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
ADVANTAGES:		
100 years of data Standardized doses Standardized treatment plan Standardized treatment time Maximum two insertions		Outpatient treatment Short administration time Standard source strength Source easily available IV conscious sedation feasible Reassess tumor size with multiple fractions Dose optimization of normal tissues Minimal staff exposure Applicator stabilized by board during treatment
DISADVANTAGES:		
Inpatient treatment Radiation exposure to staff Limited by source strength Limited sources available Spinal or general anesthesia Prolonged bedrest: *-Need for anticoagulation* *-Constipating medication* *-Need for inpatient pain control*		High risk of errors: *-Intense quality assurance* *-Intense maintenance* *-Intense physician/physicist time* >Two fractions required Treatment required on day of insertion Caution with large tumors Caution with normal tissue dose

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

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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

Liu et al, *The Cochrane Library* 2010

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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

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Int J Radiat Oncol Biol Phys, 2014

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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

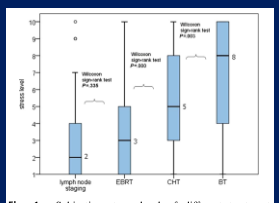


Fig. 1. Subjective stress level of different treatment modalities (1 = no stress, 10 = maximum stress). BT = brachytherapy; CHT = chemotherapy; EBRT = external beam radiation therapy.

Kirchheiner et al, *Int J Radiat Oncol Biol Phys* 2014

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

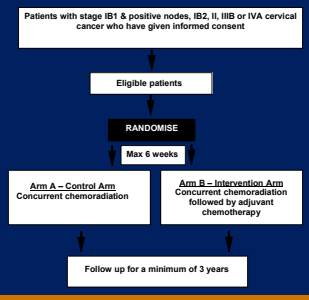
- Brachytherapy indicated for all patients receiving definitive therapy
- Integrated with EBRT for total treatment time ≤ 8 weeks
  - Allow time for shrinkage of bulky tumors from RT
- Intracavitary approach with tandem and ovoid or ring and tandem applicators common
- Interstitial implant for lower 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:
  - D_{2cc} Bladder ≤ 90 Gy EQD2
  - D_{2cc} Rectum ≤ 75 Gy EQD2
  - D_{2cc} Sigmoid ≤ 75 Gy EQD2

ABS guidelines 2012, *Brachytherapy*

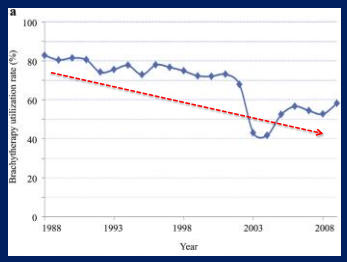
Ongoing Trial: OUTBACK (Consolidative Chemotherapy)



HDR Schedules permitted with 45 Gy EBRT:

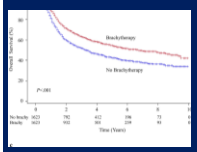
- 3 x 8.4 Gy
- 4 x 6.8 Gy
- 5 x 5.8 Gy

Concerning Trends in Cervical Cancer Brachytherapy Noncompliance

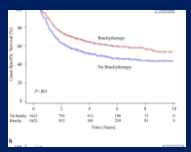


Han et al, *Int J Radiat Oncol Biol Phys* 2013

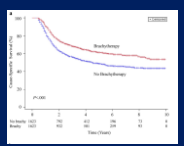
Omitting Brachytherapy Reduces Survival in Cervical Cancer



Cause-Specific Survival



Overall Survival



Non-Cancer-Related Survival

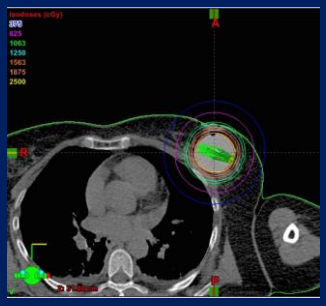
Han et al, *Int J Radiat Oncol Biol Phys* 2013

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

Tanderup et al, *Int J Radiat Oncol Biol Phys* 2014

Partial Breast HDR Brachytherapy



Patient Selection – Partial Breast

American Brachytherapy Society acceptability criteria for APBI	
Criteria	
Age	≥50 year old
Size	≤3 cm
Histology	All invasive subtypes and DCIS
Estrogen Receptor	Positive/negative
Surgical Margins	Negative
Lymphovascular space invasion	Not present
Nodal Status	Negative

ABS Consensus Statement 2013, *Brachytherapy*

ASTRO Partial Breast Selection Criteria			
Factor	**ASTRO Suitable**	**ASTRO Cautionary**	**ASTRO Unsuitable**
Patient Age	≥ 60 years	50-59 years	< 50 years
BRCA Mutation	Not present	Not present	Present
Tumor Size	≤ 2 cm	2.1-3.0 cm	> 3 cm
T Stage	T1	T0 or T2	T3-T4
Margins	Negative by ≥ 2mm	Close (< 2 mm)	Positive
Tumor Grade	Any	--	--
LVSI	No	Limited/focal	Extensive
ER Status	Positive	Negative	Negative
Multicentricity	Unicentric only	--	Present
Multifocality	Clinically unifocal, size ≤ 2 cm^3	Clinically unifocal, 2.1-3.0 cm^3	Clinically multifocal or > 3.0 cm^3
Pure DCIS	Not allowed	≤ 3 cm	> 3 cm
EIC	Not alllowed	≤ 3 cm	> 3 cm
Nodal Status	pN0	pN0	pN1-pN3
Treatment Factors	No neoadjuvant tx	No neoadjuvant tx	Neoadjuvant tx

ASTRO Consensus Statement 2009, *Int J Radiat Oncl Biol Phys*

APBI Technical Guidelines

- 34 Gy in 10 fractions twice daily
- PTV_Eval:
  - D90% ≥ 90%
  - V150 < 50 cm^3; V200 < 10 cm^3
- Skin dose < 145% of prescription

ABS Consensus Statement 2013, *Brachytherapy*

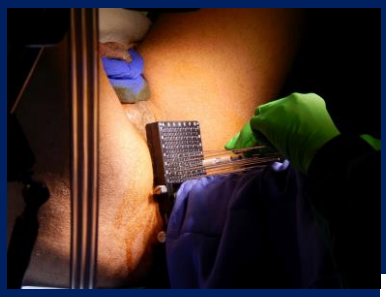
Notable APBI Clinical Trials

- 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

Hsu et al, *Int J Radiat Oncol Biol Phys* 2010, *Practical Radiation Oncology* 2014

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

Clinic/Nursing Station	Procedure Room	CT Simulator	Radiology or MRI Simulator	Shielded HDR Delivery Vault
Patient Registration & Premedication (if necessary)				
	Applicator Insertion			
Waiting		CT simulation for treatment planning		
Waiting			MRI or PET/CT if requested	
Waiting				Treatment Delivery
Discharge	Applicator Removal			
100-160 minutes	20-45 minutes	30-45 minutes	90-180 minutes	20 minutes

*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-rails brachytherapy suite at the University of Virginia Cancer Center. The procedure table contains a computed tomography (CT)-compatible insert and can accommodate leg stirrups, ultrasound attachments and an external fixator 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

UVA Rapid Workflow T&O w/ integrated Sliding Gantry CT

Radiology or MRI Simulator (Day before Brachytherapy)	Sliding Gantry CT Brachytherapy Suite
Image Acquisition CTV Delineation Image processing and transfer using commercial image-processing software and data interface	Patient Registration & Premedication (if necessary) Applicator Insertion CT simulation for treatment planning Treatment Delivery Applicator Removal Discharge
90-180 minutes patient time 15-30 minutes physician time	60-90 minutes

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?

20% 1. Tumor size 2.5 cm
20% 2. Ductal carcinoma in situ
20% 3. Positive surgical margin
20% 4. Age 51 years
20% 5. Invasive lobular carcinoma

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Answer

- Positive surgical margin is a criterion for the "unsuitable" category according to the ASTRO consensus guidelines for APBI
- Smith et al., Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *Int J Radiat Oncol Biol Phys* 2009;74(4):987-1001.

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

20% 1. 13.5 Gy x 2 fractions
20% 2. 19 Gy x 1 fraction
20% 3. 7.25 Gy x 5 fractions
20% 4. 2.5 Gy x 28 fractions
20% 5. Trick question! HDR brachytherapy monotherapy is not listed in the NCCN guidelines!

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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.
- Reference: NCCN Clinical Practice Guidelines in Oncology, Prostate Cancer. Version 2.2014.

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

20% 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.

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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, immmobilization, etc).
- Reference: Wang et al., High dose rate versus low dose rate intracavity brachytherapy for locally advanced uterine cervix cancer (Review). *Cochrane Library* 2010