Challenges in Advancing Your Prostate Practice

Chairs: André-Guy Martin, Yasuo Yoshioka, Mitchell Kamrava

Challenges Session B2

Session F2

Challenges in Advancing Your Prostate Practice

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Special thanks: C. Leland Rogers, M.D., Partner
Disclosures

John K. Hayes, Jr, MS, MD, has received consulting fees for the Elekta Advisory Board and has contracted research for Elekta.

Session F2: Challenges in Advancing Your Prostate Practice

Tasking: Are we going in the right direction? Expectations of a better cure and survival gain with brachytherapy (dose escalation)

John K. Hayes, M.D., M.S.
GammaWest Cancer Services
Salt Lake City, Utah
Challenges, Utah
Right direction to find and treat prostate cancer?

- Utah incidence: 176 cases/100,000
- U.S. average: 147 cases/100,000
- Cancer Deaths Utah Men:
  - Lung/bronchus 17.4%
  - Prostate 14.8%
  - Colon/rectum 8.4%
  - Pancreas 7.2%

Mortality
- Lung/Pr Kentucky = 4.1
- Lung/Pr Utah = 1.2

Challenges, PSA Screening
Right Direction?

- PSA screening has lead to 1.3 M new diagnoses since 1986 and “only 56,000 deaths were averted.”¹ - Scott Hensley, NPR
- Benefits of PSA screening “are still open to question. There are some proven harms associated with screening. Screening, for example, leads to unnecessary treatment in some men who are diagnosed with localized disease.”² - Otis Brawley, CMO of ACS
- “The American Cancer Society does not recommend routine screening for prostate cancer, and has not since 1997.”³ - J. Leonard Litchenfield (ACS Deputy Chief Medical Officer) October 28, 2010

With friends like these who needs enemies?

“Cancer death rates have been continuously declining for the past 2 decades. Overall the risk of dying from cancer decreased by 20% between 1991 and 2010.”

“Death rates from prostate cancer are down by 45% as a result of improvements in early detection and treatment.”

“Progress has been most rapid among middle aged black men, among whom death rates have declined by approximately 50%.”

Challenges - Screening Right Direction?

- Utah SEER Data 2007-2011
  Prostate cancer diagnosis by Gleason Score
  Gleason ≤6   45.7%
  Gleason 7    37.4%
  Gleason 8-10 12.6%
  Unknown      4.2%
  Gleason 7-10 = 50.0%!

Challenges - Screening HDR
Monotherapy Intermediate-Risk CaPr

If HDR Monotherapy can cure
19 out of 20 men with with
Intermediate risk CaPr, and
if 50% of new diagnoses are
Gleason 7-10 in Utah, does it
make sense to stop
PSA screening?

Rogers CL, Alder SC, Rogers RL, Hopkins SA, Platt ML, Childs LC, Crouch RH, Hansen RS, Hayes JK.
Challenges, Toxicity

- The USPSTF downgrading of PSA Screening was a statement on toxicity related to surgery and to external beam radiation.
- As an HDR user, both monotherapy and as boost, FU clinics are in large part toxicity free.
- How does one convince a skeptical world that HDR brachytherapy is a solution to what is going to be a big public health problem in the next decade?

Challenges to HDR Program?
Not urinary toxicity!

Side Effects: IPSS Scores

n = 284
Mean FU: 35.2 mo
(range 12.1-96.1)
Age: 70.2 yr (47-85)
PSA: 8.4 (1.0-19.7)

Box & Whiskers:
Box interquartile range (25-75%)
Line in the box is the median
Bottom of box is 25th percentile
Top of Box is 75%
If no dots: Top whisker highest in range. Bottom whisker is the lowest value.
If there are dots- whiskers only allowed to be as long as 1.5x length of box.
Dots are any values that lie outside of that, i.e. are outliers

Mean IPSS scores

p = .318
Challenges, toxicity, HDR Monotherapy
Not Urinary Incontinence

Side Effects: Incontinence (Pads)

New pad usage 22/284 (7.7%)
7 had TURP before HDR-MT (1 to 4 TURPs)
10 tremor, 2 stroke, and 1 had diffuse neuropathy

Grade 1  Grade 2  Grade 3  Grade 4
15 (68%)  5 (23%) †  2 (9%) † †  0
† 4 of 5 had TURP or tremor
† † 1 had 3 TURPs, the other 2 TURPs + tremor

7/284 (2.5%) with no TURP or neurologic compromise: 6 Gr 1, 1 Gr 2

Urinary Pad Grading Scale
Grade 0: none
Grade 1: occasional use of pads
Grade 2: ≤ daily intermittent use of pads
Grade 3: ≤ 2 pads/day, regular use of pads, self cath
Grade 4: Refractory, permanent catheter

Challenges, Toxicity, HDR Monotherapy
with rigorous dosing guidelines?

Side Effects
Bulbo-membranous Urethral Stricture

Small Prostate 15cc  Large prostate 100 cc

150%
120%
110%
105%
100%
60%
### Challenges for HDR Program

**Sexual Dysfunction?**

Side Effects: Erectile Function (IIEF-5)

Defining potency as IIEF-5 >10 (with or without aid), 67.9% were potent prior to HDR-MT. Of these 82.6% maintained potency at 2y

**Mean decrease** in IIEF-5 score 6.1

Erectile aid used by 9.2% before vs 95.7% after HDR-MT typically PDE-5 inhibitors alone

This result is similar to Vicini et al.1, who used 46Gy EBRT + HDRB, 5 Gy x 3 or 8.25-10.5 Gy x 2. With median f/u 2.8 y, potency was preserved in 73%.

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### Challenges to HDR Brachytherapy

**Program, Rectal Toxicity?**

RTOG Grade 1 toxicity occurred in 12 patients (4.2%)

None experienced rectal toxicity beyond grade 1

<table>
<thead>
<tr>
<th>ORGAN/TISSUE</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMALL/LARGE INTESTINE</td>
<td>None</td>
<td>Mild diarrhea</td>
<td>Moderate diarrhea and colic</td>
<td>Obstruction or bleeding requiring surgery</td>
<td>Necrosis Perforation Fistula</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild cramping</td>
<td>BM &gt;5 times daily</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>BM 5 times daily</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Slight rectal d/c</td>
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97.9% of patients remain Hemoccult® negative

No patient required GI intervention for an HDR side effect

Are we going in the right direction?
ALARA, Rad. Safety and Rx Gain

HDR & Androgen Suppression
Going in the Right Direction?

Biochemical Disease-Free Survival by HT

HT used (vol reduction), n=46 (16.2%)
HT not used, n=238 (83.8%)

HDR Lack of Benefit from Hormonal Therapy
WBH, CET, Kiel University

HDRB: 1260 patients
At least 1 "unfavorable characteristic"
≥cT2b, PSA>10, GS>7
EBRT 36-50 Gy, 1.8-2 Gy fx
Pelv (WBH, Kiel), Prost (CET)
HDR 22-24 Gy, 4 fx, 1 implant

HDR Boost – varying protocols
HDR planning constraints:
urethral dose <125%
posterior rectal wall <75%

Androgen Deprivation:
406 pts <6mo neoadjuvant/concurrent
in most due to poor pgx fx, but
discretionary; also for volume

Lack of benefit from a short course of androgen deprivation for unfavorable prostate cancer patients treated with
an accelerated hypofractionated regime. IJROBP 2005;62(5):1322-1331

RTOG 0815
Phase III Prospective Randomized Trial of Dose-Escalated Radiotherapy with or without Short-Term (6 months) ADT
For Patients with Intermediate-Risk Prostate Cancer

EBRT alone 79.2 Gy in 44 fractions of 1.8 Gy each
EBRT with brachy boost 45.0 Gy in 25 fractions of 1.8 Gy each
LDR seed boost if <60 cc, AUA ≤15, and no prior TURP
I-125 (110 Gy) or Pd-123 (100 Gy)

Intermediate risk: Gleason Score 7, PSA >10 but ≤20, T-Stage T2b-T2c. Pts with all 3 intermediate risk factors and ≥ 50% of their sampled biopsy cores involved will not be eligible for this study. Note: The percentage of biopsy cores involved will only be considered with respect to eligibility for those patients with all 3 of the above risk factors (i.e., patients with one or two of the above risk factors are eligible irrespective of the percentage of biopsy cores involved). Pts with Gleason score >7, PSA >20, or clinical stage > T2c are ineligible for this study.
Right direction? EBRT+/-HDR
Intermed-Risk Prostate Ca
Peter MacCallum Cancer Centre
Melbourne, Australia

2001-2006
344 patients EBRT + HDR
46 Gy / 23 + 19.5 Gy / 3
344 matched cohort EBRT alone
74 Gy / 37

NCCN Risk Groups
Low Risk none
Intermediate 203 each group
High Risk 141 each group

Hormonal therapy 59% each arm
Median f/u 60.5 months

bDFS - Entire Cohort


Comparison of PSA relapse-free survival in patients treated with ultra-high-dose IMRT versus combination HDR brachytherapy and IMRT

MSKCC
IMRT 86.4Gy/48 (n=470) vs HDRB 7Gy x3, then 1 mo later 50.4Gy/28 (n=160)
Med f/u: 53 mo IMRT 47 mo HDR + IMRT

Improved RFS on univariate analysis if: HDR, ↓T stage, ↓GS, ↓PSA, ↓NCCN risk group, no ADT

Improved on multivariate if: HDR, ↓NCCN risk group, age

Brachytherapy 2010;9:313-318
Spanish RCT (1999-2005)
445 Intermed or Hi-Risk (PSA>10 GS>6, T2b or T3)
EBRT 76 Gy/38 3D-CRT (n=222) v EBRT 46 Gy + HDR 16 Gy/2 (n=223)

<table>
<thead>
<tr>
<th></th>
<th>5y bDFS</th>
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<tbody>
<tr>
<td>EBRT</td>
<td>82.3%</td>
</tr>
<tr>
<td>EBRT+HDR</td>
<td>98.1%</td>
</tr>
</tbody>
</table>

Conclusions: Acute and late rectal complications were significantly reduced with combined treatment, and short-term PSA control better

No grade 3 or 4 rectal or urinary complications in either arm

Guix B, Bartrina I, Tello J, Lacorte T, Henriquez I, Sole J, Guix I, Galdron G, Espino M. Dose escalation with high-dose 3D-conformal radiotherapy (HD-3D-CRT) or low-dose 3D-conformal radiotherapy plus HDR brachytherapy (LD-3D-CRT+HDR-B) for intermediate-or high-risk prostate cancer: Higher PSA control with lower toxicity. JCO 2011 (suppl 7; abstr 82). Also JCO 2010; 28:15s, abst 4633

Right Direction vs.Surgery for Intermediate-Risk Prostate Ca

1746 patients
Baylor and MSKCC, 1983-2003
Single surgeon (Peter Scardino)
No EBRT, no neoadj hormonal tx
bDFS (PSA <0.4 a1996, <0.2 p1996) from date of rad prostatectomy by pre-op PSA, clinical stage, biopsy Gleason score

Systematic review 40 articles
bDFS and OS at 3, 5, & 8 yrs

Treatment  HR bRecum
EBRT v HDR  1.40
95% CI 1.31-1.51
Seeds v HDR  1.37
95% CI 1.26-1.49

Treatment  HR OS
EBRT v HDR  1.50
95% CI 1.29-1.73
Seeds v HDR  2.33
95% CI 2.04-2.66

Radiotherapy and Oncology 2009;93:168-173
Conclusion

“The combination of external beam radiotherapy and HDR brachytherapy results in a superior biochemical control and overall survival found in a systematic review on radiotherapy for prostate cancer. This outcome is mainly explained by the higher dose that can be prescribed when brachytherapy is used....”

Headed in the right direction with HDR Brachytherapy for prostate cancer?

Radiotherapy and Oncology 2009;93:168-173

Right direction? Treatment Long-term Toxicity & Cost

SEER Medicare Database 1991-2007
n = 137,427 men ≥65 years old,
Prost Ca the only cancer diagnosis

Prostatectomy 59,559 (43.3%)
EBRT 60,806 (44.2%)
Brachytherapy 17,062 (12.4%)
No pt received combined therapy

Median f/u 71 months
7.3% toxic effects requiring intervention

7.3% 8.8% 6.9% 3.7%

Treatment Related Toxicities

Right Direction? Modality
Long-term Costs

<table>
<thead>
<tr>
<th>Modality</th>
<th>Median FU 71 mo</th>
<th>Cost per Patient Year</th>
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<tbody>
<tr>
<td>EBRT</td>
<td>60,806 (44.3%)</td>
<td>$10,000</td>
</tr>
<tr>
<td>Prostatectomy</td>
<td>59,559 (43.3%)</td>
<td>$8,000, $6,412</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>17,062 (12.4%)</td>
<td>$6,000, $3,206, $2,557</td>
</tr>
</tbody>
</table>


Right Direction for Program development?

<table>
<thead>
<tr>
<th>Year</th>
<th>77787* technical</th>
<th>77787* professional</th>
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<tbody>
<tr>
<td>2008</td>
<td>$1,163.64</td>
<td>$243.31</td>
</tr>
<tr>
<td>2009</td>
<td>$529.87</td>
<td>$241.55</td>
</tr>
<tr>
<td>2013</td>
<td>$653.41</td>
<td>$238.14</td>
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<tr>
<td>2014</td>
<td>$476.33</td>
<td>$249.87</td>
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Thus this year technical reimbursement for 77787 decreased another 27.1%

* in 2008 there was no CPT 77787, rather 77784; Utah Medicare Data
Challenges, Right Direction?

“Take part or be taken apart!”

Hon. Alan K. Simpson, R-WY 1979-96

“We took part and got taken apart!”

Hon. David Wazer, Socio-economics Chair, ABS

Right Direction? HDR for CaPr

HDR Brachytherapy

- Unmatched long-term biochemical control for the majority of patients with prostate cancer
- Very favorable side effect profile
- Few adverse events. Urinary incontinence is more likely in pts with TURP, or with neurologic compromise
- Every study, including randomized trials and a large systematic review, making a direct comparison has shown advantages to HDR brachytherapy
- Androgen ablation may be unimportant, less important, or appropriate in shorter courses (e.g. GW 4 months) with HDR. This will demand further study. RTOG 0815 will help
- HDR delivers superb outcomes, optimized dosimetry, limited side effects, lack of rad exposure to others, short tx course, min time out of work, and affordability.
Right Direction? HDR for CaPr

HDR Brachytherapy

- Eliminates the need to clone Peter Grimm and Greg Merrick. I.E., the technique eliminates the need for brachytherapy superheroes. The technology can be transferred brachytherapy teams while maintaining high quality.

- Adaptable to Multiple planning methods and techniques.

- Although very high dose-fractionation schedules have been reported, 45 Gy IMRT plus 3X6.5 Gy or 6X6.5 Gy HDR MT (or its BED GY2 equivalent, is sufficient to eradicate a very high percentage of prostate tumors. Dose escalation beyond that BED is therefore not recommended.

- Medicare and the USPSTF have failed the American public as regards HDR BT for Prostate Cancer (Gleason 7-10 = 50% of new prostate diagnoses in Utah)

- Radiation oncologists working with urologists can be a powerful public health team in the upcoming epidemic of advanced prostate cancer if they incorporate HDR BT into treatment.

Challenges, Right direction in Socio-economic policy?

- Pro + Tech IMRT
- 40 fractions
- Utah Medicare
- $20,662

- Pro+Tech HDR
- 6 fx, 3 implants
- Utah Medicare
- $4,357

What is your radiation therapy department administrator going to say when you ask for money to build and staff an HDR program?
**Right Direction, Radio-Protection?**

43 × 1.8 Gy = 77.4 Gy

6 × 6.5 Gy = 39.0 Gy

12.5% of prescription dose

9.7 Gy (10.76 Gy²)

4.9 Gy (6.85 Gy²)

Integral dose strongly favors of Brachytherapy in this comparison

25% of prescription dose

19.4 Gy (23.70 Gy²)

9.75 Gy (17.67 Gy²)

About 500-1000 pelvic CT scans

**Tale of Two Doctors**

- Doctor A 2002
  - Age 56
  - PSA 60 ng/ml
  - Gleason 3+4, 3/6 sext.
  - MAB+EBRT+HDR BT
  - PSA 8/14/10 = 0.01 ng/ml

- Doctor B 2004
  - Age 56
  - PSA 13.7 ng/ml
  - Gleason 3+3, 6/6 sext.
  - 30-80% in each core
  - MAB+EBRT+HDR BT
  - PSA 10/07 = 0.03 ng/ml
  - PSA 04/08 = 0.02
  - PSA 03/10 = 0.01

Cost effective medicine?
**IMRT vs. HDR BT**

- **IMRT:** 43 x 1.8 Gy = 77.4 Gy
- **HDR BT:** 6 x 6.5 Gy = 39.0 Gy

12.5% of prescription dose

- **IMRT:** 9.7 Gy (10.76 Gy²)
- **HDR BT:** 4.9 Gy (6.85 Gy²)

About 500-1000 pelvic CT scans

25% of prescription dose

- **IMRT:** 19.4 Gy (23.70 Gy²)
- **HDR BT:** 9.75 Gy (17.67 Gy²)

Integral dose strongly favors Brachytherapy in this comparison

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**Why Payers Should like HDR MT**

- One treatment, one cure! (+/- $30K)
- No more expenses for prostate cancer care!
- Versus a too common scenario: Inappropriate radical prostatectomy (based on pre-surgical risk factors), surgery for incontinence, rising PSA, external beam radiation, rising PSA, androgen deprivation, rising PSA, chemotherapy, rising PSA, Provenge ($93,000, palliative radiation, nursing home care, hospice, death. (+/-$300K)
Tale of Two Doctors

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Cost effective medicine?

Urologic Détente?

Before Brachytherapy

After Brachytherapy
Are we going in the right direction?

Conclusions

• In world since 1986 vs. 1995 for IMRT
• Several studies now suggest benefits over other modern modalities
• May lessen the need for androgen ablation
• More accurate dose delivery vs. LDR
• Fewer Side effects vs. LDR

Are We Going in the Right Direction?

HDR Brachytherapy

• Truly Robotic vs. Robot Assisted
• Highly potent against CaP (Very favorable radiobiology, Brenner and Hall)
• In world, since 1986 vs. 1995 for IMRT
• Precise and Accurate? Yes
• Fewer Side effects than almost all treatments for prostate cancer
How to change made up minds?

• Reasoning is suffused with emotion
• The two are inseparable
• Positive and negative feelings arise faster than conscious thoughts
• By the time we are consciously reasoning, we may instead be rationalizing prior emotional commitments

Chris Mooney in “Made-up minds” In THE WEEK May 20, 2011

Made-up minds

Attitudes toward issues like the date the world will end, global warming, capital punishment, vaccines and autism, etc. are influenced by pre-existing emotional biases, as are attitudes toward prostate cancer treatment depending on one's training and experience.

True believers in their area of expertise critique each new study that challenges their views.

Chris Mooney in “Made-up minds” In THE WEEK May 20, 2011
Challenges, Prostate Cancer: How can patients get HDR BT?

Buy in by CMS
Buy in by radiation oncologists
Buy in by urologists
Buy in by patients and media
Political support by ASTRO
Political support by AUA
Buy in by Hospitals
Investment in HDR brachytherapy teams
Buy in by patient care organizations
Buy in by insurance companies
Buy in by USPSTF

Made-up minds

• Giving partisans scientific data that is relevant to their beliefs is like unleashing them in the motivated reasoning equivalent of a candy store.

• Political sophisticates are prone to be more biased than those who know less about the issues. They generate more and better reasons to explain why they are right.

• If you want to convince, don’t lead with the facts, lead with the values, so as to give the facts a fighting chance.

Chris Mooney in “Made-up minds” In THE WEEK May 20, 2011