displacement.

- To eliminate (or at least dramatically reduce) this concern, we commissioned the Varian (Vitesse) ultrasound-based intraoperative treatment method.
  - This is not to say that this is the best method, but it works well for our facility and physics workflow.

- We do 15 Gy x 1 for boost (at start of treatment) or 14 Gy x 2 for definitive (rarely, as we also offer LDR), or 19 Gy in 1 fraction for salvage.
Interstitial Brachytherapy - Workflow

1. Patient Positioning
2. Initial Image Acquisition
3. Needle Placement
4. Needle Depth Optimization/Tip Identification
5. Treatment Planning Image Acquisition
   - Aerated gel for urethral identification
6. Target/OAR Contouring
7. Needle Digitization
8. Treatment Planning
9. QA/Physics 2nd Check
10. Treatment Delivery
Interstitial Brachytherapy - Workflow

1. Patient Positioning
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10. Treatment Delivery
Patient Positioning

- This part is a bit awkward for the patient, but fortunately they are completely asleep at this point!

Interstitial Brachytherapy - Workflow

1. Patient Positioning
2. Initial Image Acquisition
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8. Treatment Planning
9. QA/Physics 2nd Check
10. Treatment Delivery
Image Acquisition - Initial

- Place 2-4 stabilizer needles in anterior lateral gland
  - *I prefer to place the periurethral and pubic arch ones at this point*
- Identify base of the prostate, and then acquire initial planning images of the seminal vesicles and prostate
Interstitial Brachytherapy - Workflow

1. Patient Positioning
2. Initial Image Acquisition
3. Needle Placement
4. Needle Depth Optimization/Tip Identification
5. Treatment Planning Image Acquisition
   - Aerated gel for urethral identification
6. Target/OAR Contouring
7. Needle Digitization
8. Treatment Planning
9. QA/Physics 2nd Check
10. Treatment Delivery
Notes on Needle Placement

- There are many ways to place the needles as well, but the most important thing is to have a **standard template** to make a safe and efficient process.
  - Generally 16 needles will be good for most prostates
  - Needles should be no closer than 5mm to each other (generally 7-10 mm) and at least 5mm from urethra
  - Posterior needles should be about 5mm from the capsule
- The exception is focal brachytherapy, where we aren’t treating a standard prostate; extra caution needed.
Needle Placement Template

- **Example**

**Central needles**  
*(make sure they cover base and apex)*

**Peripheral needles**  
*(can be outside of gland)*

**Index needle**  
*(very easy to see and judge depth)*
Interstitial Brachytherapy - Workflow

1. Patient Positioning
2. Initial Image Acquisition
3. Needle Placement
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5. Treatment Planning Image Acquisition
   - Aerated gel for urethral identification
6. Target/OAR Contouring
7. Needle Digitization
8. Treatment Planning
9. QA/Physics 2nd Check
10. Treatment Delivery
Depth Measurements
Interstitial Brachytherapy - Workflow

1. Patient Positioning
2. Initial Image Acquisition
3. Needle Placement
4. Needle Depth Optimization/Tip Identification
5. Treatment Planning Image Acquisition
   - Aerated gel for urethral identification
6. Target/OAR Contouring
7. Needle Digitization
8. Treatment Planning
9. QA/Physics 2nd Check
10. Treatment Delivery
Image Acquisition

- Identify base, and then re-acquire planning images with needles in place
- To assist with identifying the urethra, we use a mix of 30 cc acoustic jelly, 30 cc saline, and 5 cc air to make aerated contrast gel
Interstitial Brachytherapy - Workflow

1. Patient Positioning
2. Initial Image Acquisition
3. Needle Placement
4. Needle Depth Optimization/Tip Identification
5. Treatment Planning Image Acquisition
   - Aerated gel for urethral identification
6. Target/OAR Contouring
7. Needle Digitization
8. Treatment Planning
9. QA/Physics 2nd Check
10. Treatment Delivery
Final Contouring

- Contouring is assisted with MRI fusion
  - Bladder, urethra, rectum, seminal vesicles and dominant lesions within the prostate if needed
Interstitial Brachytherapy - Workflow

1. Patient Positioning
2. Initial Image Acquisition
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4. Needle Depth Optimization/Tip Identification
5. Treatment Planning Image Acquisition
   - Aerated gel for urethral identification
6. Target/OAR Contouring
7. Needle Digitization
8. Treatment Planning
9. QA/Physics 2nd Check
10. Treatment Delivery
Needle Digitization

- The most frustrating part of any HDR brachytherapy case, but absolutely critical for planning and patient safety.

[Images of medical imaging]
Interstitial Brachytherapy - Workflow

1. Patient Positioning
2. Initial Image Acquisition
3. Needle Placement
4. Needle Depth Optimization/Tip Identification
5. Treatment Planning Image Acquisition
   - Aerated gel for urethral identification
6. Target/OAR Contouring
7. Needle Digitization
8. Treatment Planning
9. QA/Physics 2nd Check
10. Treatment Delivery
Treatment Planning - Constraints

- Prostate:
  - Critical: D90 > 95%, Preferred: D90 > 98%
  - Critical: V100 > 95%, Preferred: V100 > 98%
  - V125: 55-65%; V150 < 20%; V200 < 11%

- Urethra
  - V115 = 0%

- Rectum:
  - D1cc < 70%
Interstitial Brachytherapy - Workflow

1. Patient Positioning
2. Initial Image Acquisition
3. Needle Placement
4. Needle Depth Optimization/Tip Identification
5. Treatment Planning Image Acquisition
   - Aerated gel for urethral identification
6. Target/OAR Contouring
7. Needle Digitization
8. Treatment Planning
9. QA/Physics 2nd Check
10. Treatment Delivery
QA/Plan Finalization

- Hook up catheters, length checks by the physicist
- Needle confirmations, depth checks
- In plan, review distribution (unused needles? Dwell times?)
- Export plan, MD review and approve
- QA plan, dwell times; 2\textsuperscript{nd} check
Interstitial Brachytherapy - Workflow

1. Patient Positioning
2. Initial Image Acquisition
3. Needle Placement
4. Needle Depth Optimization/Tip Identification
5. Treatment Planning Image Acquisition
   - Aerated gel for urethral identification
6. Target/OAR Contouring
7. Needle Digitization
8. Treatment Planning
9. QA/Physics 2nd Check
10. Treatment Delivery!
Prostate – Case Example

- Mr. JB presented as a 78 year old Caucasian male, with Gleason 7(4+3) prostate cancer in a single core, and cT2a (right lobe) disease, with a pre-treatment PSA of 6.2. He was otherwise in excellent health.

- Standard surgical and radiation options were presented to him, and he chose to pursue treatment on a Phase 1 dose escalation trial of hypofractionated SBRT for low- and intermediate-risk prostate cancer offered at UTSW.

  - This was back in 2010
Prostate – Case Example

- Pre-treatment imaging (CT only, at that time MRI was less available, and no Axumin/PSMA):
  - Large prostate with calcifications; no clear SVI/LAD
Prostate – Case Example

- Received 5000 cGy in 5 fractions on UTSW SBRT dose escalation trial
Prostate – Case Example

- He initially did well, with a rapid decrease in his PSA, but eventually it started to rise…
Prostate – Case Example

- Imaging of Recurrence (MRI and Axumin PET, we don’t have PSMA)
The decision was made to proceed with HDR interstitial brachytherapy for salvage of the local recurrence in the right seminal vesicle.

Given the distance from the (previously irradiated) urethra, a focal therapy in a single fraction was felt to be appropriate.
Prostate – Case Example
## Prostate – Case Example

### Dose Information

**Urethra:**
- V115\%: 0.00 cm³ [0.00 %]
- D30\%: 3.38 Gy [17.78 %]
- D1\%: 4.52 Gy [23.80 %]

**Rectum:**
- D2cm³: 5.66 Gy [29.80 %]
- D1cm³: 7.93 Gy [41.73 %]
- D0.5cm³: 9.53 Gy [50.15 %]

**GTV:**
- Total Volume: 1.71 cm³
- V200\%: 0.33 cm³ [19.19 %]
- V150\%: 0.64 cm³ [37.61 %]
- V125\%: 1.07 cm³ [62.66 %]
- V100\%: 1.67 cm³ [98.00 %]
- D90\%: 21.08 Gy [110.95 %]

**Bladder:**
- Total Volume: 112.89 cm³
- D1cm³: 9.10 Gy [47.88 %]
- D0.5cm³: 10.66 Gy [56.12 %]
Prostate – Case Example

- The patient tolerated treatment well, and his PSA trend has shown a satisfying turn!
- No significant issues with his treatment to date.
HDR Prostate Brachytherapy Team

- Radiation Oncologists
  - Michael Folkert, MD PhD
    Co-Director of Brachytherapy Service
  - Neil Desai, MD MS
  - Aurelie Garant, MD

- Physicists
  - Brian Hrycushko, PhD
    Chief HDR Brachytherapy Physicist
  - Paul Medin, PhD
    Medical Physics Residency Director

- Our Therapists, Nurses, and OR Staff!