What's New in Advanced and Metastatic Prostate Cancer Treatment

Patrick Richard, MD, MPH
Rocky Mountain Cancer Centers • 720-316-1240

Dario Pasalic, MD
Rocky Mountain Cancer Centers • 720-316-1240

Austin Poole, MD
Rocky Mountain Cancer Centers • 720-370-5363

Boulder Community Health

ROCKY MOUNTAIN™ CANCER CENTERS

2023 Prostate Cancer Summit

Treating Locally Advanced & Metastatic Prostate Cancer

Dario Pasalic, MD
Patrick Richard, MD, MPH

Radiation Oncology
Rocky Mountain Cancer Centers
Boulder, CO

Austin Poole, MD

Medical Oncology/Hematology
Rocky Mountain Cancer Centers
Boulder, CO

September 7, 2023

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Boulder Community Health

Radiation Oncology

Boulder Community Health

Patrick Richard, MD, MPH

- Tulane University School of Medicine
- Tulane University Public Health Masters
- University of Washington Residency

Appointments

- 720-316-1240

Dario Pasalic, MD

- Mayo Clinic School of Medicine
- Memorial Sloan-Kettering Cancer Center Transitional Year
- MD Anderson Cancer Center Residency

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Medical Oncology/Hematology

Boulder Community Health

Austin Poole, MD

- Wayne State University School of Medicine
  - University of Utah Residency
  - University of Utah Fellowship

Appointments

- 720-370-5363

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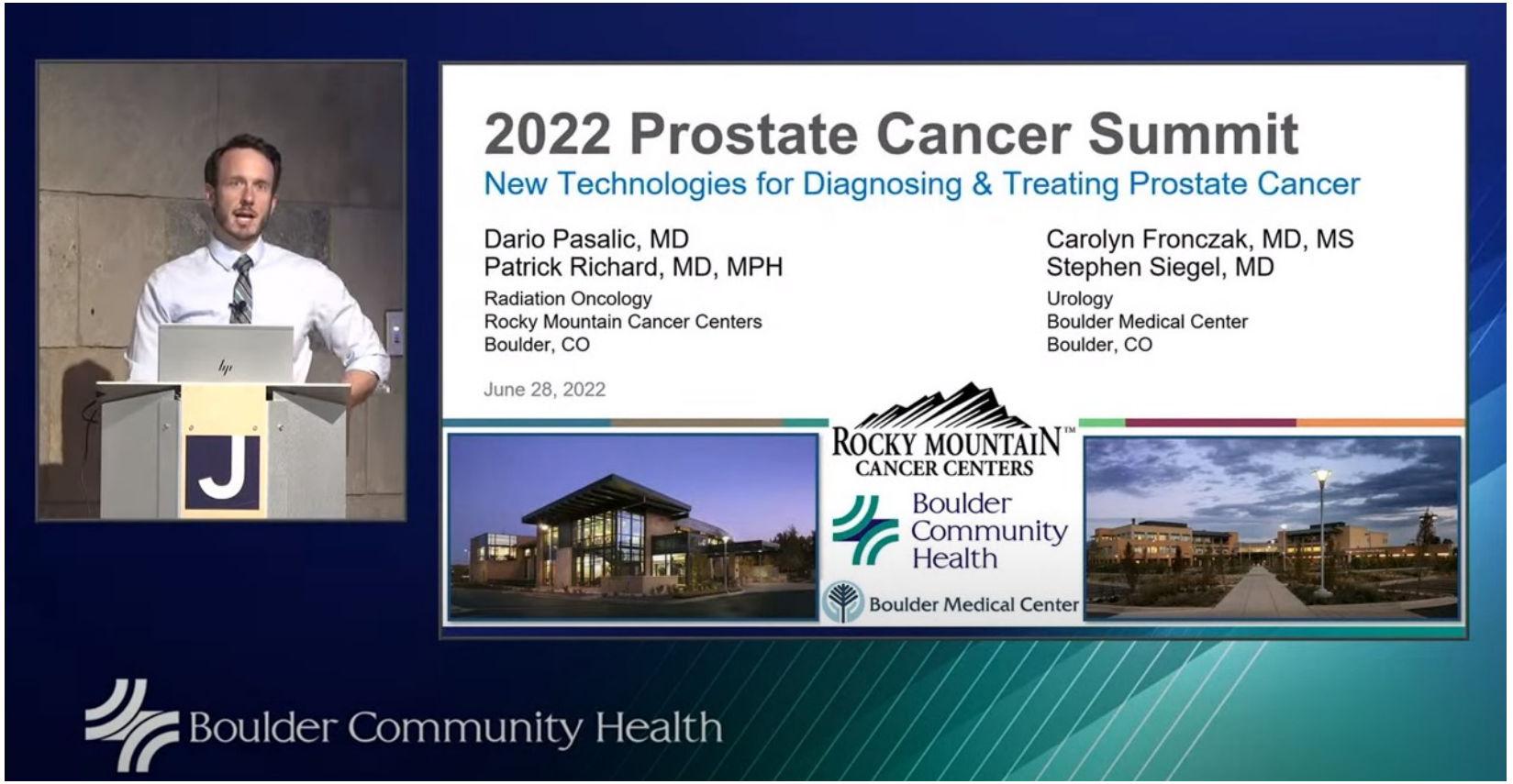
Previous Prostate Lecture

Boulder Community Health



www.bch.org/media/video-center/cancer/bch-lecture-whats-new-in-prostate-cancer-treatme/

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Upcoming Relevant Lecture

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Team Approach

Boulder Community Health

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Multidisciplinary Approach

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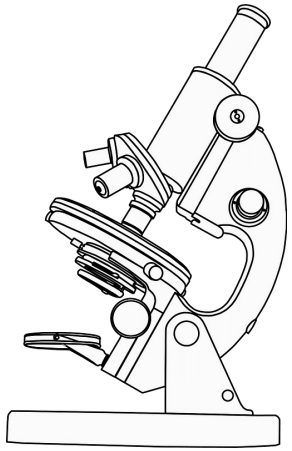
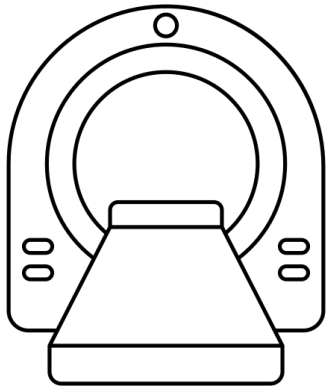
Team Approach

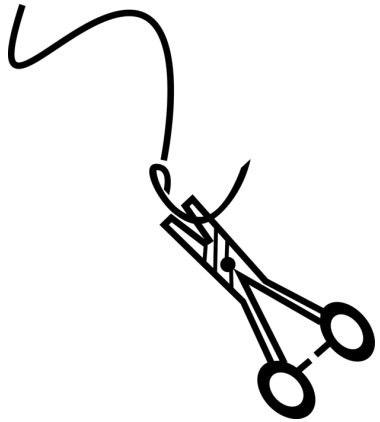
Boulder Community Health



Pathology



Radiology



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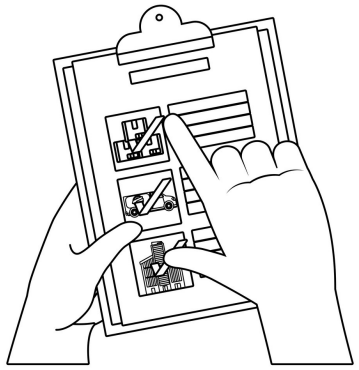
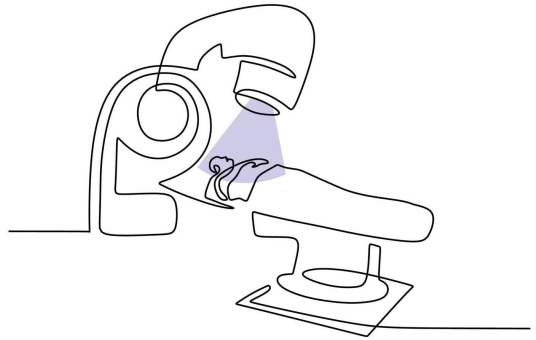


Clinical Trial Coordinator

Medical Oncology



Radiation Oncology

Multidisciplinary Approach

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Outline

Boulder Community Health

Diagnosing & Grouping

- Risk stratification
- Staging
- Imaging
- Genetic testing
- Additional work-up considerations

Treatment

- Radiation therapy
- Systemic therapy
- Radiopharmaceutical therapy

Clinical Trials

ROCKY MOUNTAIN™ CANCER CENTERS

Outline

Diagnosing & Grouping

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- Radiation therapy
- Systemic therapy
- Radiopharmaceutical therapy

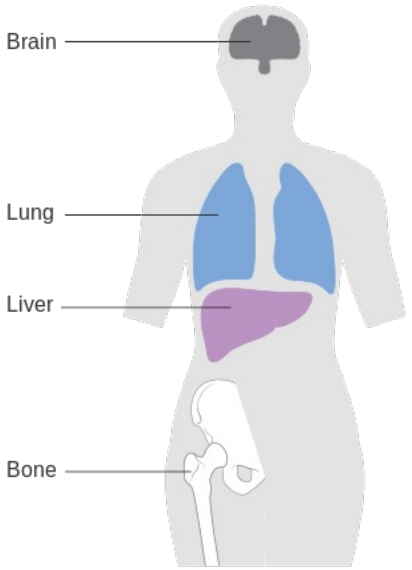
Clinical Trials

Risk Stratification

Boulder Community Health

- Main risk with prostate cancer that affects patients

Distant metastasis



Prostate cancer mortality

Estimated Deaths

Lung & bronchus	72,500	23%
Prostate	33,330	10%
Colon & rectum	28,630	9%
Pancreas	24,640	8%
Liver & intrahepatic bile duct	20,020	6%
Leukemia	13,420	4%
Esophagus	13,100	4%
Urinary bladder	13,050	4%
Non-Hodgkin lymphoma	11,460	4%
Brain & other nervous system	10,190	3%
All sites	**321,160**	

- Risk stratification
  - **Clinical** information (National Comprehensive Cancer Network [NCCN] clinical risk grouping uses PSA, Gleason score, physical exam
  - **Imaging** information (MRI, PSMA PET-CT scan, bone scan)
  - **Somatic** tumor information (e.g. Decipher testing)
  - **Genetic** germline information (e.g. Invitae panel)

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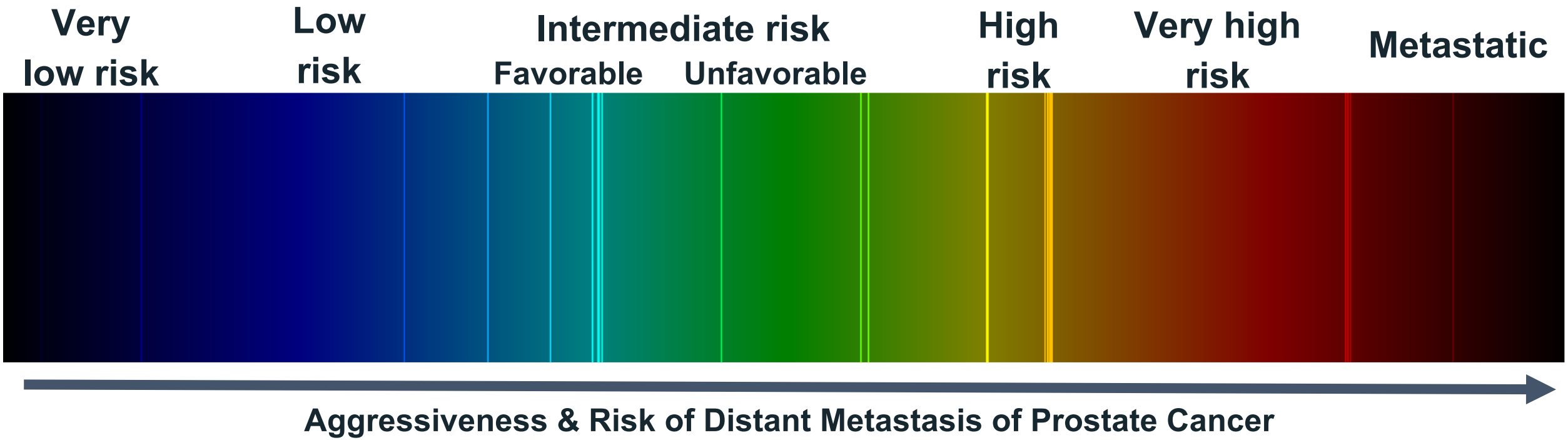
Wikipedia; American Cancer Society Surveillance Research, 2020

Clinical Risk Grouping

Boulder Community Health



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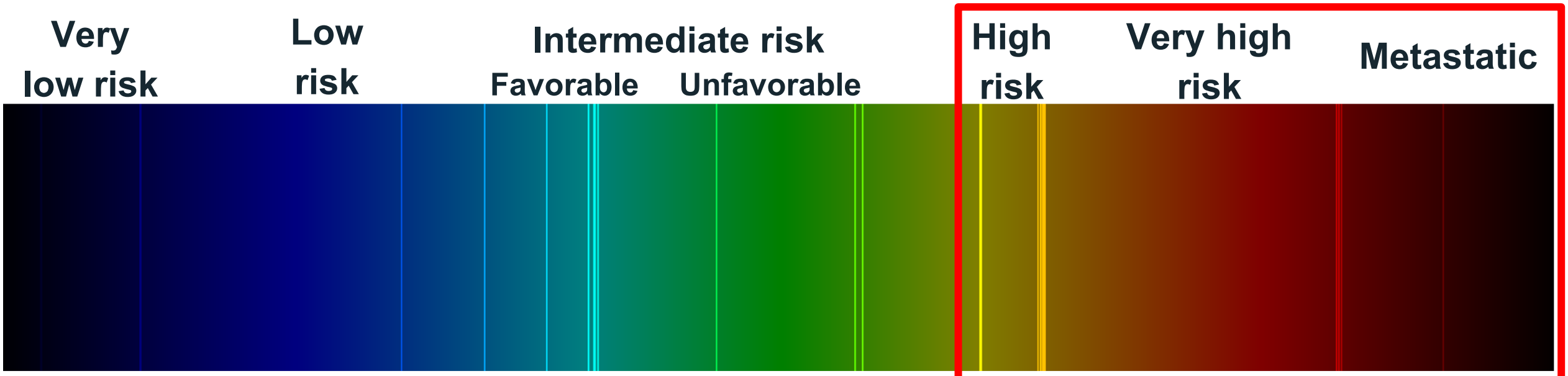
Clinical Risk Grouping

Boulder Community Health



- cT3-4 (extracapsular) (seminal vesicles)
- PSA >20
- Gleason 5
- Gleason 8-9 in ≥5 cores

- N+

- Bone
- Lung
- Brain

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Staging Studies

Boulder Community Health

- **Staging** studies determine whether cancer is **localized** to the **prostate** gland or **outside** the prostate gland
  - Involving regional pelvic **lymph nodes** or non-regional nodes
  - Involving **distant** organ (bone, liver, lungs)

- **Staging** studies usually consist of cross-sectional **imaging** to evaluate anatomy in the pelvis and other organs

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Prostate Cancer Diagnostic Imaging Options

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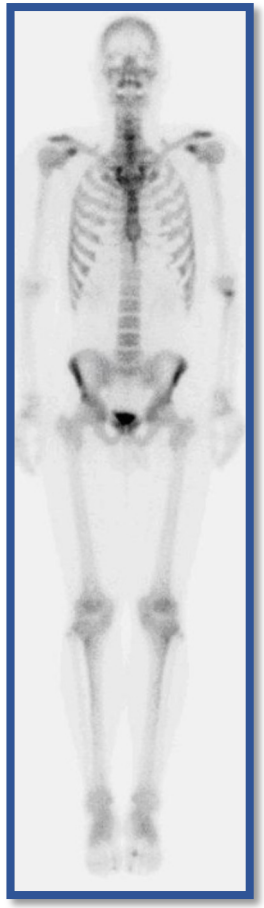
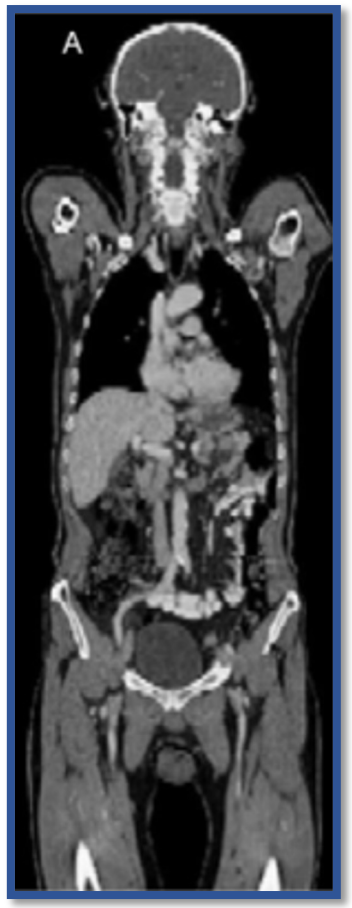


Bone scintigraphy (bone scan)

Tc99m single photon emission CT (SPECT)



Computed tomography (CT)

- **Bone scan** is a nuclear medicine scan to specifically evaluate the bone, specifically at sites of **bone turnover**
  - Technetium-99 bone scan either in a single plane or 3D reconstruction (SPECT)
  - Lacks sensitivity and specificity
  - Detection rates low especially for lower PSA
- **CT** typically given with IV contrast and evaluates abdomen and pelvis; purely assessment of **anatomy**
  - Pelvic/regional lymph nodes
  - Liver
  - Non-regional nodes in the abdominal area
- **Combining CT** results and **bone scan** results may have higher accuracy in detecting metastases

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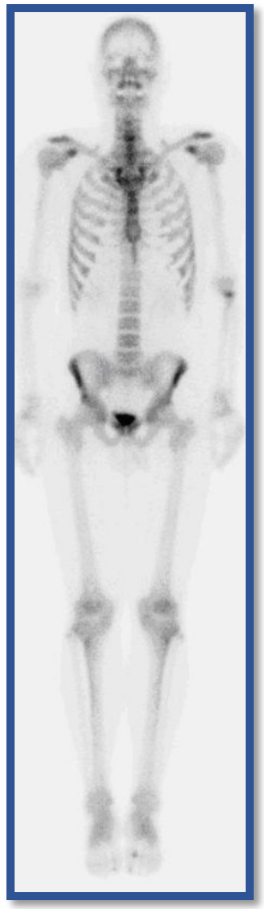
Anttinen et al., *Eur Urol Oncol* (2021)

Prostate Cancer Diagnostic Imaging Options

Boulder Community Health



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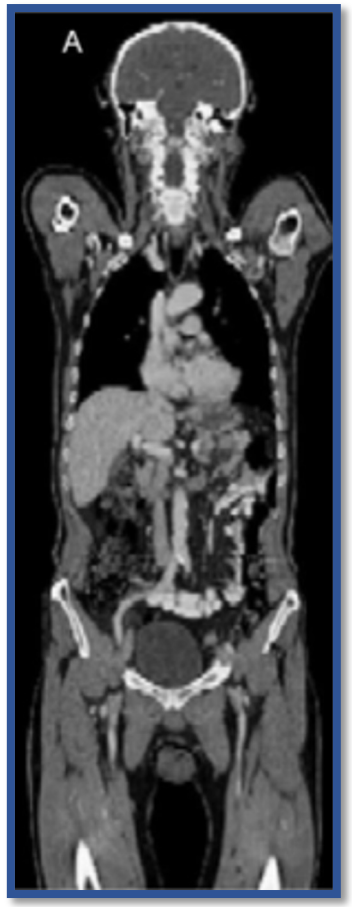

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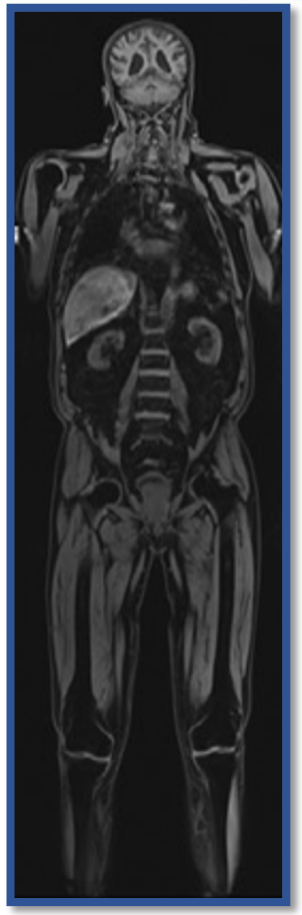

Magnetic resonance imaging (MRI)

- **Multiple MRI sequences**/parameters are used to radiographically determine whether high grade lesions are present
- Prostate Imaging Reporting and Data System (PI-RADS)

PI-RADS 1 = Very low (clinically significant cancer highly unlikely)
PI-RADS 2 = Low (clinically significant cancer unlikely)
PI-RADS 3 = Intermediate (clinically significant cancer equivocal)
PI-RADS 4 = High (clinically significant cancer likely)
PI-RADS 5 = Very high (clinically significant cancer highly likely)

- Important consideration to assess for all risk groups
  - BCH radiology offers mpMRI

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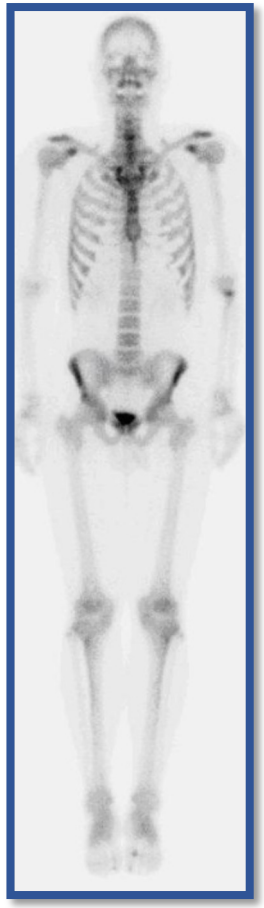
Anttinen et al., *Eur Urol Oncol* (2021)

Prostate Cancer Diagnostic Imaging Options

Boulder Community Health



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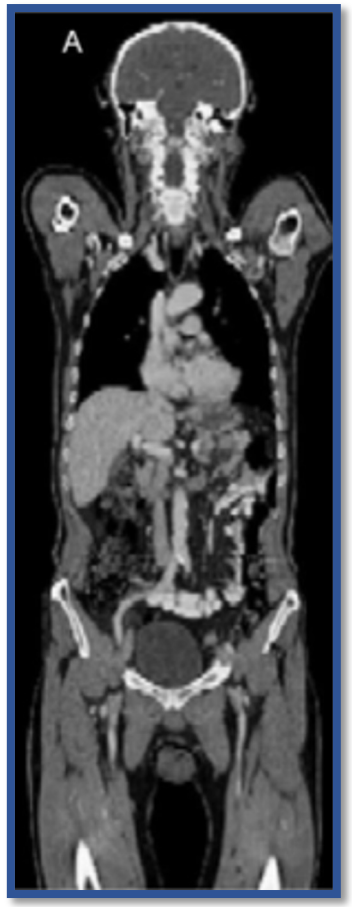
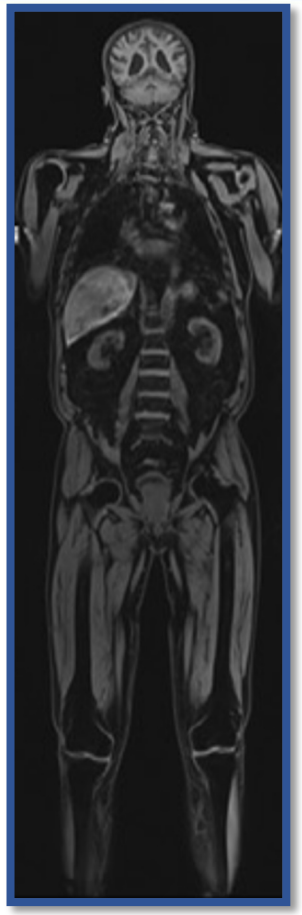
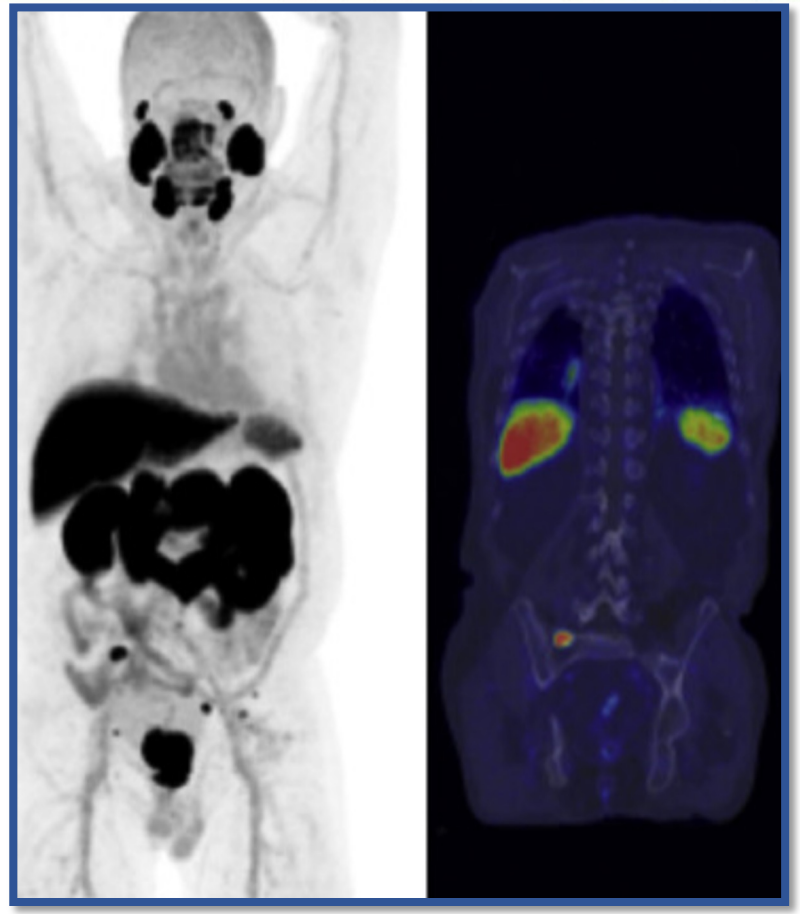


Computed tomography (CT)



Magnetic resonance imaging (MRI)



Positron emission tomography with prostate-specific membrane antigen (PET-PSMA)

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Anttinen et al., *Eur Urol Oncol* (2021)

RMCC PET-PSMA

Boulder Community Health

- **68-Ga** and **18-F-piflufolastat (Pylarify) PSMA PET** now offered in **Boulder**
  - Medicare
  - Most commercial insurances
- **RMCC-Boulder / BCH** with new joint **General Electric MI DR PET-CT** scanner
  - High spatial resolution (2mm); higher PET sensitivity; reduced CT radiation dose

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PSMA PET Appropriate Use Criteria

Boulder Community Health

Clinical Scenarios for PSMA PET

Scenario no.	Description	Appropriateness	Score
1	Patients with suspected prostate cancer (e.g., high/rising PSA levels, abnormal digital rectal examination results) evaluated for targeted biopsy and detection of intraprostatic tumor	Rarely appropriate	3
2	Patients with very-low, low-, and favorable intermediate-risk prostate cancer	Rarely appropriate	2
3	Newly diagnosed unfavorable intermediate-, high-risk, or very-high-risk prostate cancer	Appropriate	8
4	Newly diagnosed unfavorable intermediate-, high-risk, or very-high-risk prostate cancer with negative/equivocal or oligometastatic disease on conventional imaging	Appropriate	8
5	Newly diagnosed prostate cancer with widespread metastatic disease on conventional imaging	May be appropriate	4
6	PSA persistence or PSA rise from undetectable level after radical prostatectomy	Appropriate	9
7	PSA rise above nadir after definitive radiotherapy	Appropriate	9
8	PSA rise after focal therapy of the primary tumor	May be appropriate	5
9	nmCRPC (M0) on conventional imaging	Appropriate	7
10	Posttreatment PSA rise in the mCRPC setting	May be appropriate	6
11	Evaluation of response to therapy	May be appropriate	5

Jadvar et al. *Journal of Nuclear Medicine* (2022)

RMCC PET-CT Imaging Locations

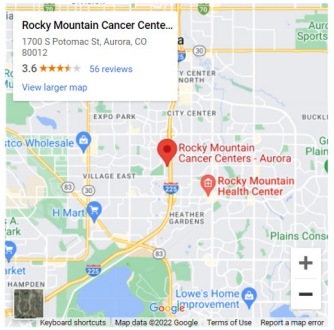
Boulder Community Health

Aurora

1700 S. Potomac St.
Aurora, Colorado 80012

REQUEST AN APPOINTMENT

Phone: 303-418-7600
Fax: 303-750-3137
Radiation Dept Phone: 303-418-7659
Radiation Dept Fax: 303-750-3096

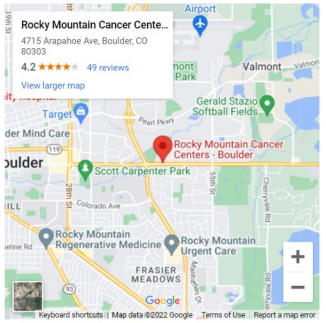


Boulder

4715 Arapahoe Ave.
Boulder, Colorado 80303

REQUEST AN APPOINTMENT

Phone: 303-385-2000
Fax: 303-267-4419
Radiation Dept Phone: 303-385-2068
Radiation Dept Fax: 303-385-2090



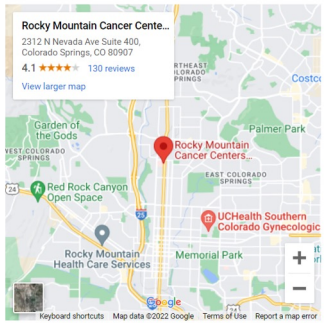
Colorado Springs - Penrose Pavilion

2312 N. Nevada Ave., Ste. 400
Colorado Springs, Colorado 80907

REQUEST AN APPOINTMENT

Phone: 719-577-2555
Fax: 719-577-2553

NEW PATIENT FORMS



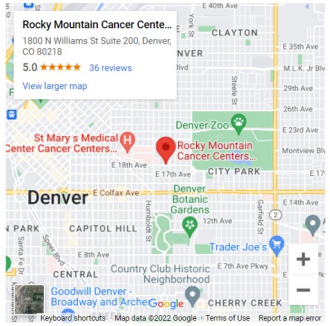
Denver - Midtown

1800 N. Williams St., Ste. 200
Denver, Colorado 80218

REQUEST AN APPOINTMENT

Phone: 303-388-4876
Fax: 303-285-5097

NEW PATIENT FORMS

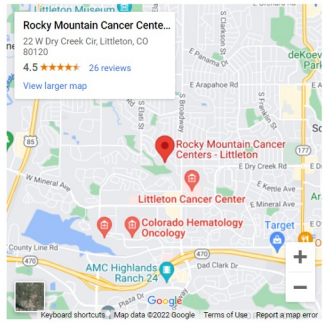


Littleton

22 W. Dry Creek Cir.
Littleton, Colorado 80120

REQUEST AN APPOINTMENT

Phone: 303-730-4700
Fax: 303-730-4790
Radiation Dept Phone: 303-730-4700
Radiation Dept Fax: 303-930-8053

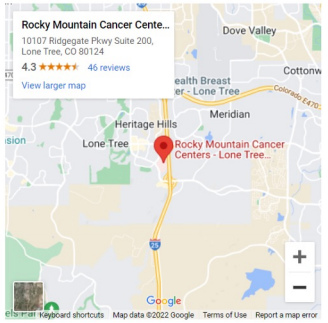


Lone Tree - Sky Ridge Medical Center

10107 Ridgegate Pkwy., Ste. 200
Lone Tree, Colorado 80124

REQUEST AN APPOINTMENT

Phone: 303-925-0700
Fax: 303-329-2599
Radiation Dept Phone: 720-225-4200
Radiation Dept Fax: 720-225-4208

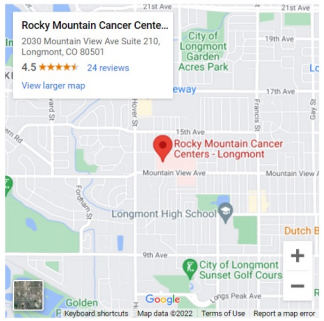


Longmont

2030 Mountain View Ave., Ste. 210
Longmont, Colorado 80501

REQUEST AN APPOINTMENT

Phone: 303-684-1900
Fax: 303-267-4470

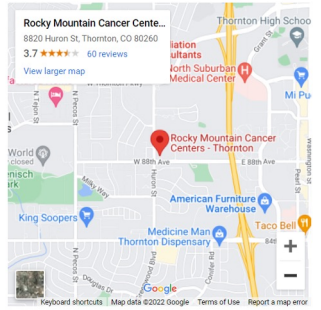


Thornton

8820 Huron St.
Thornton, Colorado 80260

REQUEST AN APPOINTMENT

Phone: 303-386-7622
Fax: 303-427-6800
Radiation Dept Phone: 303-386-7622
Radiation Dept Fax: 303-487-9350



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Genomic Risk Group

Boulder Community Health

- NCCN risk groups historically used for determining risk of local recurrence or PSA recurrence
- **More valuable** endpoints are **distant metastases** and **prostate cancer specific mortality**.
- **Decipher Test**: **22 gene genomic classifier** originally intended to determine **risk** of **distant metastases** after prostatectomy
- Genetic testing of cancer cell RNA expression of certain biomarkers.
  - Over the past 5-10 years, expanded use in certain risk groups of prostate cancer
    - Use of hormone therapy and higher dose radiation (RTOG 0126 analysis)
    - Need for adjuvant (immediate) vs. salvage radiation after prostatectomy (Den et al. *JCO* 2015)
    - Use of hormone therapy in men getting salvage radiation (RTOG 9601 analysis)
    - De-escalate or escalate hormone therapy for intermediate risk or high risk (more to come)

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Decipher Report Example

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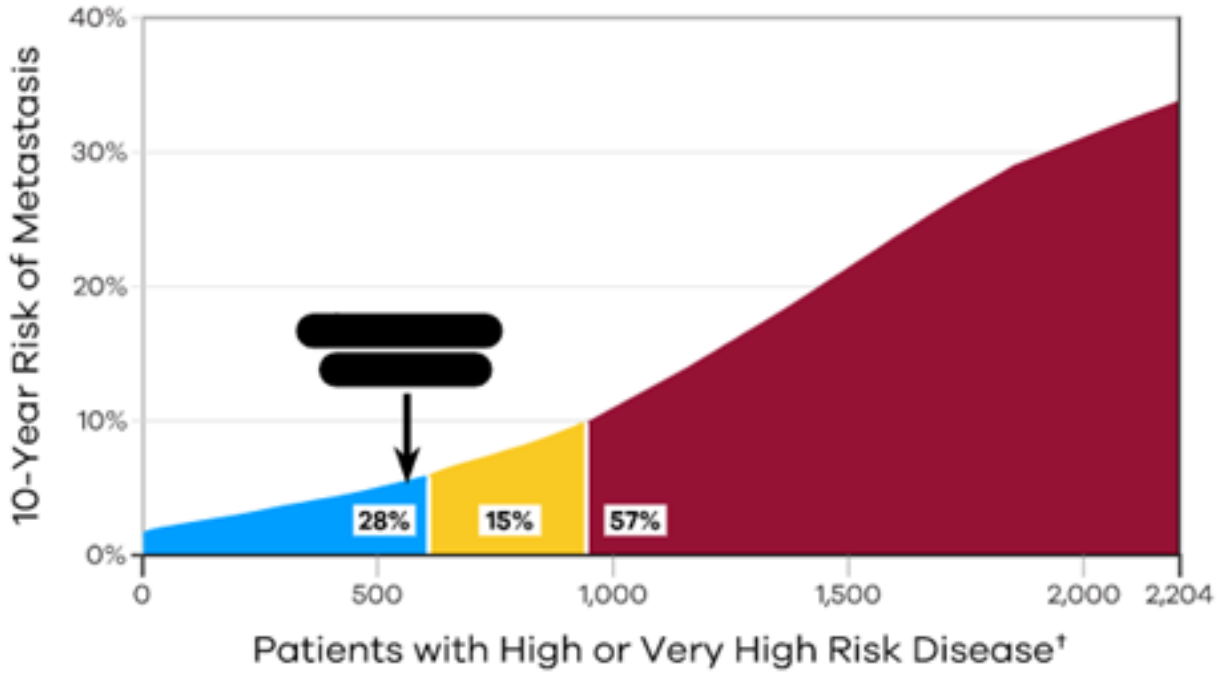

INTERPRETATION

This chart shows the 10-year risk of metastasis for 2,204 patients with similar clinical features at the time of biopsy, ordered from lowest to highest risk. Among these patients 28%, 15%, and 57% were classified as Decipher low-, intermediate-, and high-risk, respectively.

This patient has a predicted 5.3% 10-year risk of metastasis with radical therapy (e.g., radical prostatectomy or radiation therapy) and is in the 26th percentile of risk, meaning that 25 percent of men with similar clinical features have a lower Decipher score, and 74 percent have a higher Decipher score.

†Gleason 8-10, T3-T4, or PSA >20ng/mL

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Clinical-Genomic Risk Group

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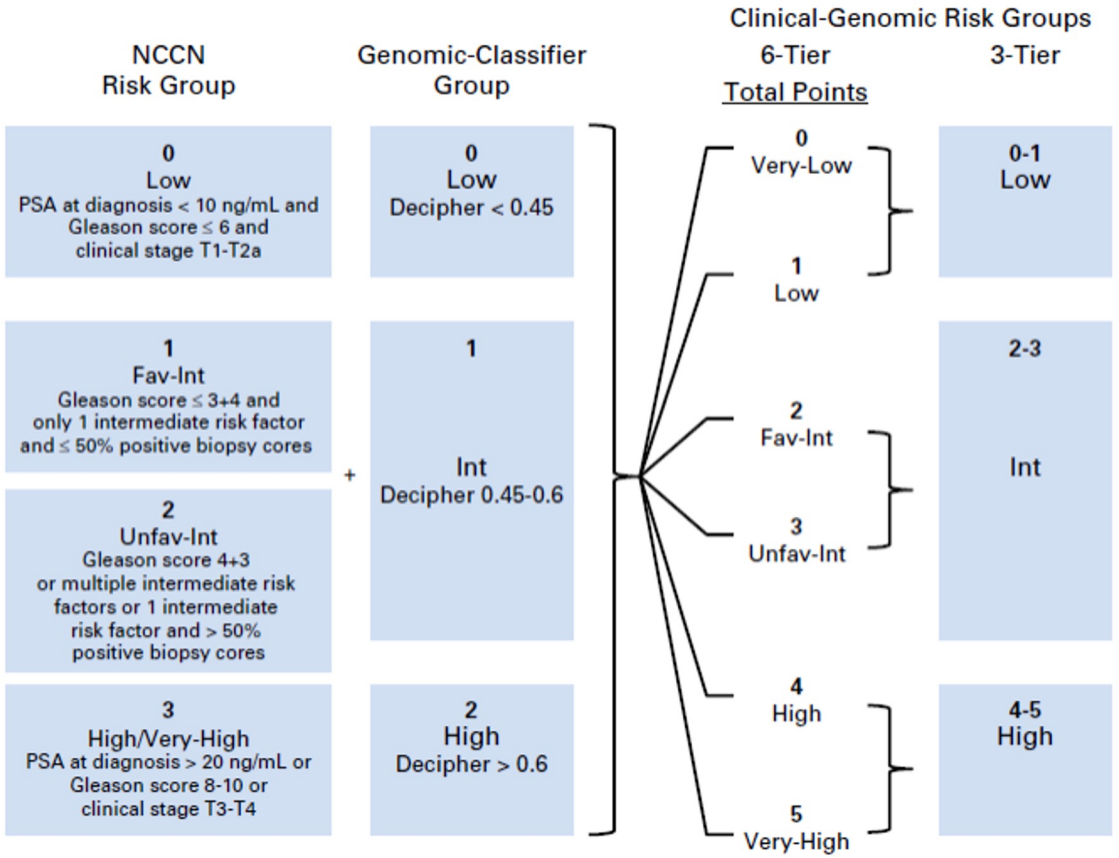
- **Combining** results of **Decipher gene testing** with **clinical factors** (PSA, physical exam, Gleason score)
- Uses genomic testing to either **upstage** the risk or **downstage** the risk



ROCKY MOUNTAIN CANCER CENTERS™

Spratt et al. *JCO (2018)*

Outline

Boulder Community Health

Diagnosing & Grouping

- Risk stratification
- Staging
- Imaging
- Genetic testing
- Additional work-up considerations

Treatment

- Radiation therapy
- Systemic therapy
- Radiopharmaceutical therapy

Clinical Trials

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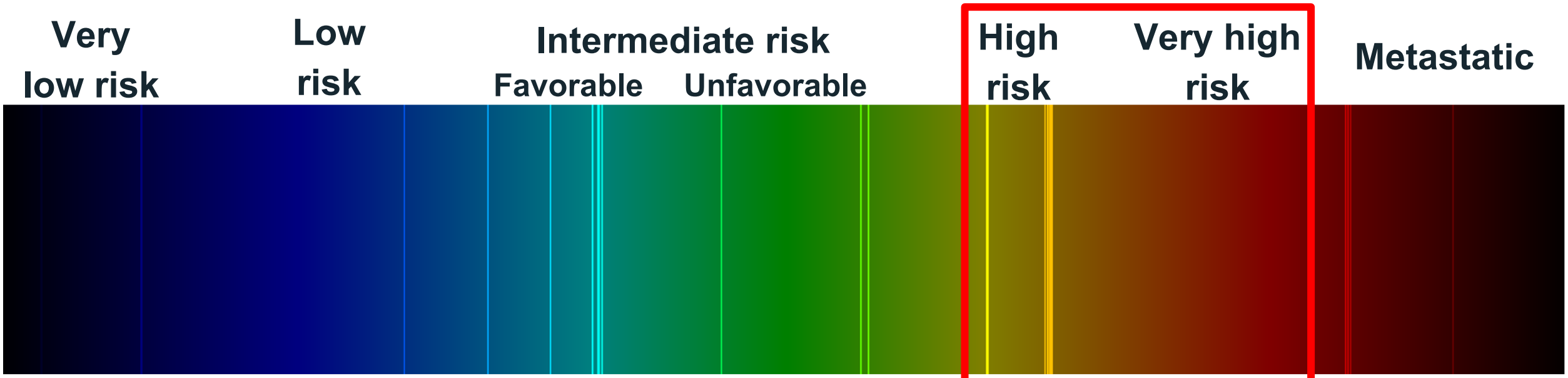
Clinical Risk Grouping

Boulder Community Health



- cT3-4 (extracapsular) (seminal vesicles)
- PSA >20
- Gleason 5
- Gleason 8-9 in ≥5 cores

- N+

- Bone
- Lung
- Brain

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Treatment: High & Very High Risk

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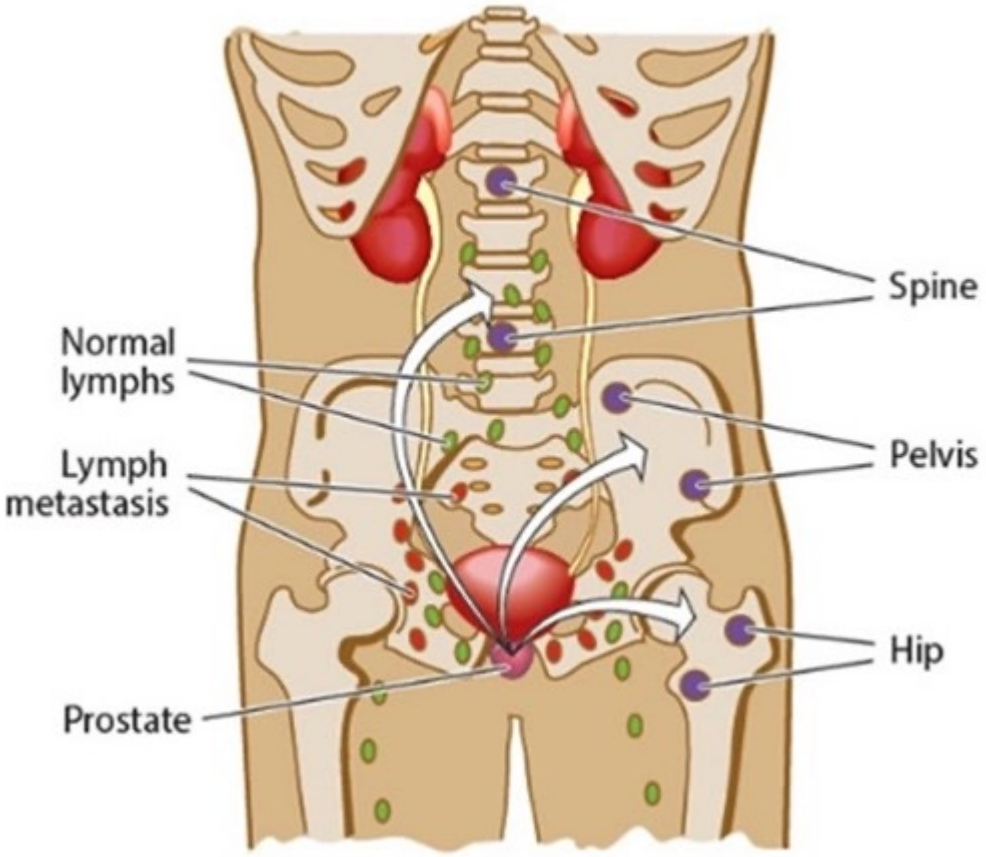

- **Distant** (Bone, lung, brain)
  - Androgen deprivation therapy
  - Anti-androgen receptor therapy
  - Chemotherapy
  - Radiopharmaceuticals

- **Local/Regional** (prostate & lymph nodes)
  - Radiation
  - Surgery

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Treatment: High & Very High Risk

Boulder Community Health

Any treatment should either **improve survival** or **improve quality of life.**

ROCKY MOUNTAIN™ CANCER CENTERS

Treatment: High & Very High Risk

Boulder Community Health

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Prostate Cancer

NCCN Guidelines Index
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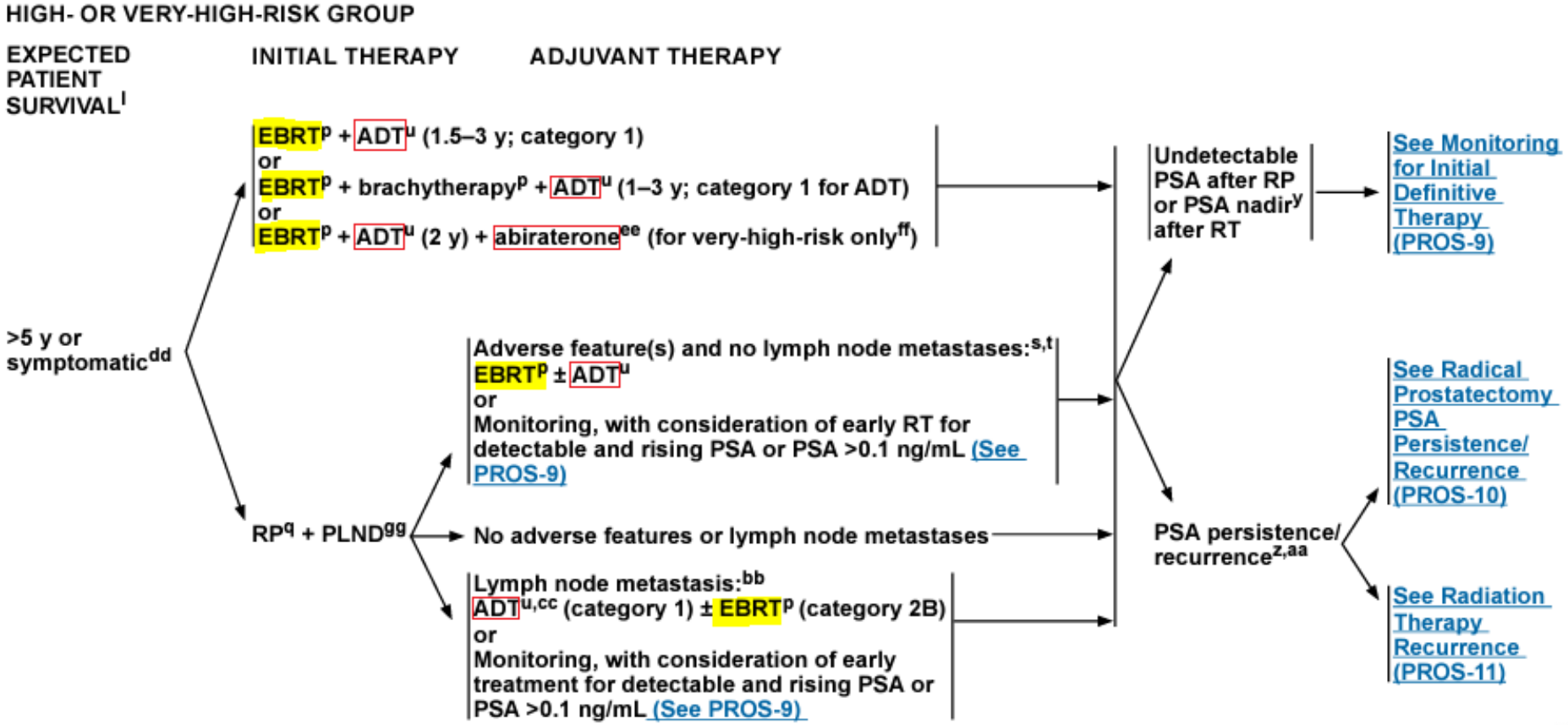

ROCKY MOUNTAIN CANCER CENTERS™

Treatment: High & Very High Risk

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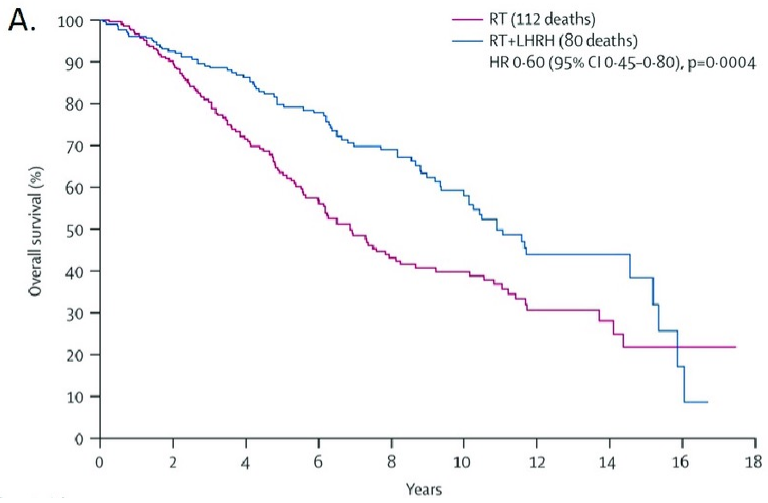
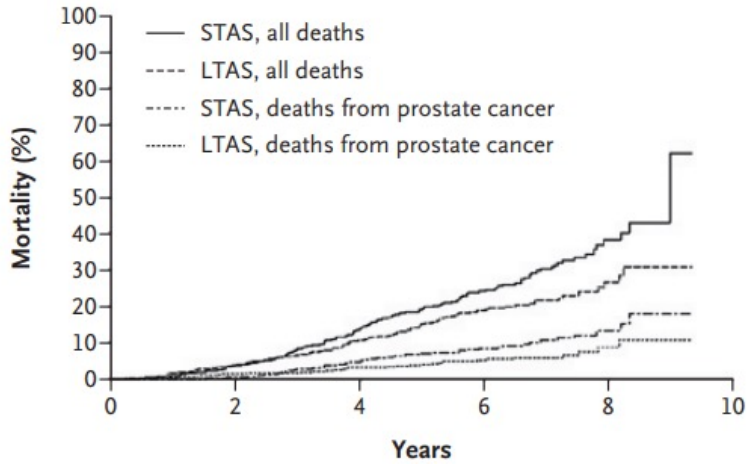
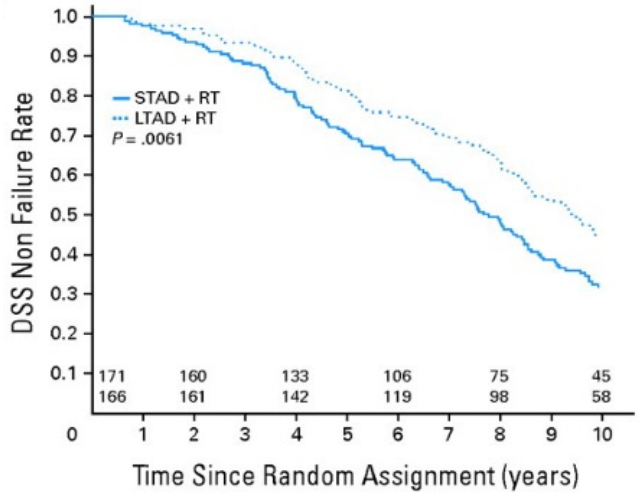
- Category 1: **Radiation + androgen deprivation therapy +/- abiraterone**

Study	Follow-Up (Years)	XRT Dose (Gy)	ADT Duration (Mo)	
EORTC 22863	9	70	36 vs 0	↑ Overall survival and disease-free survival with 36mo ADT
EORTC 22961	6	70	36 vs 6	↑ Overall survival with 36mo ADT
RTOG 9202	11	65-70	28 vs 4	↑ Overall survival with 28mo ADT among high-risk Gleason 8-10



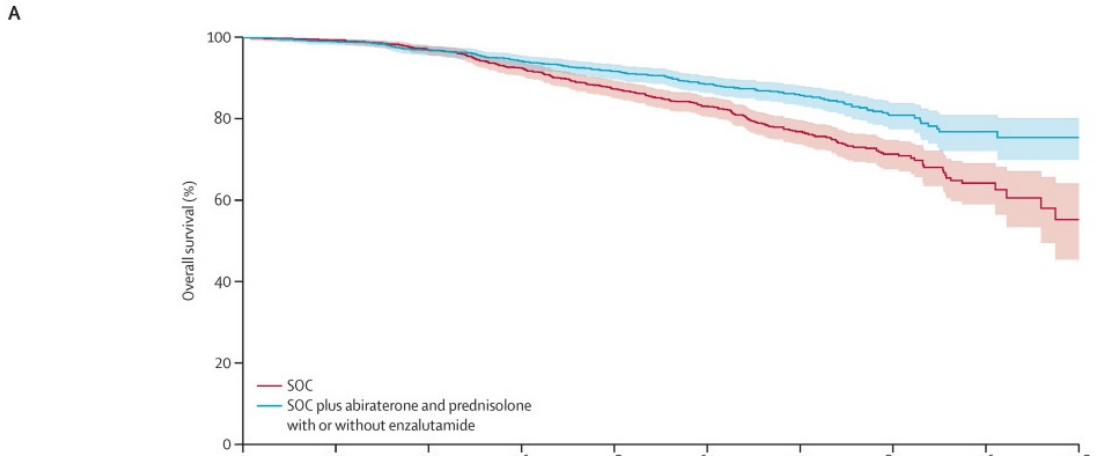




Treatment: High & Very High Risk

Boulder Community Health

- Category 1: **Radiation + androgen deprivation therapy +/- abiraterone**
- Addition of **abiraterone** to patients with **node-positive** or **node-negative with risk factors** (2 of 3 – T3-T4, Gleason 8-10, PSA ≥40) improved metastasis rates and survival



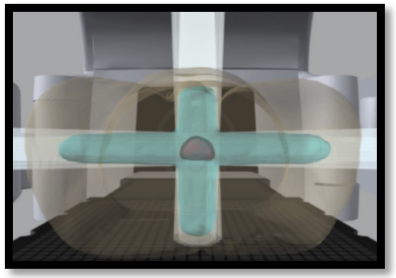
SOC										
At risk	988	974	947	901	837	610	368	200	63	10
Censored	0	8	11	14	28	216	421	568	693	742
Event	0	6	30	73	123	162	199	220	232	236
SOC plus combination therapy										
At risk	986	956	928	899	861	645	386	205	74	16
Censored	0	21	29	32	46	234	477	641	766	823
Event	0	9	29	55	79	107	123	140	146	147

ROCKY MOUNTAIN™ CANCER CENTERS

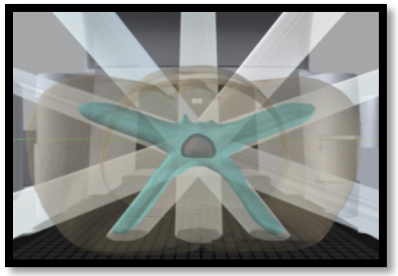
Attard et al., *Lancet* (2021)

External beam radiation therapy (EBRT)

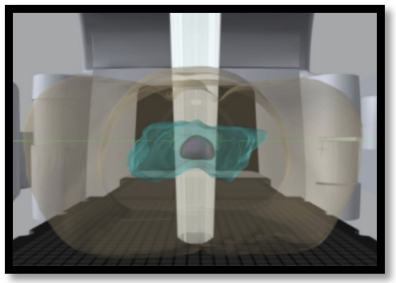
Boulder Community Health



3D-conformal (**3D-CRT**)



Intensity modulated (**IMRT**)



Volumetric modulated arc therapy (**VMAT**)

Conventional EBRT
- Small dose daily (Mon-Fri)
- 8-9 week course

Hypo-fractionated EBRT
- Larger dose daily
- 4-6 week course

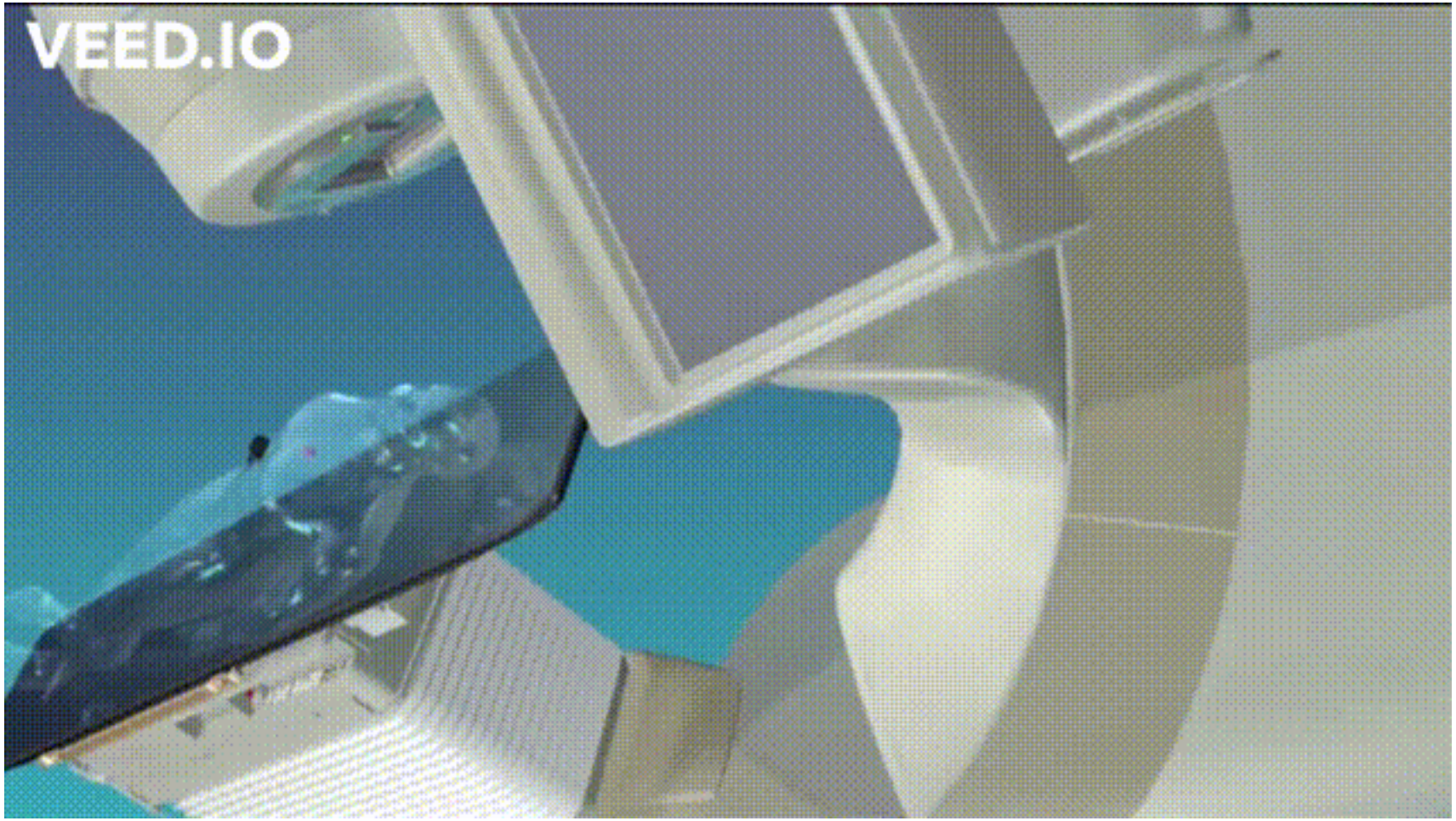
Ultra hypo-fractionated EBRT
- Stereotactic body radiation therapy **SBRT**
- Larger dose per treatment
- 5 total treatments given every other day (~2 week course)

ROCKY MOUNTAIN™ CANCER CENTERS

Leong et al., *J Med Radiat Sci* (2018)

External Beam Radiation

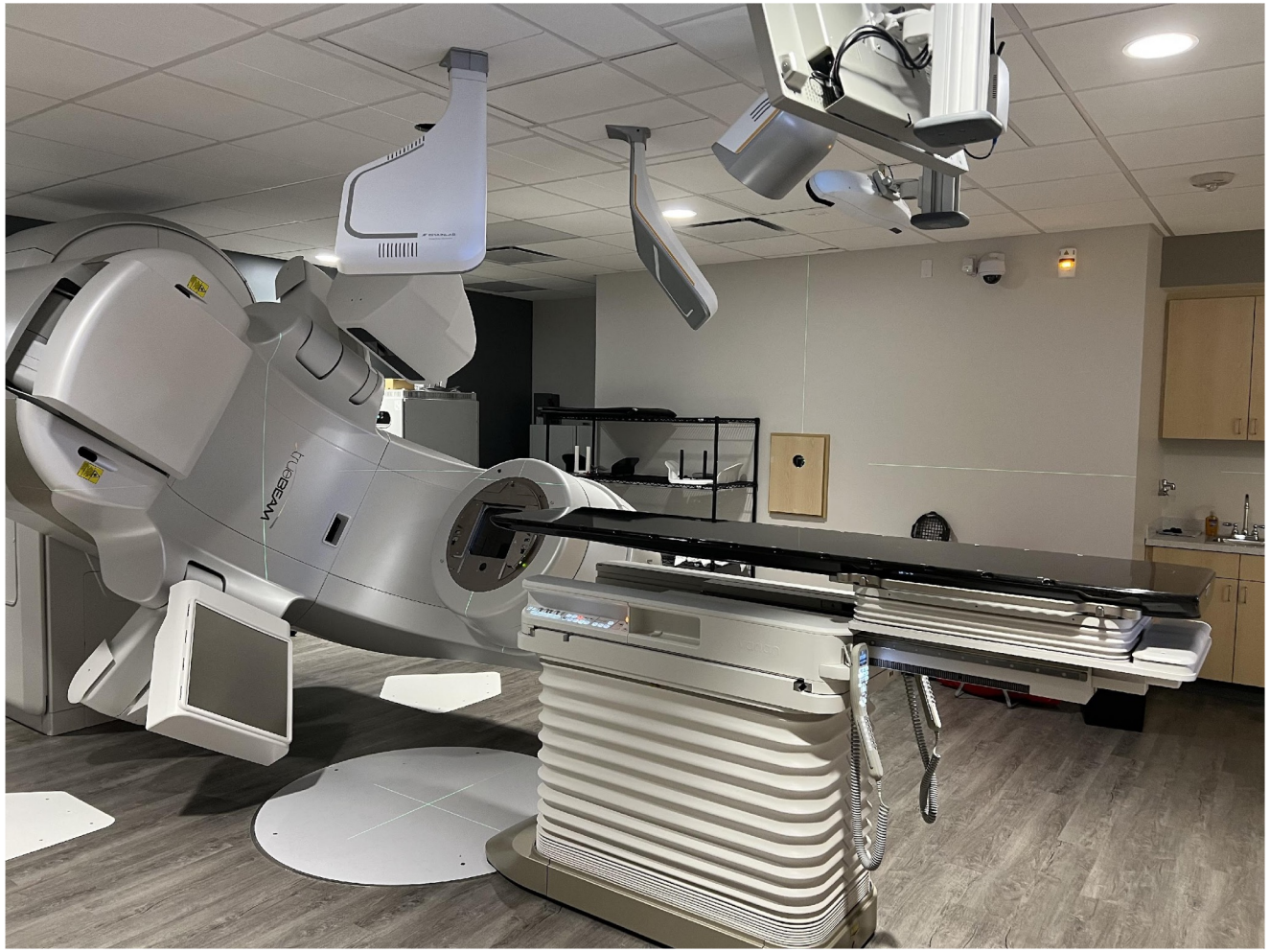
Boulder Community Health



ROCKY MOUNTAIN™ CANCER CENTERS

RMCC Technology to Deliver EBRT/SBRT

Boulder Community Health



Varian TrueBeam (Edge)

- 6-degree-of-freedom couch
  - Adjust patient position in any direction
- High definition multileaf collimators (2.5 mm)
  - Shape radiation dose with much tighter margins and dose fall-off

ROCKY MOUNTAIN™ CANCER CENTERS

RMCC Technology to Deliver EBRT/SBRT

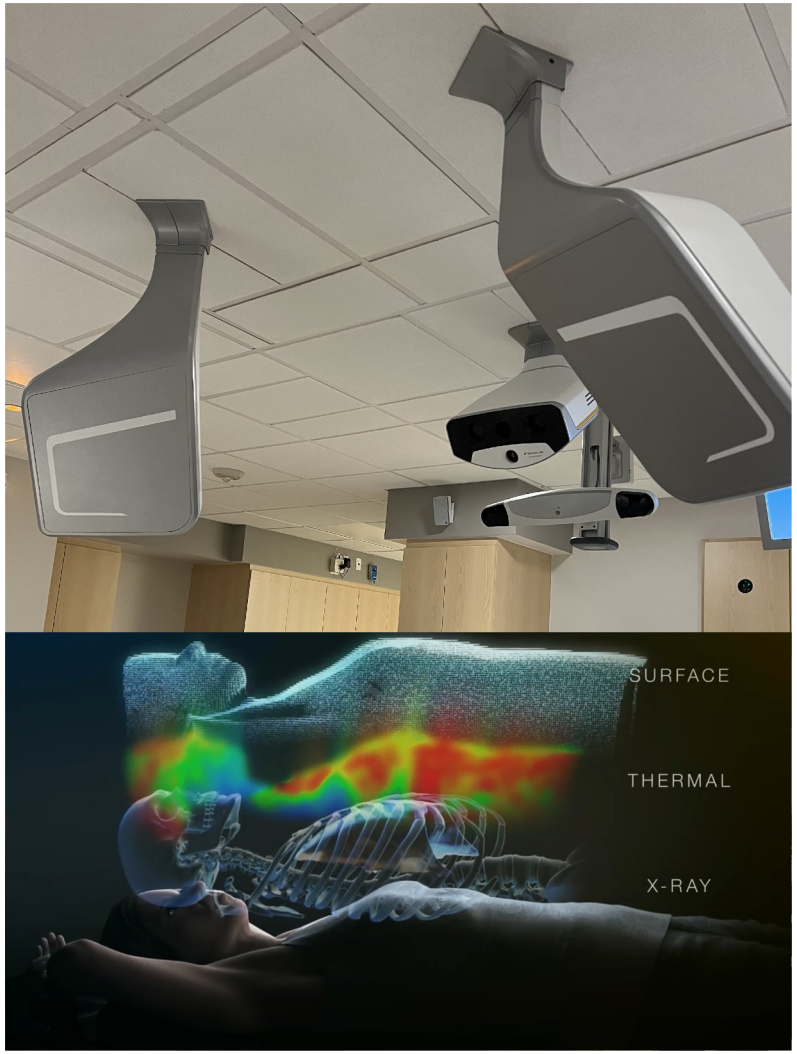
Boulder Community Health

Brainlab ExacTrac Dynamic

ROCKY MOUNTAIN™ CANCER CENTERS

RMCC Technology for Accurate & Reproducible Targeting

Boulder Community Health



Brainlab ExacTrac Dynamic

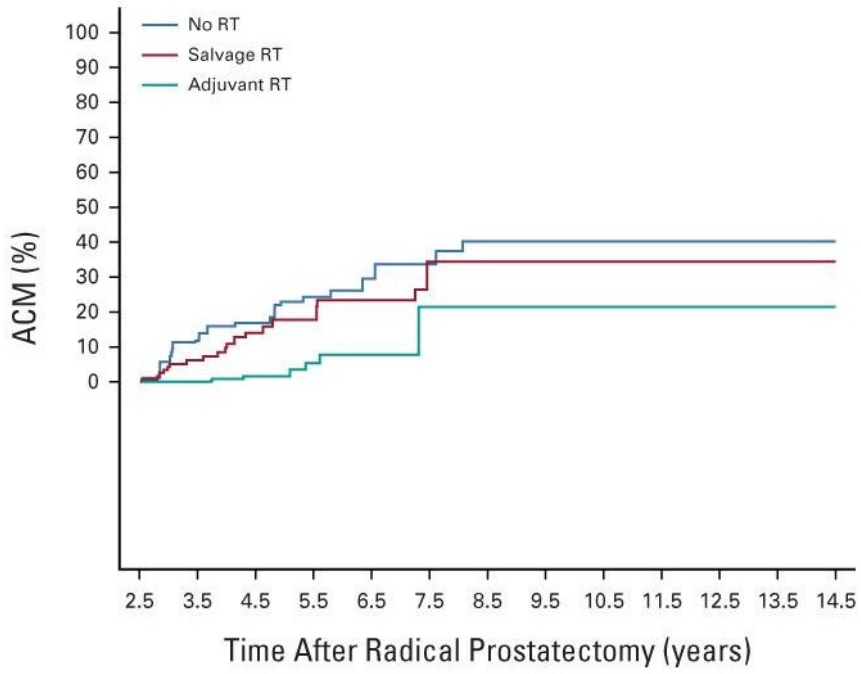
- Patient motion and position monitoring on four levels
  - Surface guidance
  - Thermal guidance
  - X-ray guidance
  - Real-time tracking/monitoring during treatment
- Allows for better precision and accuracy of setup and dose delivery

ROCKY MOUNTAIN™ CANCER CENTERS

Treatment: High & Very High Risk

Boulder Community Health

- **Unlike low / intermediate** risk disease where we know **radiation** and **surgery** lead to **equivalent** outcomes (**ProtecT** trial), **high** and **very high-risk** disease there is **no head-to-head comparison**
- Category 1: **Radiation + androgen deprivation therapy** +/- **abiraterone**
- Category 2A: **Prostatectomy + lymph node dissection**
  - High risk of needing radiation and/or androgen deprivation therapy afterwards
  - One such risk factor: Lymph node positive disease after surgery treated with immediate radiation improves survival (Category 2B)



ROCKY MOUNTAIN™ CANCER CENTERS

Tilki et al., *J Clin Oncol* (2022)

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- **Is more better?**
  - Surgery +/- radiation +/- androgen deprivation therapy vs. radiation + androgen deprivation therapy
    - Ongoing SPCG-15 trial

ROCKY MOUNTAIN™ CANCER CENTERS

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- **Is more better?**
  - Surgery +/- radiation +/- androgen deprivation therapy vs radiation + androgen deprivation therapy
    - Ongoing SPCG-15 trial
  - Radiation + androgen deprivation therapy + chemotherapy
    - D'Amico & Dana Farber Cancer Institute: No difference in overall survival
    - Sartor RTOG 0521: No difference in overall survival

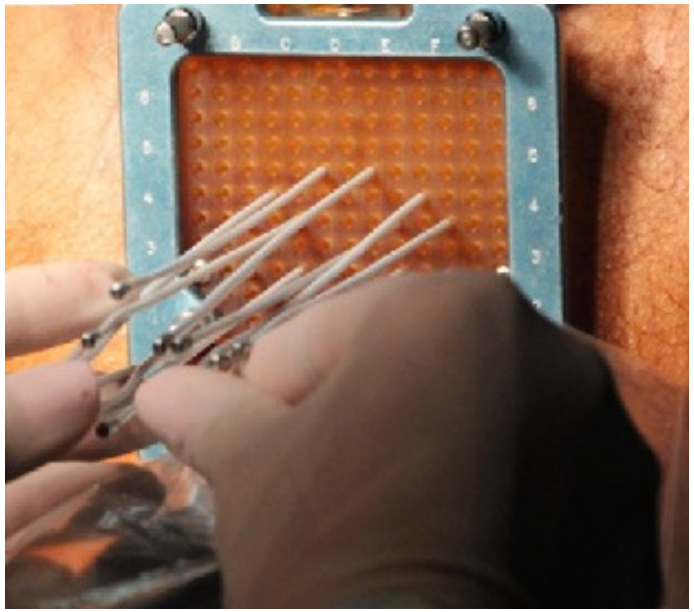
ROCKY MOUNTAIN™ CANCER CENTERS

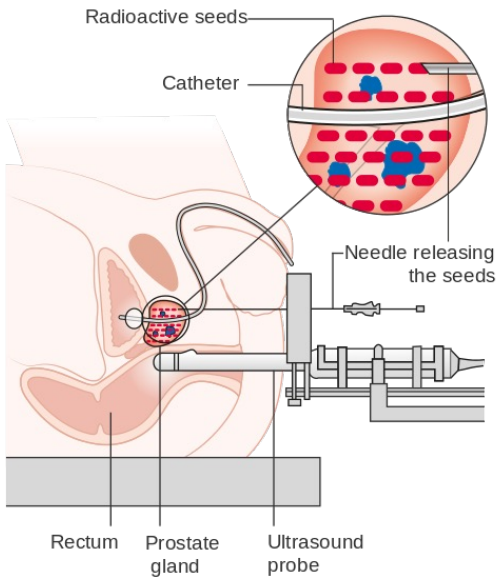
D'Amico et al., *J Clin Oncol* (2021); Sartor et al., *Eur Urol* (2023)

Treatment: High & Very High Risk

Boulder Community Health

- **Boost technique**: Increasing dose to the prostate
  - **Low dose rate brachytherapy** (permanent radioactive seed implants after external beam initially)
    - ASCENDE-RT trial: EBRT+LDR boost vs. EBRT alone
      - LDR boost with better 10-year biochemical (PSA) control rates
      - No difference in 10-year distant metastasis or overall survival
      - Higher toxicity with LDR (Grade ≥3 GU toxicity ~5% vs ~19%, worse patient-reported outcomes)





ROCKY MOUNTAIN CANCER CENTERS™

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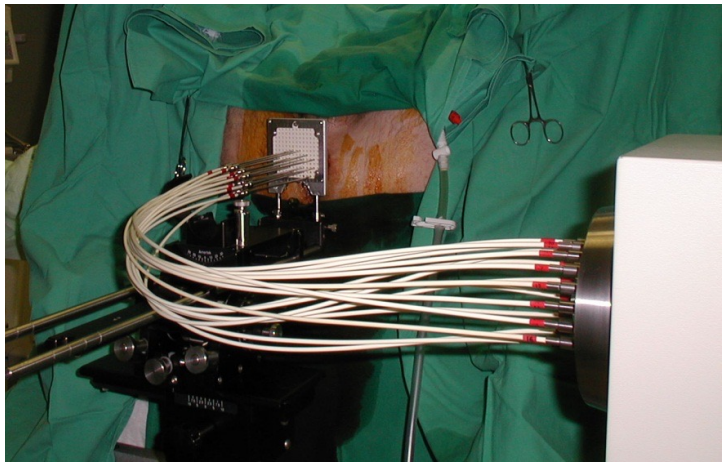
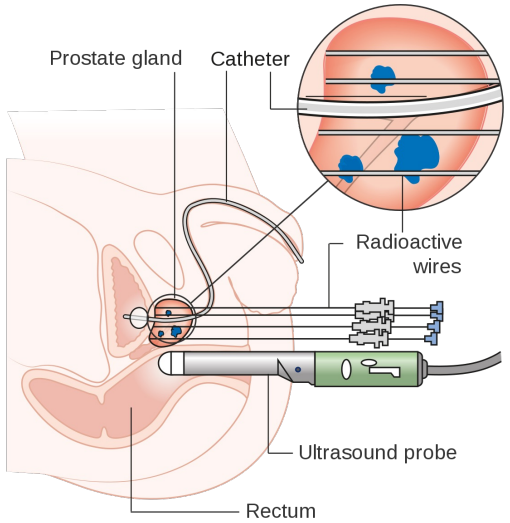
  - **High dose rate brachytherapy** (temporary catheters after external beam initially)
    - Two outpatient invasive procedures; user dependent





Treatment: High & Very High Risk

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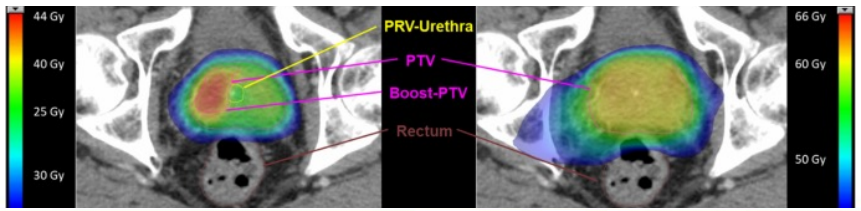
      - Higher toxicity with LDR (Grade ≥3 GU toxicity ~5% vs ~19%, worse patient-reported outcomes)
  - **High dose rate brachytherapy** (temporary catheters after external beam initially)
    - Two outpatient invasive procedures; user dependent
  - **Stereotactic boost** (SBRT/SABR after external beam initially)
    - Two to three non-invasive treatments
    - No randomized evidence comparing to other boost approaches (similar on UCSF analysis)
  - **FLAME** (focal lesion ablative micro-boost)
    - Simultaneous integrated boost CONCURRENT with external beam phase (higher dose to lesions seen on MRI)
    - Excellent 5-year biochemical control 92% (improved compared to standard dosing external boost)
    - Limited based on anatomy (urethra, bowel)



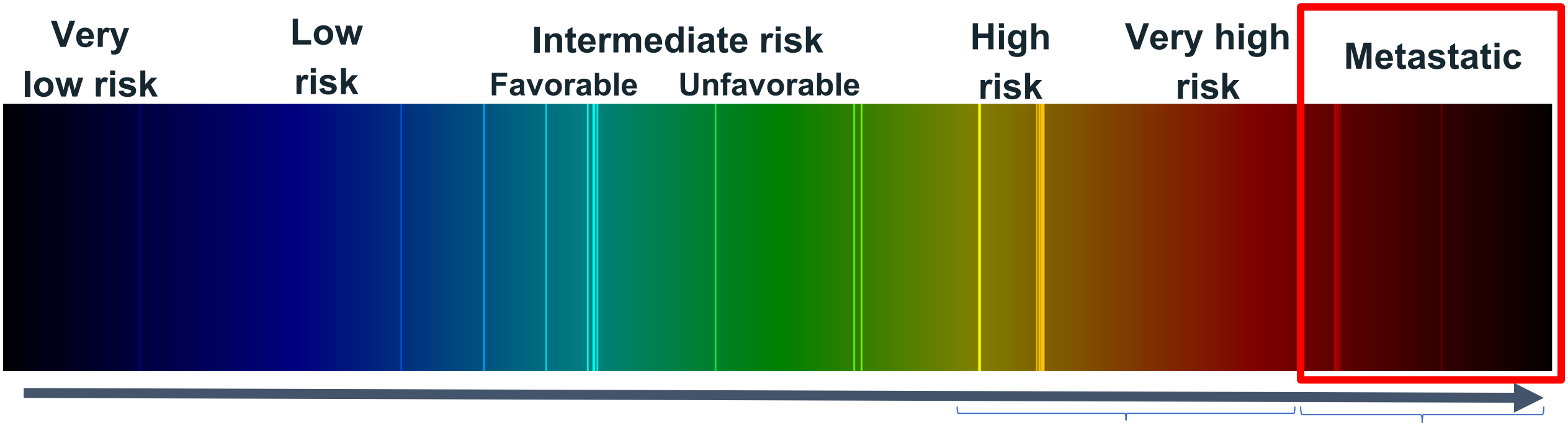
ROCKY MOUNTAIN CANCER CENTERS™

Oh et al., *IJROBP* (2023); Mendez et al., *Transl Androl Urol* (2018); Prada et al., *Radiother Oncol* (2016); Cancer Research UK; Chen et al., *IJROBP* (2021); Kerkmeijer et al., *J Clin Oncol* (2021);

Clinical Risk Grouping

Boulder Community Health

- Treating the **primary** site (prostate) and/or **metastatic sites** of disease



ROCKY MOUNTAIN™ CANCER CENTERS

Treatment: Metastatic

Boulder Community Health

- **Metastatic hormone sensitive prostate cancer (mHSPC)**
- **Metastatic castration resistant prostate cancer (mCRPC)**

ROCKY MOUNTAIN™ CANCER CENTERS

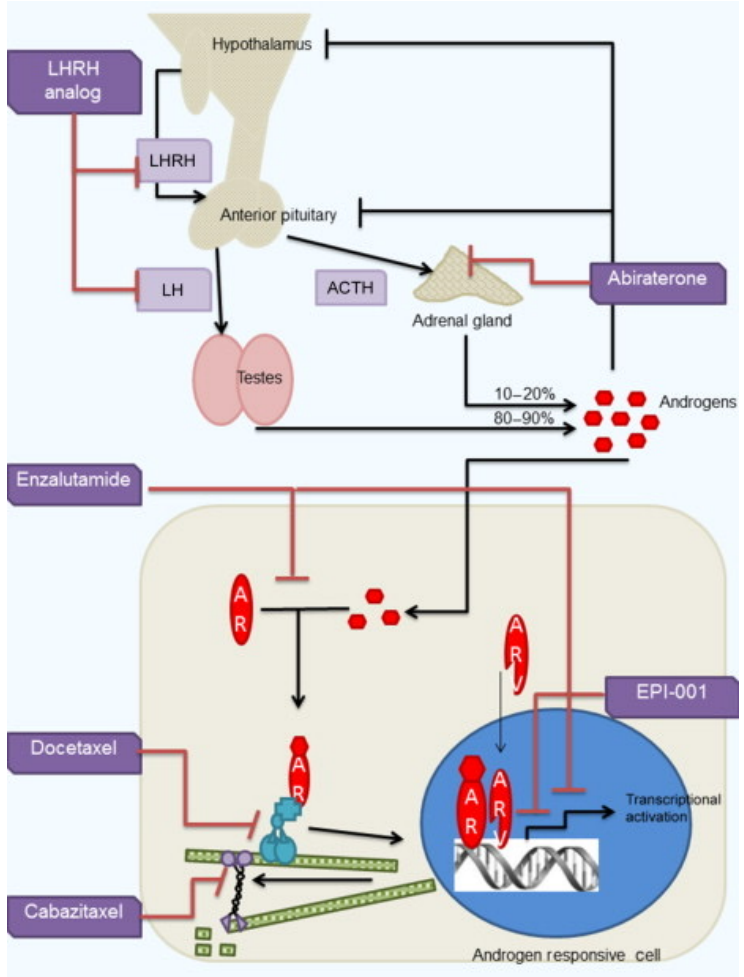
Metastatic Landscape: mHSPC

Boulder Community Health

- **ADT – Huggins and Hodges** (1941)

- **ADT + Docetaxel – CHAARTED** (2015)
- **ADT + Abiraterone – LATITUDE** (2017)
- **ADT + Apalutamide – TITAN** (2019)
- **ADT + Enzalutamide – ENZAMET** (2019)

- **ADT + Darolutamide + Docetaxel – ARASENS** (2022)



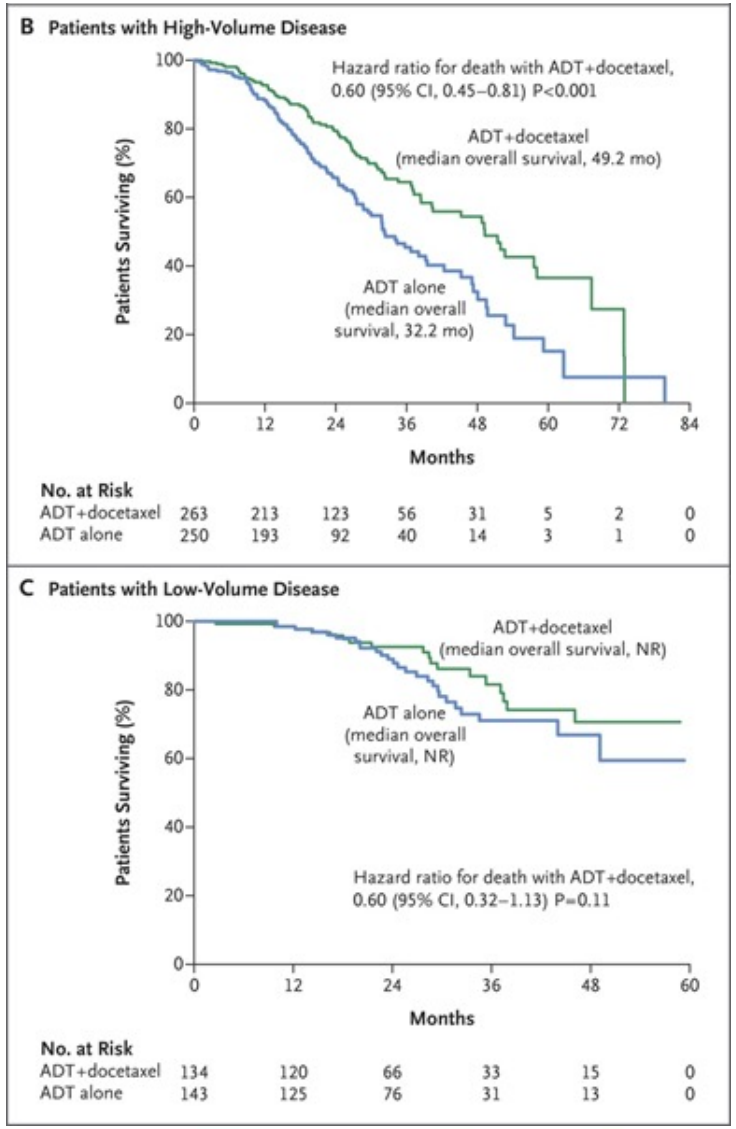
ROCKY MOUNTAIN CANCER CENTERS™

Martin et al., *Adv Cancer Res* (2015)

mHSPC: CHAARTED

Boulder Community Health

- Assess the impact of the **addition** of **six cycles** of **docetaxel to androgen-deprivation therapy** in patients with **metastatic** prostate cancer
- **High volume** disease
  - Presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis
- **Low volume** disease



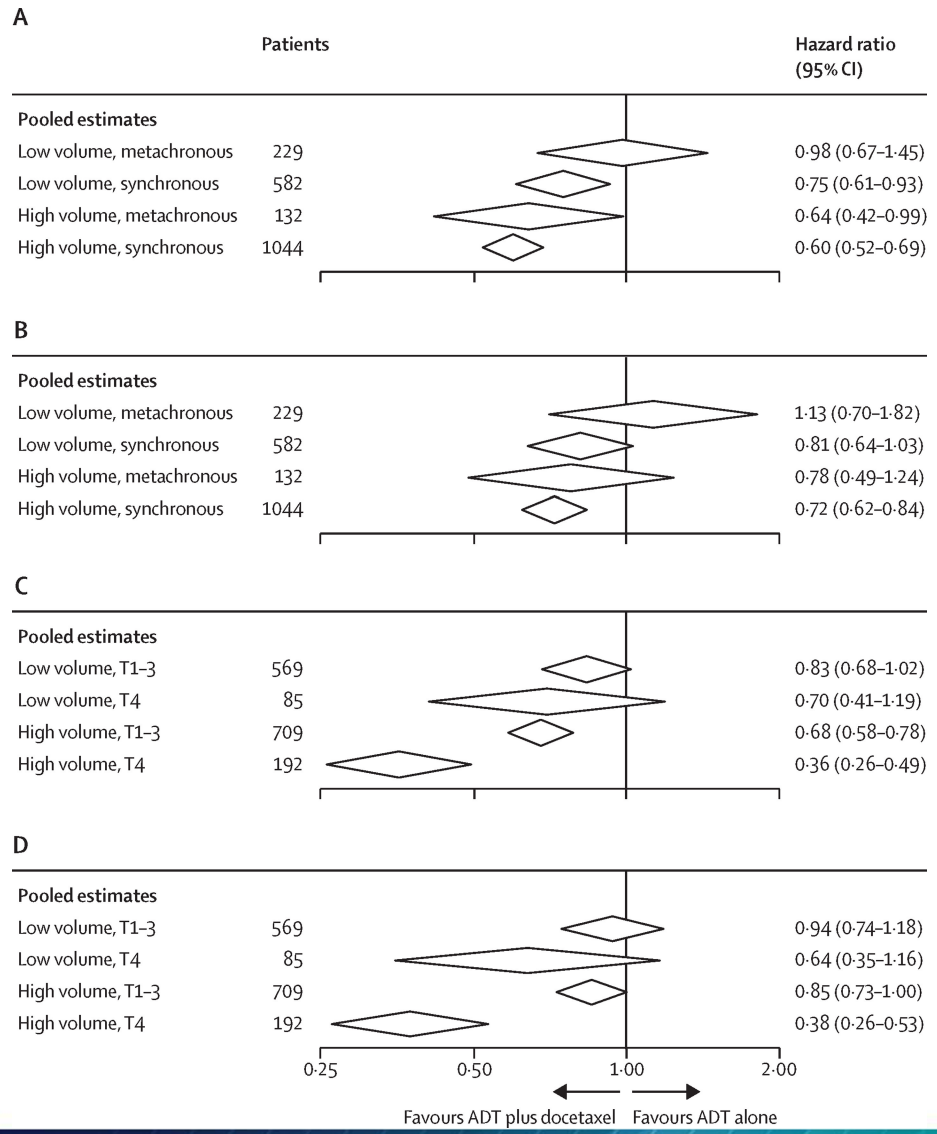
ROCKY MOUNTAIN CANCER CENTERS™

Sweeney et al., *N Eng J Med* (2015)

mHSPC: Docetaxel Meta-Analysis

Boulder Community Health

- **Meta-analysis** of addition of **docetaxel** for metastatic prostate cancer from **GETUG-AFU15**, **CHAARTED**, and **STAMPEDE** trials



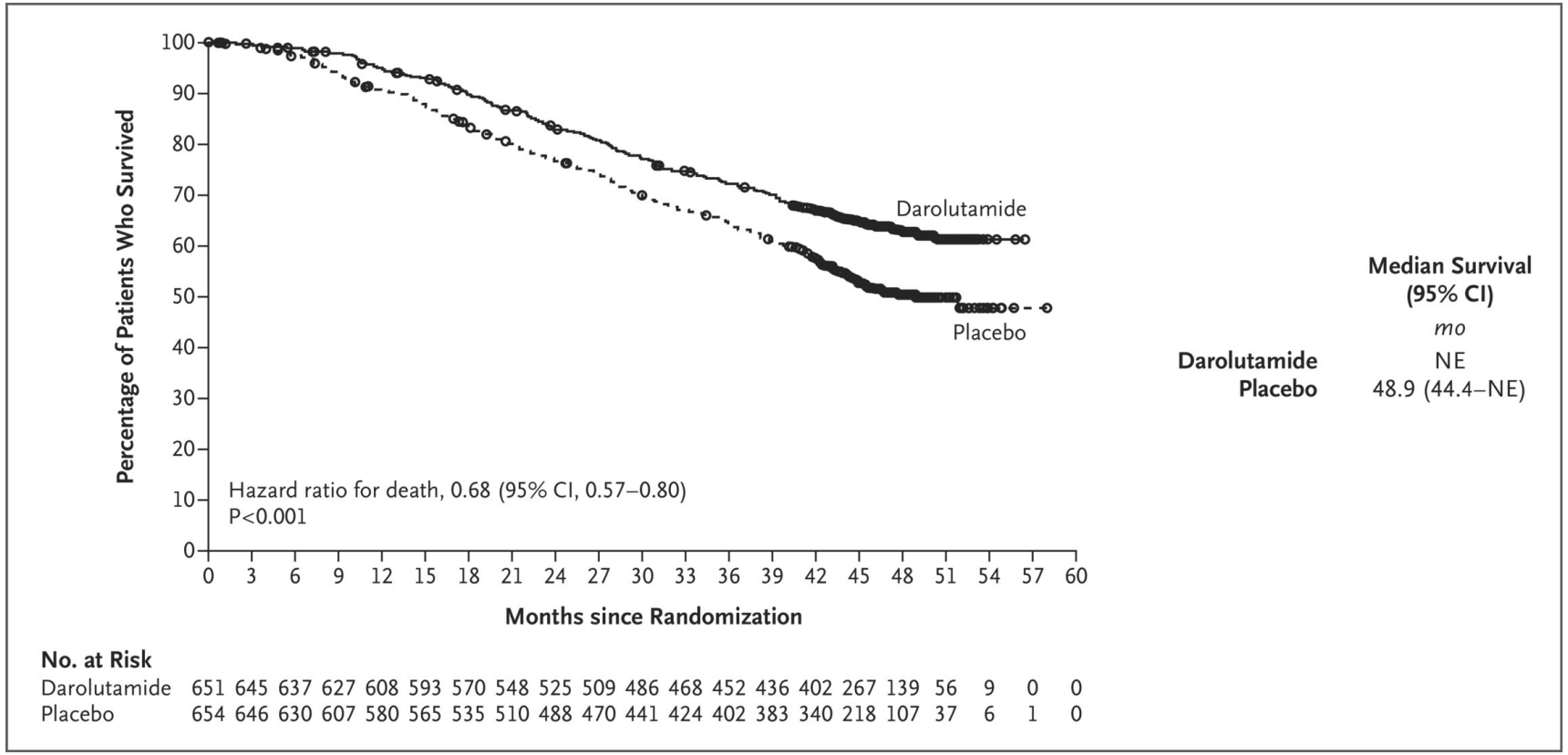
ROCKY MOUNTAIN CANCER CENTERS™

Vale et al., *Lancet Oncol* (2023)

mHSPC: ARASENS

Boulder Community Health

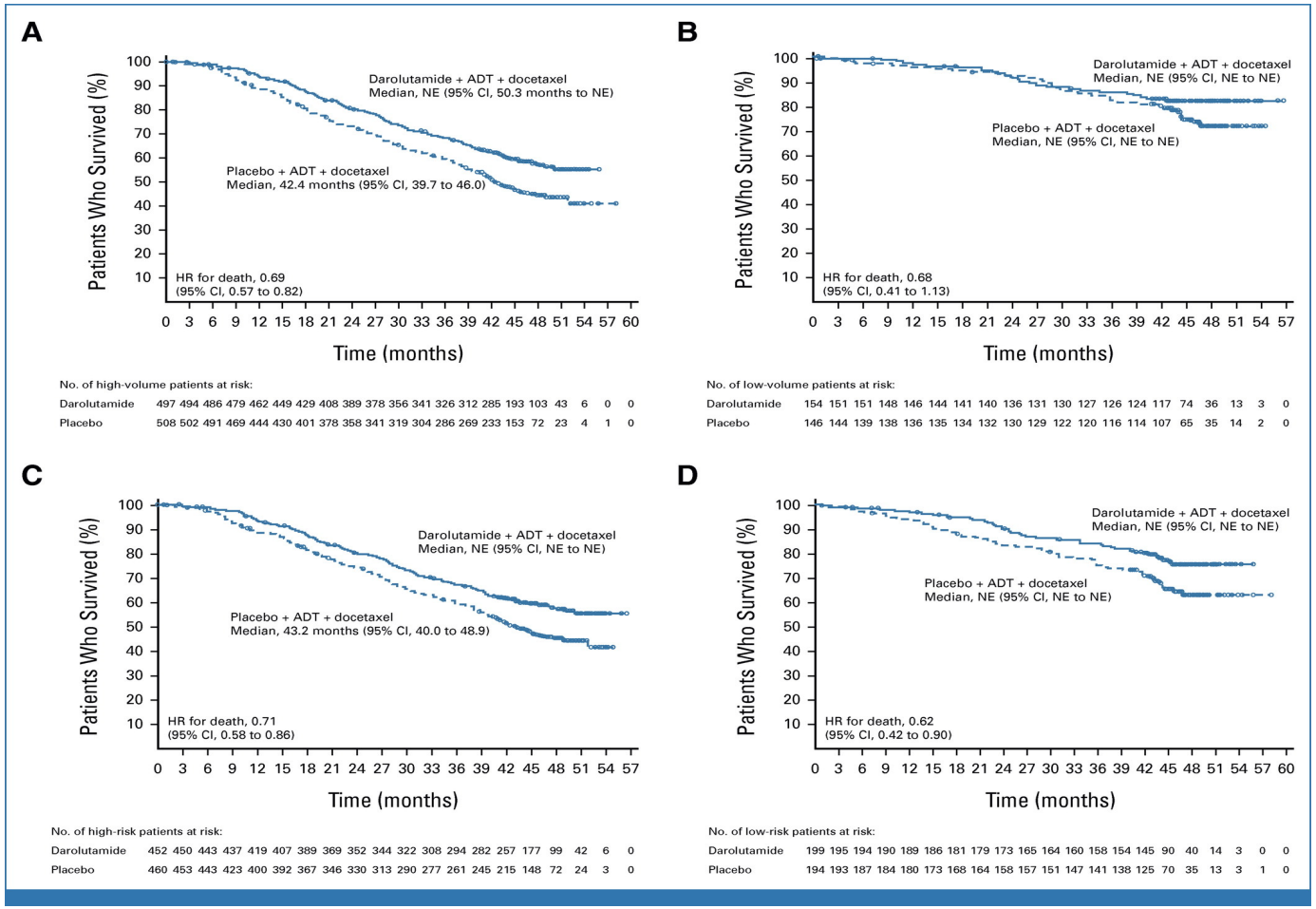
- Assess the impact of the **addition** of **darolutamide** with androgen-deprivation therapy and docetaxel with **metastatic** prostate cancer



ROCKY MOUNTAIN CANCER CENTERS™

Smith et al., *N Eng J Med* (2022)

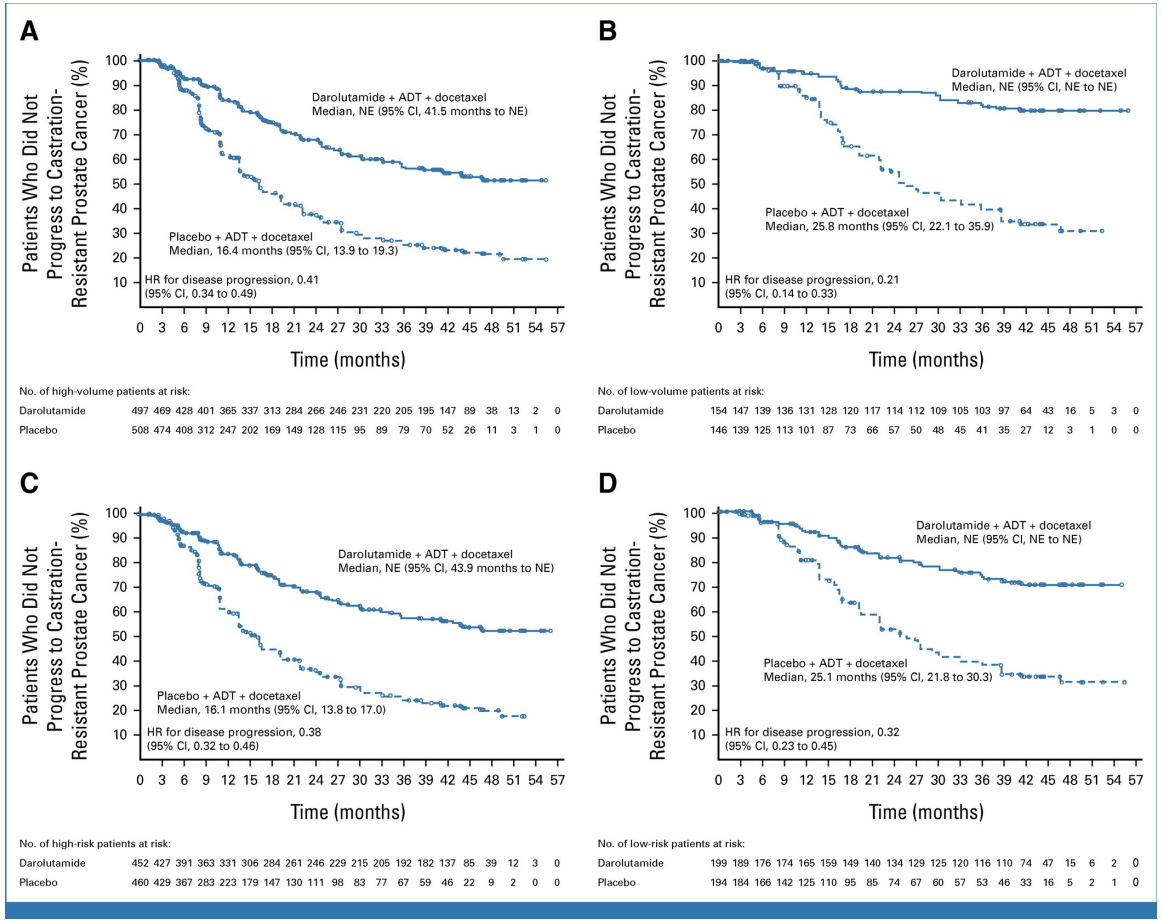
mHSPC: ARASENS



OS in subgroups of patients by (A) high-volume, (B) low-volume, (C) high-risk, and (D) low-risk disease. High-volume disease was defined as the presence of visceral metastases or ≥ 4 bone lesions with ≥ 1 beyond the vertebral bodies and pelvis. High-risk disease was defined by two of the following three risk factors: Gleason score ≥ 8, ≥ 3 bone lesions, and measurable visceral metastases.

Hussain et al., *J Clin Oncol* (2023)

mHSPC: ARASENS



Time to castration-resistant prostate cancer in subgroups of patients by (A) high-volume disease, (B) low-volume disease, (C) high-risk disease, and (D) low-risk disease in ARASENS.
High-volume disease was defined as the presence of visceral metastases or ≥ 4 bone lesions with ≥ 1 beyond the vertebral bodies and pelvis. High-risk disease was defined by two of the following three risk factors: Gleason score ≥ 8, ≥ 3 bone lesions, and measurable visceral metastases.

Hussain et al., *J Clin Oncol* (2023)

Metastatic: Effect of BRCAness

Boulder Community Health

- **BRCAness** refers to the presence of any **defect in DNA-repair genes** (BRCA1/2, FANCD2, CKD12, and ATM)
- The **relative risk** of developing **prostate cancer** for men with **germline BRCA1** mutations who are **aged <65** years is **1.8** and is **8.6** in men with germline **BRCA2** mutations
- **Loss of function in DNA-repair genes** in prostate cancer was associated with **higher incidence** of **nodal** involvement, **metastasis** or **T4** stage

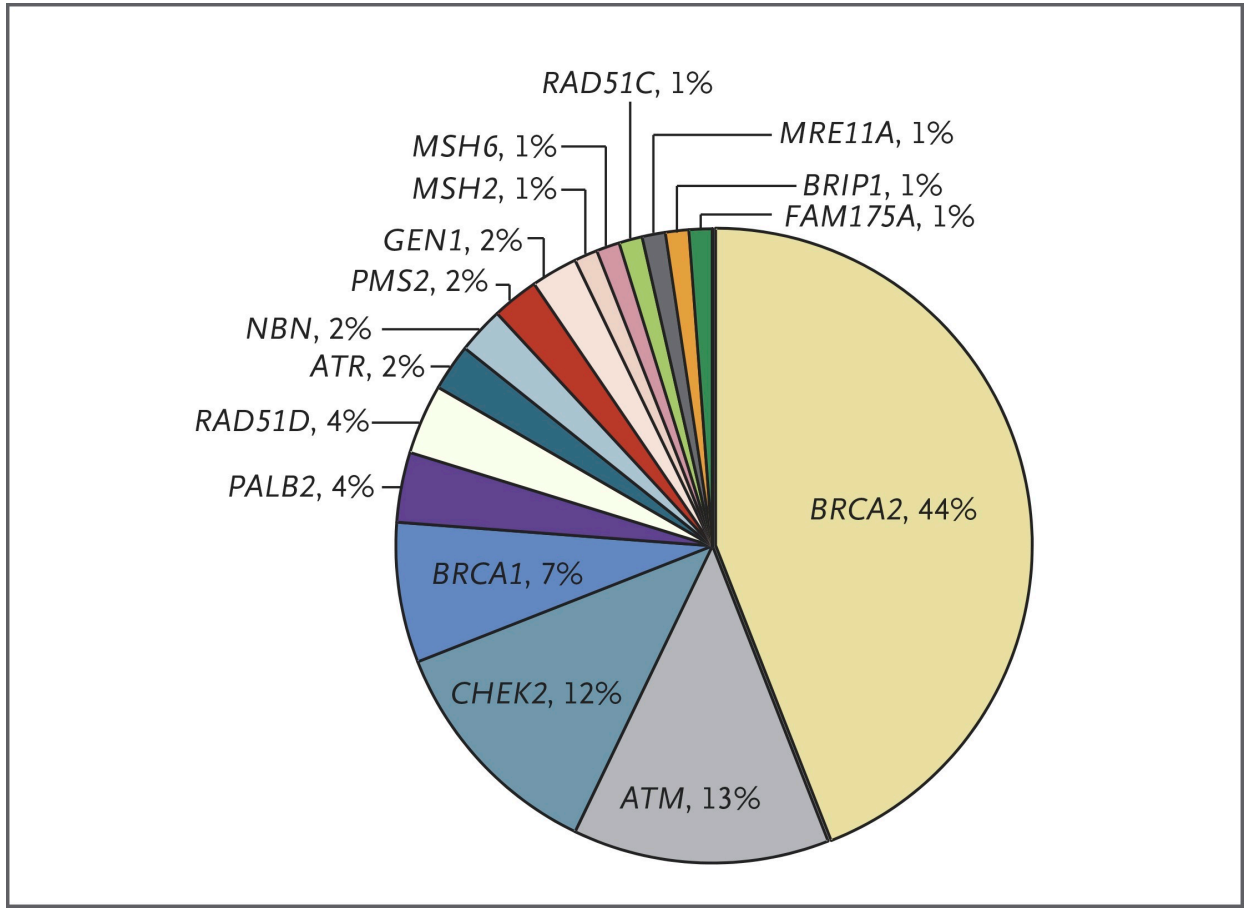
ROCKY MOUNTAIN™ CANCER CENTERS

Rimar et al., *Cancer* (2017); Castro et al., *Asian J Androl* (2012); Leongamornlert et al., *Br J Cancer* (2014)

Metastatic: Effect of BRCAness

Boulder Community Health

- Pritchard et al used **whole-exome sequencing** or **targeted next-generation sequencing** assays in a large population of men with biopsy-proven **metastatic prostate cancer** and found that **11.8% had at least 1 presumed pathogenic germline mutation**



ROCKY MOUNTAIN CANCER CENTERS™

Pritchard et al., *N Eng J Med* (2016)

mCRPC: TRITON 3

Boulder Community Health

- Randomized, controlled, phase 3 trial
- Metastatic, **castration-resistant** prostate cancer with a **BRCA1, BRCA2, or ATM** alteration and who had disease **progression** after treatment with a **second-generation androgen-receptor pathway inhibitor** (ARPI)
- Randomly assigned the patients in a 2:1 ratio to receive **oral rucaparib** (600 mg twice daily) or a **physician's choice control** (docetaxel or a second-generation ARPI [abiraterone acetate or enzalutamide]).

ROCKY MOUNTAIN™ CANCER CENTERS

Fizazi et al., *N Eng J Med* (2023)

Cross-Resistance Between Abiraterone and Enzalutamide

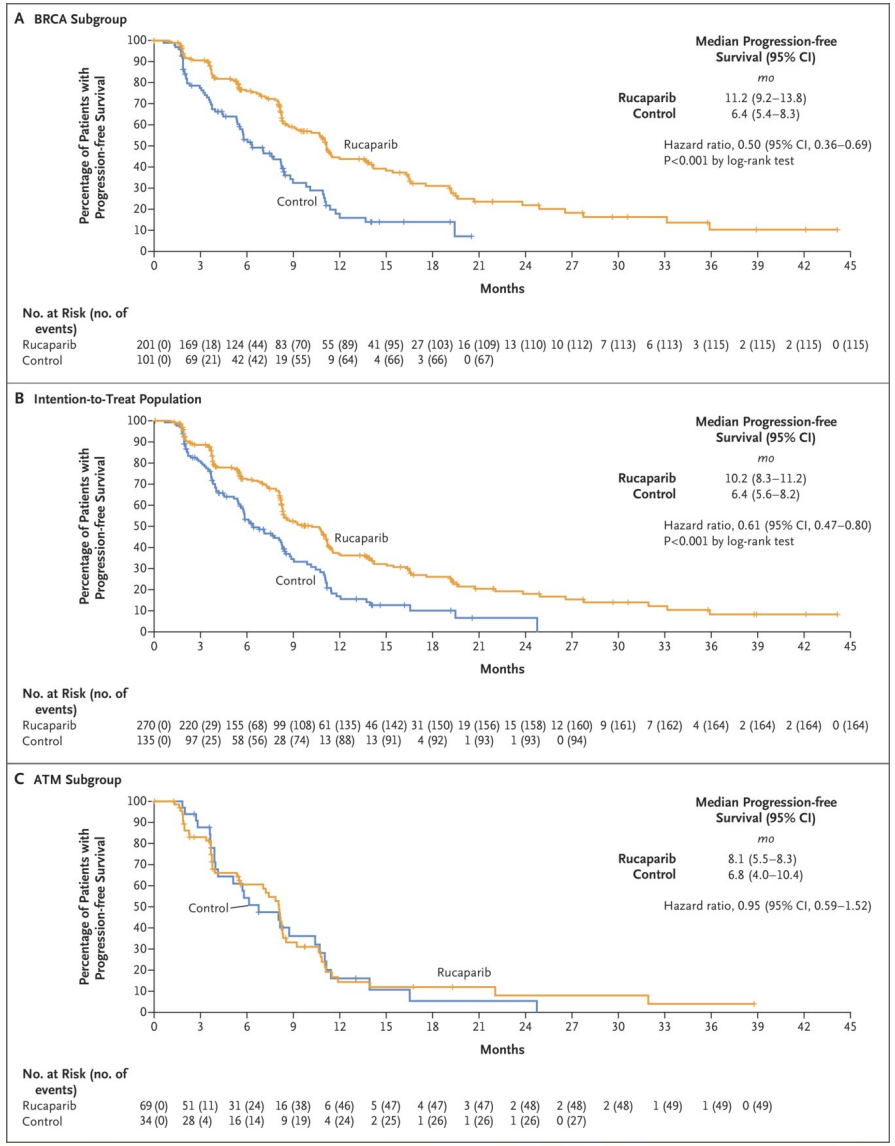
Boulder Community Health

Study	Therapy	Prior Therapy	PSA_{50} (%)	ORR (%)	PFS (months)
Noonan et al[1]	Abiraterone	Enzalutamide	4	0	3.9
Loriot et al[2]	Abiraterone	Enzalutamide	8	8	2.7
Smith et al[3]	Abiraterone	Enzalutamide			2.8
Schrader et al[4]	Enzalutamide	Abiraterone	28	3	---
Badrising et al[5]	Enzalutamide	Abiraterone	21	---	3.0
Cheng et al[6]	Enzalutamide	Abiraterone	20	---	---

ROCKY MOUNTAIN CANCER CENTERS™

Noonan et al., *Ann Oncol* (2013); Loriot et al., *Ann Oncol* (2013); Smith et al., *ASCO GU* (2014); Schrader et al., *Eur Urol* (2014); Badrising et al., *Cancer* (2014); Cheng et al., *ASCO* (2014)

mCRPC: TRITON 3



Fizazi et al., *N Eng J Med* (2023)

To Be Continued…

- **MAGNITUDE**: Abiraterone acetate/prednisone +/- niraparib
- **PROpel**: Abiraterone acetate/prednisone +/- olaparib
- **TALAPRO**: Enzalutamide +/- talazoparib

Fizazi et al., *N Eng J Med* (2023)

To Be Continued…

Boulder Community Health

- **MAGNITUDE**: Abiraterone acetate/prednisone +/- niraparib
- **PROpel**: Abiraterone acetate/prednisone +/- olaparib
- **TALAPRO**: Enzalutamide +/- talazoparib
- **COSMIC 021**:
  - Cabozantinib + Atezolizumab in mCRPC with soft tissue disease who had progressed on enzalutamide of abiraterone (132 patients)
  - 23% ORR with 3 CRs and 28 PRs
  - This phase 1 trial set stage for immunotherapy combinations which may “awaken” the immune system in an otherwise immunotherapy “cold” tumor

ROCKY MOUNTAIN™ CANCER CENTERS

Fizazi et al., *N Eng J Med* (2023)

Treatment: Metastatic

Boulder Community Health

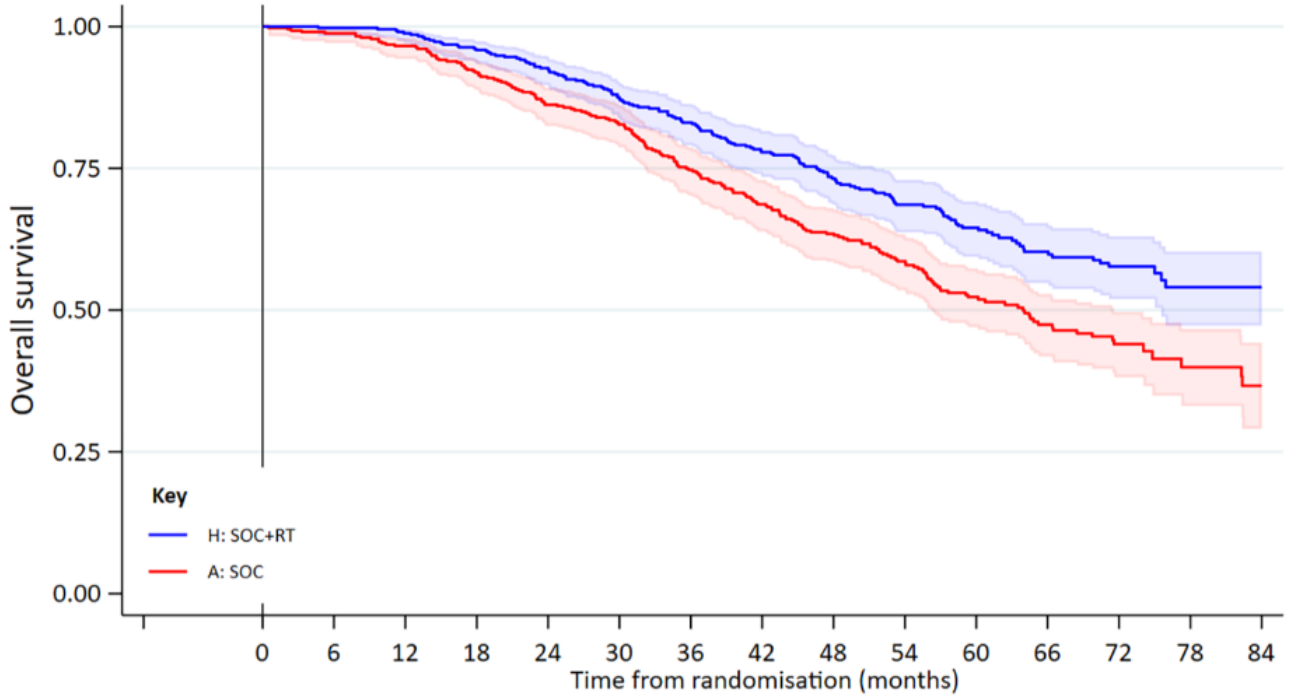
Does radiation have a role in metastatic prostate cancer?

ROCKY MOUNTAIN™ CANCER CENTERS

Treatment: Metastatic

Boulder Community Health

- **STAMPEDE** Trial
  - ↑ **Overall survival** in newly diagnosed **low-burden** (**≤3 bone mets**; no visceral) metastatic prostate cancer with addition of hypofractionated XRT (6 to 20 fractions) to the **prostate primary site** plus **standard of care systemic** treatment



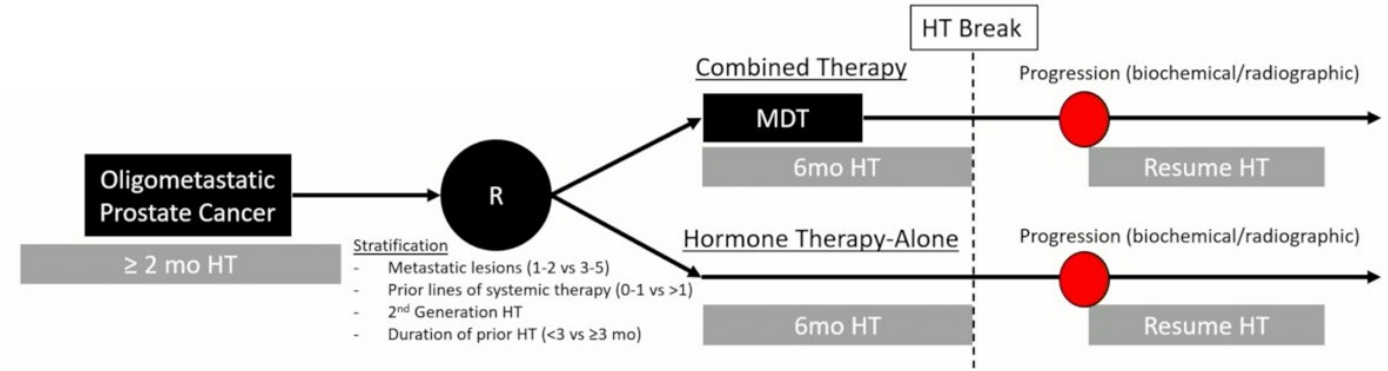
ROCKY MOUNTAIN CANCER CENTERS™

Parker et al., *PLoS Med* (2022) & *Lancet* (2018)

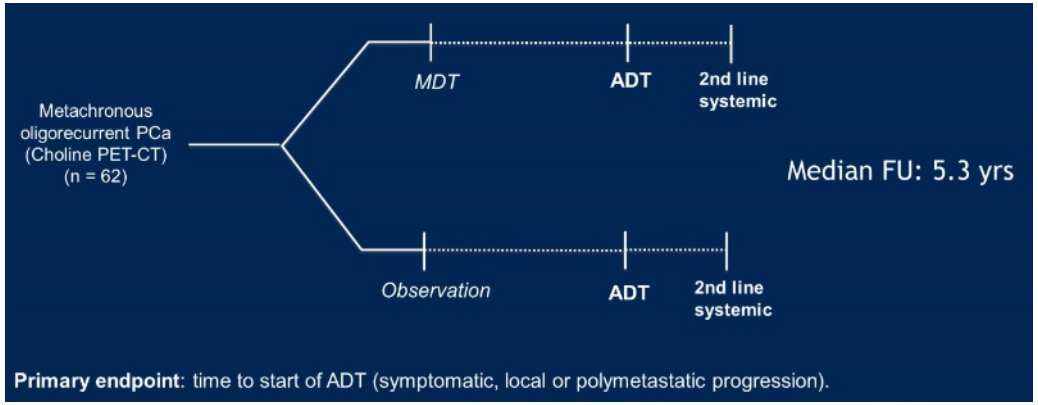
Treatment: Metastatic

Boulder Community Health

- Phase II **STOMP**, **ORIOLE**, and **EXTEND** trials
  - **STOMP** and **ORIOLE**: 1-3 metastases randomized to observation vs stereotactic radiation



  - **EXTEND**: 1-5 metastases randomized to 6mo ADT + stereotactic radiation vs 6mo ADT



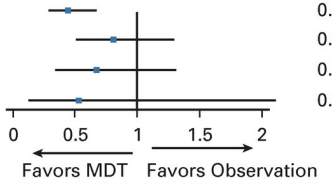
ROCKY MOUNTAIN CANCER CENTERS™

Deek et al., *J Clin Oncol* (2022); Tang et al., *JAMA Oncol* (2023)

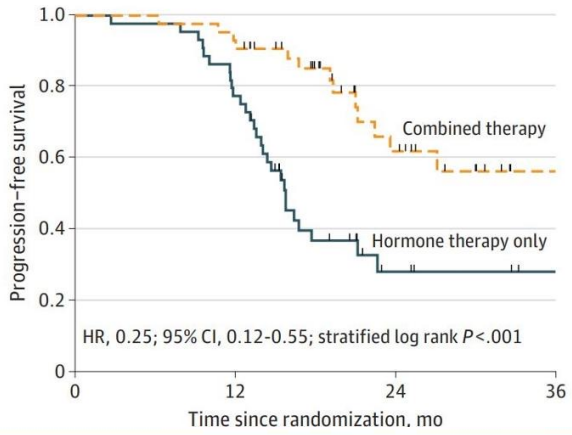
Treatment: Metastatic

- Phase II **STOMP**, **ORIOLE**, and **EXTEND** trials
  - **STOMP** and **ORIOLE**: ↑ **Median progression-free survival** and **delay to initiation of ADT** with stereotactic radiation directed at metastatic sites of disease in patients with 1-3 mets vs observation alone

Outcome	MDT Median Time to Event, months (95% CI)	Observation Median Time to Event, months (95% CI)	HR (95% CI)	*P*
PFS	11.9 (8 to 18.3)	5.9 (3.2 to 7.1)	0.44 (0.29 to 0.66)	< .001
rPFS	18.3 (12 to 36)	17 (13 to 22.8)	0.81 (0.50 to 1.29)	.37
CRPC	NR (62 to NR)	63 (53.9 to NR)	0.67 (0.34 to 1.31)	.24
OS	NR (84 to NR)	NR (73 to NR)	0.53 (0.13 to 2.11)	.36



  - **EXTEND**: ↑ **Median progression-free survival** with addition of stereotactic radiation

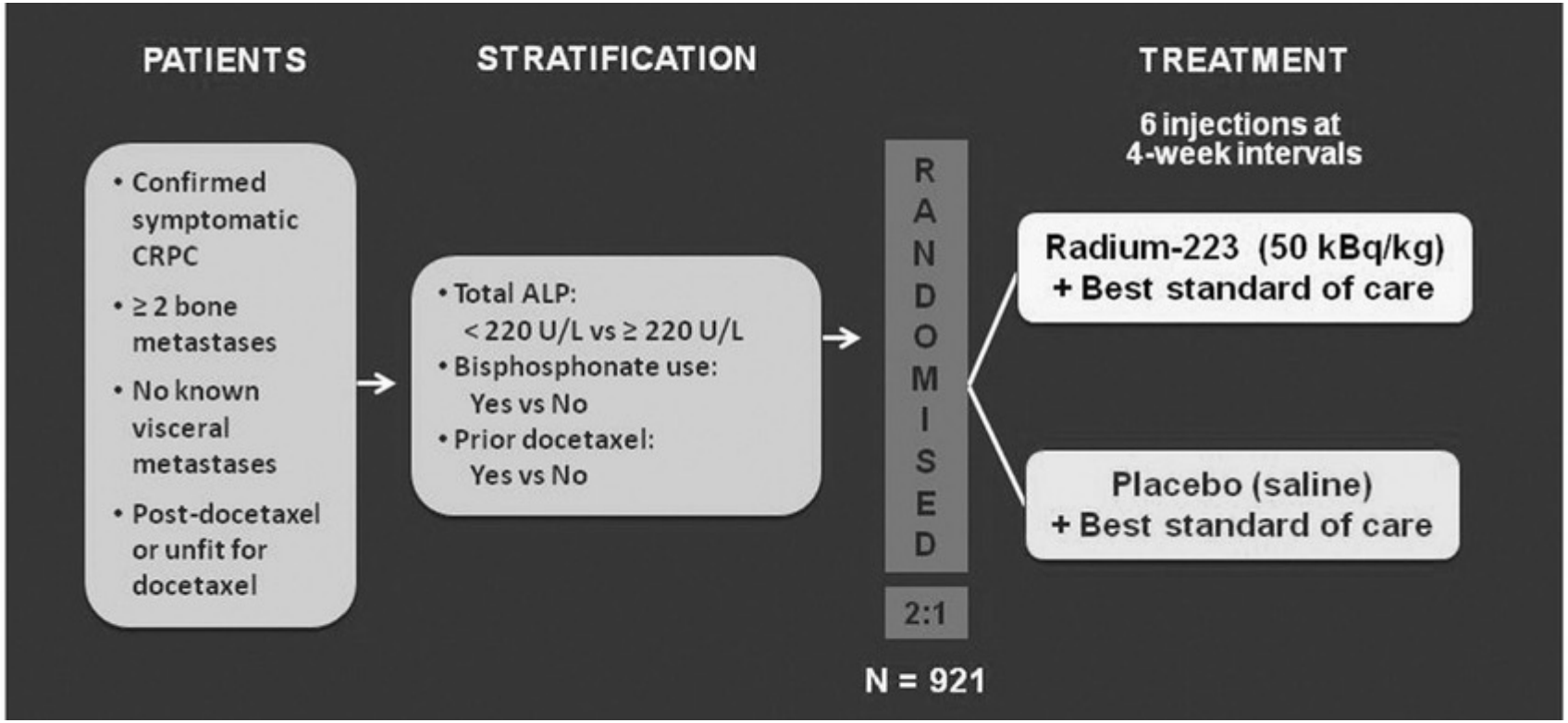


Deek et al., *J Clin Oncol* (2022); Tang et al., *JAMA Oncol* (2023)

Treatment: Metastatic

Boulder Community Health

- Phase III **ALSYMPCA** (not oligometastatic)



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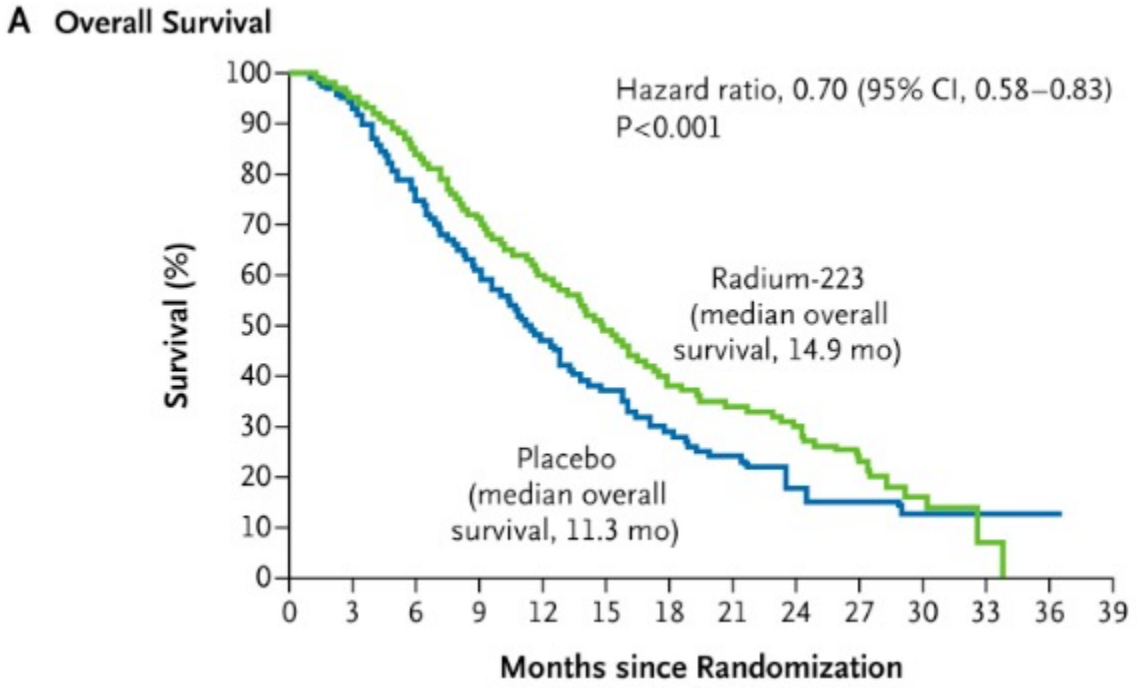
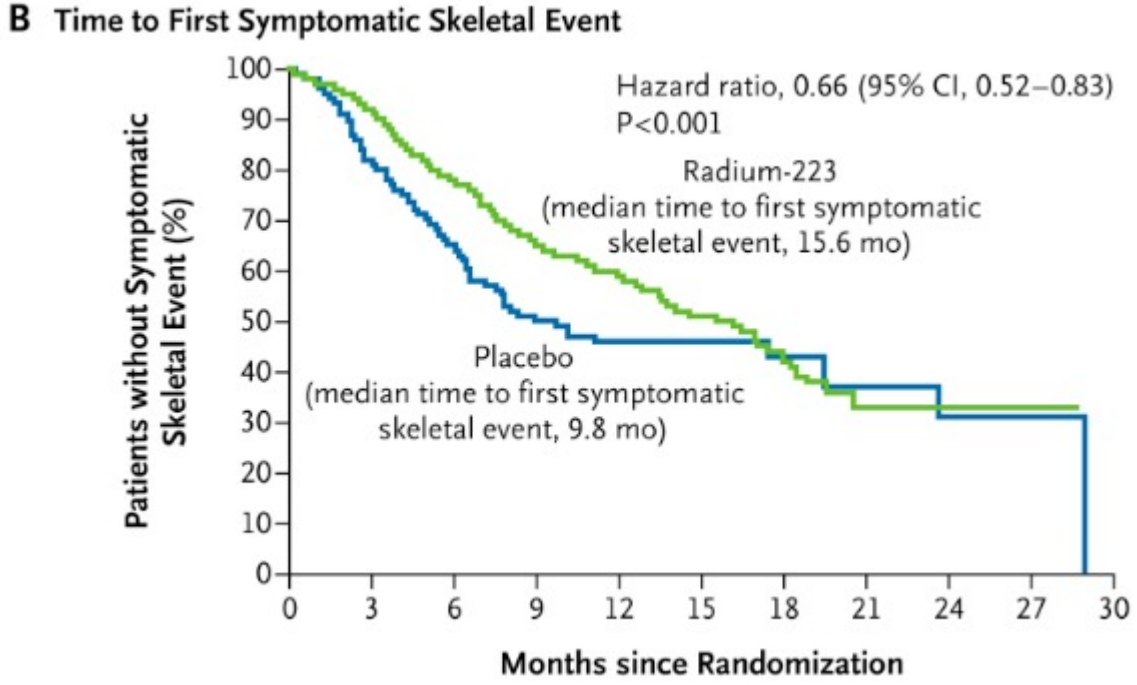
Hossein et al., *Clin Nucl Med* (2013)

Treatment: Metastatic

Boulder Community Health

- Phase III **ALSYMPCA** (not oligometastatic)
  - ↑ **Overall survival** and ↓ **skeletal events** in metastatic prostate cancer with 2+ bone metastases on skeletal scintigraphy and no known visceral metastases who received 223-Radium vs standard of care





Parker et al., *N Engl J Med* (2013)

Treatment: Metastatic

Boulder Community Health

- Phase III **VISION** (not oligometastatic)

Eligible patients

- Previous treatment with <u>both</u>
  - ≥ 1 androgen receptor pathway inhibitor
  - 1 or 2 taxane regimens
- Protocol-permitted standard of care (SOC) planned before randomization
  - Excluding chemotherapy immunotherapy, radium-223, investigational drugs
- ECOG performance status 0–2
- Life expectancy > 6 months
- PSMA-positive mCRPC on PET/CT with ^{68}Ga-PSMA-11

2:1

Protocol-permitted SOC + ^{177}Lu-PSMA-617
7.4 GBq (200 mCi) every 6 weeks
4 cycles, increasable to 6

Protocol-permitted SOC alone

Treatment → Follow-up → Final analysis

- Randomization stratified by
  - ECOG status (0–1 or 2)
  - LDH (high or low)
  - Liver metastases (yes or no)
  - Androgen receptor pathway inhibitors in SOC (yes or no)

- CT/MRI/bone scans
  - Every 8 weeks (treatment)
  - Every 12 weeks (follow-up)
  - Blinded independent central review

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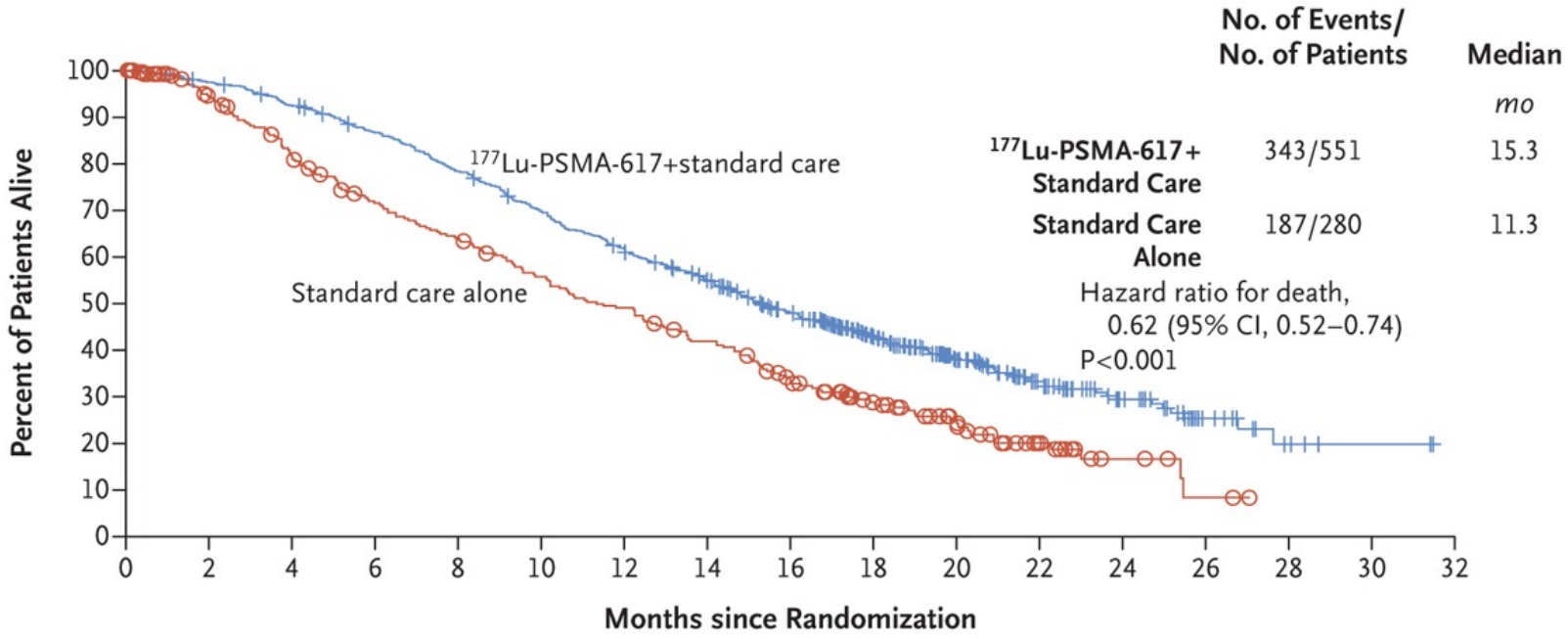
Sartor et al., *N Engl J Med* (2021)

Treatment: Metastatic

- Phase III **VISION** (not oligometastatic)
  - ↑ **Overall survival** in metastatic, castration-resistant prostate cancer with previous androgen receptor inhibitor and chemotherapy who received 177-Lu-PSMA vs standard of care alone



Sartor et al., *N Engl J Med* (2021)

Outline

Boulder Community Health

Diagnosing & Grouping

- Risk stratification
- Staging
- Imaging
- Genetic testing
- Additional work-up considerations

Treatment

- Radiation therapy
- Systemic therapy
- Radiopharmaceutical therapy

Clinical Trials

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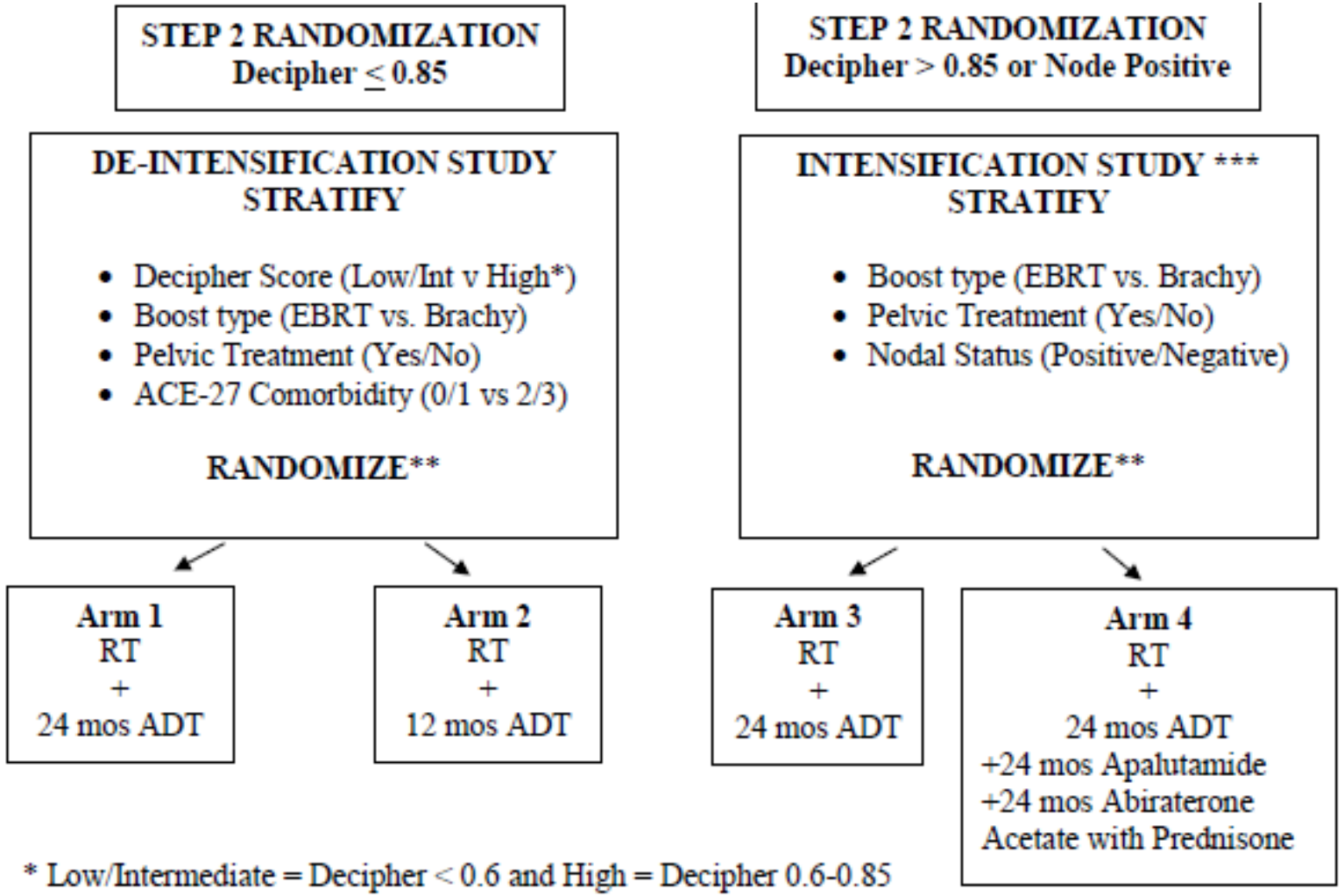
Clinical Trials

Boulder Community Health

- De-escalation vs. Escalation ADT for localized high-risk disease (PREDICT-RT)



* Low/Intermediate = Decipher < 0.6 and High = Decipher 0.6-0.85

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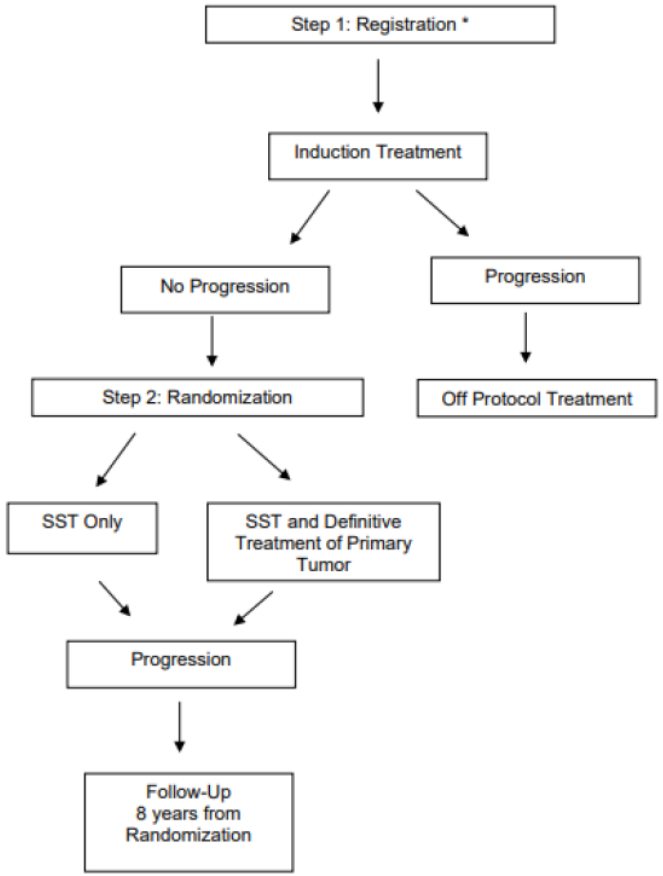
Clinical Trials

Boulder Community Health

- Role of radiation for metastatic prostate cancer
  - Treatment of prostate primary (**SWOG S1802**); oligo or non-oligometastatic
  - Metastasis-Directed Therapy (MDT) in oligometastatic disease (**NRG GU011**)

SWOG S1802



NRG-GU011

A Phase II Double-Blinded, Placebo-Controlled Trial of Prostate Oligometastatic Radiotherapy with or without Androgen Deprivation Therapy in Oligometastatic Prostate Cancer (NRG PROMETHEAN)

Schema

Recurrent Oligometastatic Prostate Cancer (detected by PET) after RT to Prostate or Radical Prostatectomy +/- Post-Operative Radiotherapy

STRATIFY

- Extrapelvic node(s) only vs Bone +/- node(s) [pelvic/extrapelvic]
- PSA Doubling Time <12 mos vs ≥ 12mos
- Fluciclovine PET vs PSMA PET

RANDOMIZE*

Arm 1	**Arm 2**
SABR + blinded placebo** for 6 months	SABR + blinded relugolix** for 6 months

*Randomization is 1:1

** Monitor according to Test Schedule; see Sections 4.2, 4.3, and 5.3.1 for progression. Salvage ADT should be delayed until metastatic progression by conventional imaging.

Clinical Trials

Boulder Community Health

- Castrate sensitive → role of androgen blocker (i.e. apalutamide/daralutamide)
  - ADT +/- Daralutamide recurrence after prostatectomy (**EA8191**)
  - ADT +/- apalutamide node positive (**NRG GU009 INNOVATE**)

- Castrate resistant → role of PARP inhibitors (DNA repair inhibitors)
  - Enzalutamide +/- rucaparib (**CASPAR** trial)

- Radiopharmaceuticals
  - Castrate resistant (chemo naïve) → Lu-PSMA-617 vs. abiraterone or enzalutamide (**PSMAfore** trial)
  - Castrate sensitive (chemo naïve) → ADT+ARPI +/- Lu-PSMA-617 (**PSMAddition** trial)

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Supportive Care/Integrative Care

Boulder Community Health

- Hormone deprivation can impact many major organ systems
  - Sexual health: lifestyle medicine
  - Muscle mass: lifestyle medicine; weight training; high protein diet
  - Bone density: calcium/Vit D; weight/resistance training
  - Cardiovascular health: lifestyle medicine (see below)
  - Joint health: acupuncture
  - Hot flashes/night sweats: acupuncture; bee pollen extract
- Lifestyle Medicine Program (CLIPP study: U of Arizona)
  - 24-week program improved weight, waist circumference, BP, cholesterol, glucose while on ADT
  - Potential down regulation of biological processes in tumorigenesis (less aggressive cancer)
- Integrative Medicine
  - Diet/nutrition: Mediterranean or whole food plant-based diet (low inflammatory)
  - Intake in omega 3 fatty acids (good fat)
  - Modified citrus pectin
  - Acupuncture: hot flashes/arthralgias from low testosterone
  - Mind body medicine (Yoga, mindfulness-based meditation): Mood changes

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Algotar et al. (2021); Ornish et al *Proc Natl Acad Sci* (2008); Abrams *JACM* (2018)

What's New in Advanced and Metastatic Prostate Cancer Treatment

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