UCSF
University of California
San Francisco

No Beam Required! HDR Brachytherapy for Prostate Cancer

2020 UCSF Mini Medical School

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Learning Objectives

- Understand basic elements of prostate cancer anatomy, presentation, diagnosis and work-up
- Describe different techniques for treating prostate cancer with radiation
- Understand advantages of brachytherapy
- Become familiar with UCSF's unique approach to HDR prostate brachytherapy

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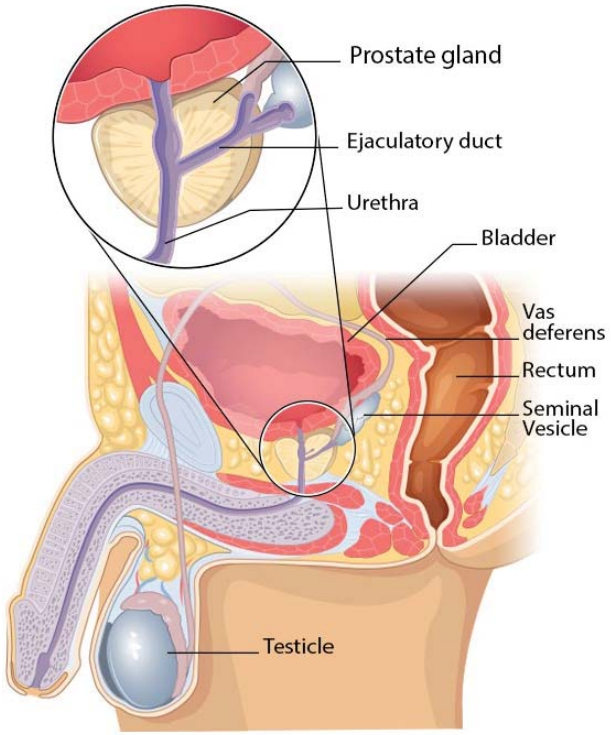
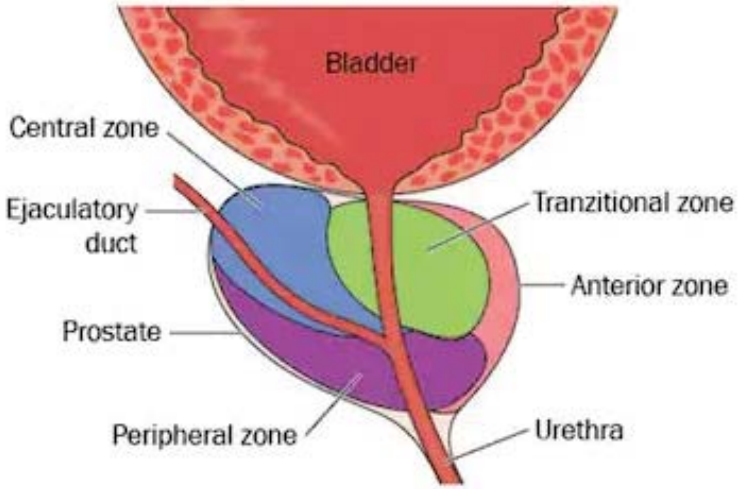
Case presentation

- A 65 year-old healthy, asymptomatic man presents with a screening serum prostate specific antigen (PSA) value of 6. He has no urinary complaints, and he takes no medications except tadalafil on occasion for erectile dysfunction.

Normal Prostate: Anatomy





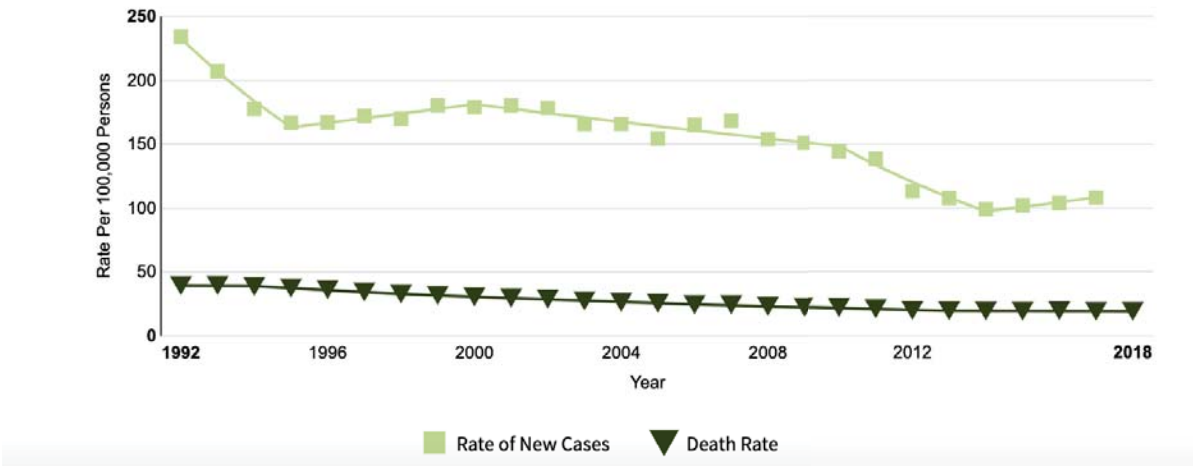
Epidemiology of Prostate Cancer

- Lifetime risk = 1 in 6 for men (the most common non-skin cancer in men)

Estimated New Cases in 2020	191,930
% of All New Cancer Cases	10.6%

Estimated Deaths in 2020	33,330
% of All Cancer Deaths	5.5%

5-Year Relative Survival
97.8%
2010–2016

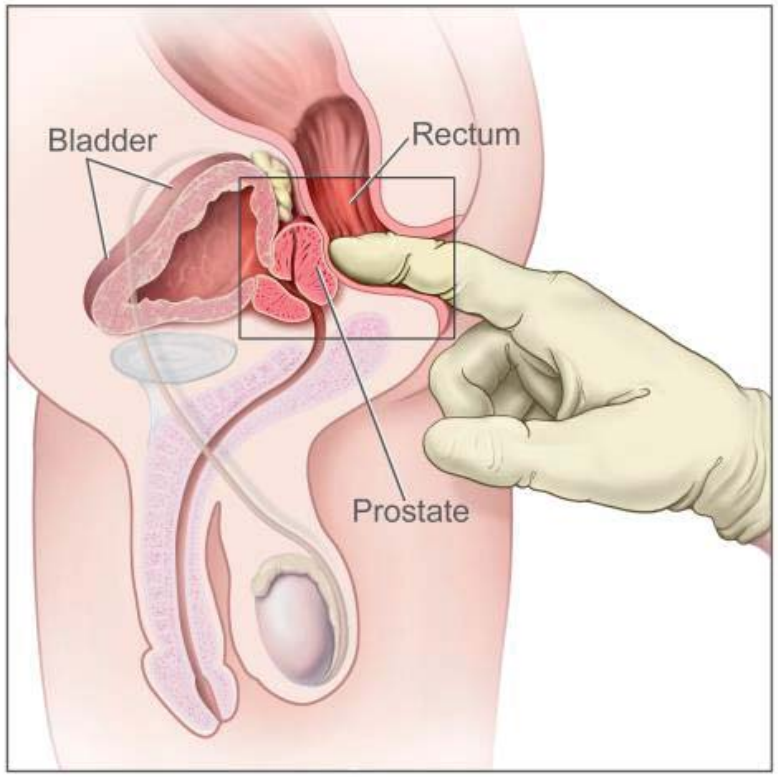


Seigel et al , CA: a cancer journal for clinicians 2020
Image from SEER.

Case presentation

- He is referred to a urologist, who performs digital rectal exam revealing a medium-sized prostate with subtle left-sided firmness. A prostate MRI is obtained, demonstrating a 1 cm in the left midgland, without evidence of cancer growth outside the prostate or spread to pelvic lymph nodes.

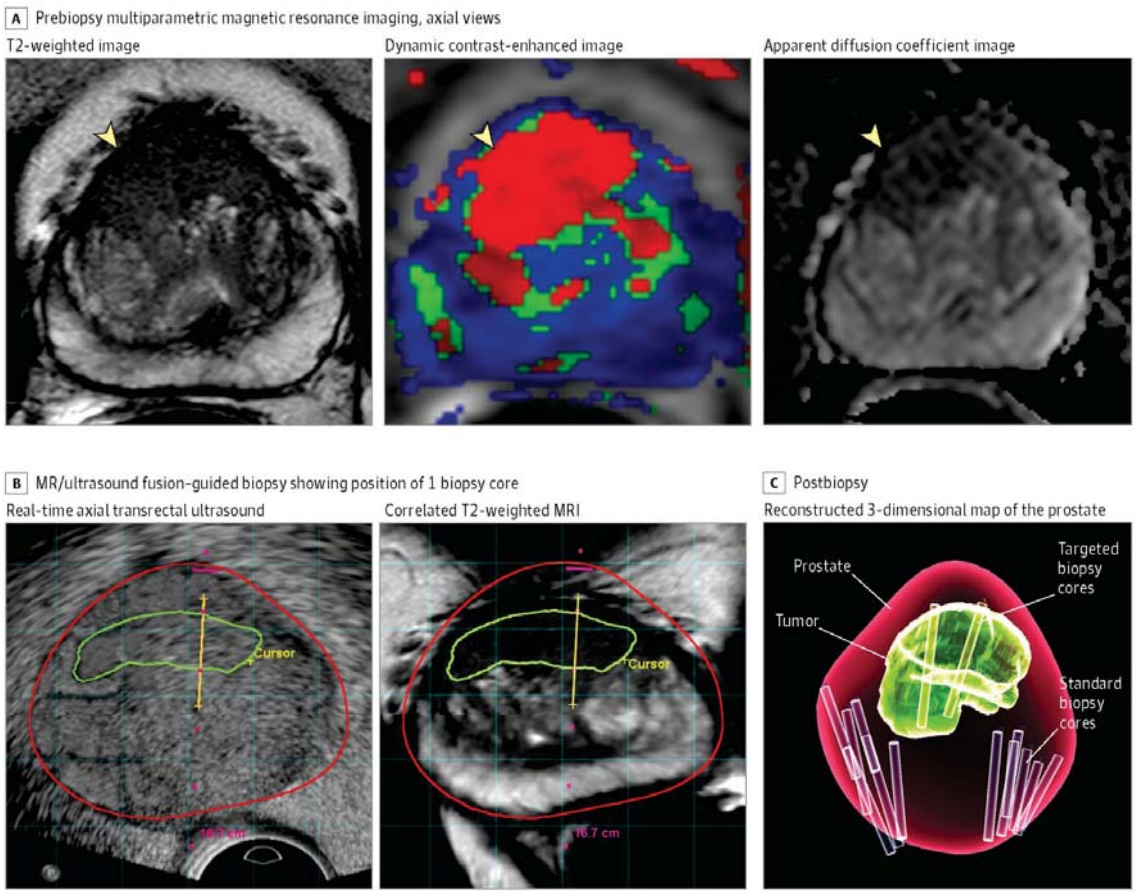
Clinical Staging: Digital Rectal Exam



T0	no evidence of primary tumor
T1	*clinically inapparent* (palpation)
T1a	incidental finding, ≤ 5%
T1b	incidental finding, > 5%
T1c	found on diagnostic biopsy
T2	*clinically apparent*, confined within prostate
T2a	≤ ½ of one lobe
T2b	> ½ of one lobe
T2c	both lobes
T3	*extends outside of prostate*
T3a	extra-capsular extension
T3b	seminal vesicle involvement
T4	fixed or invades external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

Image from wholelifeprostate.com

Prostate MRI

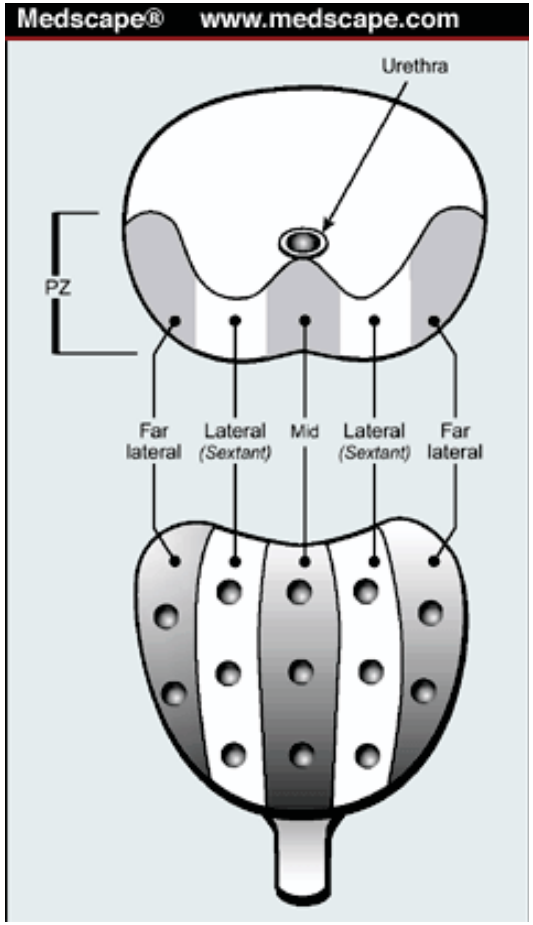


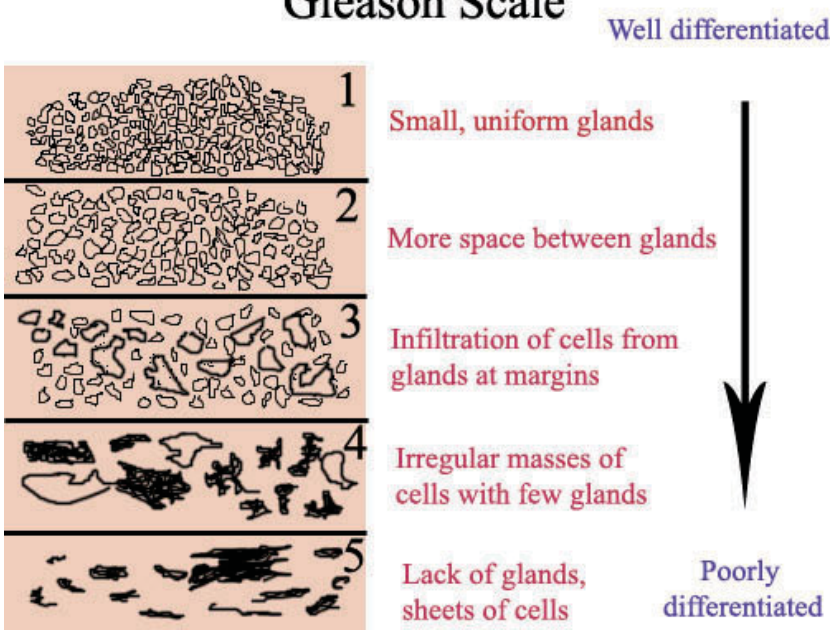
Siddiqui et al, JAMA 2015

Case presentation

- Transrectal ultrasound-guided prostate biopsy demonstrates prostate cancer (Gleason Score 3+4/Gleason Grade 2) in 3 of 16 biopsy samples

Biopsy: Gleason Score is a measure of prostate cancer aggresiveness





The Gleason score = major + minor pattern
Ex: 3+3, 3+4, 4+4, 5+4, etc

Case presentation

- His initial work-up and staging is complete. He is a 65 year-old man with newly diagnosed favorable intermediate-risk prostate cancer (PSA 6, cT2aN0, GS 3+4 with 3/16 cores positive).

- His treatment options include active surveillance, radiation therapy, and radical prostatectomy. He is referred to a radiation oncologist for further discussion.

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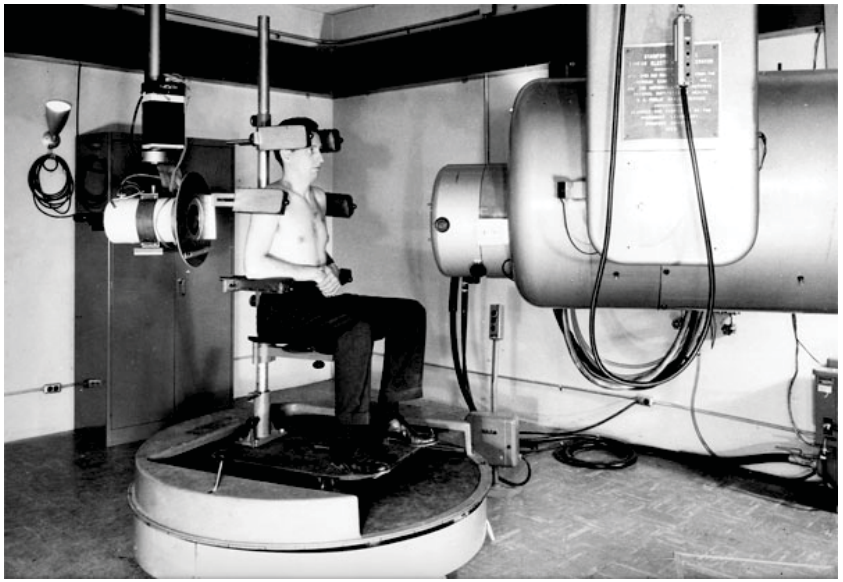
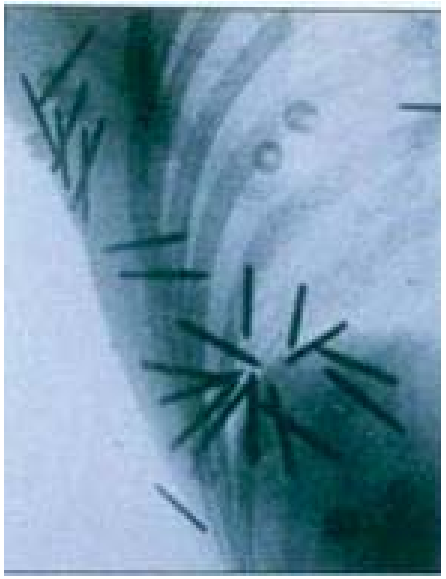
Radiation Therapy: Teletherapy vs Brachytherapy

Teletherapy
"Healing from a long distance"
External beam radiotherapy
Linear Accelerator '1.0'

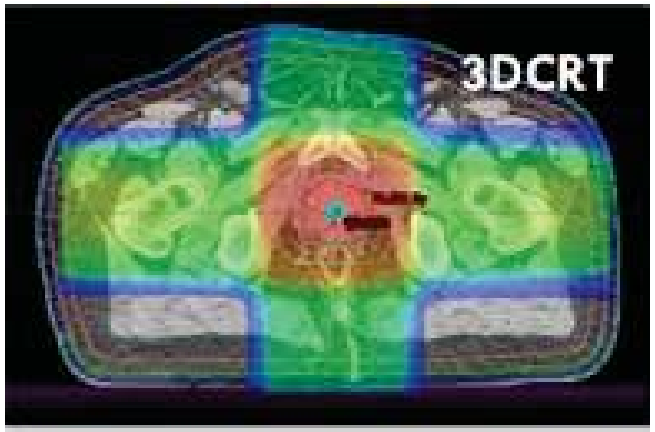


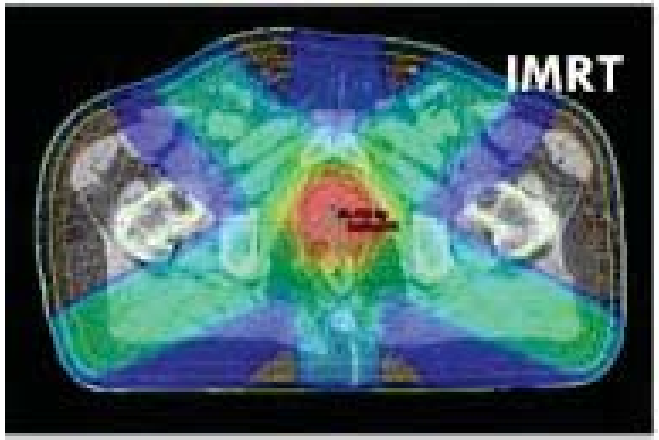
Brachytherapy
"Healing from a short distance"
Placing radioactive sources into tumor
Radium Needle

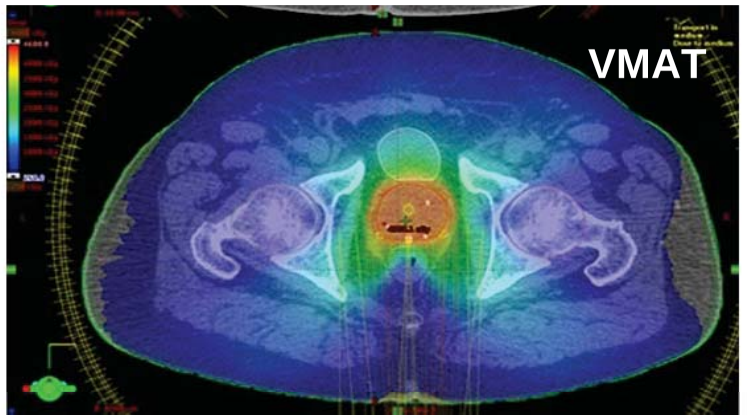


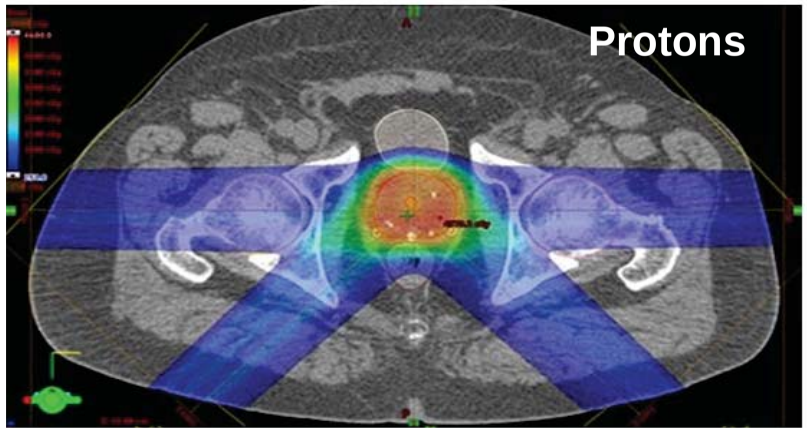
- Underlying goal of radiation oncology: Deliver therapeutic dose of radiation to the tumor while minimizing exposure to adjacent normal tissue

Teletherapy: External Beam Radiation Therapy









- External beam radiation therapy involves directing a beam of photons (X-rays) or particles (protons, carbon ions) at the tumor from outside the body. Typical EBRT plans use multiple beams or arcs converging on the target to deliver therapeutic radiation dose to the tumor

Prostate Cancer External Beam Radiation Therapy

- Randomized clinical trials have established that increasing the total radiation dose delivered (dose escalation) improves prostate cancer cure rates

- More recent trials have shown that the total dose of radiation may be reduced without losing efficacy by delivering a higher dose of radiation with each fraction (hypofractionation)

- Modern EBRT schedules for definitive treatment of prostate cancer include:
  - Conventional fractionation: 78-81 Gy in 1.8-2 Gy fractions over 8-9 weeks
  - Moderate hypofractionation: 60-70 Gy in 2.5-3.1 Gy fractions over 4-6 weeks
  - Ultrahypofractionation: 36.25-42 Gy in 6.1-8 Gy fractions over 1-2 weeks

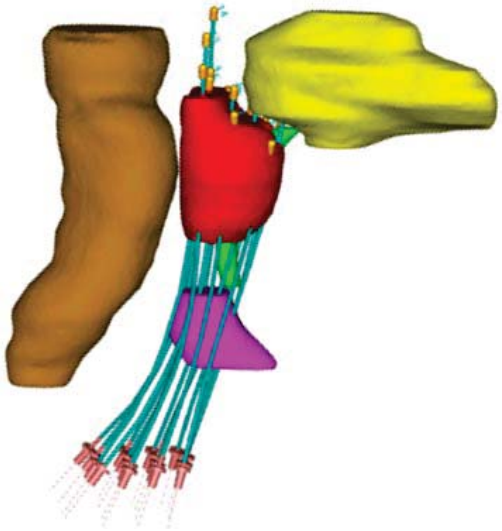
- Our patient with intermediate-risk prostate cancer, treated with any of the above EBRT regimens, would be expected to have an 85-95% cure rate at 5 years, with <5% risk of long-term severe (grade 3+) toxicity.

Prostate Cancer Brachytherapy

- Two types of brachytherapy are used for prostate cancer:

Low dose rate (LDR)
Permanent radioactive seed implantation
LDR means <2 Gy delivered per hour
Common prescription dose:
Monotherapy: 145 Gy
Boost with EBRT: 110 Gy

High dose rate (HDR)
Temporary radioactive seed implantation
HDR means >12 Gy delivered per hour
Common prescription dose:
Monotherapy: 27 Gy in 2 fractions
Boost with EBRT: 15 Gy in 1 fraction



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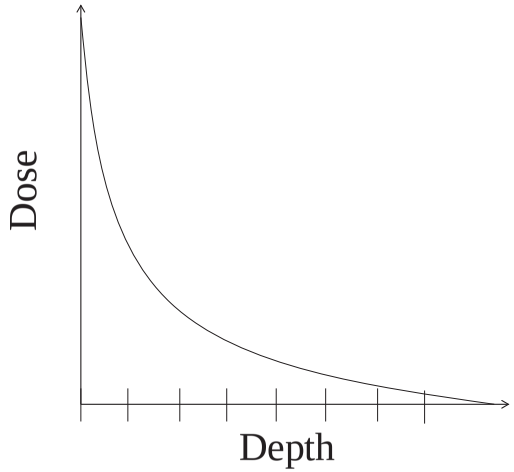
Brachytherapy

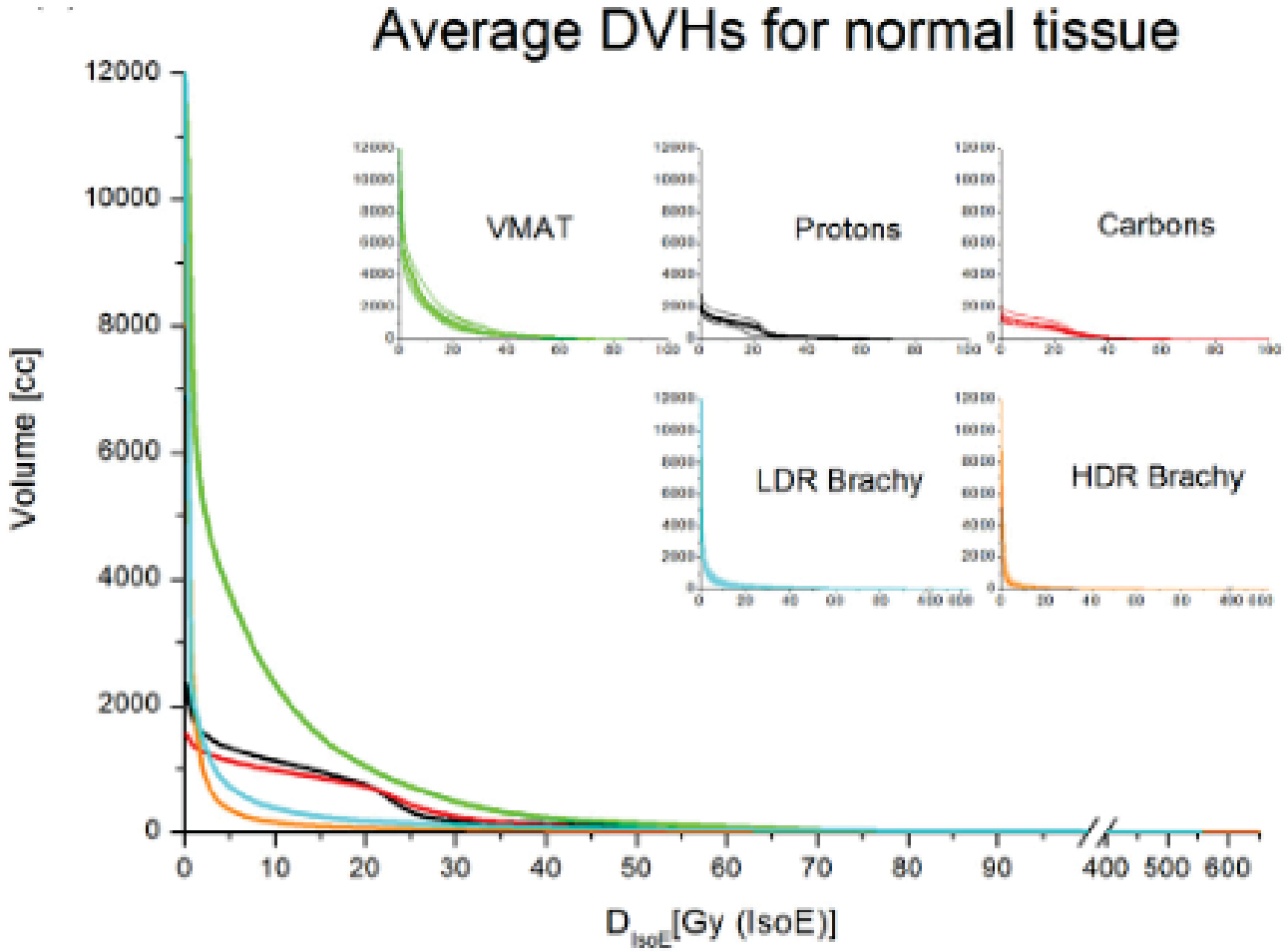
- In the setting of prostate brachytherapy, the radiation source is radionuclide-based
  - LDR brachytherapy: ^{125}I, ^{103}Pd, or ^{131}Cs
  - HDR brachytherapy: ^{192}Ir
- By taking advantage of the inverse-square law, brachytherapy enables delivery of large, ablative radiation dose to tumor while minimizing exposure to adjacent normal tissue
- The properties of brachytherapy are particularly advantageous for treating prostate cancer, which responds to dose escalation and is located directly adjacent to several critical organs (bladder, rectum, urethra, neurovascular bundles)



Brachytherapy vs EBRT: Overview

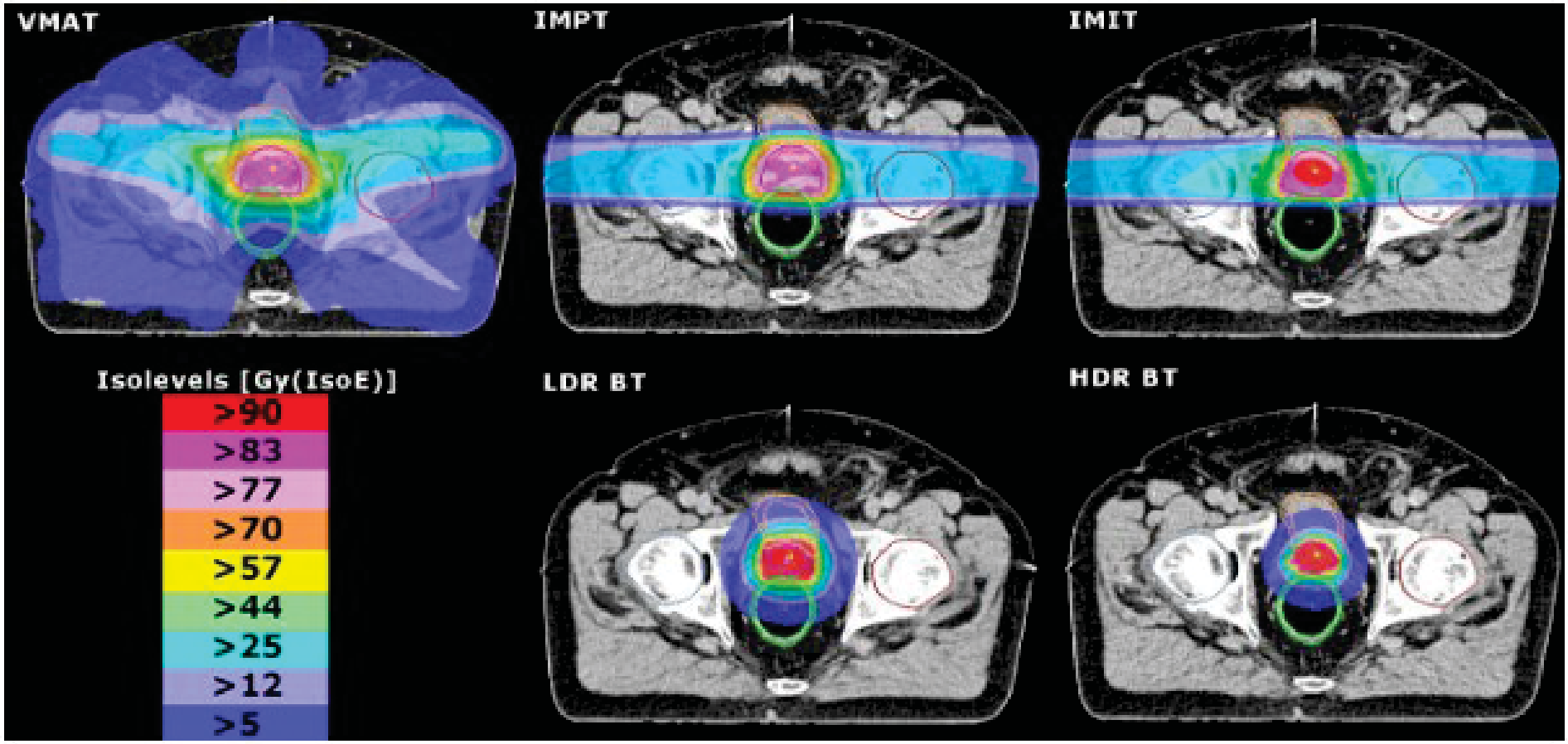
- Brachytherapy provides several advantages over EBRT for treating prostate cancer:
  - Permits extreme radiation dose escalation
  - Reduces radiation exposure to surrounding normal tissue
  - Removes intra- and inter-fraction uncertainty in radiation dose delivery
  - Treatment complete in 1-2 visits, compared to ~45 visits over 9 weeks for conventionally fractionated EBRT, improving patient convenience and reducing healthcare costs
  - Clinical studies indicate brachytherapy improves chance of long-term prostate cancer cure compared to treatment with EBRT alone

Brachytherapy vs EBRT: Dosimetric comparison



Georg et al, IJROBP 2013

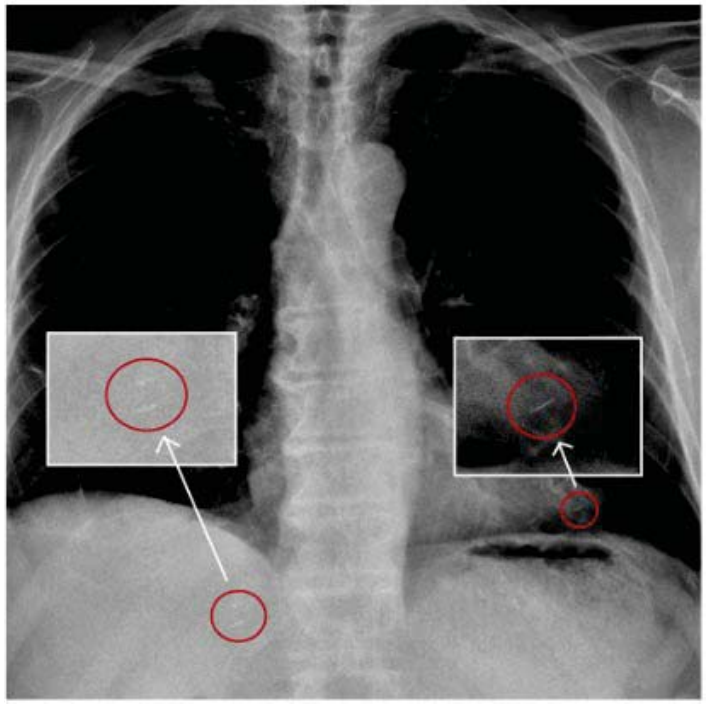
Brachytherapy vs EBRT: Dosimetric comparison



Georg et al, IJROBP 2013

HDR vs LDR Prostate Brachytherapy

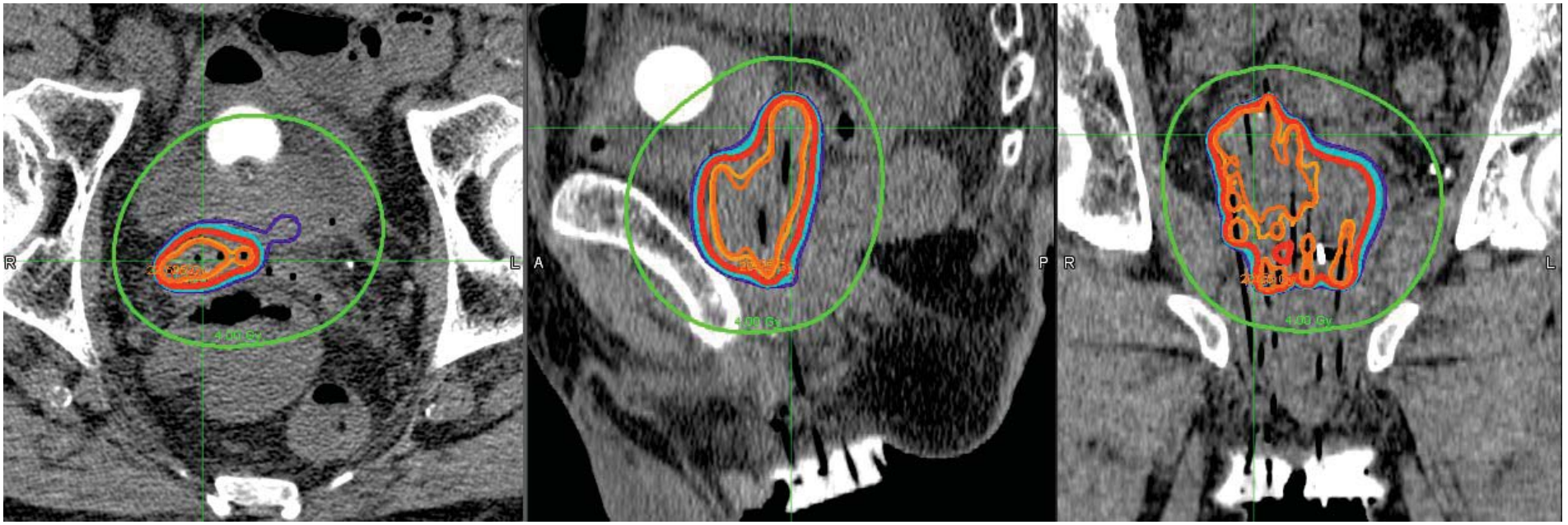
- HDR prostate brachytherapy provides several advantages over LDR brachytherapy
  - More advanced techniques for shaping radiation dose, escalating dose to tumor and reducing dose to normal tissue (bladder, rectum, urethra)
  - No need for pre-implant and post-implant dosimetry
  - Clinical studies suggest lower rates of urethral scarring after HDR brachytherapy compared to LDR
  - No restriction on ability to spend time in close proximity to pregnant women and young children after treatment
  - No possibility of seed migration or embolization



Maletzki et al, Prostate International 2018

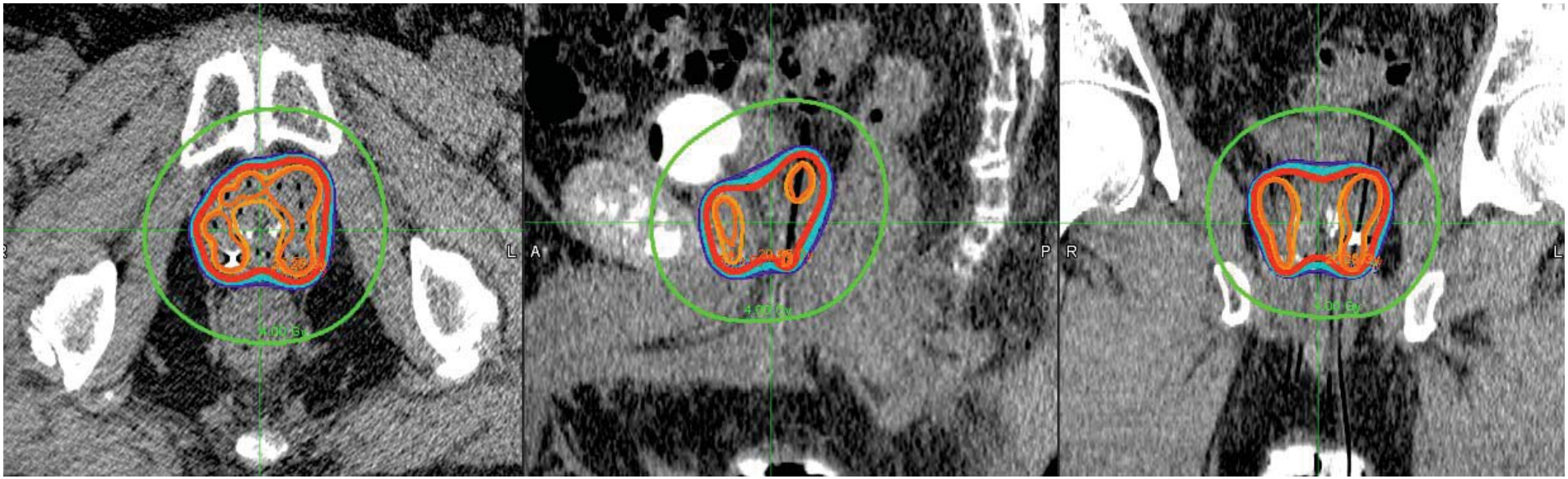
HDR vs LDR Prostate Brachytherapy

- HDR prostate brachytherapy provides several advantages over LDR brachytherapy
  - Ability to treat areas of extracapsular extension and seminal vesicle invasion



HDR vs LDR Prostate Brachytherapy

- HDR prostate brachytherapy provides several advantages over LDR brachytherapy
  - Ability to treat anterior tumors or large prostates with pubic arch interference



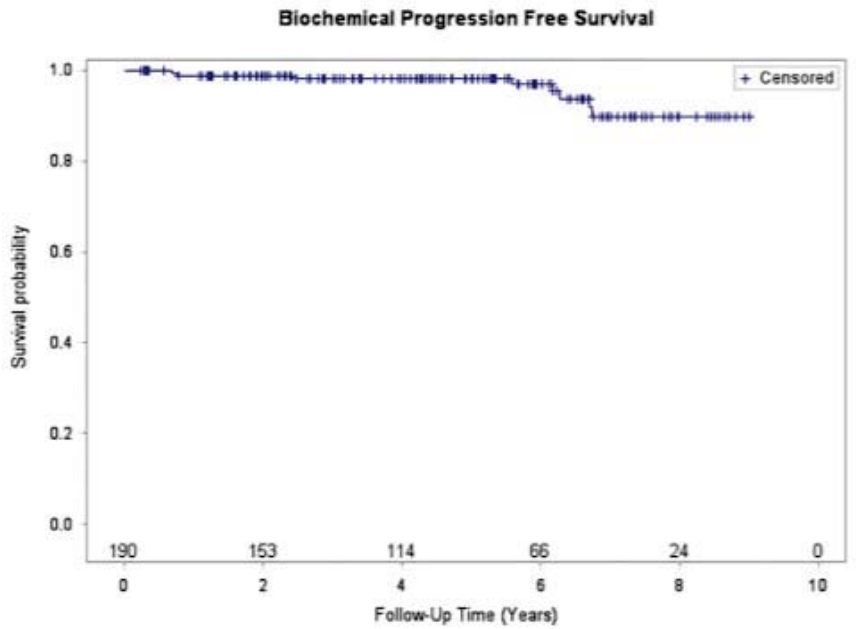
HDR prostate brachytherapy clinical outcomes: monotherapy

- HDR prostate brachytherapy monotherapy outcomes for intermediate-risk disease
  - UCLA retrospective study

Gleason score	2%, 5
	24%, 3 + 3
	62%, 3 + 4
	12%, 4 + 3
Clinical T stage	72%, T1c
	20%, T2a
	7%, T2b
	1%, T2c
Median % cores positive	25% (range, 6–100)
Risk stratification[a]	62% Favorable
	38% Unfavorable

Late (≥6 months) genitourinary and gastrointestinal toxicities (CTCAE v4.0)

Grade	*n* (%)
Genitourinary toxicities	
G0	65 (34.2)
G1	69 (36.3)
G2	36 (18.9)
G3	7 (3.7)
Unknown	13 (6.8)
Gastrointestinal toxicities	
G0	165 (86.8)
G1	12 (6.3)
G2	2 (1.1)
G3	0 (0)
Unknown	11 (5.8)

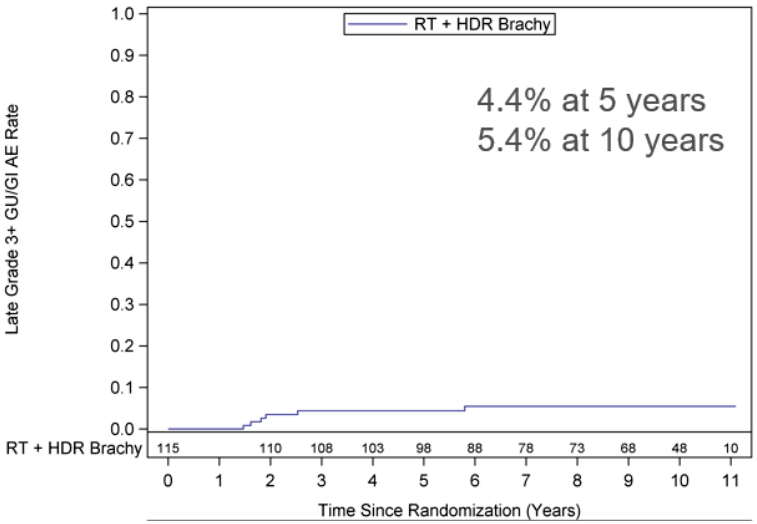


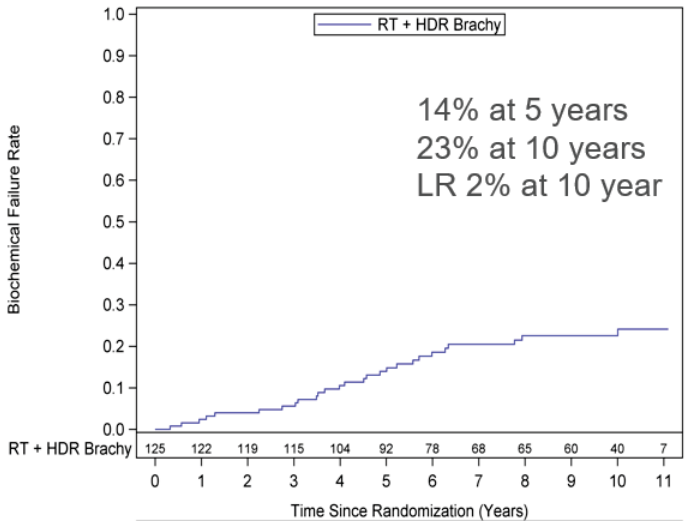
Patel et al, Brachytherapy 2017

HDR brachytherapy clinical outcomes: EBRT+brachytherapy boost

- HDR prostate brachytherapy boost outcomes for intermediate/high-risk disease
  - NRG RTOG 0321 Phase 2 prospective trial

PSA	≤10 10-20	70% 30%
Gleason Score	2-6 7 8-10	10% 72% 18%
T Stage	T1c-T2c T3a-T3b	91% 9%
Hormonal Therapy *	No Yes	57% 43%

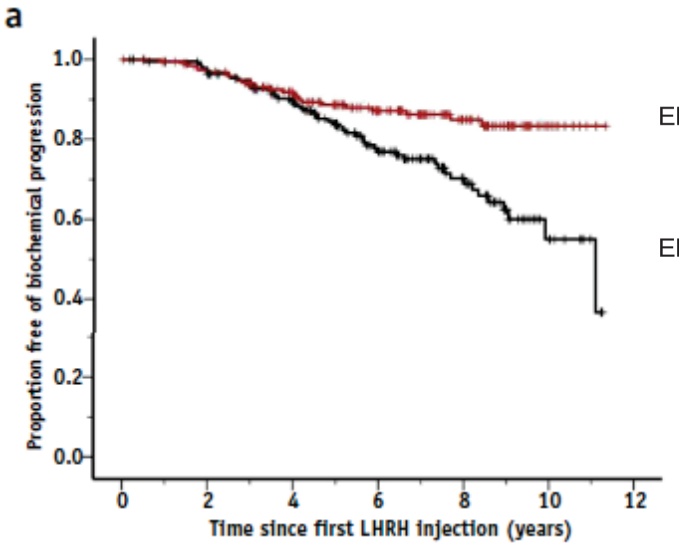




Courtesy of Dr. I.C. Hsu

EBRT alone vs EBRT+brachytherapy boost

- LDR prostate brachytherapy boost outcomes for intermediate/high-risk disease
  - ASCENDE-RT Phase 3 clinical trial



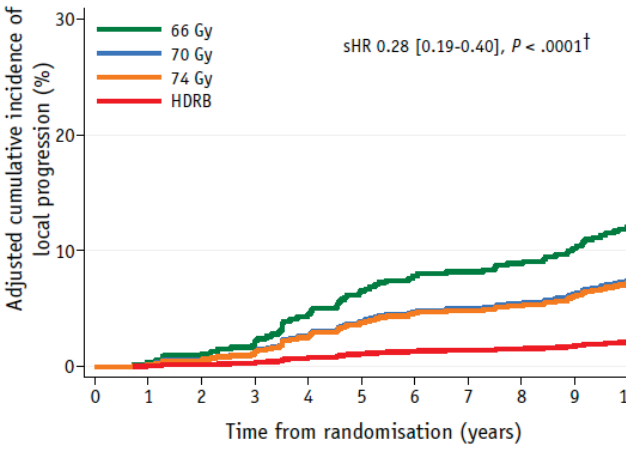
Numbers at risk:

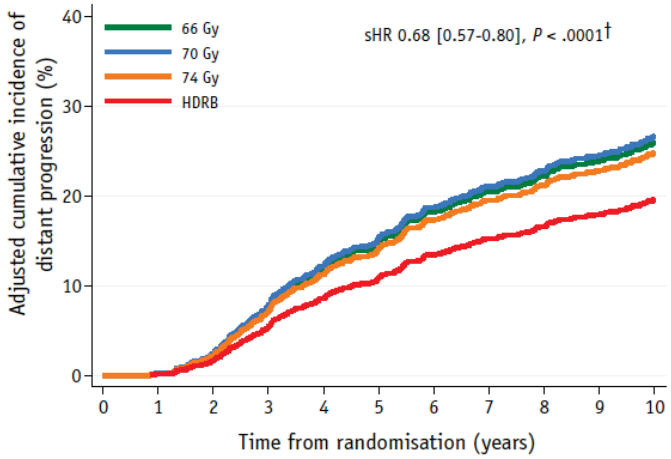
Time (yrs)	0	2	3	4	5	6	7	8	9	10
DE-EBRT	200	186	168	145	119	93	74	52	27	11
LDR-PB	198	184	168	147	127	106	86	59	38	14

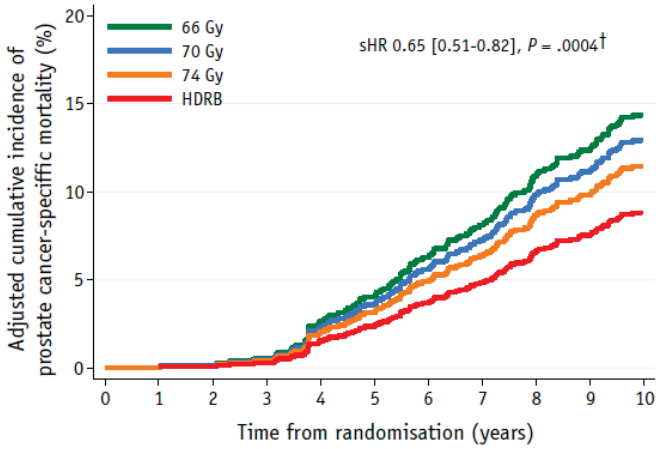
Morris et al, IJROBP 2018

EBRT alone vs EBRT+brachytherapy boost

- HDR prostate brachytherapy boost outcomes for intermediate/high-risk disease
  - TROG RADAR 03.04 Phase 3 clinical trial







Joseph et al, IJROBP 2020

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Brief History of Prostate Brachytherapy

- 1913: First described by Pasteu and Degrais
- Brought into regular use by Hugh Hampton Young (*also developed radical perineal prostatectomy*)
- 1915: Early cases using transperineal radium needles, reported by Barringer in 1924
- 1983: Introduction of image-guided (ultrasound-based) transperineal prostate brachytherapy by Holm et al.

Early Brachytherapy: Results

- Young noted:

> This article is not intended to speak of ultimate results, but we may safely say here that truly astonishing results have been obtained in some cases: disappearance of obstruction, shrinkage and great softening of certain cancers of the prostate, and extensive retrogressive changes in inoperable cancers of the bladder. Fairly large amounts of radium, in high con-

- Barringer at Memorial Hospital in New York reported on a case series (n=46) in 1924:
  - Transperineal radium needles placed under digital guidance.
  - Outcomes were poor, with local control of only 10% (per the report, "*no gross evidence of active carcinoma*"); however, only **2% of patients (n=1) had disease confined to the prostate**

Young HH, Frontz WA, J Urology 1917
Barringer BS, Ann Surg 1924
Holm et al, Urology 1990

Early Brachytherapy: Technique

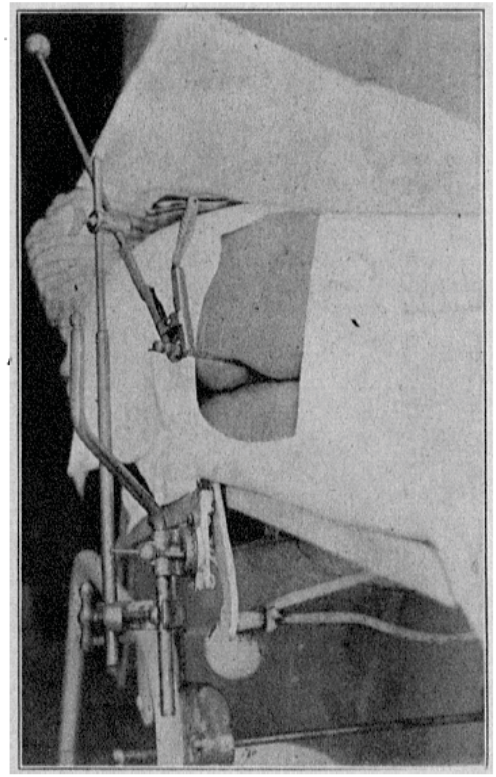


Fig. 16.—Mechanical hand in use in treating cancer of seminal vesicles and prostate through rectum.

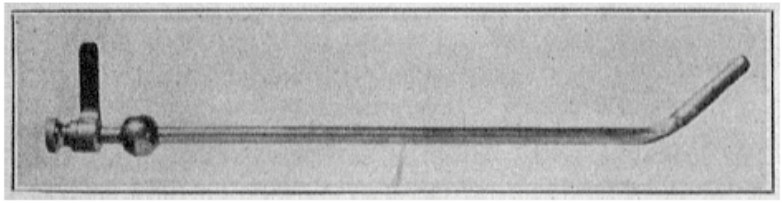


Fig. 3.—Author's Cystoscopic Radium Instrument 1 carrying a tube of radium in fenestrated platinum capsule in beak; closed with obturator.

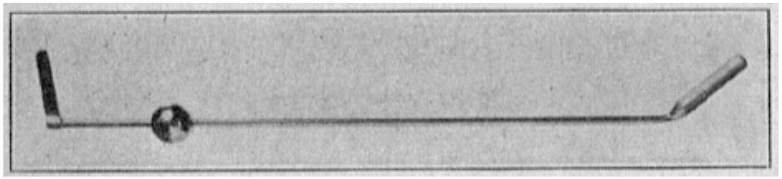


Fig. 15.—Rectal radium carrier, applied under direction of index finger in rectum, and held in place by mechanical hand or clamp.

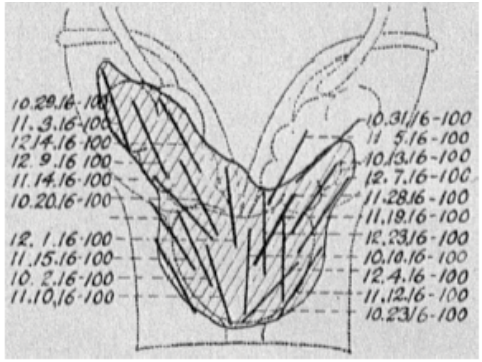


Fig. 17.—A case of cancer of the prostate and left seminal vesicle (right vesicle slightly involved). The radium treatments, each representing 100 milligram-hours, are shown, and the date of each is recorded.

Young HH, Frontz WA, J Urology 1917

History: Brachytherapy Developments

- 1983: Introduction of image-guided (ultrasound-based) transperineal prostate brachytherapy by Holm et al., and later developments in biplanar imaging.

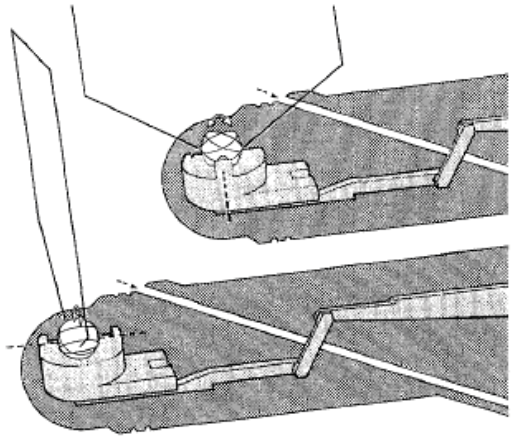
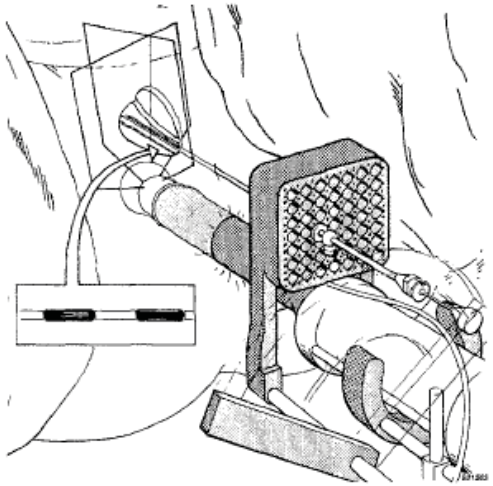


FIGURE 1. *Principle of multiplanar scanning. Top: Crystal sweeps back and forth in longitudinal mode. Bottom: Crystal sweeps from side to side in transverse mode. Arrows indicate puncture canal for transrectal biopsy (not used for seed-implantation).*

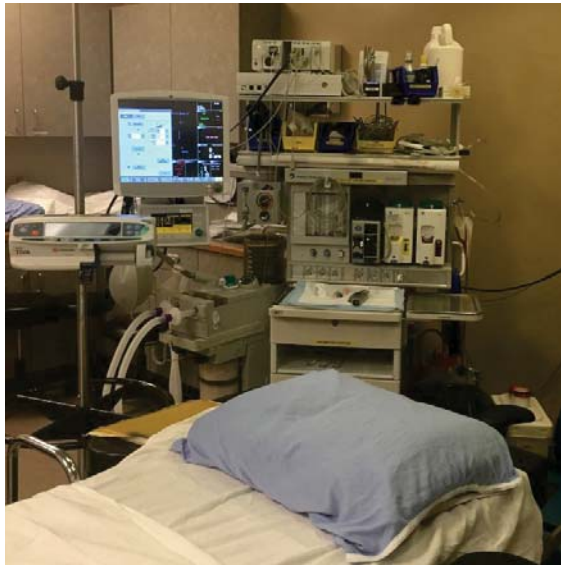


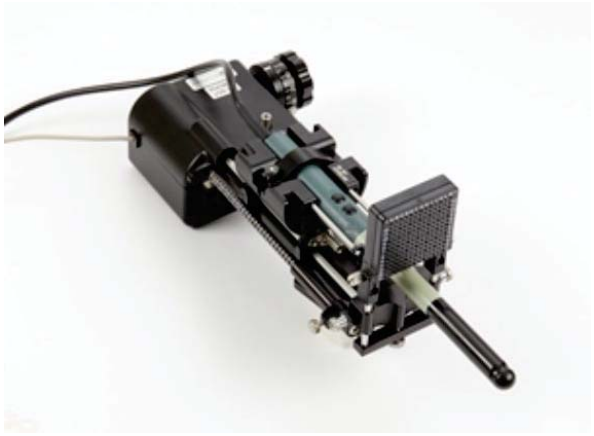
The HDR Prostate Team

- Dosimetrists
- Urologists
- Recovery Room RNs
- …

Courtesy of Deidre Betchelar

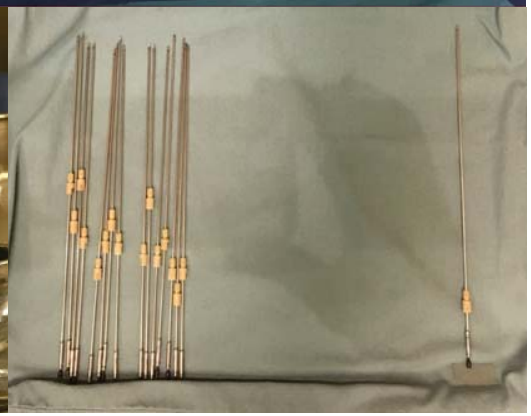
Equipment





Equipment

Equipment



HDR Prostate Supply Prep Checklist

We Bring to OR:

- ☐ Brachy Prostate Pack
- ☐ Prostate Cart
- ☐ Prolene Sutures x2
- ☐ Gold Seed Markers/Acculocs
  - ☐ Check for prior placement
- ☐ US manipulating arm
- ☐ US arm base
- ☐ US unit(w/prostate probe)
- ☐ Endocavity water standoff kit:
  - Tape for water channel
- ☐ Alcohol Gauze Jar
- ☐ 16 ISI Sterile Leur lock Catheter needles
- ☐ 4 pillows
- ☐ Dental putty in separate containers:
  - 1 scoop putty base
  - 1 scoop putty activator
- ☐ Paint pen
- ☐ Sterile marker & ruler
- ☐ Red catheter numbers
- ☐ Aquaplast grids (3 x 4.5cm aprox.)
- ☐ Striker stretcher ordered for OR by 4pm the day before.
- ☐ Patient's chart
  - Copy of brachy consent
  - Copy of procedure consent
  - HDR Prostate yellow Rx sheet
  - Radiation Oncology Admission History
  - Pathology
  - Volume Study Notes
  - Prior Acculocs?
- ☐ Sterilized friction cuffs.
- ☐ Copy of Updated Procedure
- ☐ Camera
- ☐ Catheter cutter/extra blades
- ☐ Stepper Drape
- ☐ Syringe and saline
- ☐ Zip sealed bag for patient supplies
- ☐ Pink styrofoam
- ☐ Hovermat w/ pump
- ☐ Betadine paint brush
- ☐ DVI cable

OR will Supply:

- ☐ Sterile gloves for Dr.
- ☐ Sterile instrument pack
  - Scissors
  - Needle driver
  - Pickups
  - Towel clamps
- ☐ Sterile H2O/ Saline for probe cover
- ☐ OR table
- ☐ OR Fluoro (If needed)
- ☐ Foley Catheter
- ☐ Contrast
- ☐ Cystoscope w/ 180 degree rotation

Urologist: _____

Number: _____

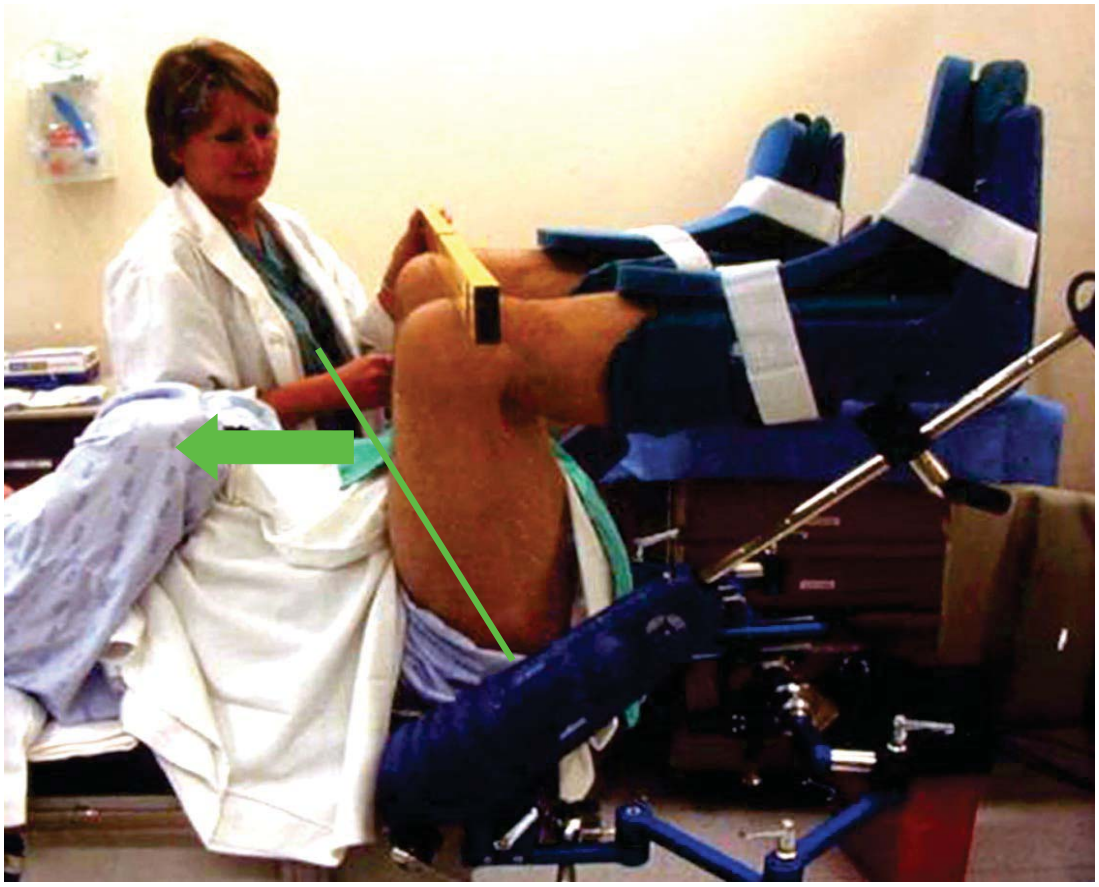
Date of Marker Placement: _____

Prior external radiation: Y or N

Courtesy J Zoberi, Washington University

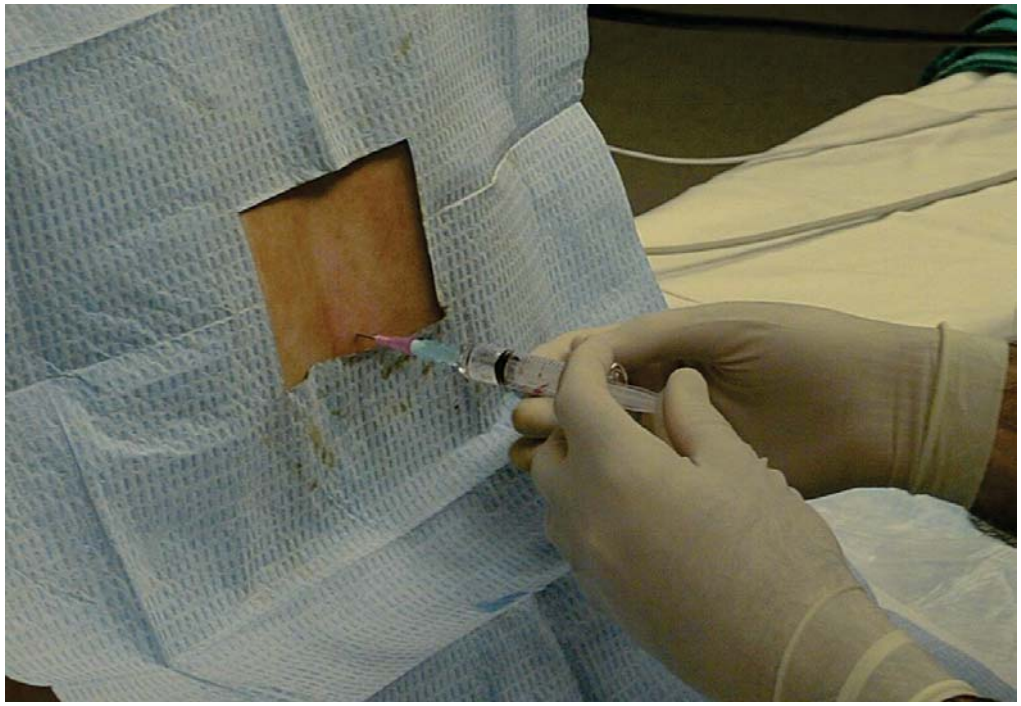
HDR Brachytherapy Workflow: Setup & Patient Positioning

Setup → Implant → Image acquisition → Needle detection → Contouring → Planning → Treatment



HDR Brachytherapy Workflow: Anesthesia – Regional or General

Spinal or Epidural

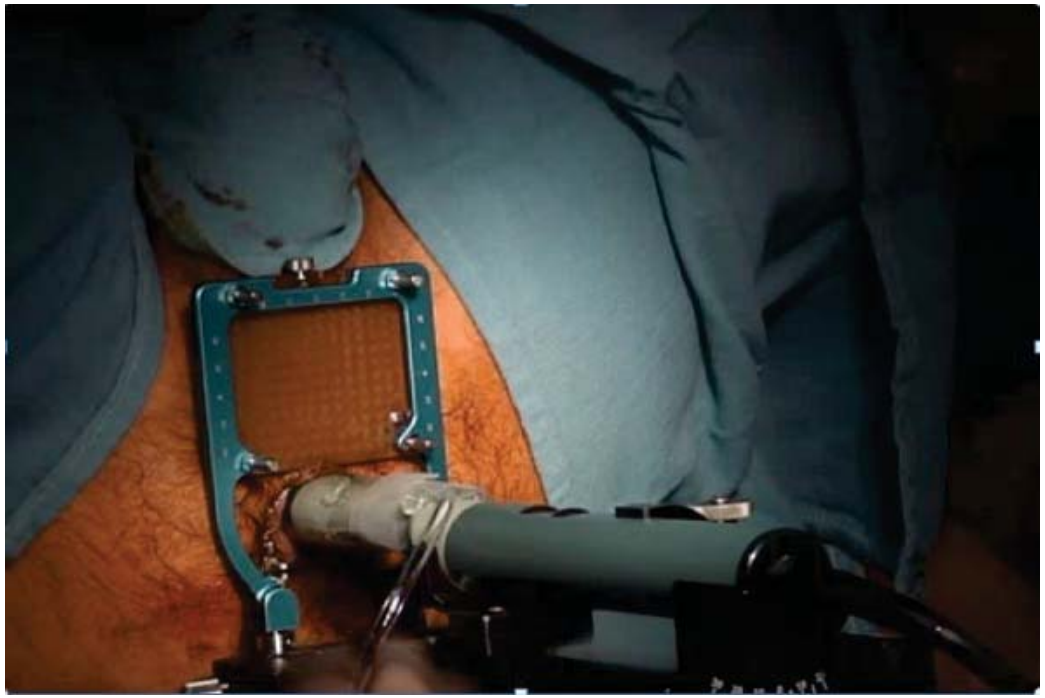


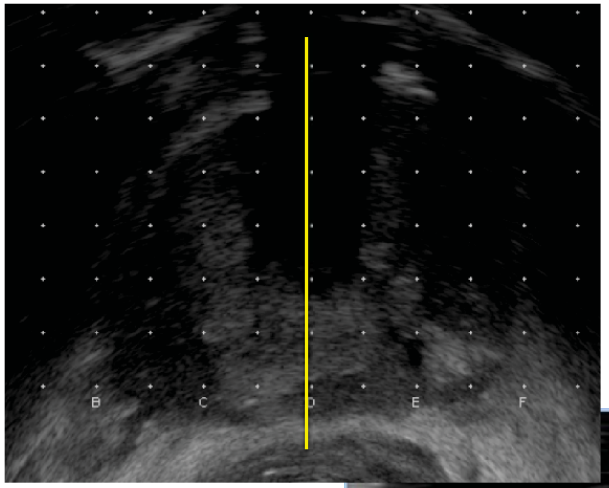
General

FJ Tornetta School of Anesthesia

HDR Brachytherapy Workflow: Implant setup

Setup → **Implant** → Image acquisition → Needle detection → Contouring → Planning → Treatment

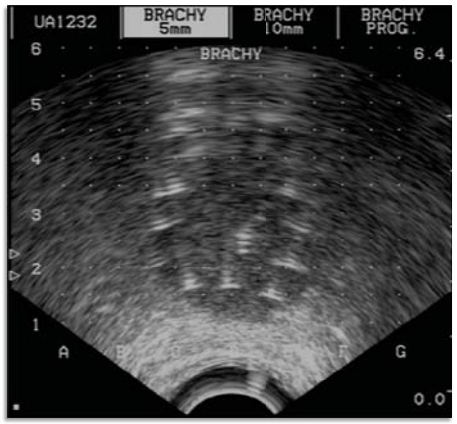


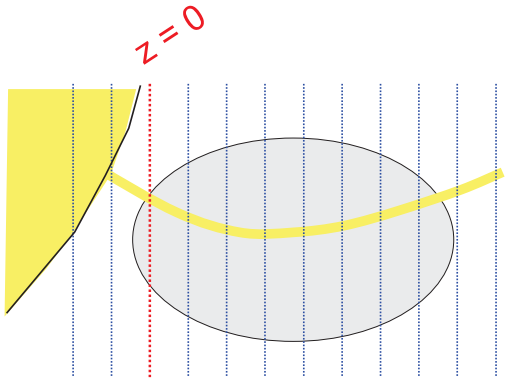


HDR Brachytherapy Workflow: Image Aquisition

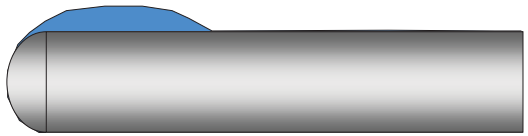
Setup → Implant → **Image acquisition** → Needle detection → Contouring → Planning → Treatment

Transversal image acquisition (2D)

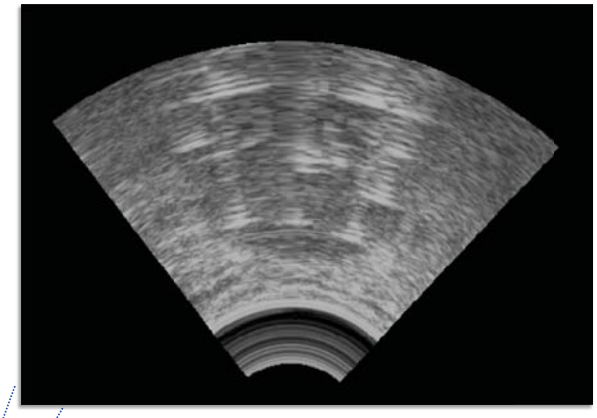


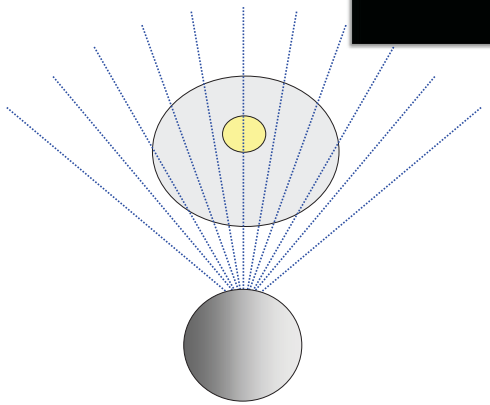


Δz=2.5mm

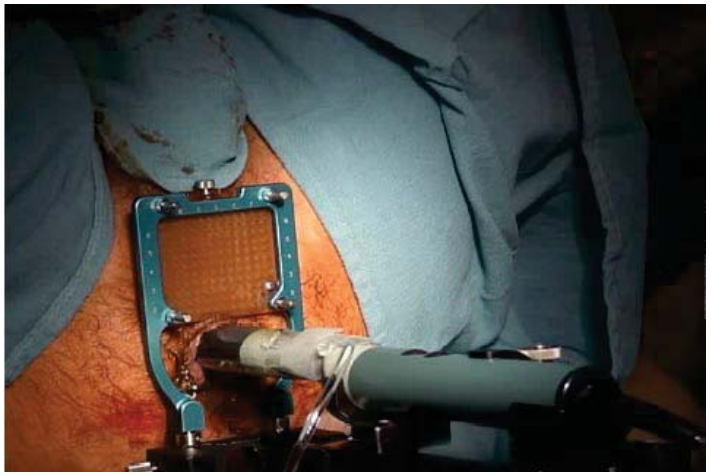


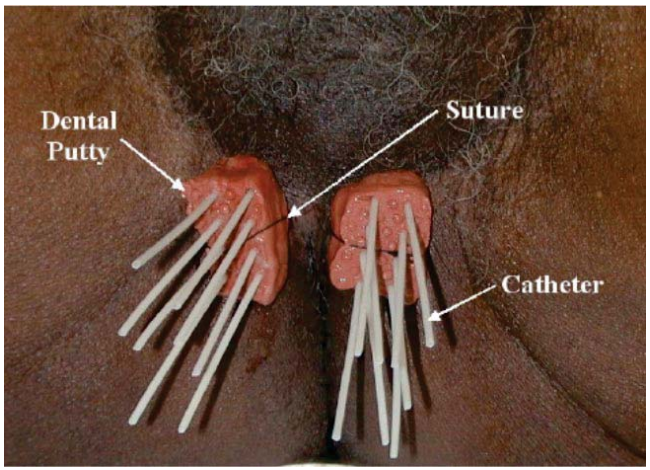
Longitudinal image acquisition (2D)





HDR Brachytherapy Workflow: Needle Placement

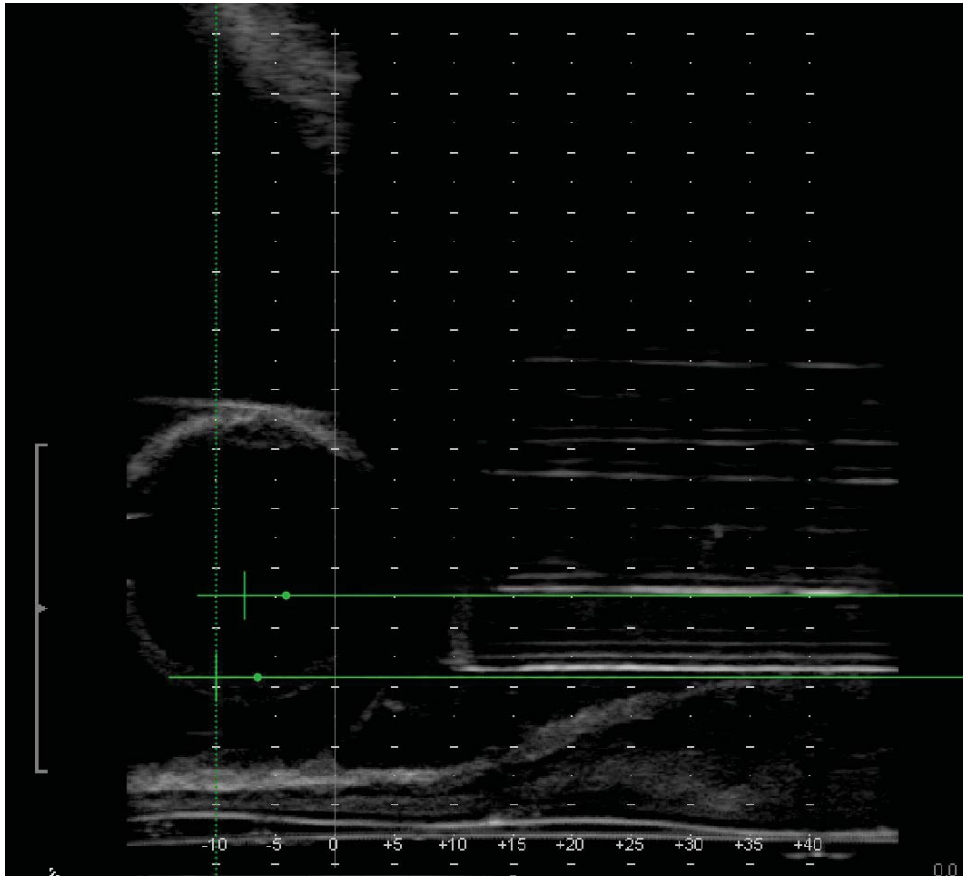




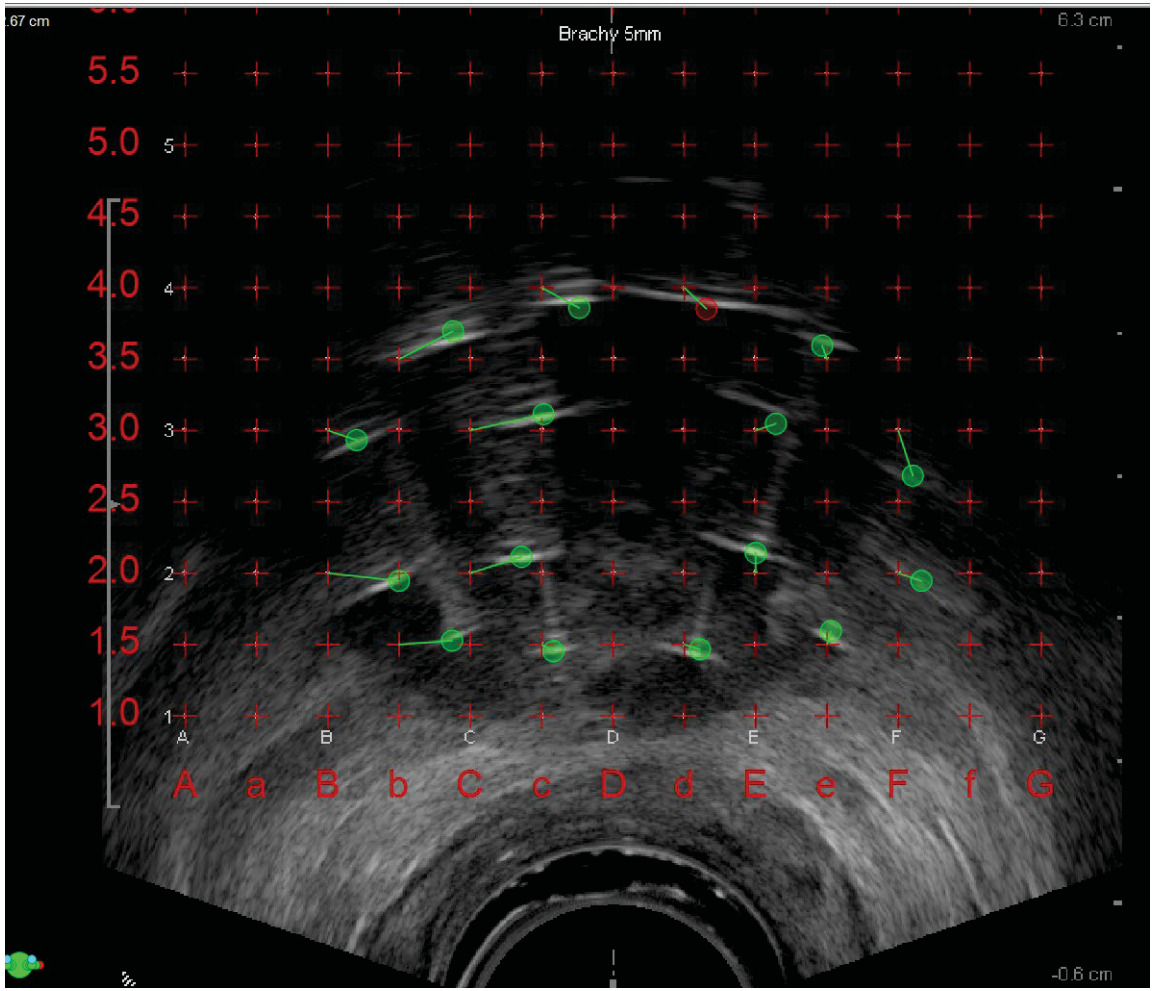
- “Fixed” templates attached to brachytherapy stand
- “Mobile” templates sutured to patient after catheter placement
- UCSF freehand technique provides most flexibility in customizing implant geometry to patient

HDR Brachytherapy Workflow: Needle placement

Setup → Implant → Image acquisition → **Needle detection** → Contouring → Planning → Treatment



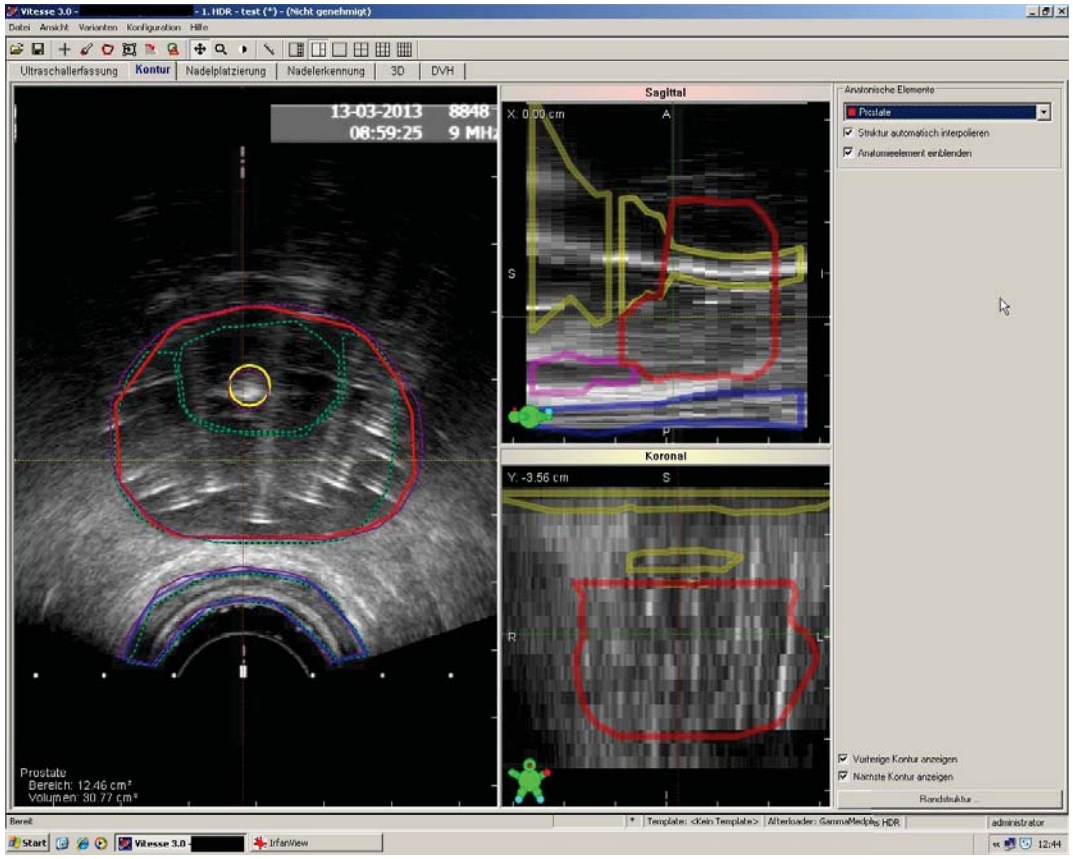
HDR Brachytherapy Workflow: Final needle placement



HDR Brachytherapy Workflow: Post-needle-placement Cystoscopy

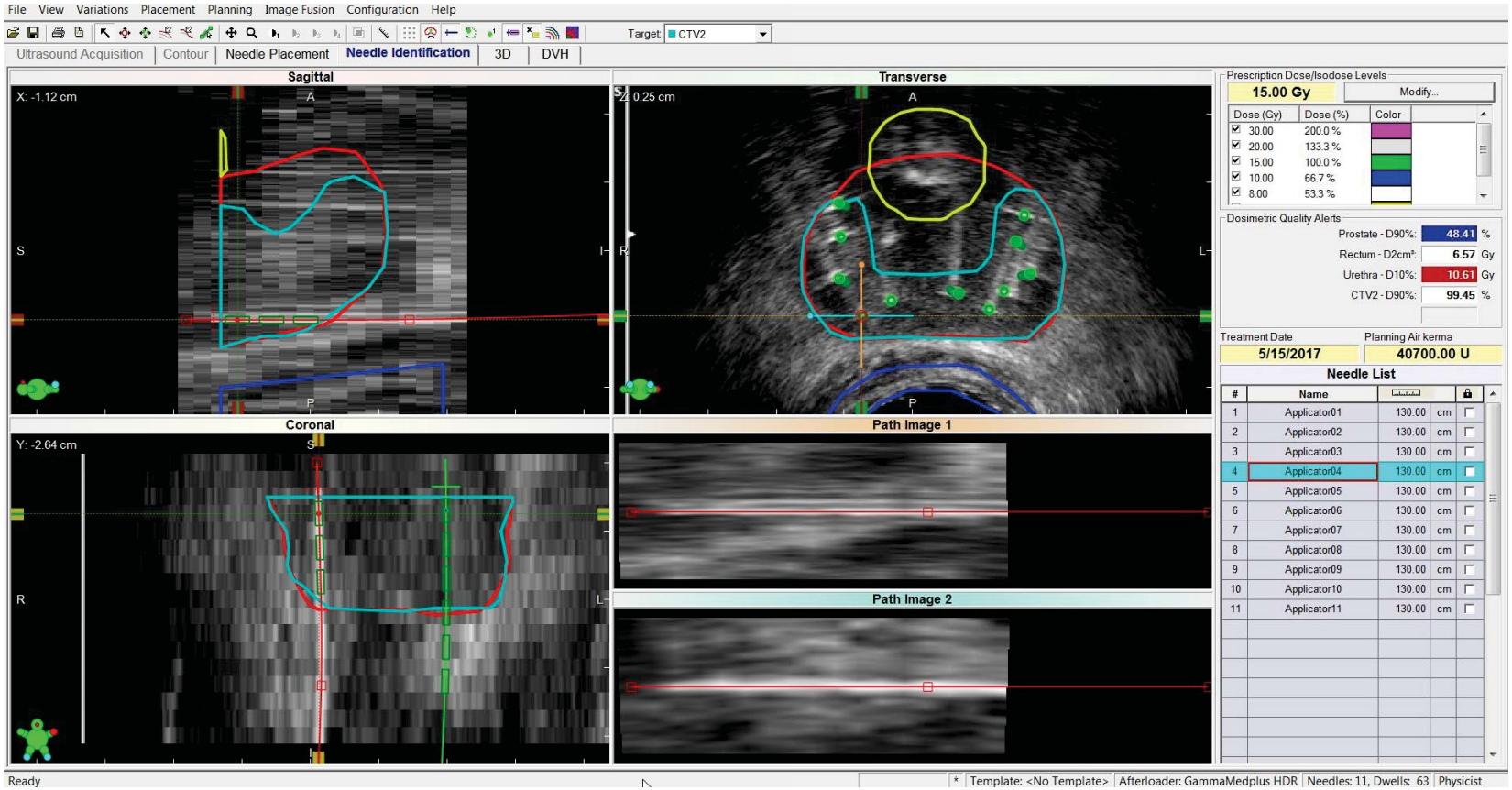
HDR Brachytherapy Workflow: Anatomy delineation

Setup → Implant → Image acquisition → Needle detection → **Contouring** → Planning → Treatment



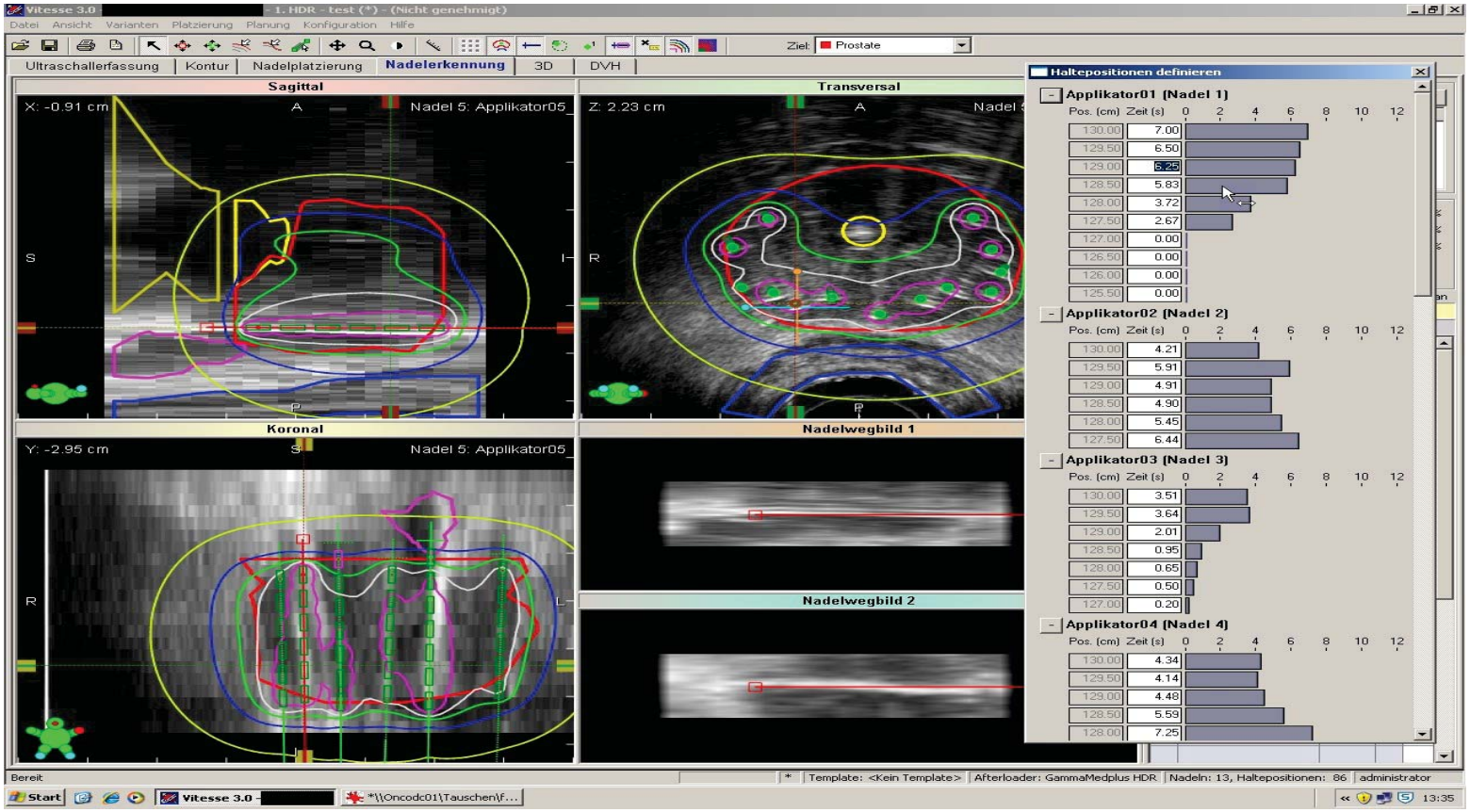
- Prostate
- Urethra
- Rectum

HDR Brachytherapy Workflow: Post-implant Dosimetry Planning



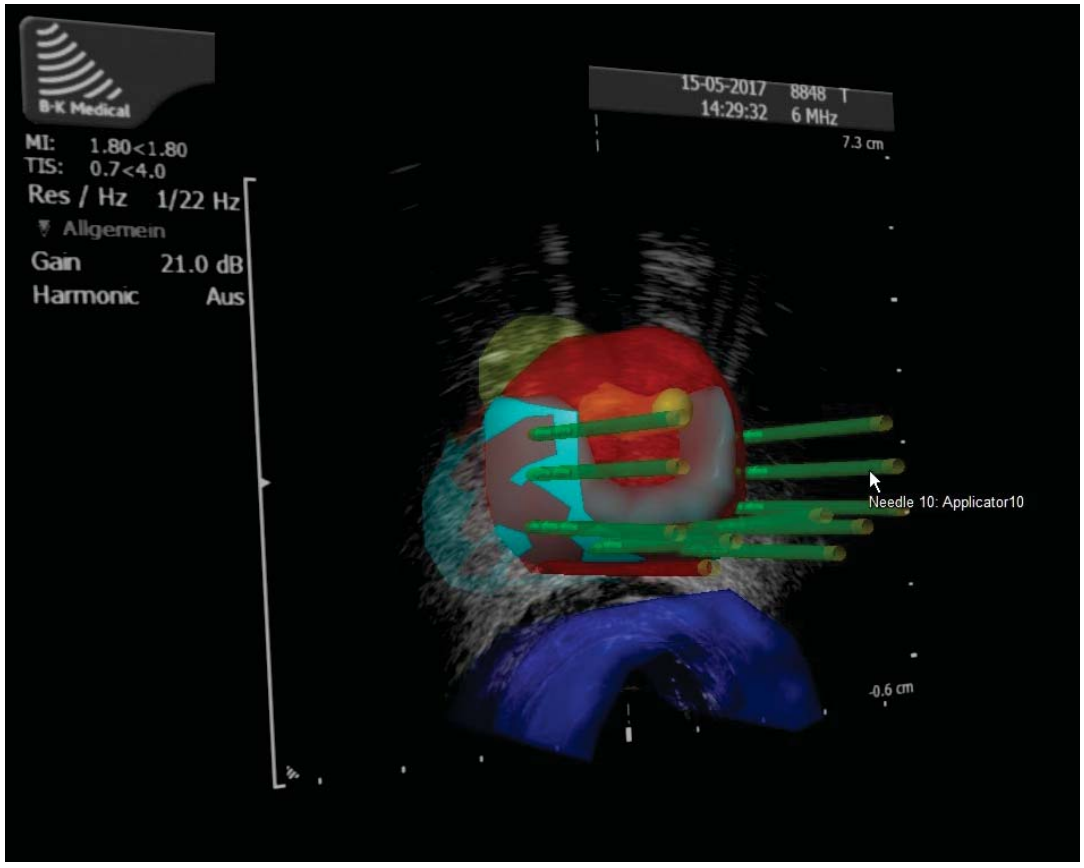
HDR Brachytherapy Workflow: Post-implant Dosimetry Planning

Setup → Implant → Image acquisition → Needle detection → Contouring → **Planning** → Treatment



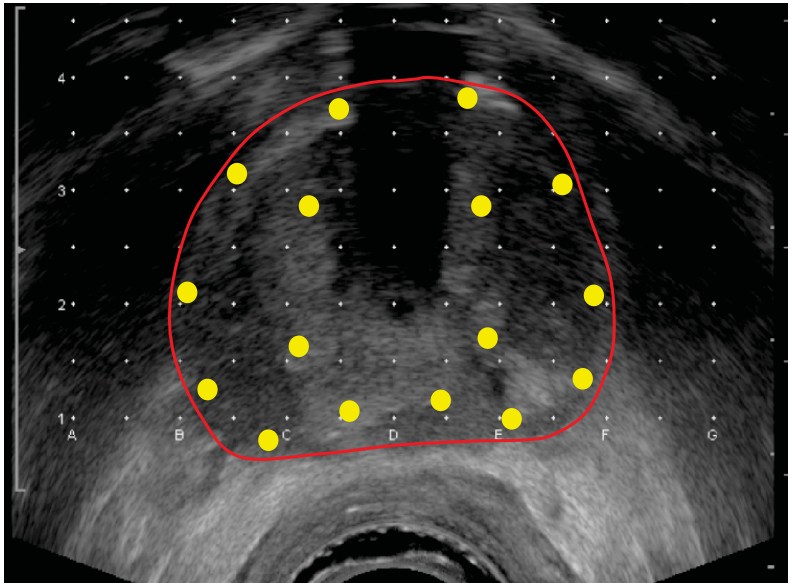
HDR Brachytherapy Workflow: Post-implant Dosimetry Planning

Setup → Implant → Image acquisition → Needle detection → Contouring → Planning → Treatment



Needle Placement Strategy

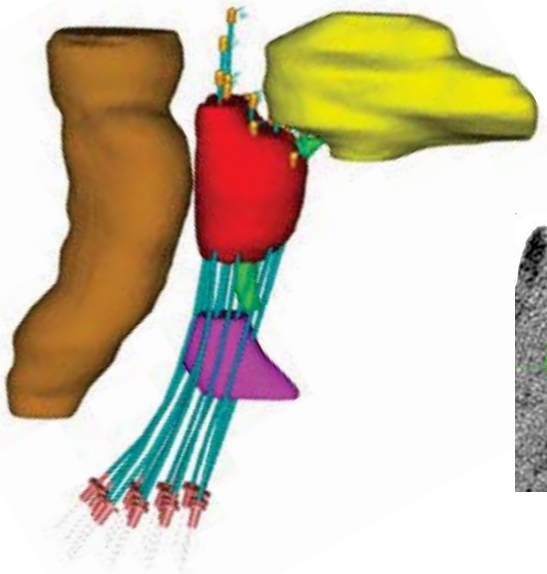
- General
  - Each implant is tailored to patient need.
  - 16 needles will cover most prostates
  - Needles should be 7-10mm apart
  - Needles should be within/on edge of capsule
- Urethra:
  - balance sparing & apical coverage
  - Keep needles ~ 5 mm from urethra
  - May be closer and needles only activated at base and apex
- Rectum
  - Keep posterior needles 5 mm within capsule
  - Keep MED-POST needles to < 10 mm apart OR
  - Consider a central D needle POST to urethra

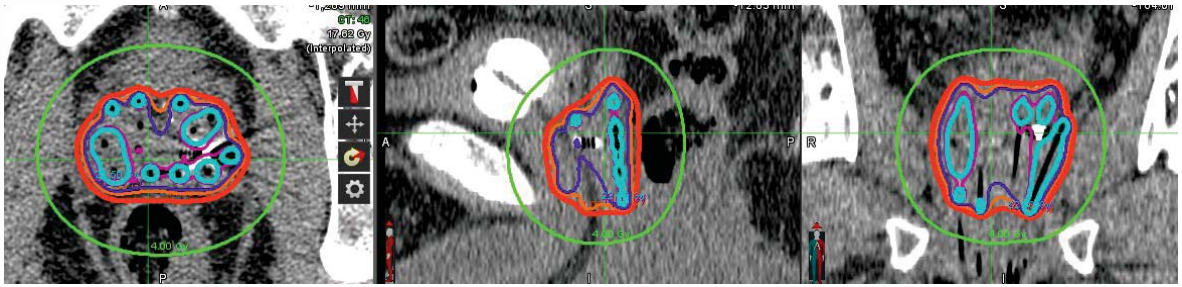


Case presentation

- Our patient is a 65 year-old man with newly diagnosed favorable intermediate-risk prostate cancer (PSA 6, cT2aN0, GS 3+4 with 3/16 cores positive)

- He elects treatment with HDR brachytherapy monotherapy at UCSF





Take Home Points

- Both teletherapy (external beam radiation) and brachytherapy (implanting radioactive sources directly into tumor) are well-established treatment options for localized prostate cancer
- Brachytherapy provides better chance of long-term prostate cancer cure than EBRT alone for men with intermediate or high risk disease
- HDR prostate brachytherapy is a safe, effective method for delivering ablative doses of radiation to eradicate prostate cancer while minimizing exposure to adjacent normal tissue
- The UCSF freehand HDR prostate brachytherapy technique overcomes technical limitations associated with template-based brachytherapy