

# Radiation for Prostate Cancer

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Grand Rounds  
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# Risk Stratification

## Clinically Localized to Prostate Gland

- Risk stratification tells you possibility of microscopic spread outside the prostate capsule, into lymph nodes, or bone

Risk Profile	Criteria <sup>†</sup>
<b>Favorable</b>	
Very Low Risk	<ul style="list-style-type: none"> <li>• T1c</li> <li>• Gleason score 6</li> <li>• PSA &lt; 10 ng/ml</li> <li>• Fewer than 3 biopsy cores positive, ≤50% cancer in any core</li> <li>• PSA Density &lt; 0.15 ng/ml/cc</li> </ul>
Low Risk	<ul style="list-style-type: none"> <li>• T1 or T2a</li> <li>• Gleason score 6</li> <li>• PSA &lt; 10 ng/ml</li> </ul>
Intermediate	<ul style="list-style-type: none"> <li>• T2b-T2c or</li> <li>• Gleason score 7 or</li> <li>• PSA 10-20 ng/ml</li> </ul>
High	<ul style="list-style-type: none"> <li>• T3a or</li> <li>• Gleason score 8-10 or</li> <li>• PSA &gt; 20 ng/ml</li> </ul>

Favorable Intermediate-Risk <sup>a</sup>	Unfavorable Intermediate-Risk <sup>b</sup>
1 intermediate-risk factor <sup>c</sup>	> 1 intermediate-risk factor
GS 3+4=7 or less	GS 4+3=7
< 50% positive biopsy cores	≥ 50% positive biopsy cores

1

2

3

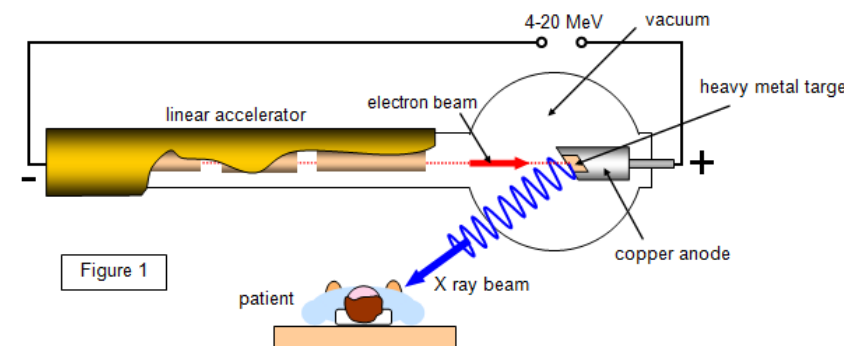
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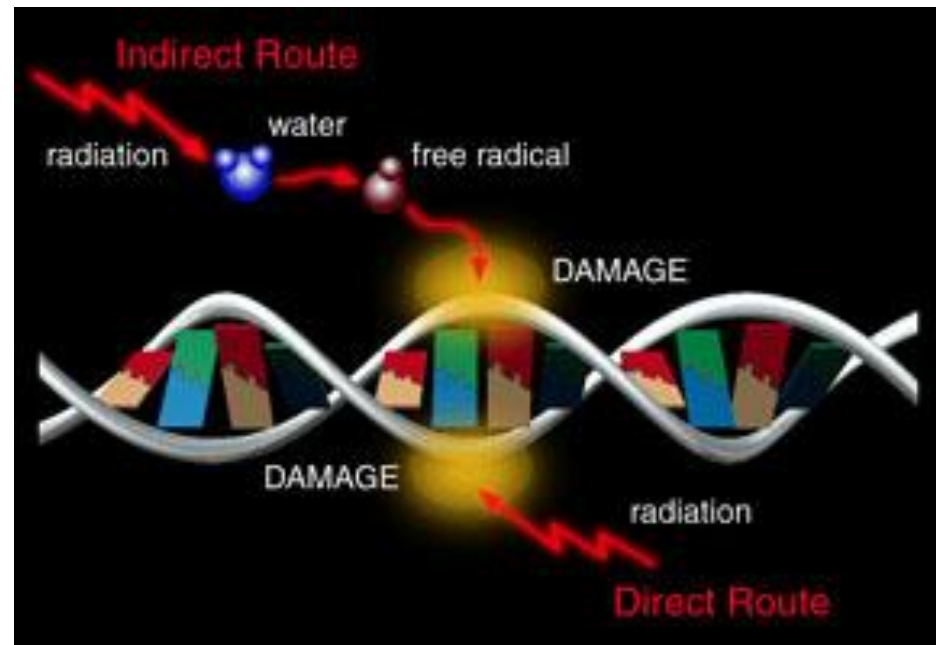
# External Beam Radiation Therapy

- Experience similar to diagnostic scan
- 5-20 min
- Gantry Head rotates around the patient and controls the shape/intensity of incident beam



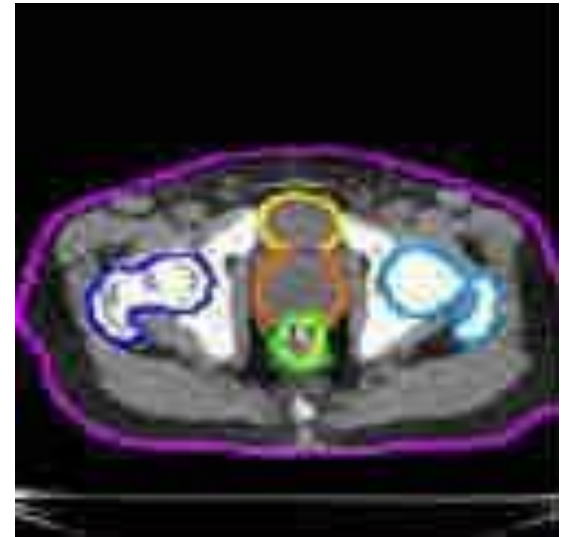
# Radiation Biology

- 2 modes of radiation-induced DNA damage
  - Direct (e.g. particulate RT such as protons)
  - Indirect: Megavoltage Xrays ionize water to form free radicals like hydrogen peroxide
- Cancer cell cannot repair DNA damage as well as normal cells
  - Treatment over many weeks allows normal body to repair DNA damage

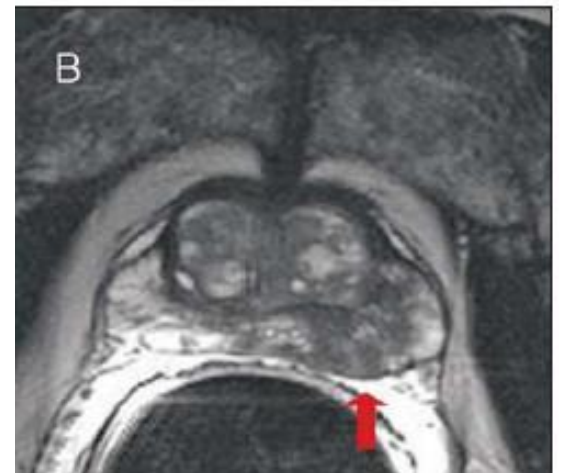


# Radiation Planning

- “CT Simulation” - Diagnostic quality CT is obtained in treatment position, MRI fused to help with targeting
- In RT planning software, labeling is performed for
  - *Targets*
    - Low risk: Prostate
    - Int Risk: Prostate and seminal vesicles (SV)
    - High risk: Prostate, SV, +/- pelvic lymph nodes
  - *Normal tissues:*
    - rectum, bladder, hip bones, bowel
- 8 mm margin is added
  - possible microscopic disease extension (ECE),
  - daily setup uncertainty, and
  - organ motion during treatment



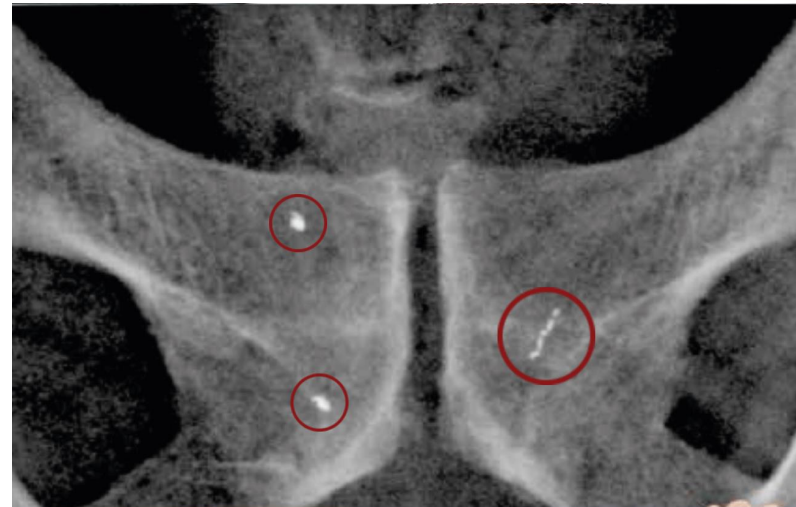
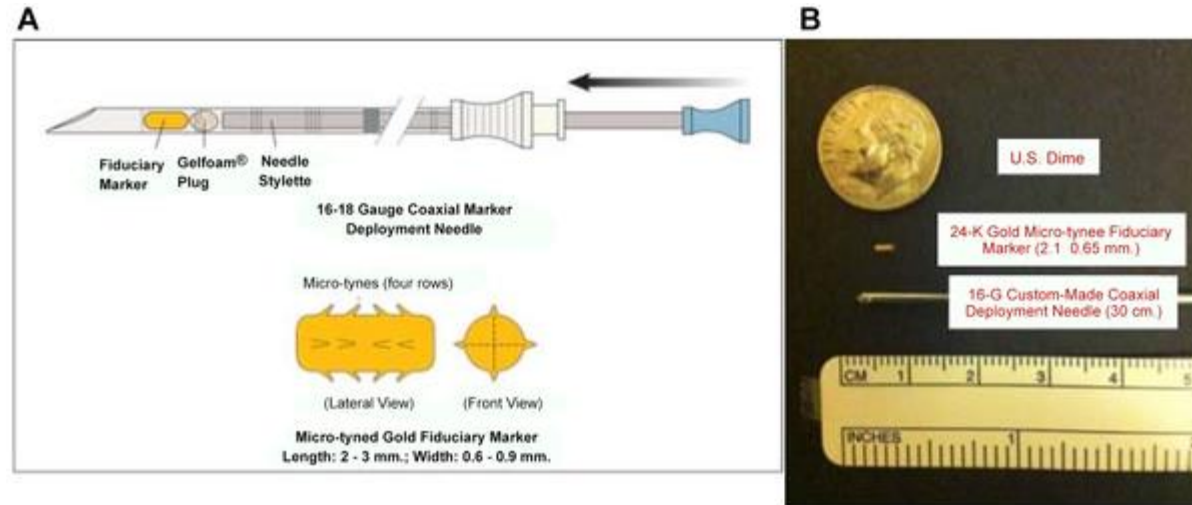
CT Simulation



MRI Prostate showing gross ECE

# Image Guided RT (IGRT)

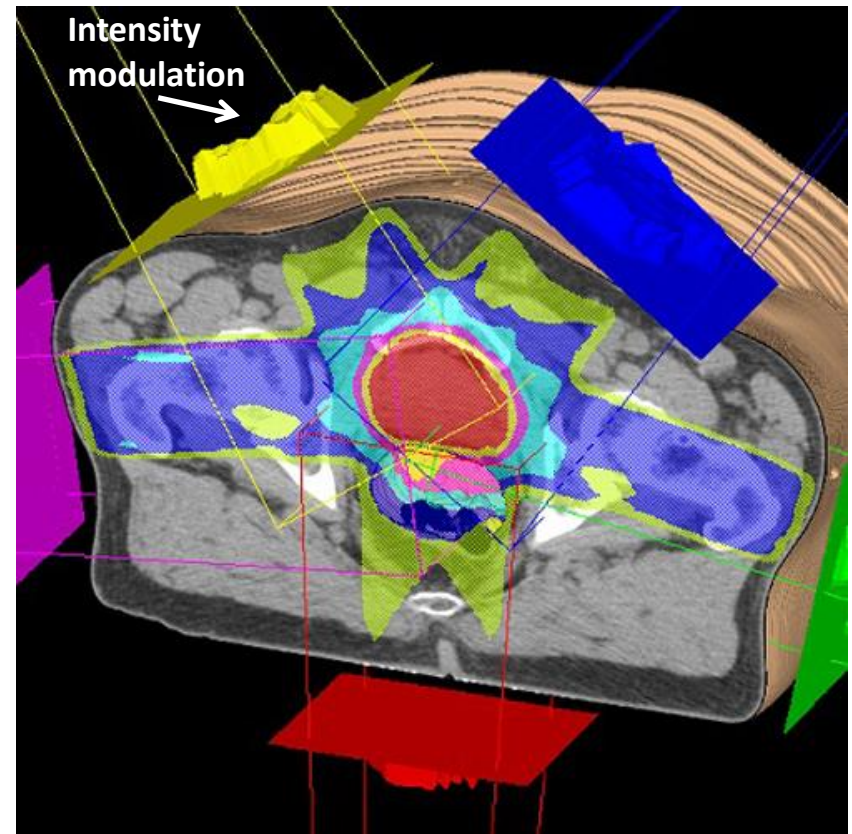
- Gold fiducial markers are placed 5-7 days prior to CT simulation
- Help to reduce setup uncertainty
- Prior to “Beam On”, daily xray is obtained and the patient is shifted to align on to the fiducial markers





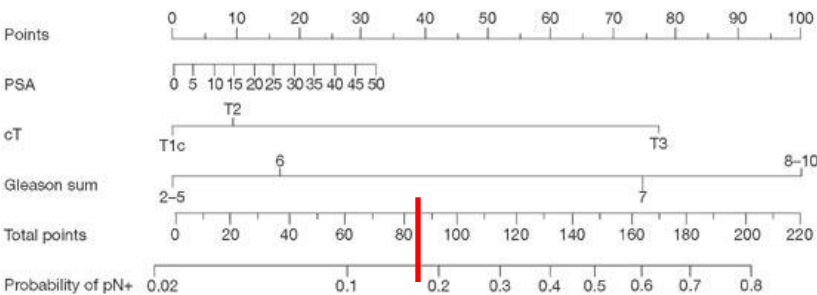
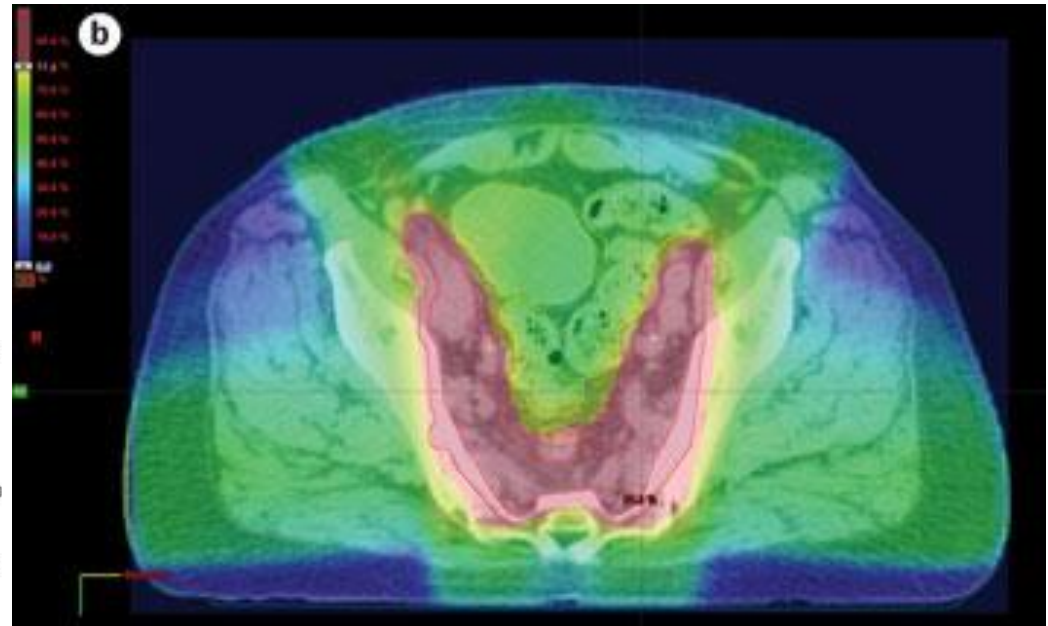
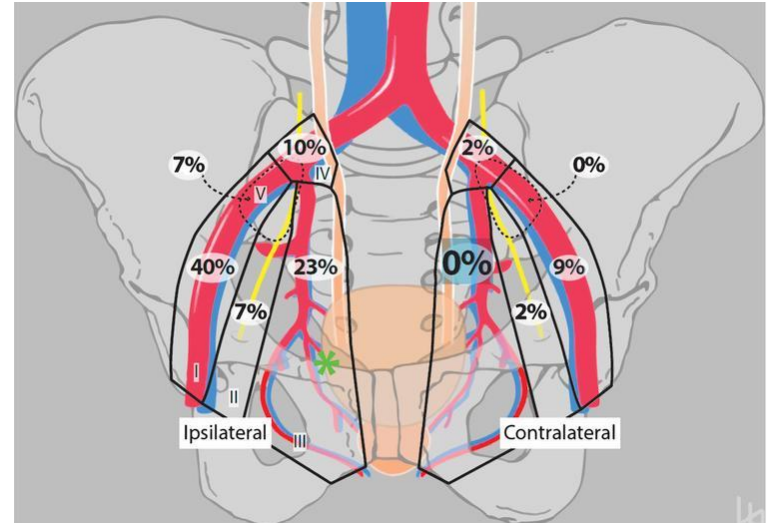
# External beam RT

- 9 weeks of daily treatment
- More precise radiation needed (e.g. IMRT) because dose escalation improves outcomes
- 5-7 intensity modulated beam angles
- arranged to conform to the target and minimize collateral normal tissue exposure



# Pelvic Nodal RT for High Risk

- The inclusion of pelvic lymph nodes for clinically localized high risk disease is controversial and is the subject of ongoing prospective study





# External Beam Radiation Side Effects

- ~50% patients experience acute/transient side effects, they gradually come on during treatment and intensify and go away 2-8 weeks after treatment completes
  - Fatigue
  - Rectal Inflammation (proctitis) = diarrhea
  - Bladder/Urethral Inflammation (cystitis/urethritis) = irritative symptoms
- Long term complications occur many months to years after treatment and are usually permanent
  - 30-40% have decreased erectile function
  - 20-30% low grade change in urinary or bowel function, modifiable with lifestyle/meds
  - 10% have mild rectal bleeding similar to hemorrhoid
  - <1% have more serious bleeding in bladder or rectum including serious injury requiring surgical intervention
  - 0.4% experience radiation-induced cancer

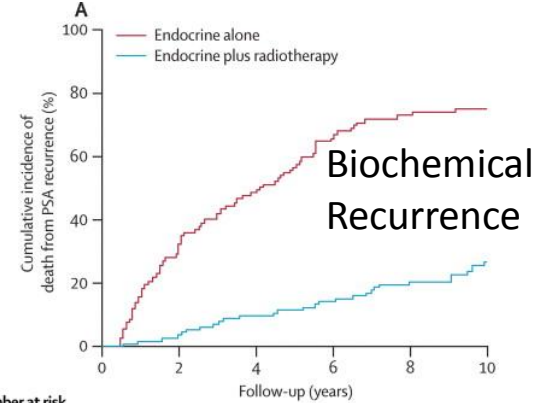
# Radiation Induced Cancer

- 2014 systematic review
  - 0.4% of patient develop radiation induced cancers, but this was with older radiation techniques
  - limited evidence for more modern techniques such as IMRT and brachytherapy is encouraging
- Important to have up to date colonoscopy

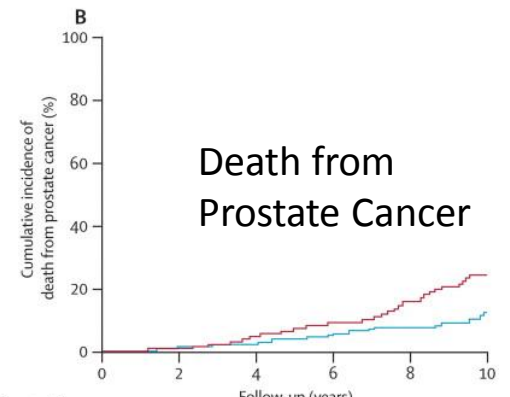


# Node+ Prostate Cancer

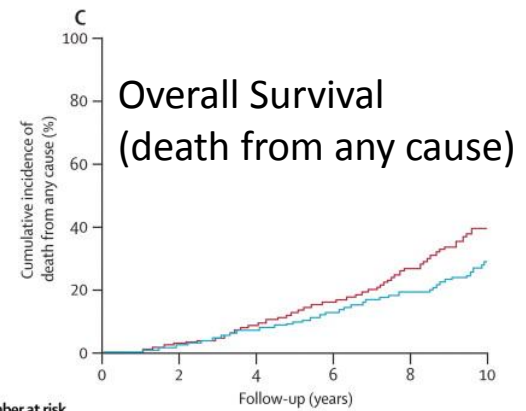
- High quality data shows **RT + ADT** improves survival over **ADT alone**
- Studies show slow/poor diffusion into community practice



Number at risk	0	2	4	6	8	10
Antiandrogen	432	296	216	149	125	119
Combination	430	412	368	341	315	303



Number at risk	0	2	4	6	8	10
Antiandrogen	439	424	400	360	336	314
Combination	436	426	405	361	359	345



Number at risk	0	2	4	6	8	10
Antiandrogen	439	424	400	368	336	314
Combination	436	426	405	381	359	345

# Postoperative Radiation

- Adjuvant Radiation: Radiation delivered within 6 months of surgery, with survival benefit for +Extracapsular Extension, +margins, +seminal vesicle invasion, or +lymph nodes
- Salvage Radiation: Radiation delivered > 6 months from surgery for a biochemical failure (PSA  $\geq 0.2$  on 2 measurements)
- Key Question: Is it better to radiate the prostate adjuvantly (based on above indications), or wait for the PSA to increase and deliver salvage RT?

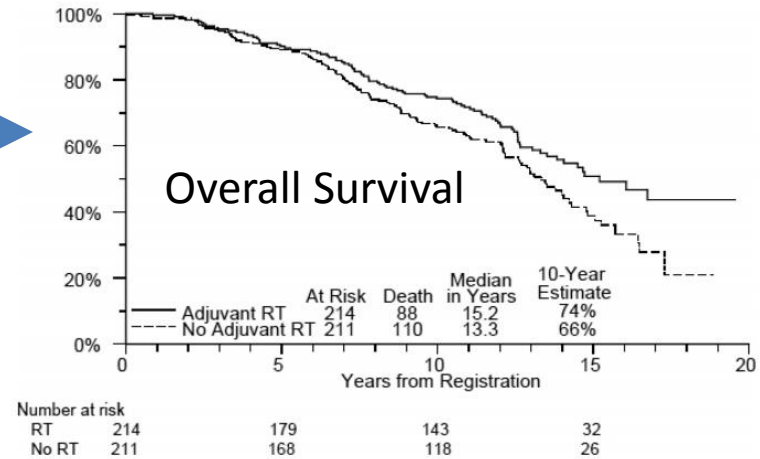
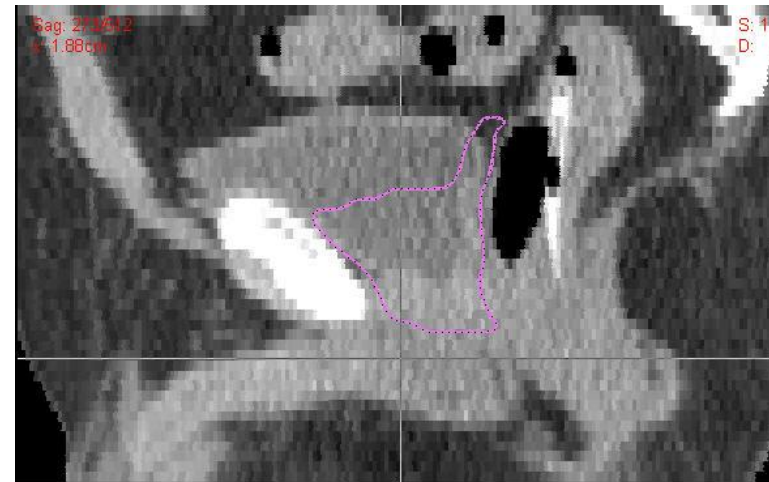
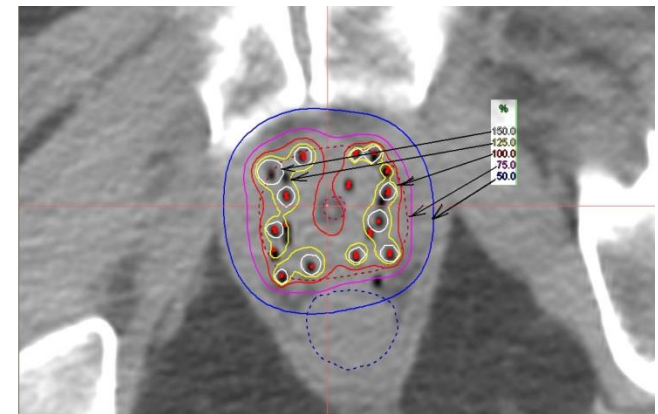
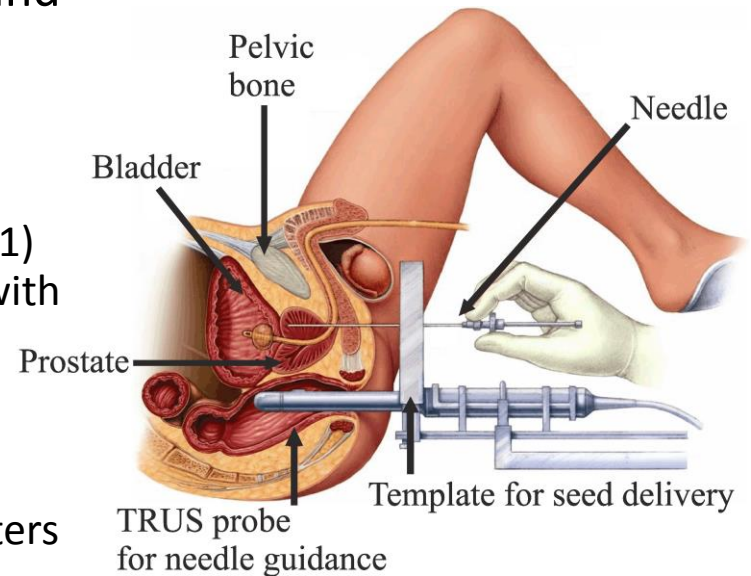


Fig. 2. Survival by Treatment Arm



# Prostate Brachytherapy

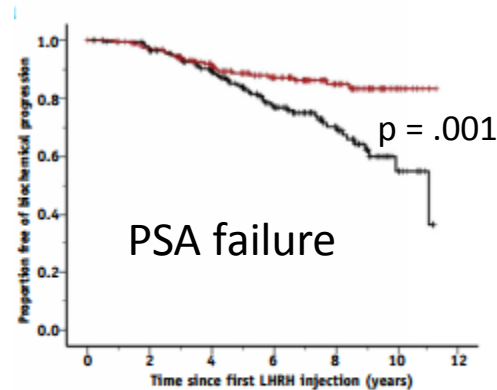
- Brachy alone is appropriate for very low, low, and favorable intermediate risk
- Low dose rate = permanent seed implant
  - 1 procedure
  - 50-70 radioactive sources (I-125, Pd-103, or Cs-131) are deposited homogeneously through the gland, with goal to spare the bladder/urethra/rectum
- High dose rate = temporary seed implant
  - (2-4 procedures)
  - Single Ir-192 source is after-loaded into the catheters to generate a customized dose cloud
- Typically does not require inpatient stay
- Side effects
  - Mainly urinary irritative/obstructive (Flomax)
  - Pain (NSAIDs)
  - Rectal toxicity less likely
  - Lowest rate of Erectile Dysfunction





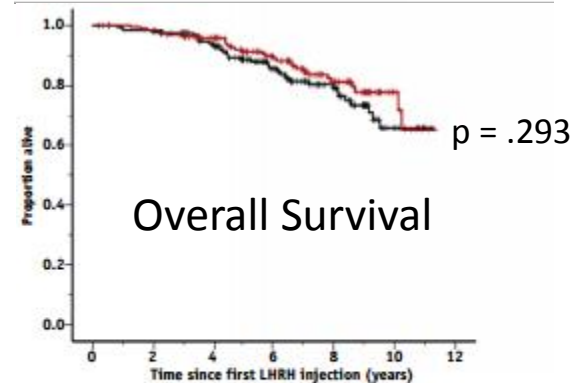
# Brachytherapy as a Boost

- Brachy boost is appropriate for unfavorable intermediate and high risk
- ASCEND-RT Trial
  - 400 pts treated to 46 Gy EBRT then randomized:
    - 32 Gy EBRT boost
    - 115 Gy brachy boost
  - 6.5 year median f/u



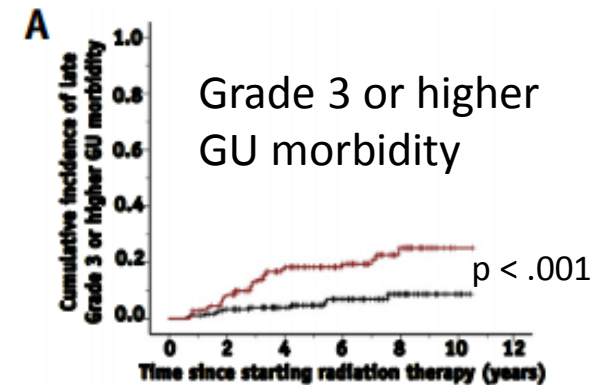
Numbers at risk:

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



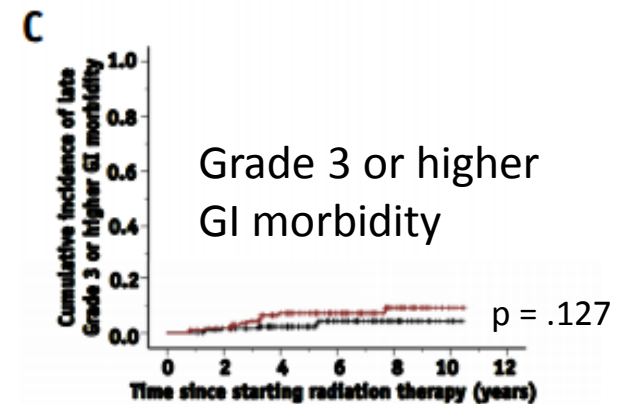
Numbers at risk:

Time (yrs)	0	2	3	4	5	6	7	8	9	10
DE-EBRT	200	192	184	161	134	109	85	66	40	16
LDR-PB	198	191	182	160	137	116	94	65	41	15



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

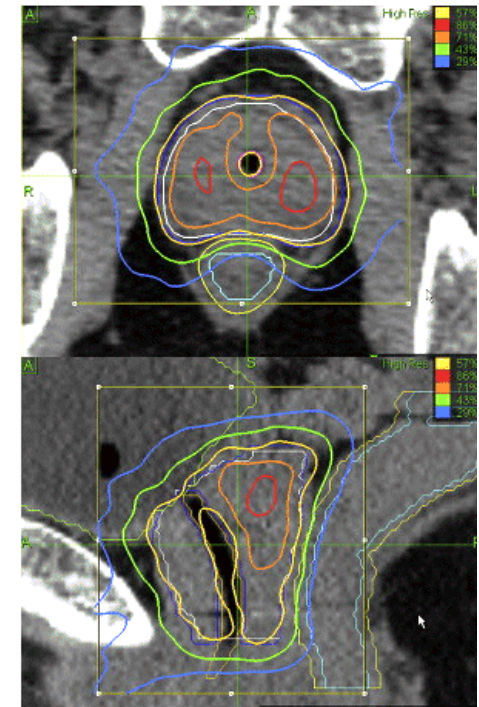


Numbers at risk:

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

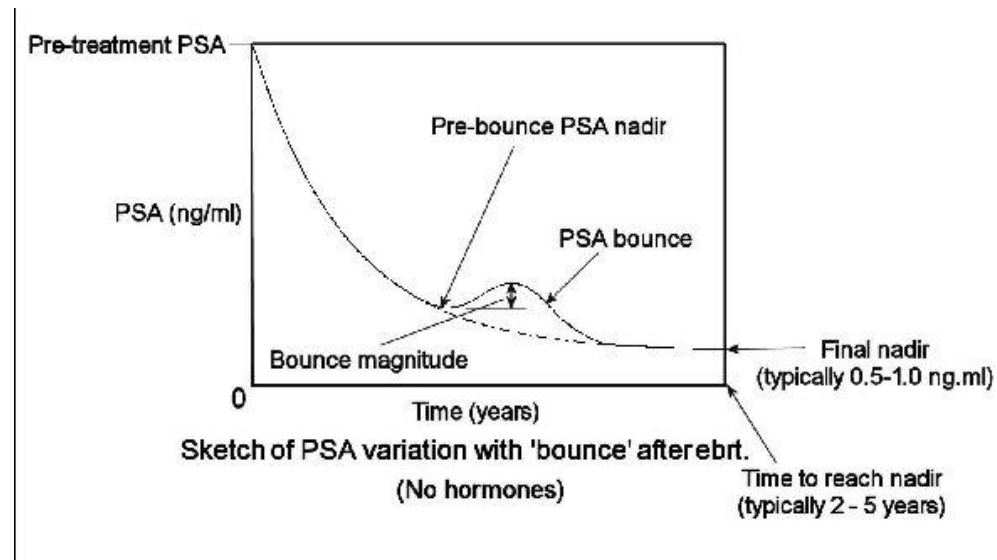
# Stereotactic Body RT (SBRT)

- 5 consecutive outpatient treatments, ~45 min/session
- Cyberknife: Uses a linac mounted on a robot to deliver hundreds of pencil beamlets from a spherical geometry
- Acute side effects are similar to external beam RT, but are of shorter duration.
- Long term side effects remain the subject of maturing prospective studies



# Follow-up after RT

- PSA nadir is lowest point and is usually reached 2-5 years after completion
- Beware of “PSA bounce” phenomenon
- Biochemical failure is defined as PSA nadir + 2.0 ng/mL

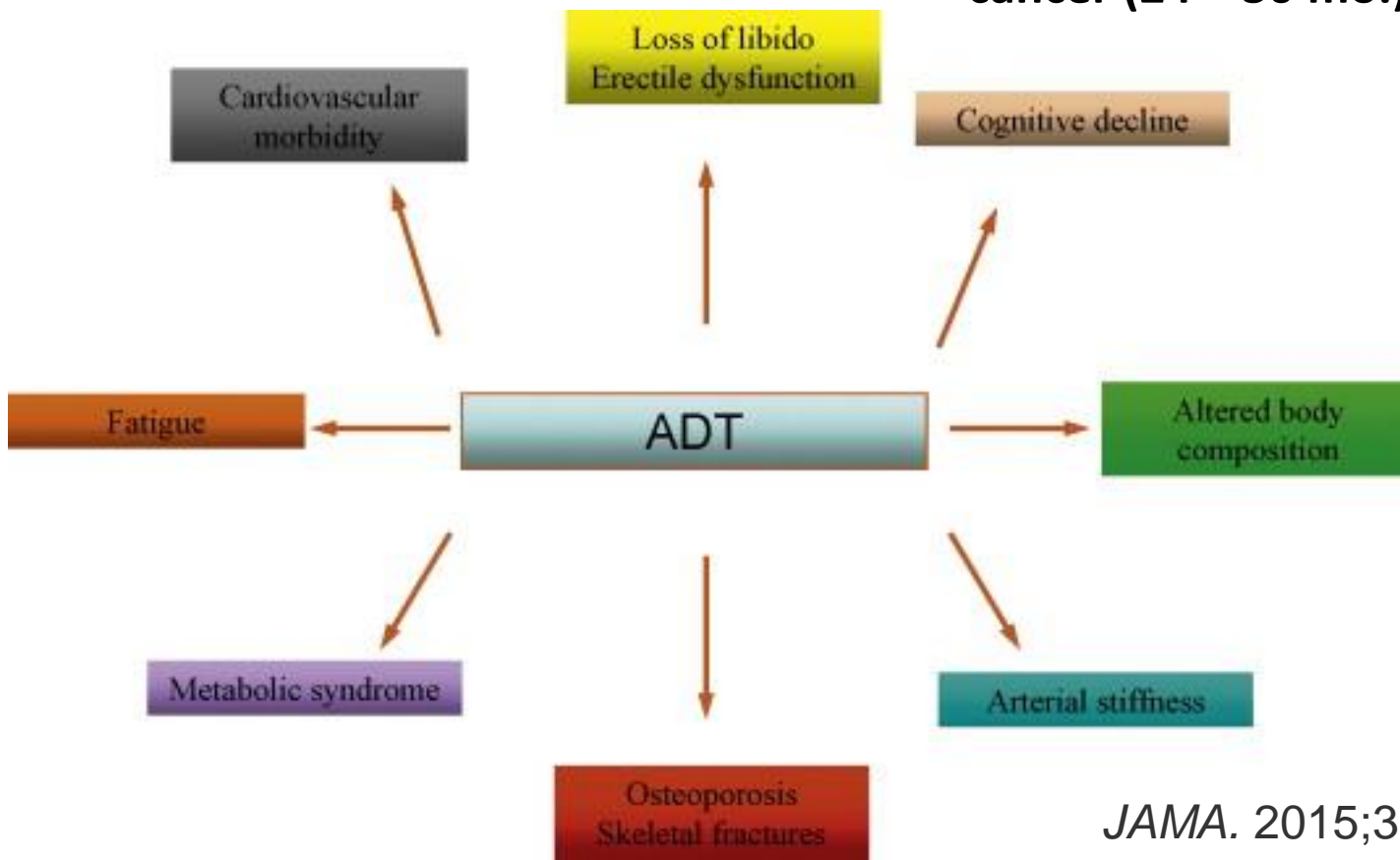


# Salvage after RT failure

- It is a myth that prostatectomy cannot be performed after external beam radiation failure
  - Important to r/o presence of metastatic disease
  - Must be performed in experienced hands
  - Associated with higher rates of morbidity
- Focal therapies such as radioactive seed implant (brachytherapy) are also options for salvage

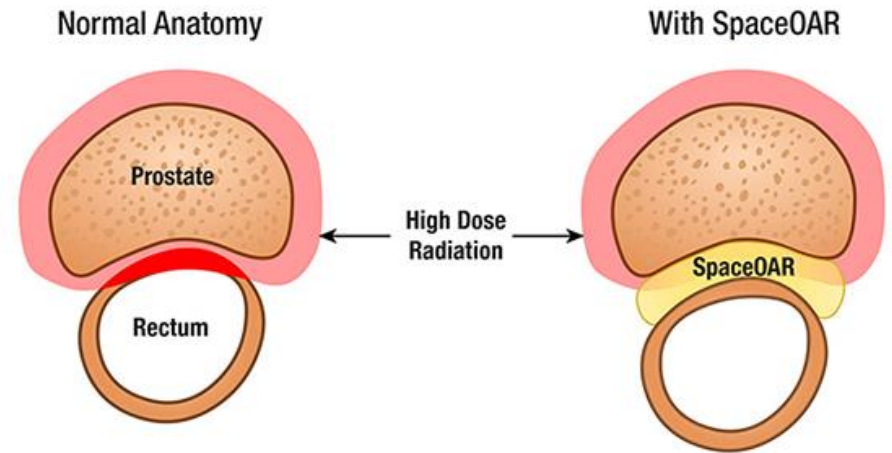
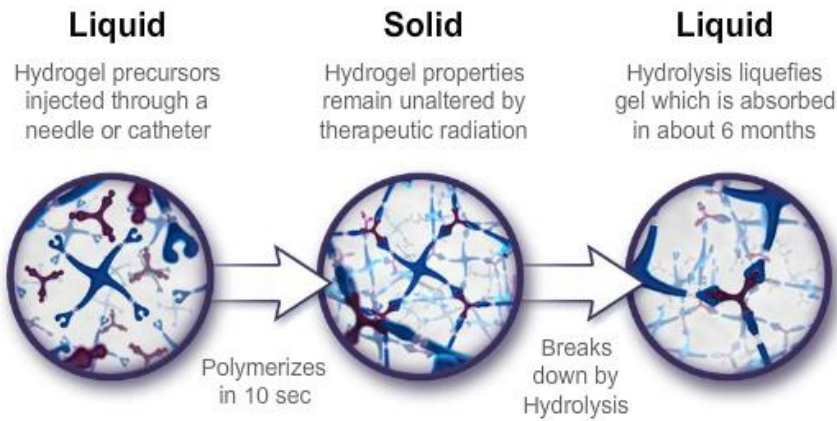
# Androgen Deprivation Therapy (ADT)

- ADT = Testosterone Inhibition (Chemical Castration)
  - Can ↓ prostate gland size
  - Sensitize cancer cell to radiation
  - Result in death of micrometastatic disease
  - **Used with RT for unfavorable intermediate (6 mo.) and high risk cancer (24 – 30 mo.)**

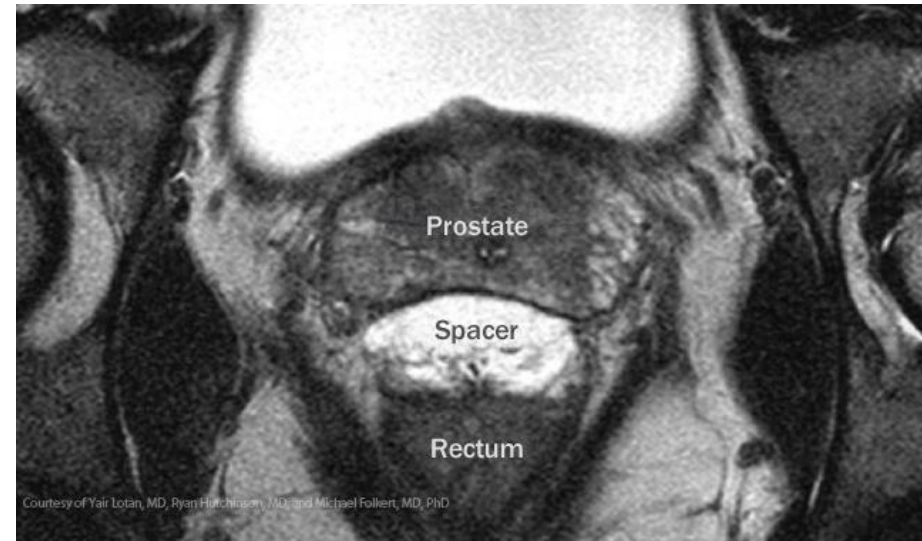




# SpaceOAR to Minimize Rectal Toxicity

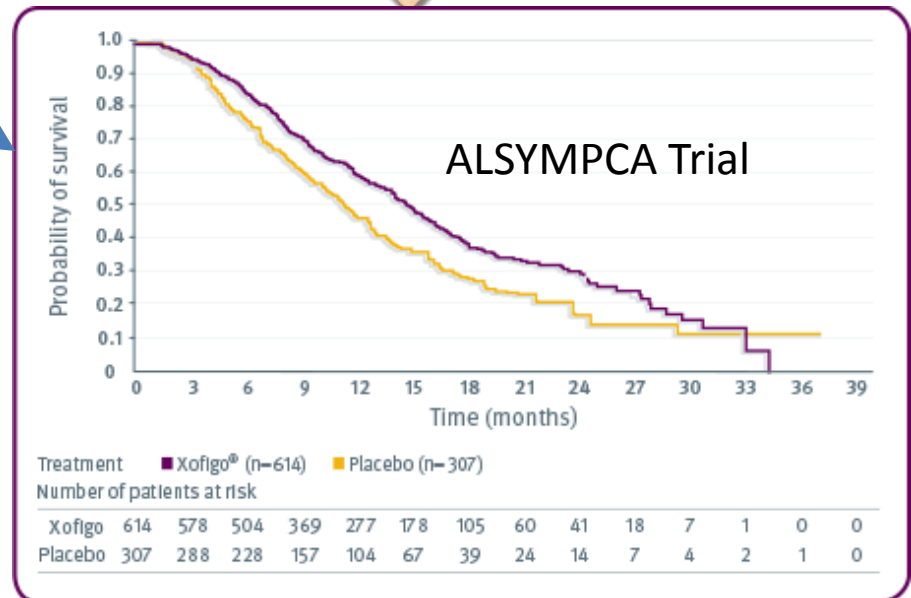
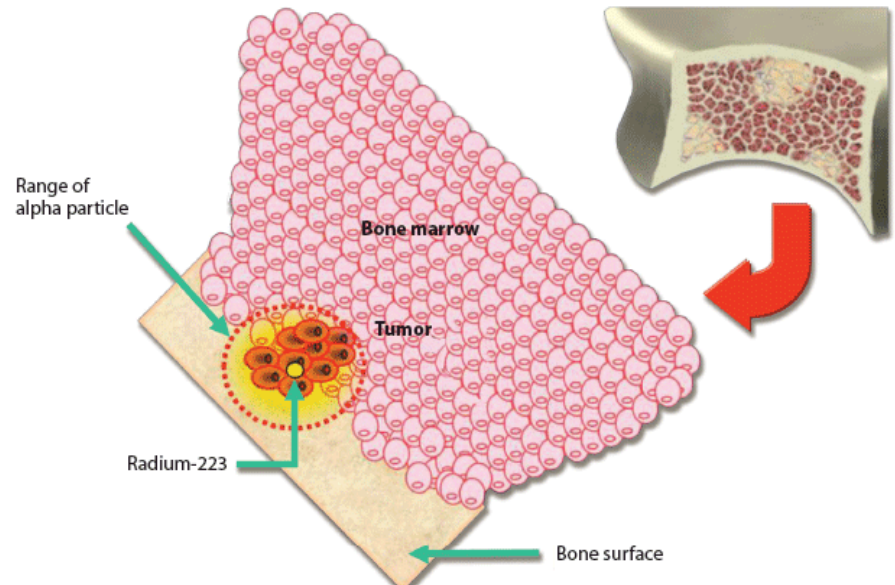


	No Spacer	Spacer
Acute Rectal Toxicity	41%	14%

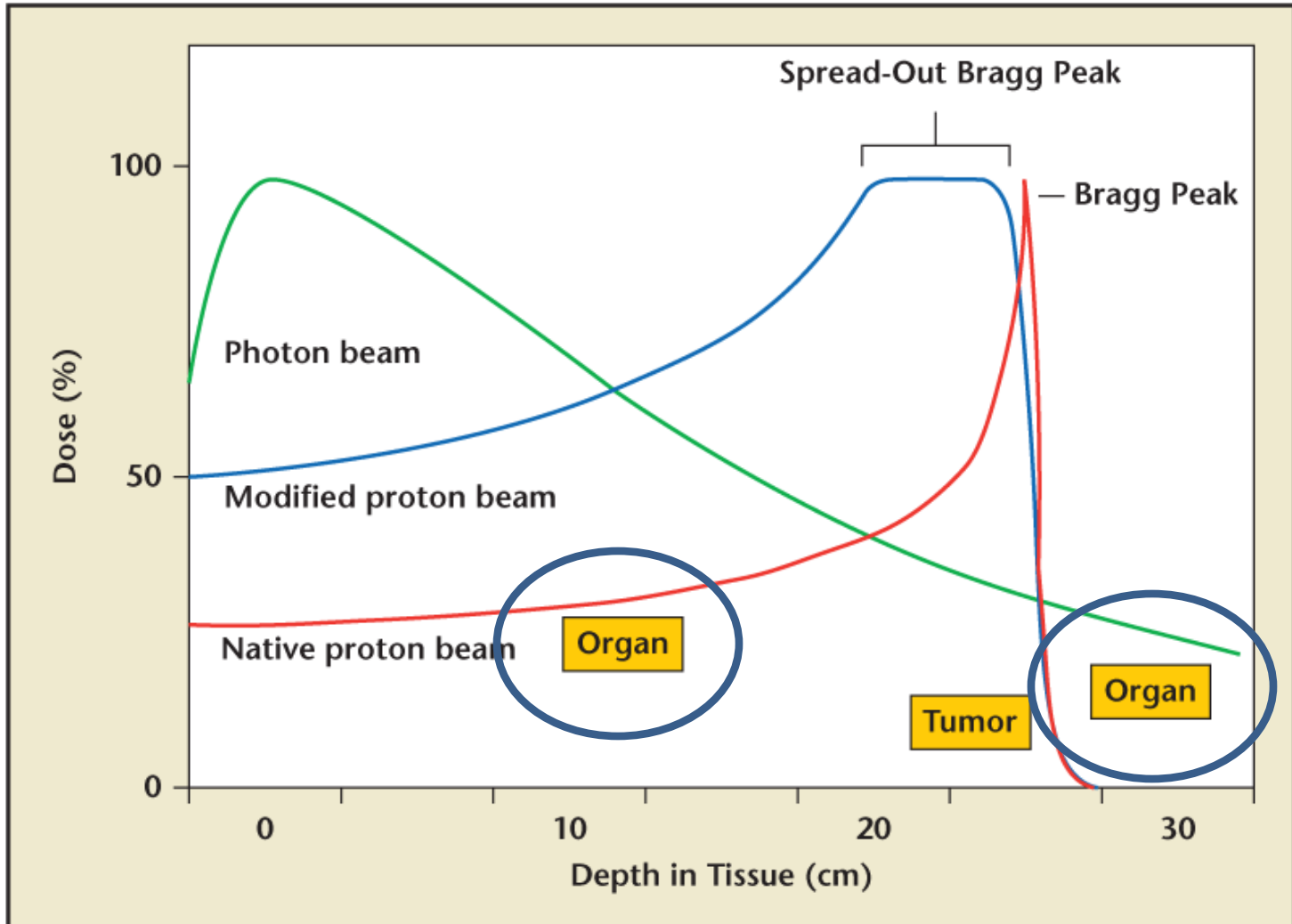


# Xofigo (Ra-223 Dichloride)

- “Liquid Radiation”, FDA approved 2013
- Calcium seeking mimetic binds to site of active bone turnover (cancer)
- Radium decays into helium ( $\alpha$  particles) with highly destructive millimeter range
  - Half life = 11 days
- Treatment consists of 6 monthly 1 minute infusions
- Associated with a survival benefit as compared with placebo
- Generally very well tolerated but side effects can include
  - n/v
  - Diarrhea
  - Decreased blood counts
  - fatigue

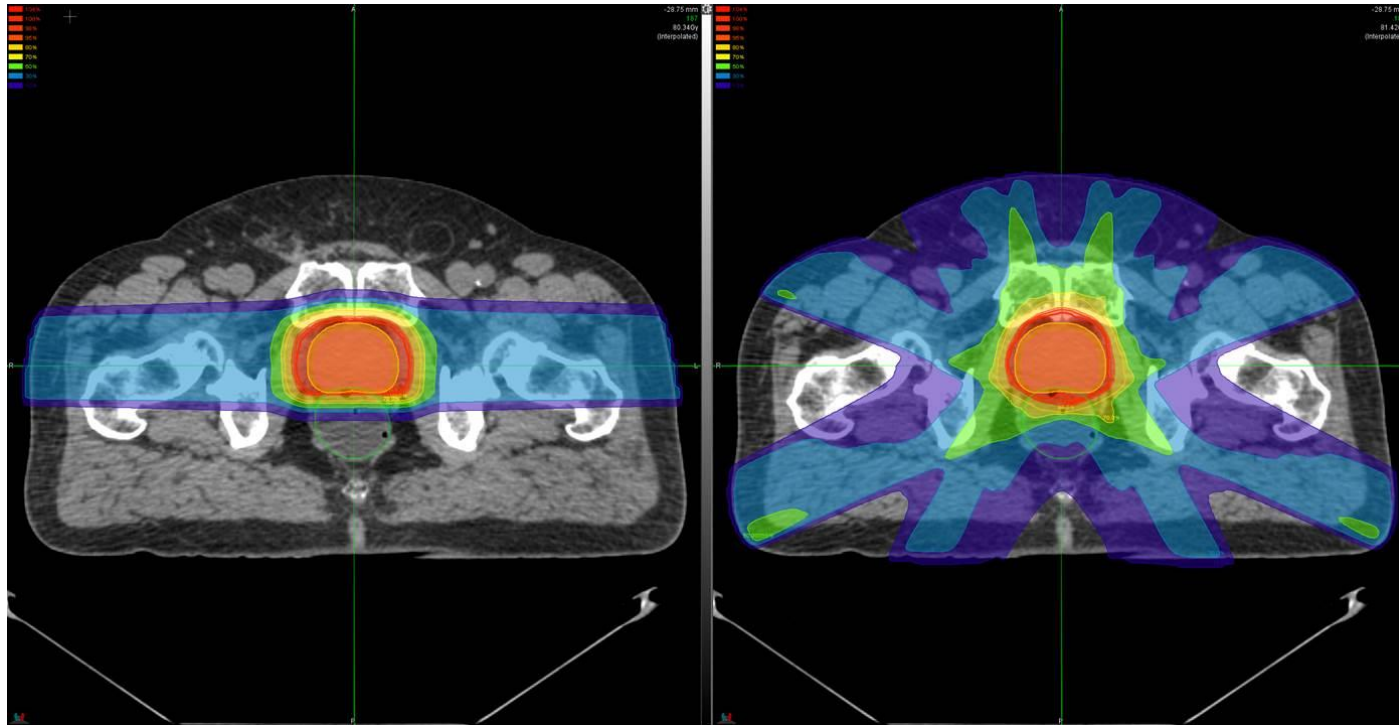


# Proton Radiation



# Proton RT

# IMRT



Proton radiation results in similar high dose exposure to normal tissues.

Pivotal Question: Does the decrease in lower radiation dose exposure yield improved clinical outcomes?

Does this justify the increased \$\$\$\$\$?





# Intensity-Modulated Radiation Therapy, Proton Therapy, or Conformal Radiation Therapy and Morbidity and Disease Control in Localized Prostate Cancer

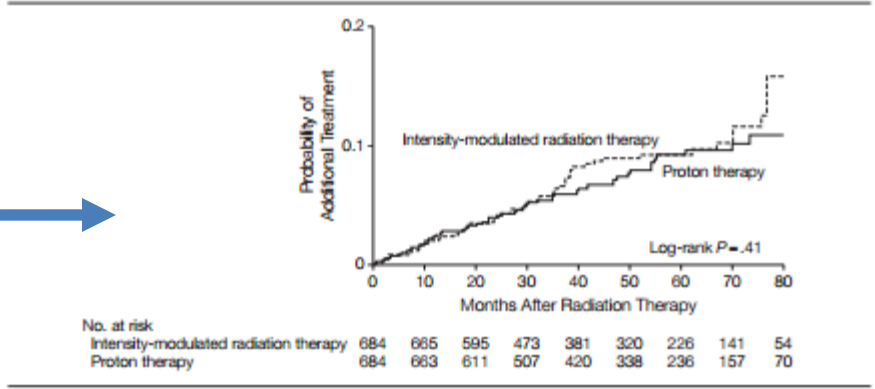
Population-based SEER data

Showed no improvement in cancer control from protons



Suggested that protons may be more dangerous in terms of rectal toxicity

**Figure 2.** Propensity Score–Matched Rates of Additional Cancer Treatment for Patients Treated With Intensity-Modulated Radiation Therapy vs Proton Therapy



**Table 6.** Outcomes for IMRT vs Proton Therapy With Propensity Score Matching and Instrumental Variable Analyses

Outcome per 100 Person-Years	Propensity Score Matched <sup>a</sup>						Instrumental Variable Analysis							
	IMRT (n = 684)			Proton (n = 684)			IMRT vs PT, Rate Ratio (95% CI)	IMRT (n = 8144) <sup>b</sup>			Proton (n = 1978) <sup>b</sup>			IMRT vs PT, Rate Ratio (95% CI)
	Total Events	100 Person-Years	Rate	Total Events	100 Person-Years	Rate		Total Events	100 Person-Years	Rate	Total Events	100 Person-Years	Rate	
Gastrointestinal events														
Procedures (including colonoscopy)	302	17	17.7	347	16.2	21.4	0.82 (0.70-0.97)	3074	169	18.2	883	41	21.6	0.60 (0.46-0.78)
Diagnoses	235	19	12.2	301	16.9	17.8	0.66 (0.55-0.79)	2620	182	14.4	714	45	16.0	0.66 (0.49-0.88)
Urinary nonincontinence events														
Procedures <sup>c</sup>	44	25	1.8	42	25.8	1.6	1.06 (0.69-1.63)	466	233	2.0	113	62	1.8	1.71 (0.87-3.36)
Diagnoses	161	22	7.5	144	22.9	6.3	1.25 (0.99-1.58)	1864	198	9.4	454	53	8.6	1.10 (0.78-1.58)
Urinary incontinence events														
Procedures	161	21	7.6	173	22.1	7.8	0.97 (0.77-1.20)	2029	194	10.5	511	51	10.0	1.06 (0.76-1.50)
Diagnoses <sup>c</sup>	75	24	3.1	82	24.8	3.3	0.96 (0.70-1.32)	816	226	3.6	200	59	3.4	1.03 (0.63-1.71)
Erectile dysfunction events														
Procedures <sup>c</sup>	21	25	0.8	36	26.2	1.4	0.61 (0.35-1.06)	206	239	0.9	70	63	1.1	0.58 (0.24-1.41)
Diagnoses	145	22	6.6	164	22.2	7.4	0.89 (0.70-1.12)	1454	208	7.0	436	53	8.3	0.78 (0.54-1.13)
Hip fracture <sup>d</sup>	21	26	0.8	18	26.6	0.7		192	239	0.8	40	63	0.6	1.42 (0.50-4.02)
Additional cancer therapy	58	26	2.2	52	27.5	1.9	1.26 (0.86-1.84)	588	252	2.3	124	67	1.9	1.60 (0.85-3.00)

Abbreviation: IMRT, intensity-modulated radiation therapy.  
<sup>a</sup>Rates shown are adjusted for the variables presented in Tables 4 and 5, using propensity scores implemented by matching.  
<sup>b</sup>Rates for IMRT and proton were adjusted with a 2-stage least-squares instrumental variable approach in which Radiation Therapy Oncology Group affiliation predicts proton use; this predicted value was subsequently used as exposure in an adjusted outcome model to estimate the effect of IMRT vs proton on the outcome.  
<sup>c</sup>Because of zero cell counts, Surveillance, Epidemiology, and End Results region was not included in propensity score–matched models.  
<sup>d</sup>Because of the small number of events and zero cell counts in some covariates in the propensity score–matched model, rate ratio could not be calculated.





# Prostate Cancer Management (in a Nutshell)

Likely to be organ confined

Risk	Treatment Options
<b>Very Low</b>	<b>Active Surveillance</b> <b>urged, All options:</b> (Surgery, EBRT, <i>Brachytherapy alone, SBRT</i> )
<b>Low</b>	<b>All options:</b> (Active Surveillance, Surgery, EBRT, <i>Brachytherapy alone, SBRT</i> )
<b>Favorable Intermediate</b>	<b>No active surveillance, otherwise all options:</b> (Surgery, EBRT, <i>Brachytherapy alone, SBRT</i> )
Unfavorable Intermediate	Surgery, EBRT +/- brachytherapy (only as a boost after EBRT), No SBRT
High	Surgery, EBRT w/ 18-24 months ADT +/- brachytherapy (as a boost)

## Abbreviations

EBRT	External Beam Radiation Therapy
SBRT	Stereotactic body radiation therapy
ADT	Androgen deprivation therapy

# Lynn Cancer Institute – Sandler Pavillion



Image: Przyborski Productions, Pittsburgh PA