Which is best  LDR or HDR for the boost

Leeds UK
March 22 2019

Mira Keyes MD FRCPC
Clinical Professor Radiation Oncology
Department of Surgery UBC
Head, BCCA prostate Brachytherapy Program
Vancouver Cancer Centre, BC Cancer  Canada
**Why Brachytherapy?**

Radiation Oncology 101

There is no radio-resistant tumors

Failure to cure localized cancer is due to:
- Inadequate dose
- Geographic miss

**Surgery:**
- Eliminate **bulk** – most common cause of RT failure

**EBRT:**
- Eliminate **microscopic disease** – most common cause of surgical failure

**BRACHYTHERAPY**
- Very high dose
- Eliminate tumor **bulk**

**EBRT and Brachytherapy**
- Eliminate both

PB is the most effective (radiation) treatment for localized PC
HDR vs LDR?

HDR – Shorter follow up than LDR, smaller studies
    Are the long term outcomes equivalent?
HDR – Various fractionation schedule
    Are they equivalent?
HDR – Toxicity is less? - Is this correct?
HDR – Less expensive? - Is this correct?
Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group


Majority LDR studies
Longer FU

Int. Risk PSA RFES @ 10y

10y PSA RFS
LDR – 70-95%
HDR+EBRT – 85-90%
LDR+ EBRT~ 85-90%
EBRT <40-60%
Surgery ~65%

http://www.pctrf.org/low-risk-results/
Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group


Majority LDR studies
Longer FU with LDR

High Risk PSA RFES @ 10y

LDR <50%
LDR+ EBRT 60-70%
HDR+EBRT 85%
LDR + EBRT+ADT 85%
EBRT+ADT <50%
Surgery 20-40%

http://www.pctrf.org/low-risk-results/
Clinical Investigation

Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): An Analysis of Survival Endpoints for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost to a Dose-Escalated External Beam Boost for High- and Intermediate-risk Prostate Cancer

W. James Morris, MD, FRCP, *† Scott Tyldesley, MD, FRCP, *† Sree Rodda, MBBS, MRCP, FRCR, * Ross Halperin, MD, FRCP, *† Howard Pai, MD, FRCP, *† Michael McKenzie, MD, FRCP, *† Graeme Duncan, MB, ChB, FRCP, *‡ Gerard Morton, MB, MRCPI, FRCP, FFRRCST, † Jeremy Hamm, MSC, † and Nevin Murray, MD, FRCP *‡

ASCENDE-RT: An Analysis of Treatment-Related Morbidity for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost with a Dose-Escalated External Beam Boost for High- and Intermediate-Risk Prostate Cancer

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Clinical Investigation

ASCENDE-RT: An Analysis of Health-Related Quality of Life for a Randomized Trial Comparing Low-Dose-Rate Brachytherapy Boost With Dose-Escalated External Beam Boost for High- and Intermediate-Risk Prostate Cancer

Sree Rodda, MBBS, MRCP, FRCR, * W. James Morris, MD, FRCP, *‡ Jeremy Hamm, MSC, † and Graeme Duncan, MB, ChB, FRCP *‡

*BC Cancer Agency, Vancouver Centre, Vancouver, British Columbia, Canada; 1Department of Surgery, University of British Columbia, Vancouver, British Columbia, Canada; 2Department of Population Oncology, BC Cancer Agency, Vancouver Centre, Vancouver, British Columbia, Canada

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Clinical Investigation

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BC CANCER
1. bPFS Absolute bPFS difference 20%

2. Absolute difference in PSA RFS is 20-40%

3. No difference in OS
Trials not powered to show OS difference
Significant association of brachytherapy boost with reduced prostate cancer-specific mortality in contemporary patients with localized, unfavorable-risk prostate cancer

Michael Xiang¹,² and Paul L. Nguyen¹

¹Department of Radiation Oncology, Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, MA

PCSM all

A) Adjusted PCSM cumulative incidence
B) Adjusted PCSM cumulative incidence

PCSM HR

C) Adjusted PCSM cumulative incidence

PCSM IR


SEER database: 52,535 pth
19.6% had EBRT + BT (1/3 HR)

Benefit for younger and HR only

PB boost increase PCSS, MFS and OS
Brachytherapy Boost Utilization and Survival in Unfavorable-risk Prostate Cancer


*Department of Therapeutic Radiology, Yale School of Medicine, New Haven, CT, USA; ‡Cancer Outcomes, Public Policy, and Effectiveness Research Center, Yale School of Medicine, New Haven, CT, USA

25,038 men in NCDB 2004 and 2012 with EBRT vs. EBRT+PB

~2000 ptss KM OS <60 y - no comorbidities
7-yr OS 85% vs 90%; p < 0.001

PB boost 5% increase in OS at 7 y
Survival Outcomes of Dose-Escalated External Beam Radiotherapy versus Combined Brachytherapy for Intermediate and High Risk Prostate Cancer Using the National Cancer Data Base

Arya Amini,* Bernard Jones, Matthew W. Jackson, Norman Yeh, Timothy V. Waxweiler, Paul Maroni, Brian D. Kavanagh and David Raben

From the Department of Radiation Oncology and Division of Urology, Department of Surgery (PM), University of Colorado School of Medicine, Aurora, Colorado

20,279 US NCDB - 2004 - 2006
• EBRT - 71% (75-81 Gy)
• EBRT + PB 29%

• 12,617 IR, 7,662 HR
• Median follow-up was 82 months

MVA
EBRT + PB - OS (HR 0.75, p <0.001). IR and HR - HR 0.73/0.76, <0.001).

Brachy Boost
Increase OS ~ 5%

Figure 1. Kaplan-Meier curves show survival outcomes between high dose EBRT (dotted curves) vs EBRT plus brachytherapy (solid curves) in patients with prostate cancer at intermediate (A) and high (B) risk.
Clinical Outcomes for Patients with Gleason Score 9–10 Prostate Adenocarcinoma Treated With Radiotherapy or Radical Prostatectomy: A Multi-institutional Comparative Analysis

Amar U. Kishan a, Talha Shaikh a, Pin-Chiueh Wang a, Robert E. Reiter c, Jonathan Said a, Govind Raghavan a, Nicholas G. Nickolas a,c, William J. Arenson d, Ahmad Sadeghi b, Mitchell Kamrava b, David Jeffrey Demanes b, Michael L. Steinberg a, Eric M. Horwitz b, Patrick A. Kupelian a, Christopher R. King a

487 pts GS 9–10 (2000 -2013)
Med FU 4.6 y
230 - EBRT, 87-EBRT + BT, 170 - RP

RT and RP - same CSS and OS
PB boots +ADT - increase MFS (40%).

RT+PB +ADT might be the optimal upfront treatment for pts with GS 9–10.
1809 pts 12 US & Norway (2000-2013) 639 RP, 734 EBRT, 436 EBRT+BT med fu 4.2-6.3y GS 9-10 43% RP pts had Salvage RT!

Figure. Adjusted Survival Curves for Prostate Cancer-Specific Survival, Distant Metastasis-Free Survival, and Overall Survival by Treatment Group, Weighted by the Inverse Probability of Treatment

PB boost increase
CS ~10%
MFS ~25%
PB boost increase

- OS by ~ 5% (ASCENDE RT 6%)
- MFS ~25-40% (GS 9-10)
- CSS ~10%

PCa has a long natural history
New treatments that increase OS
Competing risk of dying – effect of comorbidities

Mostly LDR
Brachytherapy for Patients With Prostate Cancer: American Society of Clinical Oncology/Cancer Care Ontario Joint Guideline Update

Joseph Chin, R. Bryan Rumble, Marisa Kollmeier, Elisabeth Heath, Jason Efstatiou, Tanya Dorff, Barry Berman, Andrew Feifer, Arthur Jacques,† and D. Andrew Loblaw

**LR and Low IR**
- LDR

**High - Intermediate Risk**
- LDR/HDR + EBRT + ADT

**HR**
- LDR/HDR + EBRT + ADT

**Pts in all risk groups** should be offered PB if eligible
**HR** pts receiving EBRT and ADT, should be offered PB boost (LDR/ HDR)

J Clin Oncol 35:1737-1743.
Optimal Radical Therapy for Localized Prostate Cancer: Recreation of the Self-Fulfilling Prophecy With Combination Brachytherapy?

Daniel E. Spratt, University of Michigan, Ann Arbor, MI
Peter R. Carroll, University of California San Francisco, San Francisco, CA

Self-fulfilling prophecy - now turned in a new direction: the benefit of adding brachytherapy to EBRT, and its superiority over EBRT.

1. Bias with population based studies
2. PSA RFS is not a clinically meaningful end
4. Salvage local treatment is always an option with 5% gr 3 toxicity vs. 20% ASCENDE RT
5. Isolated clinical local failures is only 10% with EBRT+ADT - over treating patients with PB
6. Quality of life and toxicity must be a high priority
PSA RFS is not a clinically meaningful end toxicity is important.

The optimal approach to treatment, may not necessarily be the one that is associated with the least morbidity, but instead the one that is most effective in preventing the need for subsequent treatment, anxiety, costs, and adverse effects of salvage.

Prevalence 5-year GU GR3 8.6% and GI Gr3 2.2%

ADT QOL ED hot flashes fatigue Anemia Loss of muscle mass Cognitive dysfunction Depression Psychiatric illness osteoporosis fractures

Metabolic syndrome
- Central and peripheral obesity
- Increase in cholesterol
- Increase in triglycerides
- HDL decreased
- Elevated blood pressure
- Elevated fasting glucose
- Elevated fasting insulin
- Decrease insulin sensitivity
- Increase diabetes by 44%
- Increase cardiovascular
  - Sudden cardiac death
- Decrease OS?

Abiraterone
- Anemia
- Fatigue
- Back pain
- Arthralgia
- Nausea
- Vomiting
- Diarrhea
- Hot Flashes
- UTI
- Fluid retention
- Hypertension
- Hypokalemia
- Hepatotoxicity
- Atrial Fibrillation

Enzalutamide
- Fatigue (Grade 3/4)
- diarrhea
- musculoskeletal pain
- headache
- hypertension
- hot flashes
- peripheral edema
- seizures

Docetaxel
- Cabazitaxel
- Ra 223
- $$$ cost
- PSMA PET

Prevalence of Incontinence
- RP RTCs 17-60%
- PIVOT 40%
- PROTECT 17%
- PCOS 18%
- SPCG RTC 60%

PSA control may be a meaningful outcome?
BCCA Brachytherapy Program

>6500 implants
Prostate cancer ‘cure’ disputed
Experts criticize B.C. Cancer Agency, saying it is exaggerating effects of its brachytherapy program

BY PAMELA FAYERMANN VANCOUVER SUN
Some prostate cancer experts are criticizing a B.C. Cancer Agency announcement for exaggerating a treatment's effects by describing it as a ‘likely cure.’ But he praised the brachytherapy program and the study.

The radiation oncologists are to be congratulated for implementing this program and delivering results on par with many other major centers in North America,” he said.

Population-Based 10-Year Oncologic Outcomes After Low-Dose-Rate Brachytherapy for Low-Risk and Intermediate-Risk Prostate Cancer

Mira Kayes, MD, FRCP(C); Ingrid Spadinger, PhD;2; Winkle Kwan, MD, FRCP(C);4; Ni McKenzie, MD, FRCP(C); Howard Pai, MD, FRCP(C);3; Tom Pickles, MD, FRCP(C);5; and Scott Tyldesley, MD, FRCP(C)

Trial of radioactive implants offers improved prostate cancer survival

A trial comparing the treatment with dose-escalated external beam radiotherapy found that it was much more successful at eliminating cancer.

Men who underwent LDR-PB were twice as likely to be cancer-free five years later.

Scientists studied 398 men with cancer that had not spread outside the prostate gland who were judged to be at high risk of treatment failure based on standard test results.

Lead researcher Professor James Morris, from Vancouver Cancer Centre in Canada, said: ‘At five years follow-up, we saw a large advantage in progression-free survival in the LDR-PB group.

‘Although, to date, overall survival and prostate cancer-specific survival do not appear to differ between the two groups, existing trends favor LDR-PB and an overall survival advantage is likely to emerge with longer follow-up.”

ACENDE RT - RTC 400 pts: 12 m ADT + EBRT ± LDR PB

Morris et al Cancer 2013
Changes in the program

Improvement in imaging and planning
- MRI for planning
- High quality new generation US
- Planning - Reducing the dose to membranous urethra
- Dose painting - DIL

Reduction of
- prescription dose to 100Gy
- Intra-prostatic volume receiving >150% of prescription

Patient selection
- Good baseline urinary function
- Comorbidity
- Age
56y old man
PSA 15, T3a? N0 M0
GS 3+4=7/10, in 7/13 cores
EBRT and PB boost July 31 2018
MRI used for planning

Jan 2019
PSA - 0.81
IPSS - 7
SHIM - 25/25
ASCENDE RT update – REDUCING TOXICITY

Update on OS and PSA RFS will be done late 2019

OPTIMAL [Optimizing Prostate cancer Treatment in Men with Advanced Local disease] – reduced toxicity

105 ASCENDE RT eligible pts:
- PSMA PET staging
- mpMRI
- Trans-prinneal saturation biopsy
- IMRT (pelvis)
- focus the ultra-high doses (150-200%) to the regions of highest tumor burden.
PSA failure definition
PSMA PET
A BIOCHEMICAL DEFINITION OF CURE FOLLOWING BRACHYTHERAPY FOR PROSTATE CANCER: A MULTI-INSTITUTION INTERNATIONAL STUDY


Objective: can the cure be defined based 10-15y FU after LDR BT using surgical PSA definition of biochemical failure.

7 international institutions - 14,496 pts
LDR BT n=11,578
ADT+ LDR n=1,965
EBRT + LDR n=498
EBRT + ADT + LDR = 455
LR - 39%
IR - 52%
Hr - 9%
<table>
<thead>
<tr>
<th>PSA range</th>
<th>Number of patients in PSA range after 4 years</th>
<th>10 y bNED (238 CFs)</th>
<th>15 y bNED (195 CFs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA≤0.2</td>
<td>7407</td>
<td>99.3</td>
<td>98.2</td>
</tr>
<tr>
<td>0.2&lt;0.5</td>
<td>811</td>
<td>96.0</td>
<td>86.8</td>
</tr>
<tr>
<td>0.5≤1.0</td>
<td>306</td>
<td>88.6</td>
<td>81.9</td>
</tr>
<tr>
<td>PSA&gt;1.0</td>
<td>487</td>
<td>61.0</td>
<td>50.1</td>
</tr>
</tbody>
</table>

Patients with a PSA ≤ 0.2 ng/ml at 4 years post LDR BT have >98% chance of remaining disease free beyond 15 years. This applies to more than 80% of patients.

We suggest that PSA ≤ 0.2 ng/ml be adopted as the biochemical definition of cure for LDR BT patients with ≥ 4 years’ follow-up.

Not validated for HDR
Objective:
evaluate patterns of recurrence after brachytherapy with PSMA PET

Eligible:
PSA failure (Nadir +2)
Candidates for salvage local therapy
No recurrence on CT or bone scan.
PSAM PET
March 2017 - August 2018, 208 - enrolled in the study open for 13 m: 35 had PB

PB  - July 20, 1998 - August, 2018, 6380 patients had PB at the BCCA
1349 had follow up PSA recorded during the same time
81 had PSA recurrence. (35/81 recurrences had PSMA PET)
Med FU was 7y
Med time to recurrence 50 m

RESULTS
68.6% - local recurrence
   80% base, 31% mid prostate and 11% apex
37.1% had SV recurrence
34.3% had nodal recurrence and
28.6% had distant metastases.
70 y IR PCa 2012
T1c, GS (3+4) = 7 (6/10 cores) iPSA 9.4.
LBL, LML, RB RA
The delay: thymoma treatment.
LDR PB 2014.

PSA nadir 2015
PSA failure 2016
PSA Nov 2018 - 5.6.
PSMA PET scan shows local recurrence
US – MR- PSMA PET fusion
Post op CT

LDR salvage - excellent dose distribution
The call of the buffalo
Conclusions

Long term outcomes in PB are mostly based on LDR

New definition of PSA PB failure - based on LDR

LDR is evolving with imaging (MRI and US)

Planning and Dose painting with LDR is feasible

Toxicity can be reduced with careful planning

OR skills will be important for both LDR and HDR
Institutional preference

Cost
- Cost of seeds
- Cost of replacing the source
- Cost of OR
- OR time
- Cost of Staff
- Physicist in the OR

Technique

Toxicity
- Dose control
- Disease bulk (SV involvement)

Have both?
- LDR monotherapy
- HDR Boost

Perception that HDR is easier to do?
Less toxicity?
A Phase III Randomized Study of Low Dose Rate compared to High Dose Rate Prostate Brachytherapy for Favorable Risk and Low Tier Intermediate Risk Prostate Cancer

HDR advantages
- Dose optimization
- Critical organ doses control
- Radioprotection - patients and staff
- Low α/β ratio HDR is cost-effective

HDR disadvantages
- Efficacy equivalent has not been established in clinical trials
- HDR shorter fu

Objective:
- QOL
- PSA nadir
- Biopsy at 36Mo

LDR PSA PFS ~ 90-95% at 5-10 years
HDR x4: PSA RFS at 5 years > 93%
HDR x1-2 - immature results

27Gy/2#
**Clinical Investigation**

**Time Course and Accumulated Risk of Severe Urinary Adverse Events After High- Versus Low-Dose-Rate Prostate Brachytherapy With or Without External Beam Radiation Therapy**

Jonathan D. Tward, MD, PhD,* Stephanie Jarosek, RN,† Haitao Chu, MD, PhD,‡ Cameron Thorpe, BS,§ Dennis C. Shrieve, MD, PhD,* and Sean Elliott, MD, MS†

*Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah; and †University of Minnesota, Minneapolis, Minnesota

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**LDR vs. HDR toxicity in SEER Database**

LDR ~12000  
HDR ~680  
LDR + EBR~ 8500  
HDR +EBRT~ 2400

**FU 4.3 y**  
Greatest risk at 2y,  
No new toxicity beyond 4 years

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**NNT to Harm:**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDR</td>
<td>52</td>
</tr>
<tr>
<td>HDR</td>
<td>26</td>
</tr>
<tr>
<td>LDR+EBRT</td>
<td>12</td>
</tr>
<tr>
<td>HDR+EBRT</td>
<td>8</td>
</tr>
</tbody>
</table>

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**Fig. 1.** Weighted cumulative incidence of grade 3 urinary adverse events by treatment. *Abbreviations: HDR = high-dose-rate brachytherapy; HDRBEAM = high-dose-rate brachytherapy with external beam radiation therapy; LDR = low-dose-rate brachytherapy; LDRBEAM = low-dose-rate brachytherapy with external beam radiation therapy.*
QUALITY - To furnish with the knowledge, skill or other accomplishments necessary for a purpose......A high level of value or excellence

Undetectable PSA (cure)
No/minimal side effect

Quality is easy to conceptualize, but difficult to quantitate
Department of VA
Office of Inspector General
Report No. 09-02815-143

- Patient selection
- US and contouring
- Planning
- Procedure - OR
- Dosimetry
- Outcomes
- Program structure and procedures
- Individual efforts

May 3, 2010 VA
APPLICATION FOR ACCREDITATION OF AN AREA OF FOCUSED COMPETENCE PROGRAM IN BRACHYTHERAPY

This questionnaire is to provide the Royal College with a complete description of the AFC program. The completed questionnaire must be signed by the AFC director and submitted to the decanal unit within the faculty of medicine responsible for oversight of AFC programs.
RESIDENT SCHOLARSHIP PROGRAM

Highlights from the 2017 HDR LDR Prostate Workshop

Anna Likhacheva, MD, MPH
Banner MD Anderson Cancer Center

2017 HDR LDR PROSTATE WORKSHOP FACULTY
The voyage of discovery is not in seeking new landscape but in having new eyes.

Marcel Proust