HDR Brachytherapy I: Overview of Clinical Application and QA

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Disclosures

• Consultant, Varian Medical Systems

Learning Objectives

• To understand the clinical aspects of HDR brachytherapy, including common clinical indications, patient selection, and evolving evidence in support of this therapeutic modality
• To review current prominent clinical trials for HDR brachytherapy
Outline

- Common indications for HDR brachytherapy
- HDR versus LDR considerations
- HDR for Cervical Cancer
- HDR for Breast Cancer
- HDR for Prostate Cancer
- Image-guided HDR brachytherapy

Broad Use of HDR Brachytherapy

- Current evidence supports HDR brachytherapy for nearly all brachytherapy indications:
- Common indications in practice:
  - GYN (cervical, uterine, vaginal, vulvar)
  - Prostate (monotherapy or boost)
  - Breast (accelerated partial breast irradiation)
  - Sarcoma (boost or monotherapy)
  - Skin (definitive)
- Less common indications: penile, head and neck, rectal, esophagus, bronchial, intraoperative, other

LDR vs. HDR

<table>
<thead>
<tr>
<th>ADVANTAGES:</th>
<th>HDR</th>
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<tbody>
<tr>
<td>300 years of data</td>
<td>Outpatient treatment</td>
</tr>
<tr>
<td>Standardized dose</td>
<td>Short administration time</td>
</tr>
<tr>
<td>Standardized treatment plan</td>
<td>Standard source strength</td>
</tr>
<tr>
<td>Minimum two insertions</td>
<td>Source easily available</td>
</tr>
<tr>
<td>Maximum source strength</td>
<td>For conscious sedation feasible</td>
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<table>
<thead>
<tr>
<th>ADVANTAGES:</th>
<th>LDR</th>
</tr>
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<tbody>
<tr>
<td>Inpatient treatment</td>
<td>High risk of errors</td>
</tr>
<tr>
<td>Radiation exposure to staff</td>
<td>Extreme quality assurance</td>
</tr>
<tr>
<td>Limited by source strength</td>
<td>Convenience of treatment</td>
</tr>
<tr>
<td>Limited sources available</td>
<td>High patient satisfaction</td>
</tr>
<tr>
<td>Spinal or general anesthesia</td>
<td>Limitation to outpatient setting</td>
</tr>
<tr>
<td>Prolonged hospitalization</td>
<td>Treatment required on do of insertion</td>
</tr>
<tr>
<td>Need for anticoagulation</td>
<td>Caution with large tumors</td>
</tr>
<tr>
<td>Coagulating resolution</td>
<td>Caution with normal tissue dose</td>
</tr>
</tbody>
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Stewart & Viswanathan, Cancer 2006
Logistical Aspects of HDR Brachytherapy Clinical Practice

- Number of insertions and amount of physician and physicist time compared to LDR
  - Potential for interfering tasks from external beam radiation therapy & clinic
  - Higher scheduling burden for staff
- Optimization in planning offers both opportunity and risk
- Some treatment courses require twice daily treatment (e.g., interstitial cervix), with patient experience similar to LDR inpatient

Cochrane Review: HDR recommended over LDR for Cervical Cancer

- 4 clinical trials included in Cochrane database review and meta-analysis of LDR vs. HDR
  - 1265 patients
- No difference in:
  - OS, DSS, LC, nodal recurrence, distant recurrence
  - Bladder and rectosigmoid complications
- Small increase in small bowel complications with HDR (HR 3.37, 95% CI 1.06-10.72, p = 0.04)
- HDR recommended based on rigid immobilization, outpatient tx, convenience, accuracy

Something to Keep in Perspective: Psychological Trauma of Treatment

Posttraumatic Stress Disorder After High-Dose-Rate Brachytherapy for Cervical Cancer With 2 Fractions in 1 Application Under Spinal/Epidural Anesthesia: Incidence and Risk Factors

Kathrin Kirchheiner, MSc,*† Agnieszka Czajka-Pepi, MSc,* Elisabeth Fasano-Seliger, MSc, PhD,* Gisela Scharbert, MD,* Léonore Wetzel, MD,* René A. Hecq, MD, PhD,* Alina Sturza, MD,* Johannes C. Dimaoulas, MD,* Wolfgang Dör, DVM, PhD,* and Richard Pötter, MD, PhD,*†
PTSD Symptoms in Brachytherapy Patients

- 30% (15/50) with acute stress disorder
- 41% (20/49) PTSD symptoms 3 months after treatment
- Immobility between fractions the most stressful factor


HDR vs LDR Summarized

- Evidence for HDR in cervical and GYN cancers is established, growing in others
  - Most practitioners view HDR vs LDR controversy as resolved
- HDR offers some patient convenience advantages as well as technical advantages
  - But there are noted downsides
- Evidence in development for many indications where HDR is nearly fully established (e.g., breast and prostate)

Brief Review of Common Indications

- Cervical Cancer
- Breast Cancer
- Prostate Cancer
Patient Selection – Cervical Cancer

• Brachytherapy indicated for all patients receiving definitive therapy
• Integrated with EBRT for total treatment time ≤ 8 weeks
  – Allow time for shrinkage of bulky tumors from RT
• Intracavitary approach with tandem and ovoid or ring and tandem applicators common
• Interstitial implant for lower vaginal or pelvic sidewall involvement

HDR Doses for Cervical Cancer Brachytherapy

• HDR regimens with 45 Gy in 25 fractions:
  – 4 x 7 Gy; 5 x 6 Gy; 6 x 5 Gy; 5 x 5.5 Gy
• Worksheet available on ABS website to facilitate conversion of HDR fractions into EQD2 (Gy)
• OAR limits:
  – D2cc Bladder ≤ 90 Gy EQD2
  – D2cc Rectum ≤ 75 Gy EQD2
  – D2cc Sigmoid ≤ 75 Gy EQD2

Ongoing Trial: OUTBACK (Consolidative Chemotherapy)

Eligible patients

Randomisation

Max 6 weeks

Arm A – Control Arm
Consolidative Chemotherapy

Arm B – Intervention Arm
Consolidative Chemotherapy + Consolidative Brachytherapy

Follow-up for a minimum of 3 years
Concerning Trends in Cervical Cancer Brachytherapy Noncompliance

Omitting Brachytherapy Reduces Survival in Cervical Cancer

Brachytherapy is NOT Optional for Cervical Cancer

- Potential reasons for decline in brachytherapy utilization include:
  - Increasing use of IMRT
  - Decreased expertise
  - Failure of clinicians who lacked resources or expertise to refer out
- Many women currently not receiving adequate treatments
- Brachytherapy essential for cervical cancer treatment
Partial Breast HDR Brachytherapy

Patient Selection – Partial Breast

| American Brachytherapy Society acceptability criteria for APBI |
|---|---|---|
| **Criteria** | **ASTRO Suitable** | **ASTRO Cautionary** | **ASTRO Unsuitable** |
| Age | ≥50 year old | ≤50 year old | < 50 years |
| Size | ≤3 cm | ≥3 cm | > 3 cm |
| Histology | All invasive subtypes and DCIS | All invasive subtypes and DCIS | All invasive subtypes and DCIS |
| Estrogen Receptor | Positive/negative | Positive/negative | Positive/negative |
| Surgical Margins | Negative | Negative | Negative |
| Lymphovascular space invasion | Not present | Not present | Not present |
| Nodal Status | Negative | Negative | Negative |

ASTRO Consensus Statement 2013, Brachytherapy

| ASTRO Partial Breast Selection Criteria |
|---|---|---|
| **Factor** | **ASTRO Suitable** | **ASTRO Cautionary** |
| Patient Age | 50-59 years | ≤50 years |
| BRCA Mutation | Not present | Not present |
| Tumor Size | 2.1-3.0 cm | > 3 cm |
| Margins | Negative by ≥2 mm | Close (< 2 mm) |
| T Stage | T3:4 | T3:4 |
| LVSI | No | Limited/focal |
| ER Status | Positive | Negative |
| Multicentricity | Unicentric only | Present |
| Multifocality | Clinically multifocal, ≤2 cm² | Clinically multifocal, 2.1-3.0 cm² |
| Pure DCIS | Not allowed | ≤3 cm |
| EIC | Not allowed | ≤3 cm |
| Nodal Status | pN0 | pN0 pN1-3 |
| Treatment Factors | No neoadjuvant tx | Neoadjuvant tx |

ASTRO Consensus Statement 2013, Brachytherapy
APBI Technical Guidelines

- 34 Gy in 10 fractions twice daily
- PTV_Eval:
  - D90% ≥ 90%
  - V150 < 50 cm³; V200 < 10 cm³
- Skin dose < 145% of prescription

ABS Consensus Statement 2013, Brachytherapy

Notable APBI Clinical Trials

- NSABP B-39:
  - Randomized trial of WBI vs APBI for Stage 0-2 breast cancer after lumpectomy (≤ 3.0 cm)
  - 3DCRT and brachytherapy (interstitial or intracavitary) permitted
  - Primary results pending, high rate of 3DCRT
- Multilumen balloon overnight trial (Khan et al):
  - 4 x 7 Gy; 3 x 8.25 Gy; 2 x 10.5 Gy
  - Ongoing (Khan et al, Oncology 2013)

Breast APBI

- Results of B-39 pending
  - My own prediction is that HDR will likely survive even if APBI inferior to whole breast RT
- Shorter fractionation schedules appealing, trials ongoing
- Evidence base growing
Prostate HDR Brachytherapy

Prostate HDR Selection Criteria

- **Monotherapy:**
  - Stage I or Stage IIA (GS 6, PSA < 15 ng/mL or GS 7, PSA < 10 ng/mL)
  - HDR more flexible for large glands (> 60 cc) and extraprostatic extension

- **Boost (added to 40-50 Gy +/- ADT):**
  - Stage IIA and higher

NCCN guidelines Version 2.2014

Prostate HDR – Prescription Details

- **Monotherapy:** 13.5 Gy x 2 fractions (NCCN)
- **Boost:** 9.5-11.5 Gy x 2 fractions; 5.5-7.5 Gy x 3 fractions; 4.0-6.0 Gy x 4 fractions (NCCN)
- **Technical Details (per RTOG 0924):**
  - Transrectal u/s guidance
  - ≥ 14 treatment catheters
  - Active dwells only within PTV
  - V75% < 1cc for bladder and rectum
  - Urethra: V125% < 1cc; V150% = 0 cc; D10 < 118%
  - PTV: V100% ≥ 90%
  - TRUS based HDR delivered with TRUS probe in patients so dosimetry accurate
RTOG 0321: Combination HDR + EBRT

- First prospective, multi-institutional trial of prostate HDR brachytherapy and EBRT
- CT-based HDR brachytherapy (8.5 Gy x 2 fx) + 45 Gy EBRT
- 129 patients from 14 institutions
- Among 112 evaluable patients, 3 acute and 4 late grade 3+ GU/GI adverse events
- Showed that higher urethral dose, larger high dose volumes, lower dose homogeneity ➞ greater toxicities

Prostate HDR

- Data increasing for monotherapy
  - Data maturing for shorter schedules (e.g., 19 Gy x 1)
  - Current evidence strongest for: 9.5 Gy x 4 fractions
    - NCCN: 13.5 Gy x 2 fractions
- Trend towards shorter schedules for boost therapy
  - 15 Gy x 1 was chosen for RTOG 0924

Prostate HDR vs LDR

- HDR better for very large glands (> 60 cc)
- HDR okay for TURP defects
- HDR has potential to be cost effective
- Accuracy and optimization may be improved since source is afterloaded after needle placement
  - Needle migration is a concern
- But...LDR is a single episode of care
Image Guided HDR Brachytherapy

Image-guided HDR Brachytherapy

- Imaging increasingly used for applicator placement and 3D treatment planning
- MRI target definition and planning increasingly common for cervical cancer and prostate
- 3D treatment planning permits volume-based prescriptions and planning constraints (vs. point-based)
- Image-guidance may introduce time delays and more steps/locations that must be considered

Process Flow Analysis: Standard T&O Brachytherapy

- Can take 2-5 hours (Mayadev et al, ABS Annual Meeting 2013)
Integrated Image-Guided Brachytherapy Procedure Spaces

- All components in one room: table, anesthesia capability, HDR afterloader and shielding, imaging
- Permits rapid workflow
- Less opportunity for applicator motion or migration

Figure 1. CT on radioutherapy suite at the University of Virginia Cancer Center. The procedure table contains a computed tomography (CT) compatible insert and can accommodate leg stiffness, ultrasound attachments and an external fixture to hold applicators in place. Full anesthesia capability is available. The room is shielded for high-dose-rate treatment delivery, so all components of CT-based treatment planning and delivery can be performed without moving the patient.

Orcutt et al (Showalter), Future Oncology 2014

<table>
<thead>
<tr>
<th>UVA Rapid Workflow T&amp;O w/ integrated Sliding Gantry CT</th>
<th>Sliding Gantry CT Brachytherapy Suite</th>
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<tbody>
<tr>
<td>Radiology or MRI Simulator (Day before Brachytherapy)</td>
<td></td>
</tr>
<tr>
<td>Image Acquisition</td>
<td>Patient Registration &amp; Premedication</td>
</tr>
<tr>
<td>CTV Delineation</td>
<td>(if necessary)</td>
</tr>
<tr>
<td>Image processing and transfer using commercial image</td>
<td>Applicator Insertion</td>
</tr>
<tr>
<td>processing software and data interface</td>
<td>CT simulation for treatment planning</td>
</tr>
<tr>
<td></td>
<td>Treatment Delivery</td>
</tr>
<tr>
<td></td>
<td>Applicator Removal</td>
</tr>
<tr>
<td></td>
<td>Discharge</td>
</tr>
<tr>
<td>90-180 minutes patient time</td>
<td>60-90 minutes</td>
</tr>
<tr>
<td>15-30 minutes physician time</td>
<td></td>
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UVA CT-on-Rails HDR Suite Experience

- Tandem and ovoid case in 1-1.5 hours on average
- Interstitial case from placement to first treatment in 1.5 hours
- Ongoing trial of breast HDR brachytherapy IORT with multilumen balloon (12.5 Gy x 1)
- Efficient workflow
- No patient transfers with applicator in place
- Has required institutional choices for workflow related to complementary imaging

Orcutt et al. (Showalter), Future Oncology 2014; Jones et al. (Showalter), Brachytherapy 2014

Clinical Aspects of HDR Brachytherapy

- HDR brachytherapy has broad range of indications
- Strong evidence, with growing foundation for prostate and breast
- Image-guided brachytherapy increasingly used
- Logistical and process-based challenges important for safety and quality

Acknowledgements

- UVA Brachytherapy team:
  - Bruce Libby, PhD (physics)
  - Ray Van Ausdal, PhD (physics)
  - Tyler Watkins, PhD (physics)
  - Grace Moyer, CMD (dosimetry)
  - Donna Lash, RN (nursing)
- Stan Benedict, PhD (formerly at UVA)
Which of the following characteristics would place a patient into the “unsuitable” category for accelerated partial breast irradiation?

- Tumor size 2.5 cm (20%)
- Ductal carcinoma in situ (20%)
- Positive surgical margin (20%)
- Age 51 years (20%)
- Invasive lobular carcinoma (20%)

Answer

- Positive surgical margin is a criterion for the “unsuitable” category according to the ASTRO consensus guidelines for APBI.

Which dose-fractionation schedule is listed in NCCN guidelines as an option for prostate HDR brachytherapy when delivered as monotherapy?

- 13.5 Gy x 2 fractions (20%)
- 19 Gy x 1 fraction (20%)
- 7.25 Gy x 5 fractions (20%)
- 2.5 Gy x 28 fractions (20%)
- Trick question! HDR brachytherapy monotherapy is not listed in the NCCN guidelines!
Answer

• 13.5 Gy x 2 fractions is the fractionation schedule cited in the current NCCN guidelines. Note that this is 1 additional insertion beyond that required for LDR monotherapy.


Which of the following statements is true regarding comparisons of HDR versus LDR brachytherapy for locally advanced cervical cancer?

1. HDR and LDR brachytherapy have not been directly compared in any prospective clinical trials.
20%

2. There are no significant differences in tumor control or treatment related complications with the exception of a slight increase in small bowel complications with HDR.
20%

3. HDR brachytherapy has inferior local tumor control compared to LDR brachytherapy.
20%

4. HDR brachytherapy has similar tumor control rates, but dramatically worse outcomes for rectum, bladder and small bowel complications.
20%

5. LDR is better than HDR in all aspects that have been compared.
10%

Answer

• There are no significant differences in tumor control or treatment related complications with the exception of a slight increase in small bowel complications with HDR. The Cochrane Database review recommends HDR based on these findings and the additional advantages of HDR brachytherapy (outpatient, immobilization, etc).