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THE UNIVERSITY OF BRITISH COLUMBIA

Risk Stratification & Treatment Options for Prostate Cancer

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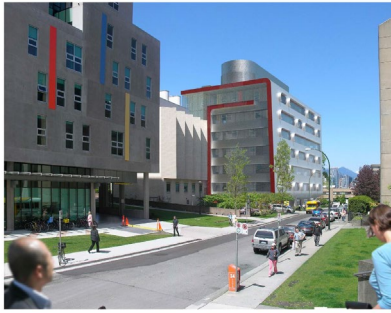

M.H. Mohseni Institute of Urologic Sciences

RESEARCH TREATMENT

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Faculty/Presenter Disclosure

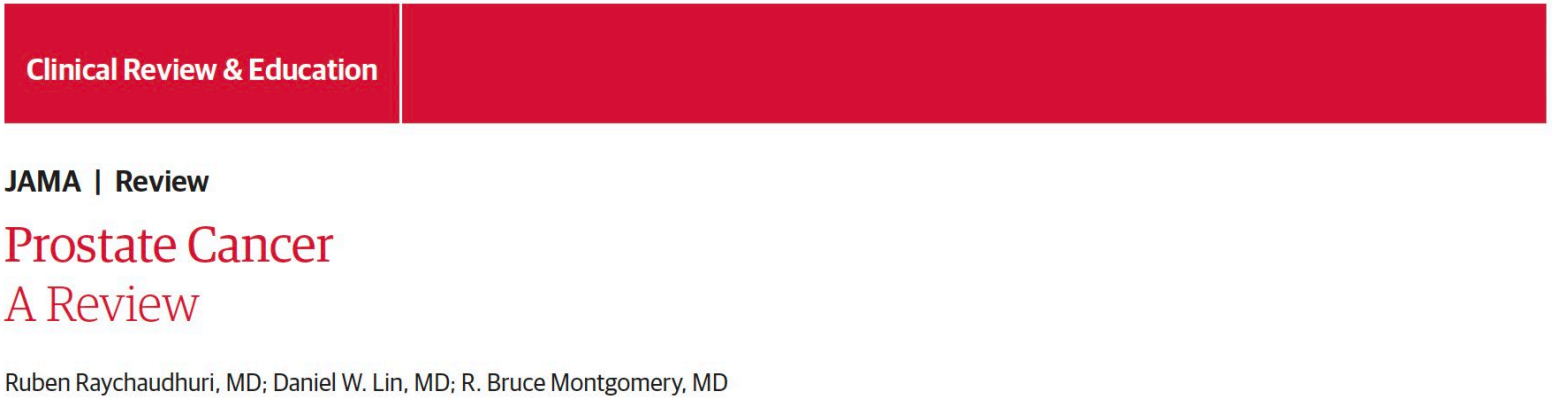
- **Faculty/Presenter:** Martin Gleave

- **Relationships with financial sponsors:**
  - **Grants/Research Support:** CIHR; PCF; PCC; CFI; BCKDF; NIH; NCI; Janssen; Astellas; Bayer
  - **Speakers Bureau/Honoraria:** None
  - **Consulting Fees:** Astellas, AZ, Bayer, GDx, Janssen, Sanofi, Pfizer, MDX
  - **Patents**: >200 (OGX-011, OGX-427; ST-CP; ST-POP; SEMA3C; VPC22826)
  - **Founder**: OncoGenex Technologies; Sustained Therapeutics; Sikta Pharma

Mitigating Potential Bias

- I diagnosis and treat men across the spectrum of prostate cancer from diagnosis to local and systemic therapies, including supportive and end of life care

- I am a urologist who performs radical prostatectomies

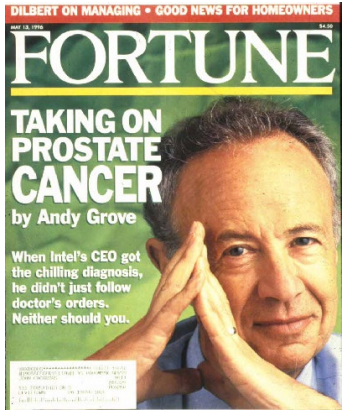


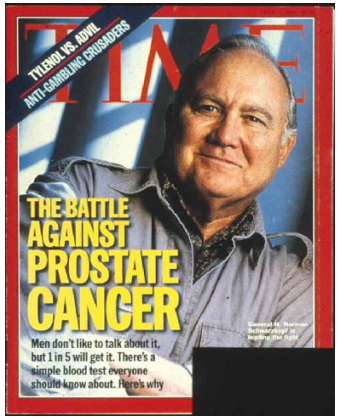
Learning Objectives

Upon successful completion of this activity participants will be able to:

- Understand risk stratifiers of men with PCa
- Describe treatment options for men with localized PCa
- Describe treatment options for men with recurrent or met PCa
- Council men and their families on side effect profiles of these treatments.

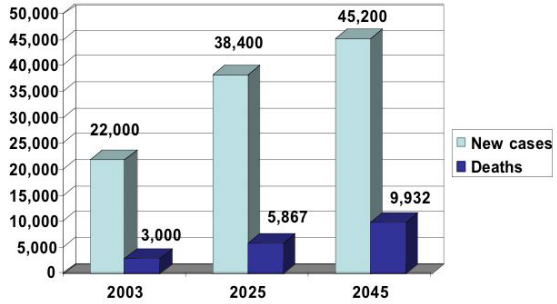
Prostate Cancer and the Ageing Male





- Cancer is our #1 killer and greatest fear
- PCa is the most common male cancer and 2nd leading cause of cancer deaths
- Incidence rises rapidly with age in an ageing population

Health Canada Projections



- **2 main challenges:**
  - **Over-detection and over-treatment of low risk cancers**
  - **Progression to lethal castrate resistant state**

Prostate Cancer Statistics in Canada - 2024

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- **27,900 cases, or 22% of all new cancer cases in men.**
- **5,000 deaths, or 11% of all cancer deaths in men.**
- **On average, 76 Canadian men will be diagnosed with, and 14 will die from, prostate cancer every day.**

50% decline in PCa death rate since 1995

- **earlier detection**
- **improved imaging**
- **multimodal local therapies**
- **better systemic therapies**

Optimizing Outcomes in PCa

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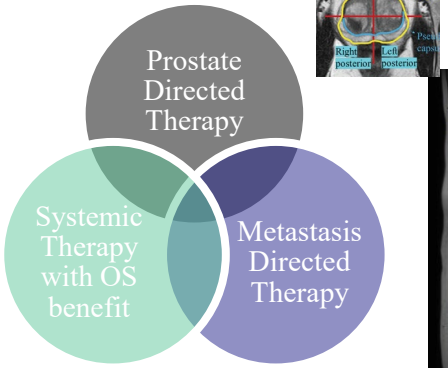
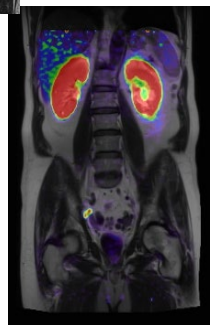
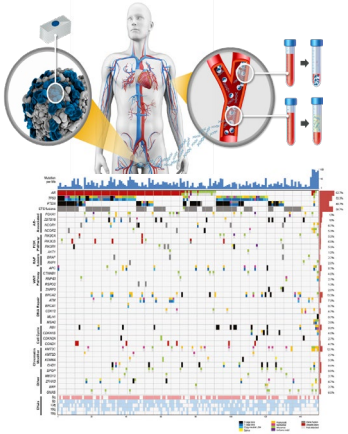
Convergent Incrementalism

- **Early Detection – PSA + MRI**
- **Risk Stratification**
  - volume pattern 4,5; PSA; biomarkers; imaging
- **Curative Techniques**
  - Surgery, radiotherapy
- **Multi-modal Therapy Integration:**
  - BCR: PSA- and image-guided early salvage therapy
  - Metastasis-directed therapies
  - ARPI Neoadjuvant strategies
- **More potent AR pathway inhibitors**
  - Other targeted therapies – PARPi, PSMA RLT







- **Biomarkers –**
  - **Prognostic, predictive**

➢ **Improve outcomes**

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PSA and PCa Detection

- Performance characteristics of PSA improved now with MRI.
- Evaluation of elevated PSA with prostate biopsy now improved with guided transperineal approach
- Risk of detecting low grade PCa with overtreatment now mitigated by active surveillance
- Treatment outcomes with high risk PCa now improved with better risk stratification, imaging, and multimodal therapy
- Treatment associated with bladder, bowel and sexual dysfunction now decreasing with improved techniques

Diagnosing Prostate Cancer "Early"

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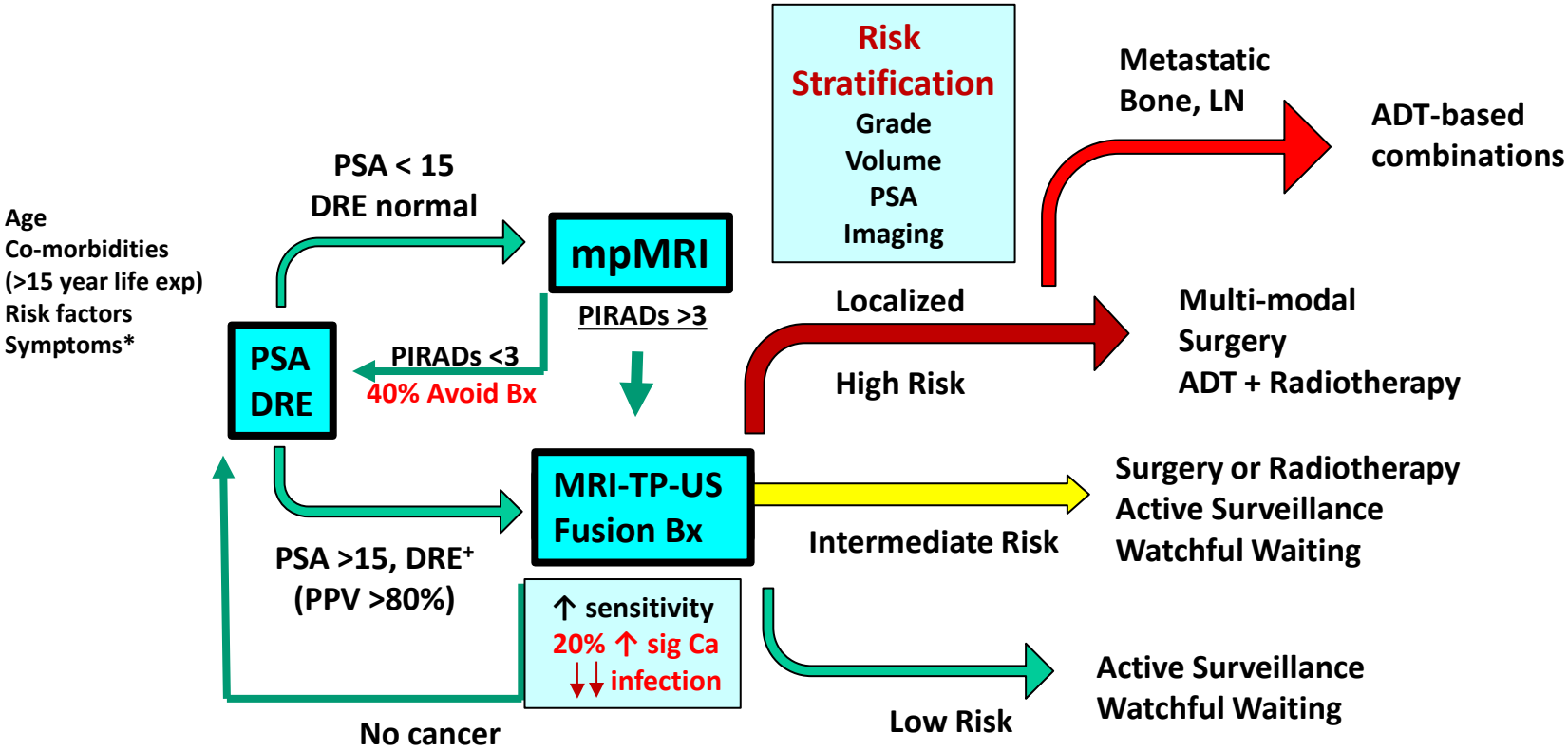
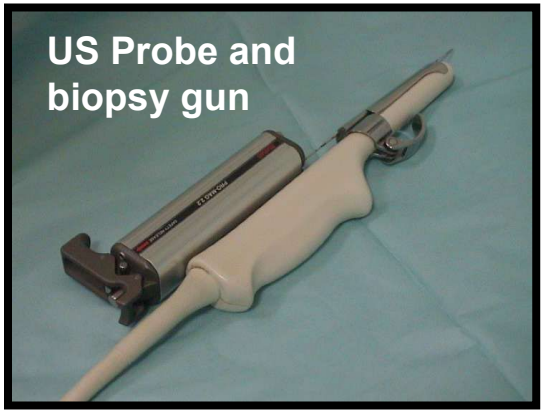
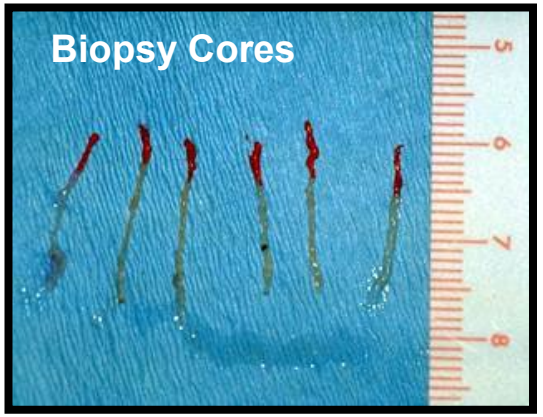


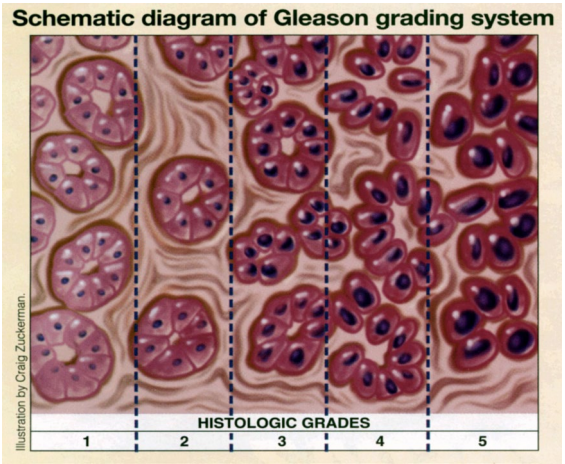
Ahmed HU et al (PROMIS). The Lancet. 2017 Feb 25;389(10071):815–22
Kasivisvanathan V et al. N Engl J Med. 2018 May 10;378(19):1767–77

Prostate Biopsy and Risk Stratification





- Gleason score low vs grade
- Quantify amount of PCa in biopsy
  - Number (%) of +ve cores
  - Linear extent/% of cancer in core(s)
  - Extracapsular disease
  - Aggressive patterns



Diagnosis

Risk Stratification Localised PCA

Risk	Low	Intermediate	High
PSA	0-10	10.1-20	>20
Stage	T1C, T2a	T2b	T3
Gleason	6	7	8-10
		Volume of pattern 4 or 5	

Active Surveillance

Surgery or Radiation ADT with RT

D'Amico, J Urol, 1998

Defining Risk in "Localized PCa"

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vLR → LR → Low-Int → High –Int → Low-High → Int-High → High-High → M1a

T*	T1c, 2	T1c, 2	T1c, 2	T1c, 2	T1c, 2, 3	T1c, 2, 3	T1c, 2, 3	Tx
N	N0	N0	N0	N0	N0	N0	N1	N1
M	M0	M0	M0	M0	M0	M0	M0	PSMA PET
GG**	3	3	3+4	4+3; 3+4	4+4; 4+3	4+5; 4+4	5+5; 4+5	GP 4 or 5
# cores[a]	<3	>3	<3	<3; >3	<3; >3	<3; >3	<3; >3	any
PSA	<10	<10	<10	10-20	10-20; >20	10-20; >20	10-20; >20	PSA > 10

*MRI risk features
**Histologic variants

[a] vol of cancer in cores:
depends on type of bx – MRI targeted +/- systematic (6 cores of MRI ROI vs 12 cores + 2 additional of MRI ROI)

Refining Risk – Challenges, Advances

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- **Multifocal, multiclonal origins underpin intra-patient spatial heterogeneity**
- **Imperfect imaging and biopsy under-sampling limit accuracy of prognostic subgrouping**

  - Clinical T stage highly subjective
  - Grade-defined high risk can be misleading
    - Low volume GG4 vs high volume GG3
  - Need to consider core lengths; Gleason Grade and variants
    - **Most important - volume of pattern 4, presence of pattern 5;**
    - **Other estimates of volume - PSA >20; PSMA N status**

Prostate Cancer is Highly Heterogeneous (multifocal, multiclonal)

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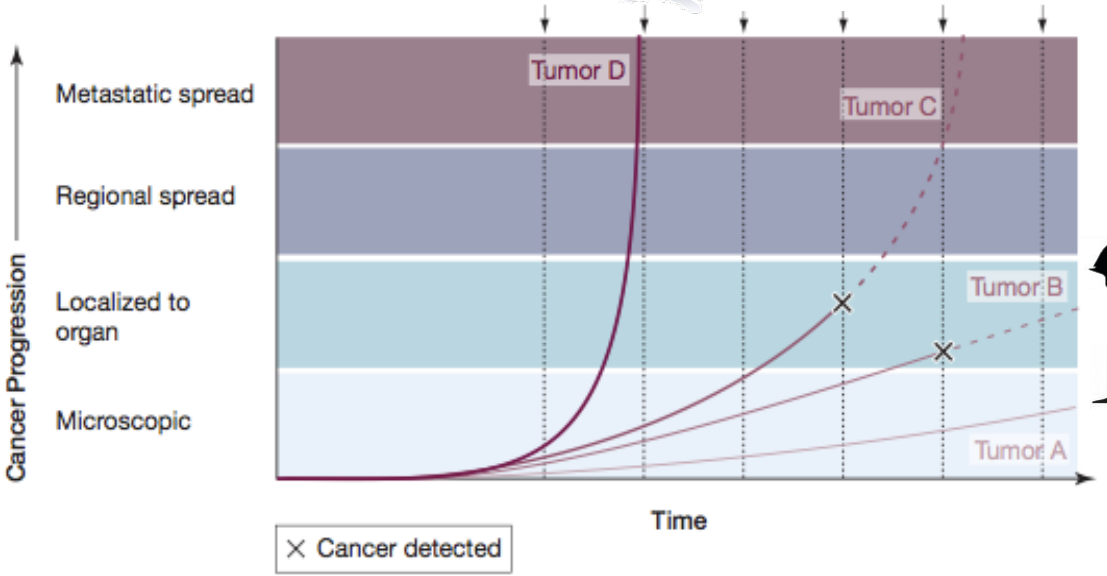
- High frequency of genomic alterations
- (loss of PTEN, p53, RB)

- Multimodal therapy for cure

Gleason 4 or 5
PSA >10

Higher volume pattern 4
PSA 10 - 20

- Surgery or Radiotherapy



Low volume
Gleason pattern 4

Gleason 3+ 3
PSA <10

Low frequency of genomic alterations (ETS fusions, SPOP)

- Active Surveillance

The Balancing Act…

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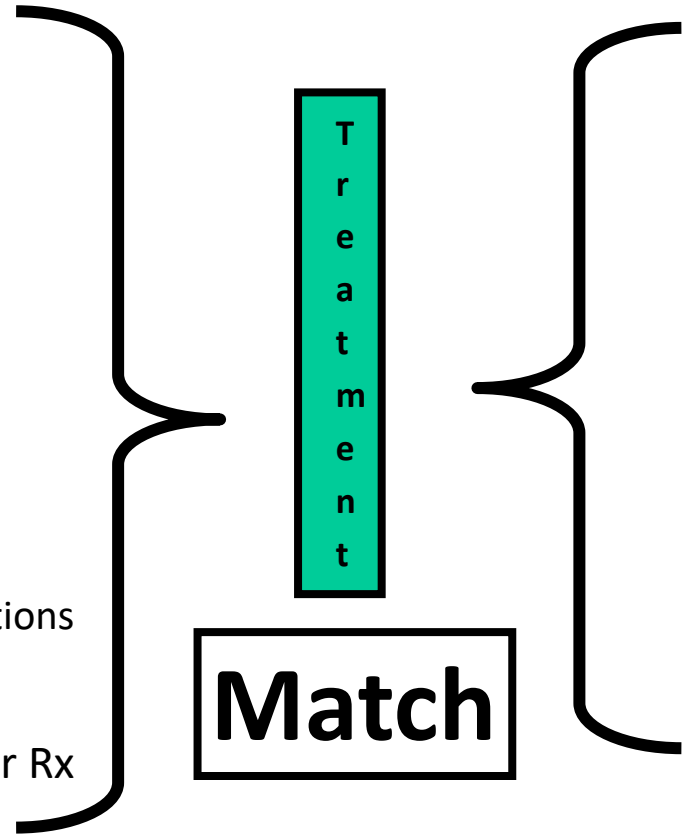
- identify those who need treatment
- decrease the risk of death & morbidity

- Avoid unneccessary treatment
- Maintain QoL
- Cost Effectiveness

Individual patient counselling is key!

Individualize

- Patient
  - Age, life exp
  - Co-morbidities
  - Risk tolerance
  - preferences
- Tumor
  - Grade
  - Volume/stage
  - PSA
  - Genomic alterations
- QoL
  - AE from PCa or Rx
  - Longevity



Active Surveillance

Surgery

Conformal RT

Brachytherapy

ADT

Focal Therapy

- HIFU, Cryo, ICE

Watchful waiting

Optimal Treatment Of Localized Prostate Cancer

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- ***Low Risk:***
  - **Active surveillance**
- ***Intermediate Risk:***
  - **Active surveillance for select low tier**
  - **RP and RT/ADT have *similar* rates of PSA recurrence**
- ***High Risk:***
  - **RP and RT/ADT have *similar* rates of BCR**
  - **RP has lower rates of metastases, PCA deaths >10 yrs**
    - **(earlier detection of recurrence, earlier post op salvage RT)**

*Presence of LUTS/retention prioritizes RP
*Side effects quantitatively similar, qualitatively distinct

Active Surveillance is not Watchful Waiting

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- **Active surveillance**

  Consists of deferring treatment in patients candidate for an immediate radical treatment

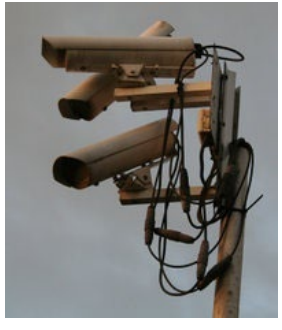
  Implies revisiting periodically the patient status and treating in case of progression

- PSA/DRE q 6 monthly
- MRI +/- re-bx ~ q 2 years
- Progression – grade, PSA, Sx
- ~20% progress q 5 years

Ideal for low risk and selected low tier intermediate risk with > 10 yr life expectancy

- **Watchful waiting**

  is delaying treatment until symptoms occured in patients not candidate or refusing a radical treatment



For elderly asymptomatic men with co-morbidities, short life expectancy

Need to

-manage expectations, anxiety

-develop methods to reduce F/U biopsy (Canary Protocol active at UBC)

JAMA

Home | JAMA | Vol. 331, No. 24

Original Investigation FREE

Cite Permissions Metrics

Long-Term Outcomes in Patients Using Protocol-Directed Active Surveillance for Prostate Cancer

Lisa F. Newcomb, PhD[1,2]; Jeannette M. Schenk, PhD[1]; Yingye Zheng, PhD[3]; Menghan Liu, MS[3]; Kehao Zhu, MS[3]; James D. Brooks, MD[4]; Peter R. Carroll, MD, MPH[5]; Atreya Dash, MD[6]; Claire M. de la Calle, MD[2]; William J. Ellis, MD[2]; Christopher P. Filson, MD, MS[7,8]; Martin E. Gleave, MD[9]; Michael A. Liss, MD, PhD[10]; Frances Martin, MD[11]; Jesse K. McKenney, MD[12]; Todd M. Morgan, MD[13]; Maria S. Tretiakova, MD[14]; Andrew A. Wagner, MD[15]; Peter S. Nelson, MD[16]; Daniel W. Lin, MD[1,2]

Author Affiliations | Article Information

JAMA
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2024;331;(24):2084-2093. doi:10.1001/jama.2024.6695

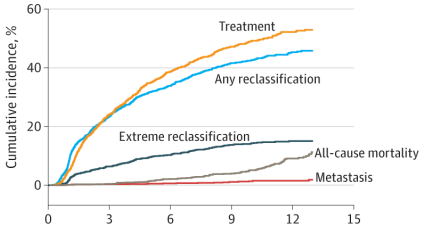
2155 men with localized PCa, median fu 7.2 years, median age 63 years

10 years after diagnosis, 49% of men remained free of progression or treatment, less than 2% developed metastatic disease, and less than 1% died of their disease.

Later progression and treatment during surveillance were not associated with worse outcomes.

In general – risk of progression (grade, PSA) was ~20% every 5 years

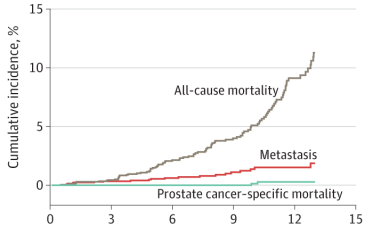
A Reclassification, treatment, metastasis, and all-cause mortality in the full cohort



No. of participants at risk

Treatment	2155	1421	819	505	218
Any reclassification	2155	1300	720	422	175
Extreme reclassification	2147	1402	807	492	212
All-cause mortality	2155	1849	1262	864	394
Metastasis	2155	1843	1254	852	388

B Metastasis, all-cause mortality, and prostate cancer-specific mortality in the full cohort



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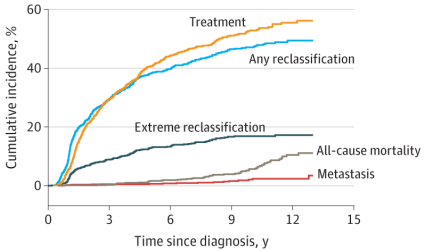
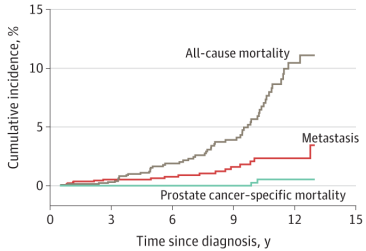
C Reclassification, treatment, metastasis, and all-cause mortality in the subcohort



No. of participants at risk

Treatment	1403	863	436	255	74
Any reclassification	1403	782	380	211	58
Extreme reclassification	1397	847	427	249	74
All-cause mortality	1403	1208	767	494	161
Metastasis	1403	1202	761	484	155

D Metastasis, all-cause mortality, and prostate cancer-specific mortality in the subcohort



No. of participants at risk

All-cause mortality	1403	1208	767	494	161
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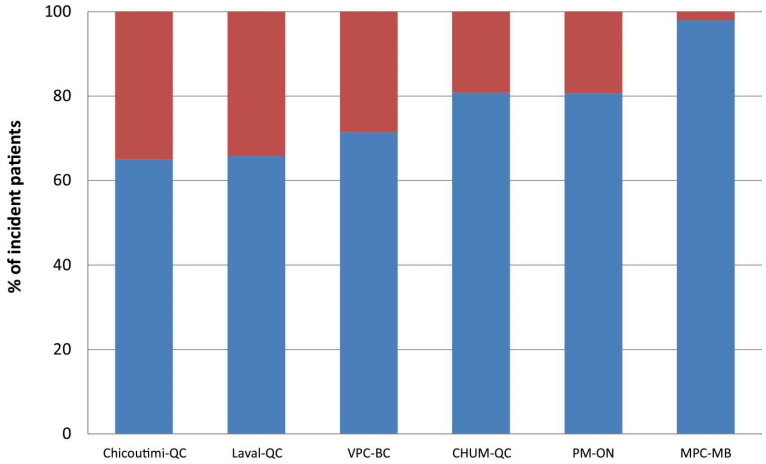
Proportion of men with low risk PCa receiving Active Surveillance

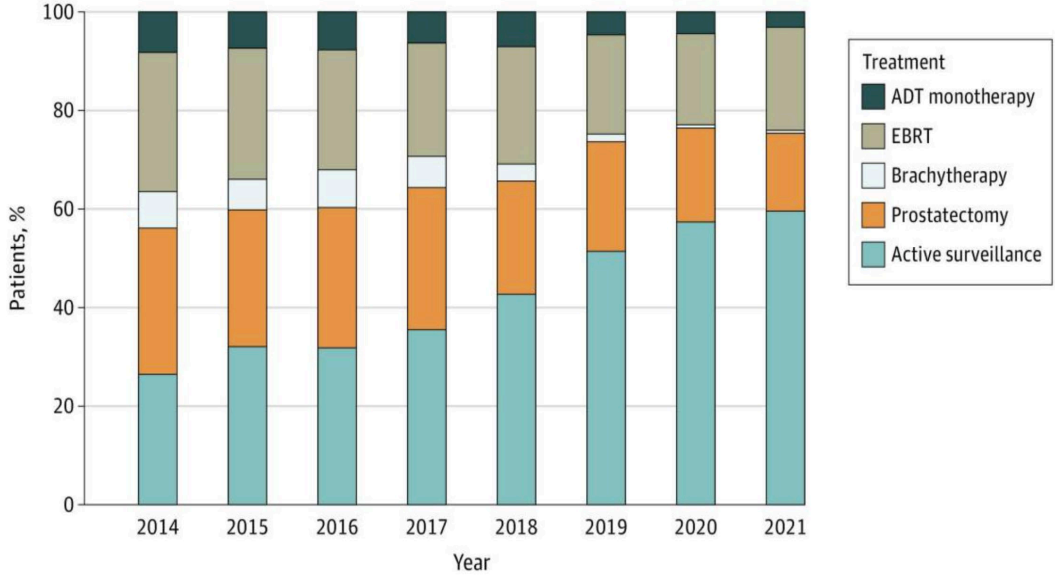
Canada - 2010



Upfront therapy, n (%)	21 (35)	32 (34)	37 (28)	60 (19)	26 (19)	1 (2)
Chose initial AS, n (%)	39 (65)	62 (66)	93 (72)	252 (81)	109 (81)	49 (98)

604 of 781 (77.3 %) of the low-risk patients received AS as initial management

Trends in U.S.



N Timilshina et al., World J Urol (2017) 35:595–603

Optimal Treatment Of Localized Prostate Cancer

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*Presence of LUTS/retention prioritizes RP
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Optimizing Outcomes in High Risk Localized PCa

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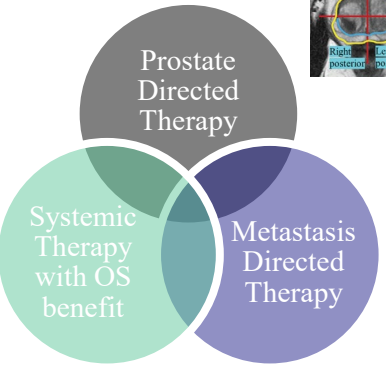
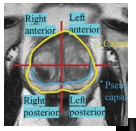
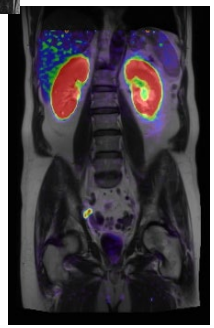
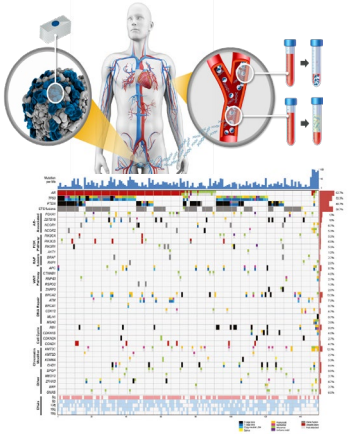
Convergent Advances

- **Early Detection – PSA + MRI**
- **Risk Stratification**
  - volume pattern 4,5; PSA; biomarkers; imaging
- **Technique**
  - Surgery, radiotherapy









- **Biomarkers –**
  - **Prognostic, predictive**

- **Multi-modal Therapy Integration:**
  - Post-op: PSA- and image-guided early salvage therapy
  - Metastasis-directed therapies
  - ARPI Neoadjuvant strategies

➢ **Improve outcomes**

Evolution of Therapies for Localized CaP

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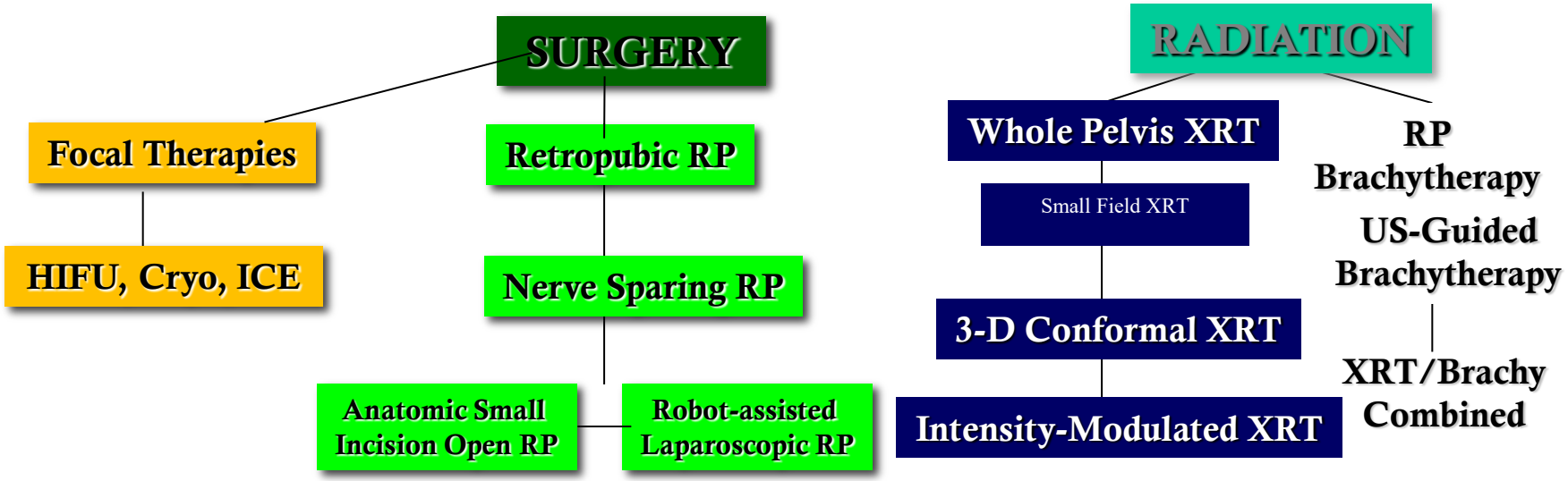

High cure rates in low-intermediate risk diseases

~ 50% impotence rates
5 - 10% stress incontinence

~ 50% impotence rates
10% urgency incontinence

Radical Prostatectomy (+ PLND)

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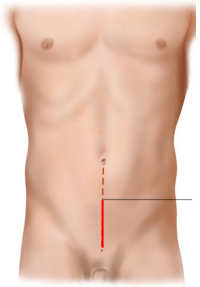
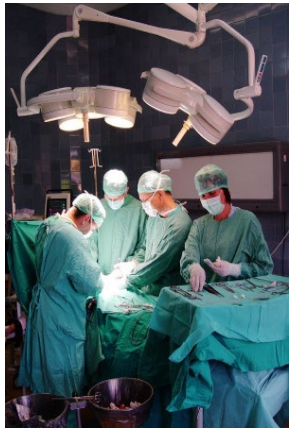
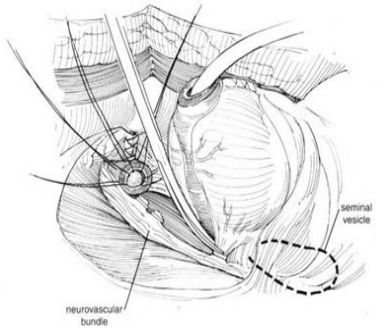
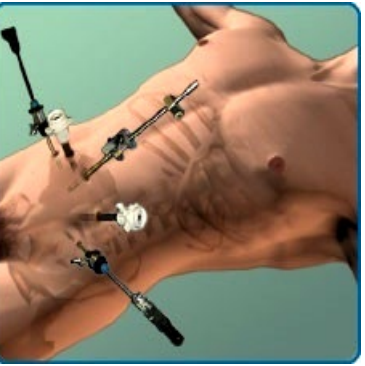
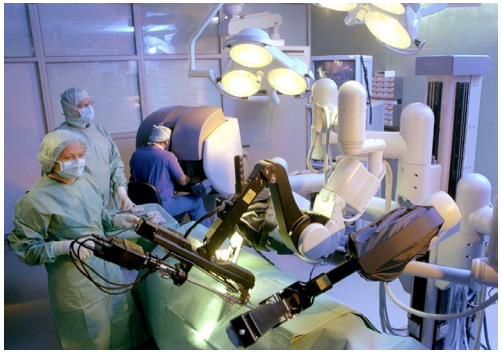


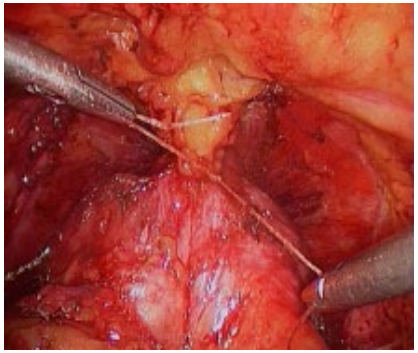




- 2-3 hour surgery
  - Small incision length, Local anesthesia
  - Watertight anastomosis, No drain,
  - Transfusion 1%
- Postoperative
  - Ketorolac infusion, no opiods,
  - Pathway for discharge postop day 1
  - Catheter out day 7, Full activity week 4







Open vs Robot-assisted Laparoscopic RP for Prostate Cancer

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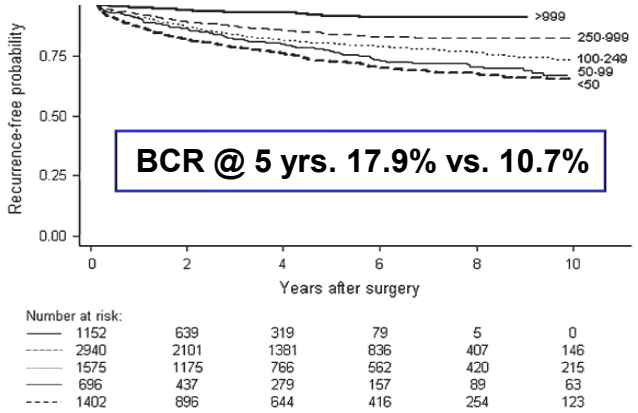
- **Overall and serious postoperative complication rates similar.**
  - ***90% overnight stay; < 1% transfusion rate***
- **Urinary and sexual quality of life similar**
  - 5-10% risk of SUI; ~50% potency with nerve-sparing
- **Postoperative pain similar**
  - Tylenol + advil for analgesia; No narcotics
- **Oncological outcomes similar**
  - Cost of procedure 2x with RALP
- **Outcomes most dependent on surgeon/hospital volume**
  - ~50% of RP in BC performed at VGH by 3 uro-oncologists

JNCI 2007

ARTICLE

The Surgical Learning Curve for Prostate Cancer Control After Radical Prostatectomy

Andrew J. Vickers, Fernando J. Bianco, Angel M. Serio, James A. Eastham, Deborah Schrag, Eric A. Klein, Alwyn M. Reuther, Michael W. Kattan, J. Edson Pontes, Peter T. Scardino



Laparoscopic and robot-assisted vs open radical prostatectomy for the treatment of localized prostate cancer: a Cochrane systematic review.
Ilic D et al. BJU Int. (2018)

Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study.
Yaxley JW et al. Lancet. (2016)

Gagnon et al Can J Urol 2014

Radical Prostatectomy Improves Survival

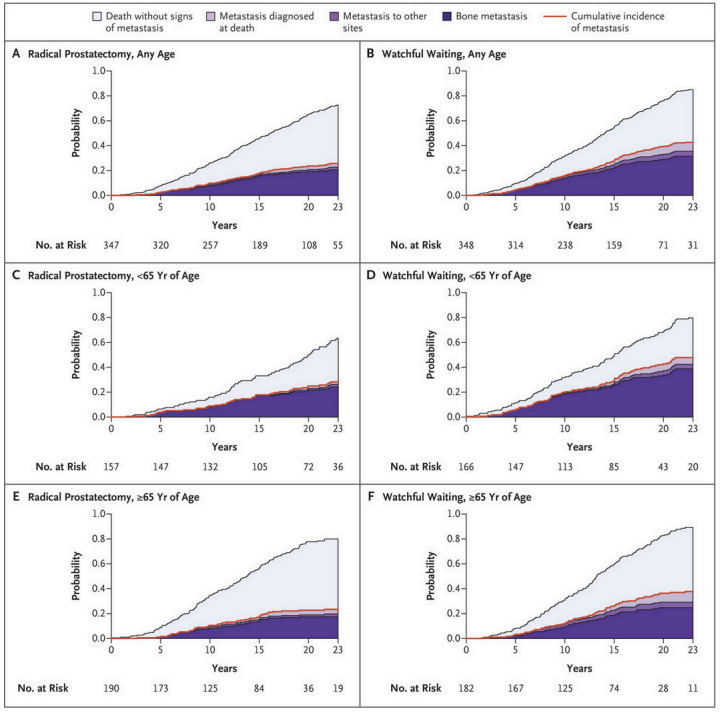
NEJM 379;24 2018

The NEW ENGLAND JOURNAL of MEDICINE

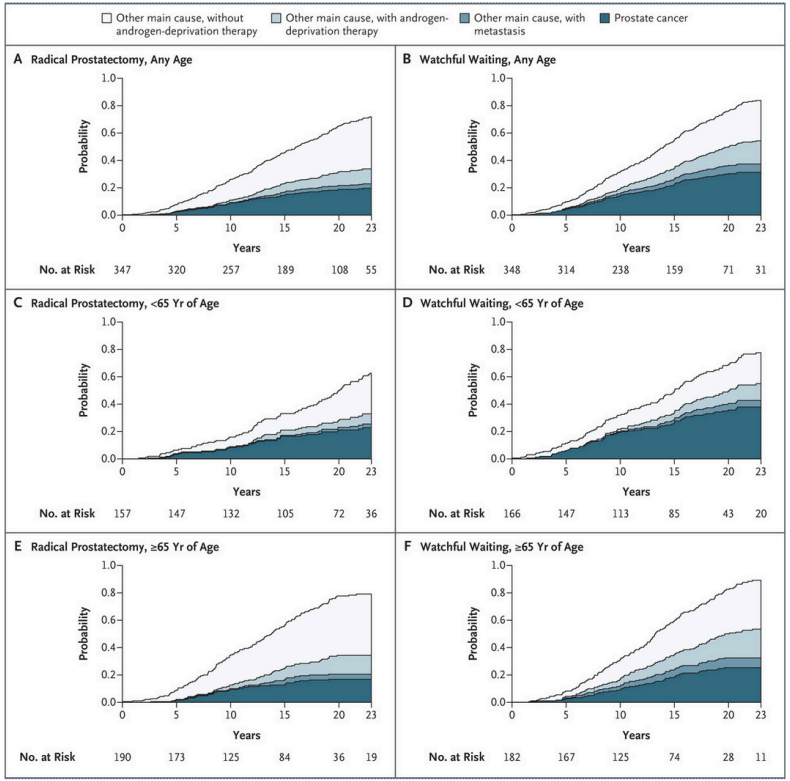
ORIGINAL ARTICLE

Radical Prostatectomy or Watchful Waiting in Prostate Cancer — 29-Year Follow-up

Anna Bill-Axelson, M.D., Ph.D., Lars Holmberg, M.D., Ph.D., Hans Garmo, Ph.D., Kimmo Taari, M.D., Ph.D., Christer Busch, M.D., Ph.D.,



- NNT to treat to avert one death from any cause was 8.4.
- At 23 years, mean of 2.9 years of life were gained with RP
  - Gain in life years much higher with Gleason >7 cancers



Radiation Therapy

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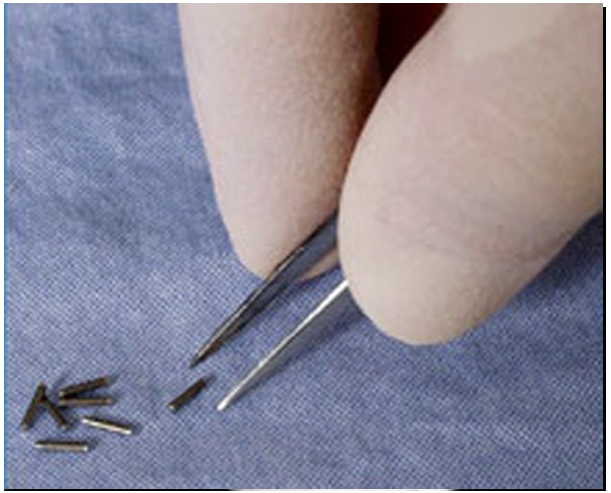
Conformal external beam

Brachytherapy



- **Option as monotherapy in intermediate risk PCA**
- **For high risk, IMRT combined with ADT, +/- brachy boost**

Role of Androgen Deprivation Therapy with Radiotherapy

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- **Randomized Phase III trials show benefit of combined RT + ADT vs either RT or ADT monotherapy in high risk localized PCA**

Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial

Lancet 2011; 378: 2104-11
Published Online November 3, 2011
DOI:10.1016/S0140-

Padraig Warde*, Malcolm Mason*, Keyue Ding, Peter Kirkbride, Michael Brundage, Richard Cowan, Mary Gospodarowicz, Karen Sanders, Edmund Kostashuk, Greg Swanson, Jim Barber, Andrea Hiltz, Mahesh K B Parmar, Jinka Sathya, John Anderson, Charles Hayter, John Hetherington, Matthew R Sydes†, Wendy Parulekar†, for the NCIC CTG PR.3/MRC UK PR07 investigators

- **Duration of combined ADT + RT dependent on cancer risk:**
  - **-Low Tier High risk: IMRT with 6 months ADT**
  - **-High Risk: IMRT plus 18 months of ADT**

- **Intermediate risk: IMRT/brachy monotherapy**

Patient-reported Quality of Life: Prostatectomy vs Radiotherapy

Prevalence of Patient-Reported Bother

One Year after Treatment, by HRQOL Domain

Percent of patients reporting "moderate" or "big" problem

HRQOL Domain	Prostatectomy (n=602)	Brachy (n=311)	External RT (n=292)
Sexual	49%	30%	31%
Urinary	7%	21%	9%
Bowel/Rectal	2%	11%	11%
Vitality/Hormonal	11%	13%	19%

Accrual: 1206 pts, 614 spouses (2003-2006)

Sanda et al, NEJM 358:1250, 2008

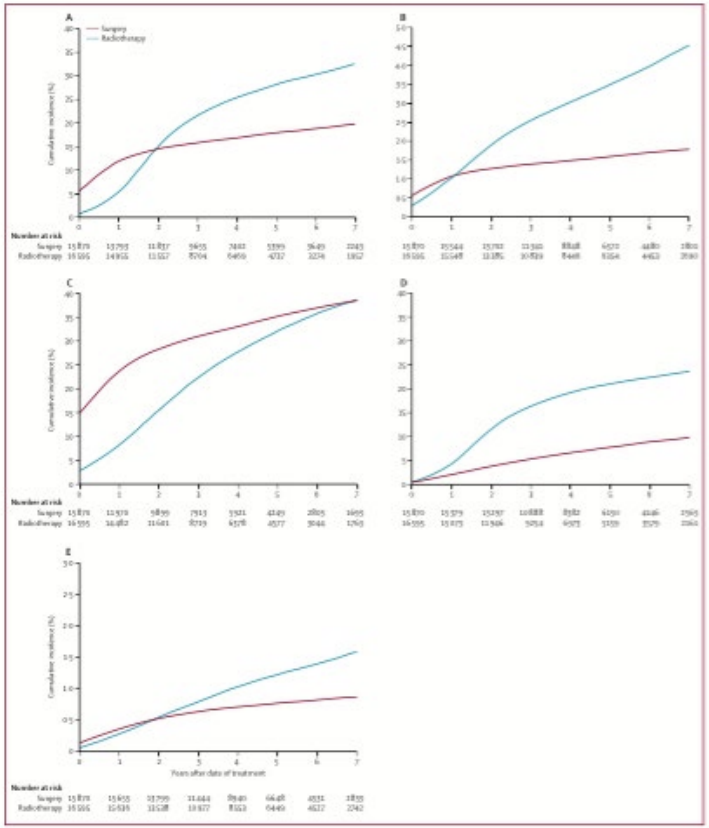
Incidence of complications other than urinary incontinence or erectile dysfunction after RP or XRT: a population-based cohort study.

Nam R et al, Lancet Oncol. 2014 Feb;15(2):223-31

All hospital admissions

Minor GU procedures

Open surgical procedures



Hospitalization LOS > 1 day

Rectal procedures

Complications after prostatectomy or radiotherapy for prostate cancer: results of a population-based, propensity score-matched analysis. Urology. 2015 Mar;85(3):621-7

Optimal Treatment of Localized Prostate Cancer

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- Prostatectomy and radiotherapy both curative options
  - No randomized trials successfully accrued
- 13/14 studies using propensity adjustment, 6 with > 10,000 pts favor RP over radiation
  - Systematic bias/imbalance in unmeasured confounding variables
  - Prostate cancer mortality difference?
    - More and longer use of ADT with RT (CV AE's)?
    - Second malignancies with RT ?

1. Tewari A J Urol 2007 Mar;177(3):911-5.
2. Albertsen PC et al, J Urol. 2007 Mar;177(3):932-6
3. Merglen A Arch Intern Med. 2007 Oct 8;167(18):1944-50.
4. Zelefsky MJ, JCO 2010 Mar 20;28(9):1508-13.
5. Cooperberg M, Cancer 2010 116(22):5226-34
6. Kibel A, J Urol. 2012 Apr;187(4):1259-65.
7. Abdollah F, Int J Urol. 2012 Sep;19(9):836-44;
8. Nepple K, Eur Urol. 2013 Sep;64(3):372-8.
9. Hoffman R, JNCI 2013;105:711-718
10. Shao Y, Lu-Yao G. Eur Urol. 2014 Apr;65(4):693-700.
11. Lee JY, Ann Surg Oncol. 2014 May 20
12. Sooriakumaran P BMJ. 2014 Feb 26;348
13. Dorr M EAU 2014
14. Sun M, Karakiewicz PI BJU Int 2014 113(2):200-8.

Incidence of 2nd Malignancies in PCa After Brachytherapy or Prostatectomy at Extended Follow-up: BC Data

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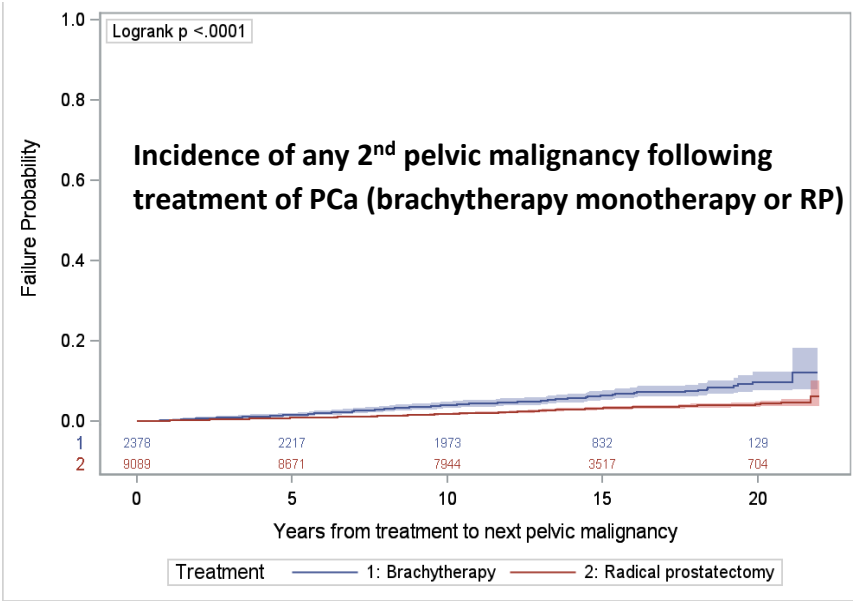

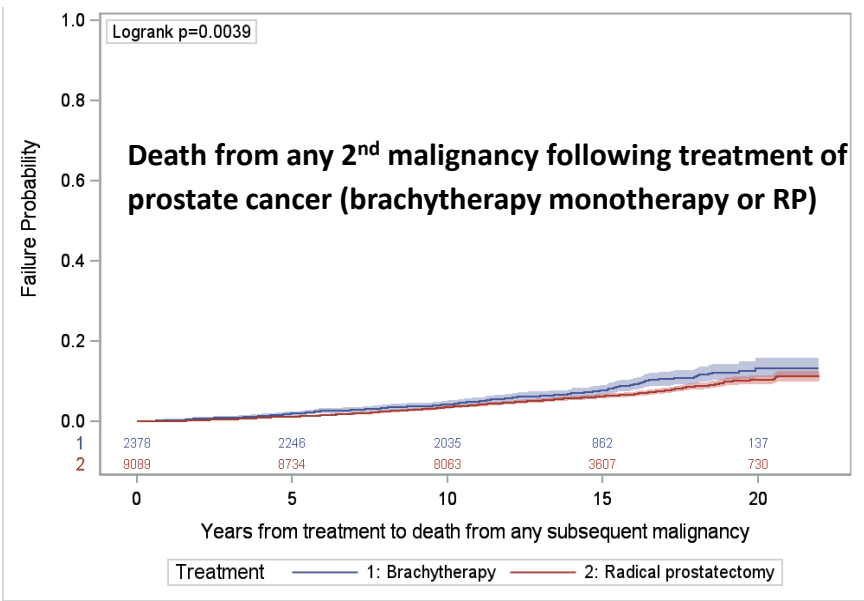

- **2378 brachy and 9089 RP pts median follow-up 14years**
- **absolute risk of pelvic SMN at 15 and 20 years was 6.4% and 9.8 % after BT, and 3.2% and 4.2% after RP**

St-Laurent MP et al, J Urol 2024

Propensity adjusted studies - is surgery better?

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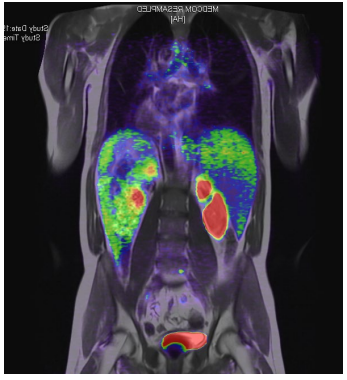
- 13/14 studies using propensity adjustment favor RP over radiation
- Likely some systematic bias/imbalance in unmeasured confounding variables
- Prostate cancer mortality difference?
  - More and longer use of ADT with RT (CV AE's)
  - Second malignancies with RT

➢ RP + PLND defines extent of disease, allows detection & options for salvage Rx

- Earlier and more frequent salvage therapy for BCR
  - Phoenix criteria BCR post RT – rising above 2
  - Post RP – rising > 0.2
    - » Increasingly PSMA PET directed
    - » enables access to 2 or more curative therapies



Prostate Cancer Disease States

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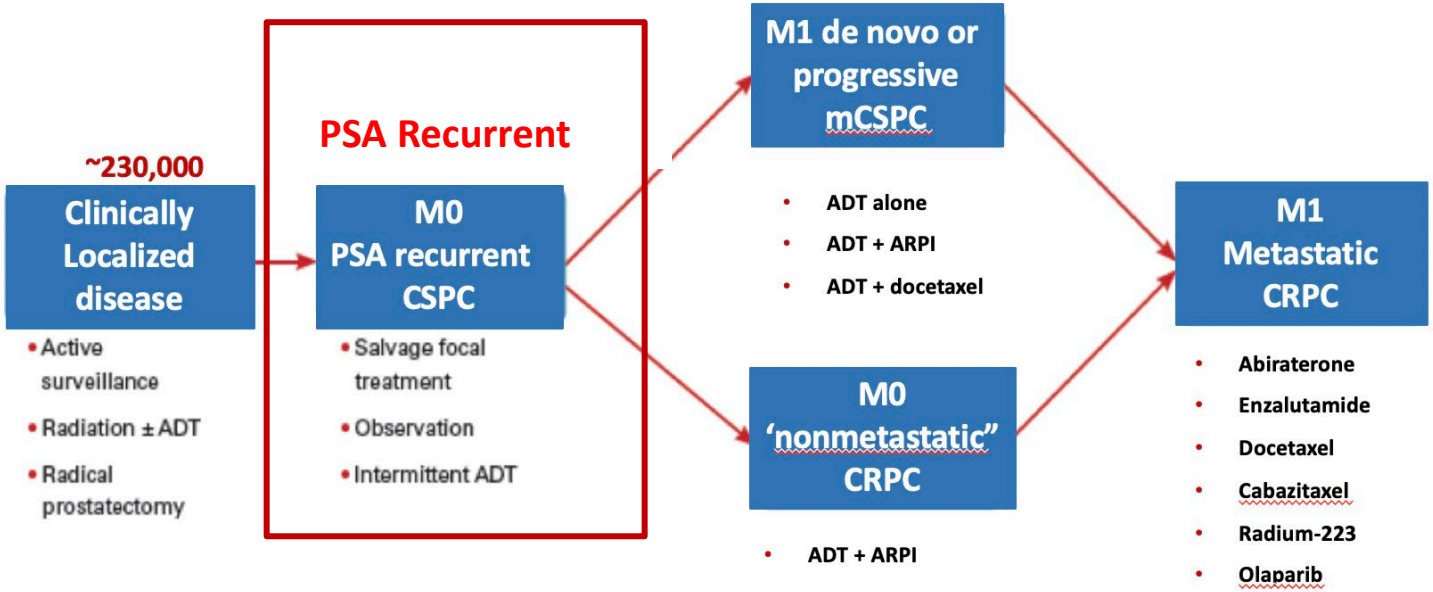

Figure 1. Clinical Disease States of Prostate Cancer

ADT = androgen deprivation therapy; CRPC = castration-resistant prostate cancer; HSPC = hormone-sensitive prostate cancer.

Data from: Chen et al. J Clin Oncol. 2016.[2]

PSA and Biochemical Relapse after Local Therapy

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1. Impact of BCR on oncological outcomes

- low and high risk BCR gps
- pathologic risk factors, timing, PSAdt

Guidelines – Prostate Cancer

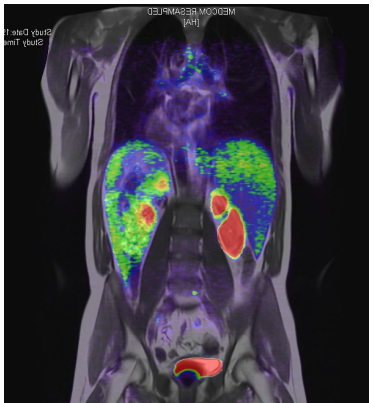
Biochemical Recurrence in Prostate Cancer: The European Association of Urology Prostate Cancer Guidelines Panel Recommendations

Thomas Van den Broeck[a,], Roderick C.N. van den Bergh[b], Erik Briers[c], Philip Cornford[d], Marcus Cumberbatch[e], Derya Tilki[f,g], Maria De Santis[h,i], Stefano Fanti[j], Nicola Fossati[k,l], Silke Gillessen[m,n,o], Jeremy P. Grummet[p], Ann M. Henry[q], Michael Lardas[r], Matthew Liew[s], Malcolm Mason[t], Lisa Moris[a,u], Ivo G. Schoots[v], Theodorus van der Kwast[w], Henk van der Poel[x], Thomas Wiegel[y], Peter-Paul M. Willemse[z], Olivier Rouvière[A], Thomas B. Lam[B,C], Nicolas Mottet[D]*

Eur Urol, 2019

2. PSMA PET imaging to guide salvage RT or lymph node dissection

- Image-guided salvage (vs adjuvant) radiotherapy (+ ADT) or LND in patients post RP
- threshold sensitivity post-RP 0.4 ng/ml



3. Systemic Rx - ADT

- **Timing (earlier better in high risk BCR)**
- **Intermittent (preferable, as in PR-7)**
- **Intensification - ARPI doublets (EMBARK)**

Multi-modal Therapy in Biochemical Recurrent PCa

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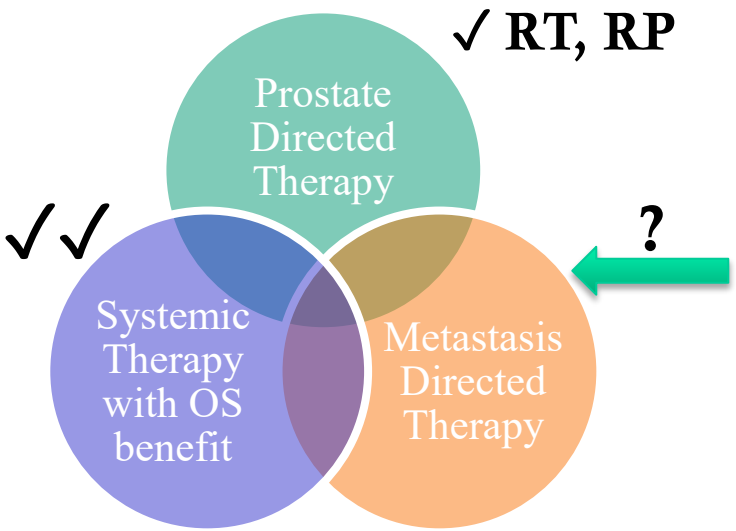
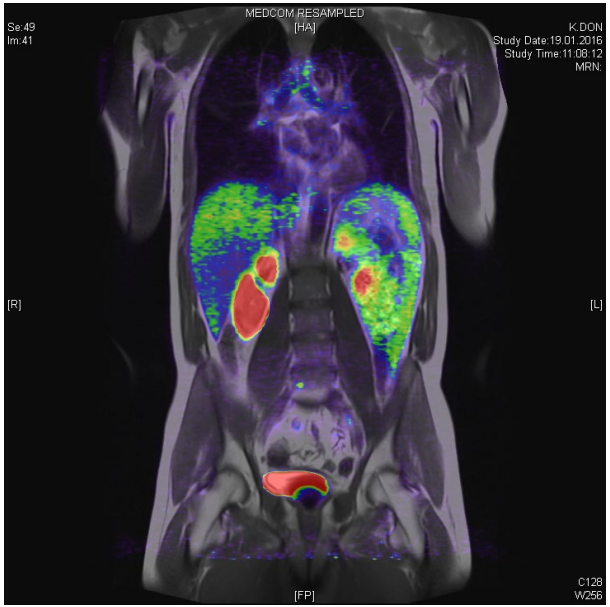




50-year-old

RP 2012 for Gleason 4+5=9, pT2, margin negative, N1 Pca

PSA increased to 1.7
- ADT + salvage RT

Second PSA relapse
Referred for PSMA PET

SBRT on COMET 2016

Convergent advances –
surgery, RT, drug combinations
imaging and biomarkers

Prognostic, predictive
Improve outcomes

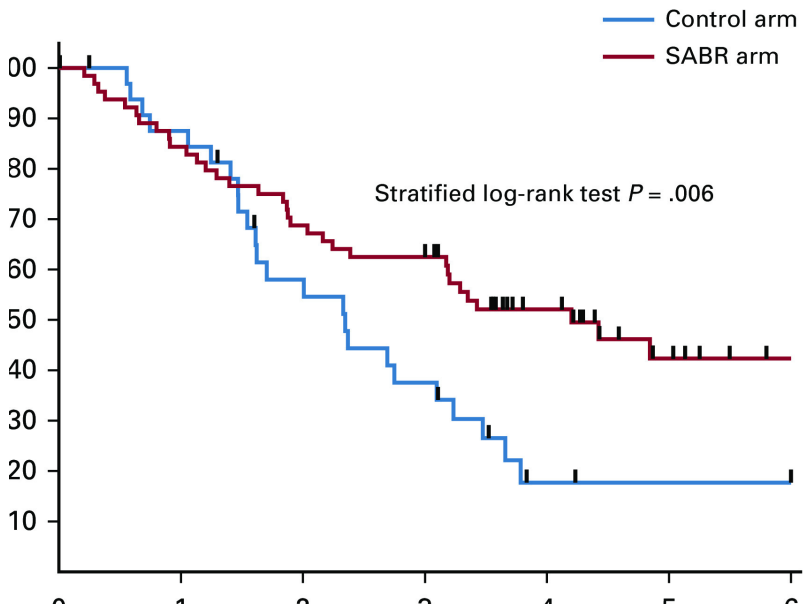
- PSA 2025 <0.01 on ADT

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

J Clin Oncol. 2020 Sep 1; 38(25): 2830–2838.
Published online 2020 Jun 2. doi: 10.1200/JCO.20.00818

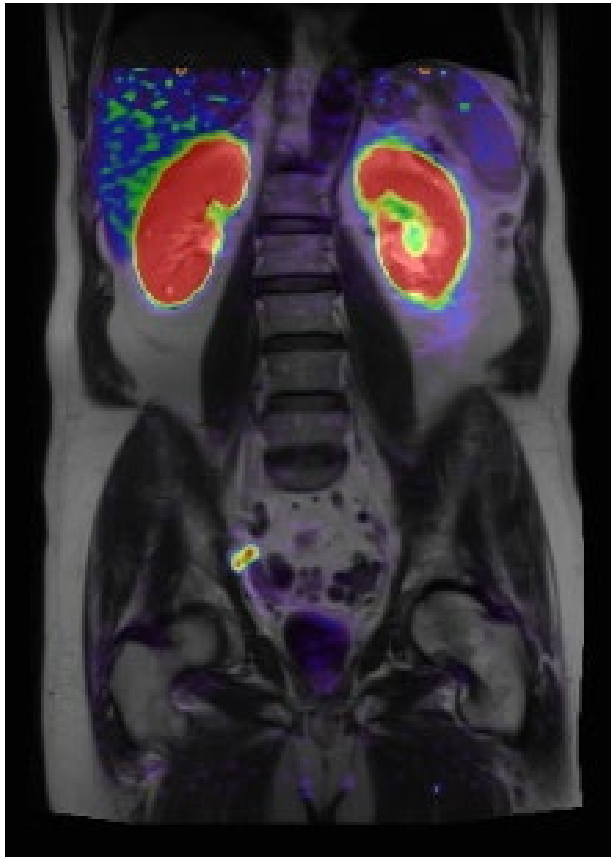
PMCID: PMC7460150
PMID: 32484754

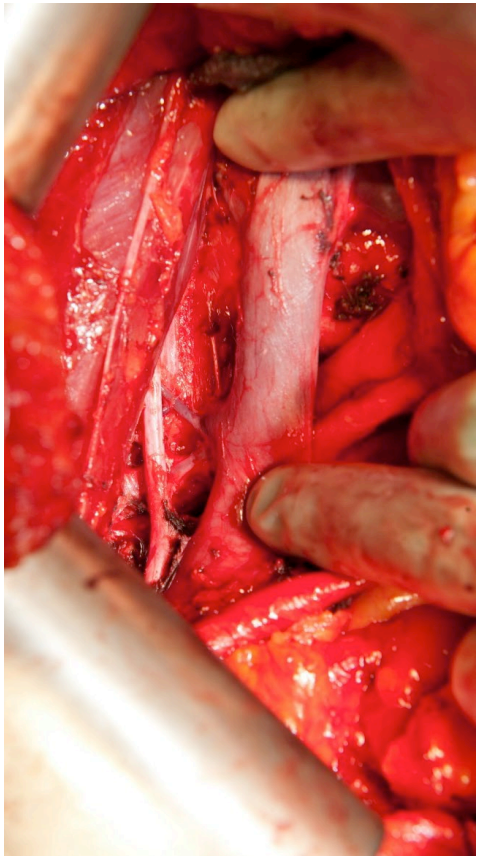
Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial



- **99 pts with 1–5 metastatic lesions and a controlled primary tumor randomized to receive SoC +/- SBRT to all oligometastatic sites**
- **5 yr OS for all cancers 17.7% vs 42.3%**
- **16 patients with PCa**
- **~ 60% in both arms received systemic therapy after MDT.**
- **MDT improved median PFS (5.4 to 11.6 months, *P* = 0.001) and OS (28 to 50 months, *P* = 0.006); no significant change in QOL**

Image-guided Salvage-Lymphadenectomy





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Eur Urol, 2019

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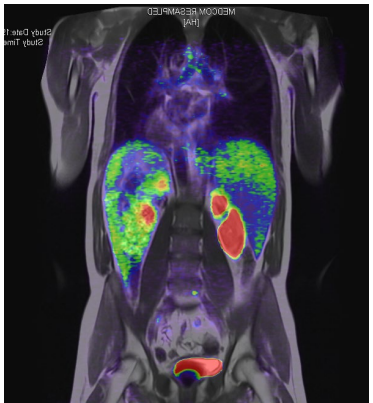
- Image-guided salvage lymph node dissection



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- **Timing (earlier better in high risk BCR)**
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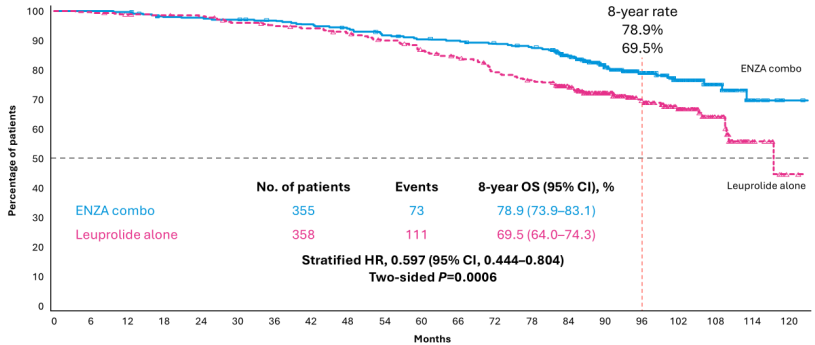
- **Intensification - ARPI doublets (EMBARK)**

EMBARK: A Phase 3 RCT of ENZA or Placebo Plus Leuprolide and ENZA Monotherapy in High-Risk BCR Prostate Cancer (NEJM 2025)

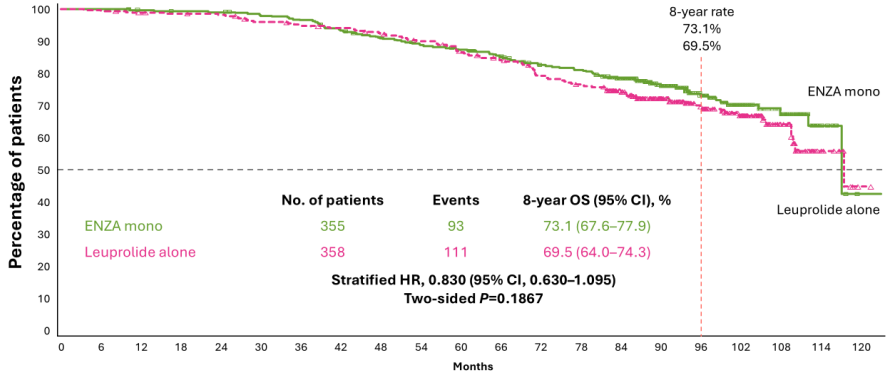
- Neal D. Shore,[1] Murilo de Almeida Luz,[2] Ugo De Giorgi,[3] Martin Gleave,[4] Geoffrey T. Gotto,[5] Gabriel P. Haas,[6] Miguel Ramirez-Backhaus,[7] Antti Rannikko,[8] Jamal Tarazi,[9] Swetha Sridharan,[10] Jennifer Sugg,[6] Yiyun Tang,[11] Ronald F. Tutrone, Jr.,[12] Balaji Venugopal,[13] Arnauld Villers,[14] Henry H. Woo,[15] Fabian Zohren,[16] Stephen J. Freedland[17]

Risk of death 40.3% lower for ENZA combo compared with leuprolide alone



The 8-year OS rate was 78.9% (95% CI, 78.9–83.1) in the ENZA combination group and 69.5% (95% CI, 64.0–74.3) in the leuprolide alone group.

Risk of death 17.0% lower for ENZA mono vs leuprolide alone did not reach statistical significance



The 8-year OS rate was 73.1% (95% CI, 67.6–77.9) in the ENZA monotherapy group and 69.5% (95% CI, 64.0–74.3) in the leuprolide alone group.

Prostate Cancer Disease States

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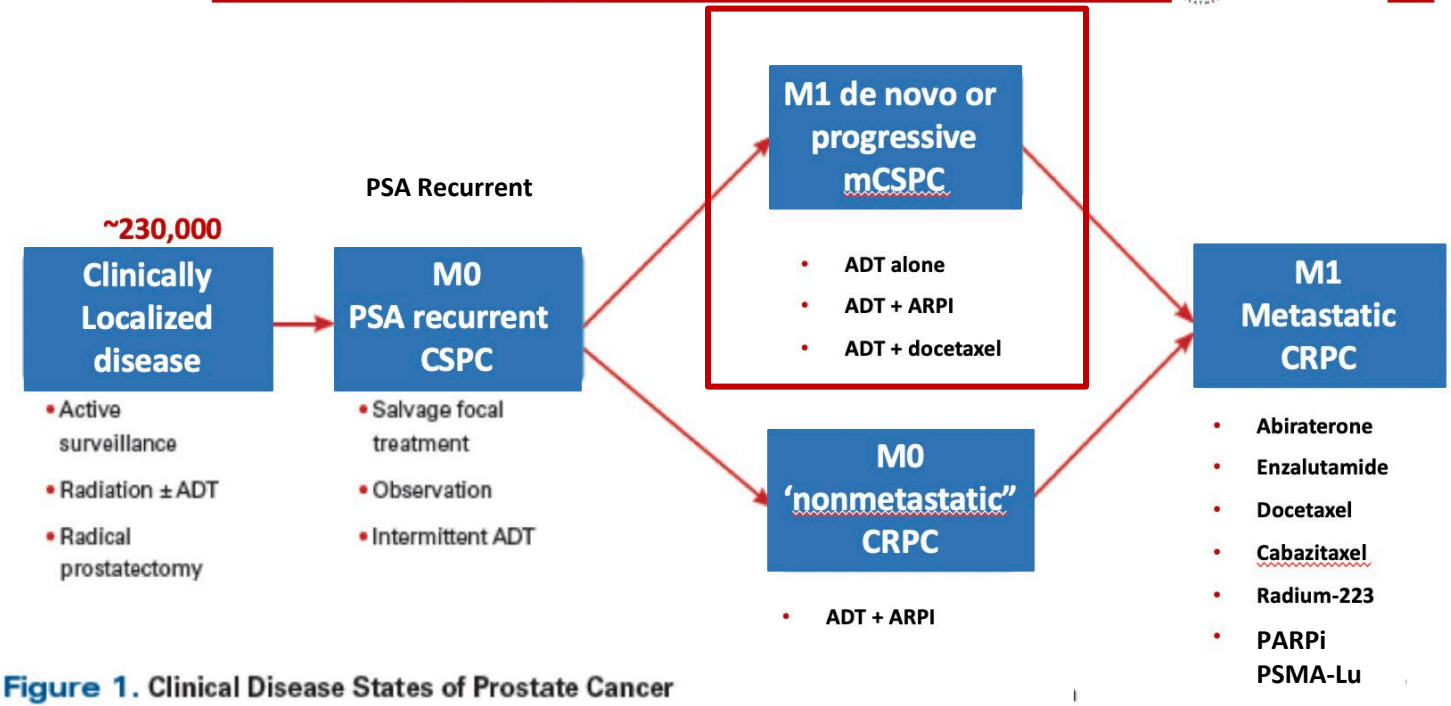

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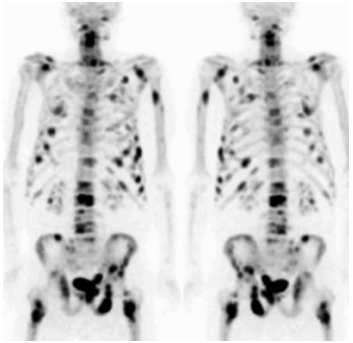

Metastatic Castrate Sensitive Prostate Cancer

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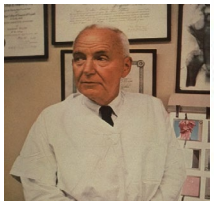
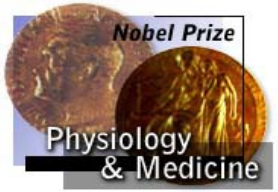
- **PCA metastasis are bone predominant, also lymph nodes**
- **Androgens/AR is main driver pathway in PCA**





Charles Huggins, Nobel Laureate, 1966

-Canadian born Urologist at U of Chicago

- **ADT is the cornerstone of treatment for mCSPC**
  - **Orchiectomy or LHRHa (eg. Zoladex, luprolide)**
- **For unfit patients - ADT alone**
- **For fit patients with high volume metastatic disease:**
  - Add docetaxel or abiraterone, enzalutamide or apalutamide
- **For low volume metastatic disease:**
  - Add AR pathway inhibitor (abiraterone, enzalutamide, apalutamide)
  - Consider treating primary tumor (eg. RT) with ADT + ARPI
  - Consider focal targeting of oligo-mets in selected pts

James N, Lancet, Dec 2015
Fizazi K, N Engl J Med. 2017;377(4):352-360
James ND, N Engl J Med. 2017;377(4):338-351.

Chi K, NEJM July 2019
Davis I, NEJM Aug 2019

The Androgen Receptor (AR) is the Driver of Progression Castrate Sensitive and Resistant Prostate Cancer

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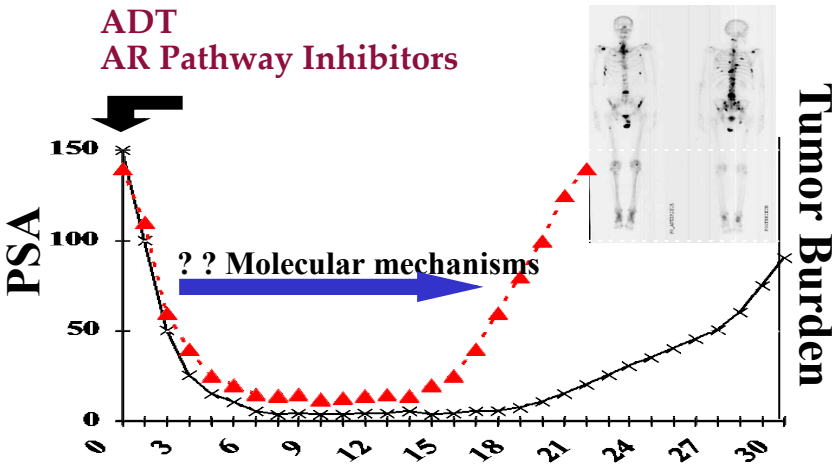
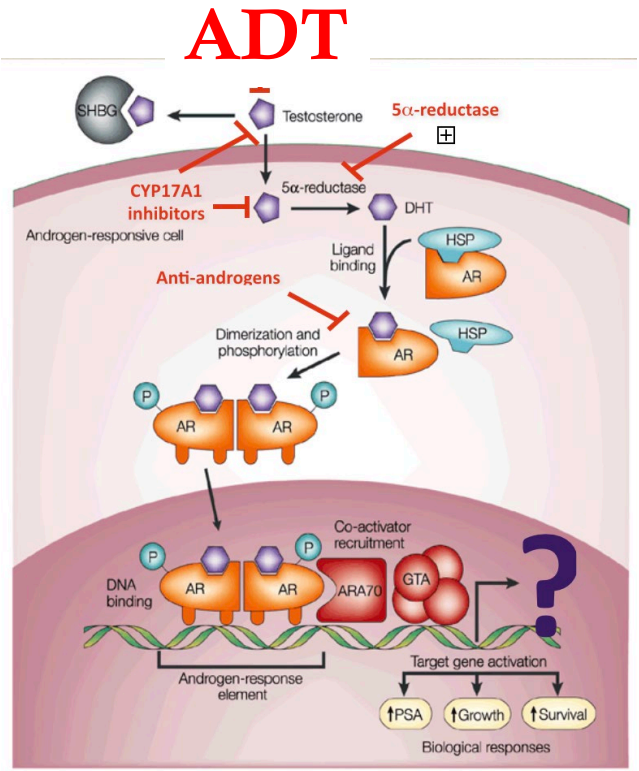
The Problem:
Acquired Treatment Resistance (CRPC)

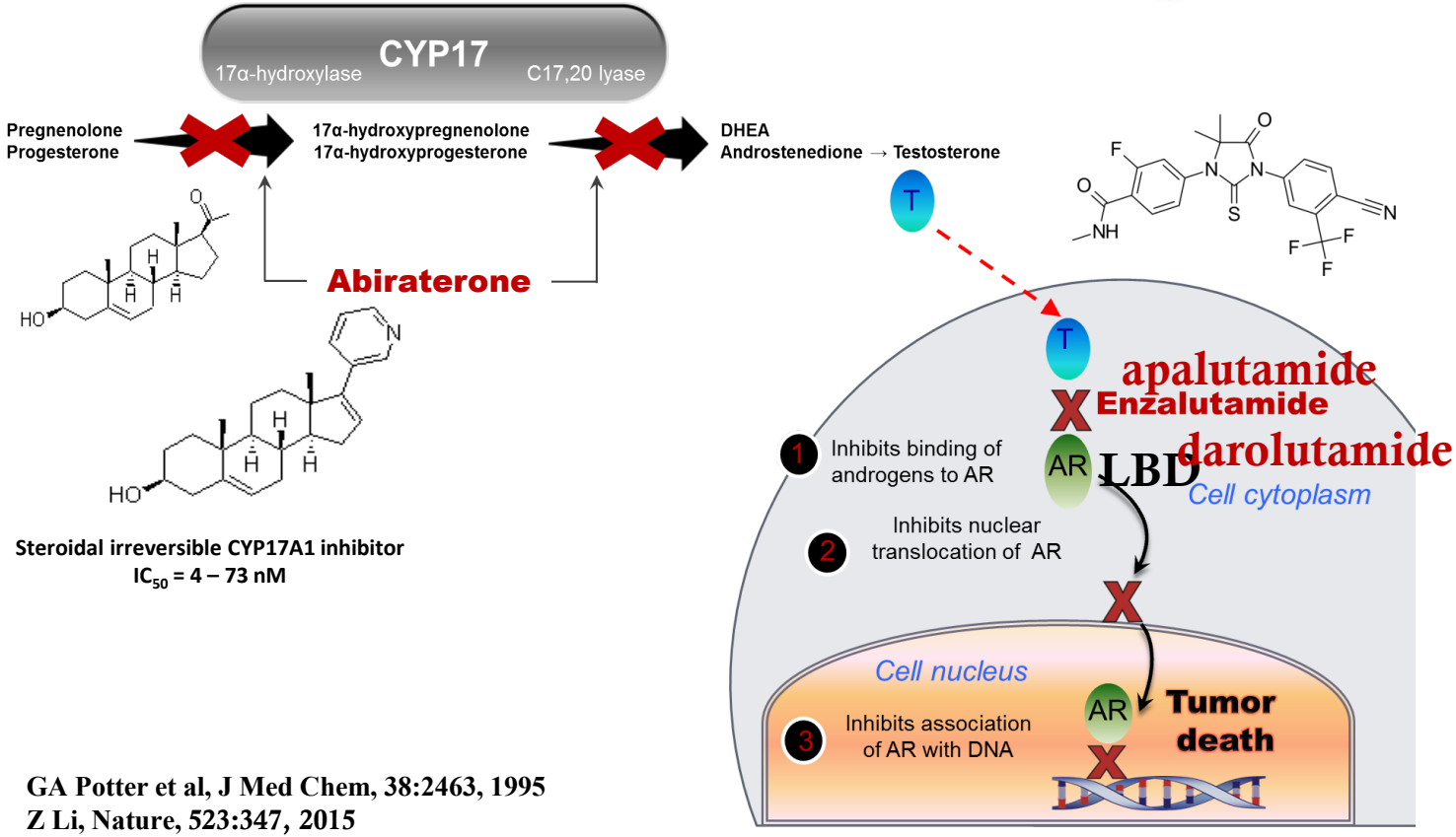




1. Montgomery RB, et al. Cancer Res. 2008;68:4447-4454;
2. Stanbrough M, et al. Cancer Res. 2006;66:2815-2825;
3. Locke JA, et al. Cancer Res. 2008;68:6407-6415.

Nature Reviews | Cancer

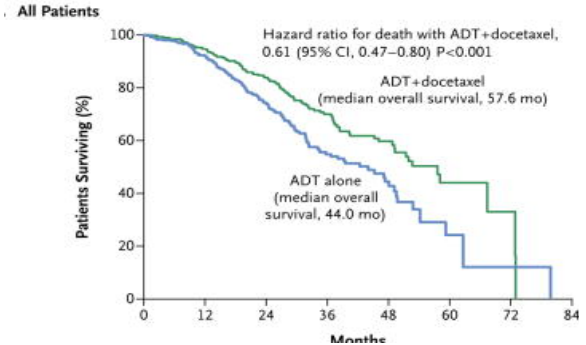
AR Pathway Inhibitors for Advanced PCa



GA Potter et al, J Med Chem, 38:2463, 1995
Z Li, Nature, 523:347, 2015
C Tran et al, Science 324:787, 2009

ARPI Doublets Prolong Overall Survival in mCSPC

Docetaxel

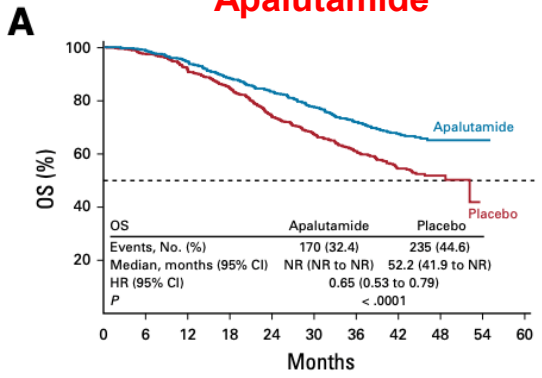


Sweeney et al. N Engl J Med. 2015 Aug 20;373(8):737-46

CHAARTED
HR: 0.62

f/u time
28.9 mo

Apalutamide

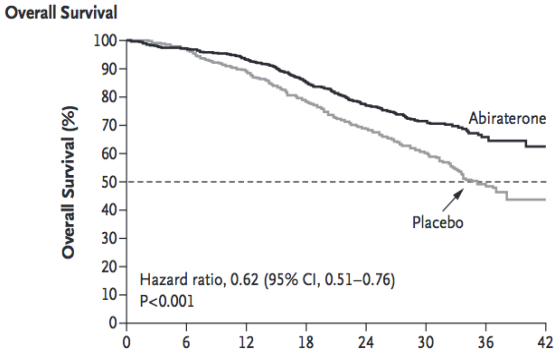


Chi KN, et al. *N Engl J Med* 2019;381:13;

TITAN
HR: 0.65

f/u time
22.7 mo

Abiraterone

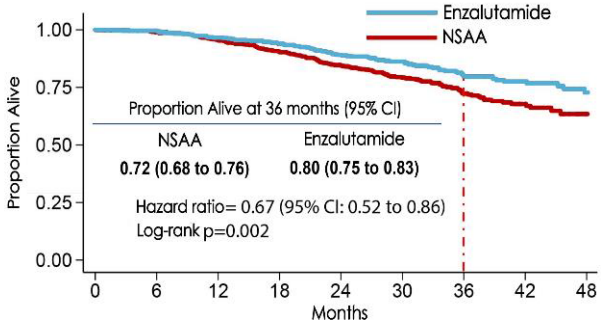


Fizazi K, et al. N Engl J Med 2017; 377:352-360;

LATITUDE
HR: 0.62

f/u time
30.4 mo

Enzalutamide

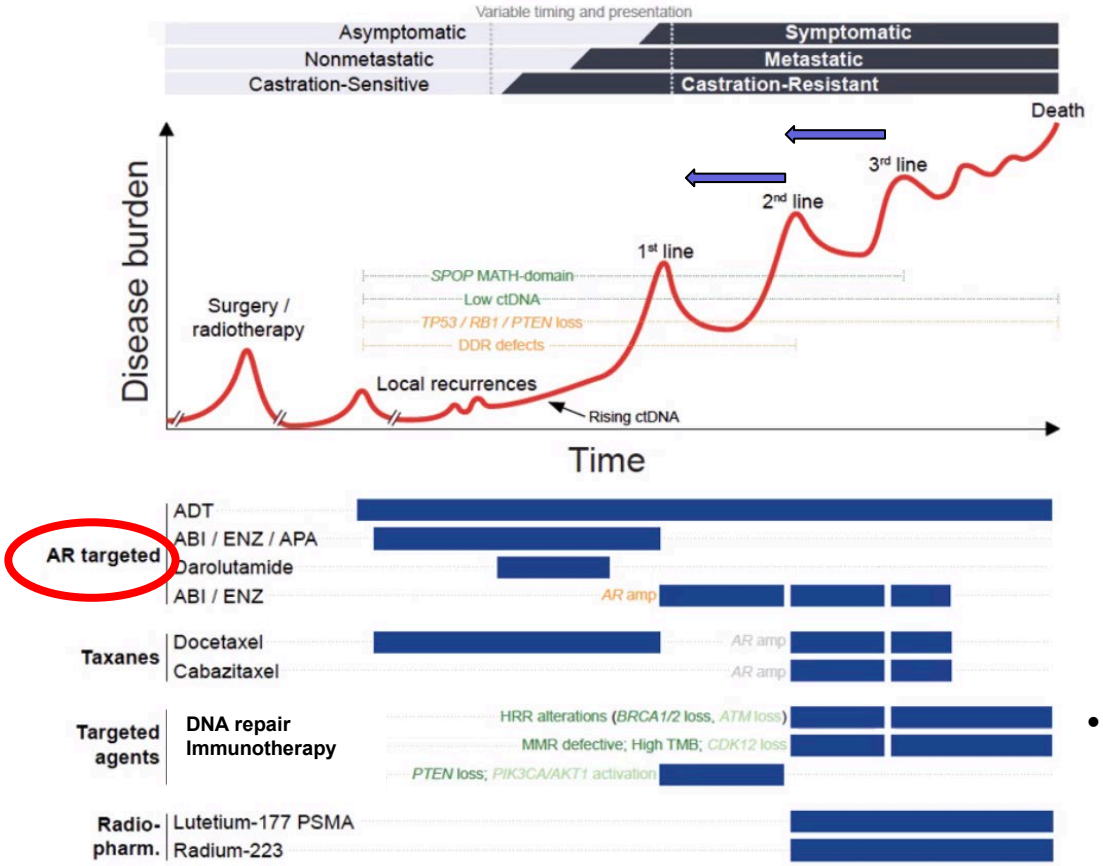


Davis ID, et al. *N Engl J Med* 2019;381:121

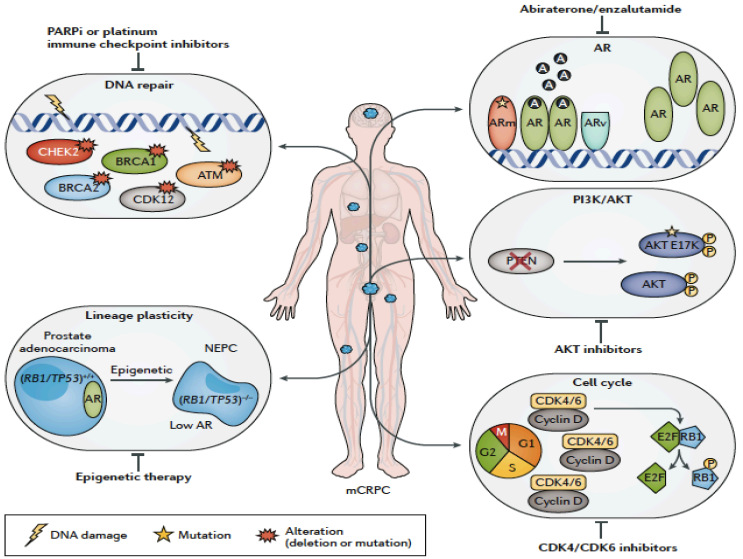
ENZAMET
HR: 0.67

f/u time
34 mo

Treatment Landscape in Advanced PCA: 2025



Genomic Hallmarks of mCRPC

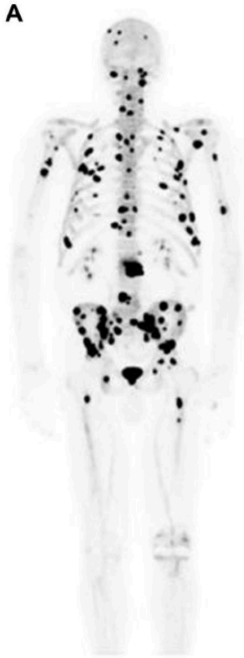


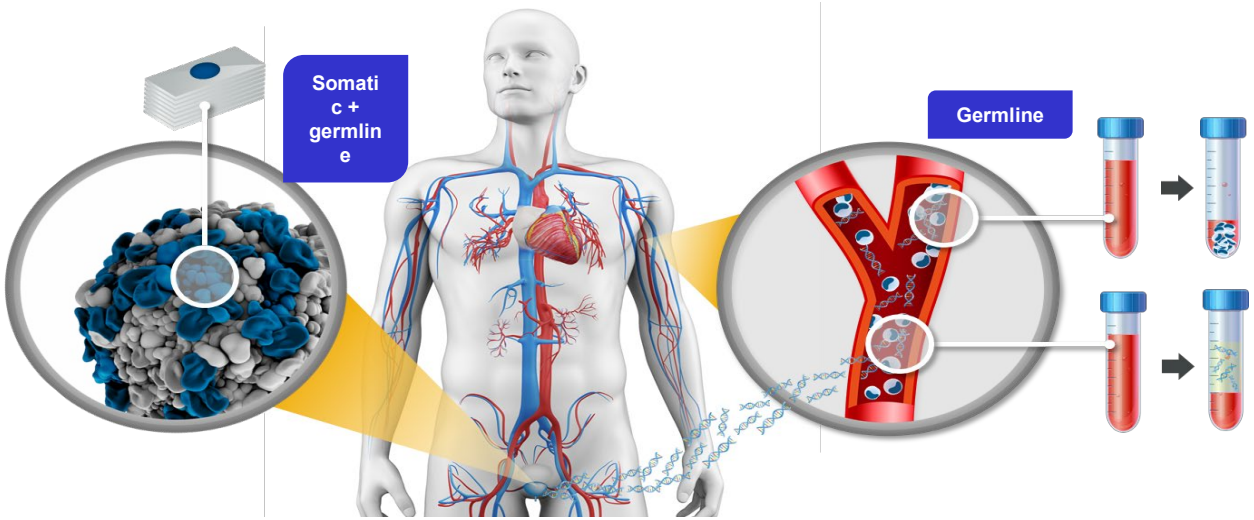
Ku et al ; Nature Reviews Urology, 2019 Quigley DA et al, Cell. 2018;174(3):758

Robinson D et al. *Cell.* 2015;161(5):1215-1228.

- **Biomarkers help guide:**
  - Optimal sequencing of ARPI vs docetaxel in met PCa
  - Selection for targeted or immuno- therapies
  - Defining/detecting treatment resistance

Detecting/Defining Resistance
Limitations of Metastatic Tissue Biopsy in mPCa -Tissue is an Issue





Sumiyoshi *et al.*, Prostate Cancer and Prostatic Diseases 2021

- **inter-patient heterogeneity underpins basis for precision oncology, BUT inter-tumor heterogeneity complicates profiling of single biopsies especially mCRPC bone mets**

Hence the need for "Liquid Biopsies":

- **Homogenizes heterogeneity, while still capturing inter-tumoral heterogeneity**

Plasma ctDNA tracks PCA genome in met PCa patients treated with AR inhibitors

Clin Cancer Res, 21:2315, 2015
Clinical Cancer Research
Personalized Medicine and Imaging

Androgen Receptor Gene Aberrations in Circulating Cell-Free DNA: Biomarkers of Therapeutic Resistance in Castration-Resistant Prostate Cancer

Arun A. Azad[1], Stanislav V. Volik[2], Alexander W. Wyatt[1], Anne Haegert[1], Stephane Le Bihan[1], Robert H. Bell[1], Shawn A. Anderson[1], Brian McConeghy[1], Robert Shukin[1], Jenny Bazov[1], Jack Youngren[1], Pamela Paris[2], George Thomas[2], Eric J. Small[3], Yuzhuo Wang[2,4], Martin E. Gleave[1,3], Colin C. Collins[1,2], and Kim N. Chi[1,3]

Original Investigation

Genomic Alterations in Cell-Free DNA and Enzalutamide Resistance in Castration-Resistant Prostate Cancer

Alexander W. Wyatt, DPhil; Arun A. Azad, MD; Stanislav V. Volik, PhD; Matti Annala, MSc; Kevin Beja, BSc; Brian McConeghy, BSc; Anne Haegert, BSc; Evan W. Warner; Fan Mo, PhD; Sonal Brahmbhatt, BSc; Robert Shukin, BSc; Stephane Le Bihan, PhD; Martin E. Gleave, MD; Matti Nykter, PhD; Colin C. Collins, PhD; Kim N. Chi, MD

JAMA Oncol, May 5, 2016

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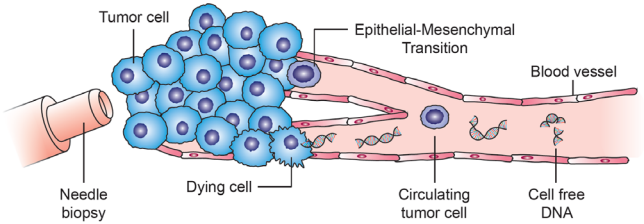
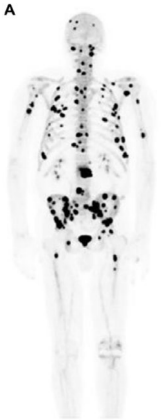
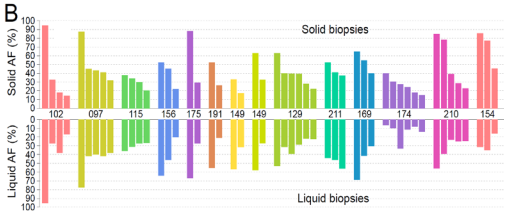
Alex Wyatt

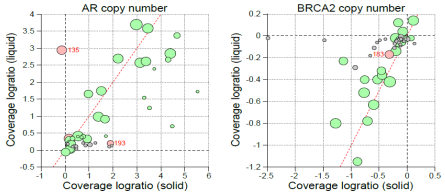


- First to use ctDNA to define prostate cancer genome from plasma
  - AR^{mut} and/or AR^{amp} detected in ~50%
  - Identified actionable alterations in DNA repair, PI3K, CTNNB1, MSI
- ctDNA highly concordant with metastatic mCRPC tissue biopsy
  - surveys intra-patient heterogeneity better than biopsy of a single metastatic site





Similar mutation profiles, ctDNA vs tissue



Similar Gene copy numbers

OXFORD
JNCI J Natl Cancer Inst (2017) 110(1): djx118
doi: 10.1093/jnci/djx118
First published online June 29, 2017
Article

ARTICLE

Concordance of Circulating Tumor DNA and Matched Metastatic Tissue Biopsy in Prostate Cancer

Alexander W. Wyatt*, Matti Annala*, Rahul Aggarwal, Kevin Beja, Felix Feng, Jack Youngren, Adam Foye, Paul Lloyd, Matti Nykter, Tomasz M. Beer, Joshi J. Alumkal, George V. Thomas, Robert E. Reiter, Matthew B. Rettig, Christopher P. Evans, Allen C. Gao, Kim N. Chi†, Eric J. Small†, Martin E. Gleave†

Towards evaluating precision oncology with liquid biopsies and Umbrella Trials in mCRPC

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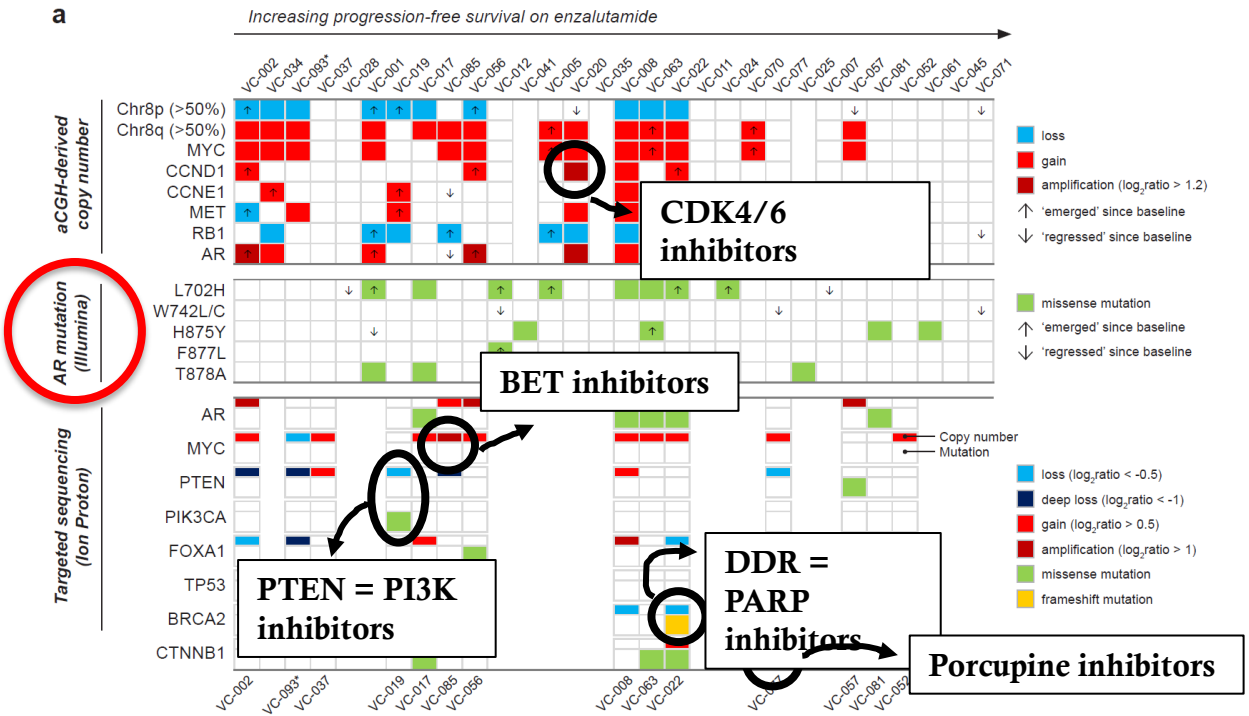
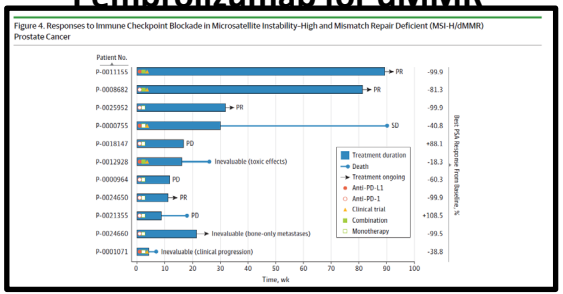


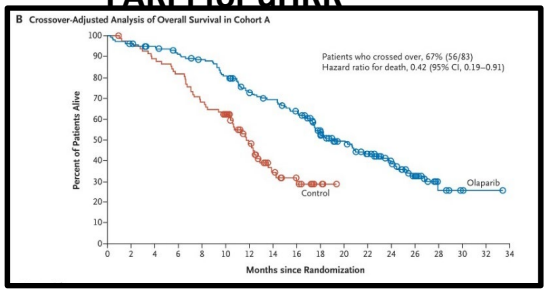
Wyatt et al; Cancer Discovery 2018
Herberts C, Annala M, et al Nature 2022

New Era of Precision Medicine in Prostate Cancer: Genomic and Imaging Biomarkers

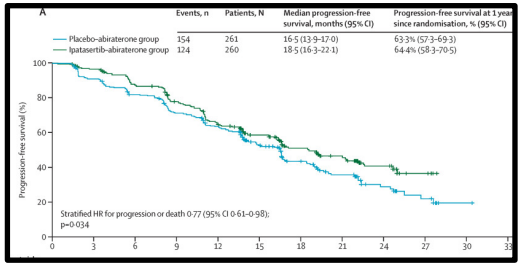
Pembrolizumab for dMMR



PARPi for dHRR

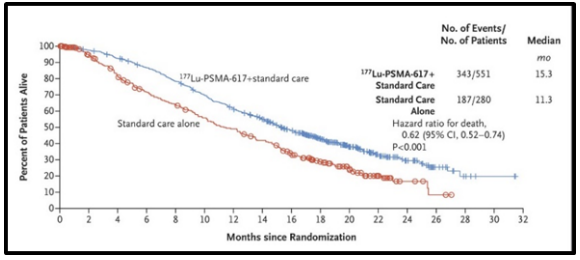


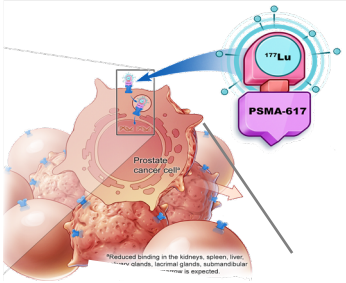
AKTi for PTEN^{def}

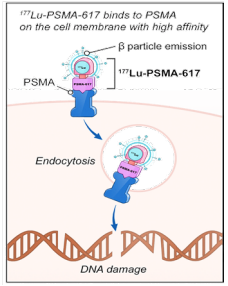


improved rPFS in PTEN-def mCSPC

Lu-PSMA-617 for PET-PSMA+







- **PARPi combinations moving upstream**
- **More ADC's and RL's under development**

W. Abida, et al. JAMA Oncol. 2019;5(4):471-478; M. Hussain, et al. N Engl J Med 2020; 383:2345-2357; O. Sartor, et al. N Engl J Med 2021; 385:1091-1103

DNA repair : Role of "PARP" inhibition and BRCA Alterations in Contextual Lethality

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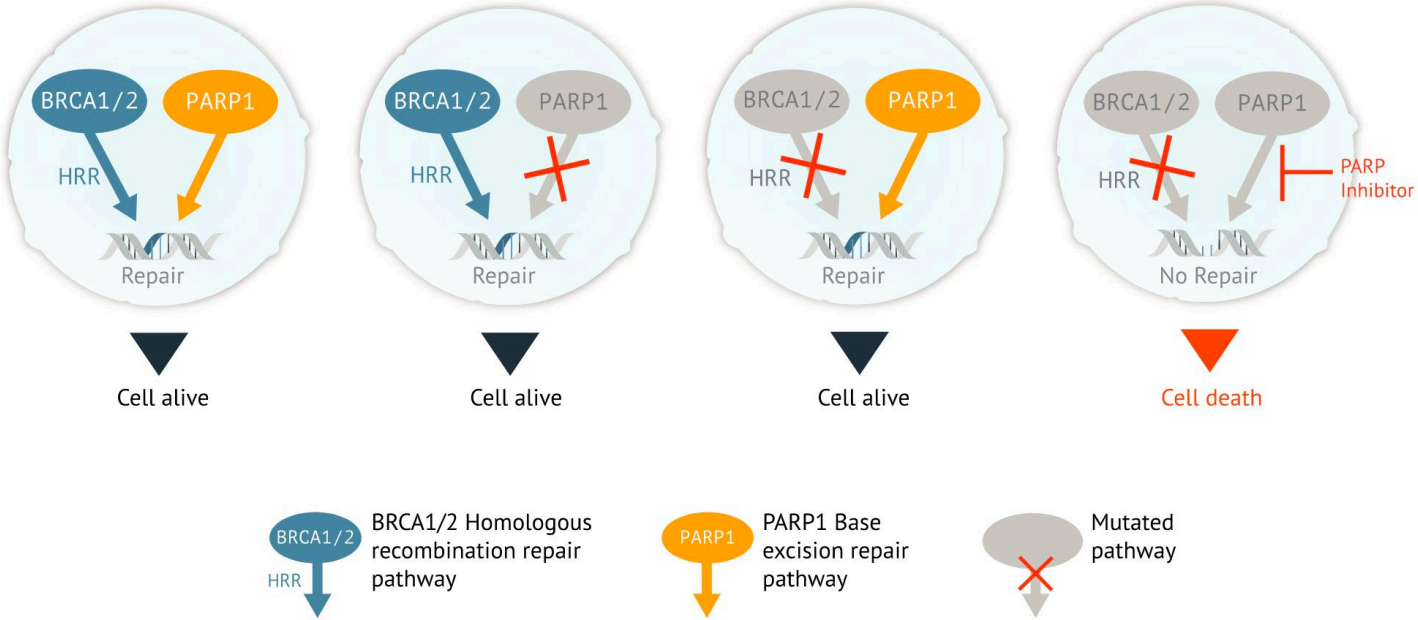
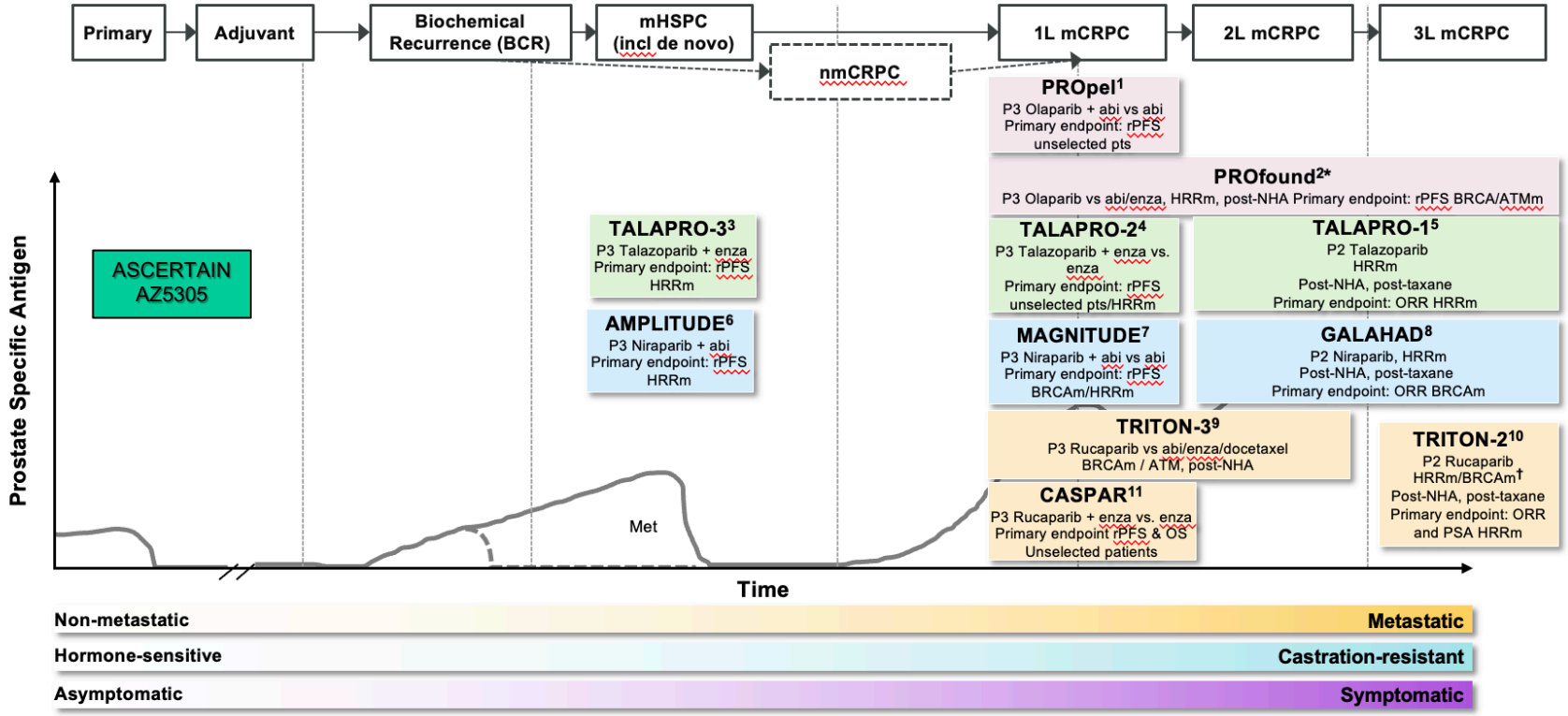


There are multiple trials investigating the use of PARP inhibitors in prostate cancer[1–11]



*As a result of the data from PROfound, olaparib monotherapy was approved for the treatment of adult patients with deleterious or suspected deleterious germline and/or somatic *BRCA* or *ATM* mutated metastatic castration-resistant Prostate Cancer (mCRPC) who have progressed following prior treatment with an NHA (Health Canada approval), or for HRRm mCPRC adult patients who have progressed following prior treatment with enzalutamide or abiraterone (FDA approval), or for mCRPC patients with mutations in only *BRCA1/2* after progression on an NHA (EMA approval)

†As a result of the data from TRITON2, rucaparib monotherapy was approved by the FDA only for the treatment of mCRPC in patients with a BRCA1/2m who have disease progression after treatment with prior AR-directed therapy and prior taxane

abi=abiraterone; enza=enzalutamide; P2=phase 2; P3=phase 3; BCR=biochemical recurrence; FDA=US Food and Drug Administration; HRRm=homologous recombination repair mutation; mCRPC=metastatic castration-resistant prostate cancer; met=metastasis; mHSPC=metastatic hormone-sensitive prostate cancer; NHA=new hormonal agent; nmCRPC=non-metastatic castration-resistant prostate cancer; rPFS=radiographic progression free survival; OS=overall survival; ORR=objective response rate; PSA=prostate-specific antigen

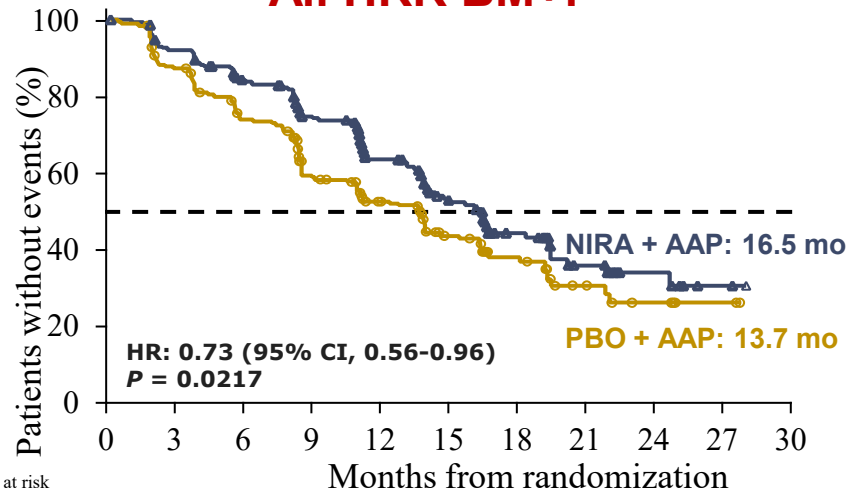
Please see slide notes for references.

MAGNITUDE: Double-Blind, Placebo-Controlled RCT in L1 mCRPC

Prospectively selected biomarker cohorts designed to test HRR BM+ and HRR BM–

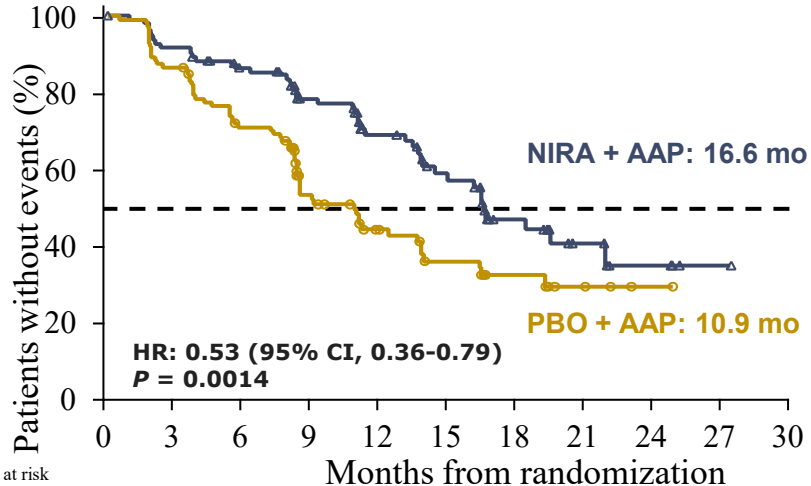
HRR BM+ – NIRA + AAP Significantly Reduced the Risk of Progression or Death

All HRR BM+:



No. at risk											
NIRA + AAP	212	192	167	129	96	64	45	21	10	2	0
PBO + AAP	211	182	149	102	78	53	35	15	9	2	0

BRCA1/2mut



No. at risk											
NIRA + AAP	113	103	90	65	45	31	18	9	4	1	0
PBO + AAP	112	97	77	43	28	20	11	5	2	0	0

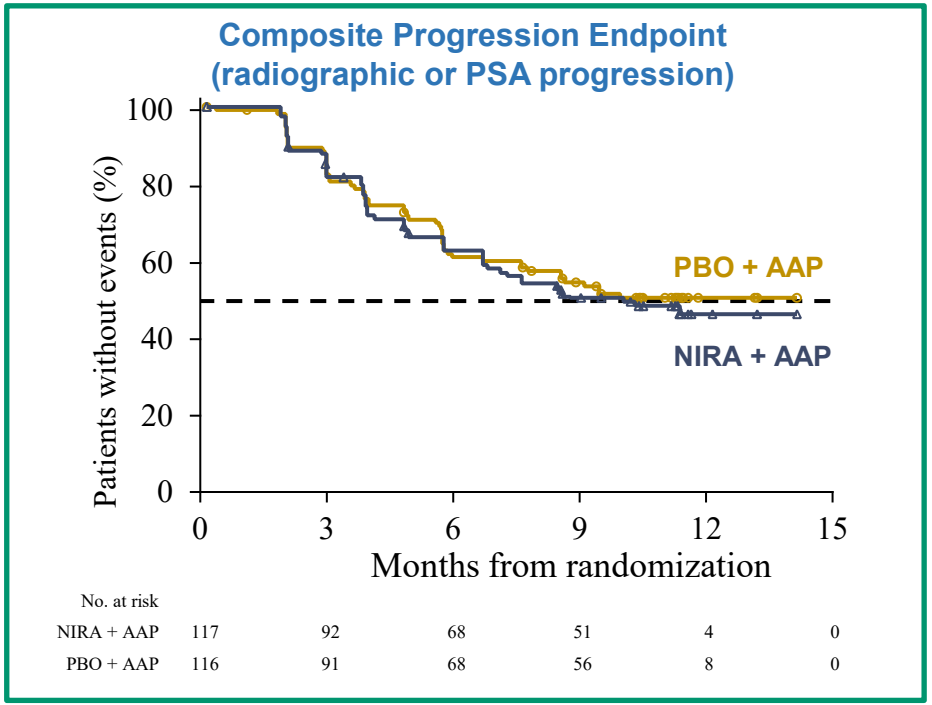
Median follow-up 18.6 months

Chi K et al. J Clin Oncol 2023 Mar 23;

MAGNITUDE: Double-Blind, Placebo-Controlled RCT in L1 mCRPC

Prospectively selected biomarker cohorts designed to test HRR BM+ and HRR BM⁻

HRR BM⁻: Prespecified Early Futility Analysis: No Benefit of NIRAPARIB + AAP in HRR BM⁻



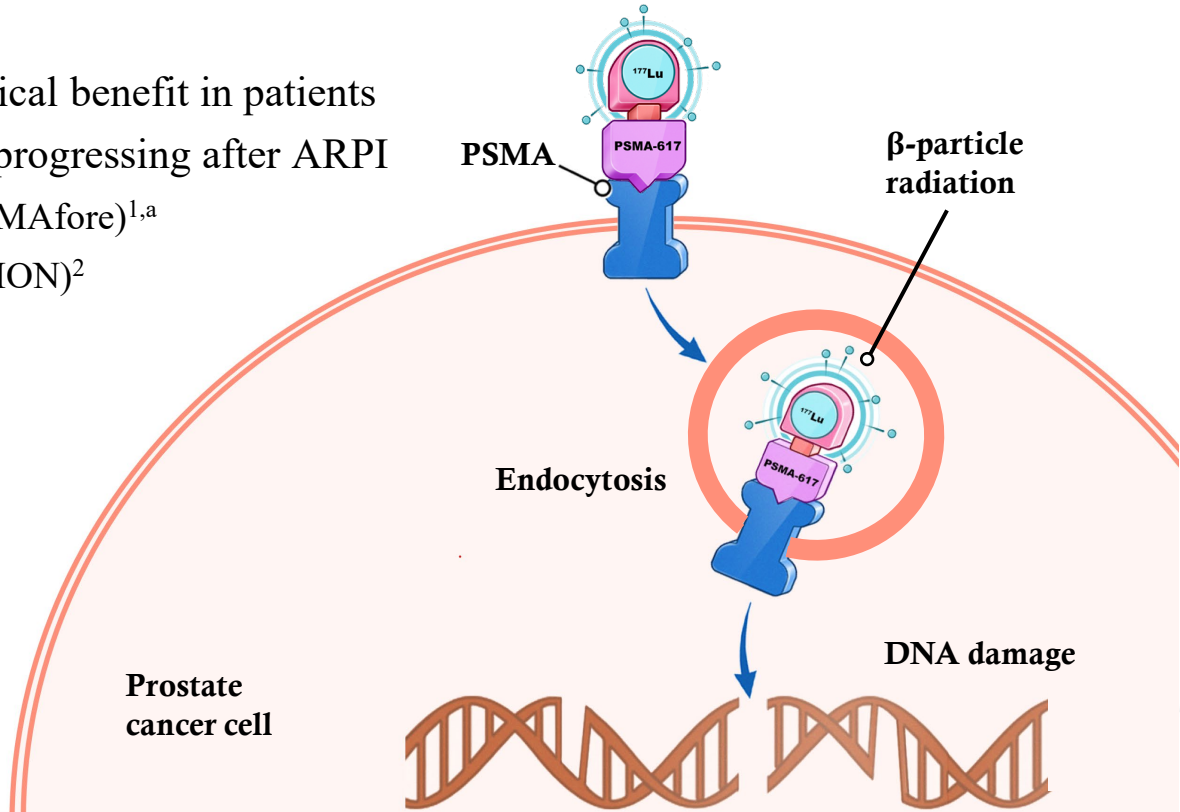
- Composite endpoint[a] (N = 233) was met, with a HR = 1.09[b] (95% CI 0.75-1.59) [futility was defined as ≥1]
- Additional grade 3/4 toxicity was observed using NIRA + AAP vs PBO + AAP
- With added toxicity and no added efficacy in HRR BM⁻ mCRPC, the IDMC recommend stopping enrollment in this cohort

[b]Breakdown of composite endpoint events
83 PSA events (HR = 1.03, 95% CI 0.67-1.59)
65 rPFS events (HR = 1.03, 95% CI 0.63-1.67)

Chi K et al. J Clin Oncol 2023 Mar 23;

^{177}Lu-PSMA-617

- [^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) is a PSMA-targeted radioligand therapy
- ^{177}Lu-PSMA-617 provides clinical benefit in patients with PSMA-positive mCRPC progressing after ARPI
  - in the taxane-naive setting (PSMAfore)[1,a]
  - in the post-taxane setting (VISION)[2]



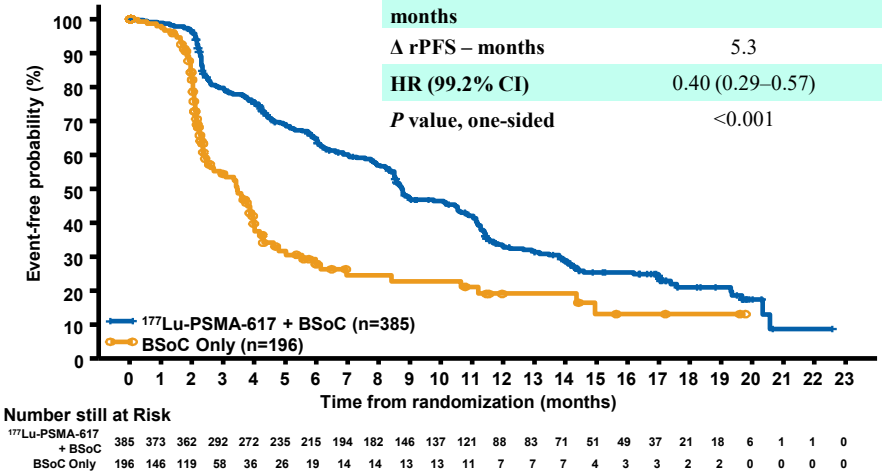
1. Morris M *et al. Lancet* 2024;404:1227–39
2. Sartor O *et al. N Engl J Med* 2021;385:1091–103

Lutetium post ARPI/Taxane mCRPC (VISION)

^{177}Lu-PSMA-617 - PSMA-targeted radioligand therapy

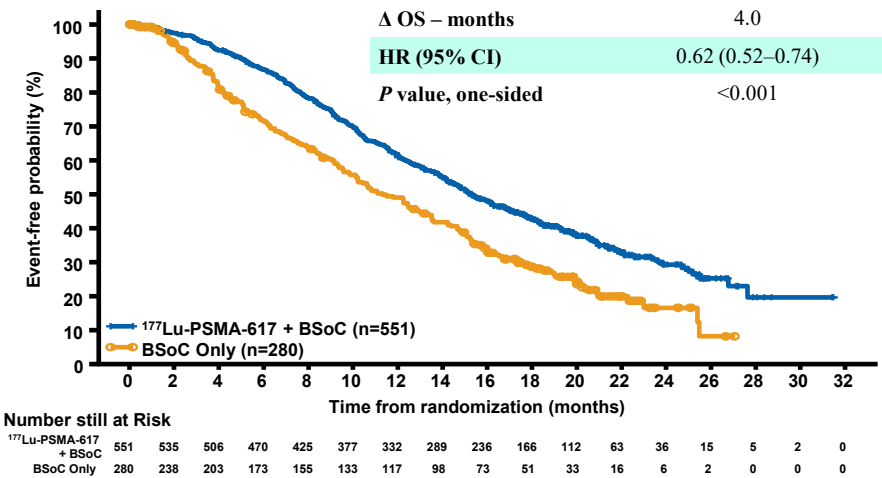
rPFS

	^{177}Lu-PSMA-617	BSoC
Median rPFS – months	8.7	3.4
Δ rPFS – months	5.3	
HR (99.2% CI)	0.40 (0.29–0.57)	
P value, one-sided	<0.001	



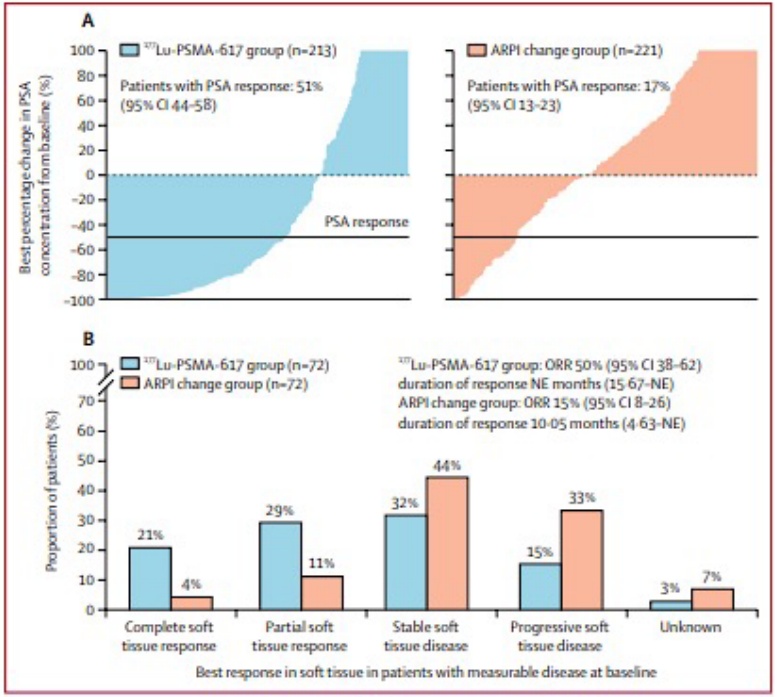
Overall Survival

	^{177}Lu-PSMA-617	BSoC
Median OS – months	15.3	11.3
Δ OS – months	4.0	
HR (95% CI)	0.62 (0.52–0.74)	
P value, one-sided	<0.001	



Morris M, et al. Oral presentation at the 2021 ASCO Annual Meeting; June 6, 2021; Abstract LBA4. Sartor et al. NEJM 2021

PSMAfore: Phase 3 RCT of Lu-PSMA-617 vs ARPI switch for taxane-naive mCRPC



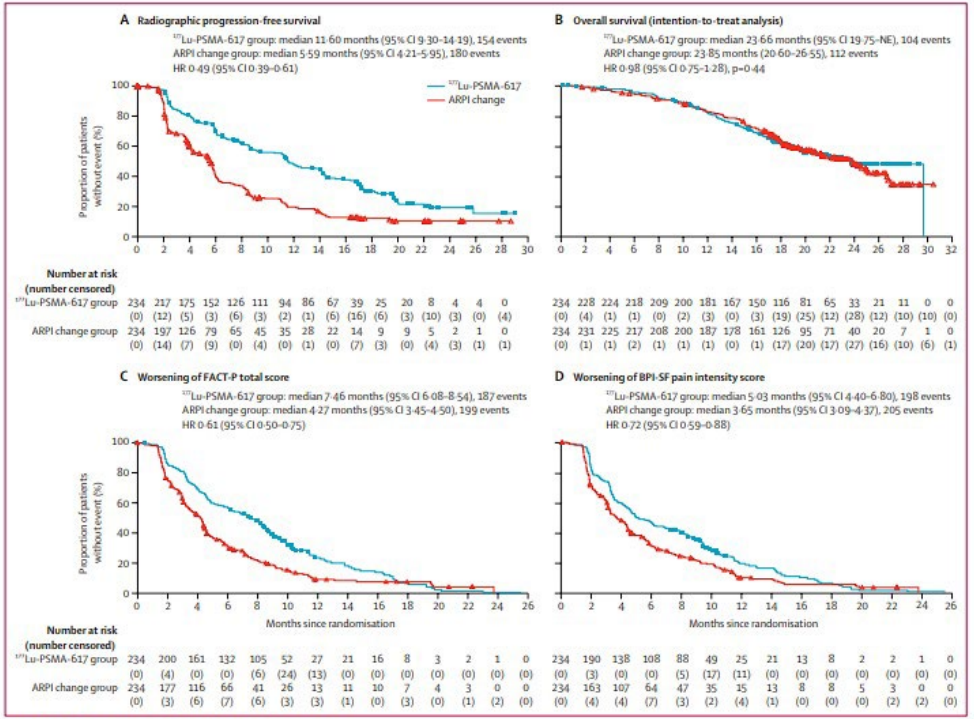


Figure 2: **Time-to-event endpoints at the time of third data cutoff**

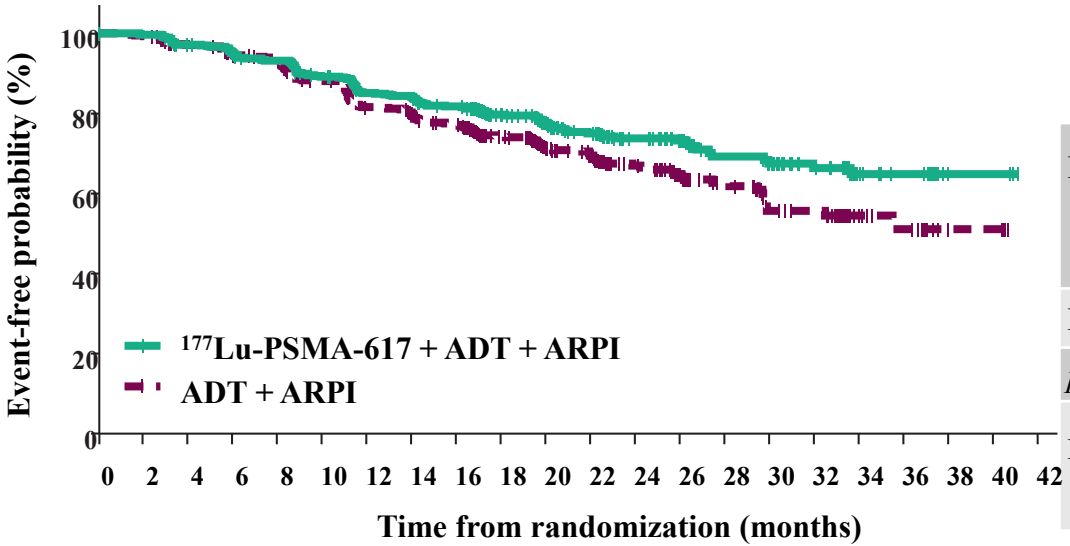
(A) Updated radiographic progression-free survival (see appendix 1 p 10 for primary analysis); events were radiographic disease progression (determined by blinded independent central review per the Prostate Cancer Clinical Trials Working Group 3-modified[14] Response Evaluation Criteria in Solid Tumours v1.1) or death. (B) Overall survival (intention-to-treat analysis; three patients died before receiving ^{177}Lu-PSMA-617). (C) Time to worsening of FACT-P total score; events were a decrease of ≥10 points,[40,41] clinical disease progression, or death. (D) Time to worsening on BPI-SF pain intensity scale; events were an increase of ≥2 points,[40,41] clinical disease progression, or death. See appendix 1 (p 9) for the schedule of investigations. ARPI=androgen receptor pathway inhibitor. BPI-SF=Brief Pain Inventory—Short Form. FACT-P=Functional Assessment of Cancer Therapy—Prostate. HR=hazard ratio. NE=not estimable. PSMA=prostate-specific membrane antigen.

No difference in OS to date

Morris MJ, et al. Lancet. 2024 Sep 28;404(10459):1227-1239. doi: 10.1016/S0140-6736(24)01653-2. Epub 2024 Sep 15. PMID: 39293462.

^{177}Lu-PSMA RLT in mCSPC: PSMAddition

rPFS by BIRC –primary endpoint was met



Number of patients still at risk

572	558	539	524	512	485	458	452	436	337	252	212	153	134	79	73	59	23	18	3	3	0
572	550	527	507	495	461	424	408	391	304	225	195	134	99	74	50	47	19	15	4	4	0

	^{177}Lu-PSMA-617 + ADT + ARPI (N = 572)	ADT + ARPI (N = 572)
Events – n (%) rPD Death without rPD	139 (24.3) 112 (19.6) 27 (4.7)	172 (30.1) 152 (26.6) 20 (3.5)
HR (95% CI)	0.72 (0.58, 0.90)	
p value	0.002[a]	
Median rPFS (95% CI) – months	NR (NE, NE)	NR (29.7, NE)

[a] Significance threshold at rPFS IA2: 0.009 (one-sided; stratified log-rank test); information fraction, 74.4%
CI, confidence interval; IA, interim analysis; NE, not estimable; NR, not reached

PCa Disease States and the Evolving Treatment Landscape

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Early Detection

Clinically localized disease
- Active surveillance
- Radiation ± ADT
- Radical prostatectomy

Neoadjuvant ARPI

PSA Recurrent

Nonmetastatic HSPC
- Salvage focal treatment
- Observation
- Intermittent ADT

ADT + ARPI

Late Detection

Metastatic HSPC

ARPI Doublets

ADT + docetaxel

Selective local or MDT

Nonmetastatic CRPC

ARPI

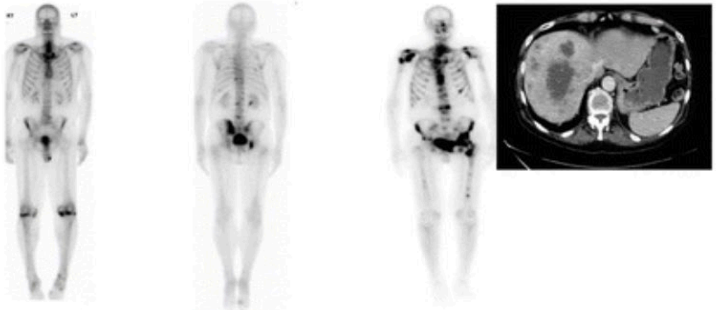
Metastatic CRPC
- ARPI switch
- Docetaxel, Cabazitaxel
- Radium-223
- PARPi for HRR+
- PSMA-Lu

Disease burden

- FUTURE
  - AKT inhibitor
  - ADCs, bispecifics
  - AR PROTACs
  - Alpha-RLT

Clinical Factors Within States:
Disease-related symptoms/pain
Visceral vs. non-visceral metastases
Prior therapy exposure

Goals:
Develop molecular taxonomy
Risk stratification



Optimizing Outcomes in Localized PCa

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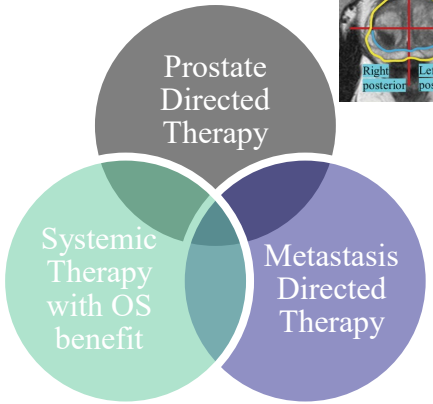
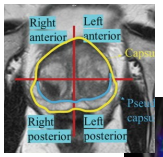
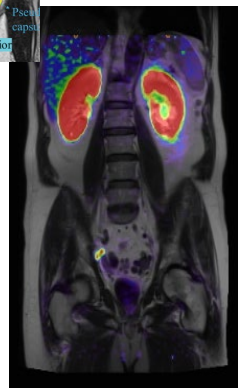
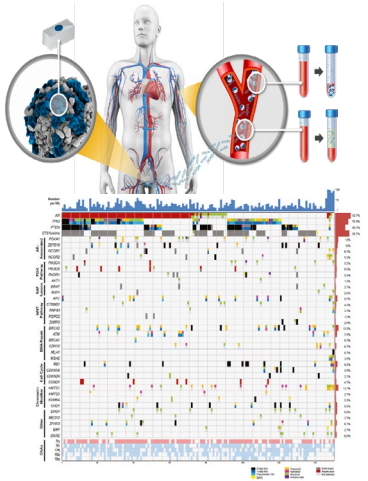
Convergent Advances

- **Early Detection – PSA + MRI**
- **Risk Stratification**
  - volume pattern 4,5; PSA; biomarkers; imaging
  - Uncouple Dx from Rx: Active Surveillance for Low Risk
- **Technique**
  - Surgery, radiotherapy









- **Imaging and Biomarkers –**
  - **Prognostic, predictive**

➢ **Improve outcomes**

- **Multi-modal Therapy Integration:**
  - Post-op: PSA- and image-guided early salvage therapy
  - Metastasis-directed therapies
  - ARPI doublets prolong survival

Evolving Treatment Strategies for Metastatic PCa

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- **ARPI doublets are the foundation of mPCa treatment**
  - Consider prostate- and metastasis-directed therapies in selected oligometastatic cases
  - Consider ARPI triplets for fit pts with de novo high volume PCa (Rx intensification)
- **ctDNA enables serial monitoring of treatment-induced genomic adaptations**
- **Molecular sub-classification of PCA key to segmenting cancer heterogeneity**
  - Prognostic and Predictive biomarkers = Select optimal drug therapy (PARPi, PSMA-Lu, PDL-1)
    - ➢**Key to precision oncology approaches**

Clinical Review & Education

JAMA | Review

Prostate Cancer
A Review

Ruben Raychaudhuri, MD; Daniel W. Lin, MD; R. Bruce Montgomery, MD