

Prostate Brachytherapy

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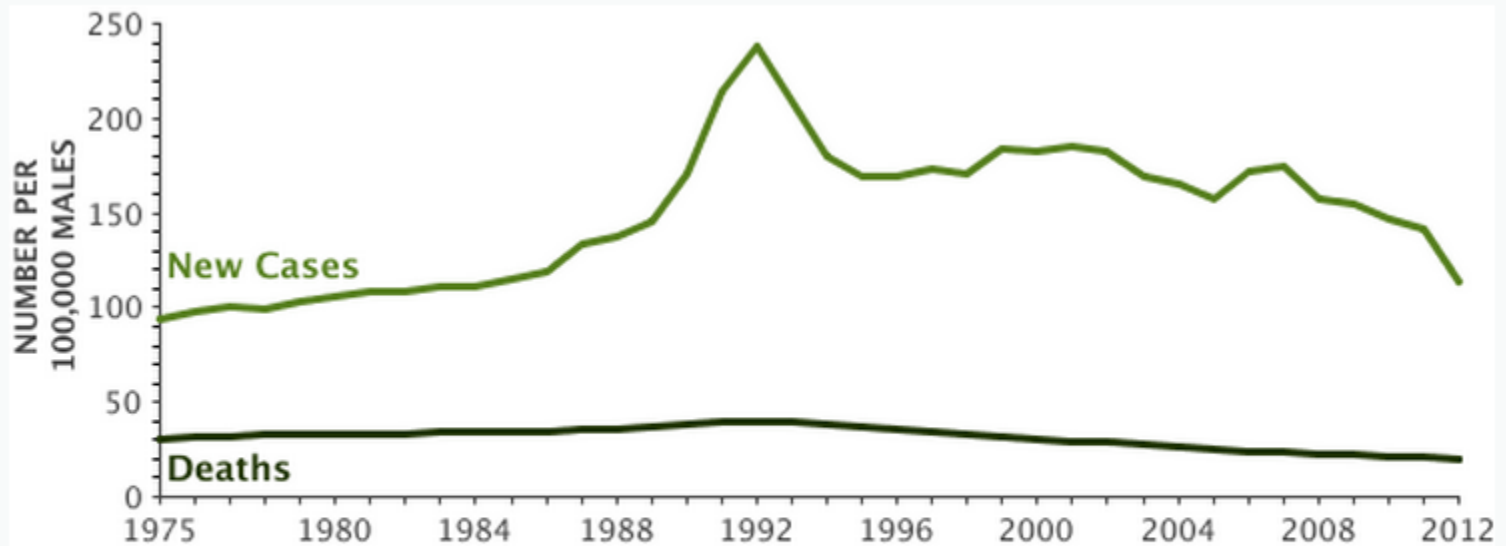
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Outline

- Intro to prostate cancer
- History of brachytherapy
- Patient selection for prostate brachytherapy
- LDR techniques and isotopes
- HDR techniques
- Dose prescriptions and constraints
- Brachytherapy outcomes
- Toxicity of brachytherapy
- Toxicity management

Epidemiology

- #1 non cutaneous cancer, Lifetime risk = 1 in 6 for men
- Median age of Dx =70 yrs
- Risk factors: age, AA race, obesity, high dietary intake of fat



Year	1975	1980	1985	1990	1995	1999	2003	2007
5-Year Relative Survival	66.0%	70.2%	74.9%	88.4%	95.7%	99.2%	99.1%	99.7%

Presenting symptoms

- The majority of patients with organ-confined disease are asymptomatic on presentation
- Baseline urinary or erectile symptoms should be taken into account with PSA, DRE and imaging findings (if available)
- Standardized assessments of urinary and erectile symptoms include the AUA Symptom Score and the Sexual Health Inventory for Men (SHIM)

AMERICAN UROLOGICAL ASSOCIATION (AUA) SYMPTOM SCORE

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your Score
Incomplete emptying – It does not feel like I empty my bladder all the way.	0	1	2	3	4	5	
Frequency – I have to go again less than two hours after I finish urinating.	0	1	2	3	4	5	
Intermittency – I stop and start again several times when I urinate.	0	1	2	3	4	5	
Urgency – It is hard to wait when I have to urinate.	0	1	2	3	4	5	
Weak stream – I have a weak urinary stream.	0	1	2	3	4	5	
Straining – I have to push or strain to begin urination.	0	1	2	3	4	5	
	None	1 time	2 times	3 times	4 times	5 times or more	Your Score
Nocturia – I get up to urinate after I go to bed until the time I get up in the morning.	0	1	2	3	4	5	

Total AUA Symptom Score

Total score: 0-7 mild symptoms; 8-19 moderate symptoms; 20-35 severe symptoms

SEXUAL HEALTH INVENTORY FOR MEN (SHIM)

1. How do you rate your confidence that you could get and keep an erection?		VERY LOW	LOW	MODERATE	HIGH	VERY HIGH
		1	2	3	4	5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?	NO SEXUAL ACTIVITY	ALMOST NEVER OR NEVER	A FEW TIMES (MUCH LESS THAN HALF THE TIME)	SOMETIMES (ABOUT HALF THE TIME)	MOST TIMES (MUCH MORE THAN, HALF THE TIME)	ALMOST ALWAYS OR ALWAYS
	0	1	2	3	4	5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	DID NOT ATTEMPT INTERCOURSE	ALMOST NEVER OR NEVER	A FEW TIMES (MUCH LESS THAN HALF THE TIME)	SOMETIMES (ABOUT HALF THE TIME)	MOST TIMES (MUCH MORE THAN, HALF THE TIME)	ALMOST ALWAYS OR ALWAYS
	0	1	2	3	4	5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	DID NOT ATTEMPT INTERCOURSE	EXTREMELY DIFFICULT	VERY DIFFICULT	DIFFICULT	SLIGHTLY DIFFICULT	NOT DIFFICULT
	0	1	2	3	4	5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	DID NOT ATTEMPT INTERCOURSE	ALMOST NEVER OR NEVER	A FEW TIMES (MUCH LESS THAN HALF THE TIME)	SOMETIMES (ABOUT HALF THE TIME)	MOST TIMES (MUCH MORE THAN, HALF THE TIME)	ALMOST ALWAYS OR ALWAYS
	0	1	2	3	4	5

Add the numbers corresponding to questions 1-5.

TOTAL: _____

The Sexual Health Inventory for Men further classifies ED severity with the following breakpoints:

1-7 Severe ED

8-11 Moderate ED

12-16 Mild to Moderate ED

17-21 Mild ED

Clinical Staging

DRE



AJCC 8th Ed. Clinical T (cT)

- T0** no evidence of primary tumor
- T1** **clinically inapparent** (palpation or imaging)
A *incidental, $\leq 5\%$*
B *incidental, $> 5\%$*
C *Found on **dx bx** (e.g. after high PSA)*
- T2** **clinically apparent, still within** prostate
A *$\leq \frac{1}{2}$ **one lobe***
B *$> \frac{1}{2}$ **one lobe***
C ***both lobes***
- T3** **extends outside**
A *ECE*
B *SV involvement*
- T4** fixed, or invades ext sphincter, rectum, bladder, levator muscles, and/or pelvic wall

Clinical Staging

N staging

N Category	N Criteria
NX	Can't assess
N0	No nodes
N1	Mets in RN

M staging

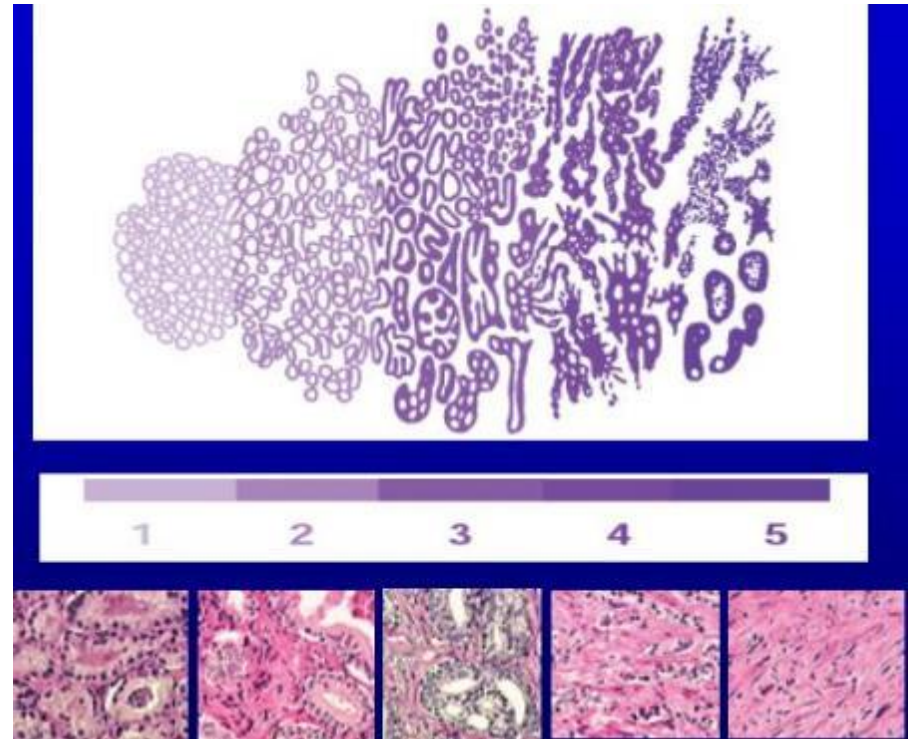
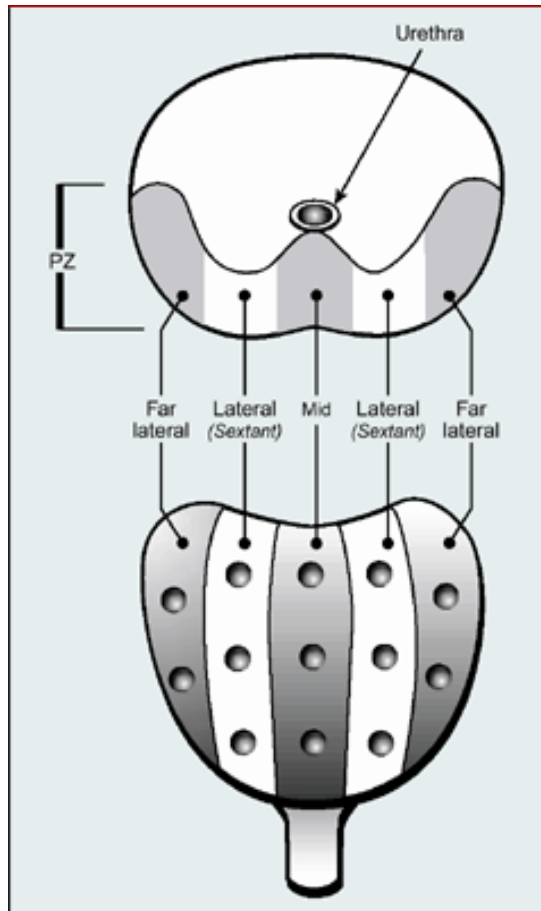
M Category	M Criteria
M0	No mets
M1a	Non-RN
M1b	Bone mets
M1c	Other mets

AJCC 8th Ed. Prognostic Grouping

T	N	M	PSA	Grade Group	Stage
cT1a-2a pT2	0	0	< 10	1	I
cT1a-2a	0	0	≥ 10-20	1	IIA
cT2b-c	0	0	< 20	1	IIA
T1-2	0	0	< 20	2	IIB
T1-2	0	0	< 20	3-4	IIC
T1-2	0	0	≥ 20	1-4	IIIA
T3-4	0	0	Any	1-4	IIIB
Any	0	0	Any	5	IIIC
Any	1	0	Any	Any	IVA
Any	Any	1	Any	Any	IVB

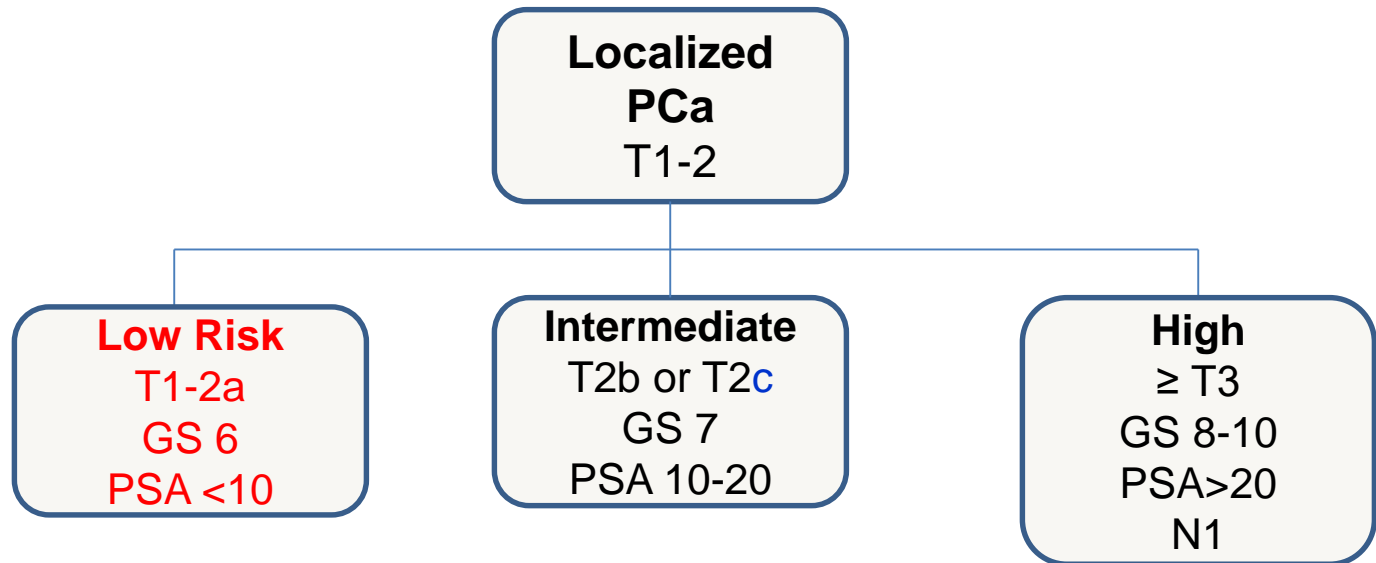
Gleason Score

TRUS-guided biopsy



The Gleason score = major + minor pattern

Risk stratification



Brachytherapy alone

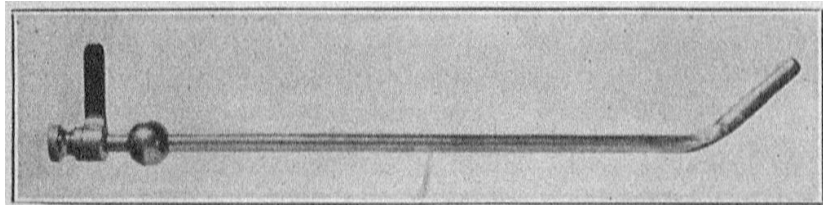


Brachytherapy as a boost to
the prostate with external beam radiation

History of Brachytherapy

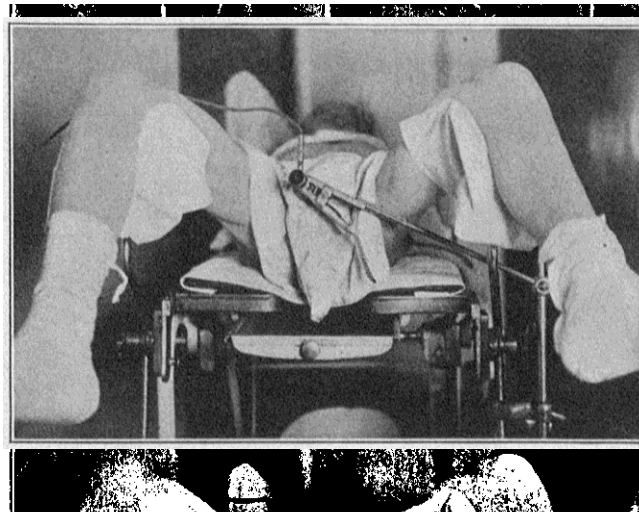
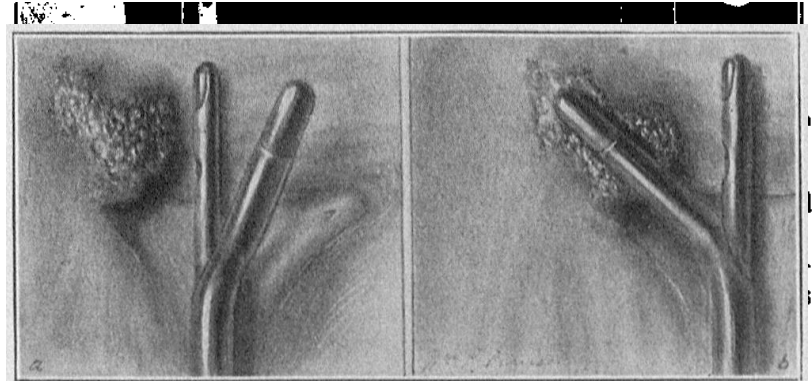
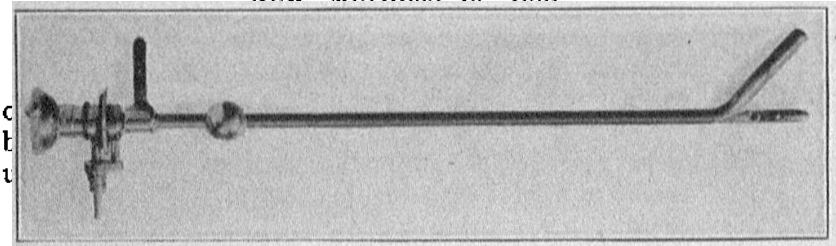
- 1895: Discovery of Xrays
- 1913: First described by Pasteu and Degrais
- Brought into regular use by Young (radical perineal prostatectomy)
- 1915: Early cases using transperineal radium needles, reported by Barringer in 1924
- 1983: Introduction of image-guided (ultrasound-based) transperineal prostate brachytherapy by Holm et al.

when that little description is necessary. The small, straight
cystoscope which is used in my cystoscopic rongeur (Fig. 2)



THE USE OF RADIUM IN CANCER OF THE PROSTATE
AND BLADDER

A. PRESENTATION OF NEW INSTRUMENTS AND
NEW METHODS OF USE *



which react well, the prostate is a sclerosed mass and is only too rare.

the low percentage of actual cures by radiation of the prostate, it would seem that this germicidal treatment were better.

Obstruction in Advanced Cases.—One of the

- Outcomes were poor:
 - Local control: 10%
- 2% of patients had disease confined to the prostate

Patient Selection: American Brachytherapy Society (ABS) Guidelines

- Absolute contraindications
 - Limited life expectancy (<10 years)
 - Unacceptable operative risks
 - Distant metastases (disease spread)
 - Absence of rectum, precluding TRUS guidance
 - Large TURP defects, precluding seed placement and acceptable dosimetry
 - Ataxia telangiectasia

Patient Selection: ABS Guidelines

- Relative contraindications
 - Significant difficulties with urination
 - History of prior pelvic radiotherapy
 - Transurethral resection defects
 - Large prostate and prostate bulging into the bladder
 - Gland size $>60 \text{ cm}^3$ at time of implantation
 - Inflammatory bowel disease

Patient Selection:

ABS Recommendations

Table 4

Suggested treatment schema for low-, intermediate-, and high-risk disease for PPB

Risk group per NCCN	Brachytherapy alone?	Combined with EBRT?	Combined with androgen deprivation?
Low	Yes	Not favored	Not favored
Intermediate	Optional	Optional	Optional
High	No	Yes	Favored

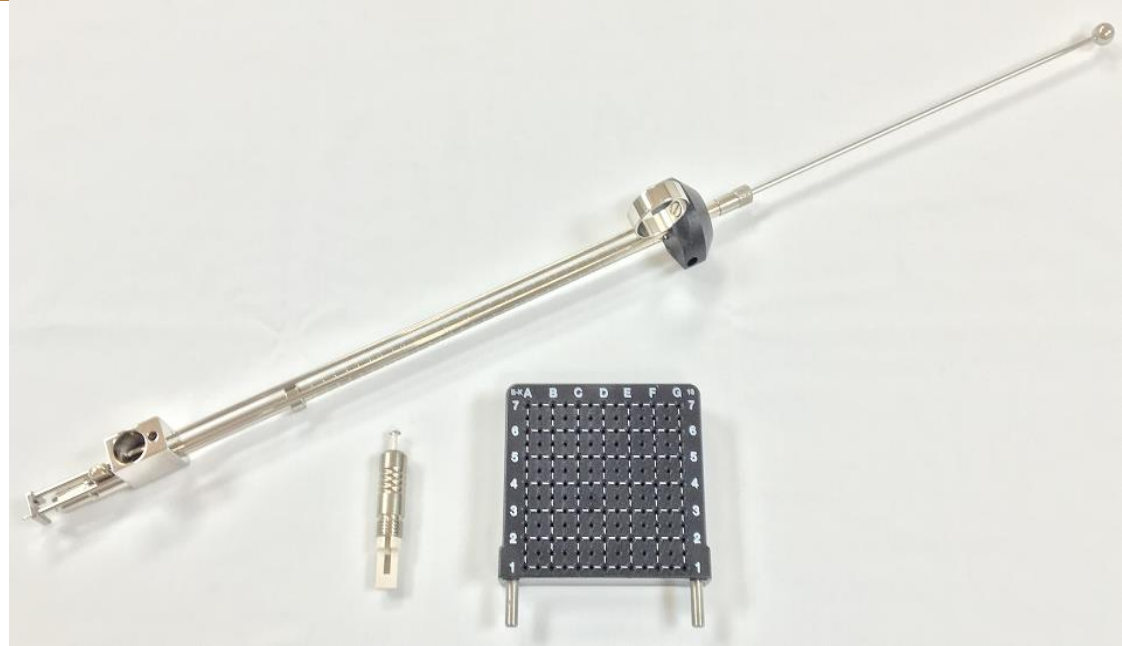
NCCN = National Comprehensive Cancer Network; EBRT = external beam radiation therapy; PPB = permanent prostate brachytherapy.

Brachytherapy

- Low dose rate (LDR): permanent seeds
- High dose rate (HDR): transient seeds

LDR Techniques

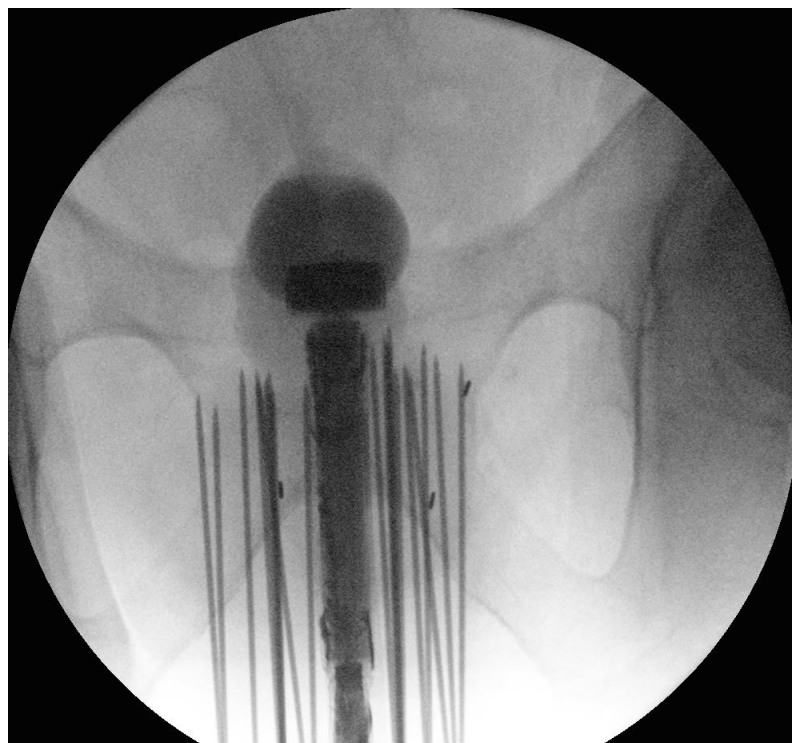
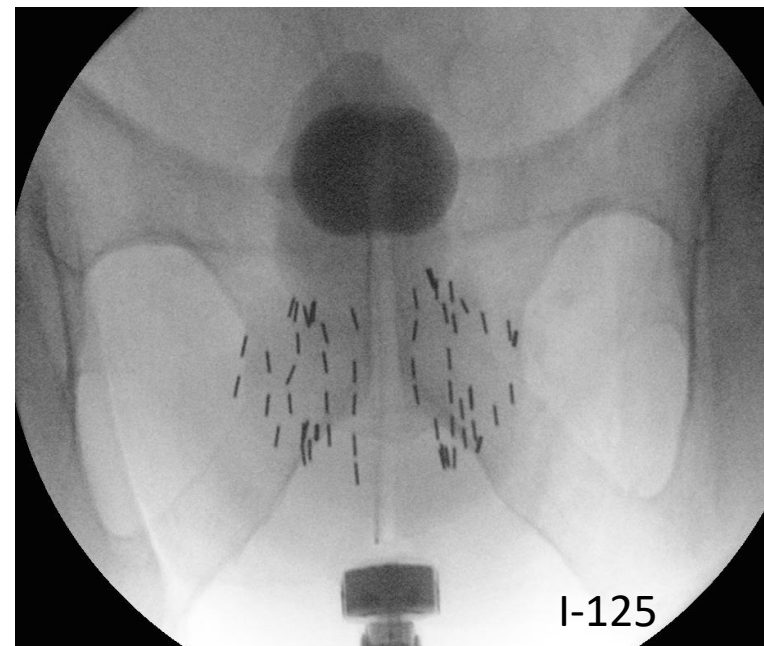
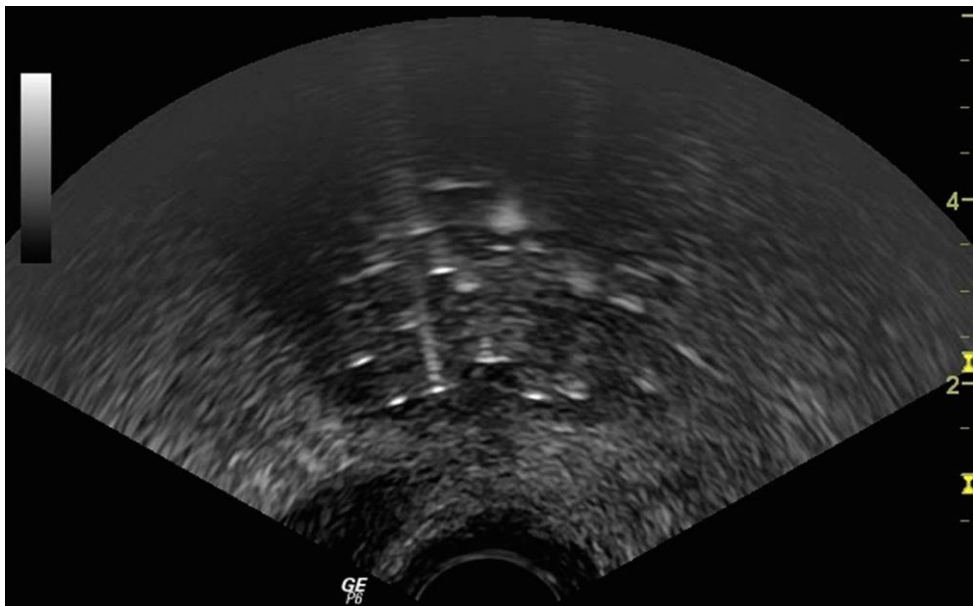
- Transperineal approach with ultrasound image guidance as per Holm et al.
- Attached template grid and real-time image guidance allow for accurate needle placement and adjustment.
- Fluoroscopy can also be used to monitor seed deposition as complementary to TRUS.
- Seeds are delivered through needles into the prostate through various methods (Mick applicator, stranded seeds)



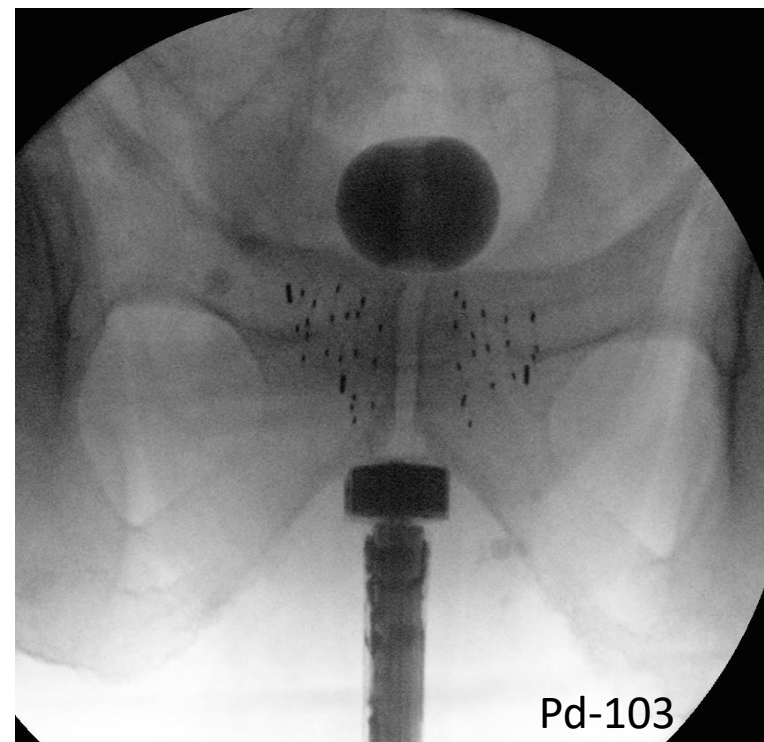
Figures courtesy of Dr. Folkert

LDR Isotopes

- Iodine-125 (I-125) (1965)
 - Electron capture decay
 - $T_{1/2}$: 59.4 days
 - Energies: 27.4 – 35.5 keV (avg 27.4 keV)
 - Dose rate: 5-7 cGy/h
- Palladium-103 (Pd-103) (1986)
 - Electron capture decay
 - $T_{1/2}$: 17 days
 - Energies: 20.1 and 23 keV
 - Dose rate: 18-20 cGy/h
- Cesium-131 (Cs-131) (2004)
 - Electron capture decay
 - $T_{1/2}$: 9.7 days
 - Energies: 29.5 – 34.4 keV (avg 30.4 keV)

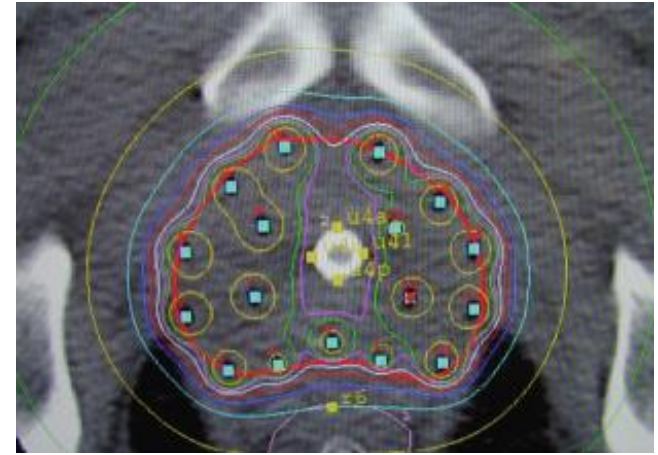


Figures
courtesy of
Dr. Folkert



HDR Techniques

- Needles or guide catheters are held in place in template sutured to perineum
- Ultrasound, CT, or MRI obtained for treatment planning
- Remote afterloader is attached to needles or catheters and treatment is delivered



Constraints:

ABS and AAPM Guidelines

- Prostate
 - D90 (min dose covering 90% target): in Gy and %
 - V100 (% of target receiving 100% Rx): in %
 - V150 (% of target receiving at least 150% Rx): in %
- Urethra
 - UV150 (in volume)
 - UV5 (urethral max dose): <150%
 - UV30 (clinically sig volume of urethra): <125%
- Rectum
 - RV100: <1 cc on Day 1, <1.3 cc on Day 30
- Prostate
 - D90: >100% Rx
 - V150: <=50%
- Urethra
 - D10: <150% Rx
 - D30: <130% Rx
- Rectum
 - D_{2cc} : <reference Rx dose
 - $D_{0.1cc}$ (D_{max}): <150% of reference Rx dose

LDR Brachytherapy Outcomes: Versus Other Modalities

- Difficult to do randomized trials comparing brachytherapy monotherapy to radical prostatectomy
 - SPIRIT trial failed to accrue.
- Studies suggest prostate brachytherapy is at least equivalent to radical prostatectomy (Peschel and Colberg, Lancet 2003).

EBRT+brachytherapy boost: Combination Therapy Outcomes

EBRT vs. EBRT plus brachytherapy

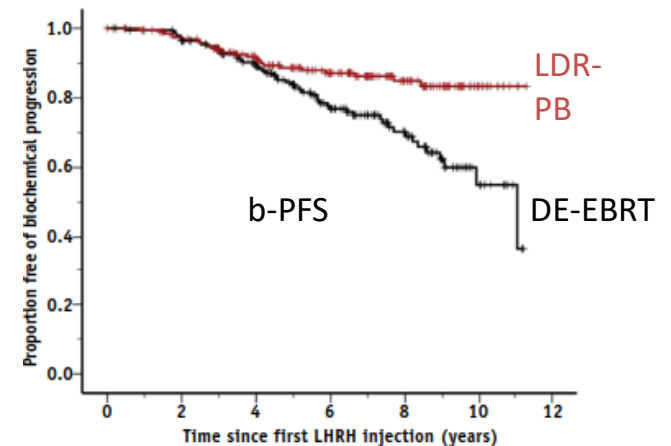
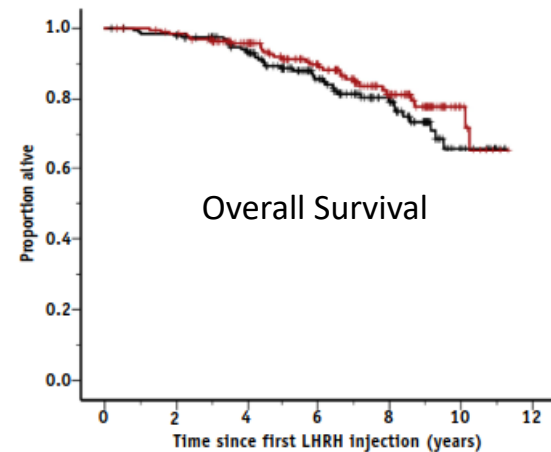
Phase III clinical trials of EBRT vs. EBRT plus brachytherapy

Authors	Year	N	Median followup	Risk groups	Outcomes		
					EBRT	Combo	Significance
Sathya <i>et al.</i> (83)	2005	104	8.2 years	Low: 0%	5 yr bRFS:		
				Intermediate: 40%	39%	71%	SS
				High: 60%	Post-tx biopsy positive:		
Hoskin <i>et al.</i> (40)	2012	218	7.1 years	Low: 5%	51%	24%	SS
				Intermediate: 42%	7-yr bRFS		
				High: 53%	48%	66%	SS
ASCENDE-RT (59)	2015	398	6.5 years	Low: 0%	9-yr bRFS		
				Intermediate: 31%	58%	78%	SS
				High: 69%			

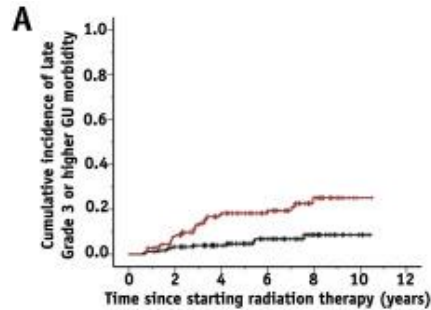
EBRT = external beam radiation therapy; bRFS = biochemical recurrence-free survival; SS = statistically significant.

ASCENDE-RT: EBRT vs EBRT+LDR boost

- 400 pts with high (276) and intermediate risk (222) disease from 2002-2011
- Treatment
 - Both received 8 mon of neoadjuvant ADT and whole pelvis EBRT (46Gy/23F)
 - DE-EBRT: EBRT boost 32Gy/16F to a total of 78Gy
 - LDR-B: I-125 LDR boost prescribed to minimum peripheral dose of 115Gy
- Primary end point: relapse free survival (nadir+2ng/ml threshold)
- Median follow up: 6.5 years

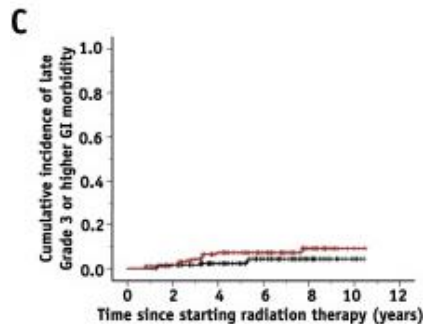
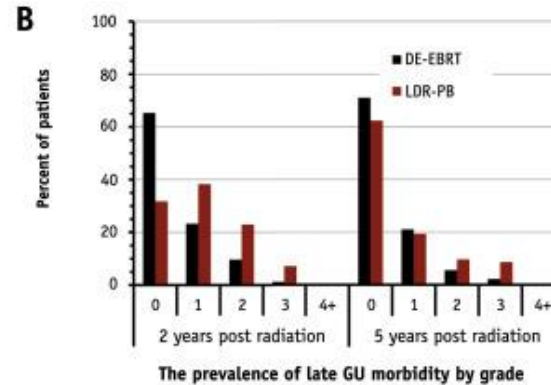


ASCENDE-RT: Toxicity



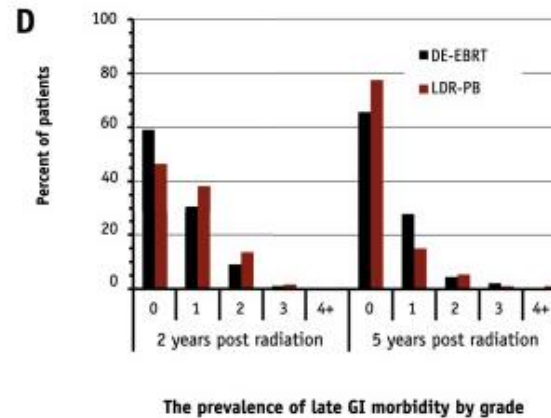
Numbers at risk:

Years	0	2	4	6	8	10
DE-EBRT	195	167	125	79	41	8
LDR-PB	188	158	109	69	28	1



Numbers at risk:

Years	0	2	4	6	8	10
DE-EBRT	195	172	129	80	41	9
LDR-PB	188	168	119	80	36	4



Late grade 3 GU and GI toxicity for Dose-Escalation

Table 4 Comparing late grade 3 GU and GI toxicity reported for radiation dose-escalation studies for prostate cancer

Study	Median follow-up (y)	Late GU toxicity grade 3 (%)	Late GI toxicity grade 3 (%)
EBRT + LDR-PB studies: combination arm			
Albert et al (8)	2.8	N/A	30 (rectal bleeding)
Wong et al (9)	4.8	18	5
Spratt et al (10)	5.3	1.4	1.4
CALGB 99809 phase 2 study (11)	6.0	3	0
RTOG 00-19 phase 2 study* (12)	8.2	~ 15	~ 15
ASCENDE-RT (LDR-PB arm)	6.5	18.4	8.1
HDR + EBRT studies: combination arm			
Aluwini et al (13)	6.2	4	1
Sathya et al (14)	8.2	13.7	3.9
Hoskin et al (15)	7.3	31	7
Agoston et al (19)	5.1	14	2
Ghadjar et al (20)	5.1	10.9	0
EBRT alone dose-escalation studies: dose-escalation group			
M. D. Anderson (1)	8.7	4	7
MRC RT01 (2)	5.2	4	10
Dutch CKVO96-10 (3)	5.8	13	5
PROG95-09 (18)	8.9	2	1
ASCENDE-RT (DE-EBRT arm)	6.5	5.2	3.2

Large range in late grade 3 GU and GI morbidity (1.4% to 30%) limited by differences in morbidity scoring systems, length of follow up, eligibility characteristics, radiation field and ADT duration.

RTOG 0321: EBRT+HDR boost

- Long-term patient outcome following treatment with external beam radiation therapy (EBRT) and prostate high dose rate (HDR) brachytherapy from a prospective phase II, multi-institutional collaborative trial conducted by NRG Oncology/RTOG
 - Clinically localized prostate cancer without prior history of TURP or hip prosthesis were eligible for this study.
 - All patients were treated with a combination of EBRT and one HDR implant delivering RT in 2 fractions.
- 129 patients
 - median age was 68
 - 43% of patients received hormonal therapy.
 - There were 6 (5%) patients with grade 3 GI/GU AEs, and no late grade 4-5 GI/GU AEs.
 - The single Grade 3 GI AE was proctitis. The grade 3 GU AEs were: cystitis (n=1), pollakiuria (n=1), renal/genitourinary-other (n=1), urethral stricture (n=1), urinary incontinence (n=1), and urinary retention (n=2).
 - Five- and 10-year overall survival rates were 95% and 76%.
 - The biochemical failure rates: 5-year and 10-year rates of 10% and 15%

EBRT vs. EBRT plus brachytherapy: food for thought

- Retrospective studies
 - Selection bias similar to RP vs. EBRT (patients with advanced age, multiple comorbidities, presence of gross ECE or bulky seminal vesicle invasion, large prostate volume, worse baseline urinary toxicity are less likely to undergo brachytherapy).
- Randomized controlled studies
 - No survival benefit
 - 2-4 fold increased \geq grade 3 GU toxicity
 - Suboptimal systemic therapy (ADT timing, duration and utilization)
 - Multiple trials have demonstrated effective salvage brachytherapy

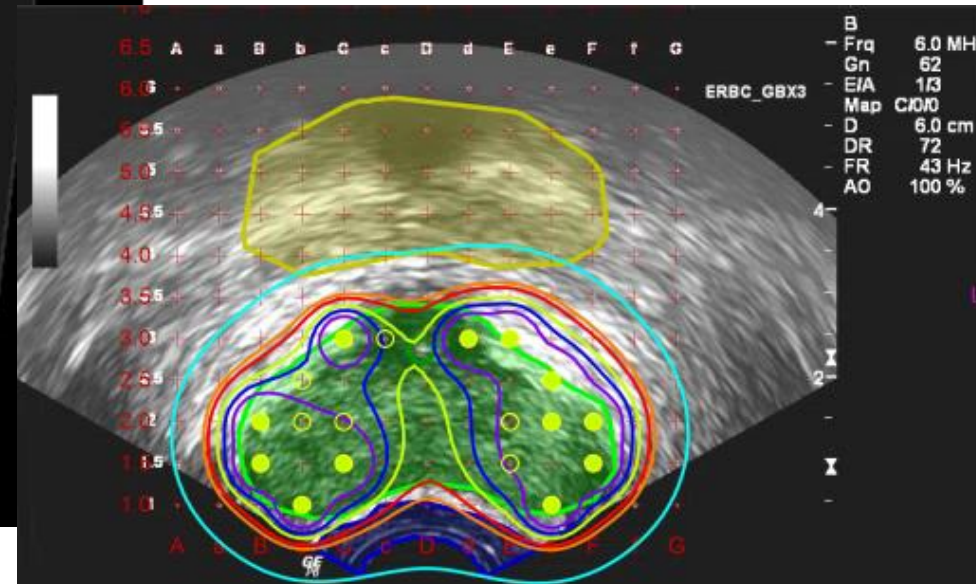
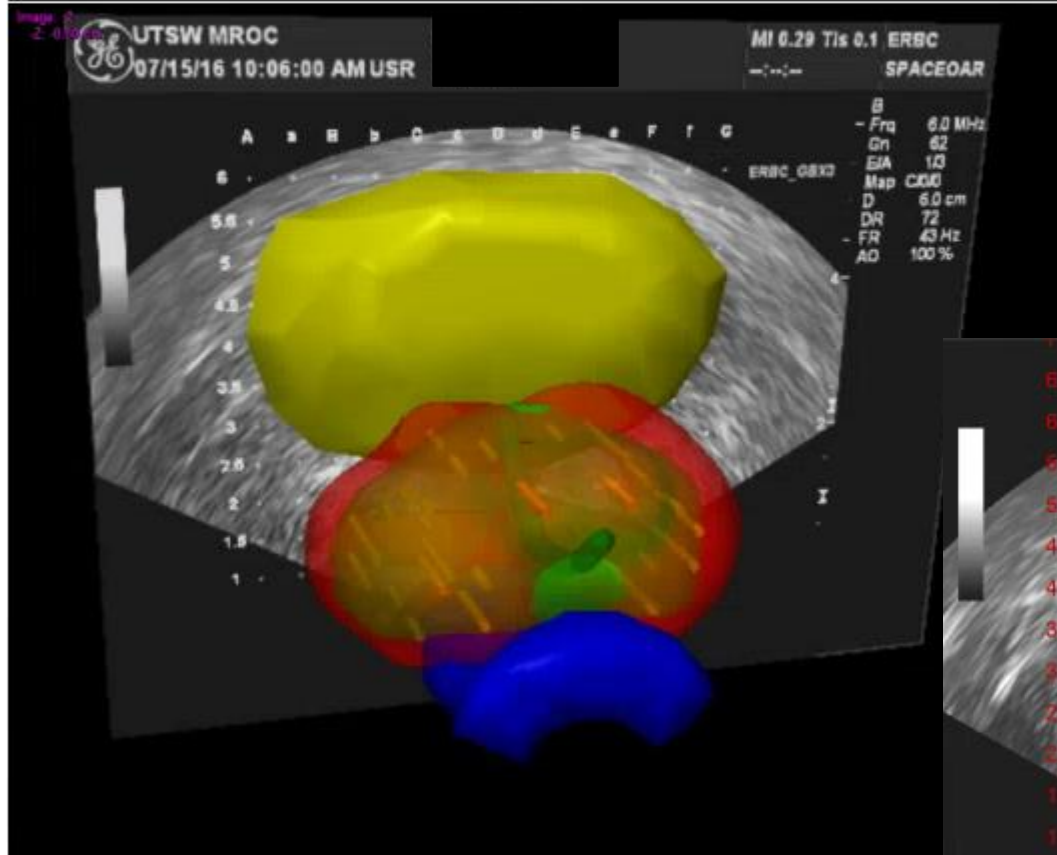
Cost Effectiveness

- Observation vs initial tx for low risk disease using Medicare scales
 - Observation was more cost-effective than initial treatment
 - If treated, prostate brachytherapy was most effective and least expensive initial therapy
 - Avg lifetime costs, age 65:
 - Watchful waiting: \$24,520
 - Prostate brachytherapy: \$35,374
 - Radical prostatectomy: \$38,180
 - Active surveillance: \$39,894
 - IMRT: \$48,699

Case: Plan Review

Dept. ID:	Study: Prostate I125 Monotherapy	Source: I-125 (AgX100)
	Variation: mike	Comment:
	Images: 11	Sources: 51
	Template: B-K Standard	Anisotropy: Factors (Line Model)
Procedure Date: 8/26/2016	Prescription Dose: 144.0 Gy	Source Activity: 0.566 U [0.446 mCi]
Not approved by physician		Total Activity: 28.866 U [22.729 mCi]
Not approved by physician		Not approved by physicist

Isodose Surface	144.00 [100.00 %]
Gy [% of Prescription Dose]	



The University of Texas Southwestern Medical Center
NOTIFICATION TO AUTHORITIES
RADIOACTIVE MATERIAL PROCEDURE

(Name) Da has undergone a

RADIATION ONCOLOGY IMPLANT PROCEDURE on

(date) 8/26/16 at Clements University Hospital.

The Patient received radioactive seeds during the course of the procedure a may activate radiation detection equipment until the given time period as li below. For further information, contact Radiation Oncology at:

(phone) 214-645-8525

Or UTSW Radiation Safety at (214) 648-2250 during normal working hours. After hours only general information may be available from the Institutional Police Department at

214-648-8311

The patient received the following radioisotope(s) and may activate radiation detection equipment for the following amount of time after the procedure:

<input type="radio"/> Technetium-99m 2 ½ days	<input type="radio"/> Thallium-201 30 days	<input type="radio"/> Indium-111 28 days
<input type="radio"/> Gallium-67 33 days	<input type="radio"/> Iodine-131 80 days	<input type="radio"/> Iodine-123 300 days
<input type="radio"/> Phosphorus-32 14.29 days	<input checked="" type="radio"/> Iodine-125 180 days	

VALID ONLY WITH EXPIRATION AND SIGNATURE

EXPIRES 2/26/17 Signed [Signature]



The University of Texas Southwestern Medical Center
Department of Radiation Oncology

**HOME GUIDELINES FOR PATIENTS IMPLANTED
WITH RADIOACTIVE I-125 SEEDS**

Radioactive I-125 seeds have been implanted into your prostate. The external radiation level around you is low; allowing us to release you from the medical center after the implant procedure has been completed.

The radioactive material that is emitting radiation is contained in a sealed capsule (seed), so the radioactivity does not circulate in your blood, urine, or any other body fluids. Therefore, you cannot contaminate anyone or anything. This means that linen, clothing, tableware, dishes, and toilet facilities may be used by others without taking any special precautions. Moreover, the seeds do not interfere with pacemakers or microwave ovens.

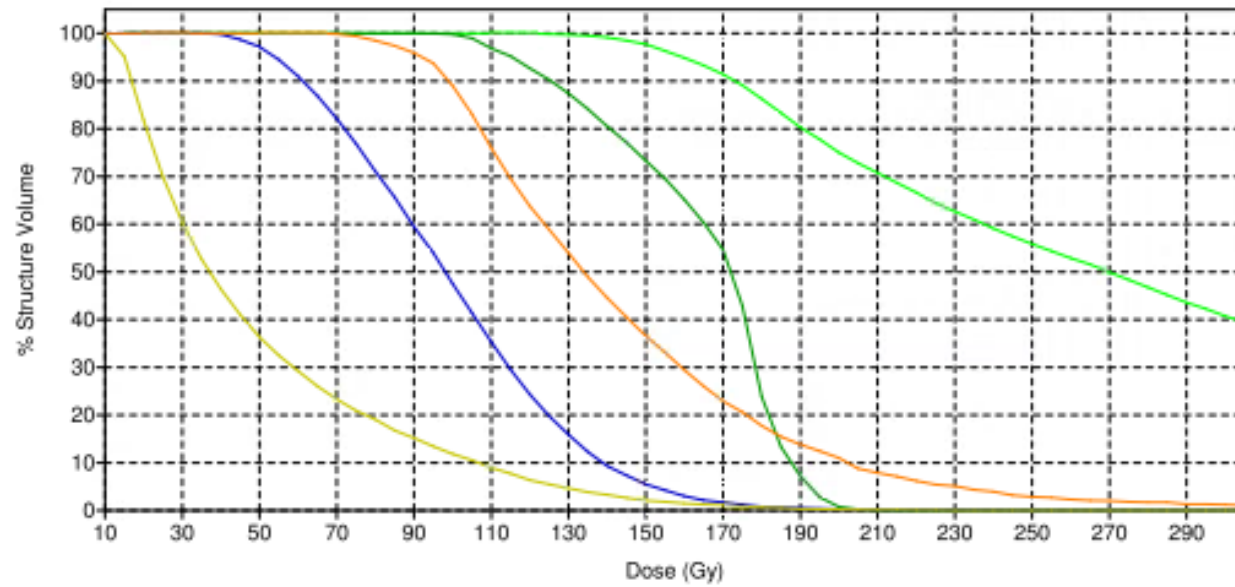
It is possible that a seed may be passed during urination or ejaculation. Although such an occurrence is rare, it is recommended not to grasp the seed with your fingers or hands, instead use a spoon or tweezers to pick up the seed and flush it down the toilet. It is recommended not to resume sexual activity for 1 week after the implant procedure. Use a condom for at least the first five ejaculations, and longer if you have already lost a seed this way.

Some very sensitive security monitors can detect the low levels of radiation emitted from your body in the first months after the implantation. These security instruments are able to detect radiation at levels well below those that are of concern to health. These radiation monitors are typically located at the entry/exit of nuclear plants, nuclear research centers, some waste disposal areas, and some scrap metal factories/yards. In addition, they are now more frequently in use in airports and at border crossings. In some cities, police officers are equipped with such monitors. If you trigger the alarm of such a monitor, show your notification card.

FOR ADDITIONAL INFORMATION OR EMERGENCY ASSISTANCE CONTACT:

Radiation Oncology – 214-645-8525 (8:00 am to 5:00pm weekdays)
Physician: Michael Folkert – office 214-645-2112; pager 214-786-7875
Physicist: Arnold Pompos – office 214 645 7663; pager 214 822 -3555; cell 603-362-7863

Cumulative DVH



PostProcedure f/u

- Void test (wait until patient genuinely wants to urinate –do not make them strain)
- Watch for blood clots/pinkish tint is ok
- If no void, need to go home with foley (<1%) and return within 3 days for another void test
- Flomax for 1 month (+Abx if not given preOp) (+Anti-inflammatory)
- f/u in 1 month

Thank You