Predicting (and avoiding) Morbidity in LDR Prostate Brachytherapy

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University of British Columbia
BCCA CSI
Categories of Morbidity

- **Urinary**
  - IPSS
  - retention
  - stricture
- **Rectal**
  - bleeding
  - fistula
- **Sexual**
  - erectile function
Functional/technical considerations

• Prostate volume
  – Total volume
  – Volume with respect to body habitus
  – Transition zone volume/ TZ index

• Voiding function
  – IPS score
  – Voiding study/ flow rate & post void residual

• TURP before or after

• Hormonal therapy to downsize

• Planning aspects
  – seed activity (# seeds/needles)
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Factors</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee</td>
<td>2000</td>
<td>91</td>
<td>vol &gt;35 cc</td>
<td>p&lt;0.05</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td># needles</td>
<td>p&lt;0.04</td>
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<tr>
<td>Locke</td>
<td>2002</td>
<td>62</td>
<td>volume</td>
<td>p=0.02</td>
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<tr>
<td>Crook</td>
<td>2002</td>
<td>150</td>
<td>volume/hormones</td>
<td>p=0.003</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=0.007</td>
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<tr>
<td>Hineman-Mulroy</td>
<td>2004</td>
<td>116</td>
<td>preH vol hormones</td>
<td></td>
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<tr>
<td>Henderson</td>
<td>2004</td>
<td>255</td>
<td>volume urodynamics IPSS</td>
<td>p&lt;0.05</td>
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<tr>
<td>Kelly</td>
<td>2006</td>
<td>111</td>
<td>volume/ IPSS</td>
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<tr>
<td>Martens</td>
<td>2006</td>
<td>207</td>
<td>volume/PFR&lt;10ml/s</td>
<td>p=0.009</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>p=0.004</td>
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# Predictors of Retention

<table>
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<tr>
<th>author</th>
<th>year</th>
<th>n</th>
<th>factors</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Keyes</td>
<td>2009</td>
<td>712</td>
<td>Volume, # needles, IPSS, HT</td>
<td>MVA</td>
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<tr>
<td>Mabjesh</td>
<td>2007</td>
<td>655</td>
<td>Volume, IPSS</td>
<td>OR: 6.8 OR: 3.1</td>
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</tbody>
</table>
Prostate size

• no absolute limit
  – can you get under the pubic arch?
  – how well do they pee?
Prostates > 60 cc

- require larger number of seeds & needles (↑ risk urinary morbidity)
- technically difficult b/o PAI
- no absolute cut-off for size/ depends on relationship to pubic arch
  - with small frame, may get PAI @ 40-45 cc, while in large frame 65 cc OK
- Hip-position and TRUS probe-angle important
The big prostate

a. check for PAI
b. flatten the probe
c. hyperflex the hips
To improve access under pubic arch:

*Hip angle more acute and flatten probe*
Pubic arch interference
Pubic arch interference

Relates to body habitus, race and frame size
- Blacks and Asians: narrow pubic arch
- broad shoulders more important than height
Functional/technical considerations

Transition zone

TZ index = TZ vol/PV
Transition zone data

- Predicts retention (multivariate)  *Thomas 2000:*
- Predicts IPSS peak & normalization  *Merrick 2001*
- Post H TZ predicts catheter dependence  *Hinerman-Mulroy 2004*
- TZI < 35% AUR 4%, > 55% AUR 28%  *Crook 2002*
Subjective feeling of being “empty”
Frequency of < 2 hour intervals
Interrupted stream
Having to push or strain to start
Weak stream
Difficulty postponing urination
# of times up at night

Very subjective!
IPSS: experience at PMH n=1100

- Median IPSS at baseline: 5
- at 5 years: 6
- at 10 years: 3
- Median time for return to normal: 12 mo
- By 2 years: 71% returned to normal
- By 3 years: 83%
- FLARE: IPSS > 15 and ▲ ≥ 5 over nadir
  35%; peak time 16-24 mo
- Keyes et al IJROBP 2009: n=712; 30% nadir +8
  52% nadir +5
Experience based on urethral dose constraints

- catheter for post plan CT
- identify on each slice from base to apex
- DVH for UD5 (dose to 5% in cGy)
  - mean 210 Gy (SD 30) (goal < 150%)
- UD30 (dose to 30% in cGy)
  - mean 188 Gy (SD 22) (goal < 125%)
- UV150 (vol. cc receiving 150% of prescribed dose) less helpful (should be 0)
% of men with elevated IPSS

3.9%
Voiding study

Shape of the curve
Peak flow: 23.8 ml/sec
Voided volume: 330 ml
• Age \( p=0.38 \)
• **Voided volume** \( p=0.64 \)
• IPSS \( p=0.85 \)
• **PVR** \( p=0.37 \)

• Prostate size \( p<0.001 \)
• Hormones \( p<0.001 \)
• **PFR** \( p=0.011 \)

• **Multivariate analysis**
  – PFR \( p=0.003 \)
  – Prostate volume \( p=0.005 \)
Voiding studies

Volume: 148 ml, max flow 8.2 ml/sec

Volume: 316 ml, max flow 13.2 ml/sec

PVR: 320 ml

PVR: 204 ml
Case: Mr. RC

- Age 55
- PSA 5.5
- TRUS 29 cc
- Bx: 3/15 cores positive GS 6/10 (all \approx 5 \%)
- IPSS 9/35, IIEF 19/25

First void: 310 cc @ 11 cc/sec, PVR 180 cc
**First void**: 310 cc @11 cc/sec, PVR 180 cc

Sent back to urologist for median lobe resection

6 mo post brachy: no retention/ no problems
Functional/technical considerations
To TURP or not to TURP

- **Merrick** *IJROBP 2004*: n = 27 pre and/or post implant TURP
  - Pre implant TURP better with similar urinary QOL to non TURP patients
  - Post implant TURP: 50% had significant urinary dysfunction

- **Wallner** *IJROBP 1997*: 19 men with prior TURP med 3 yrs prev (2 mo – 15 yrs), only 1 mild stress incontinence post brachy

- **Mabjeesh** *Urology 2007*: 13 post implant channeling TURP after 6 mo; no incontinence (n=655)
Limit size of resection!

Small TURP

Big TURP: this patient is incontinent!
Prior TURP

- large TURP defect → seed loss and poor dosimetry
- possible ↑ risk of urethral necrosis, stricture, urinary incontinence
- exclude those with large or poorly healed TURP defect
- small TURP OK with peripheral loading
- allow minimum 3 months for healing
Case: Mr. PS

- Age 62
- PSA ↑ 5.9 → 7.3
- TRUS 58 cc
- Bx: 3/12 cores positive GS 6/10 10-15%
- Wife is a GP
- IPSS 19/35
- IIEF 19/25 (priority)
First void: PFR 7.8 ml/sec, PVR 270 cc

Sent back to urologist for limited TURP...

BT 18 mo ago, IPSS now 9/35, IIEF 17, PSA 0.2
Planning around a TURP
urethral identification

- opacify with aerated gel
- allows you to plan around it and keep dose to < 125% of prescription dose
- catheter distorts prostate and doesn’t show you extent of the defect
Hormonal down-sizing

BCCA: 65% had 6 mo of HT
n=1006, 1998-2003
Morris et al, Urology 2009

n=150; 31% had HT retention: 13%
24% if HT vs. 8.7%

Factors influencing risk of acute urinary retention after TRUS-guided permanent prostate seed implantation

Juanita Crook, M.D.,* Michael McLean, M.D.,* Charles Catton, M.D.,* Ivan Yeung, Ph.D.,† John Tsihlias, M.D.,‡ and Melania Pintilie, M.Sc.§
Risk of retention according to HT & prostate volume

Initially used HT in ~ 30%
now <1%, overall 10%

Risk of retention according to HT & prostate volume

- No prior hormone
- Prior hormone
Planning aspects

- 0.32 mCi per seed (0.4 U)
- use higher activity in larger prostates to keep # of seeds and needles reasonable
Classic Seattle plan
Preplan parameters

- margin 5mm cephalad and caudad and anteriorly, 3 mm laterally and same as prostate capsule posteriorly
- 25-30% of seeds are extracapsular
- D90 ~ 120-125%
- V100 > 99%, V150: 55-60%, V200: 15-18%
Modified to reduce central trauma

<table>
<thead>
<tr>
<th>Number of Needles</th>
<th>Seeds per needle</th>
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<tbody>
<tr>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

### Plan Summary

- **Total Activity [U]**: 43.04
- **Total Activity [mCi]**: 33.89
- **Total Needles**: 27
- **Total Seeds**: 102
- **Extra Seeds**:
- **Total Seeds to Order**: 38
"normal" activity: 0.32 mCi/0.422 U
32 needles/142 seeds
“High” activity seeds: 0.39 mCi/0.51U
28 needles/127 seeds

Plan Summary

<table>
<thead>
<tr>
<th>Total Activity [U]</th>
<th>63.12</th>
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</thead>
<tbody>
<tr>
<td>Total Activity [mCi]</td>
<td>49.70</td>
</tr>
<tr>
<td>Total Needles</td>
<td>28</td>
</tr>
<tr>
<td>Total Seeds</td>
<td>127</td>
</tr>
<tr>
<td>Extra Seeds</td>
<td></td>
</tr>
<tr>
<td>Total Seeds to Order</td>
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</table>
Rectal toxicity

Plan in such a way as to minimize risk
Be honest in post plan evaluation
KNOW your rectal doses!
## Factors influencing rectal dose

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect</th>
<th>What to do</th>
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<tbody>
<tr>
<td>timing</td>
<td>↓ RV100 if day 0 or day 1</td>
<td>be consistent</td>
</tr>
<tr>
<td>BMI</td>
<td>↓ RV100 if high BMI</td>
<td>wary of low BMI</td>
</tr>
<tr>
<td>rectal content</td>
<td>↑ RV100 if full rectum</td>
<td>scan empty</td>
</tr>
<tr>
<td></td>
<td></td>
<td>avoid constipation</td>
</tr>
<tr>
<td>length of source</td>
<td>↑ RV100 if long source train</td>
<td>be accurate in length</td>
</tr>
<tr>
<td>activity</td>
<td>↑ RV100 if ↑ activity</td>
<td>insert deeper</td>
</tr>
<tr>
<td>probe &lt;</td>
<td>↑ RV100 if probe not</td>
<td>follow post caps</td>
</tr>
</tbody>
</table>
Timing: When do we contour?

Dose in Gray to 1 cc of anterior rectal wall

Difference between day 1 and day 30: p= 0.002
(Wilcoxon Signed Ranks Test )

Day 1  Day 8  Day 30
1cc_Day1  1cc_Day8  1cc_Day30
Anatomic variation in degree of rectal contact

- Han and Wallner 2001
- Pre-implant CT scans define 3 groups
- 100% (9/9) of proctitis pts in group C vs 39% (7/18) of controls

Influenced by BMI and constipation
Scan with empty rectum for consistency

Rectal wall CT

Rectal wall MRI
Snapshot of a Dynamic process

Rectal wall CT

Rectal wall MRI
Rectal DVH

- 1cc: 123 Gy
- 2cc: 87 Gy
- 145 Gy (prescribed dose) to 0.49 cc
- Do not use D10 or D30 since dose to % of the organ depends on contouring limits
Fitting the literature results to your own experience... Han and Wallner IJROBP 2001

- 9 proctitis of 160 cases (6/9 comb EBRT)
- each matched to 2 controls by prostate size, isotope, prostate dose
- all 9 had “full contact” anatomy
- controls: 39% full, 33% partial, 28% none
- RV100: 0.6 cc non-bleeders vs. 2.5 cc proctitis p=0.00008 (Day 0 scan)
Fitting the literature results to your own experience… Snyder, Stock, Stone 2001

- $n=212$, Iodine 125 only
- 22 cases grade 2 proctitis
  - 14% in year 1, 72% year 2, 14% year 3
- $RV100 \leq 1.3$ cc: 5% proctitis vs. 18% $p=0.001$
  - 8% $> 1.3 - 1.8$ cc
  - 25% $> 2.3$ cc $p=0.002$
Fitting the literature results to your own experience... Snyder, Stock, Stone 2001

Dose/Rectal volume with < 5% risk

Grade 2 proctitis risk
< 1.3 cc vs. > 1.3 cc
Rectal toxicity

• document RV100 on post plans
• strive to keep < 1 cc
• probably doesn’t matter if rectal wall or just outer contour
• MR-CT fusion a very useful tool to accurately evaluate seed placement relative to prostate contours
MRI-CT fusion
Overestimation of prostate length on postplan prevents correction of technique.
MRI-determined prostate vs. CT-determined

MRI

CT
Length 6 cm
Sexual function

• recorded as 1/0 +/- PDE5’s for all patients at each visit
  – 84% potent pre BT
  – 82.5% potent at last follow-up (82.8% with follow-up > 5 yrs)

• since 2005, baseline IIEF and annually
  – 83.4% > 15 @ baseline
  – 84.4% @ 2 yrs and 3 yrs

• PDE-5’s discussed with every patient, samples offered and use encouraged
Neurovascular bundles on TRUS
Penile bulb on MRI
Time-of-flight non contrast MR angiograms of Internal Pudendal Arteries
Relation of IPA and penile bulb to brachytherapy dose

Lateral view
Mean peak dose 17 Gy

Posterior view

Gillan, Crook et al, IJROBP 2006
SPIRIT: *Surgical Prostatectomy vs. Interstitial Radiation Intervention Trial*

- Phase III randomized trial comparing RP and BT for favourable risk prostate cancer
- Closed May 2004 due to poor accrual
- Trial-specific educational session attended by 263 eligible men of whom 190 underwent RP or BT by choice or on trial

<table>
<thead>
<tr>
<th>RP</th>
<th>BT</th>
</tr>
</thead>
<tbody>
<tr>
<td>62</td>
<td>94</td>
</tr>
</tbody>
</table>

Trial: 34

QOL Cohort
QOL cohort study

- Median follow-up 5.2 years (3.2-6.5)
- Cancer-specific 50 item EPIC (Expanded Prostate cancer Index Composite)
- SF-12 PCS/MCS (Physical/Mental Component Score)
- Response rate 88.4%
  - 6 lost/16 declined
## Results: assessment of QOL @ 5 years

<table>
<thead>
<tr>
<th></th>
<th>BT</th>
<th>RP</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (chose/randomized)</td>
<td>86/15</td>
<td>52/15</td>
<td></td>
</tr>
<tr>
<td>age</td>
<td>61.5</td>
<td>59.5</td>
<td>0.06</td>
</tr>
<tr>
<td>Bowel domain</td>
<td>93.0</td>
<td>94.3</td>
<td>0.43</td>
</tr>
<tr>
<td>Hormonal domain</td>
<td>93.5</td>
<td>90.0</td>
<td>0.09</td>
</tr>
<tr>
<td>SF-12 PCS</td>
<td>55.8</td>
<td>55.5</td>
<td>0.37</td>
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<tr>
<td>SF-12 MCS</td>
<td>45.4</td>
<td>44.2</td>
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<tr>
<td>Urinary Domain</td>
<td>91.8</td>
<td>88.1</td>
<td>0.02</td>
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<tr>
<td><strong>Sexual domain</strong></td>
<td>52.3</td>
<td>39.7</td>
<td><strong>0.002</strong></td>
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<tr>
<td><strong>Satisfaction</strong></td>
<td>93.6</td>
<td>77.2</td>
<td>&lt;<strong>0.0001</strong></td>
</tr>
</tbody>
</table>
Specific questions with significant differences

- Urinary
  - Frequency of leakage
  - Urinary control
  - Problem with leakage

- Sexual
  - Ability to have an erection $p=0.0007$
  - Reach orgasm $p=0.048$
  - Quality of erection $p=0.0002$
  - Frequency of erection $p=0.003$
Anonymous patient-reported data consistent with entire BT experience @ PMH

• Erections firm enough for sexual activity were reported by 79% of men treated with BT compared to 48% of those treated by RP (p=0.0002)

• 66% had erections at least half the time when they wanted as compared to 40% of men after surgery (p=0.003).
Summary: urinary morbidity

- Prostate and transition zone volume, voiding function, and HT are inter-related.
- Large prostates can be safely implanted:
  - excellent voiding function
  - minimize operative trauma by using higher activity seeds and fewer central needles
- Strictures usually @ membranous urethra:
  - don’t over estimate length @ planning
  - don’t over-implant apex
Summary: rectum

Rectum:

• contour inner and outer wall
• contour all slices with seeds
• report as dose to fixed volume (1cc, 2cc) OR volume (cc) receiving certain dose levels (100% = RV100, 150% = RV150, 200% = RV200)
Summary: sexual

Penile bulb

- hard to identify on CT
- easily contoured on MR
- need more data
- encourage those centers using MR to routinely contour and report
Conclusions

• Your way of planning and executing an implant is probably unique
• Technique can only be disseminated through fellowship training (6-12 months)
• The toxicity of others may not be relevant to what you do (but may provide clues)
• Study your own results. Know your toxicity and what it relates to. Tweak your technique and see what happens!
Conclusion

THE DEVIL IS IN
THE DETAILS

Courtesy of R Stock