UC San Diego Health

Contemporary management of localized prostate cancer

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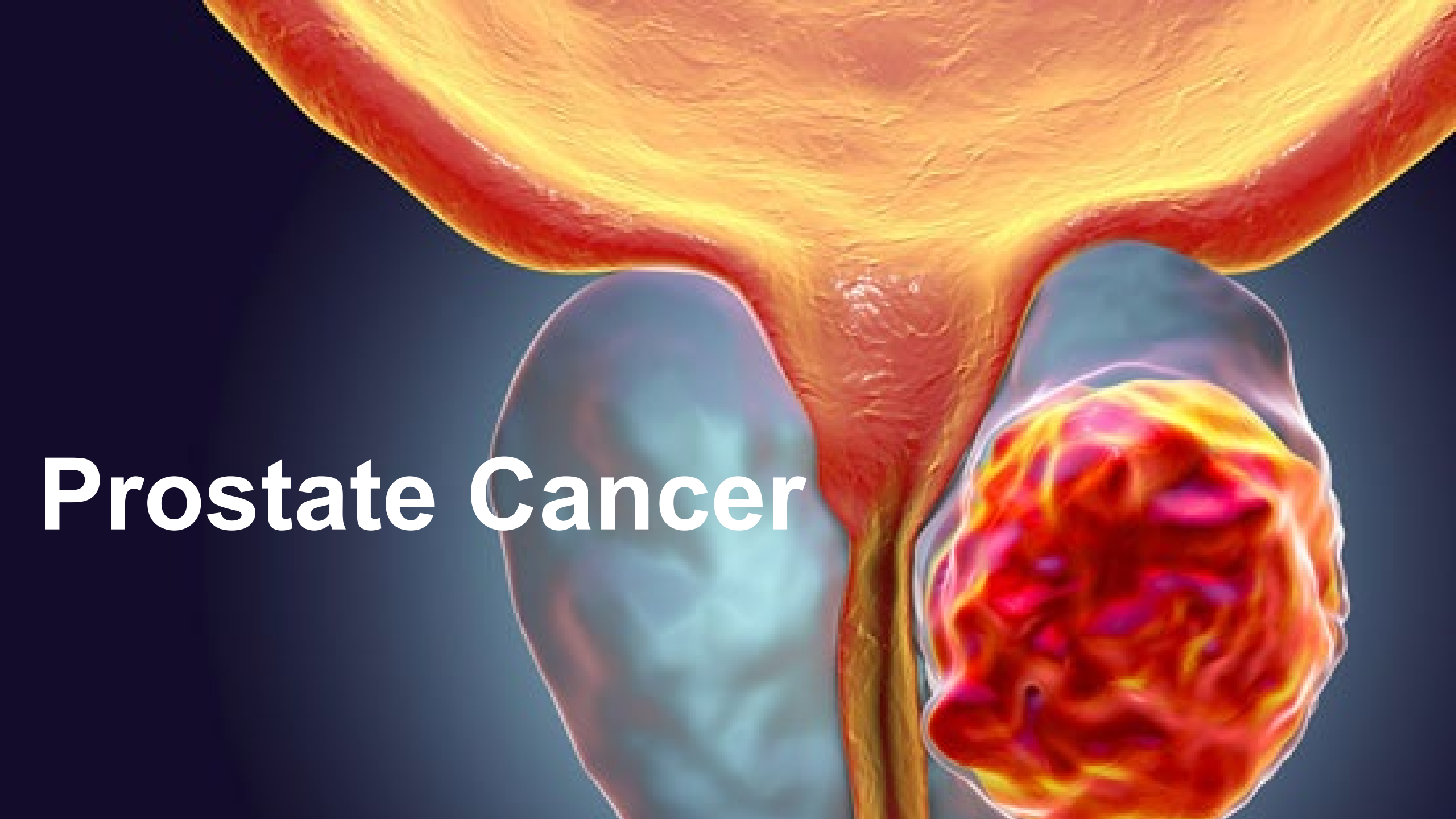
Prostate Cancer



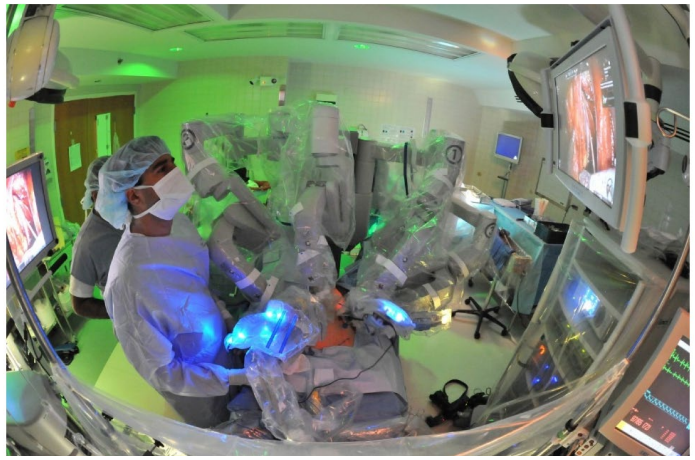
Prostate cancer in the press

The Washington Post

To Your Health

Almost all men with early prostate cancer survive 10 years, regardless of treatment

By Laurie McGinley September 14



The New York Times

ARCH

Teaching Your Child Emotional Agility

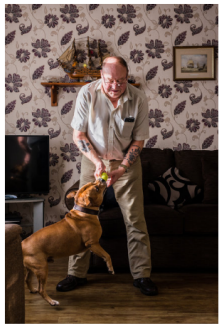
Copper Sinks and Faucets May Stem Hospital Infections

Toxins Linger in Homes Long After Smokers Quit

HEALTH

Prostate Cancer Study Details Value of Treatments

By DENISE GRADY SEPT. 14, 2016



Robert Boulton, a prostate cancer patient, was initially assigned to receive active monitoring but switched to radiation treatment after four years, when his P.S.A. went up.

Alexander Atack for The New York Times

A new study offers important information to men who are facing difficult decisions about how to treat prostate cancer in its early stages, or whether to treat it at all.

Researchers followed patients for 10 years and found no difference in death rates between men who were picked at random to have surgery or radiation, or to rely on "active monitoring" of the cancer, with treatment only if it progressed.

Death rates from the cancer were low over all: only about 1 percent of patients 10 years after diagnosis.

But the disease was more likely to progress and spread in the men who opted for monitoring rather than for early treatment. And about half the patients in the study who had started out being monitored wound up having surgery or radiation.

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TIME

LATEST MAGAZINE VIDEOS

Prostate Cancer Treatment Doesn't Save More Lives Than Active Surveillance

HEALTH CANCER

Prostate Cancer Treatment Doesn't Save More Lives Than Active Surveillance

THE WALL STREET JOURNAL.

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ELECTION 2016

VP Candidates Defend Their Running Mates

Trump's Buzz Challenges Clinton's Organization

Lobbyists as Directors Test Rules for Corporate Boards

Hurricane Matthew Threatens Florida, the Carolinas

U.S.

With Early Prostate Cancer, Forgoing Treatment Makes No Difference

Skepticism even within Urologic Oncologists

WHITMOREISMS: MEMORABLE QUOTES FROM WILLET F. WHITMORE, JR, M.D.

JAMES E. MONTIE AND JOSEPH A. SMITH, JR

The current state of prostate cancer may not be good medicine but it sure is good business.

There are more people making a living from prostate cancer than there are dying from it.

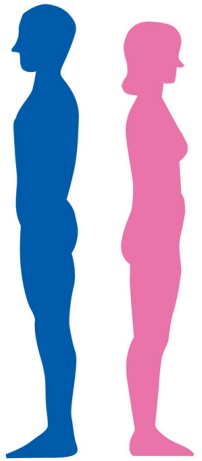
Prostate Cancer: Epidemiology

- In the United States
  - #1 cause of cancer in men
  - ~250,000 new cases per year
  - 26% of all cancer diagnoses!
  - 12% lifetime risk of prostate cancer

  - #2 case of cancer death in men
  - ~34,130 deaths / year

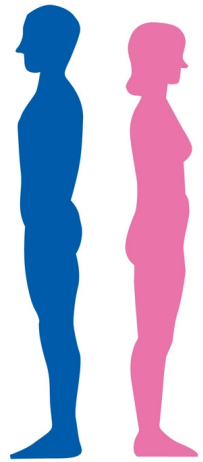
Estimated New Cases

Males			Females		
Prostate	248,530	26%	Breast	281,550	30%
Lung & bronchus	119,100	12%	Lung & bronchus	116,660	13%
Colon & rectum	79,520	8%	Colon & rectum	69,980	8%
Urinary bladder	64,280	7%	Uterine corpus	66,570	7%
Melanoma of the skin	62,260	6%	Melanoma of the skin	43,850	5%
Kidney & renal pelvis	48,780	5%	Non-Hodgkin lymphoma	35,930	4%
Non-Hodgkin lymphoma	45,630	5%	Thyroid	32,130	3%
Oral cavity & pharynx	38,800	4%	Pancreas	28,480	3%
Leukemia	35,530	4%	Kidney & renal pelvis	27,300	3%
Pancreas	31,950	3%	Leukemia	25,560	3%
All Sites	**970,250**	**100%**	**All Sites**	**927,910**	**100%**



Estimated Deaths

Males			Females		
Lung & bronchus	69,410	22%	Lung & bronchus	62,470	22%
Prostate	34,130	11%	Breast	43,600	15%
Colon & rectum	28,520	9%	Colon & rectum	24,460	8%
Pancreas	25,270	8%	Pancreas	22,950	8%
Liver & intrahepatic bile duct	20,300	6%	Ovary	22,950	5%
Leukemia	13,900	4%	Uterine corpus	12,940	4%
Esophagus	12,410	4%	Liver & intrahepatic bile duct	9,930	3%
Urinary bladder	12,260	4%	Leukemia	9,760	3%
Non-Hodgkin lymphoma	12,170	4%	Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,500	3%	Brain & other nervous system	8,100	3%
All Sites	**319,420**	**100%**	**All Sites**	**289,150**	**100%**

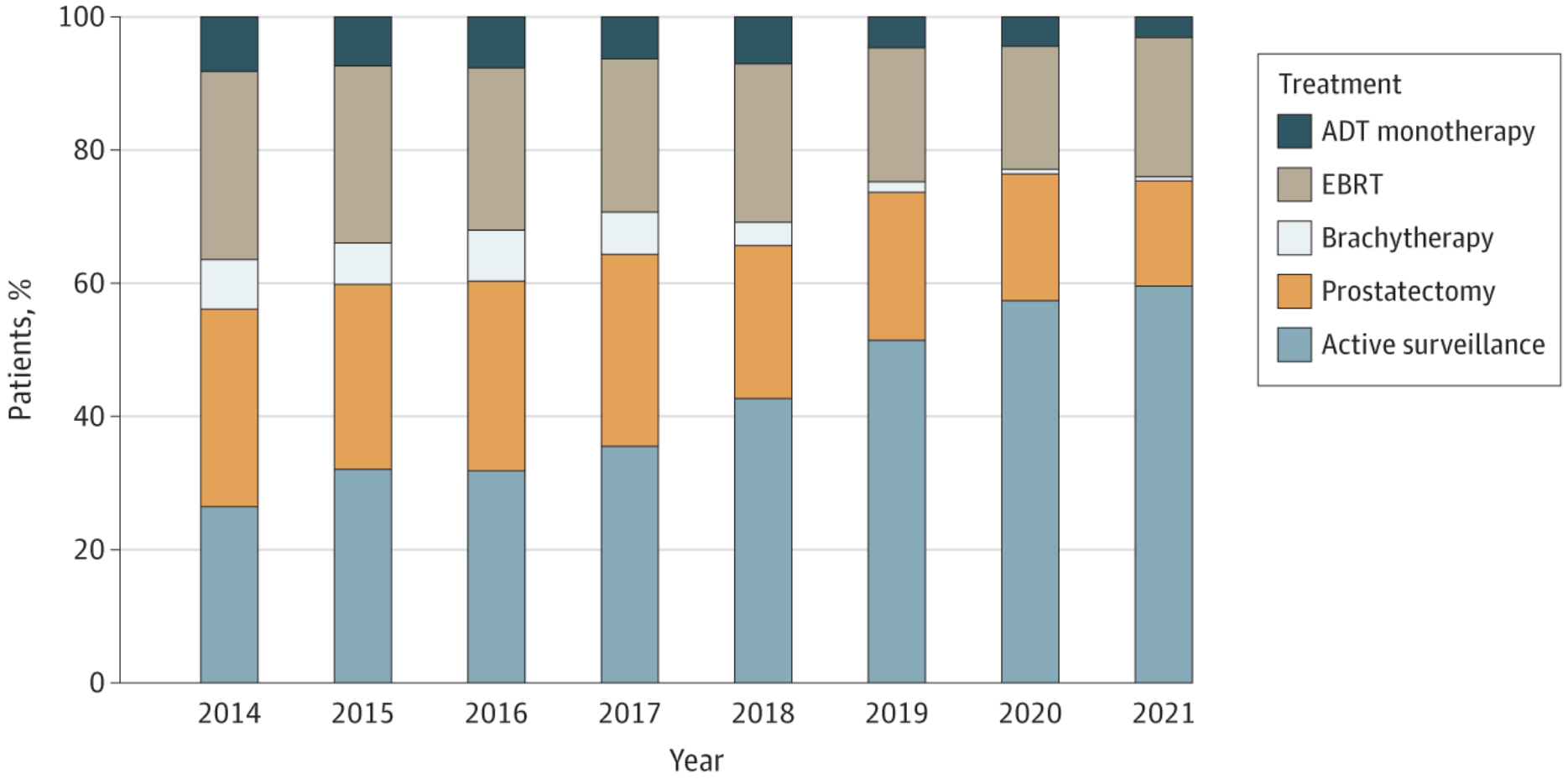


Siegel et al. Cancer 2021

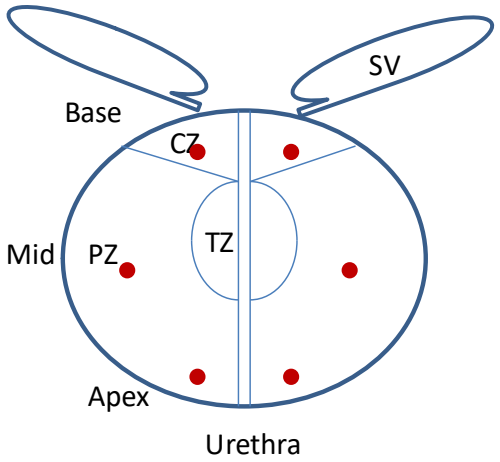
JAMA Network™

From: **Time Trends and Variation in the Use of Active Surveillance for Management of Low-risk Prostate Cancer in the US**

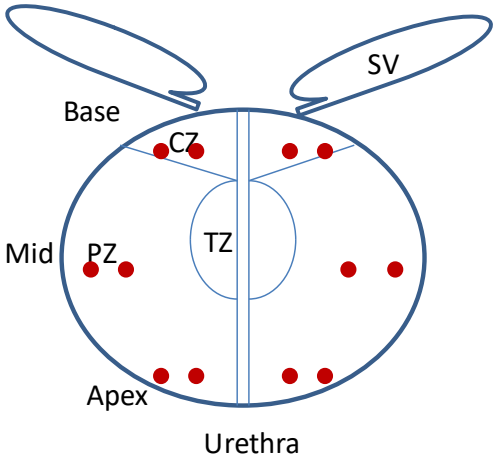
JAMA Netw Open. 2023;6(3):e231439. doi:10.1001/jamanetworkopen.2023.1439



PSA/Diagnosis of prostate cancer

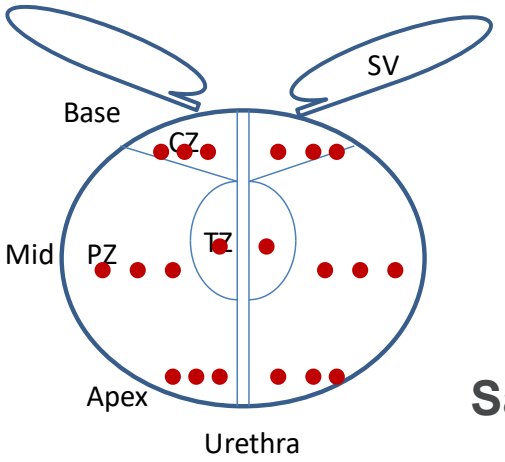


Sextant



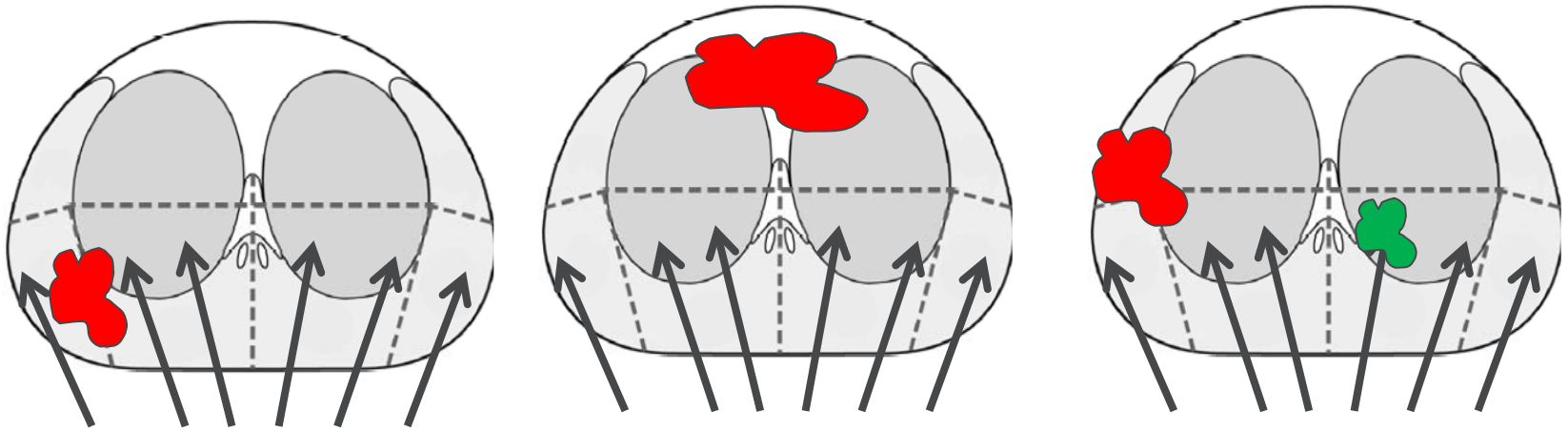
12-core

Biopsy techniques have relied on *random* sampling of the prostate gland



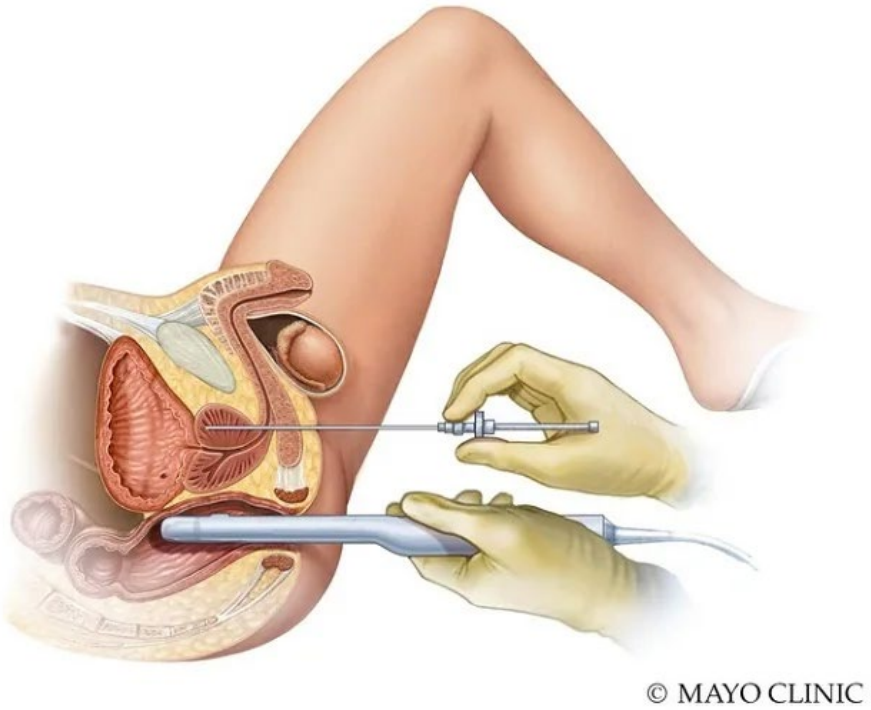
Saturation

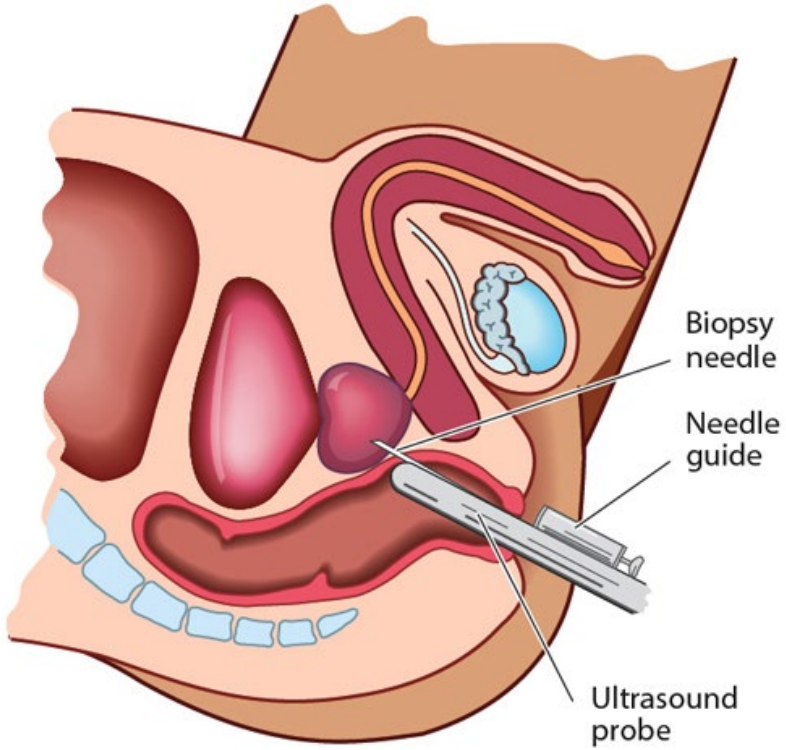
Some clinically significant cancers are missed because of sampling error of the biopsy, and many men are diagnosed with clinically insignificant disease.



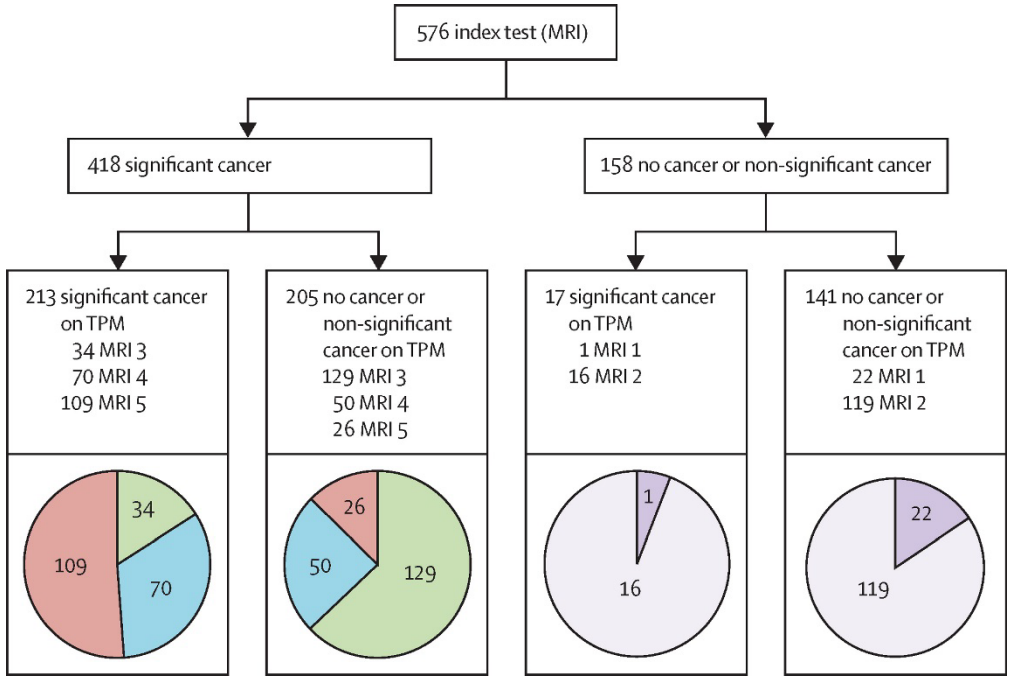
PSA Screening: Accuracy

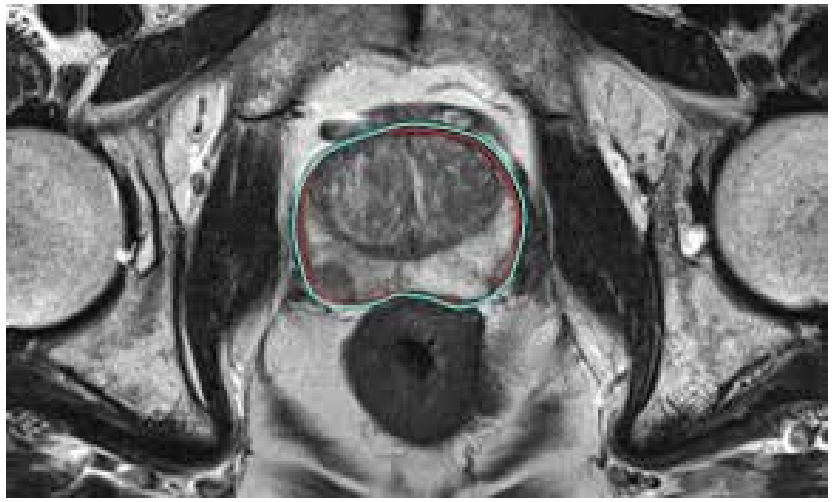
- **Old-Paradigm**
  - **Annual PSA check**
  - **If PSA greater than 3-4 -> repeat -> if persistent -> TRUS Biopsy**





MRI for prostate cancer screening



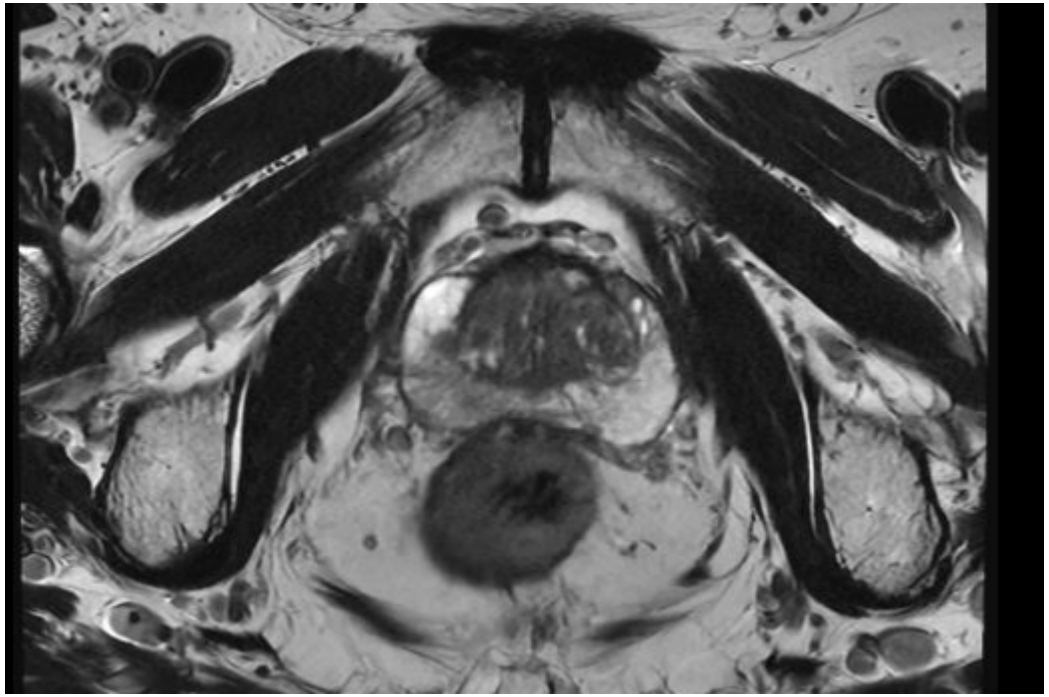


Sensitivity 93% (95% CI 88–96), positive predictive value 51% (46–56), specificity 41% (36–46), negative predictive value 89% (83–94).

Lancet 2017: Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study

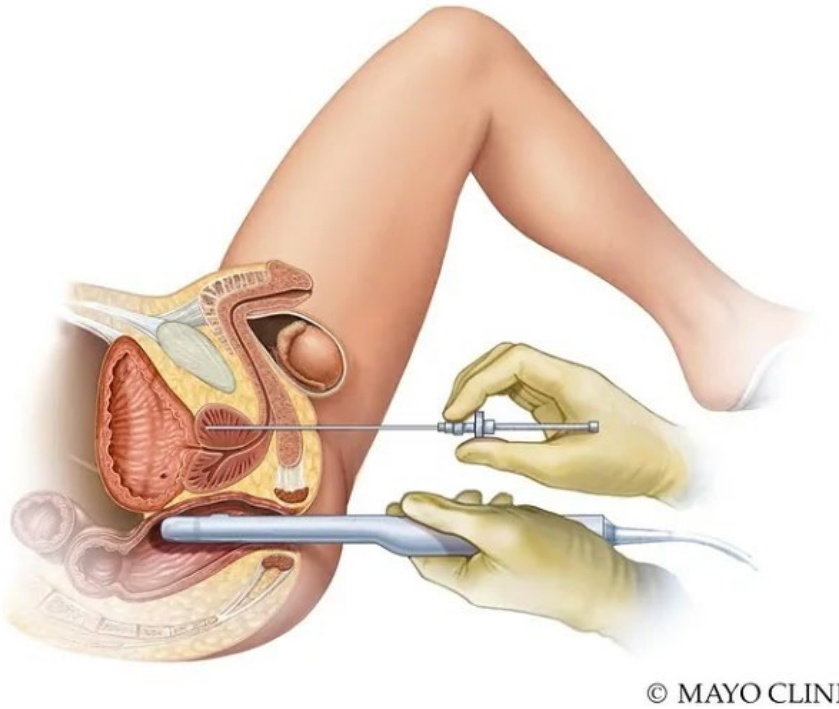
Sample Case 1

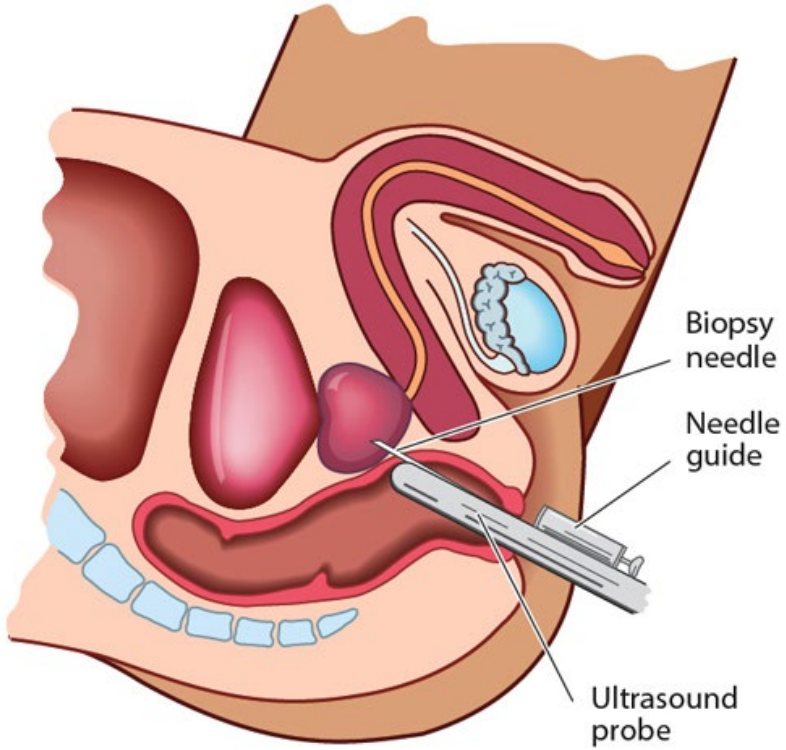
- 69 man with a PSA of 6.21, repeat PSA 6.26 January 2023. Prostate MRI read as no suspicious lesions.
  - ExoDX Urine Test (PSA Adjunct) shows increased lifetime risk of developing prostate cancer, Prostate volume 37.8, PSA Density 0.16
  - TRUS prostate biopsy shows inflammation and no evidence of prostate cancer
  - Planned for repeat PSA in 12 months



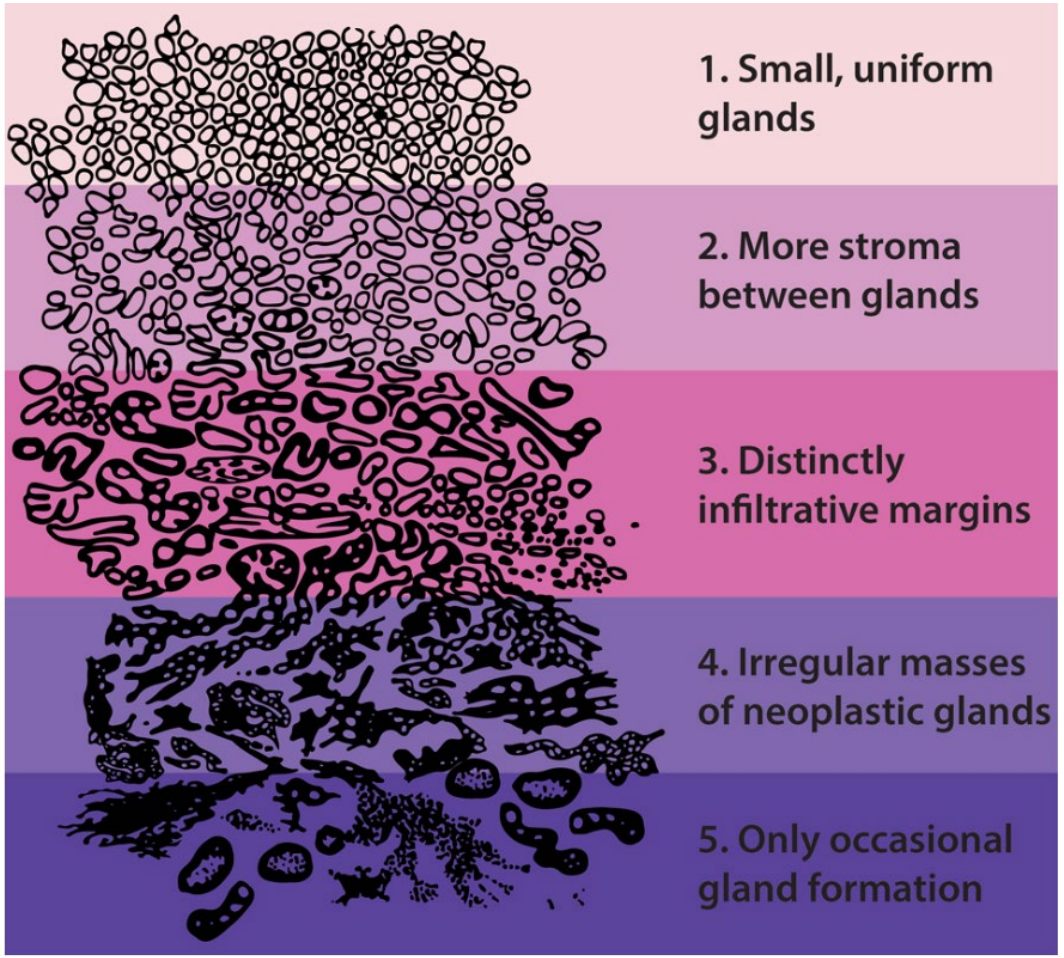
Contemporary evaluation of PSA

- Screening smarter (imaging, biomarkers) →
  - Avoidance of biopsies
  - Decreased diagnosis of clinically insignificant prostate cancer
  - Enrichment for higher risk/significant prostate cancer





GLEASON PATTERN



Grade 1: Well-differentiated (***not contribute to score***)

Grade 2: Moderately differentiated (***not contribute to score***)

Grade 3: moderate-poorly differentiated

Grade 4: Poorly differentiated, marked anaplasia

Grade 5: minimal resemblance of normal cells

Primary Grade: dominant tumor pattern

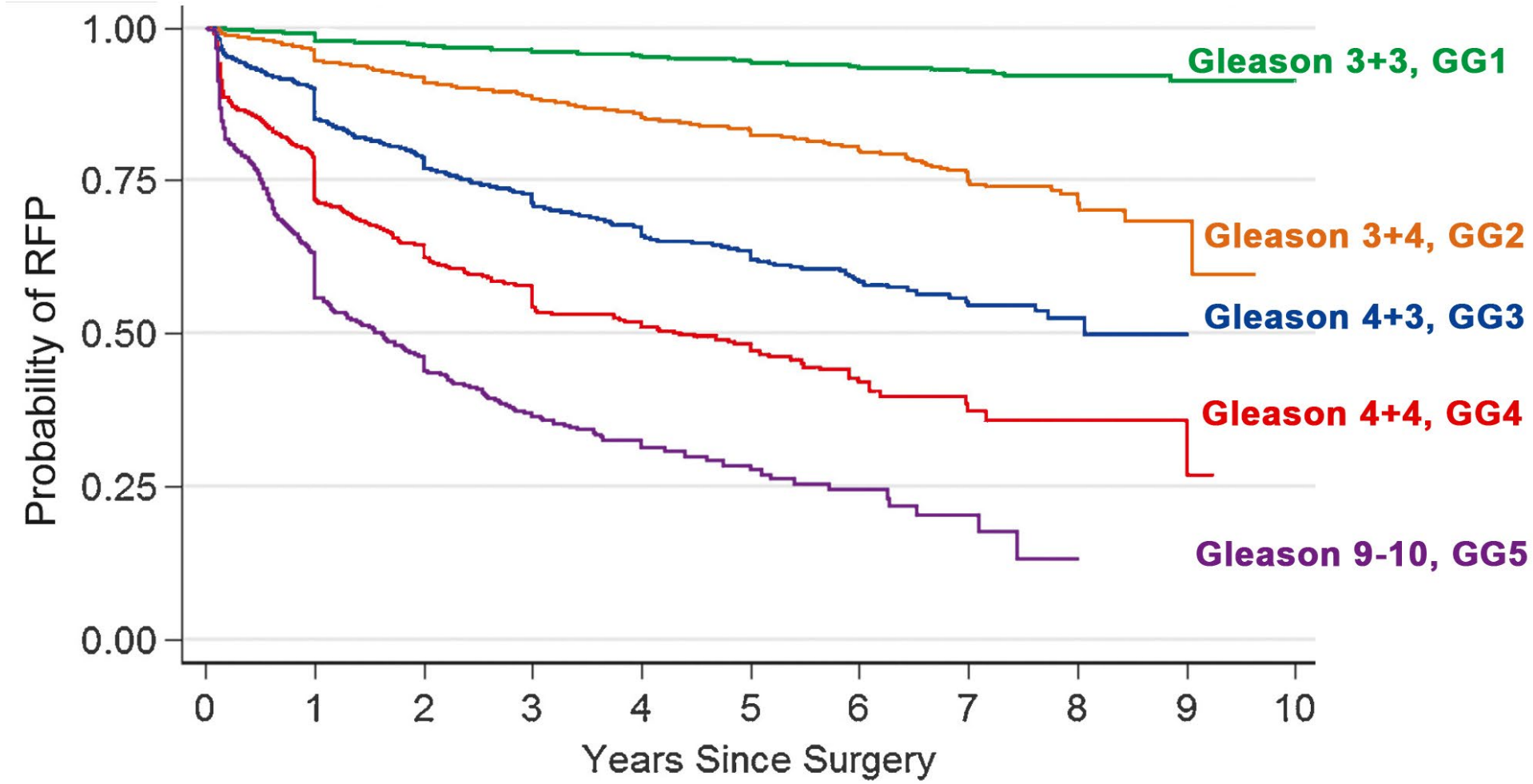
Secondary Grade: next most frequent pattern

GLEASON SCORE = Primary Grade + Secondary Grade (6-10)

van Leenders et al., Am J Surg Pathol. 2020

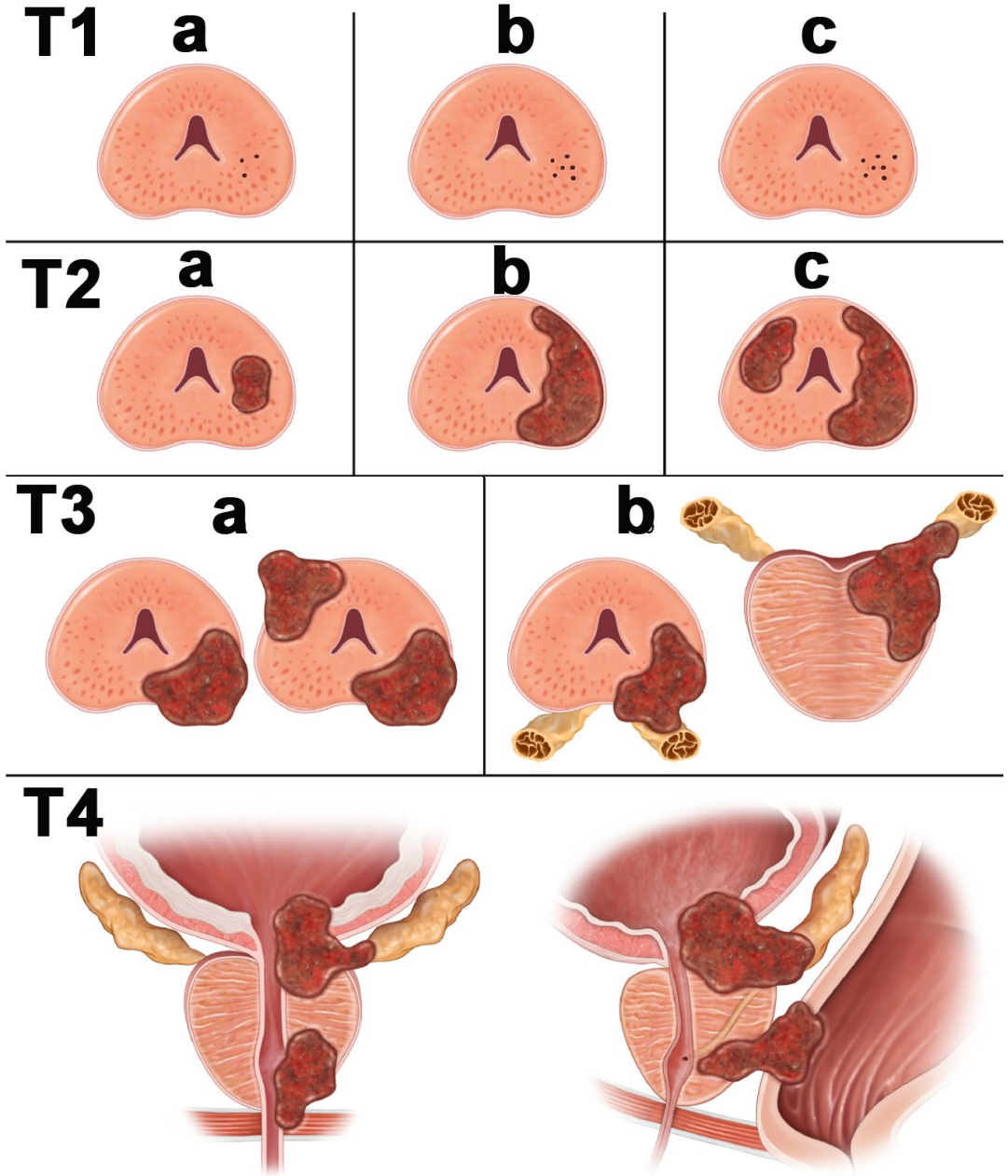
www.training.seer.cancer.gov

GRADE GROUPS



Epstein et al., European Urology. 2016
Epstein et al., Am J Surg Pathol. 2016

Tumor Staging



T1: <5% histological involvement

T2: confined palpable tumor

T3: extra-prostatic extension

T3b: seminal vesicle involvement

T4: invasion adjacent structures

NCCN 3.2023

Surasi et al., Semin Ultrasound CT MR. 2020

RISK STRATIFICATION for Localized Disease

Risk Group	Clinical/Pathologic Features		
Very low[f]	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[g] • PSA density <0.15 ng/mL/g		
Low[f]	Has all of the following but does not qualify for very low risk: • cT1–cT2a • Grade Group 1 • PSA <10 ng/mL		
Intermediate[f]	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRFs): ▸ cT2b–cT2c ▸ Grade Group 2 or 3 ▸ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (eg, <6 of 12 cores)[g]
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥ 50% biopsy cores positive (eg, ≥ 6 of 12 cores)[g]
High	Has no very-high-risk features and has exactly one high-risk feature: • cT3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL		
Very high	Has at least one of the following: • cT3b–cT4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5		

3 Main Factors:

- Clinical tumor stage
- PSA
- Grade Group/Gleason pattern

NCCN Guidelines 3.2023

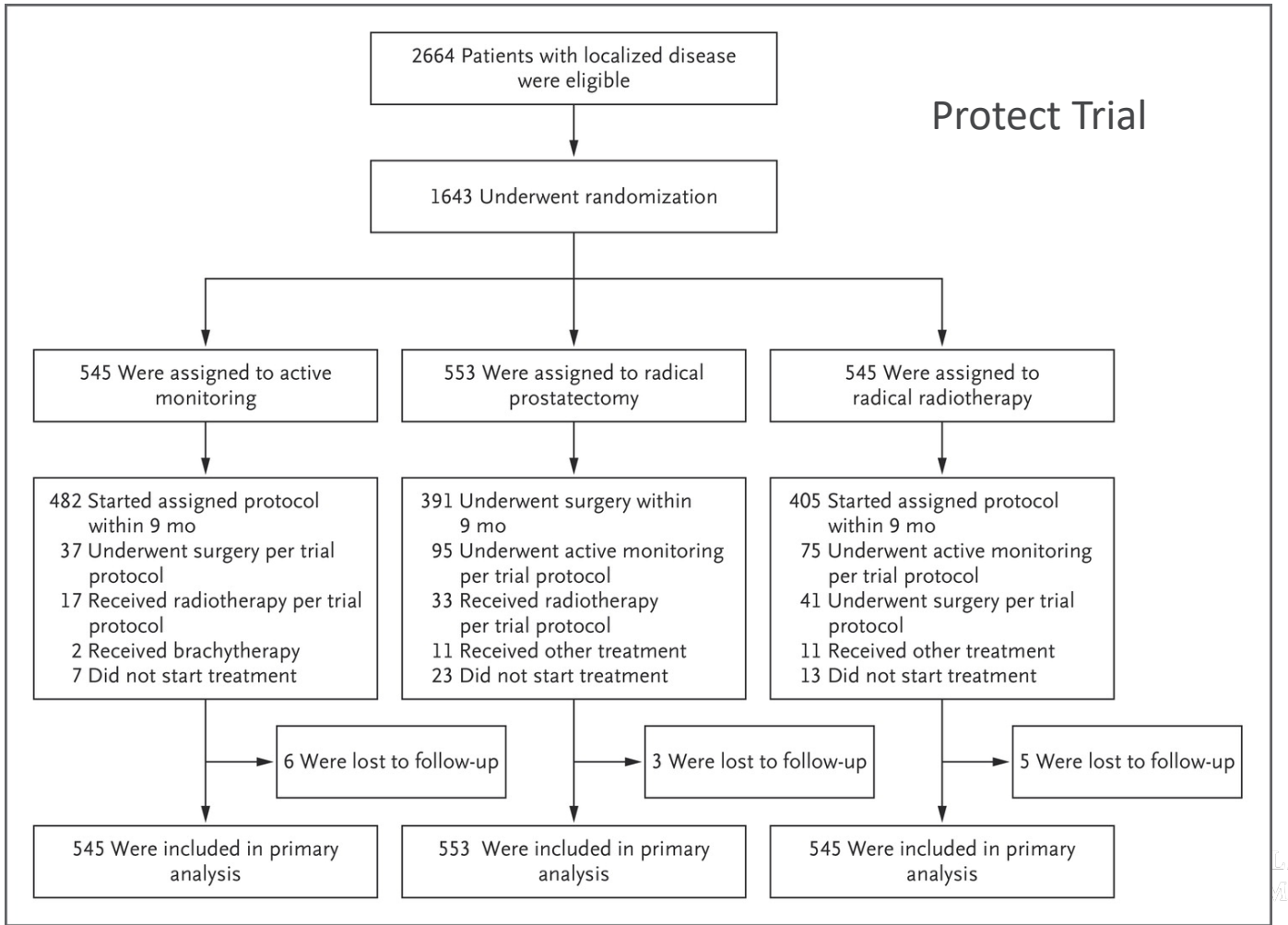
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer

1999-2009

Protect Trial



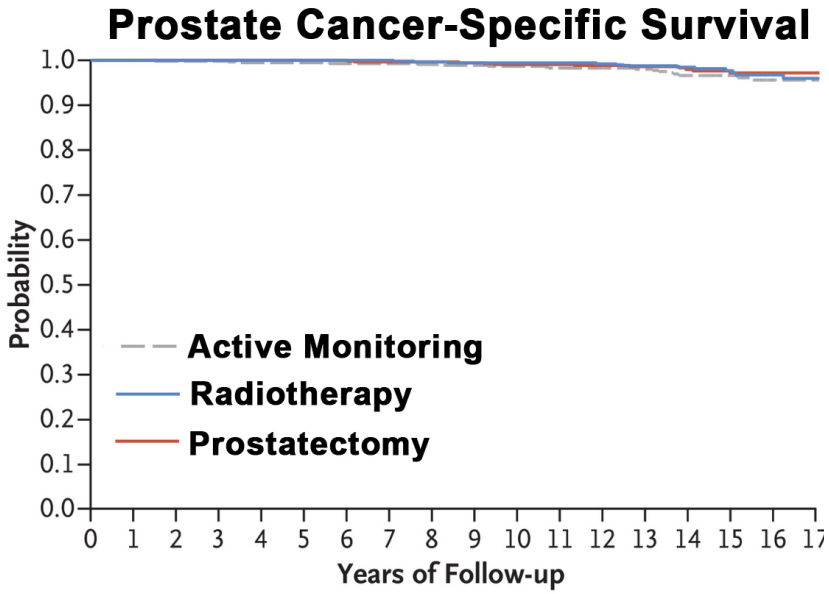
Hamdy FC et al. N Engl J Med 2016

Baseline characteristics stratified by study arm of PROTECT participants

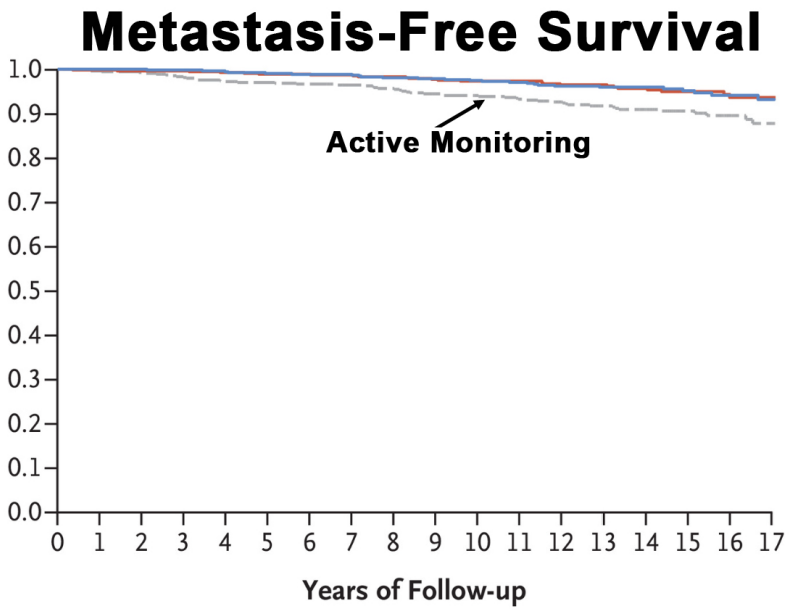
	Active monitoring protocol (n=545)	Surgery (n=553)	Radiotherapy protocol (n=545)
Mean age in years at randomisation (SD[1])	62 (5)	62 (5)	62 (5)
White ethnic origin (%)	535 (99)	542 (99)	529 (98)
African-Caribbean origin (%)	2 (0.4)	3 (0.5)	5 (0.9)
Married or living with partner (%)	457 (84)	458 (84)	460 (85)
Managerial / professional occupation (%)	229 (43)	229 (42)	226 (42)
Known family history prostate cancer (%)	43 (8)	32 (6)	44 (8)
Median PSA[2] in ng/ml (IQR[3])	4.7 (3.7, 6.7)	4.9 (3.7, 6.7)	4.8 (3.7, 6.7)
PSA[2] 10+ ng/ml (%)	57 (10)	57 (10)	58 (11)
Gleason score			
6	421 (77)	422 (76)	423 (78)
7	111 (20)	120 (22)	108 (20)
8-10	13 (2)	10 (2)	14 (3)
Missing	0	1	0
Clinical stage			
T1c	410 (75)	410 (74)	429 (79)
T2	135 (25)	143 (26)	116 (21)

ProtecT

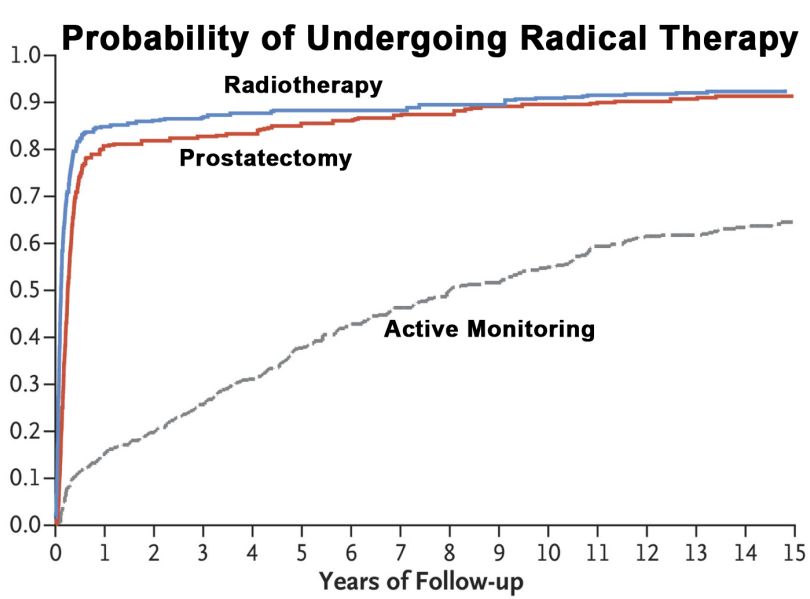
- 1643 men (median age 62) followed for 15 years
- Majority (66%) low risk, 24% intermediate risk, 10% high risk localized PCa
- Equally Randomized to active surveillance vs prostatectomy vs radiation



CSS = 97% for all 3 groups



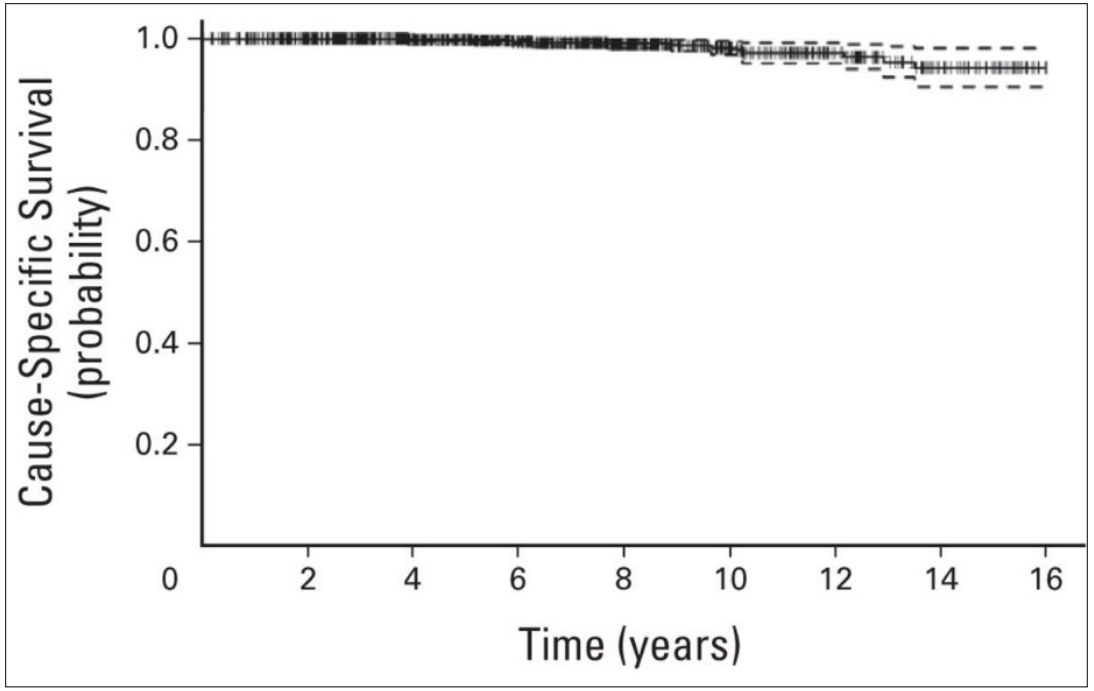
AS arm had ~2X relative risk of distant metastasis



61% of AS patients eventually received radical Tx

Hamdy et al., NEJM 2023

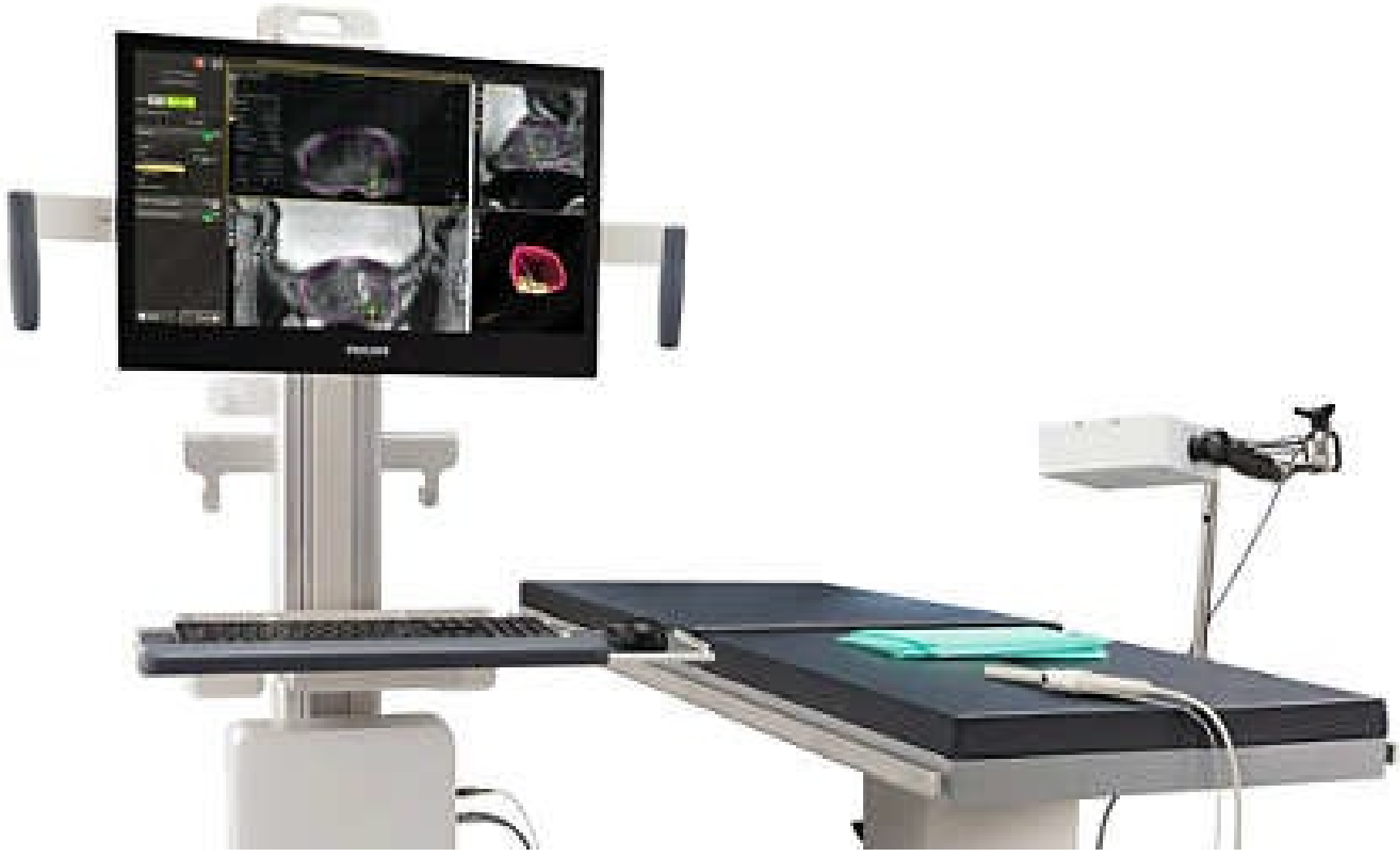
CARE OPTIONS– VERY LOW-/LOW RISK



7. Clinicians should recommend **active surveillance as the best available care option** for **very low-risk localized prostate** cancer patients. (Strong Recommendation; Evidence Level: Grade A)
8. Clinicians should recommend **active surveillance** as the preferable care option for most **low-risk localized prostate cancer** patients. (Moderate Recommendation; Evidence Level: Grade B)

Klotz 2015

UroNav MRI TRUS Fusion



RISK STRATIFICATION

The Panel incorporated contemporary Grade Group categorizations to subcategorize intermediate-risk group into "*favorable*" (Gleason 3+4, Grade Group 2) and "*unfavorable*" (Gleason 4+3, Grade Group 3) categories to facilitate decision-making

Gleason Score	Grade Group*
3+3	1
3+4	2
4+3	3
4+4	4
4+5, 5+4, or 5+5	5

*Grade Group = Contemporary Pathology Consensus Based on Gleason Score and Adopted by WHO, 2016

Zumsteg 2013, 2016; Mathieu 2017

FAVORABLE VS UNFAVORABLE INTERMEDIATE RISK SUB-GROUPS

PCa Intermediate Risk Sub-Group	Pathology Grade Group	PSA (ng/ml)	Clin Stage (DRE)
Favorable	1	10-20	T1-T2a
	2 (3+4=7)	<10	
Unfavorable	2 (3+4=7)	<10	T2b
	2 (3+4=7)	10-20	Any T1-2
	2 (4+3=7)	<20	Any T1-2

(Amount of Pca on biopsy not included in sub-categorization due to lack of such strata in RCT evidence)

Zumsteg 2013, 2016; Mathieu 2017

CARE OPTIONS– INTERMEDIATE RISK

Intermediate Risk	**PSA 10-<20 ng/ml OR Grade Group 2-3 OR clinical stage T2b-c** • Favorable: Grade Group 1 (with PSA 10-<20) OR Grade Group 2 (with PSA<10) • Unfavorable: Grade Group 2 (with either PSA 10-<20 or clinical stage T2b-c) OR Grade Group 3 (with PSA < 20)

Considerable variability in the clinical behavior of intermediate risk prostate cancer

Tumor volume
Percentage Pattern 4
Adverse histology
Genomic Risk Classifier
MRI findings
Patient comorbidity
Patient compliance

- **Surgery**
- **Focal therapy**
- **Radiation**
- **+/- ADT**

CARE OPTIONS– INTERMEDIATE RISK

16. Clinicians should **discuss active surveillance, radical prostatectomy or radiotherapy** as **standard treatment options** for patients with favorable intermediate-risk localized prostate cancer. (Strong Recommendation; Evidence Level: Grade A)

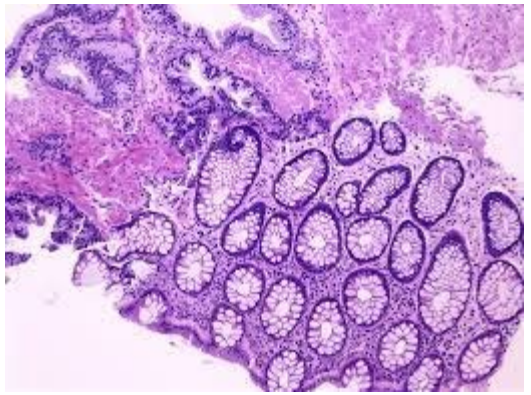
17. Clinicians should inform patients with **unfavorable intermediate-risk prostate cancer AND > 10 YEAR LIFE EXPECTANCY that prostatectomy and XRT + 4-6 months of ADT are standard options**

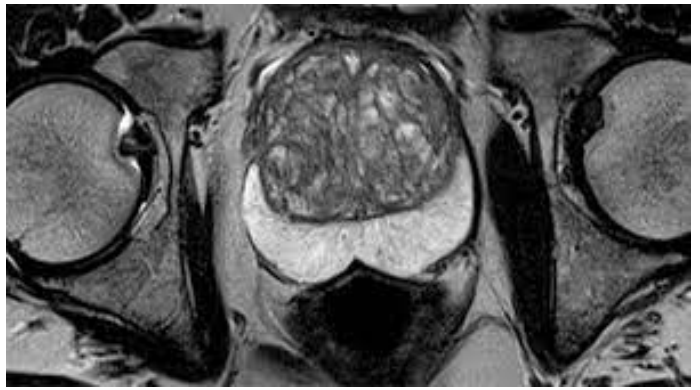
PSMA pet staging for uIR and high risk patients

Bill-Axelson 2014

Surveillance: Selection is key!

- **Tumor volume**
- **Percentage Pattern 4**
- **Adverse histology**
- **Genomic Risk Classifier**
- **MRI findings**
- **Patient comorbidity**
- **Patient compliance**





SelectMDx™ for Prostate Cancer

Decipher® PROSTATE GENOMIC CLASSIFIER

Adverse Disease Features in Gleason Score 3 + 4 "Favorable Intermediate-Risk" Prostate Cancer: Implications for Active Surveillance

	Gleason upgrade				Gleason downgrade				Non–organ confined				Unfavorable disease			
	OR	95% CI		*p*	OR	95% CI		*p*	OR	95% CI		*p*	OR	95% CI		*p*
Age	1.06	1.02	1.09	**<0.001**	0.97	0.94	1.00	0.05	1.03	1.00	1.06	**0.04**	1.05	1.02	1.08	**<0.001**
Log_2 PSA density	1.83	1.17	2.85	**0.007**	0.67	0.51	0.89	**0.006**	1.04	0.79	1.35	0.79	1.14	0.90	1.44	0.29
Clinical stage																
cT1	Ref.				Ref.				Ref.							
cT2a	1.13	0.84	1.52	0.43	0.52	0.32	0.84	**0.007**	1.95	1.32	2.88	**<0.001**	1.74	1.23	2.46	**0.002**
Positive cores, % (cont)	0.99	0.99	1.01	0.55	0.98	0.97	0.99	**0.007**	1.02	1.01	1.03	**<0.001**	1.02	1.01	1.02	**<0.001**
Positive cores, %																
<50	ref				Ref.				Ref.				Ref.			
≥50	0.96	0.57	1.62	0.88	0.76	0.45	1.28	0.3	1.87	1.22	2.85	**0.004**	1.57	1.06	2.31	**0.02**
Surface area, % (cont)	1.01	1.00	1.02	**0.03**	0.98	0.97	0.99	**<0.001**	1.02	1.01	1.03	**<0.001**	1.02	1.01	1.02	**<0.001**
Surface area, %																
<50	Ref.				Ref.				Ref.				Ref.			
≥50	0.87	0.29	2.63	0.8	2.62	0.69	9.94	0.16	1.60	0.58	4.44	0.36	1.09	0.47	2.55	0.84
Tumor bilaterality																
No	Ref.				Ref.				Ref.				Ref.			
Yes	0.70	0.43	1.13	0.15	0.86	0.55	1.36	0.52	1.32	0.87	1.99	0.19	1.00	0.69	1.45	0.99
Perineural invasion																
No	Ref.				Ref.				Ref.				Ref.			
Yes	1.37	0.91	2.07	0.13	0.59	0.36	0.96	**0.03**	2.50	1.75	3.56	**<0.001**	1.89	1.36	2.62	**<0.001**

CI = confidence interval; OR = odds ratio; PSA = prostate-specific antigen; Ref = reference.
Boldface shows $p < 0.05$.

- Age
- PSA Density
- Percentage Pattern 4
- Core involvement

UC San Diego Health

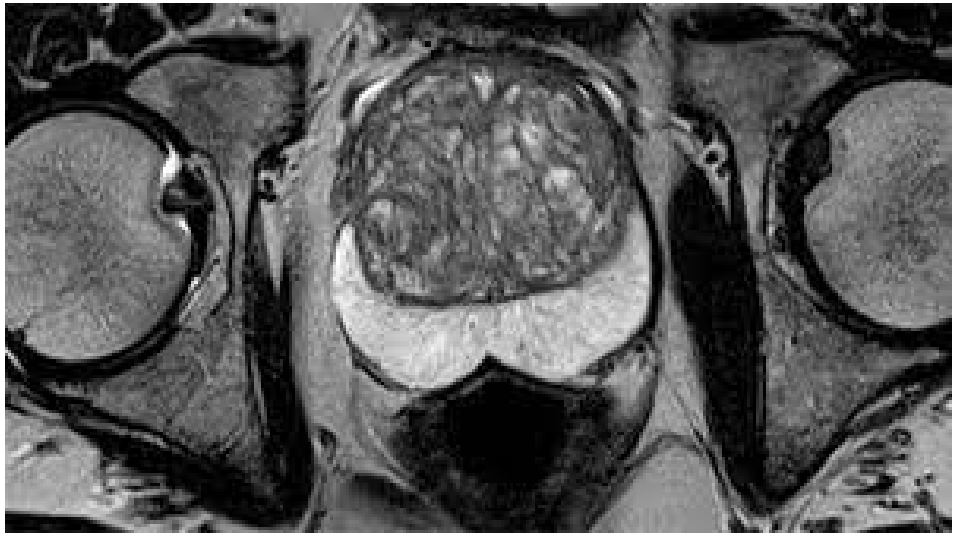
Adverse Pathology and germline characteristics

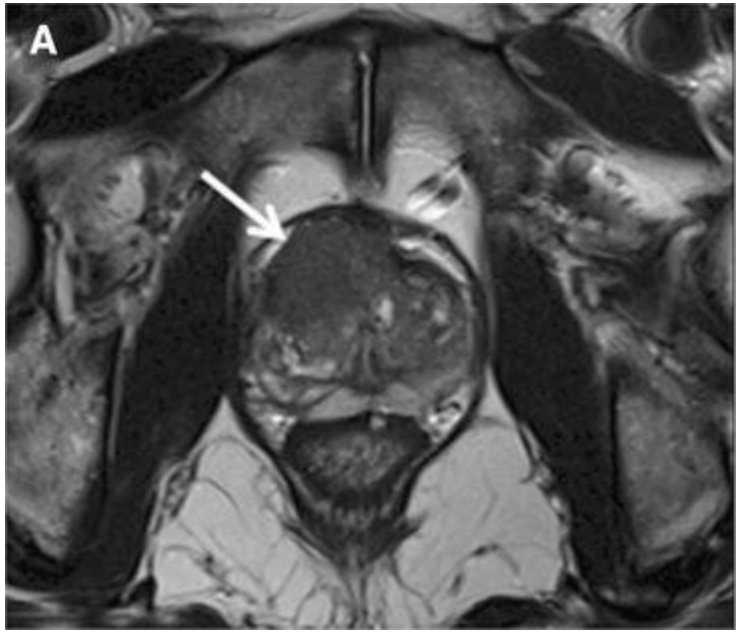
- **Standardized Reporting of cribiform and intraductal histology in Pathology Consensus Statements**

- **Hereditary GERMLINE considerations**
  - **BRCA1/BRCA2**
  - **Ashkenazi Jewish Ancestry**
  - **DNA Damage Repair Mutations**

MRI features

- **Guide confirmatory biopsies**
- **Assess Adverse features**
  - **Extraprostatic Extension**
  - **Large Tumor Volume**
  - **Multifocal Disease**
- **Good Negative Predictive Value**
- **Low rates of undergrading/staging**

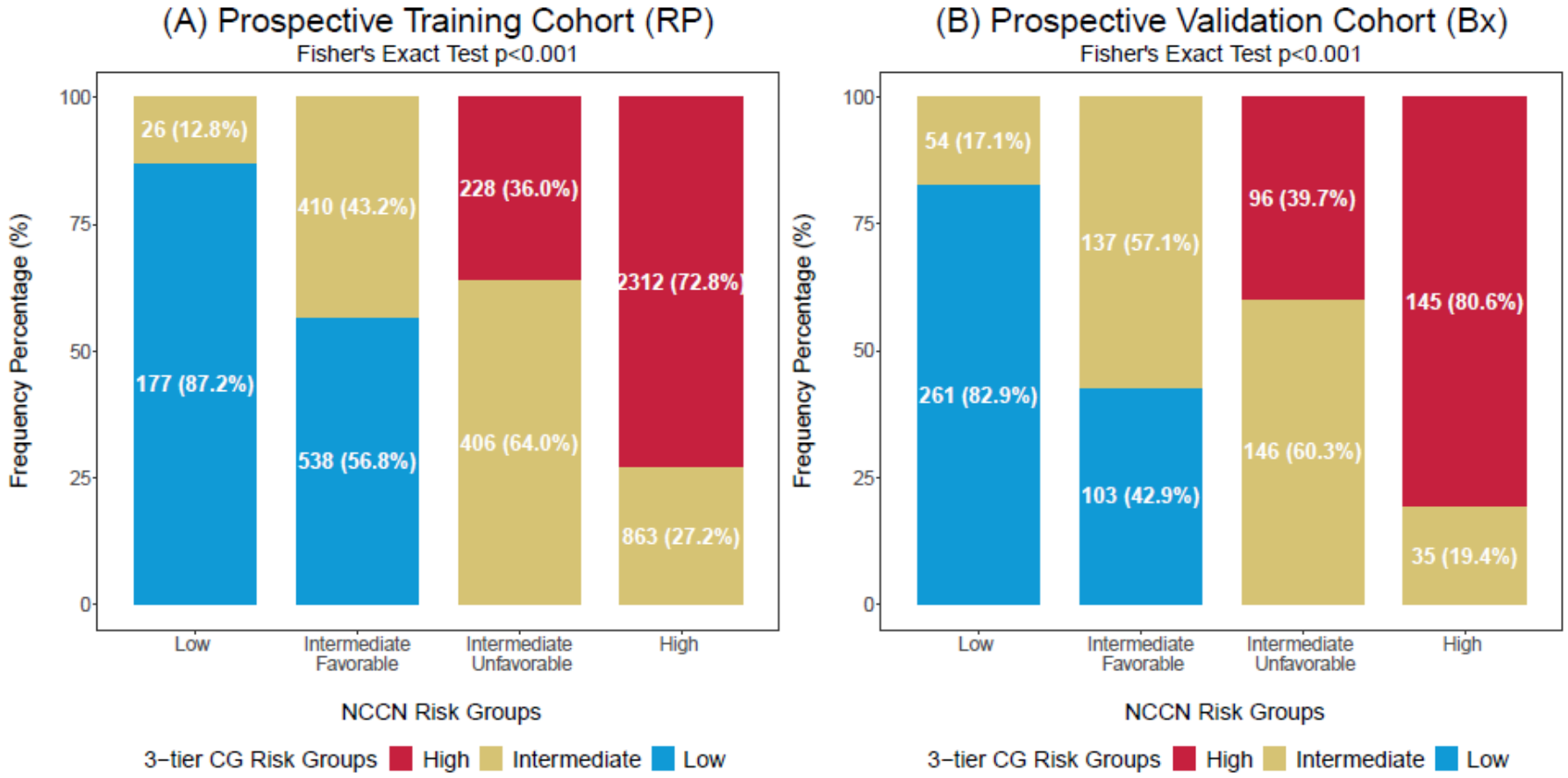




PROMIS (NEJM)
PRECISION (LANCET)

Genomic Risk Classifiers

- **Use molecular Characteristics to augment NCCN risk groups**

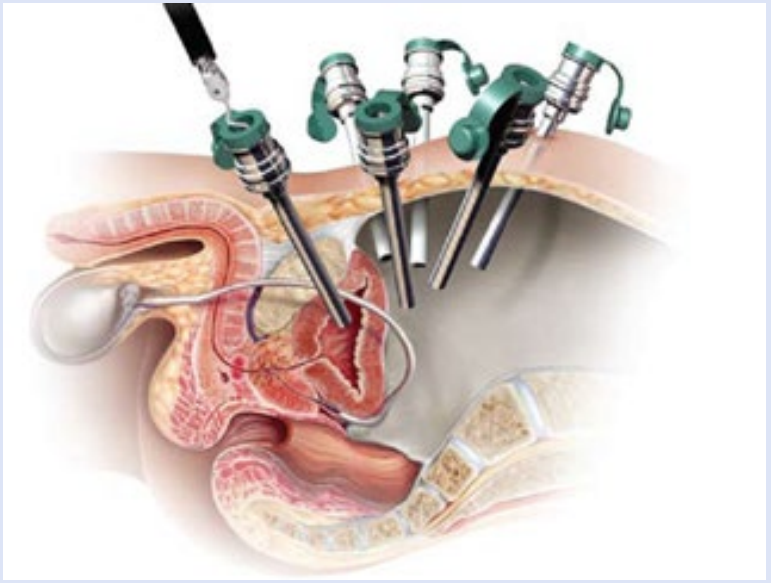


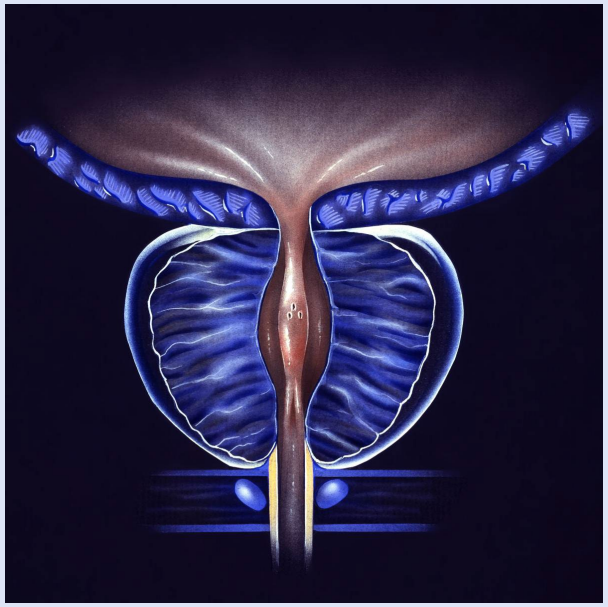
Considerable variability in the clinical behavior of intermediate risk prostate cancer

Tumor volume
Percentage Pattern 4
Adverse histology
Genomic Risk Classifier
MRI findings
Patient comorbidity
Patient compliance

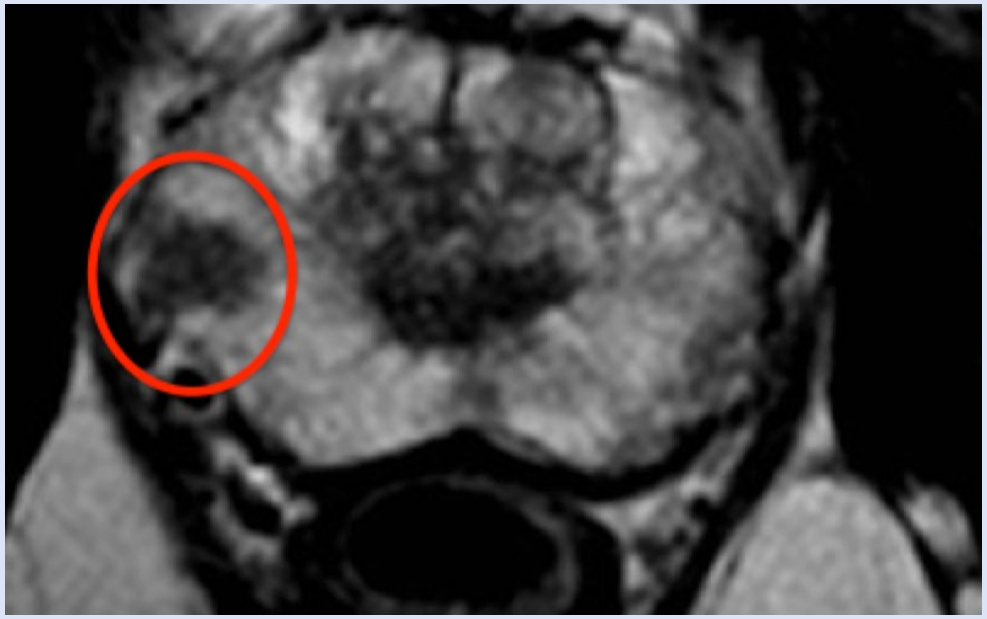
- **Surgery**
- **Focal therapy**
- **Radiation**
- **+/- ADT**

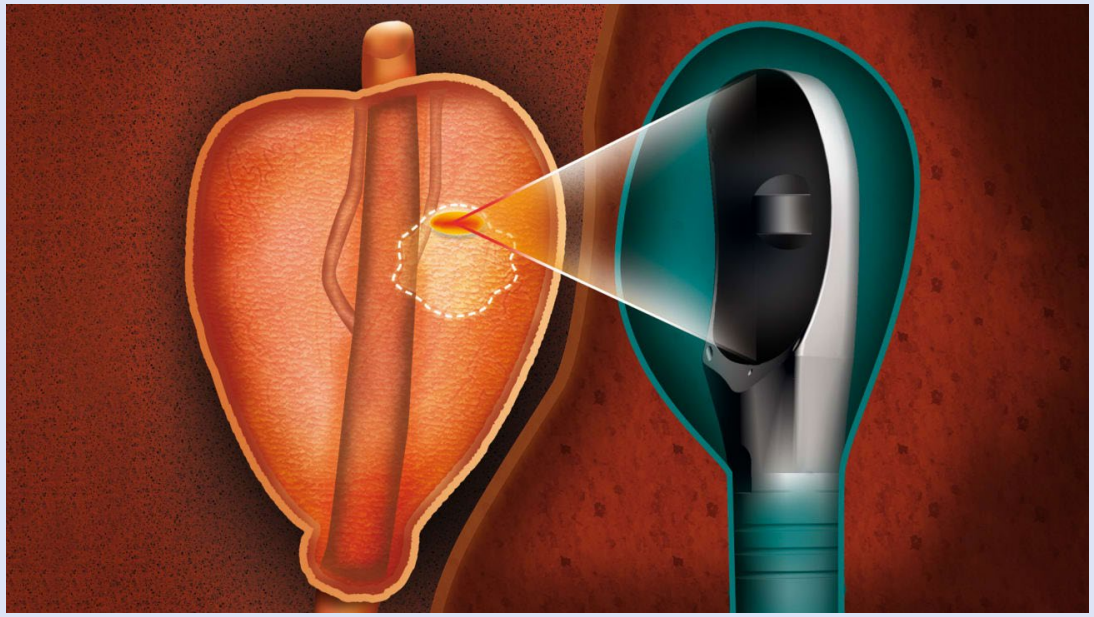
Robotic Prostatectomy





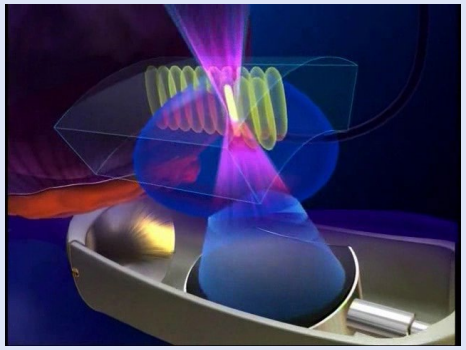
Focal Treatment for Focal Disease – Do We Really Need to do Radical Prostatectomies or Whole Gland Radiation ?



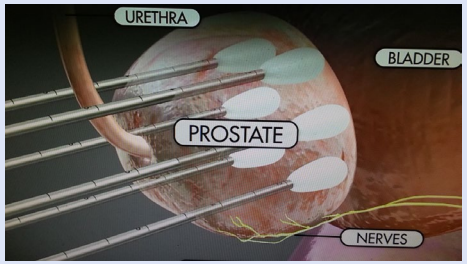


Focal therapy modalities

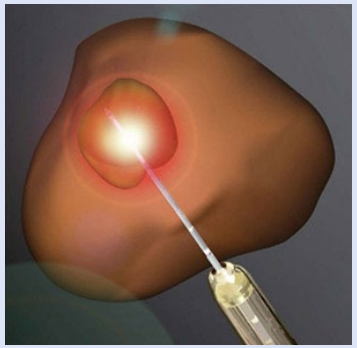
HIFU/TULSA



Cryotherapy

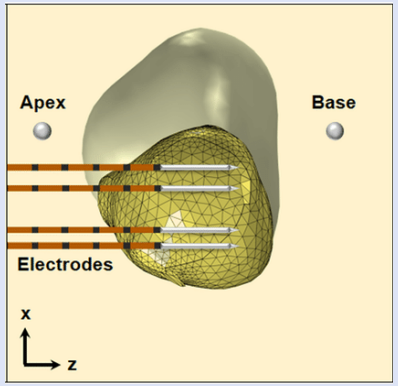


Laser

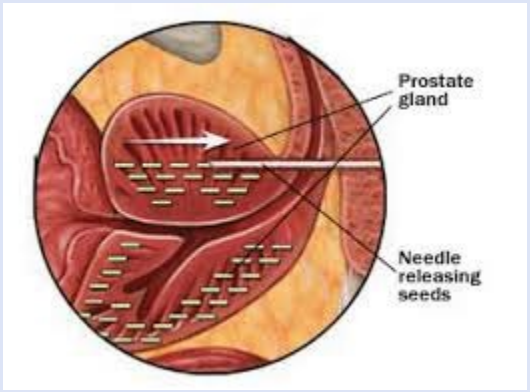


Photodynamic Therapy

IRE



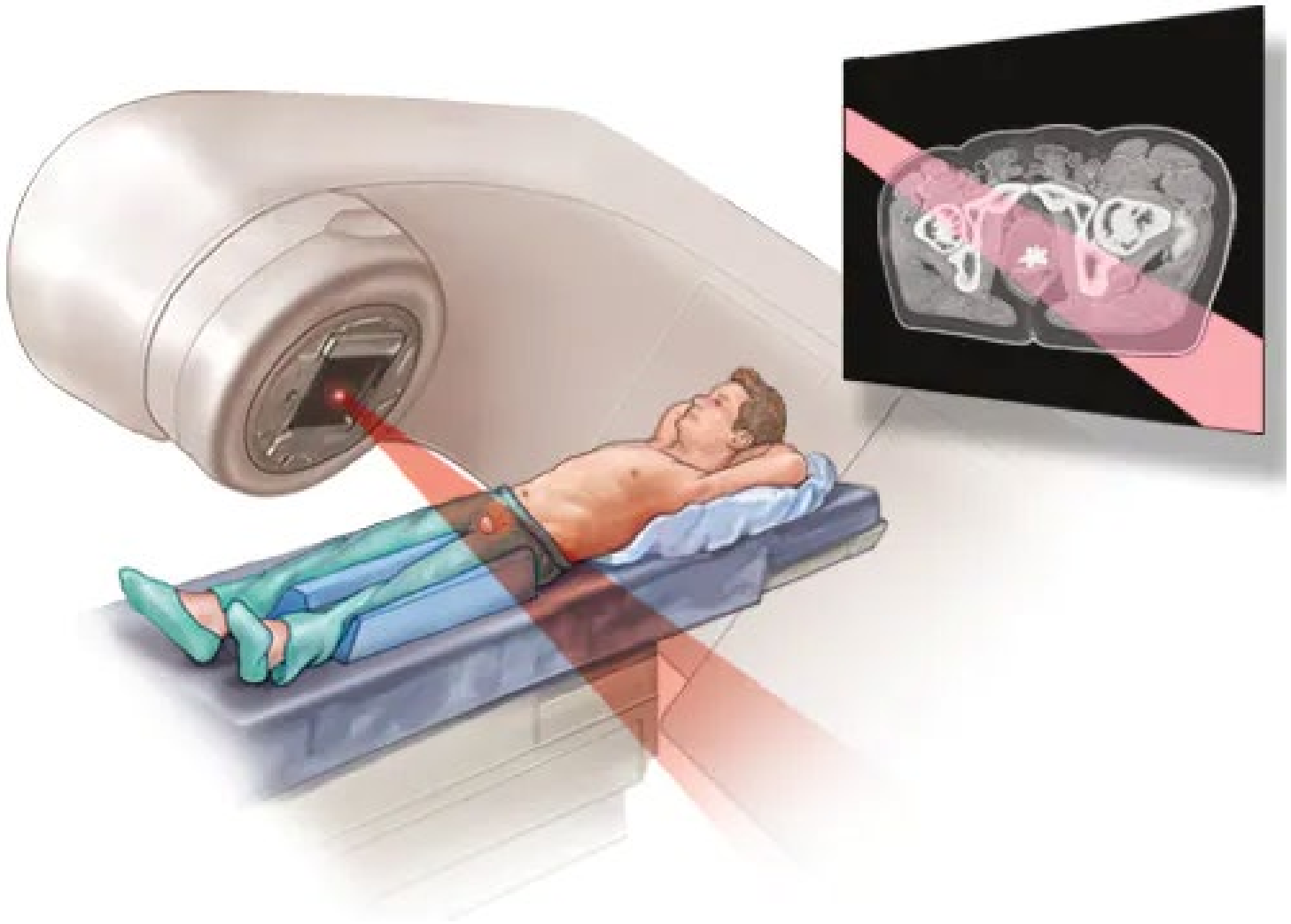
Radiation



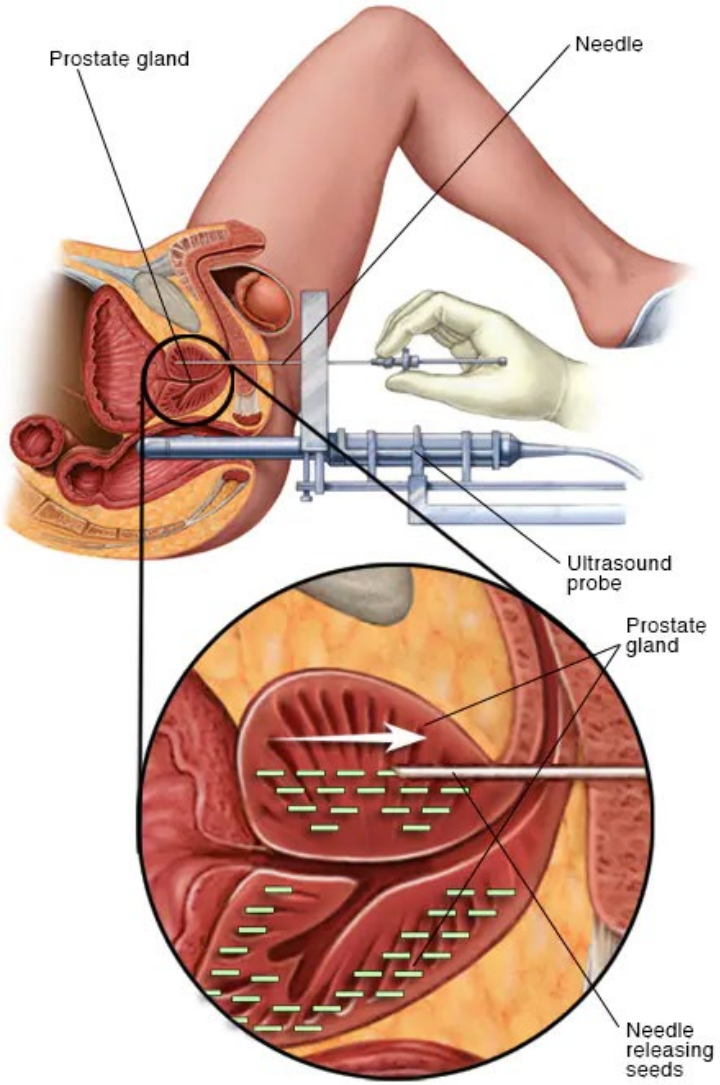
Focal therapy Conclusions

- Focal therapy is a promising option for patients with localized low and intermediate risk prostate cancer.
- Potential for recurrence is likely inherent to most treatments and should be part of counseling
- Complication rate is low and acceptable.
- Long-term oncologic outcomes need to be investigated
- Salvage option also

External Beam Radiotherapy (EBRT)

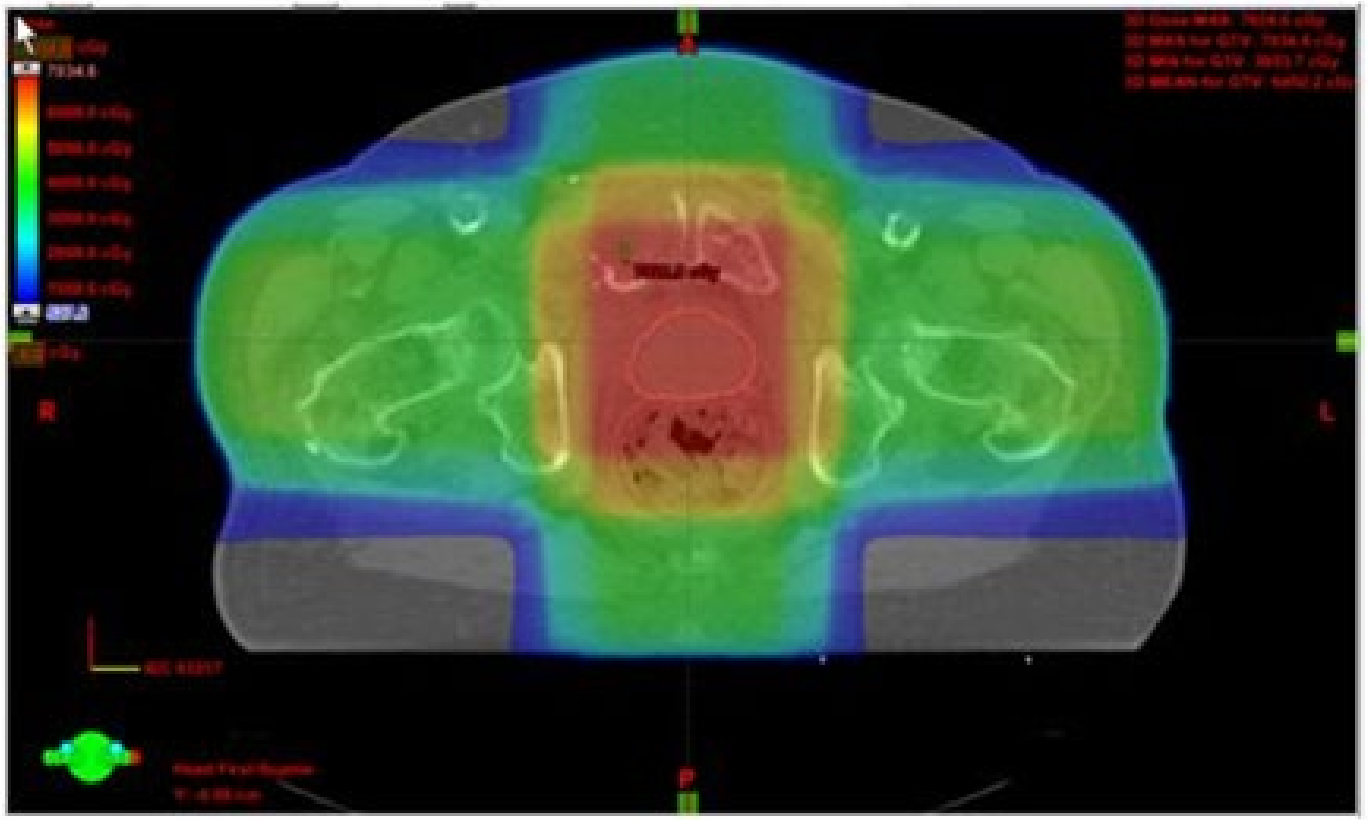


Brachytherapy



Older Radiotherapy Technique

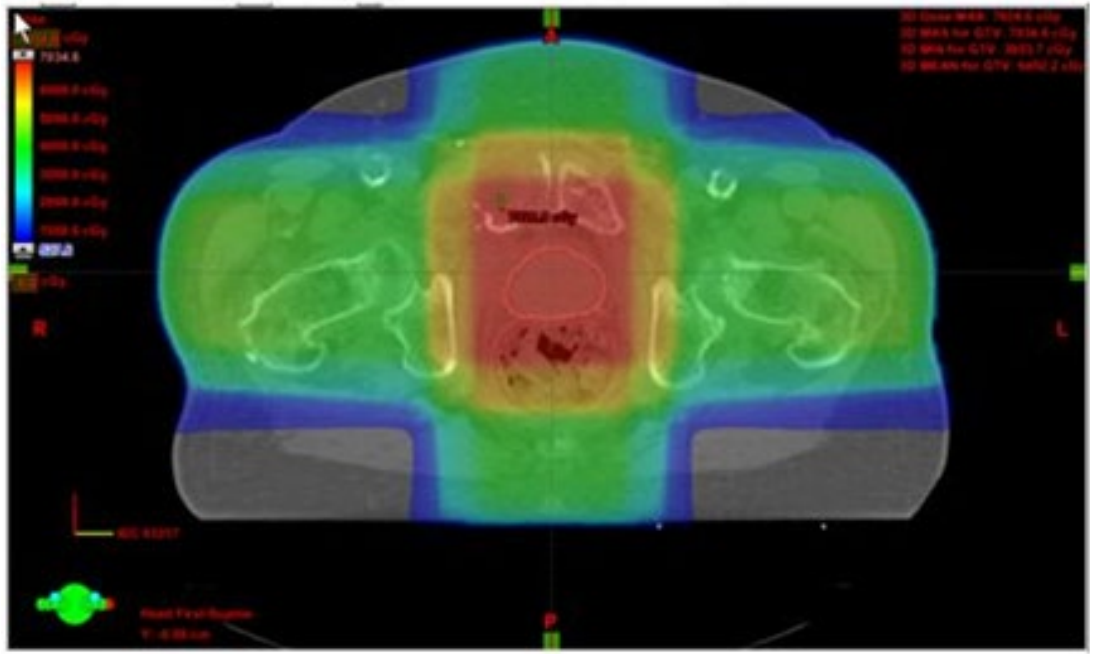
"4-field Box"



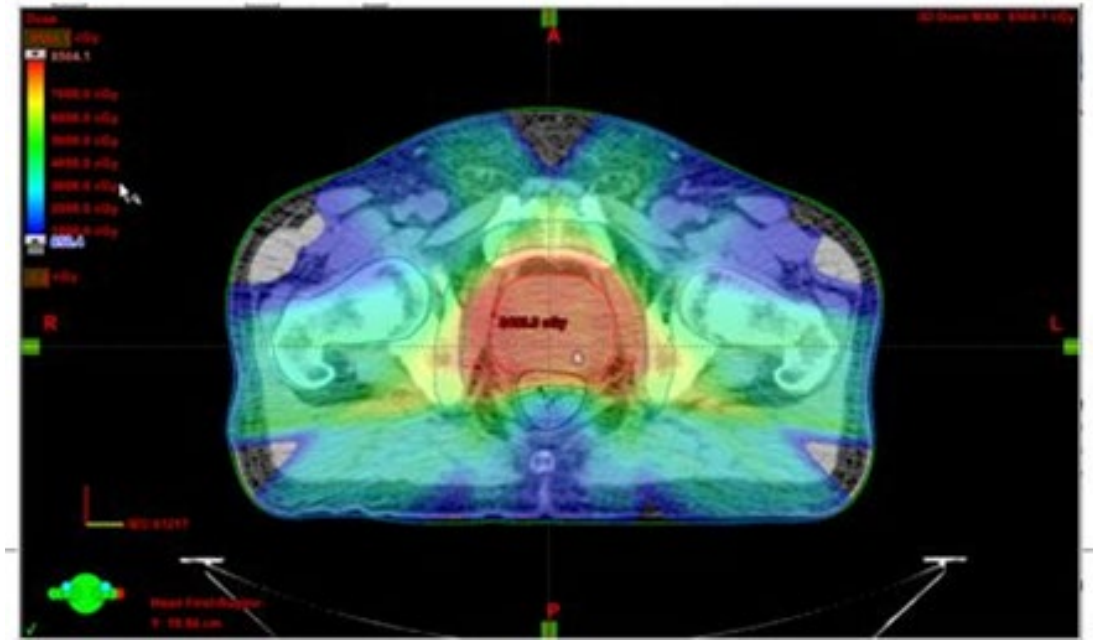
- Older imaging techniques limited the precision of the treatment
- Relied on "fractionation" and lower total radiation dose to limit side effects

Intensity Modulated Radiation Therapy (IMRT)

“4-field Box”



IMRT



IMRT Era

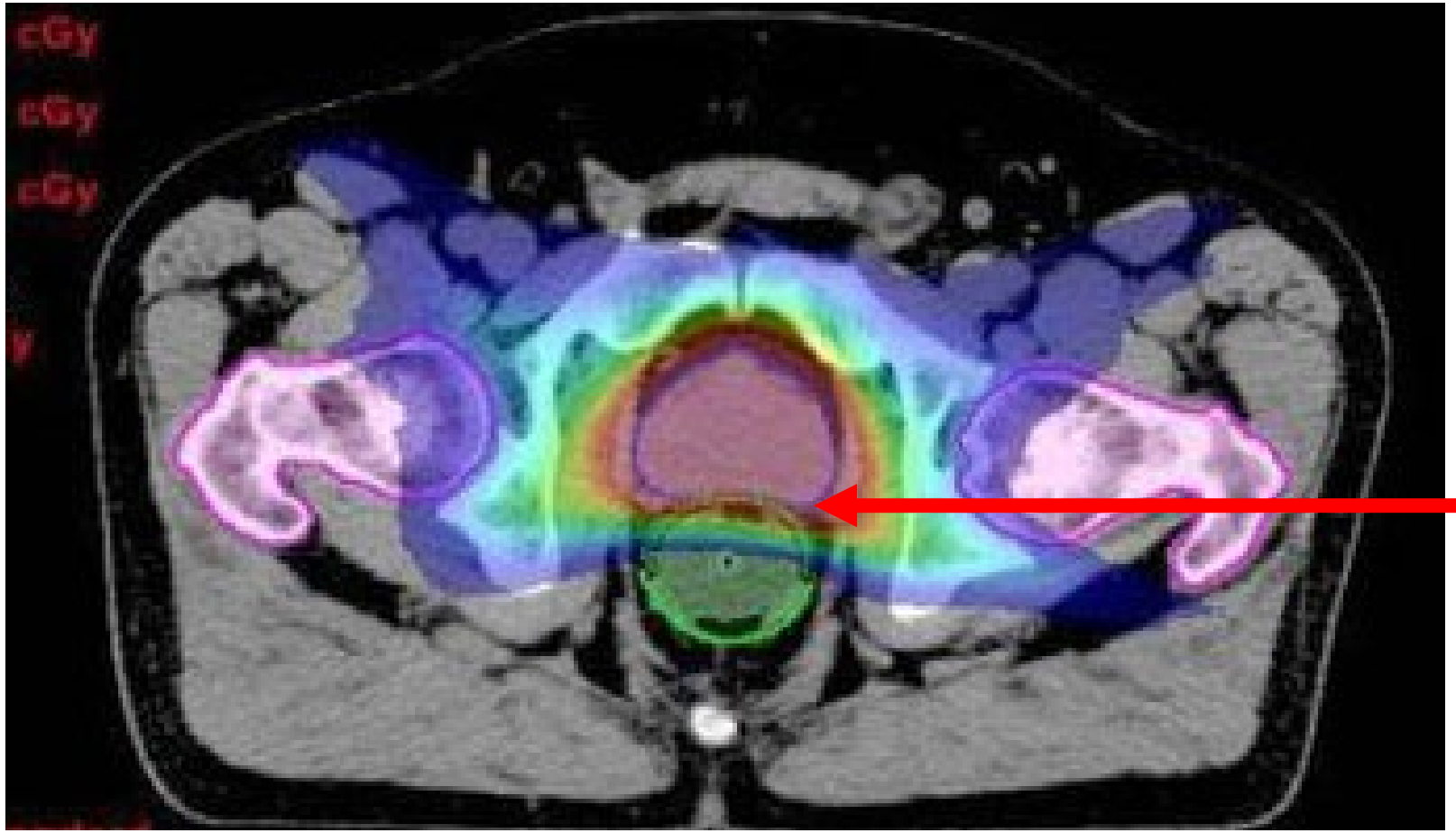
IMRT reduces radiation dose to normal tissues

Dose escalation – 78 Gy in 39 fractions

Hypofractionation – Fewer total treatments

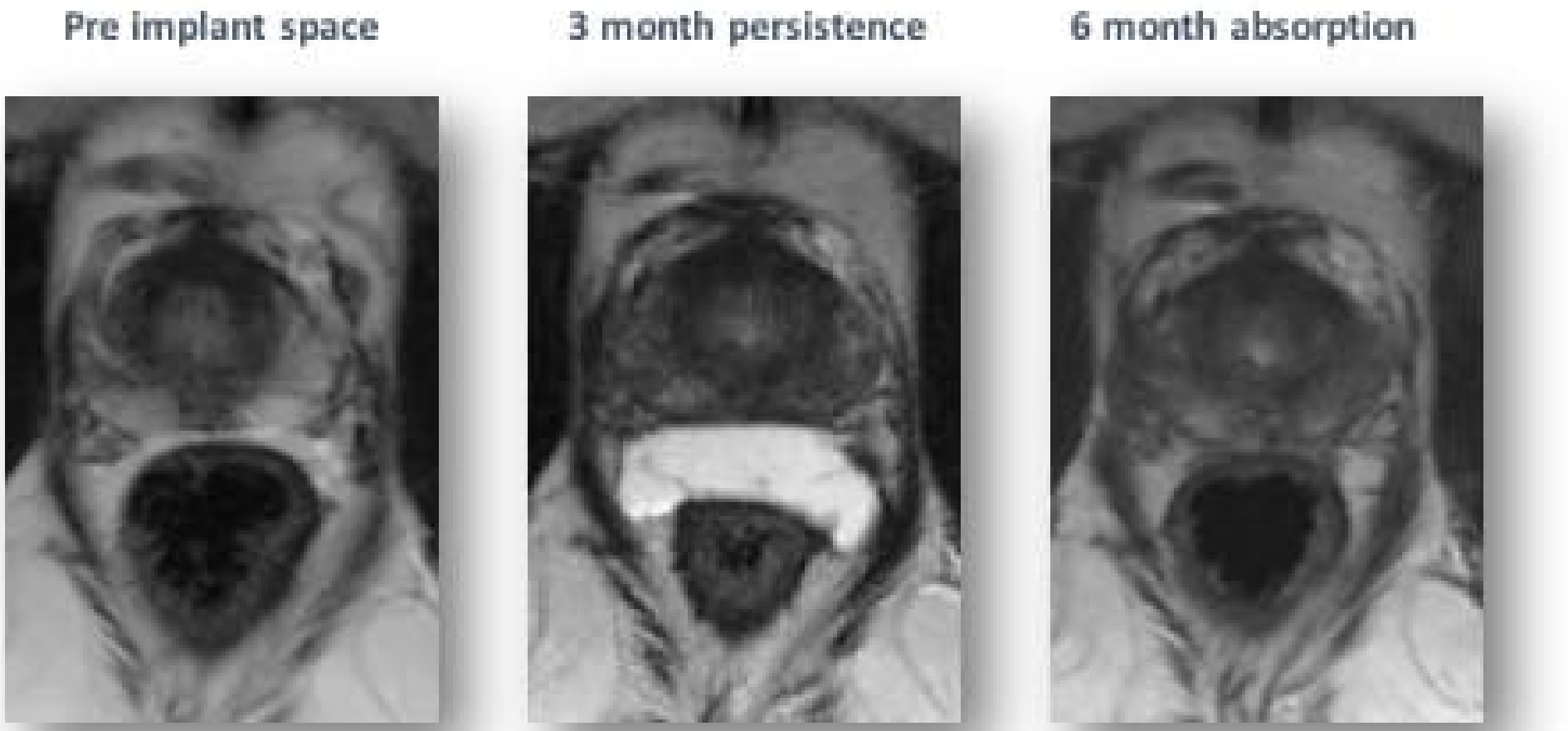
a) 70 Gy in 28 fractions b) 60 GY in 20 fractions

SBRT 35-40 Gy in 5 fractions

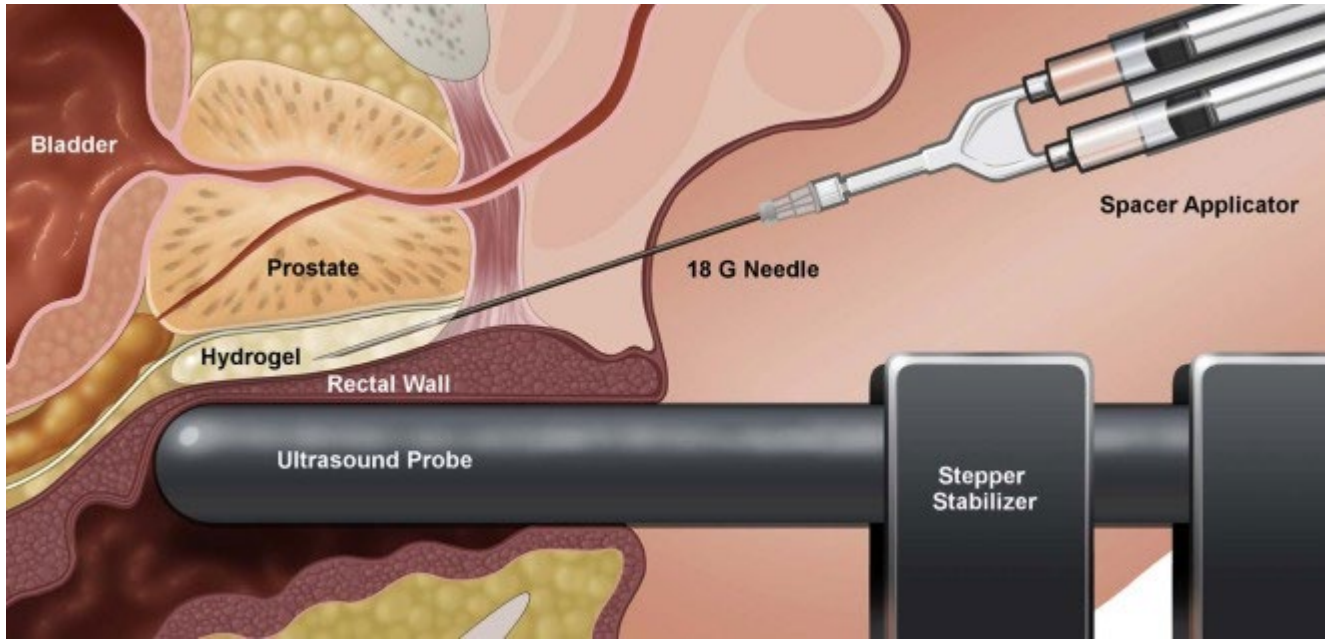


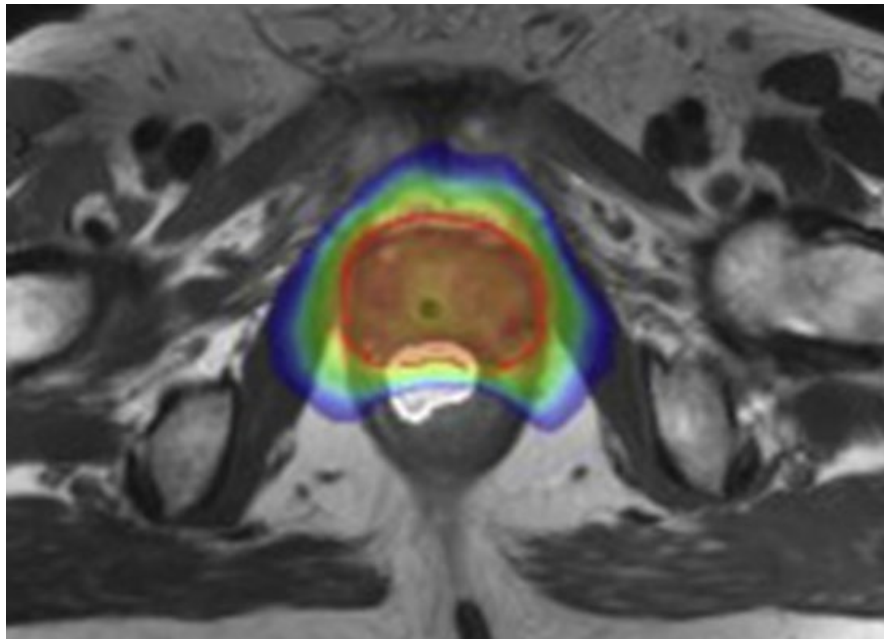
Rectum and Prostate are in close proximity

Hydrogel Spacer



Hydrogel Spacer





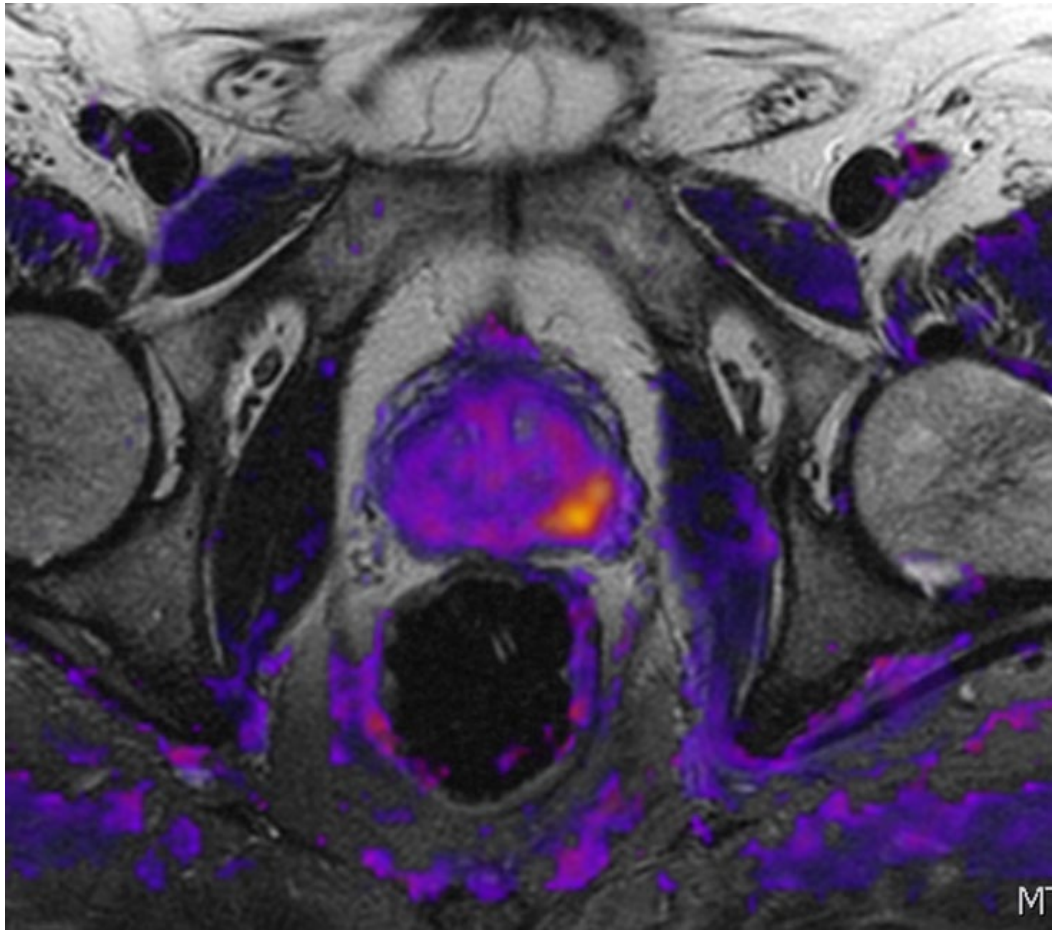
Radiation with a Hydrogel Spacer – For Everyone?

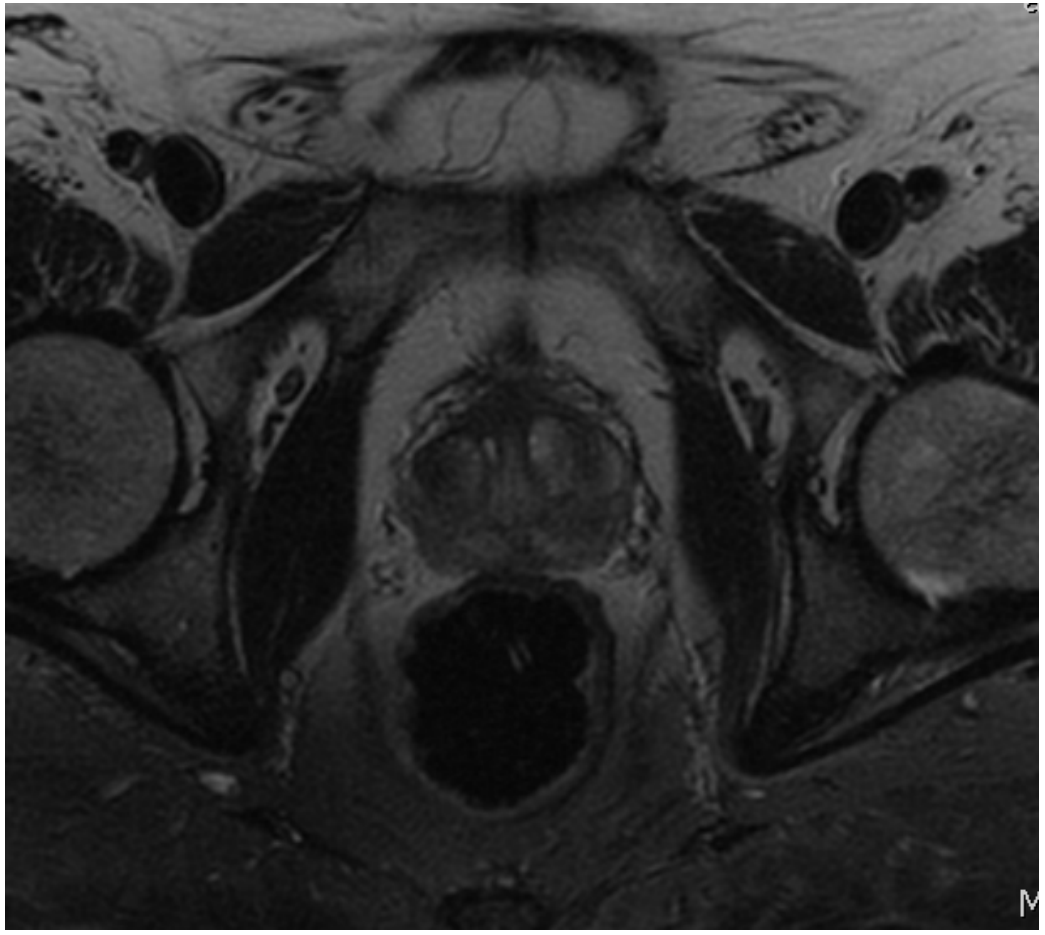
Table 3. Gastrointestinal and Genitourinary Toxic Effects by CTCAE, Version 5.0

	Acute toxic effect (within 3 mo)		6-mo Toxic effect	
CTCAE	Spacer	Control	Spacer	Control
No.	136	65	136	65
Gastrointestinal				
0	114 (84.4)	36 (55.4)	129 (99.2)	57 (91.9)
1	17 (12.6)	20 (30.8)	1 (0.8)	5 (8.1)
2	3 (2.2)	9 (13.8)	0	0
3	1 (0.7)	0	0	0

Mariados et al.
JAMA Onc 2023

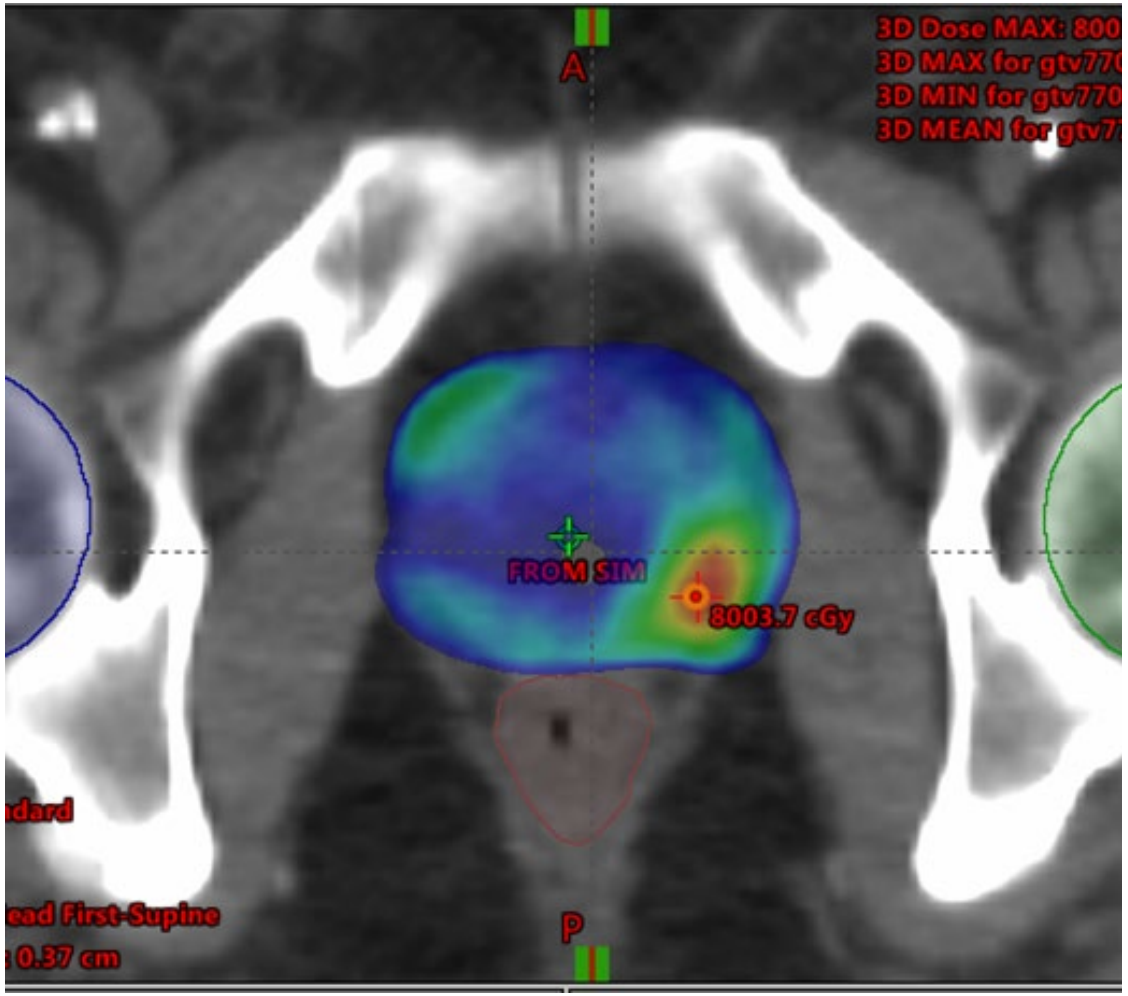
MRI for Prostate Cancer Treatment

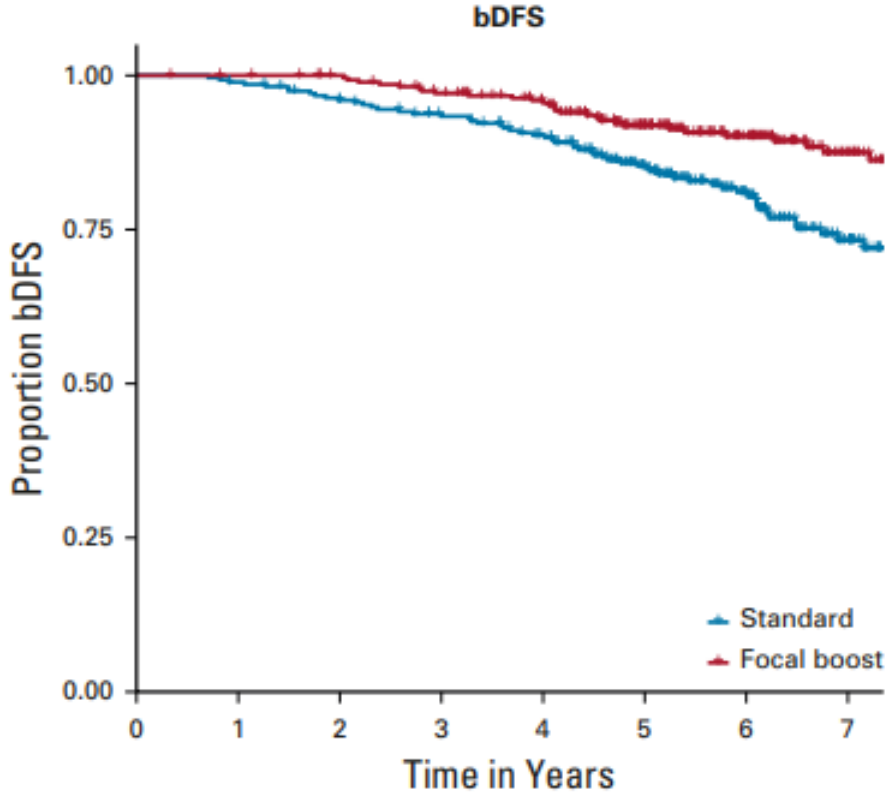




Axial T2 image with and without RSI cellularity index

Focal Radiotherapy Boost





N at risk (cumulative events)

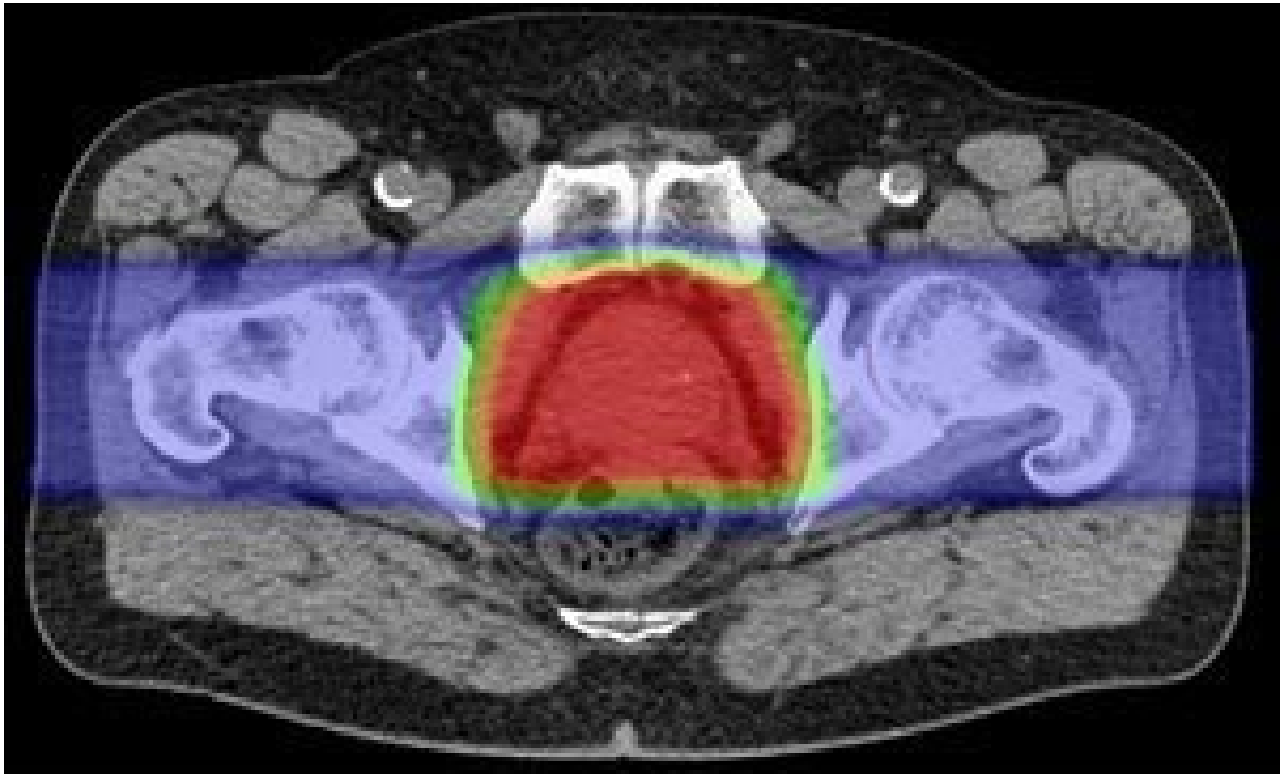
Standard	276 (0)	272 (3)	260 (11)	247 (17)	229 (26)	182 (38)	127 (46)	67 (56)
Focal boost	281 (0)	279 (0)	274 (0)	261 (8)	244 (11)	188 (21)	135 (24)	80 (27)

Cumulative censoring

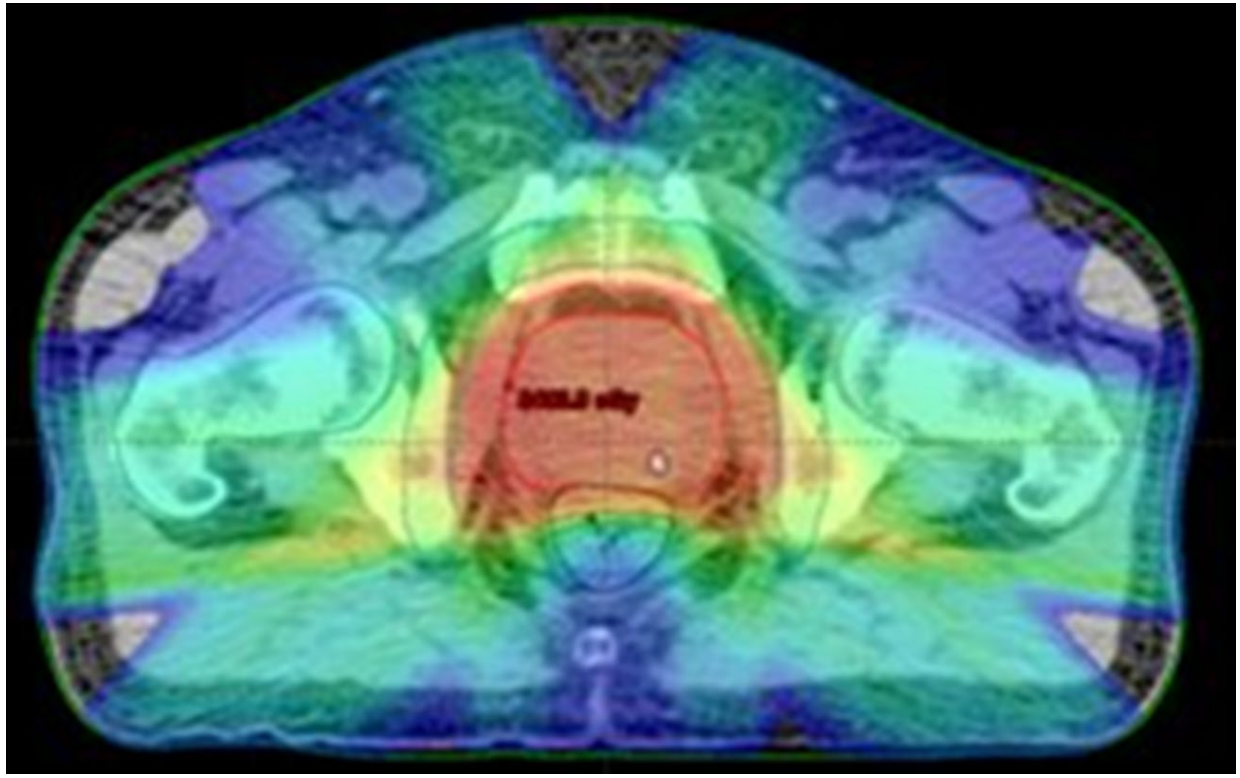
Standard	0	1	5	12	21	56	103	153
Focal boost	0	2	7	12	26	72	122	174

Kerkmeijer JCO 2021

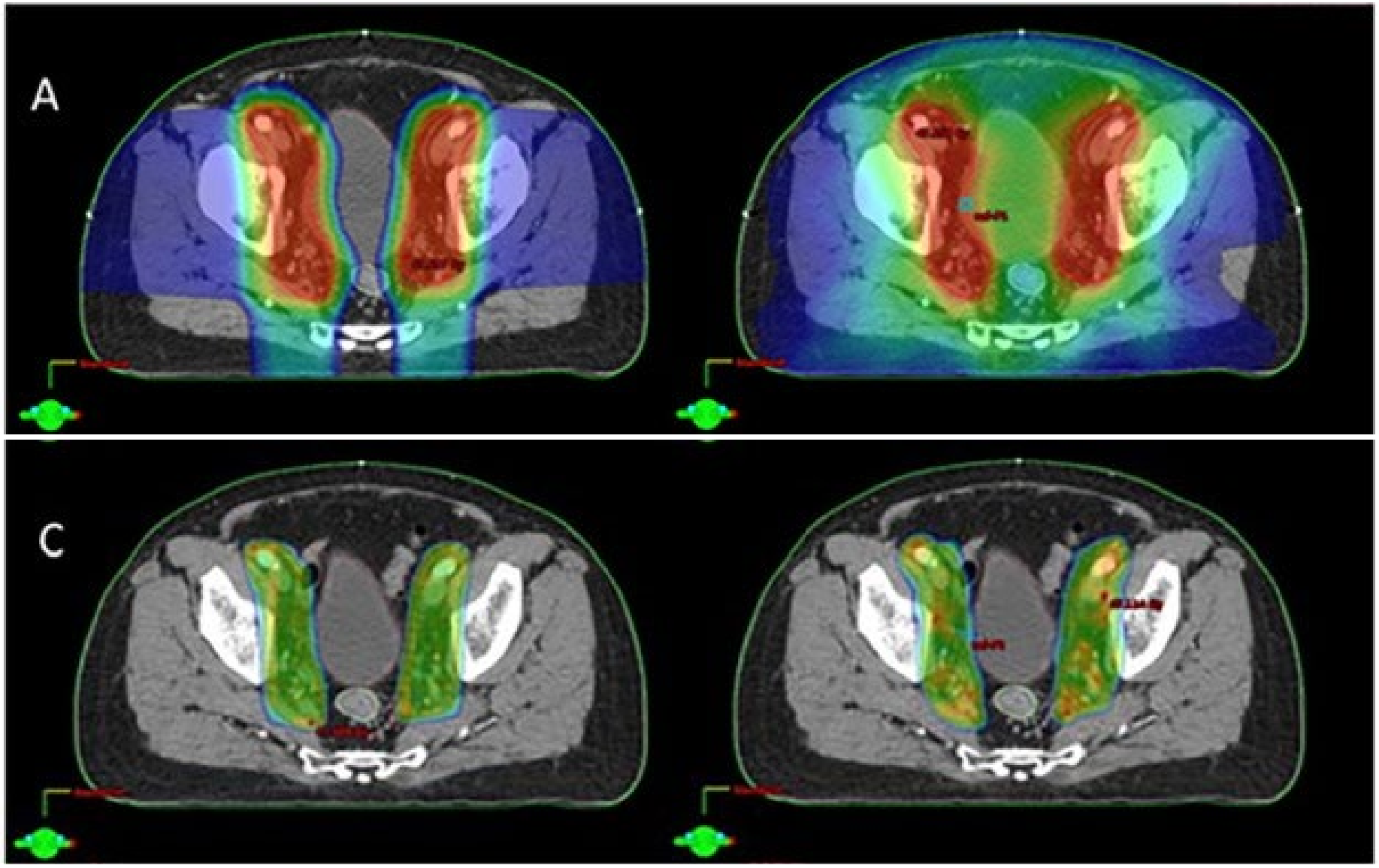
Proton Therapy



IMRT



Proton Therapy IMRT



- Total dose
- Filtered to show high dose only

Proton Therapy Conclusion

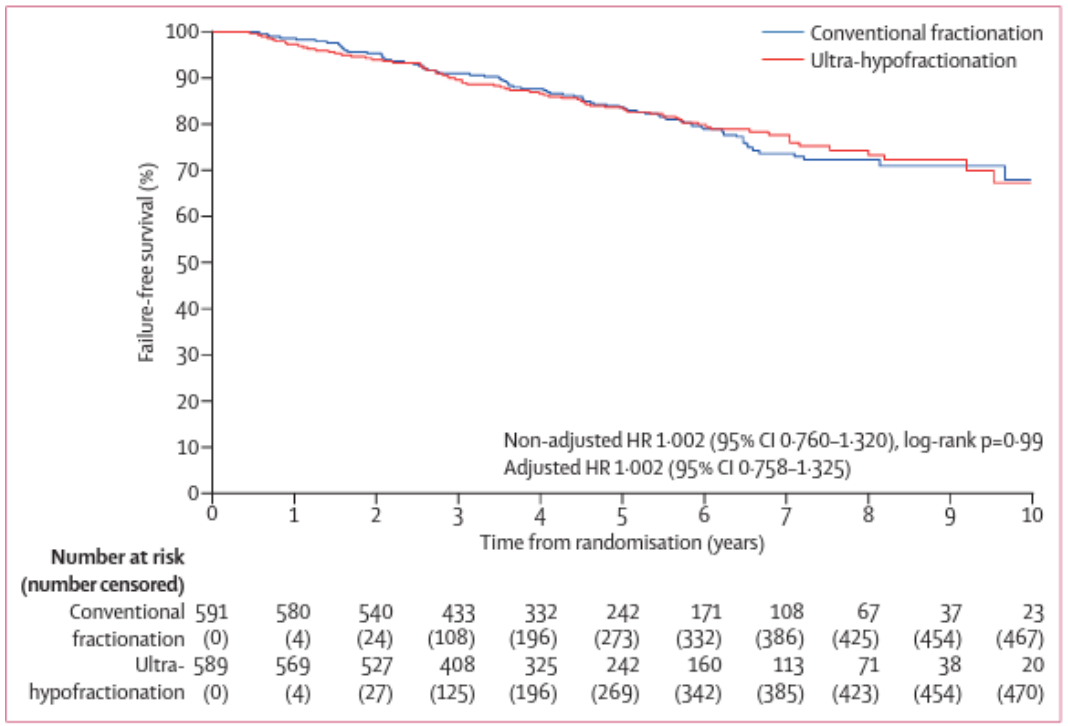
- Proton therapy often has superior dosimetry
- Limited data comparing outcomes
- Likely advantages in certain situations but not others

Stereotactic Body Radiotherapy (SBRT)

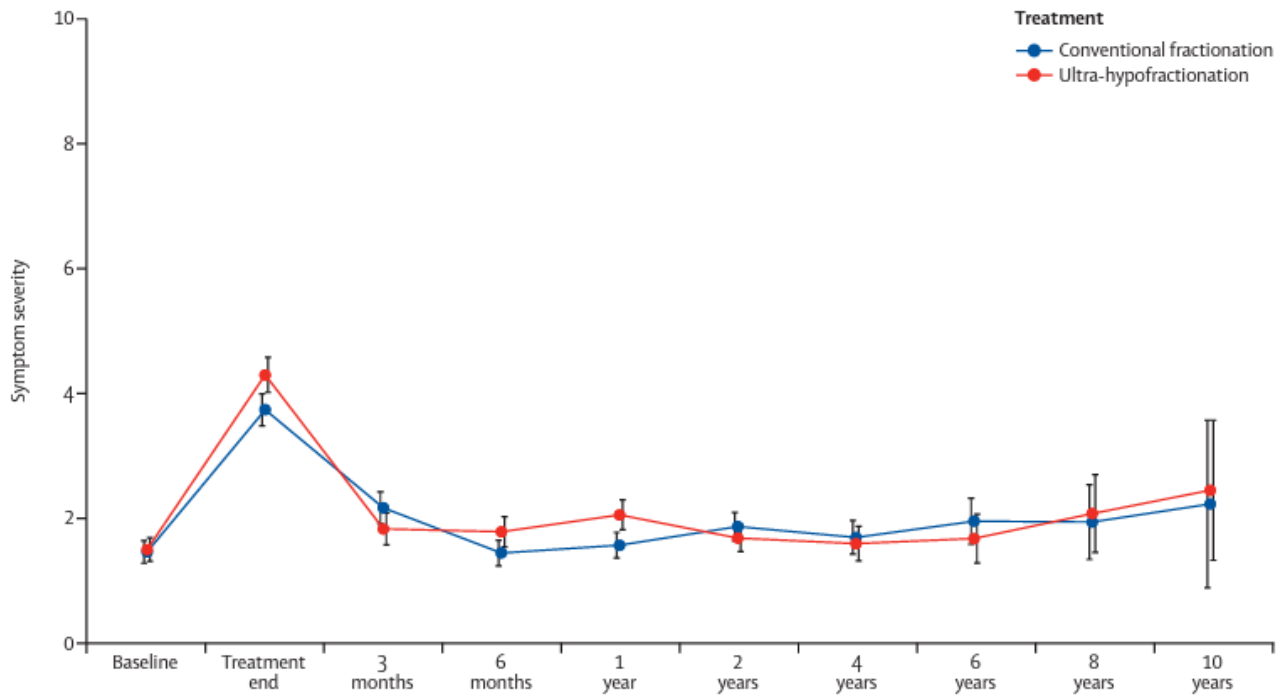
- SBRT = Definitive radiotherapy with high-dose external radiation given in a total of 5 treatments
- Sometimes also known as stereotactic ablative radiotherapy (SABR)

Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial

Anders Widmark, Adalsteinn Gunnlaugsson, Lars Beckman, Camilla Thellenberg-Karlsson, Morten Hoyer, Magnus Lagerlund, Jon Kindblom, Claes Ginman, Bengt Johansson, Kirsten Björnlinger, Mihajl Seke, Måns Agrup, Per Fransson, Björn Tavelin, David Norman, Björn Zackrisson, Harald Anderson, Elisabeth Kjellén, Lars Franzén, Per Nilsson

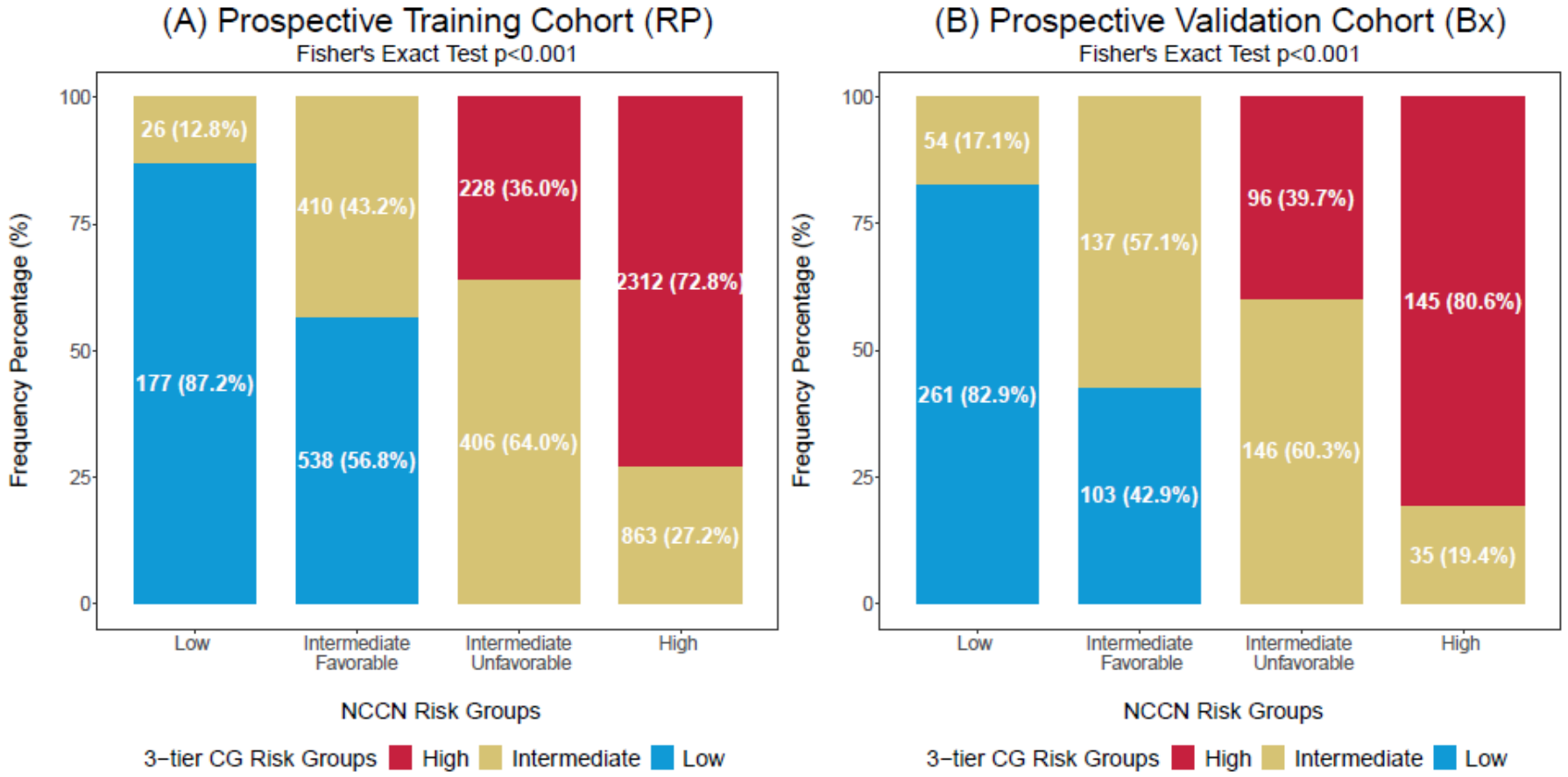


Patient Reported GU Problems



Genomic Risk Classifiers

- **Use molecular Characteristics to augment NCCN risk groups**

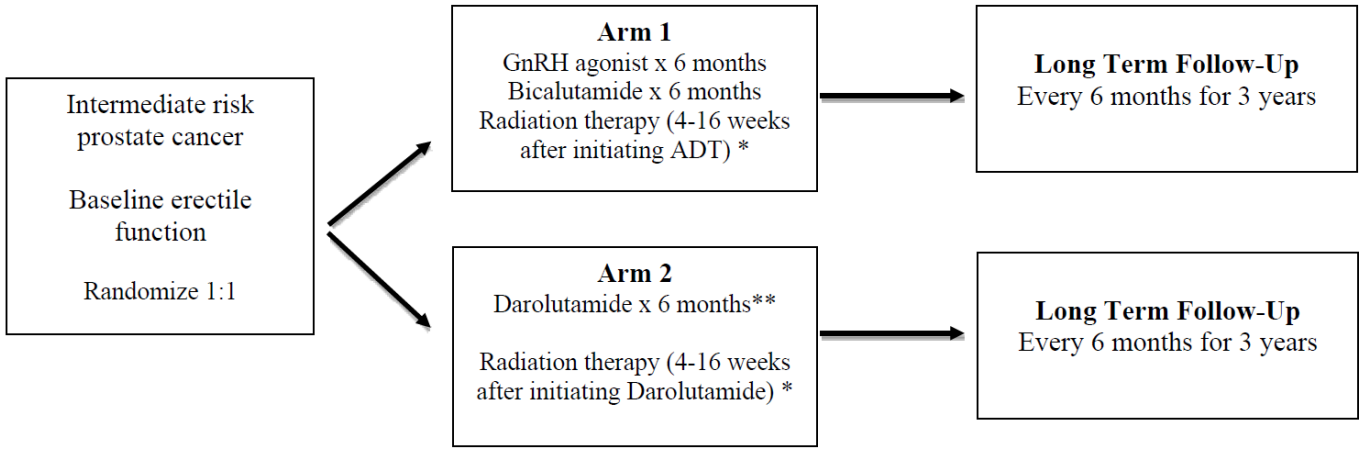


ADT modulation: INTREPID

INTREPId (INTermediate Risk Erection PreservatIon Trial): A Randomized Phase II Trial of Radiation Therapy and Darolutamide for Prostate Cancer

- Phase 2 randomized trial
- Stratification
  - Decipher low/intermediate vs high risk
  - RT modality (EBRT vs SBRT/combination RT)
  - Age ≥ 65 vs < 65

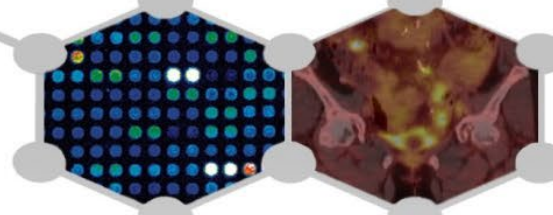
**One cycle/month is 28 days



ADT modulation: INTREPID

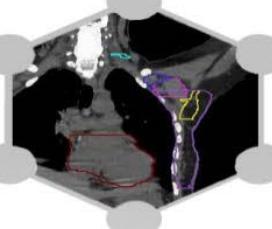
INCLUSION CRITERIA:

- NCCN intermediate risk prostate cancer defined as clinical T2b-T2c, Gleason 7, or PSA 10-20 ng/mL.
- Successful acquisition of a genomic classifier Decipher score (Decipher Biosciences, Vancouver, BC) from archived tissue.
- Good erectile function as assessed by EPIC-26 questionnaire



NRG ONCOLOGY

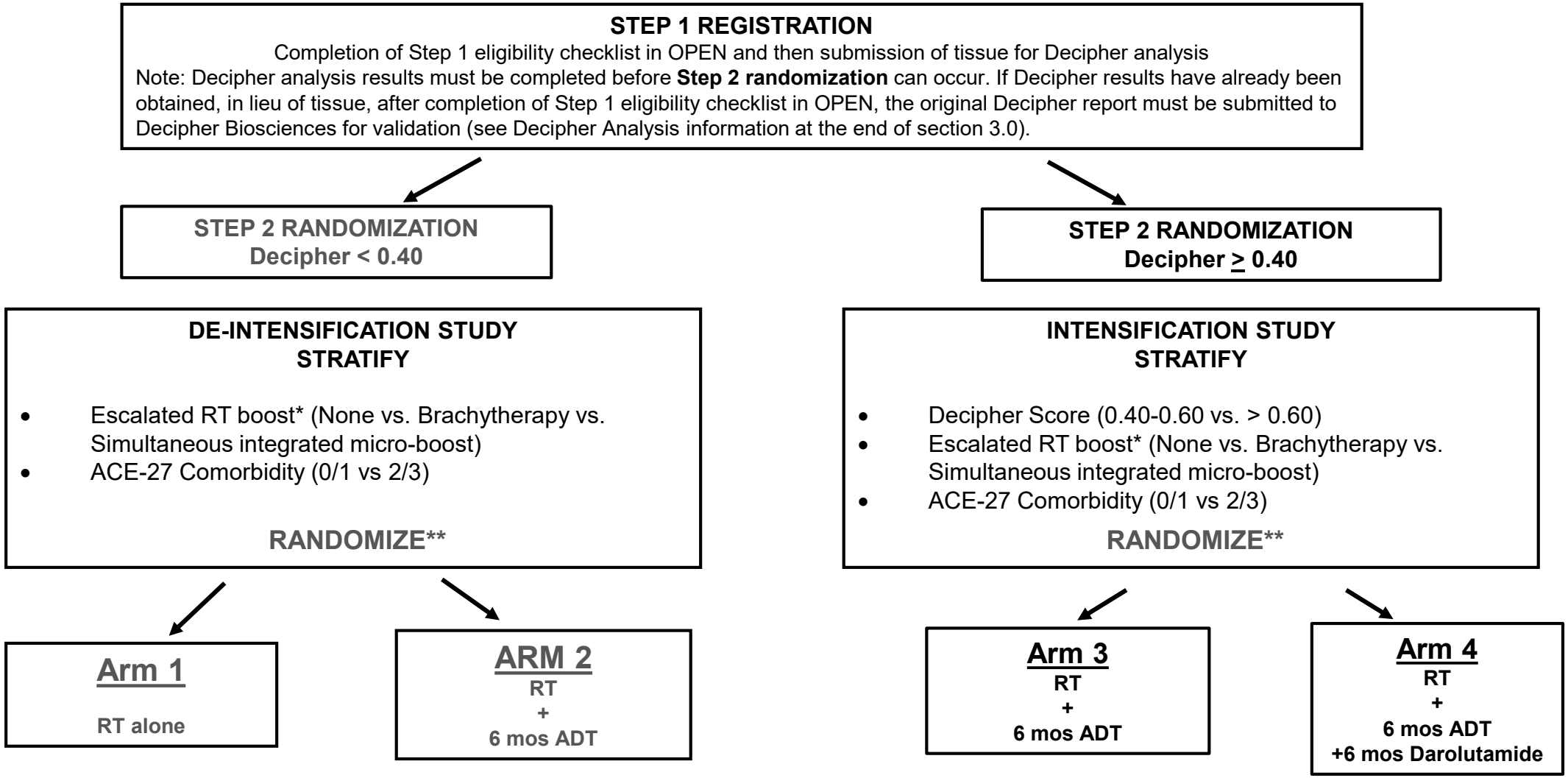
Advancing Research. Improving Lives.™



NRG-GU010

PARALLEL PHASE III RANDOMIZED TRIALS OF **G**ENOMIC-RISK STRATIFIED **U**NFAVORABLE **I**NTERMEDIATE RISK PROSTATE CANCER: **D**E-INTENSIFICATION **A**ND I**N**TENSIFICATION **C**LINICAL TRIAL **E**VALUATION (**GUIDANCE**)

Study Schema



* For Escalated RT boost definition see Section 5.2 Establishing Treatment Approaches

**Randomization is 1:1

RT = radiation therapy; SBRT=stereotactic body radiotherapy; ADT =androgen deprivation therapy

NRG ONCOLOGY™

Key Eligibility Criteria

- Biopsy(+) prostate adenocarcinoma within 270 days prior to registration
- No prior hormonal therapy or pelvic radiotherapy
- Unfavorable intermediate risk prostate cancer, defined as having ALL the following criteria:
  - Has at least one intermediate risk factor (IRF):
    - PSA 10-20 ng/mL
    - Clinical stage T2b-c by American Joint Committee on Cancer (AJCC) 8th edition*
    - Gleason Score 7 (Gleason 3+4 or 4+3 [ISUP Grade Group 2-3])
  - Has ONE or more of the following 'unfavorable' intermediate-risk designators:
    - >1 IRF
    - Gleason 4+3=7 (ISUP Grade Group 3)
    - ≥50% of biopsy cores positive*
  - Absence of high-risk features (Gleason 8-10 [ISUP Grade Group 4-5], PSA>20, cT3-4 by digital exam or gross extra-prostatic extension on imaging)

NRG ONCOLOGY™

**Note: See protocol for details on prioritizing DRE over imaging assessment of T-stage and counting multiple biopsies from lesion targeted sampling as one positive biopsy only in % positive core assessment.*

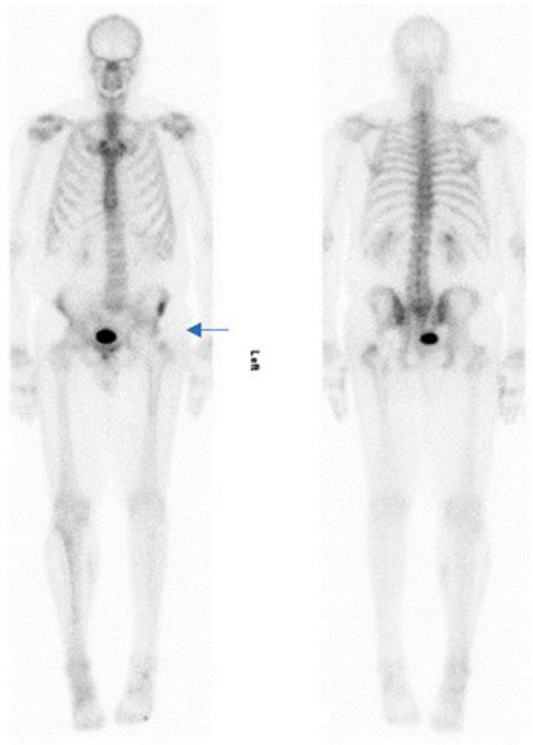
CARE OPTIONS–HIGH RISK

17.Clinicians should inform patients with **high-risk prostate cancer AND > 10 YEAR LIFE EXPECTANCY that prostatectomy and XRT + 18-24 months ADT are standard options**

General Information	
Age	59 years
Pretreatment PSA	14 ng/mL
Gleason Pattern	
Primary Gleason at biopsy	Pattern 4
Secondary Gleason at biopsy	Pattern 5
Biopsy Gleason score	9
Clinical Tumor Stages	
Clinical Tumor Stage (AJCC Version 7, 2010)	T2a
Biopsy Cores	
Number of positive biopsy cores	6 cores
Number of negative biopsy cores	6 cores
Percentage of positive biopsy cores	50.00%

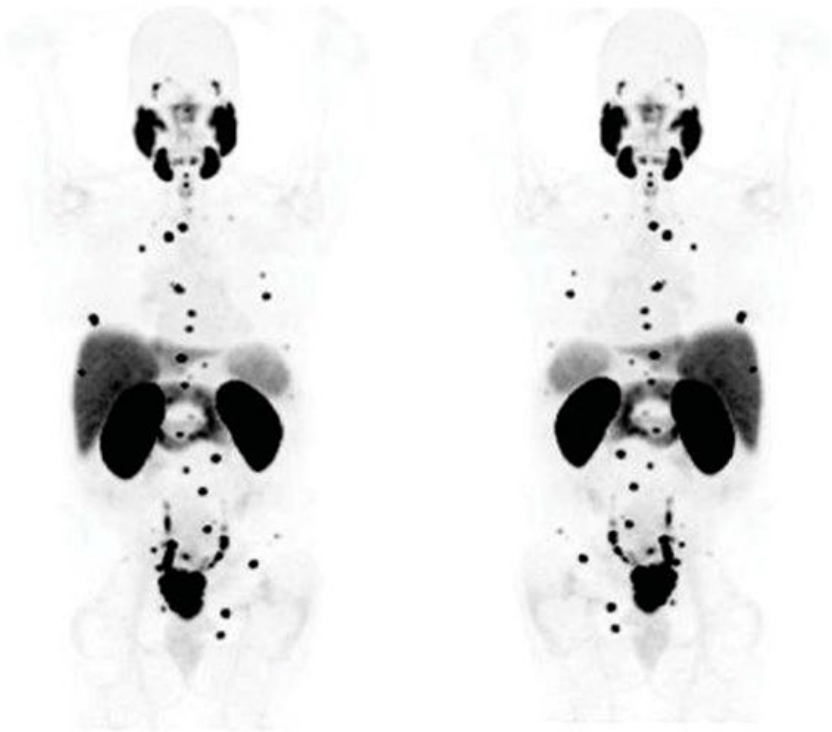
Jones 2011

Conventional imaging vs PSMA



Anterior Posterior

Bone Scintigraphy



Anterior
^{18}F-DCFPyL-PET/CT

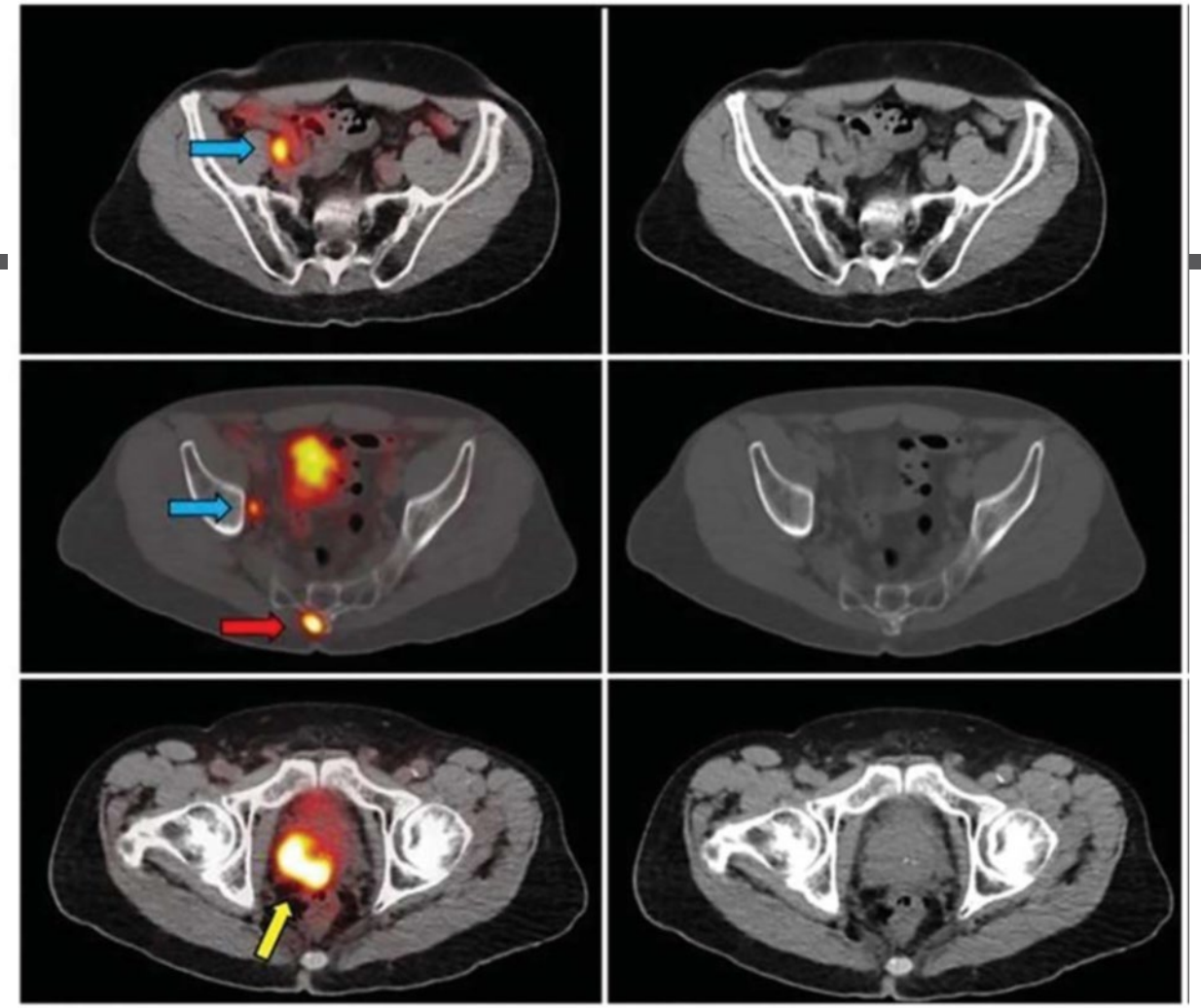
Posterior
^{18}F-DCFPyL-PET/CT

Maximum Intensity Projection Images

PSMA PET for Pretreatment Staging

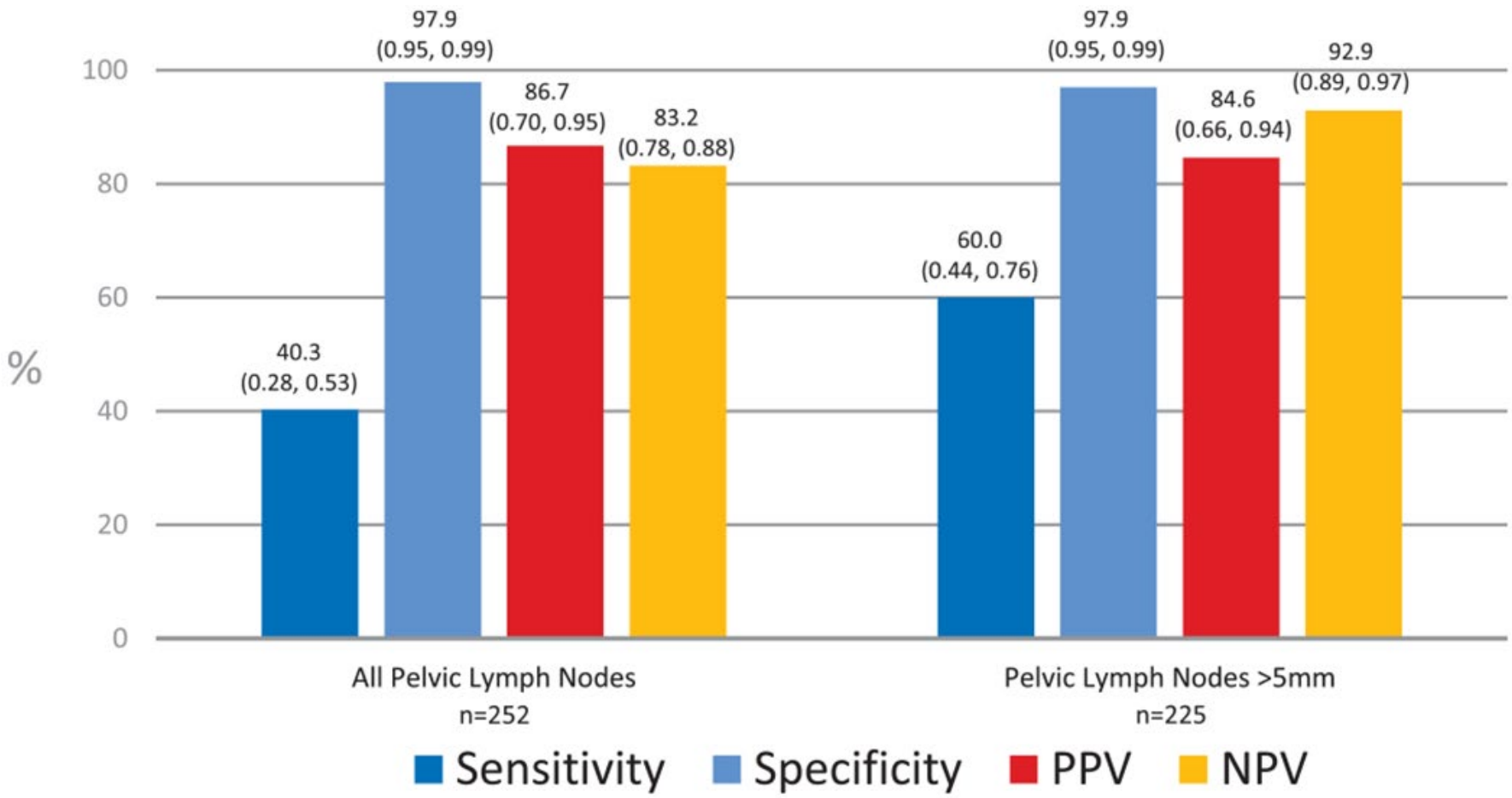
77 yo, PSA 7.1, GG 4+5
Conventional imaging negative

PSMA PET:
2 positive pelvic LNs
1 bone met in sacrum
Lesion in prostate

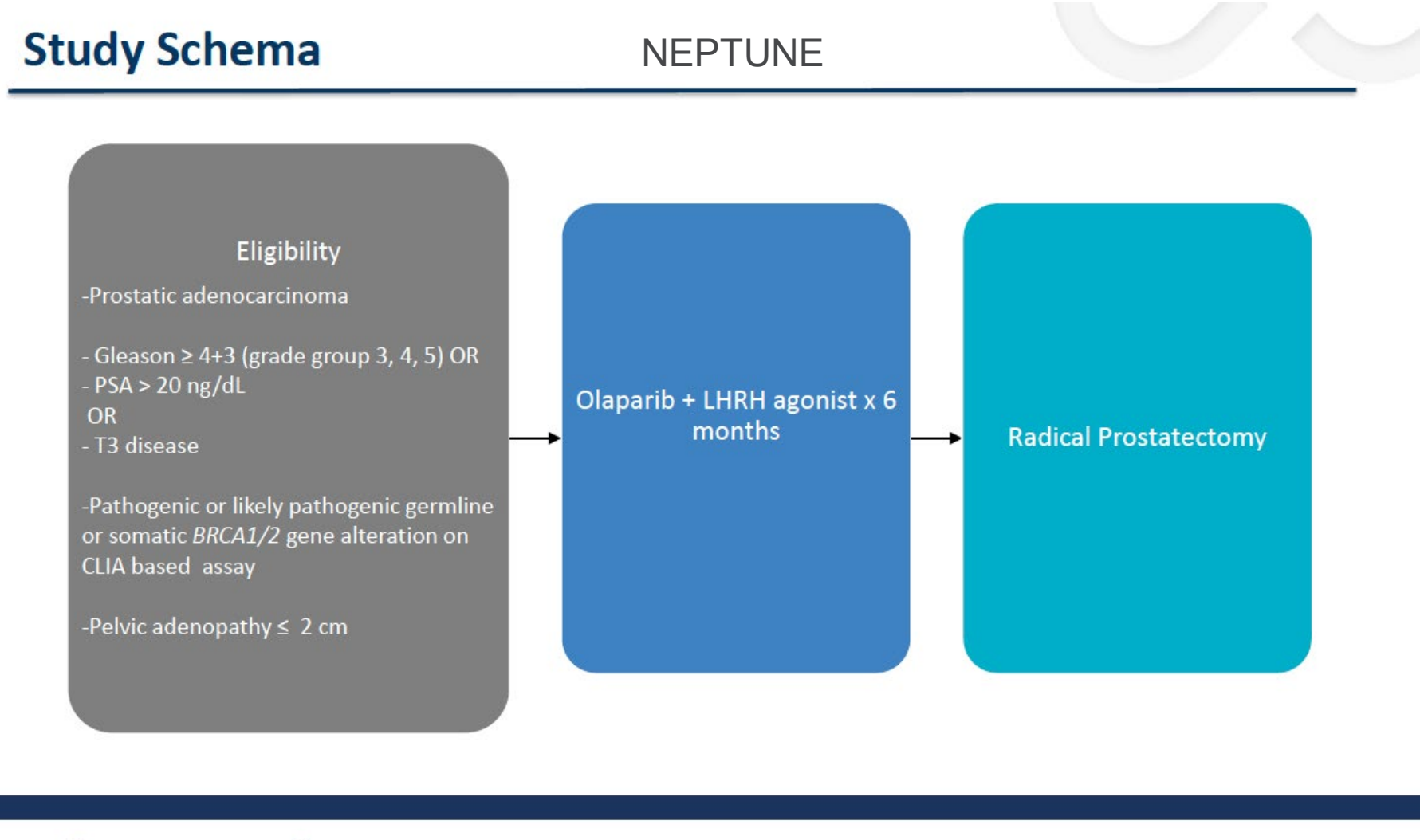


Kuppermann et al. J of Urology 2022

PSMA performance



Neoadjuvant therapy prior to prostatectomy: NEPTUNE



hoosier SM
CANCER RESEARCH NETWORK

Neoadjuvant therapy prior to prostatectomy: Proteus

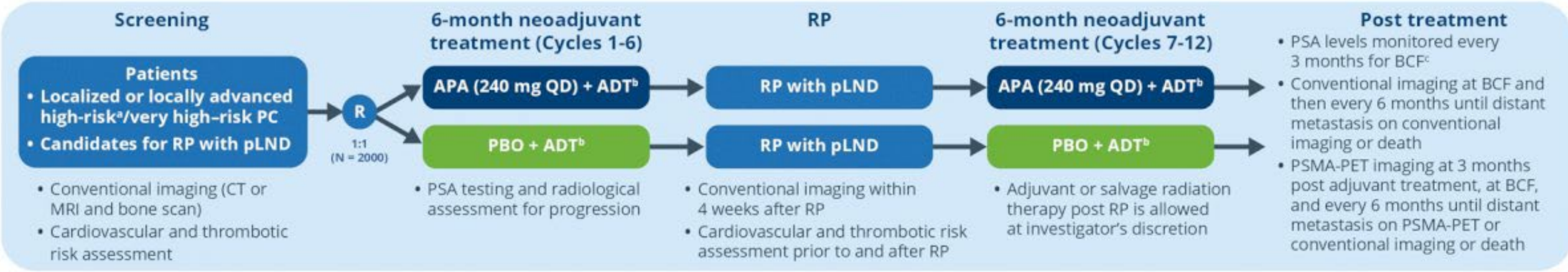
INCLUSION CRITERIA:

•Gleason Sum Score >=4+3 or =Grade Groups [GG] 3 5) AND >=1 of the following 4 criteria:

• a) Any combination of Gleason Score 4+3 (= 3) and Gleason Score 8 (4+4 or 5+3) in >= 6 systematic cores (with >=1 core Gleason Score 8 [4+4 or 5+3] included)

•b) Any combination of Gleason Score 4+3 (=GG 3) and Gleason Score 8 (4+4 or 5+3) in >=3 systematic cores and Prostate-specific antigen (PSA) >=20 ng/mL (with >= 1 core Gleason Score 8 [4+4 or 5+3] included);

•c) Gleason Score >=9 (=GG 5) in at least 1 systematic or targeted core; d) At least 2 systematic or targeted cores with continuous Gleason Score >=8 (=GG 4), each with > 80 percent (%) involvement



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NRG-GU009: PARALLEL PHASE III RANDOMIZED TRIALS FOR HIGH RISK PROSTATE CANCER EVALUATING DE-INTENSIFICATION FOR LOWER GENOMIC RISK AND INTENSIFICATION OF CONCURRENT THERAPY FOR HIGHER GENOMIC RISK WITH RADIATION (PREDICT-RT*)

Prostate RNA Expression/Decipher To Individualize Concurrent Therapy with Radiation

ClinicalTrials.gov Identifier NCT# 04513717
NCI Version Date: (October 29, 2020)

Principal Investigator:
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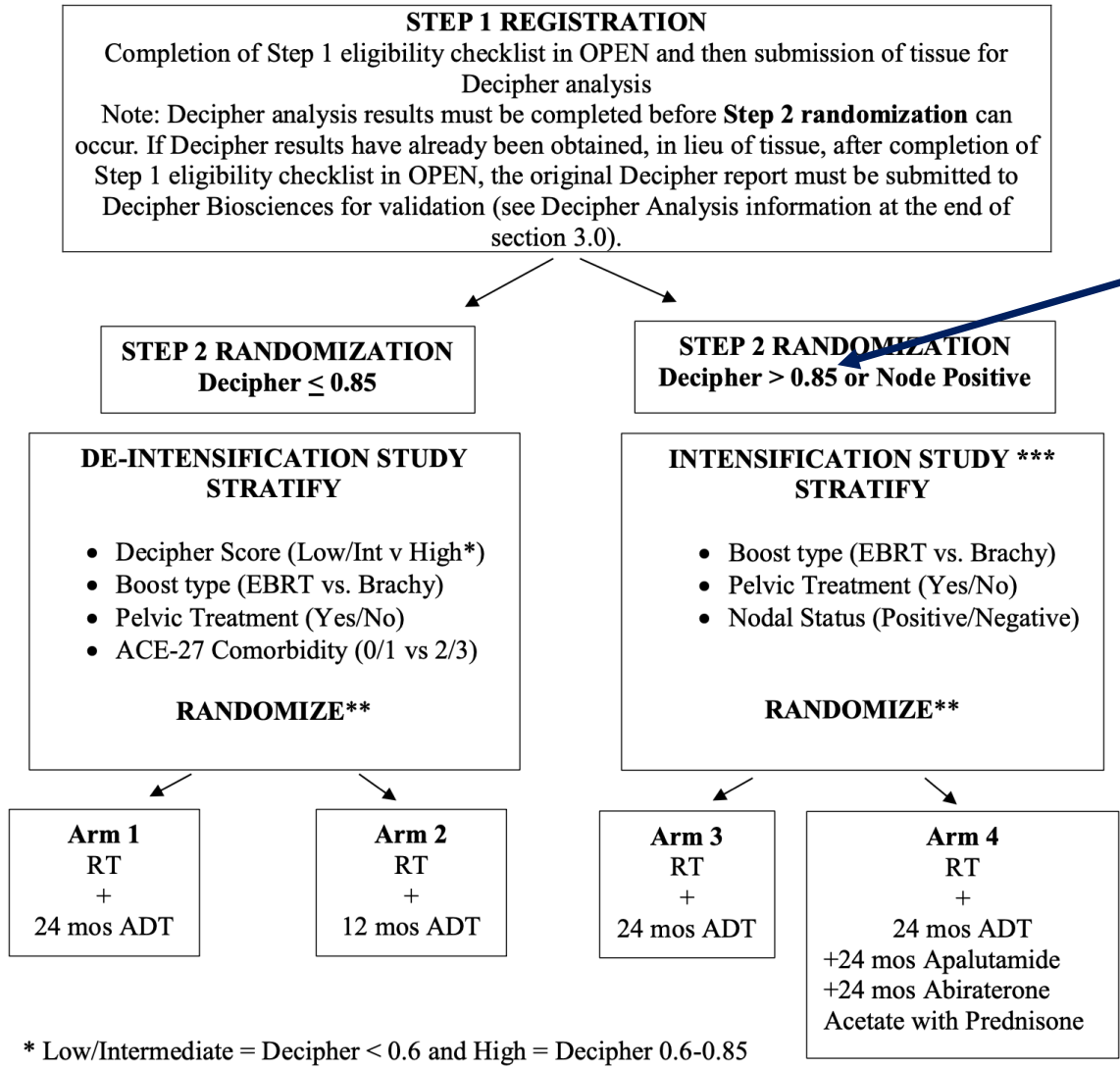
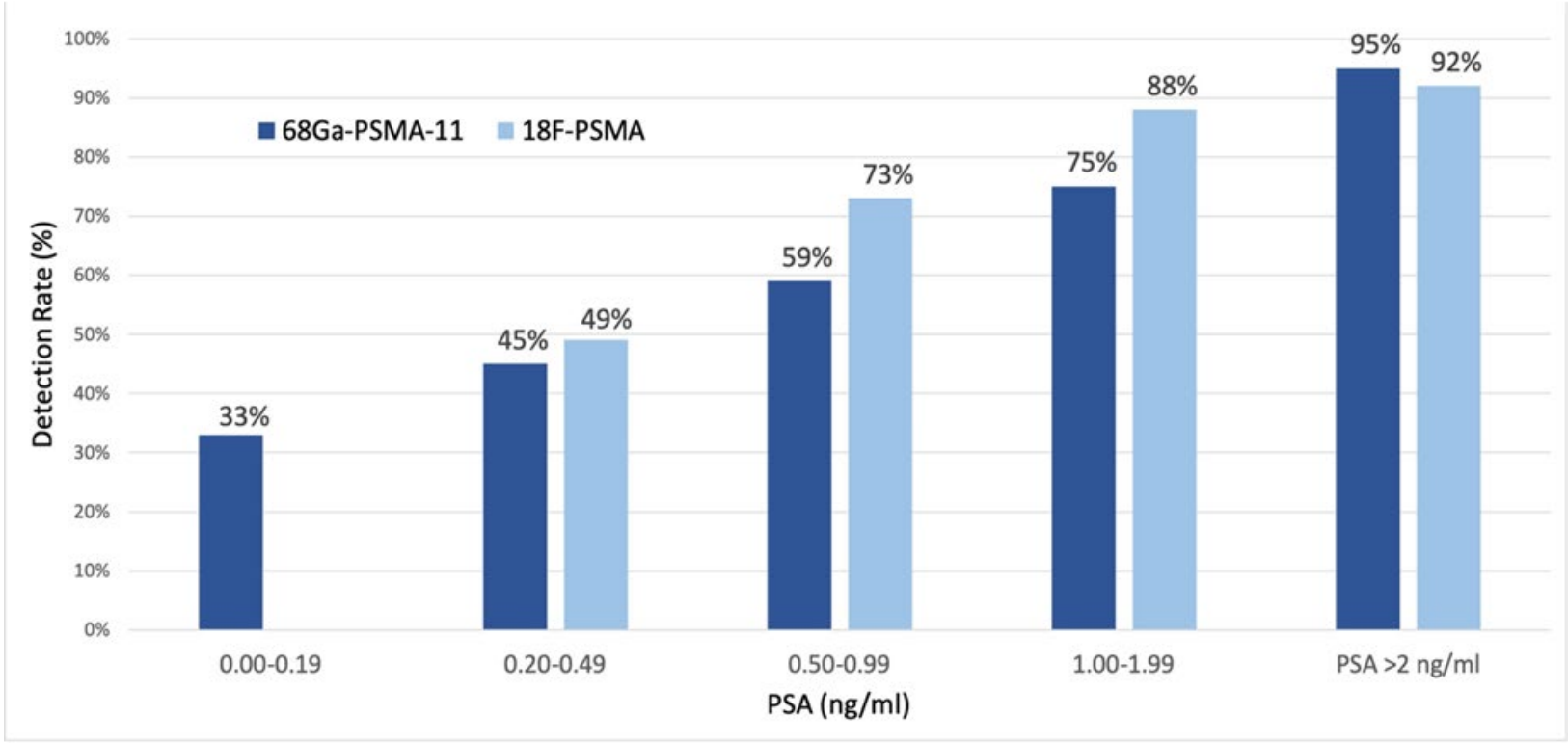
NRG-GU009
SCHEMA



Upper 1/3 of Decipher

* Low/Intermediate = Decipher < 0.6 and High = Decipher 0.6-0.85
**Randomization is 1:1
*** Up to 200 patients who consent to imaging sub study will receive F-18 PET. See Section 4.0 and 11.3 for more details and time points.
Note:
A radiation treatment approach change post registration involving the pelvic lymph node treatment or prostate boost type stratification factors will result in a protocol deviation.
RT = radiation therapy; ADT = androgen deprivation therapy

CARE OPTIONS–Biochemical recurrence



Kuppermann et al. J of Urology 2022

Phase III Study of Local of Systemic Therapy INtensification DIrected by PET in Prostate CAncer Patients with Post-ProstaTEctomy Biochemical Recurrence (INDICATE) (EA8191)

ECOG-ACRIN
cancer research group
Reshaping the future of patient care

Neha Vapiwala, MD FACR
Professor, Radiation Oncology
University of Pennsylvania
EA8191 Study Chair

Hypothesis and Objectives

Hypothesis: PET scan-based treatment intensification with either enhanced systemic therapy or with metastasis-directed radiation for cytoreduction will improve progression-free survival (PFS) relative to standard of care (SOC) therapy for post-prostatectomy BCR.

Primary Objectives

1. For patients without PET-evidence of extrapelvic metastases, *to evaluate whether the addition of enhanced systemic therapy to SOC salvage therapy could prolong PFS*.
2. For patients with PET-evidence of extrapelvic metastases, *to evaluate whether the addition of metastasis-directed RT to enhanced systemic therapy and SOC salvage therapy could prolong PFS*.

NB: SOC salvage therapy = pelvic RT + 6 months of GnRH agonist

Enhanced systemic therapy = 6 months of Apalutamide + GnRH agonist

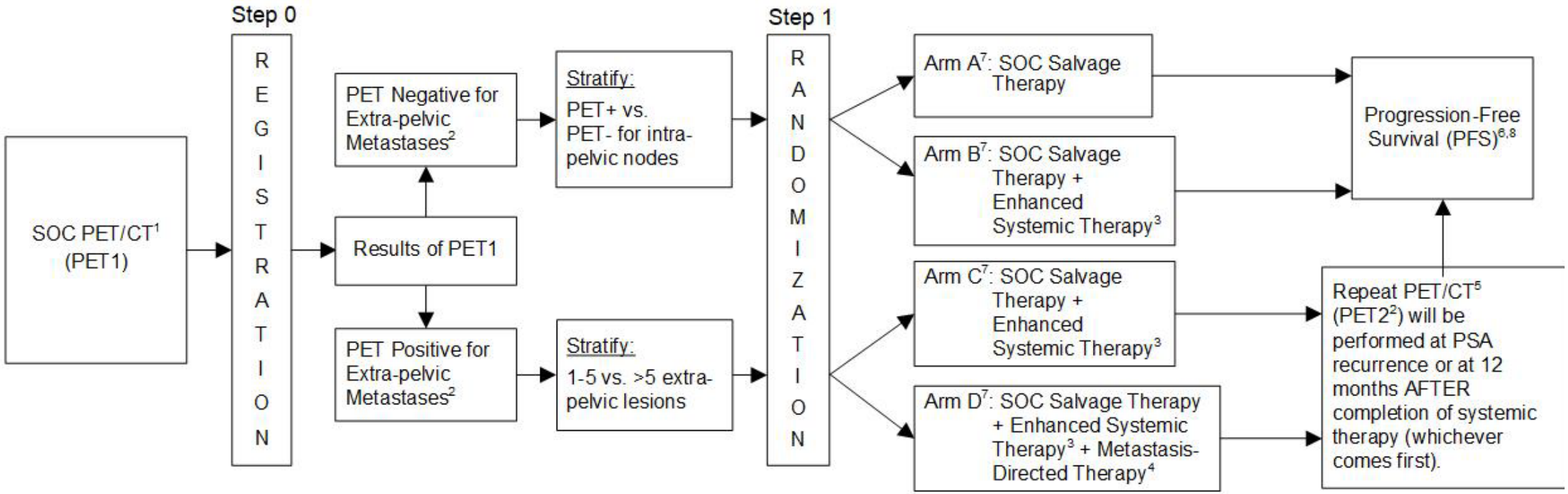
Key Eligibility

1. Biochemical recurrence (BCR) after RP, rising PSA defined as follows:
   - If time to BCR (defined as time to first detectable PSA after RP) is <12 months, a minimum PSA level of 0.2ng/mL and a confirmatory reading of ≥0.2 ng/mL is required, per the AUA definition (includes patients with persistent PSA reading of ≥0.2 ng/mL).
   - If time to BCR is ≥12 months, a minimum absolute PSA of 0.5 ng/mL is required.
     - NOTE: Qualifying PSA values per above must be collected at least 4 weeks after RP, with confirmatory persistent or elevated PSA collected at any subsequent time point.

2. Negative or equivocal for extrapelvic metastases by conventional imaging modalities (CIM) (i.e., bone scan, pelvic CT/MRI) within 12 weeks prior to registration. Extra-pelvic metastases = any osseous and/or any extrapelvic soft tissue, lymph nodes and organ (superior to common iliac bifurcation, outside standard prostate bed + pelvic nodal RT fields).

3. Baseline PET/CT scan (AXUMIN scan or FDA approved PSMA PET/CT scan) completed after Step 0 registration and prior to Step 1 randomization OR ≤12 wks prior to Step 0

Schema



*Note: ^{18}F-fluciclovine (Axumin) will be used as current clinically available SOC PET/CT

Conclusions

- Novel technologies, enhanced biomarkers, effective systemic therapies changing the face of localized prostate cancer

- Clinical trials ushering in precision medicine across disease states

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Thank you!

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UC San Diego Health