HDR vs. LDR
Is One Better Than The Other?

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Learning Objectives

• Indications for prostate brachytherapy
• Identify pros/cons of HDR vs LDR prostate brachytherapy
• Prostate Brachytherapy
  – Superior form of conformal radiotherapy
  – Tightest achievable dose distribution of any modern radiotherapy treatment
  – Allows for dose escalation far beyond what is safe with EBRT alone
For EBRT and BT the clinical target volume (CTV) is generally defined as the prostate +/- SV (depending on risk) plus a small margin – to encompass potential ECE for example.

- For EBRT an additional margin of 3-7mm is typically added to create the planning target volume (PTV) to which the radiotherapy dose is prescribed.
- PTV accounts for target motion and daily setup inaccuracy so that we never miss the target.
- For BT (LDR or HDR) – there is no PTV margin, as the treatment moves with the prostate.
Prostate Brachytherapy Indications

NCCN guidelines v.2.2017

- **Monotherapy**
  - Very low risk patients with LE ≥ 20 yrs
  - Low-Risk patients with LE ≥10 yrs
  - “selected patients with low-volume intermediate risk cancers”

- **Brachy Boost + EBRT**
  - Intermediate-Risk
    - EBRT (40-50 Gy) + Brachy Boost ± ST-ADT (4-6 mos)
  - High-risk, Very High Risk
    - EBRT (40-50 Gy) + Brachy Boost ± LT-ADT (2-3 years)

- **Salvage of LR after radiation failure**
Patients with:
- A very large or very small prostate
- Symptoms of bladder outlet obstruction (high IPSS)
- Prior TURP

are more difficult to implant and may suffer increased risk of side effects.

- Neoadjuvant ADT may be used to shrink the prostate to an acceptable size.
  - However, increased toxicity would be expected from ADT and prostate size may not decline.

- Post-implant dosimetry should be performed to document the quality of the implant. (for LDR)
Brachytherapy Dose Recommendation

NCCN guidelines v 2.2017

- The recommended prescribed doses for LDR monotherapy
  - 145 Gy for I-125
  - 125 Gy for Pd-103.

- The corresponding boost doses after 40 to 50 Gy EBRT are:
  - 110 Gy for I-125
  - 90-100 Gy for Pd-103

- High-dose rate (HDR) brachytherapy can be used alone or in combination with EBRT (40–50 Gy) instead of LDR.

- Commonly used HDR boost regimens include:
  - 9.5 to 11.5 Gy x 2 fractions
  - 5.5 to 7.5 Gy x 3 fractions
  - 4.0 to 6.0 Gy x 4 fractions.

- A commonly used regimen for HDR monotherapy is:
  - 13.5 Gy x 2 fractions
 HDR vs. LDR

Clinical outcomes

• Efficacy and toxicity
  – No prospective randomized trials comparing HDR vs. LDR in either monotherapy or boost situations
  – Single modality prospective and retrospective single institution series show excellent and comparable oncologic outcomes and toxicity data for both methods
  – Retrospective series looking at toxicity data support shorter overall duration of acute GU toxicity for HDR vs LDR and similar rates of late toxicity
  – Clinical data has significantly longer FU with LDR given that HDR is much newer technique.
  – HDR monotherapy has excellent results with median FU in the 6-7 year range
LDR prostate brachytherapy
- Multiple small relatively weak radioactive sources are **permanently** implanted into the prostate through a TRUS guided, transperineal, interstitial approach.
- Sources are spatially arranged to deliver a specific dose to the prostate and limit doses to nearby organs at risk (bladder, rectum, urethra)
- Dose is delivered as the sources decay over relatively long period of time (2-10 months)

HDR prostate brachytherapy
- Hollow needles/catheters are placed into the prostate with a similar, TRUS-guided transperineal approach.
- Imaging and treatment planning is then performed
- Treatment is delivered by sending a single, high activity radiation source **temporarily** to different stopping positions in each needle to deliver a relative large dose of radiation to the prostate over several minutes.
Workflow

Logistics have a major influence on ability to deliver HDR

• LDR techniques
  – Pre-planned
  – Real-time planning
  – Can be delivered in any OR or surgery center (no special shielding required)

• HDR techniques
  – CT based dosimetry
  – US based dosimetry (real time)
    • Requires a shielded room for treatment delivery
My Current HDR workflow

- OR – 1.5 hours
  - General anesthesia induced, patient positioned, Foley placed and prepped
  - Fiducial markers, brachytherapy needles placed under TRUS guidance, template sutured to perineum and locked
  - Patient returned to supine position, recovered from anesthesia
- PACU – Fentanyl PCA started, 30-45 minutes observation by Anesthesia service
- CT simulation – 5-10 minutes
  - Scan reviewed, needles adjusted and re-scan if necessary
- HDR treatment planning/optimization/physics QA (1-1.5 hours)
- HDR treatment delivery (15-20 min)
- Implant removal under MAC (5 min)
- Recovery in PACU/discharge home (1-2 hours)
Optimal HDR workflow

Shielded Brachytherapy Suite

- In Room CT-on-rails
- US planning
- Entire procedure done while patient under anesthesia (2-2.5 hours)
  - Implant
  - Imaging
  - Planning/QA
  - Treatment Delivery
  - Implant removal
- 1-2 hours recovery in PACU
• HDR catheters are easy to visualize with TRUS
• Can be safely implanted outside the prostate capsule and into the seminal vesicles without the risk of seed migration
• HDR has potential for significantly improved dose coverage for known T3 disease
• While LDR dose is commonly prescribed up to 3mm outside the capsule, coverage of gross ECE and especially extensive SVI is limited due to potential migration of seed placed outside prostate or in SV
• Irregular geometry of TURP defect can be an issue for LDR
• There may be “missing tissue” where seeds should be implanted for optimal dose distribution
• The stable catheter matrix used in HDR and higher energy of the source gives more flexibility to provide better coverage while sparing the re-epithelialized mucosa of the TURP defect from hot spots
HDR vs LDR

Radionuclide Characteristics

- **LDR**
  - Most commonly uses $^{125}$I or $^{103}$Pd
  - Relatively lower energy
    - Source placement critical
    - No room shielding required

- **HDR**
  - Significantly higher energy source
    - Dosimetry more forgiving
    - Requires shielded room for treatment delivery

<table>
<thead>
<tr>
<th>Radio- nuclide</th>
<th>Half-life (days)</th>
<th>Average Energy (keV)</th>
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<tbody>
<tr>
<td>$^{125}$I</td>
<td>59.4</td>
<td>28.4</td>
</tr>
<tr>
<td>$^{103}$Pd</td>
<td>17.0</td>
<td>20.7</td>
</tr>
<tr>
<td>$^{131}$Cs</td>
<td>9.7</td>
<td>30.4</td>
</tr>
<tr>
<td>$^{192}$Ir</td>
<td>73.8</td>
<td>380</td>
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HDR provides multiparametric dose optimization through modulation of
- Needle geometry (placement)
- Dwell position
- Dwell time

Compared to LDR, HDR is “High Density”
- For the same size prostate typical HDR implant has 2x the number of dwell positions vs. LDR seeds
- Seeds are typically all the same strength, but the dwell time at each HDR position can be varied as a continuous variable

Most practitioners experienced with both techniques agree that this allows HDR planning to produce consistently more robust dose coverage and normal tissue sparing.
High-Dose-Rate Prostate Brachytherapy Consistently Results in High Quality Dosimetry

Evan C. White, MD, Mitchell R. Kamrava, MD, John Demarco, PhD, Sang-June Park, PhD, Pin-Chieh Wang, PhD, Oluwatosin Kayode, MS, Michael L. Steinberg, MD, and D. Jeffrey Demanes, MD

California Endocurietherapy at UCLA, Department of Radiation Oncology, David Geffen School of Medicine at the University of California at Los Angeles, Los Angeles, California


**Fig. 2.** First vs second implant dosimetry.
HDR vs LDR

Radiobiological considerations

Fractionation

- Most RT treatments are significantly fractionated
  - Give small doses repeated daily over several weeks
  - Takes advantage of:
    - Normal tissue damage repair
    - Redistribution of cancer cells into more radiosensitive phases of the cell cycle (G2-M)
    - Reoxygenation of the tumor
- $\alpha/\beta$ ratio used to describe the dose response of different tissues to radiation
  - Most tumors as well as early responding tissues (skin, mucosa) have an $\alpha/\beta$ ratio $\geq 10$
  - Most late-responding normal tissues (connective tissue, muscle, bladder, rectum) have an $\alpha/\beta$ ratio $\sim 3-5$
- When the $\alpha/\beta$ ratio of the Tumor is greater than surrounding normal tissues:
  - More fractionation increases BED to tumor $>\text{BED OARs}$
- When the $\alpha/\beta$ ratio of the Tumor is less than surrounding normal tissues
  - Hypofractionation increases BED to tumor $>\text{BED OARs}$
HDR vs LDR

Radiobiologic Considerations

Biologically equivalent dose (Gy)

Sample dose regimen
(Total Gy) / (# fractions) / (Gy per fraction)

HDR-BT boost, two sample schedules shown:
- sum of HDR-BT and CFRT
- sum of HDR-BT and HFRT

HDR-BT monotherapy
"modern" (i.e. post-2001) HFRT monotherapy
Dose escalated CFRT monotherapy

Higher BED theorized to improve outcome
Lower BED theorized to decrease toxicity

α/β

prostate cancer, per hypothetical reports
late-responding issues (i.e. for late toxicity)
early-responding issues (i.e. for early toxicity)
HDR vs LDR
Radiation Safety

• LDR treatment
  – Exposure to Staff
    • Room survey after procedure
  – Safety precautions for patient after implant
    • Condom use
    • Airports
    • Limiting exposure to children, pregnant women and partners

• HDR treatment
  – No exposure to staff
  – No radioactive material left inside patient
The dose in an LDR implant is planned precisely (whether preplanned, or optimized with real-time techniques in the OR),

However, during the lifetime of the dose delivery, anatomic changes can occur which have the potential to alter the 3D-dose delivery

- Edema from the implant which resolves during delivery
- Shrinkage of the gland from continued hormone effect of ongoing ADT in higher risk cases

With HDR, the dose is **fully delivered** within minutes to hours of simulation/planning

- More confidence that dose I see in the plan was delivered to where it was supposed to go
Both are excellent forms of conformal radiotherapy
Operator experience and training are crucial
LDR main advantages
  – Single procedure
  – No shielding required
  – Longer term data – especially for monotherapy
HDR main advantages
  – No radiation safety concerns for staff or family members
  – Can more reliably treat ECE/SVI
  – Immediate dose delivery and quicker resolution of acute side effects.
British Columbia Cancer Agency (2013-~2018)

- Phase 3 RCT
- Study Population: Unfavorable intermediate Risk and High Risk Prostate Cancer
- Both arms receive 46Gy/23Fx EBRT, Then randomized to:
  - LDR boost – $^{125}\text{I}$ – 115Gy
  - HDR boost – $^{192}\text{Ir}$ – 15Gy x 1
- Outcomes:
  - PSA recurrence free survival
  - QOL (EPIC, IPSS, IIEF) at 6 and 36 months
RTOG 0815 - recently closed to accrual
  - Phase 3 RCT
  - Study population: Intermediate Risk Prostate Cancer
    - Both arms receive Dose escalated RT with either:
      - EBRT alone (79.2 Gy @ 1.8Gy/Fx)
      - EBRT (45Gy/25Fx) + LDR boost (110Gy - $^{125}$I or 100Gy $^{103}$Pd)
      - EBRT (45Gy/25Fx) + HDR boost (10.5Gy x 2)
    - Randomized to:
      - Arm 1: RT alone
      - Arm 2: RT + 6 months ADT (anti-androgen + LHRH agonist/antagonist)
  - Outcome Measures:
    - OS advantage to adding ADT?
    - Effects of ADT on locoregional failure, distant metastasis, BRFS, PCSM
    - Estimation of magnitude of benefit of ADT with different RT modalities (EBRT alone, LDR or HDR boost)
    - HRQOL metrics

HDR vs. LDR – Ongoing studies
References

- NCCN Prostate Cancer Clinical Practice Guidelines, version 2.2017